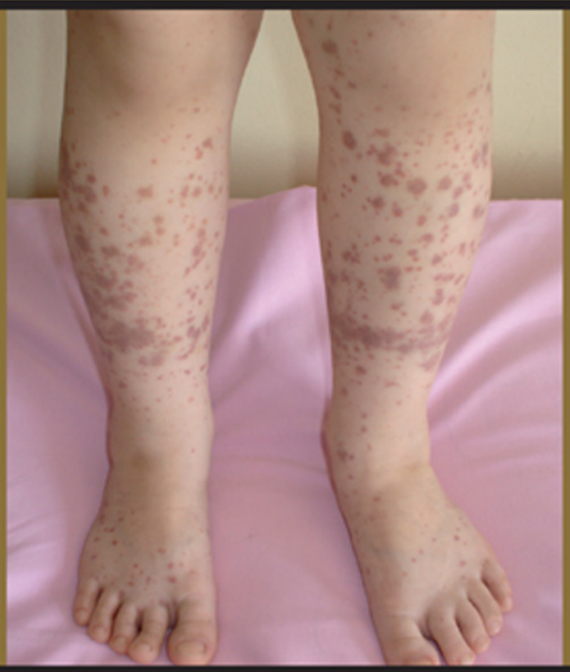
HANDBOOK OF SYSTEMIC AUTOIMMUNE DISEASES
Series Editor: Ronald A. Asherson
Volume 6



Pediatrics in Systemic Autoimmune Diseases

Edited by
Rolando Cimaz & Thomas Lehman

Handbook of
Systemic Autoimmune Diseases

Volume 6

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Handbook of
Systemic Autoimmune Diseases

Volume 6

Pediatrics in Systemic Autoimmune Diseases

Edited by:

Rolando Cimaz
Université Claude Bernard, Lyon, France
Hopital Herriot, Lyon, France
Ospedale Meyer, Florence, Italy

Thomas J.A. Lehman
Hospital for Special Surgery, New York, USA

Series Editor

Ronald A. Asherson

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Paris – San Diego – San Francisco – Singapore – Sydney – Tokyo

Elsevier
Radarweg 29, PO Box 211, 1000 AE Amsterdam, The Netherlands
Linacre House, Jordon Hill, Oxford OX2 8DP, UK

First edition 2008

Library of Congress Cataloging-in-Publication Data
A catalog record for this book is available from the Library of Congress

British Library Cataloguing in Publication Data
A catalogue record for this book is available from the British Library

ISBN: 978-0-444-52971-8
ISSN: 1571-5078

Printed and bound in The Netherlands

08 09 10 11 12 10 9 8 7 6 5 4 3 2 1

Preface

The systemic autoimmune diseases of childhood have always represented a special problem for the physicians and scientists who care for the affected children and study their diseases. Some conditions such as Kawasaki disease are virtually unique to childhood, while systemic lupus erythematosus, progressive systemic sclerosis and juvenile onset spondyloarthropathies may be thought of as the early onset of the same disease which is seen in adults. The autoinflammatory disorders appear to be of clear genetic origin, accounting for their frequent discovery in childhood. For many other conditions such as juvenile dermatomyositis the relationship between the condition seen in children and that seen in adults is less certain. Even within conditions such as juvenile idiopathic arthritis it has become increasingly evident that we are dealing with not one, but many different diseases with only a small percentage of the children having a disease which resembles one seen in adults. It is abundantly clear that children and the majority of their systemic autoimmune diseases are not just "younger/smaller versions of what is seen in adults."

Despite the obvious differences between the autoimmune diseases in adults and in children, in the past the majority of the scientific work that pediatric practitioners must rely on has been drawn from the adult experience. This is changing and there is a new and rapidly expanding cadre of young scientists trained to deal with the specific problems of pediatrics. In this volume we have gathered input from a variety of experts around the world. Each was asked to provide the latest information available in a format that would give the clinician both a clear understanding of what has been done in the past and a scientific basis for deciding what to do for the next afflicted child in their care.

The care of children with systemic autoimmune diseases is moving forward at a rapid pace. This volume will provide a good starting point for physicians and scientists new to the field and for anyone looking for the most up to date summary of a particular disease. While many questions are answered, many more are raised for which we do not yet have the answers. We hope our readers will be inspired to their own research and help to answer them.

Thomas J.A. Lehman and Rolando Cimaz

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Series Editor

Prof. Ronald A. Asherson

Professor Ronald A. Asherson, MD, FACP, MD (Hon) (London), FCP (SA), FACR, is Professor of Immunology (Hon), at the School of Pathology, University of the Witwatersrand, as well as being Consultant Rheumatologist at the Rosebank Clinic in Johannesburg, South Africa. He is also a Visiting Professor at the Systemic Autoimmune Diseases Unit at the Hospital Clinic, Barcelona, Spain where he regularly visits and coordinates research projects.

Professor Asherson qualified in Medicine at the University of Cape Town in 1957 and, after completing his internship, became H/P to Professor Sir Christopher Booth at the Hammersmith Hospital, London, in 1960. In 1961 he accepted a Fellowship at the Columbia Presbyterian Hospital in New York, returning in 1962 to become Registrar and then Senior Registrar till 1964 at Groote Schuur Hospital in Cape Town. After 10 years as a Clinical Tutor in the Department of Medicine, he returned to the United States and was appointed as Assistant Clinical Professor of Medicine at the New York Hospital—Cornell Medical Centre under the late Professor Henry Heineman. From 1981 to 1986 he was associated with the Rheumatology Department at the Royal Postgraduate Medical School of London. It was at that time that he developed his interest in Connective Tissue Diseases and Antiphospholipid Antibodies.

In 1986 he moved to the Rayne Institute and St. Thomas' Hospital in London, where he was appointed Honorary Consultant Physician and Senior Research Fellow. In 1991 he took a sabbatical at St. Luke's Roosevelt Hospital Center in New York, working with Professor Robert Lahita. In 1992 he returned to South Africa for private practice in Johannesburg.

In 1998 he was elected as Fellow of the American College of Physicians (FACP) as well as a Founding Fellow of the American College of Rheumatology (FACR). From 1988 to 1991 he served on the Council of the Royal Society of Medicine in London. In 1992 he was co-winner of the European League Against Rheumatism (EULAR) Prize and in 1993 was the co-recipient of the International League Against Rheumatism (ILAR) Prize, both for his research on antiphospholipid antibodies. In 1994 he was elected a Fellow of the Royal College of Physicians (FRCP) of London. In 2002 he was awarded an Honorary Doctorate in Medicine from the University of Pleven in Bulgaria.

Professor Asherson has been an invited speaker at many universities and International conferences both in the USA and in Europe. He is the author of more than 300 papers on connective tissue diseases and has contributed to more than 30 textbooks of medicine, rheumatology, and surgery as well as having co-edited "*Problems in the Rheumatic Diseases*", the "*Phospholipid Binding Antibodies*", two editions of "*The Antiphospholipid Syndrome*" and "*Vascular Manifestations of the Systemic Autoimmune Diseases*". He is currently engaged in research on connective tissue diseases, particularly on the antiphospholipid syndrome together with colleagues in the USA, Spain, France, and Israel and is in clinical practice in South Africa. In 1999, he was the co-recipient of the Juan Vivancos Prize in Spain and in 2003 was the co-recipient of the Abbott Prize, awarded at the European League Against Rheumatism (EULAR) International Meeting, held in Lisbon, Portugal.

His original description of the "Catastrophic Antiphospholipid Syndrome" and the publishing of more than 40 papers on this new disease was rewarded by the attachment of the eponym "Asherson's Syndrome" to

this condition at the November 2002 International Phospholipid Conference held in Sicily. He has established the first International Committee to study survivors of this syndrome.

He is currently editing a series of 12 volumes entitled ''The Handbook of Systemic Autoimmune Disease'' (Elsevier,) and in September of 2003 was Co-Chairman of the First Latin American Congress on Autoimmunity, held in the Galapagos Islands, Ecuador. He co-chaired and participated in a Session at the Milan Conference on ''Heart, Rheumatism and Autoimmunity'' held in February 2004.

He was awarded an Honorary Fellowship of the Slovakian Rheumatology Association in 2005 and was made an Honorary Life Member of the South African Rheumatism Association in the same year in recognition of his contributions to the study of the Antiphospholipid Syndrome. In 2006 was made a Life member of the South African Medical Association. He was appointed Professor of Immunology (Hon) in the School of Pathology at the University of the Witwatersrand in April of 2006.

Volume Editors

Thomas J. A. Lehman, MD

Dr. Lehman graduated from the University of California at Berkeley in 1970, then *cum laude* from Jefferson Medical College of Thomas Jefferson University in Philadelphia in 1974. He completed his residency in Pediatrics at Childrens Hospital of Los Angeles between 1974 and 1976 and the University of California San Francisco (VMC campus) in 1976–1977. This was followed by a two-year fellowship in Pediatric Rheumatology with Dr. Virgil Hanson at Childrens Hospital of Los Angeles. From 1981 to 1983, Dr. Lehman served as a medical staff fellow in the Arthritis Branch at the National Institutes of Health with an emphasis on the care of patients with systemic lupus erythematosus and animal models of juvenile rheumatoid arthritis.

In 1983 Dr. Lehman returned to Los Angeles as assistant professor of Pediatrics at the University of Southern California in the Division of Rheumatology at Childrens Hospital of Los Angeles. In 1987 he became an associate professor of Pediatrics at Cornell University school of medicine and chief of the division of pediatric rheumatology at the Hospital for Special Surgery in New York. In 1995 he was promoted to full professor.

Dr. Lehman is the author of more than 50 peer-reviewed publications in pediatric rheumatology and many invited manuscripts and textbook chapters devoted to the diagnosis and treatment of childhood rheumatic diseases. He serves on review committees for the NIH, the FDA, the Lupus Foundation, the Canadian Arthritis Society, the March of Dimes, and the Veterans Administration as well as being on the editorial board and a manuscript reviewer for multiple journals.

Rolando Cimaz

Rolando Cimaz works as a pediatric rheumatologist since 2005 at the Hospices Civiles de Lyon (Hopital Edouard Herriot) and is Maitre de Conférences des Universités at Université Claude Bernard-Lyon I in Lyon, France.

He graduated from Milan University in Italy in 1987, and is a specialist in Pediatrics (1991) and in Rheumatology (2003). He has been Professore a Contratto for Milano University (1999–2005), as well as visiting professor, University of British Columbia, Canada (2000). He did his Fellowship in Pediatric Rheumatology in Dallas, Texas, in 1993–1994.

His main interest is pediatric rheumatology, in particular osteoporosis, antiphospholipid antibodies, and neonatal lupus. Currently he is involved in several research projects, nationally and internationally.

He has been in the Council of the Pediatric Rheumatology European Society (treasurer) from 1999 to 2005. He is a member of the American College of Rheumatology, the Italian Society of Pediatrics, the French Society of Pediatric Inflammatory Diseases and the French Society of Pediatric Ortophedics.

He is a co-author of more than 120 articles and 150 abstracts, as well as 18 book chapters, all in the field of pediatric rheumatology. He has also acted as reviewer for several journals: *Pediatric Rheumatology Online Journal*, *Lupus*, *Archives de Pédiatrie*, *Journal of Rheumatology*, *Clinical and Experimental Rheumatology*, *Lancet*, *Pediatrics*, *Journal of Pediatrics*, *Scandinavian Journal of Rheumatology*, *American Journal of Kidney Diseases*, *Rheumatology*, *European Journal of Pediatrics*, *European Journal of Pain*, *Vaccine*, *Pediatric Infectious Disease Journal*, *Arthritis Care and Research*, *Arthritis and Rheumatism*, *Annals of the Rheumatic Disease*.

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List of Contributors

Alexa Adams
Division of Pediatric Rheumatology, Cornell University Hospital for Special Surgery, New York, NY, USA

Tadej Avčin
Department of Allergology, Rheumatology and Clinical Immunology, University Children's Hospital Ljubljana, University Medical Centre, Ljubljana, Slovenia

Antonio Brucato
Department of Internal Medicine, Ospedali Riuniti, Bergamo, Italia

Rubén Burgos-Vargas
Rheumatology Department, Hospital General de México, Mexico City, Mexico

Rebecca ten Cate
Department of Pediatrics, Leiden University Medical Center, Leiden, The Netherlands

Rolando Cimaz
Department of Pediatrics, Hopital Edouard Herriot and Université Lyon 1, Lyon, France and Department of Pediatrics, Anna Meyer Children's Hospital, University of Florence, Firenze, Italy

Koert Dolman
Department of Pediatrics, Academic Medical Centre, Amsterdam, The Netherlands

Ali Duzova
Department of Pediatrics, Hacettepe University, Faculty of Medicine, Ankara, Turkey

Fernanda Falcini
Department of Pediatrics, Anna Meyer Children's Hospital, University of Florence, Firenze, Italy

Flavio Fantini
Pediatric Rheumatology Unit, Chair and Department of Rheumatology, Gaetano Pini Institute of Milan, Milano, Italy

Ivan Foeldvari
Klinikum Eilbek, Dehnhaide 120, 22081 Hamburg, Germany

Joost Frenkel
Department of Paediatrics, Division of Rheumatology, Allergy, Immunology, University Medical Centre, Lundlaan 6, 3584 EA Utrecht, The Netherlands

Valeria Gerloni
Pediatric Rheumatology Unit, Chair and Department of Rheumatology, Gaetano Pini Institute of Milan, Milano, Italy

Hermann J. Girschick
Universitäts-Kinderklinik Würzburg, Germany

Maria Odete Esteves Hilário
Pediatric Rheumatology Unit, Department of Pediatrics, Universidade Federal de São Paulo, Brazil

Hal M. Hoffman
Division of Rheumatology, Allergy and Immunology, University of California—San Diego School of Medicine, San Diego, CA, USA

Hans-Iko Huppertz
Prof. -Hess-Kinderklinik, Klinikum Bremen-Mitte, Sankt-Jürgen-Strasse, Bremen, Germany

Isabelle Koné-Paut
Department of Pediatrics and Pediatric Rheumatology, Bicêtre University Hospital, Le Kremlin Bicêtre, France

Loes M. Kuijk
Department of Paediatric Immunology, University Medical Centre Utrecht, Utrecht, The Netherlands

Ronald M. Laxer
The Hospital for Sick Children, University Avenue, and University of Toronto, Toronto, Ont., Canada

Thomas J.A. Lehman
Division of Pediatric Rheumatology, Cornell University Hospital for Special Surgery, New York, NY, USA

Emma MacDermott
Division of Pediatric Rheumatology, Cornell University Hospital for Special Surgery, New York, NY, USA

Susan Maillard
Great Ormond Street Hospital, NHS Trust, Institute of Child Health, University College London, London WC1N 1EH, UK

Alberto Martini
Dipartimento di Pediatria, Università di Genova and Pediatria II, Istituto G. Gaslini, Genova, Italy

Bénédicte Neven
Department of Paediatric hemato-immunology and rheumatology, Hopital Necker-Enfants Malades, Paris, France

Seza Ozen
Department of Pediatrics, Hacettepe University, Faculty of Medicine, Ankara, Turkey

Clarissa Pilkington
Great Ormond Street and University College Hospitals and Juvenile Dermatomyositis Research Centre, Institute of Child Health, UCL, London, UK

Irene Pontikaki
Pediatric Rheumatology Unit, Chair and Department of Rheumatology, Gaetano Pini Institute of Milan, Milano, Italy

Berent J. Prakken
Wilhelmina Children's Hospital University Medical Centre, Lundlaan 6, 3584 EA Utrecht, The Netherlands

Angelo Ravelli
Dipartimento di Pediatria, Università di Genova and Pediatria II, Istituto G. Gaslini, Genova, Italy

Carlos D. Rose
Department of Pediatrics, Thomas Jefferson University, Division of Rheumatology duPont Children's Hospital, Wilmington, DE, USA

Rayfel Schneider
The Hospital for Sick Children, University Avenue, and University of Toronto, Toronto, Ont., Canada

Maria Teresa Ramos Ascensão Terreri
Pediatric Rheumatology Unit, Department of Pediatrics, Universidade Federal de São Paulo, Brazil

Carine H. Wouters
Pediatric Rheumatology Unit, University Hospital, Leuven, Belgium

Nico M. Wulffraat
Wilhelmina Children's Hospital University Medical Centre, Lundlaan 6, 3584 EA Utrecht, The Netherlands

Francesco Zulian
Department of Pediatrics, Rheumatology Unit, University of Padova, Padova, Italy

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Rolando Cimaz and Thomas Lehman, editors

CHAPTER 1

Oligoarticular and Polyarticular Juvenile Idiopathic Arthritis

Rebecca ten Cate[a,*], Koert Dolman[b]

[a]*Department of Pediatrics, Leiden University Medical Center, Leiden, The Netherlands*
[b]*Department of Pediatrics, Academic Medical Centre, Amsterdam, The Netherlands*

1. Introduction

When a child under the age of 16 years has arthritis with a duration exceeding 6 weeks the diagnosis of juvenile idiopathic arthritis (JIA) is probable. Other diseases need to be excluded especially in the absence of commonly found serological factors as antinuclear antibodies (ANA).

JIA is a heterogeneous group of diseases and only the subtype with IgM rheumatoid factor (RF) is thought to be the equivalent of adult rheumatoid arthritis (RA).

In the past, several names have been given to chronic arthritis in childhood such as juvenile RA and juvenile chronic arthritis. Since an ILAR work force (last revised in 2007) proposed the name juvenile idiopathic arthritis (JIA) this name has been adopted, both in Europe as in the USA. Seven subtypes of JIA are recognized (Table 1) (Petty et al., 1998).

Usually children with JIA are first seen by an orthopedic surgeon or a pediatrician and referred to a pediatric rheumatologist in a later stage (Cuesta et al., 2000).

As damage to the joints can be prevented by early and adequate medical therapy permanent post-academic education on the subject of rheumatic diseases in childhood is mandatory in order to obtain early referral of children with a suspicion of inflammatory arthritis.

Having (a child with) JIA creates a considerable burden for the child, the family, friends, and school (Duffy, 2005) and interventions have been developed to reduce the impact of the disease (Akikusa and Allen, 2002). The importance of adequate patient and parent information and education is emphasized.

1.1. Definitions

Oligoarticular JIA is defined as arthritis in 1–4 joints during the first 6 months with exclusion of

- Psoriasis, diagnosed by a dermatologist in at least one first or second grade family member;
- HLA-B27 associated disease in at least one first or second grade family member;
- presence of RF;
- arthritis in a boy older than 8 years and HLA-B27 positive; and
- systemic JIA.

Table 1
Subtypes of Juvenile Idiopathic Arthritis (ILAR-classification)

Systemic
Polyarticular RF negative
Polyarticular RF positive
Oligoarticular
Persistent
Extended
Psoriatic arthritis
Enthesitis-related arthritis
Other arthritis

*Corresponding author.
Tel.: +31-715264131; Fax: +31-715248198.
E-mail address: R.ten_Cate@lumc.nl (R. ten Cate).

DOI: 10.1016/S1571-5078(07)06005-9

IgM RF negative polyarticular JIA is defined as arthritis in five or more joints during the first 6 months with negative tests for IgM RF and exclusion of systemic JIA.

IgM RF positive polyarticular JIA is defined as arthritis in five or more joints during the first 6 months and presence of the IgM RF on two occasions with an interval of 3 months with the exclusion of systemic JIA.

2. Prevalence/epidemiology

Joint pain, joint swelling, and morning stiffness are not uncommon in childhood. However, only a minority of children with these symptoms, suggestive of arthritis are diagnosed with JIA by objective criteria and thorough physical examination performed by an experienced pediatrician or (pediatric) rheumatologist. The exact incidence and prevalence of JIA is unknown. Studies on these topics have shown different results, influenced by the different populations that have been studied as well as ethnicity and environmental factors (Nielsen et al., 1999). Also seasonal variation has been described. The incidence probably varies from 1 to 20 per 100,000 in the population (Gare, 1999; Moe and Rygg, 1998). Using the American College of Rheumatology (ACR) criteria, the prevalence of JIA also shows a considerable variability ranging from 8 to 150 per 100,000 (Oen and Cheang, 1996; Gare, 1999). Several studies on the prevalence of JIA have suggested that these figures might underestimate the true prevalence. Close examination of the children under study and restriction to those who are at risk, will probably lead to a considerably increase in the prevalence of JIA.

Although JIA can be divided into different subgroups with different peak incidences of age, it is obvious that despite these differences, generally more girls than boys develop JIA except the systemic onset type.

3. Etiology and pathogenesis

JIA probably has a multifactorial etiology. Genetic predisposition, environmental influences, provoking infections, hormonal factors, and vulnerability in childhood are involved in the development of JIA (Mason and Reed, 2005; Olson, 2003). The genetic predisposition includes multiple genes that are related to immunity and inflammation.

HLA class I and class II alleles are both associated with an increased risk to develop JIA. Early-onset oligoarticular JIA in girls is related to the class I antigen HLA-A2. Persistent and extended oligoarticular JIA are associated with class II antigens HLA-DRB1*08 and HLA-DRB1*11, DQA1*04, DQA1*05, and DQB1*04. Enthesitis-related JIA is associated with HLA-B27 (class I) and the class II antigens HLA-DRB1*01 and HLA-DQA1*0101. Systemic-onset JIA is related to HLA-DRB1*11 (Prahalad, 2004; Forre and Smerde, 2002; Thomson and Donn, 2002). The genetic predisposition also includes genes that are related to cytokine production (Fishman et al., 1998; Rosen et al., 2003).

Many immunological factors are involved in the pathogenesis of this autoimmune disease. Cytokine production, T-lymphocytes, immune complexes (ICs), and immunodysregulation all lead to inflammation of the joint. However, it is still a matter of debate whether JIA predominantly is an immunogenetically determined disease or an antigen-driven immunological response (Moore, 1999).

Cytokines that are involved in the pathogenesis are TNF-α, IL-1, IL-2, IL-4, IL-6, IL-7, and IL2R (Mangge et al., 1999; Woo, 2002). Concentrations of these cytokines are increased, both in plasma as well as in the synovial fluid. In systemic JIA IL-6 levels increase during active disease and correlate with fever, hypergammaglobulinemia, acute phase proteins like CRP, anemia and thrombocytosis (Fishman et al., 1998). The effect of IL-6 is prolonged after forming a complex with its soluble receptor, sIL-6R. IL-1α and IL-1β both are particularly involved in oligoarticular and polyarticular JIA and related to disease activity. Increase of IL-1α has been detected in plasma and increase of IL-β in synovial fluid. Soluble TNF-α is also increased in plasma as well as synovial fluid (Mangge et al., 1995).

Bacterial infections not only can cause reactive arthritis, but are also involved in the development of JIA. In children with JIA humoral as well as

cellular immune responses against bacterial heat shock proteins (HSP) have been described. These HSP are highly conserved proteins of bacterial origin and have been demonstrated in plasma and synovial fluid of JIA patients. T-lymphocyte responses to HSP-60 were demonstrated before remission of JIA and it thus has been speculated that induction of immunotolerance to specific T-cells might be beneficial for JIA patients and nasal administration of HSP-60 might be used as future immunotherapy (Puga Yung et al., 2003; van Eden et al., 2005; Albani and Prakken, 2006).

Complement activation is also involved in the pathogenesis of JIA. Complement components of both, the classical pathway (C4) and the alternative pathway (Bb), showed increased levels and correlated with disease activity (Jarvis et al., 1994, Aggarwal et al., 2000). Mannose binding lectin (MBL) is a major component of the lectin route of complement activation. Mutations in the *MBL2* gene result in deficient MBL plasma concentration (Turner, 1996; Gadjeva et al., 2001). An increased frequency of mutations in exon 1 of the *MBL2* gene has been demonstrated in RA and JIA patients, indicating a possible role of MBL deficiency in the pathogenesis of JIA (Jacobson et al., 2001; Saevarsdottir et al., 2001). It can be speculated that MBL deficiency leads to an impaired innate immunity, and subsequent increased risk of infections. The prolonged presence of infectious agents in the host may alter the immunologic repertoire, resulting in inflammatory disease. The possible causative role of infection in JIA is also been demonstrated by increased incidence of chronic arthritis in patients with hypogammaglobulinemia, IgA deficiency, and C2 deficiency (Davies et al., 2001). It should be noted that bacterial cell wall fragments as well as bacterial DNA have been detected in the synovial tissue, where they could promote synovial inflammation (van der Heijden et al., 2000).

Furthermore, MBL deficiency might lead to defective clearance of ICs and apoptotic cells, as seen in individuals with C1q deficiency. MBL and C1q are molecules with similar characteristics. Another possibility is that MBL is involved in the recognition of an infectious agent in the pathophysiology of the disease. Low or absent MBL serum concentration leads to decreased complement activation and ineffective clearance of the pathogen or pathogen-derived antigens.

Circulating ICs have been demonstrated in JIA. These ICs have been detected in plasma and synovial fluid and revealed complement activation as well as cytokine secretion potential. The ICs correlated with disease activity and systemic features of JIA (Jarvis, 1998). The activating capacity of ICs is related to their size. Although often undetectable in plasma of JIA patients, immunoglobulin M (IgM) RF is bound to the ICs and concentration of this RF related to disease activity (Jarvis et al., 1992).

The T-lymphocyte mediated immune response is important in chronic inflammation. T-lymphocytes are the most prominent mononuclear cells in synovial fluid. The T-lymphocytes can be differentiated in CD4 (helper/inducer) and CD8 (suppressor/cytotoxic) cells with different functional abilities. The results of different studies on the possible pathogenetic role of CD4+ and CD8+ T-lymphocytes have been inconsistent. Increased CD8+ T-lymphocytes have been demonstrated in systemic and polyarticular JIA, however other studies showed decreased CD8+ T-lymphocytes, especially in systemic disease (Murray et al., 1996; Gattorno et al., 1997; Raziuddin et al., 1998). Decreased CD4+ T-lymphocytes might be due to autoantibodies in JIA patients with active disease. It has been suggested that disturbed function of CD8+ T-lymphocytes play a role in the pathogenesis of JIA, resulting in the production of autoantibodies. Although decreased CD4+/CD8 ratio has been described, others found normal CD4/CD8 ratios (Murray et al., 1998). The pathogenetic importance of defective T-lymphocyte regulation is demonstrated by increased HLA-DR antigens and very-late-activation antigen-1 (VLA-1), indicating T-lymphocyte activation. In general, synovial T-lymphocytes reveal increased activation markers. Several studies reported no differences in T-lymphocytes derived from synovial fluid or plasma. T-lymphocyte proliferation appeared to be correlated with disease activity, and increased in JIA patients with active disease, but was normal in patients with inactive disease (Mangge and Schauenstein, 1998).

Disturbed Th1/Th2 interaction has also been suggested to be involved in the pathogenesis of JIA (Woo, 1998). Increased production of IFN-γ by synovial T-lymphocytes indicated marked Th1 response. Others have found mixed Th-lymphocyte response in systemic JIA (Raziuddin et al., 1998).

B-cell concentration is normal in oligoarticular and polyarticular JIA, however, generally increased in patients with systemic JIA. Total levels of IgG might be elevated and a diversity of autoantibodies can be detected in sera of JIA patients. The increased IgG levels are partly due to nonspecific inflammation. Possible ocular involvement is reflected by the presence of ANA (Adib et al., 2005).

The pathogenesis of JIA is also influenced by psychological factors. Dysregulation of the autonomic nervous system is related to impaired immunologic response and possible development of autoimmune disease (Kuis et al., 1996).

The clinical heterogeneity probably reflects different pathogenetic mechanisms in the JIA subtypes.

4. Clinical manifestations

When taking a history from (parents of) children with JIA pain is usually not a major symptom at onset (McGhee et al., 2002) but the parents of young children may have noticed a regression in the motor phase of their child (Ansell, 2000). Especially an asymmetric pattern is alarming. Swelling of the knee or ankle is often noticed by chance when parents are undressing or bathing the child. Other signs at onset can be behavioral problems, limping or refusal to walk. In older children, especially in those with (IgM RF positive) polyarticular JIA, pain can be a presenting symptom. General malaise, low-grade fever, and fatigue can be present in severely affected children, mostly in those with polyarticular JIA. Morning stiffness and stiffness after spending much time in the same position are common. The onset of JIA may be acute but usually is insidious.

At physical examination the general condition of the child should be noticed. They may look anemic and, when suffering from systemic features, ill and painful. Length and weight should be measured regularly as general growth impairment points at active disease and this may be aggravated by the use of glucocorticoids.

In children with IgM RF positive polyarticular JIA rheumatoid nodules at the extensor surface of the elbows or at the lateral sides of the feet can be found.

Asymmetrical diffuse edema of hands or lower leg and ankle in a sock-like form can be found in some children with polyarticular JIA (Bardare et al., 1997). This lymphedema is usually nonpitting and not painful.

In children with JIA that develop chronic anterior uveitis (CAU) before the onset of arthritis secondary changes in the eyes can be noticed. Irregular pupils that do not respond properly to light may reflect the presence of synechiae. Calcifications of the cornea may be present in the form of band keratopathy.

Signs of arthritis are local swelling, increased temperature, pain elicited by movement, and limitation of motion. Local discoloration is very unusual except over the small joints in the hands and feet (Gedalia et al., 1989) and when present over a knee or ankle should be a reason for reconsideration of the diagnosis.

Establishing arthritis can be difficult especially in young children with puppy fat. An observation by an experienced child physiotherapist or the use of ultrasound can be helpful.

In children with oligoarticular JIA asymmetric swelling of large joints like the knee, ankle, and elbow are most frequent, while in children with polyarticular JIA symmetric involvement of the small joints of the hands and feet is more common. In children with IgM RF swelling around the styloid processus of the ulnar can be prominent.

In children with persistent oligoarticular JIA the number of joints involved remains four or less throughout the course of the disease. In extended oligoarticular JIA the arthritis shows extension to polyarthritis after the first 6 months.

Several severe complications may develop in children with oligoarticular and polyarticular JIA.

Impaired growth and delay of puberty may be the result of disease activity (Saha et al., 1999) and the use of glucocorticoids aggravates the

impairment of linear growth. Muscle atrophy and leg length discrepancy by accelerated local growth are frequent findings in longstanding asymmetric arthritis (Vostresj and Hollister, 1998).

Decreased bone mineral content can be observed in a quarter of children with early onset JIA (Lien et al., 2005). Osteopenia can be detected in adolescents with early-onset JIA (Lien et al., 2003).

Cardiac manifestations are rare but may be the cause of significant morbidity, especially valvular disease in RF positive polyarticular JIA (Bultink et al., 2002).

Parenchymal lung disease is an infrequent finding, but pulmonary function is impaired in some children with JIA (Knook et al., 1999).

Temporomandibular involvement is common in children with oligoarticular and polyarticular JIA. Because of the high prevalence and discrepancy between clinical signs and presence of arthritis in the temporomandibular joint regular orthodontic evaluation and orthopantomograms are recommended to enable early intervention (Twilt et al., 2004). Involvement of the temporomandibular joints may lead to impaired opening of the mouth and retrognathia (Twilt et al., 2004).

CAU is reported in up to 20% of patients with JIA and is the main secondary disease in JIA. It is strongly associated with the presence of ANA. All children with JIA need to be screened with regular intervals (see Table 2) as this type of uveitis is asymptomatic until complications develop. The classic presentation of CAU is an anterior, non-granulomatous, uni- or bilateral uveitis. Slit-lamp examination is necessary to detect the inflammatory cells in the anterior chamber of the eye. It is therefore essential that all children with JIA are seen by an ophthalmologist at regular intervals.

Early detection and treatment of CAU is of major importance to avoid sight-threatening complications including band keratopathy, synechiae, cataract, glaucoma, macular edema, decreased vision, phthisis bulbi, and blindness (Boer, 2003). Young age of onset (arthritis and uveitis), active uveitis at the time of onset of arthritis and high uveitis activity at the time of diagnosis is associated with a higher risk of sight-threatening complications. The recommended frequency is listed in the Table 2.

Table 2
Recommended frequency of ophthalmological investigation in children with persistent or extended oligoarticular JIA according to the American Academy of Pediatrics (1993)

Subtype of arthritis	Onset of arthritis (years of age)	
	<7[a]	≥ 7[b]
Persistent oligoarticular		
+ANA	H[c]	M
−ANA	M	M
Extended oligoarticular		
+ANA	H[c]	M
−ANA	M	M

Notes: H: high risk = every 3–4 months ophthalmological investigation; M: medium risk = every 6 months ophthalmological investigation; and L: low risk = every 12 months ophthalmological investigation (all other patients with JIA).

[a] All patients are regarded low risk 7 years from onset of arthritis; ophthalmological investigation yearly.

[b] All patients are regarded low risk 4 years from onset of arthritis; ophthalmological investigation yearly.

[c] All patients with high risk are regarded medium risk 4 years from onset of arthritis.

Generally patients with JIA are divided into high- and low-risk groups depending on known risk factors for uveitis. Risk factors are young age of onset, female gender, oligoarticular onset of JIA, and presence of ANA. Onset of arthritis usually precedes the onset of uveitis, but uveitis may also start first. The risk of developing uveitis is the highest shortly after onset of arthritis and decreases gradually after the first year.

5. Diagnostic investigations

In all children with chronic arthritis a full blood count is indicated.

In most children with oligoarticular JIA normal hemoglobin levels are found. In some children with oligoarticular JIA with high disease activity and in children with polyarthritis moderate normocytic, hypochromic anemia can be present characteristic of the chronic anemia of inflammation (Bertero and Caligaris-Cappio, 1997). Anemia and raised platelet count are associated with a less favorable prognosis. In a child with other systemic

features like fever, skin rash, and lymph node enlargement other diagnoses like systemic JIA, other autoimmune diseases (systemic lupus erythematosus (SLE)), or malignancy should be considered.

The leukocyte count usually is normal. In children with active disease leukocytosis may be present. During treatment with sulfasalazine or methotrexate a low leukocyte count may represent drug-induced bone marrow suppression. In a child with possible JIA a low leukocyte count could be the key to another diagnosis such as SLE or leukemia.

Platelets are within the normal range in most children with oligo- and polyarticular JIA, but may be raised in children with high disease activity.

The acute phase reactants (ESR, CRP) can be normal in children with JIA, but may be raised at onset of the disease and during exacerbations (Giannini and Brewer, 1987).

Blood chemistry is at onset of JIA usually not abnormal. The level of serum urea can increase during the use of non-steroidal anti-inflammatory drugs (NSAIDs). Liver function tests need to be carefully followed during the use of sulfasalazine and methotrexate.

In the diagnostic phase broad screening for infectious causes of arthritis is indicated as a variety of micro-organisms may induce arthritis (see differential diagnosis). The onset of JIA and its exacerbations are frequently preceded by infections (Pugh et al., 1993).

In children with active (poly)arthritis a raised IgG can be present. During treatment with sulfasalazine the level of IgA may decrease (van Rossum et al., 2001).

ANA are found in ~75% of children with oligoarticular JIA and in 50% of children with polyarticular JIA. Their presence is strongly associated with the risk to develop CAU. A positive ANA is rare in children, but can be a temporary false positive finding in infections (streptococci, viral). Antibodies to dsDNA are usually not found. When they are detected the child could have SLE. Antibodies to extractable nuclear antigens (anti-ENA) are rarely present; anti-ENA may indicate other autoimmune diseases such as mixed connective tissue disease (MCTD).

Tests for the IgM RF are less frequently positive in children with JIA than in adults with RA. In 5–10% of children with JIA IgM RF can be detected during the course of the disease. Their presence is associated with onset of disease in girls around 13 years of age with clinical signs as in RA, progressive disease and early erosions. Anti-cyclic citrullinated peptide antibodies can be detected in the sera of patients with JIA but almost exclusively in the subset of children with IgM RF-positive disease (van Rossum et al., 2003a).

Serum complement levels usually are within the normal ranges, but may be elevated at onset and during exacerbations of the illness.

Analysis of the synovial fluid may provide valuable information in the diagnostic phase of a child with monoarthritis. The number of leukocytes reflects the severity of inflammation. A low leukocyte count ($< 2 \times 10^9$) is unlikely in infectious arthritis and suggests a mechanical disorder of the joint. Gram preparation and culture are indispensable to rule out infection. PCR for *Borrelia burgdorferi* and *Mycobacterium tuberculosis* are available.

In children with oligoarticular and polyarticular JIA the synovial fluid is yellow with decreased viscosity. The white cell count is usually around $20{,}000 \times 10^9\,L^{-1}$ with predominantly polymorphonuclear neutrophils and mononuclear cells.

In a child with a chronic monoarthritis without circulating ANA a synovial biopsy is rarely necessary to exclude local abnormalities of the synovial membrane when MRI findings are insufficient to make a diagnosis. In children with JIA the histological finding is a non-specific chronic inflammation.

For the follow-up of radiological damage by JIA plain X-rays are used. At onset of the disease usually only soft tissue swelling and periarticular osteopenia can be detected. During the course of the disease various radiological abnormalities may develop (van Rossum et al., 2003b). Ossification centers can develop earlier by increase of blood flow in the involved extremity resulting in overgrowth, but eventually premature closing of the epiphysis may lead to stunting of bone growth. Loss of cartilage can be reflected by narrowing of the joint space. Development of erosions in an

early stage can be present in children with IgM RF polyarticular JIA, but erosions can also be detected in children with longstanding active disease. A radiological scoring system for children with JIA has been developed (van Rossum et al., 2005).

For specific problems in individual joints ultrasound or MRI can be helpful.

6. Differential diagnosis

Joint complaints are relatively frequent in childhood, but usually self-limiting and seldom require referral to a hospital. For a correct differential diagnosis, clear difference must be made between myalgia, arthralgia, arthritis, and possible involvement of the bones.

Reactive arthritis often has an acute onset and will recover with or without medication within approximately 6 weeks. Duration of the arthritis of more than 6 weeks is called chronic arthritis. The most frequent cause of chronic arthritis in childhood is JIA. Not only infection or inflammatory diseases can cause joints complaints, other possibilities include traumatic, metabolic, hematological, malignant, and even psychogenic causes (Malleson, 1997).

Infectious or bacterial arthritis is an acute illness, also called septic arthritis (Ross, 2005). The child with septic arthritis is often very ill with high fever, and refuses to use the involved joint. One of the most important characteristics is the extreme pain. The bacteria enter the joint either by hematological spread or directly by penetration of the skin. Physical examination should always include inspection of the skin to detect a porte d'entrée which might lead to identification of the micro-organism. The micro-organisms that are most frequently involved are *Staphylococci* and *Streptococci*. When bacterial arthritis is suspected, puncture of the joint to obtain synovial fluid should be performed for analysis on leukocyte count and bacterial culture.

It should be taken into account that osteomyelitis in the vicinity of a joint may give a clinical picture that is similar to that of infectious arthritis without yielding a positive culture of the synovial fluid (Frank et al., 2005).

Another micro-organism that can cause arthritis is *Borrelia burgdorferi* (Hengge et al., 2003). Lyme arthritis is often preceded by erythema migrans, myalgia and arthralgia, that can be followed by recurrent as well as chronic arthritis (Huppertz, 2001). Only in the minority of the patients a tick bite is remembered. After the erythema migrans, arthritis can develop even after months, often starting in one or both knees in episodes (Eppes, 2003). Chronic arthritis occurs in approximately 20% of patients with Lyme arthritis, most frequent as mono-arthritis of the knee. Diagnostic tests include polymerase chain reaction (PCR) of synovial fluid and serology. The presence of anti-*Borrelia* IgG antibodies is not definite proof of Lyme arthritis because 5% of the adult population have positive IgG antibodies due to asymptomatic infection in the past. Anti-*Borrelia* IgM antibodies become positive after approximately 6 weeks and are present during months, IgG antibodies can be detected during years. Lyme-arthritis has a good prognosis with complete recovery with antibiotic therapy (Weinstein and Britchkov, 2002).

Arthritis can also develop after viral infections, i.e., parvovirus, rubella, hepatitis B, as well as viruses of the herpesgroup, adenoviruses, and para-myxoviruses (Calabrese and Naides, 2005). Most of these viral infections will lead to reactive arthritis and detection of the virus in the synovial fluid is often negative. Viral arthritis generally completely resolves within 6 weeks although chronic duration is possible. Arthritis can develop even after vaccination. Clinical presentation, viral exanthema, and duration of the arthritis are helpful in the diagnosis of possible viral arthritis.

Mycoplasma pneumonia is another micro-organism that can be associated with arthritis as well as spondylarthropathy in children (Harjacek et al., 2006). Important symptoms include fever, cough, headache, and myalgia. Approximately 30% of the children with *M. pneumonia* infection will develop arthritis.

Reactive arthritis can develop after viral infections, *Neisseria meningitidis* infection, as well as gastro-enteritis by *Salmonella*, *Shigella*, *Campylobacter*, or *Yersinia* (Flores et al., 2003; Leirisalo-Repo, 2005).

Reiter's syndrome is an example of reactive arthritis, associated with HLA-B27, characterized by arthritis, conjunctivitis, and urinary tract infections (Pepmueller and Moore, 2000; Toivanen and Toivanen, 1999).

Acute rheumatic fever (ARF) is caused by Group A beta-hemolytic *Streptococci* (GABHS) (Carapetis et al., 2005). It develops approximately 3 wk after the GABHS infection, characterized by angina, high fever, illness, and headache. A sore throat is not always present. Arthritis is present in 80% of the patients, often with acute onset, painful polyarticular, migrating from one joint to another, and preferentially involving the large joints of the lower extremities (Lennon, 2004). The diagnosis of ARF is made according to the Jones criteria. Carditis with possible heart failure is an important complication of ARF that occurs in 50% of the patients. Mitral and aortic valve stenoses can develop. Other complications include Sydenham's chorea, subcutaneous noduli, erythema marginatum, and (cutaneous) vasculitis (Tani et al., 2003).

Reactive arthritis can develop after a streptococcal infection without fulfilling the Jones criteria. This arthritis is often less severe, not migrating, however with a longer duration. Not only GABHS but also other *Streptococci* species can cause this form of arthritis (Mackie and Keat, 2004). Diagnostic tests include bacterial culture of the throat, nose and/or ears, as well as anti-streptolysin-O-antibody titer and anti-Dnase-B (Ahmed and Ayoub, 2001; Petersel and Sigal, 2005).

Polyarthritis can be the first clinical sign of autoimmune diseases like SLE, juvenile dermatomyositis (JDM), scleroderma, Sjögren syndrome (SS), MCTD, and systemic vasculitis. Apart from arthralgia, arthritis and myalgia, these autoimmune diseases are characterized by organ involvement and positive autoimmune serology.

Hemophilia as well as sickle cell disease are both hematological disorders with possible involvement of the joints. Vaso-occlusive episodes can be very painful and difficult to distinguish from arthritis (Avina-Zubieta et al., 1998).

Malignancies like lymphoma, Hodgkin disease, osteosarcoma, Ewing sarcoma, as well as neuroblastoma can lead to bone pain, arthralgia, and/or swelling of the joints. Bone and joint pain during the night is one of the most characteristic clinical signs for malignancy. Differentiation between systemic JIA and malignancy can be difficult when general malaise, fever, anemia, and leukocytosis are present (Cabral and Tucker, 1999).

Another group of diseases that can present with arthritis, as well as arthralgia or myalgia, are the periodic fever syndromes like familial mediterranean fever (FMF), hyper IgD syndrome, tumor necrosis factor receptor-1 associated periodic syndrome (TRAPS), Muckle-Wells syndrome, and pFAPA (fever, aphtous stomatitis, pharyngitis, and adenitis) (McDermott and Aksentijevich, 2002; Padeh, 2005; Stojanov and Kastner, 2005).

Other possible causes of arthritis and arthralgia in childhood include orthopedic conditions such as coxitis fugax, Perthes disease, epiphysiolysis, Osgood-Schlatter disease, chondromalacia, hypermobility syndromes, and trauma (Grahame, 2000).

7. Treatment

The treatment of children with JIA is mostly medical but physiotherapy and other non-pharmacological therapies also form a major component. Many children are referred to a rehabilitation center where these therapies can be organized in a multidisciplinary way.

There are not many anti-rheumatic drugs that are used based on evidence but progress is made in extending the spectrum of effective drugs (Hashkes and Laxer, 2005). The availability of biologic therapies has made a significant difference for children that appeared to be refractory to all previous used anti-rheumatic drugs.

To measure efficacy of medical treatment a definition of improvement (Giannini et al., 1997) has been developed using a core set of outcome variables and a definition of remission has been proposed (Wallace et al., 2004, 2005).

As early cartilage loss is demonstrated in children with JIA and prognosis is not as favorable as was thought previously, treatment nowadays is more vigorous. In absence of clear prognostic

factors medical treatment still consists of a combination of NSAIDs with a disease modifying antirheumatic drug (DMARD). Illustrative algorithms for children with oligoarticular and polyarticular JIA can be found in the paper by Hashkes and Laxer (2005).

7.1. Drugs used in children with JIA

NSAIDs are effective in suppressing fever and signs of inflammation as pain and stiffness. Naproxen, ibuprofen, and indomethacin are frequently used. Pseudoporhyria can occur with the propionacid derivatives like naproxen and ibuprofen and can induce scarring of sun-exposed areas. Indomethacin can cause headache and malaise in some children.

As DMARDs hydroxychloroquine, sulfasalazine, methotrexate, and leflunomide are used. Regular blood checks are advised, especially liver function tests. Retinopathy can rarely occur as adverse reaction to hydroxychloroquine. Ophthalmological follow up is advised every 6 months.

Sulfasalazine is effective and safe in children with oligoarticular and polyarticular JIA, but not well tolerated in about one third of children (van Rossum et al., 1998). Sulfasalazine may induce or worsen low levels of IgA (van Rossum et al., 2001).

Methotrexate has gained the position of gold standard for RA and is also very effective in children (Giannini et al., 1992). It is given once a week as tablets or subcutaneous injection. The use of folic acid can decrease nausea, malaise, and mucosal ulcerations (Hunt et al., 1997). In some children anti-emetics are necessary to alleviate the weekly misery of methotrexate. During treatment with methotrexate vaccination with life attenuated viruses should be avoided.

Leflunomide is tolerated well by most children but has slightly less efficacy than methotrexate (Silverman et al., 2005).

The use of systemic glucocorticoids should be restricted to life-threatening complications. In some children low to medium doses glucocorticoids are used to bridge the interval between start and moment of effectiveness of DMARDs.

Glucocorticoids are mainly used as intra-articular injection with good results (Hertzberger-ten cate et al., 1991; Padeh and Passwell, 1998) and no short-term adverse effects on the cartilage (Huppertz et al., 1995). Leakage to the system may induce secondary Cushing syndrome (Gondwe et al., 2005). Triamcinolon hexacetonide has shown to be superior to triamcinolone acetonide judged by the duration of remission (Zulian et al., 2004).

The biologicals have extended the therapeutic arsenal for children with resistant JIA. To hamper TNF-α both soluble receptors (etanercept) and blocking antibodies (infliximab, adalumimab) are available, but for the use in children only etanercept is registered. The eligible child has to fail on sufficiently high dosed methotrexate or show unacceptable side effects. Approximately 75% of children with longstanding, resistant, polyarticular course JIA responded to etanercept in a blinded randomized controlled trial (Lovell et al., 2000). The clinical improvement lasts in the majority of patients for over 2 years (Lovell et al., 2003) without significant adverse events (Horneff et al., 2004).

In the near future the development of other anti-cytokine directed strategies holds great promises for the treatment of children with resistant JIA although the concern about infections and long-term consequences remains (Carrasco et al., 2004).

Autologous stem cell transplantation was used as an experimental treatment in children with therapy refractory polyarticular and systemic JIA (De Kleer et al., 2004). In recent years less children were candidates for this procedure as a consequence of the effectiveness of biologicals.

Progress has been made in the treatment of the complications of JIA. The experimental use of recombinant human growth hormone restores linear growth and improves body composition in children with glucocorticoid induced impaired growth and severe osteoporosis (Simon et al., 2003; Grote et al., 2006).

The treatment of uveitis consists of topical and systemic drugs. Topical steroids are the first choice of treatment and sometimes are combined with mydriatic agents. Subtenon injections of steroids can be used. A large group of patients with uveitis

needs systemic treatment to achieve adequate disease control. Systemic glucocorticoids are effective, but the use should be minimized because of the harmful effects on bone and growth. Systemic glucocorticoids may also contribute to cataract formation and glaucoma. Intravenous pulses of methylprednisolone (30 mg/kg per dose with a maximum of 1 g) may be effective at lower risk of side effects. NSAIDs can have shown to have some supplementary anti-inflammatory effect. Methotrexate and cyclosporine A can be effective and glucocorticoid-sparing, but reports about the use of immunosuppressive drugs are scarce (Agle et al., 2003). Other agents that are reported to have some effect in smaller series are mycophenolate mofetil, intravenous immunoglobulins, and anti-TNF-α drugs. Immunomodulatory therapy started early in the course of uveitis is associated with a better visual acuity (Yu et al., 2005). Several cases of a flare of uveitis or de novo development of uveitis are reported during the use of etanercept (Horneff et al., 2004).

8. Prognosis

Ongoing arthritis was found in almost half of the patients with polyarticular JIA after 10 years (Wallace and Levinson, 1991) and also oligoarticular-onset JIA has been shown to be a severe disease with frequent complications (Guillaume et al., 2000). This was of course before the era of anti-TNF treatment. In 2003, Fantini reported that 75% of their patients with a minimum follow-up of 10 years did not reach remission (Fantini et al., 2003). The course of the disease and outcome depend on the category of JIA and the presence of IgM RF or ANA (Wallace et al., 2005; Felici et al., 2005). Patients with ANA positive JIA seem to constitute a homogeneous subgroup (Ravelli et al., 2005) and ocular complications determine visual prognosis in this subgroup (de Boer et al., 2003; Yu et al., 2005). The prognosis of IgM RF polyarticular JIA can be compared with that of RA in adults. Prolonged efficacy of etanercept and decreased rate of radiographic progression may improve the outcome in these patients (Genovese et al., 2005).

At this moment JIA remains a chronic disease with considerable psychosocial impact that often extends into adulthood, although functional outcome has improved over the years (Oen et al., 2002).

Key points

- JIA is not a single disease but a heterogeneous group of disorders that have in common only the presence of (chronic) synovial inflammation. Current classification is a work in progress.
- Oligoarticular and polyarticular JIA have a wide differential diagnosis, that mostly include infections, especially at the beginning of disease, inherited and metabolic disorders, orthopedic conditions, and others.
- JIA probably has a multifactorial etiology. Genetic predisposition, environmental influences, provoking infections, hormonal factors, and vulnerability in childhood are involved in its development.
- Current standard treatment for oligoarticular JIA include NSAIDS and intra-articular triamcinolone; for polyarticualr disease second line drugs including methotrexate and anti-TNF agents are often used.
- Despite the therapeutic advances, at the present time JIA remains a chronic disease with considerable psychosocial impact that often extends into adulthood, although functional outcome has improved over the years.

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Handbook of Systemic Autoimmune Diseases, Volume 6
Pediatrics in Systemic Autoimmune Diseases
Rolando Cimaz and Thomas Lehman, editors

CHAPTER 2

The Juvenile-Onset Spondyloarthritides

Rubén Burgos-Vargas*
Rheumatology Department, Hospital General de México, Mexico City, Mexico

1. Introduction

The spondyloarthritides (SpA) comprise a group of rheumatic diseases—which includes ankylosing spondylitis (AS), reactive arthritis (ReA), subsets of psoriatic arthritis (PsA), Crohn's disease as well as ulcerative colitis, and undifferentiated SpA—strongly linked to the human leukocyte antigen (HLA)-B27 that affect 0.23–1.8% of the population (Akkoc and Khan, 2006). Usually, SpA commences at the age of 25 years, but in a variable proportion of cases initial symptoms occur in childhood or adolescence constituting the juvenile-onset group. Excepting the prevalence of certain clinical symptoms at onset and severity of the disease, juvenile- and adult-onset SpA are rather similar.

1.1. Concept

Juvenile-onset SpA may be regarded as a group of HLA-B27-associated disorders characterized by enthesitis and arthritis affecting the lower extremities, and, in a variable proportion of cases, the sacroiliac and spinal joints (Burgos-Vargas, 2002). In some cases, extra-articular manifestations occur and in some other bacterial infections may trigger the disease.

The clinical events that take place throughout childhood, adolescence, and adulthood in patients with juvenile-SpA are unique and may evolve from monoarthritis to complex forms of disease, including inflammatory and proliferative phenomena at peripheral and axial entheses and joints accompanied by extra-articular manifestations. The clinical spectrum spans from undifferentiated conditions to syndromes or diseases that either fulfill specific diagnostic criteria or correspond with the clinical picture of diseases described in adults (Burgos-Vargas et al., 1997). Juvenile-onset undifferentiated SpA include children with isolated episodes of arthritis, enthesitis, tendonitis, or dactylitis and those with the combination of arthritis and enthesitis, for example, the idiopathic form of the seronegative enthesopathy and arthropathy (SEA) syndrome (Rosenberg and Petty, 1982). Differentiated forms are syndromes and diseases characterized by structural changes (e.g., radiographic sacroiliitis, spinal disease, or tarsal ankylosis), extra-articular manifestations (e.g., infectious diarrhea, urethritis, cervicitis, psoriasis, and inflammatory bowel disease [IBD]), or laboratory findings (e.g., bacteriologic or serologic demonstration of infection) consistent with AS, ReA, subsets of PsA, Crohn's disease, as well as ulcerative colitis, and rare forms such as ankylosing tarsitis.

In patients with juvenile-onset SpA, symptoms may overlap at some time during the course of the disease. In fact, there is a disease continuum characterized by changes that includes the relevance of each manifestation within the clinical picture, the degree of disease activity and damage as well as diagnosis and classification throughout the time.

*Corresponding author.
Tel.: + 10350615; Fax: + 10350615
E-mail addresses: burgosv@attglobal.net, burgosv@prodigy.net.mx (R. Burgos-Vargas).

DOI: 10.1016/S1571-5078(07)06006-0

1.2. Nomenclature, classification, and diagnosis

The use of both the term juvenile-onset SpA and the European Spondyloarthropathy Study Group (ESSG) classification criteria (Dougados et al., 1991) is consistent with the concept of SpA developed in the adult population in spite of the fact that not all children—and certainly not all adults—develop axial disease. Such consistency has a major role in patient transition from childhood and adolescence to adulthood as well as in the approach of the society and health policy makers. Although the ESSG criteria have been validated in children (Prieur et al., 1993) it is important to consider that inflammatory back pain (IBP)—one of the two ESSG major criteria—rarely occurs in children and adolescents (Table 1).

Enthesitis related arthritis (ERA) refers to one of seven subgroups of juvenile idiopathic arthritis (JIA) proposed by the International League of Associations for Rheumatology (ILAR) (Petty et al., 1998, 2004). Although ERA enlists the most important features of juvenile-onset SpA as inclusion criteria, the list of exclusions prevent the classification of PsA, ReA, and IBD within the same group. Unfortunately, the concepts behind SpA and ERA are not the same (Burgos-Vargas et al., 2002b).

The distinction between the different types of juvenile-onset SpA depends on the specificity of clinical, laboratory, and radiographic signs at a given time. Clinical overlapping may occur and therefore diagnosis may change during the course of the disease.

Juvenile-onset SpA diagnosis relies on criteria and clinical descriptions pertaining to adult-onset populations, for example, the modified New York criteria for AS (Van der Linden et al., 1984), and those for ReA (Kingsley and Sieper, 1996). In contrast, the description of SEA syndrome (Rosenberg and Petty, 1982) as well as Vancouver (Southwood et al., 1989) and ILAR criteria for PsA (Petty et al., 2004) were developed in children and adolescents. Criteria for juvenile AS (Calabro et al., 1980; Hafner, 1987) and atypical SpA (Hussein et al., 1989) have also been developed for children, but are not used.

Table 1
The European Spondylarthropathy Study Group (ESSG) and the International League of Associations for Rheumatology (ILAR) classification criteria for spondyloarthropathies and enthesitis related arthritis subgroup of juvenile idiopathic arthritis

ESSG classification criteria (Dougados et al., 1991)	ILAR proposed classification criteria (Petty et al., 2004)
Inflammatory spinal pain or synovitis, asymmetric or predominantly lower limbs and one or more of the following criteria	Arthritis and enthesitis, or arthritis or enthesitis with at least two of the following
1. Positive family history	1. The presence of or a history of sacroiliac joint tenderness and/or inflammatory lumbosacral pain
2. Psoriasis	2. The presence of HLA-B27 antigen
3. Inflammatory bowel disease	3. Onset of arthritis in a male over 6 years of age
4. Urethritis, cervicitis, or acute diarrhea within 1 month before arthritis	4. Acute (symptomatic) anterior uveitis
5. Buttock pain alternating between right and left gluteal areas	5. History of ankylosing spondylitis, enthesitis related arthritis, sacroiliitis with inflammatory bowel disease, Reiter's syndrome, or acute anterior uveitis in a first-degree relative
6. Enthesopathy	
7. Radiographic sacroiliitis	
Exclusions	
None	1. Psoriasis or a history of psoriasis in the patient or first-degree relative
	2. The presence of IgM rheumatoid factor on at least two occasions at least 3 months apart
	3. The presence of systemic JIA in the patient

2. Epidemiology

The incidence and prevalence of juvenile-onset SpA may be influenced by ethnic or geographic factors. The incidence in American and Canadian children ranges from 1.44 to 2.10 per 100,000 (Denardo et al., 1994; Malleson and Fung, 1996), but in Western Canadian Indians (Rosenberg et al., 1982), particularly Inuit (Oen et al., 1986), Alaskan Inupiat (Boyer et al., 1998) and Yupik Amerindians (Boyer et al., 1990) figures may reach 24.0 per 100,000 children. In contrast, the frequency of juvenile-onset SpA in other countries is relatively low (Gare et al., 1987; Kiessling et al., 1998; Kaipainen-Seppanen and Savvolainen, 1996; Arguedas et al., 1998; Moe and Rygg, 1998). Juvenile forms approaches 50% of Mexicans, Indians, North Africans, and Asians with SpA (Lau et al., 1998; Huang et al., 2003), but less than 21% of white Caucasians.

While the juvenile rheumatoid arthritis (JRA) to juvenile-onset SpA ratio at the end of the 1990s ranged from 1.4:1 to 2.6:1 (Denardo et al., 1994; Malleson and Fung, 1996; Bowyer et al., 1996; Symmons et al., 1996) the ratio reported by Rosenberg (2005) approached 1.0. Long-term follow-ups of HLA-B27 positive children with juvenile chronic arthritis (JCA) or JRA children have shown that 66–84.6% of them actually have AS or undifferentiated SpA (Hall et al., 1987; Sheerin et al., 1988; Flato et al., 2002). Juvenile or adult-onset SpA is seen in approximately 20% of first-degree relatives of patients with juvenile-onset SpA (Ansell et al., 1969; Burgos-Vargas et al., 1990).

Juvenile-onset SpA occurs more frequently in boys than in girls, particularly in the prepubescent years and in children with juvenile-onset AS, but the proportion of juvenile-onset SpA in girls increases with age. Although juvenile-onset SpA may appear at any age, most cases are found between the ages of 6 and 12 years.

3. Pathogenesis

The etiology of SpA, including the juvenile-onset forms is still unknown. In contrast to most autoimmune diseases, the pathogenesis of SpA is not linked to B lymphocytes hyperactivity, autoantibody production, or to HLA-DR mediated genetic susceptibility. Nevertheless, two major factors—genetic susceptibility and bacterial infections—have been implicated in the pathogenesis of the disease. Additionally, mechanical factors and probably growth and development influence the appearance and severity of SpA.

SpA, including juvenile-onset SpA are strongly linked to HLA-B27, particularly B*2705, the original B27 molecule (López-Larrea et al., 1995; Reveille and Brown, 2006). The HLA-B27 association of SpA is linked to family aggregation and SpA prevalence in the general population, but the mechanisms by which HLA-B27 confers susceptibility to disease is still unknown. None of the hypothesis postulated thus far satisfactorily explains the disease. The arthritogenic peptide hypothesis (Benjamin and Parham, 1990; Fiorillo et al., 2000; Ramos and Lopez de Castro, 2002; Boyle et al., 2004) postulates that the HLA-B27 molecule is able to bind a unique bacterial or self antigenic peptide (not yet identified, but supposedly present in the joints), which is then presented to an HLA-B27-restricted cytotoxic (CD8+) T cell. HLA-B27 modulates the production of cytokines and influences both bacterial invasion of cells and killing of bacteria (Saarinen et al., 2002; Inman and Payne, 2003). As result, intracellular survival of arthritogenic bacteria is prolonged. HLA-B27 homodimers, which form as result from B27 misfolding at the endoplasmic reticulum and misfolded protein accumulation (Dangoria et al., 2002; Bird et al., 2003) are likely to act as receptors to humoral or cell-mediated autoimmune responses or as pro-inflammatory targets. Lastly, it has been also postulated that the HLA-B27 molecule might be recognized and presented by HLA-class II heterodimers to CD4+ lymphocytes after intracellular bacterial infection (Popov et al., 2002).

Because the risk conferred by HLA-B27 to genetic susceptibility of SpA is less than 40% and furthermore the risk conferred by the major histocompatibility complex (MHC) is less than 50%, the role of other genes has been studied (Reveille and Brown, 2006). While

HLA-DRB1*08, HLA-DPB1*0301, and LMP2 gene polymorphism have been positively associated with juvenile-onset SpA (Ploski et al., 1995; Maksymowych et al., 1997a, b). HLA-B44, B14, and DR5 do so in the opposite direction (Silva-Ramirez et al., 2005). In adults, associations with HLA-DRB1*01 and DRB1*04 alleles (Brown et al., 1998; Said-Nahal et al., 2002) as well as tumor necrosis factor (TNF) (McGarry et al., 1999; Hohler et al., 1998) heat shock protein (HSP) (Vargas-Alarcon et al., 2002), and low molecular weight protein (LMP) polymorphisms (Vargas-Alarcon et al., 2004) have been described. Genome-wide screens have implicated non-MHC regions including chromosomes 2q, 3p, 5, 9q, 10q, 11q, 16q, 17p, and 19q (Laval et al., 2001; Zhang et al., 2004; Miceli-Richard et al., 2004).

In addition to immunogenetic factors, ReA and other SpA have been linked to bacterial infections. Evidence in juvenile-onset SpA includes the presence of antibodies against bacterial peptidoglycan in children with juvenile-onset AS (Burgos-Vargas et al., 1986), increased T cell responses to enteric bacteria (Sieper et al., 1992) and human heat shock protein 60 (HSP60) in patients with HLA-B27 positive pauciarticular JCA (Life et al., 1993), and synovial T cell response of children with HLA-B27 who have JCA indistinguishable from ReA (Southwood and Gaston, 1993). The search for bacterial DNA in the synovial fluid of patients with undifferentiated SpA or AS has revealed *Salmonella*, *Shigella*, *Chlamydia*, *Campylobacter*, and *Mycobacterium* tuberculosis (Pacheco-Tena et al., 2001).

On the other hand, the existence of humoral and T cell immune responses to the aggrecan G1 domain, a normal constituent of the enthesis, and other molecules, mainly link protein, in human and animal models, as an alternate explanation of localization of disease in patients with SpA (Zou et al., 2005). Finally, there are additional factors that should be considered in the pathogenesis of juvenile-onset SpA, including age, (e.g., maturity of the immune and endocrine systems and bacterial exposure), mechanical factors, and concomitant disease.

4. Clinical manifestations

4.1. General aspects

Arthritis and/or enthesitis at peripheral sites occur in nearly all patients and rarely at spinal and sacroiliac joint at onset (Fig. 1). In some cases, the distinction between arthritis and enthesitis might pose certain difficulties from the clinical point of view. Furthermore, the digital pressure of metatarsophalangeal (MTP) joints may be tender in healthy children (Sherry and Sapp, 2003). Throughout the course of the disease, the severity, duration, and consequences of arthritis and enthesitis may not parallel each other. The pattern of arthritis and enthesitis, particularly at peripheral sites, differs very little among patients with specific diagnoses, but the presence of HLA-B27 and disease duration appear to influence their development. During episodes of disease activity, many patients have transient sacroiliac joint and spinal symptoms. The severity and duration of disease activity influence disease outcome.

Juvenile-onset SpA may affect the functional capacity of children, adolescents, and adults. The consequences of disease activity and structural damage result in diverse degrees of pain, stiffness, loss of movement, functional impairment, and harm to quality of life. Because of the predominant lower limb involvement of juvenile-onset SpA, most patients have limitation with walking, standing, climbing stairs, and running.

Nearly 60% of children with SpA have moderate-to-severe limitations by 10 years of disease (Calin and Elswood, 1988; Flato et al., 1998; Minden et al., 2000; Packham and Hall, 2002). Patients with disease activity for 5 years or more have significant functional impairment. The probability of remission reaches only 17% after 5 years of disease duration. Childhood Health Assessments Questionnaires (CHAQ) scores of children with juvenile-onset SpA are both high at the beginning of disease and throughout long-term follow-up (Selvaag et al., 2005). In comparison with adults, patients with juvenile-onset AS require more hip replacements, more patients are in functional

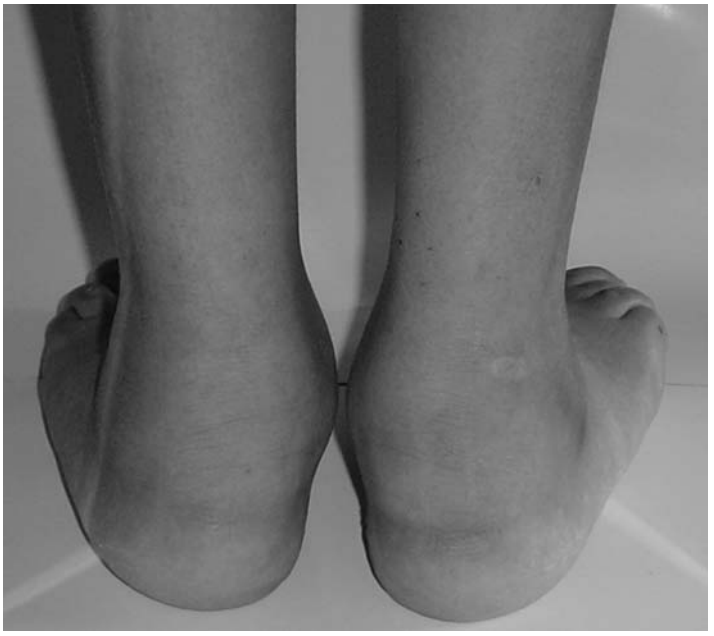

Figure 1. Massive swelling of the posterior aspect of the ankle joint, including the retrocalcaneal bursae and the posterior peroneal and tibial tendons in a 15-year-old boy with juvenile-onset AS.

classes III and IV, and the mean Bath ankylosing spondylitis functional index (BASFI) score is higher (García-Morteo et al., 1983; Calin and Elswood, 1988; Stone et al., 2005).

4.2. Arthritis

The most frequent sign of juvenile-onset SpA is peripheral arthritis. At onset, most patients have unilateral or asymmetric mono or oligoarthritis involving the knee, mid-tarsus, and ankle; rarely, the feet, MTP or interphalangeal (IP) joints, the hips, or any joint of the upper extremity.

The course of arthritis is variable: while some patients have a single or very few episodes of mono or oligoarthritis lasting 3–6 months, other develop recurrent episodes of oligo or polyarthritis for longer periods, followed by partial or complete remission, with little, or no structural damage at all. There are also children who develop severe and persistent bilateral polyarthritis (usually between 5 and 10 joints) and structural damage (Burgos-Vargas and Vázquez-Mellado, 1995; Burgos-Vargas et al., 1996). The frequency of hip, MTP, and foot IP joints involvement as well as some joints of the upper extremities, particularly the shoulder increases during the course of the disease. Peripheral arthritis is more severe and lasts longer in patients with AS.

Most patients with chronic disease, particularly AS or ankylosing tarsitis, or those with Crohn's disease, ulcerative colitis, and PsA having axial involvement correspond to these categories.

Arthritis presents with pain and swelling accompanied by reduced mobility. Long-term consequences include joint contractures, muscle atrophy, distorted alignment of the bones, and joint deformities.

4.3. Enthesitis

Enthesitis refers to the inflammatory involvement of tendon, ligament, joint capsule, and fascia insertions into the bone as well as to the involvement of adjacent anatomical structures, specifically sesamoid and periosteal fibrocartilage, bursae, and

fat pads (Benjamin and McGonagle, 2001). Although both types of entheses—fibrocartilaginous and fibrous—may be involved in SpA, enthesopathy of the former is much more characteristic of SpA. In fibrocartilaginous entheses, the ligaments and tendons attach to long and short bones and spinal apophyisis and epiphysis. In fibrous entheses, ligaments and tendons attach to long bones metaphysis and diaphysis. Although osteocartilaginous proliferation of entheses and enthesophyte formation may occur within inflamed joints (e.g., in the sacroiliac joints), they frequently develop in extrarticular sites (e.g., in the calcaneus attachments of Achilles tendon and plantar fascia) (Benjamin et al., 2004).

Enthesitis presents with pain on standing and walking, and foot swelling. Physical examination reveals pressure tenderness at the Achilles' tendon and plantar fascia attachments to the posterior and inferior aspect of the calcaneus, or along functional entheses such as the longitudinal apposition of the peroneal and tibialis anterior and posterior, as well as extensor hallucis longus tendons to the tarsal bones. Enthesitis may also occur at the tibial anterior tuberosity, greater trochanter, iliac crest, and ischion, but their frequency is lower than that of the feet. Soft tissue swelling results from inflammation of tendon sheaths and adjacent bursae.

The course of enthesitis is variable. In some patients, the episodes of active inflammation are unique, last longer than those of arthritis (approximately 6–12 months), and involve one or few entheses (Burgos-Vargas and Vázquez-Mellado, 1995; Burgos-Vargas et al., 1996, 2002a). Some children have recurrent episodes of enthesitis followed by partial or complete remission; others develop severe and persistent enthesitis involving many sites, particularly the feet. Persistent enthesitis is associated with bone overgrowth, enthesophytosis, bone bridging, and ankylosis. Less frequently, it causes subcortical bone cysts and erosions at tendon attachments.

4.4. Imaging

Radiographs of involved joints, particularly those of the foot and hips may show osteopenia, joint space narrowing, and ankylosis (Azouz and Duffy, 1995; Kleinman et al., 1977). Erosions and destructive changes are rare, but enthesophytosis and bone bridging, particularly in the feet, are commonly seen. When present, erosions are usually seen on the margins or the articular surface in small joints, for example, the MTP. In the sacroiliac joints, radiographic changes include subchondral sclerosis and irregularities of the articular surface in the lower third of the iliac bones, which may progress to erosions, joint space narrowing, bone bridging, and complete fusion of the sacroiliac bones (Fig. 2). Although it has been argued that bone growth plates in children interfere with the radiographic evaluation of the sacroiliac joints, it has been shown that regardless of age persistently symptomatic children have radiographic sacroiliitis. In contrast, spinal syndesmophytosis and ligamentous calcification are non-reversible changes appearing many years after onset.

Magnetic resonance imaging (MRI), particularly of the spinal and sacroiliac joints and ultrasongraphy of the peripheral joints are useful methods in detecting disease activity. The former may show bone edema adjacent to entheses and joints, which is attributed to inflammation, increased synovial fluid in the joints, subtle cartilage and subchondral bone erosions, and enthesophytes (Laxer et al., 1992; Bollow et al., 1998).

4.5. Histopathology

TNF is prominently expressed in the synovial membrane of peripheral joints (Grom et al., 1996). TNF expression correlates with T cell and macrophage infiltrates. Other findings include high levels of CD8-activated cells, TNF-β, γ interferon, and interleukins 2, 4, and 6 (Grom et al., 1996; Murray et al., 1996, 1998). Inflammatory infiltrates at the midtarsal entheses are not prominent, but bone proliferation (C. Pacheco-Tena, unpublished observations, 2002) and mucopolysaccharide deposits may be found (Jiménez-Balderas et al., 2000). Enthesopathy appears associated with inflammatory infiltrates in the interface between the zones of calcified fibrocartilage and subchondral bone (also called metaplasic bone or

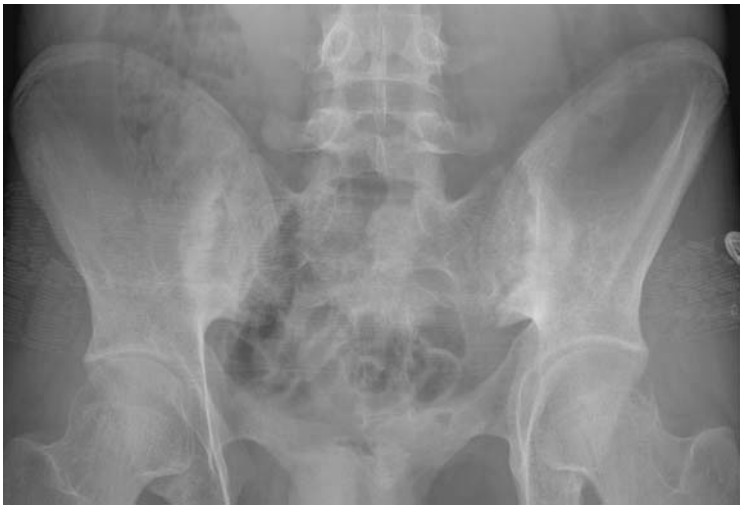

Figure 2. Grade 3 bilateral sacroiliitis in a 14-year-old boy with 6 years disease duration. There is subchondral sclerosis of the iliac bone, joint surface irregularities, which include some erosions on both sides, and joint space narrowing of the hips. (From Burgos-Vargas, 2006 with permission from Elsevier.)

type II chondroid bone), but it may also be an extension of the inflammation of the bone marrow. Interestingly, osteocartilaginous proliferation and enthesophytosis (bone spurs and bridging) may occur during the growth and development of bone, particularly under the effect of trauma or mechanical stress.

5. Clinical forms

5.1. Isolated signs of disease and SEA syndrome

The most common of these forms is peripheral arthritis, specifically monoarthritis or oligoarthritis of the lower extremities. Most cases seem to have recurrent episodes of pain and swelling, which are sometimes attributed to trauma or extreme exercise. In the past, most of these children were diagnosed as oligoarticular JRA or JCA.

Differential diagnosis between SpA and other forms of JIA is a challenge, but demographics (age at onset and gender), family history (HLA-B27—or SpA-associated disorders), clinical pattern (asymmetric, lower limb involvement, sparing of the hands), and HLA type (HLA-B27) orientate the diagnosis (Rosenberg, 1982; Burgos-Vargas and Vázquez-Mellado, 1995). Likewise, the differentiation from toxic hip synovitis, tuberculosis of the hip, and joints and tendons of the fingers, internal derangements of the knee, ankle strain, and bone tumors may be difficult. Apart from HLA-B27 investigation, the use of MRI may reveal sacroiliac joint inflammation in children with neither symptoms nor radiographic changes.

Isolated episodes of enthesitis, tenosynovitis, and dactylitis (Fig. 3) in single or multiple sites of the lower extremities, particularly the plantar fascia, and less frequently, the Achilles insertions to the calcaneus may occur in HLA-B27 children (Gerster and Piccini, 1985; Siegel and Baum, 1988; Olivieri et al., 1990; Olivieri and Pasero, 1992). Tenosynovitis of the hip and foot may also occur, and dactylitis may involve the hands or feet. Acute uveitis, mucositis, skin disease (excluding psoriasis), or heart disease are likely to occur as unique manifestations of disease in children who later develop SpA, but their frequency is unknown.

SEA syndrome (Rosenberg, 1982), the combination of enthesopathy and arthritis or arthralgia, may present as a form of idiopathic disease or as part of a well-defined SpA. Despite importance of SEA syndrome from the historical and conceptual

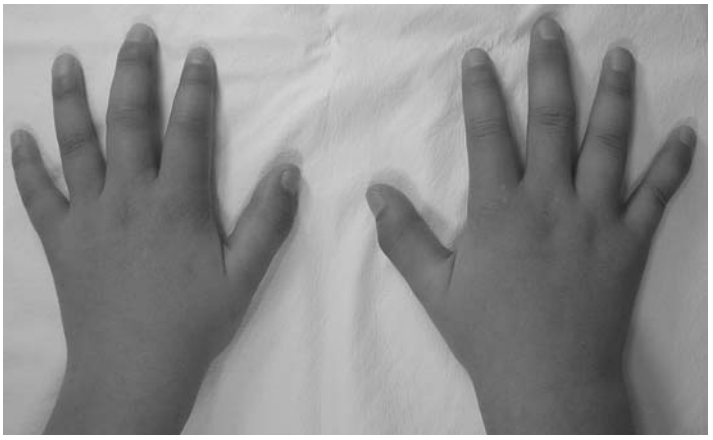

Figure 3. Nine-year-old boy with undifferentiated SpA of 6 months duration characterized by peripheral arthritis and enthesitis that predominantly involved the lower limbs. In addition, he had prominent involvement of the hands which consisted of swelling of both PIP1 joints and left DIP5 joint and diffuse swelling (dactylitis) of the 2nd and 3rd fingers of the right hand. This patient had neither psoriasis nor infection as trigger.

perspective, the term is rarely used today. Nevertheless, long-term follow-ups of SEA syndrome in the Mexican and Canadian populations indicate that 70–90% fulfill definite AS criteria within 10 years of disease onset (Burgos-Vargas and Clark, 1989; Cabral et al., 1992). Shorter follow-ups yield lower figures (Jacobs et al., 1982; Olivieri et al., 1992).

Extra-articular manifestations in patients with SEA síndrome include non-specific IBD, acute uveitis, and systemic symptoms, as well as atlanto-axial subluxation, cardiac conduction disturbances, and pulmonary function test abnormalities (Burgos-Vargas, 2006).

5.2. Reactive arthritis

ReA is a form of rheumatic disease triggered by an infection. Although ReA has been described following viral, parasitic, and a number of bacterial infections, this term is usually restricted to HLA-B27-associated ReA triggered by arthritogenic bacteria such as *Salmonella*, *Yersinia*, *Campylobacter*, *Shigella*, and *Chlamydia*. Reiter's syndrome (a term which tends not to be used anymore) refers to the coincidence of arthritis, conjunctivitis, and urethritis or cervicitis, and is actually a form of ReA with prominent extra-articular manifestations.

Causative organisms are essentially the same that trigger ReA in adults, but the relative frequency of each micro-organism may differ (Burgos-Vargas and Vázquez-Mellado, 2005). For example, the prevalence of ReA triggered by *Salmonella* and *Yersinia* in children is much higher than that of *Chlamydia*. ReA in children rarely develops after epidemics by *Salmonella* and *Campylobacter* and their prevalence is lower in comparison with that found in adults: ReA develops in 5–10% (Russell, 1977; Leino et al., 1980; Hoogkamp-Korstanje and Stolk-Engelaar, 1995) of children with yersiniosis and none to 8.0% children after *Salmonella* outbreaks (Mattila et al., 1994; Rudwaleit et al., 2001).

ReA predominantly involves the joints and entheses of the lower extremities, resembling the pattern seen in adults with ReA or undifferentiated SpA (Hussein, 1987; Burgos-Vargas and Vázquez-Mellado, 2005). Some patients with *Salmonella* and *Yersinia* ReA present with polyarthritis affecting the small joints of the hands (Taccetti et al., 1994; Kanakoudi-Tsakalidou et al., 1998). The arthropathy and enthesopathy of children with ReA, particularly HLA-B27 negatives or those with *Yersinia* or *Campylobacter* infection, are usually mild-to-moderate and leave no structural

damage in most cases. ReA in children with HLA-B27 is in contrast a chronic disease that may evolve into AS (Russell, 1977; Rosenberg and Petty, 1979; Hussein, 1987; Cuttica et al., 1992).

Regardless of bacteria, infection may be asymptomatic or produce slight to moderate symptoms in a mean of 2–4 wk before the onset of arthritis. In some children, infection is only suspected by detecting serum antibodies, but in others, infection may be a severe event. Since ReA diagnosis is based on the identification of the infection that triggered the disease, any retrospective clinical or laboratory data should be properly evaluated. There is still no definitive method to diagnose infection in retrospect.

Extra-articular manifestations include aphtous stomatitis, conjunctivitis, erythema nodosum (particularly in *Yersinia* ReA), circinate balanitis, keratoderma blenorrhagica (which may clinically and histologically resemble psoriasis), anterior uveitis, urethritis and cervicitis (particularly in adolescents with sexually acquired ReA), aortic insufficiency, myocarditis, and pericarditis.

5.3. Juvenile-onset ankylosing spondylitis

In juvenile-onset AS, individuals younger than 16 years have involvement of the sacroiliac and spinal joints. The diagnosis is made according to adult-onset criteria referring to spinal symptoms and radiographic sacroiliitis (Table 2) (Van der Linden et al., 1984). IBP, the most characteristic symptom of axial involvement in SpA, is usually accompanied by morning stiffness and improves with exercise, but not with rest; patients awake with pain and rarely manifest alternating buttock pain. The prevalence of IBP in children with SpA is very low, yet in adolescents it occurs more frequently (Burgos-Vargas and Vázquez-Mellado, 1995; Burgos-Vargas et al., 1996). Decreased spinal mobility and reduced chest expansion are also signs of axial involvement in SpA considered in the diagnosis of AS. As mentioned before, radiographic sacroiliitis of the AS type may be seen in children and adolescents with persistent axial disease (Burgos-Vargas et al., 1996).

Most patients with juvenile-onset AS had isolated conditions, mainly arthritis, or SEA syndrome in the initial years of disease and axial involvement occurs later on (Burgos-Vargas, 2006). During the initial 6 months, most patients with juvenile-onset AS have oligoarthritis, but by the end of the first year the majority has polyarthritis (Burgos-Vargas and Vázquez-Mellado, 1995). Some patients have involvement of the upper extremity joints during this period. Enthesopathy has a remarkable predominance for the lower extremities. Exacerbations and remissions of arthritis and enthesitis are certainly coincident, but in general, enthesitis is more severe and persists longer.

Few patients present with axial symptoms and radiographic sacroiliitis within 2–3 years of disease fulfilling AS criteria (Burgos-Vargas et al., 1996). HLA-B27 children with polyarthritis and polyenthesitis are more prone to do so. Usually, the prevalence of spinal or sacroiliac joint pain and stiffness, reduced anterior spinal flexion or chest expansion—compared with normal values

Table 2
The modified New York classification criteria for ankylosing spondylitis (Van der Linden et al., 1984)

Clinical criteria
Low back pain and stiffness for at least 3 months, which improves with exercise, but is not relieved by rest
Limited lumbar spinal motion in sagittal (sideways) and frontal (forward and backwards) planes
Chest expansion decreased relative to normal values corrected for age and sex
Radiologic criteria
Bilateral sacroiliitis grade 2–4
Unilateral sacroiliitis grade 3 or 4
Definite AS, if one radiologic criterion is associated with at least one clinical criterion
Probable AS, if three clinical criteria are present or one radiologic criterion is present without any clinical criterion

(Burgos-Vargas et al., 1985, 1993)—increases after 2.5 years of disease and reaches a maximum 5–10 years after onset (Burgos-Vargas et al., 1989; Burgos-Vargas and Vázquez-Mellado, 1995). Axial symptoms first occur in the lumbar and thoracic spine, and less frequently, in the neck and sacroiliac joints. As in adult-onset patients, spinal pain in children seems to improve with movement, yet some others notice worsening.

Compared with adult-onset AS, juvenile-onset AS patients have a higher prevalence of peripheral arthritis and enthesitis, and a lower prevalence of axial disease at onset (Marks et al., 1982; Burgos-Vargas, 1989; Baek et al., 2002).

Systemic features, particularly in the active phase of disease, occur in 5–10% of patients and consist of high-grade fever, weight loss, muscle weakness and atrophy, fatigue, lymph node enlargement, leukocytosis, or anemia. Up to 27% have one or more attacks of non-granulomatous acute uveitis (Ansell, 1980; Schaller et al., 1969; Ladd et al., 1971; Burgos-Vargas et al., 1988) and around 80% have non-specific IBD. Cardiovascular manifestations are rare, but include aortic valve insufficiency, non-specific conduction disturbances, and fewer miscellaneous findings (Gore et al., 1982; Stamato et al., 1995; Jiménez-Balderas et al., 2001). One series of cases reported amyloidosis in 3.8% of patients (Ansell, 1980). Atlantoaxial subluxation has also been reported (Reid and Hill, 1978; Thompson et al., 1982).

5.4. Juvenile-onset psoriatic arthritis

Juvenile-onset PsA is defined as the association of arthritis and psoriasis in individuals 16 years of age or younger. According to ILAR criteria (Petty et al., 2004), the definition might also include patients who have either arthritis or psoriasis and dactylitis, nail pitting, or family history of psoriasis (Table 3). In the ILAR criteria, the presence of any data suggesting SpA excludes the diagnosis of PsA. This is a very controversial issue since SpA classification includes PsA as in the list of conditions within the group. Moreover, a variable proportion of patients with juvenile PsA have SpA stigmata either in the initial years of the disease or in the adult age (Shore and Ansell, 1982; Southwood et al., 1989; Truckenbrodt and Häfner, 1990).

Juvenile-onset PsA is more frequent in girls than boys; the age at onset of arthritis is between 7 and 11 years and at the onset of psoriasis between 9 and 13 years, but ranges may be wider. HLA-A2, HLA-B17, HLA-DR1, and HLA-DR6 are weakly associated with the disease as a whole, oligoarthritis with HLA-DR5 and HLA Drw8, severe arthritis with HLA-A11 and HLA-B7, and associations of male gender, age >6 years, and spinal disease with HLA-B27 have been described (Southwood et al., 1989; Hamilton et al., 1990).

Arthritis is the initial manifestation in 50% of cases, psoriasis in 40%, and arthritis and psoriasis in 10%. In general, psoriasis appears within 2

Table 3
ILAR definition of PsA (Petty et al., 2004)

Arthritis and psoriasis, or arthritis and at least two of the following
1. Dactylitis
2. Nail pitting or onycholysis
3. Psoriasis in a first-degree relative
Exclusions
Arthritis in an HLA-B27 positive male beginning after the sixth birthday
Ankylosing spondylitis, enthesitis related arthritis, sacroiliitis with inflammatory bowel disease, Reiter's syndrome, or acute anterior uveitis, or a history of one of these disorders in a first-degree relative
The presence of IgM rheumatoid factor on at least two occasions at least 3 months apart
The presence of systemic JIA in the patient

years of arthritis, but in some patients the interval is much longer. At onset, 70% of children with juvenile-onset PsA have oligoarthritis (Shore and Ansell, 1982; Southwood et al., 1989; Truckenbrodt and Häfner, 1990). The knees, ankles, feet, as well as proximal and distal IP of both hands and feet are frequently affected. In a short time, most patients develop polyarthritis. Several patterns of hand and foot involvement have been described and dactylitis is relatively common (Roberton et al., 1996). During the course of the disease, the frequency of wrist, metacarpophalangeal (MCP), MTP, elbow, and less often hip disease increases. Radiographic changes include osteopenia and joint space narrowing, periostitis, erosions, destructive changes, or ankylosis of the hand, cervical spine, and hip joints. Regarding axial involvement, the cervical segment is more frequently involved than other spinal segments, yet clinical and radiographic involvement of the sacroiliac joints and spine occur throughout follow-up.

Most children have slight or mild skin psoriasis lesions in the scalp, umbilicus, extensor surfaces of limbs, nasal cleft, and nails. Severe and disseminated forms of psoriasis are rare. Nevertheless, skin manifestations might vary or combine in the same patient during the course of the disease; around 80% have psoriasis vulgaris, 30% have guttate, and less than 2% have pustular psoriasis. Nail psoriasis include pits and striae, and rarely, nail thickening or lysis. In most patients, the severity of the skin disease does not parallel the severity of arthritis. Extra-articular manifestations include chronic iridocyclitis in 15% of patients, and fever, pericarditis, IBD, or amyloidosis in very few cases.

5.5. The arthropathy of IBD: Crohn's disease and ulcerative colitis

Crohn's disease and ulcerative colitis may be associated with peripheral or axial arthritis. Crohn's disease is a transmural disease that involves the mucosa and regional lymphatics of the colon, distal ileum, and other segments of the digestive tube, with characteristic lesions consisting of non-caseating granulomas. Ulcerative colitis is a diffuse, inflammatory process consisting of neutrophils with crypt abscesses that involves the colonic mucosa. Diagnoses are usually based on clinical, radiographic, endoscopic, and often histopathologic studies, but their differentiation from other causes of IBD, particularly *Yersinia* infection is difficult. Approximately 18–30% of patients with Crohn's disease, and 15% of those with ulcerative colitis, have onset of disease before the age of 20 (Farmer and Michener, 1979; Ferguson and Sedgwick, 1994).

Children and adolescents with Crohn's disease and ulcerative colitis may have peripheral arthritis and sacroiliac or spinal disease at the time of presentation of gastrointestinal symptoms or later on (Lindsley and Schaller, 1974). The frequency of peripheral arthritis is approximately 9% in patients with Crohn's disease and is approximately 10–20% in patients with ulcerative colitis. Arthritis involves the peripheral joints of the lower, and seldom the upper extremities. Single (~50% of cases) or recurrent attacks of mono or oligoarthritis lasting less than 4 wk occur throughout the course of the disease. Less than 50% of patients with peripheral arthritis have parallel exacerbations of joint disease and gut symptoms (Lindsley and Schaller, 1974). Although some patients have joint erosions and structural changes, this type of arthritis does not lead to permanent functional limitation or joint damage.

Interestingly, the peripheral arthritis of patients with juvenile-onset Crohn's disease and juvenile-onset ulcerative colitis does not resemble that of most juvenile-onset SpA. Spondylitis (which is indistinguishable from idiopathic AS) and radiographic sacroliitis are rare, and is found at an older age in patients with juvenile-onset Crohn's disease and juvenile-onset ulcerative colitis than peripheral arthritis.

Non-specific IBD changes occur in up to 80% of patients with juvenile-onset SpA and are associated with erosive disease and a high risk of progression to AS. Although non-specific IBD rarely causes symptoms, repeated histopathologic, as well as radionuclide, studies of the gut may reveal acute and chronic inflammatory changes in the mucosa and submucosa of the terminal ileum and

colon resembling Crohn's disease and ulcerative colitis in more than two-thirds of the patients (Mielants et al., 1987).

5.6. Ankylosing tarsitis

This term refers to a set of clinical and radiographic findings, including some inflammatory (joint synovitis, enthesitis, tenosynovitis, and bursitis) and proliferative (periostitis, enthesophytosis, and bony ankylosis) manifestations originally described in patients with HLA-B27 who had juvenile-onset SpA (Burgos-Vargas and Granados-Arriola, 1990; Burgos-Vargas, 1991). This condition seems equivalent to clinical, radiographic, and perhaps histopathologic features of the spinal and sacroiliac joints in patients with AS. The clinical characteristics of ankylosing tarsitis are midfoot swelling associated with soft tissue swelling around the malleoli, Achilles tendon, and remaining areas of the feet, decreased mobility of tarsal, ankle, and MTP joints, pes planus (much less frequently pes cavus), and hyperextension of the MTP joints. Radiographic features include diffuse osteopenia of the tarsal bones, joint space narrowing or ankylosis involving most tarsal joints, bone cysts, erosions, and osseous proliferation at the enthesis (Fig. 4). MRI shows hyperintensive signals in bones, synovial sheaths, bursa, and rarely joint space (Fig. 5). Histopathologic findings include slight inflammatory changes, but striking osteocartilaginous proliferation. Ankylosing tarsitis may occur in patients with undifferentiated juvenile-onset SpA or as a stage previous to radiographic sacroiliitis in patients with juvenile-onset AS.

6. Therapeutic approach

The therapeutic approach of children and adolescents with juvenile-onset SpA is aimed to reduce the intensity and duration of signs and symptoms that particularly relate to inflammation. Ideally, therapeutic measures should also reduce the structural consequences of the disease, yet there is no evidence thus far that any treatment may do so.

Pharmacologic treatment is mainly based on the therapy of other forms of juvenile arthritis and adult-onset SpA. Non-steroidal anti-inflammatory drugs (NSAIDS) and in some cases, glucocorticoids, provide symptomatic relief (Table 4). Indomethacin, ibuprofen, naproxen, diclofenac, and meloxicam may reduce pain and swelling in most patients, but in those who do not respond to NSAIDS and persist with inflammatory activity, oral glucocorticoids may be of some benefit. Likewise, most patients receiving intra-articular or intra-lesional glucocorticoids improve after one or two injections. Exceptionally, glucocorticoids may be administered by either the intramuscular or the intravenous routes.

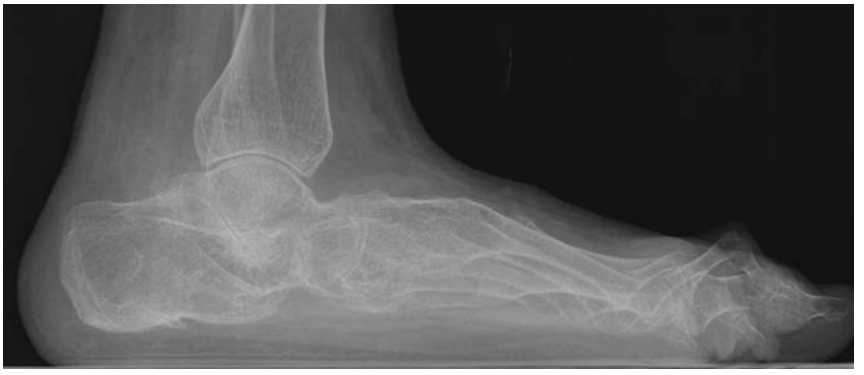

Figure 4. Complete fusion of the tarsal bone and enthesophytosis of the calcaneus in a 15-year-old boy with juvenile-onset AS.

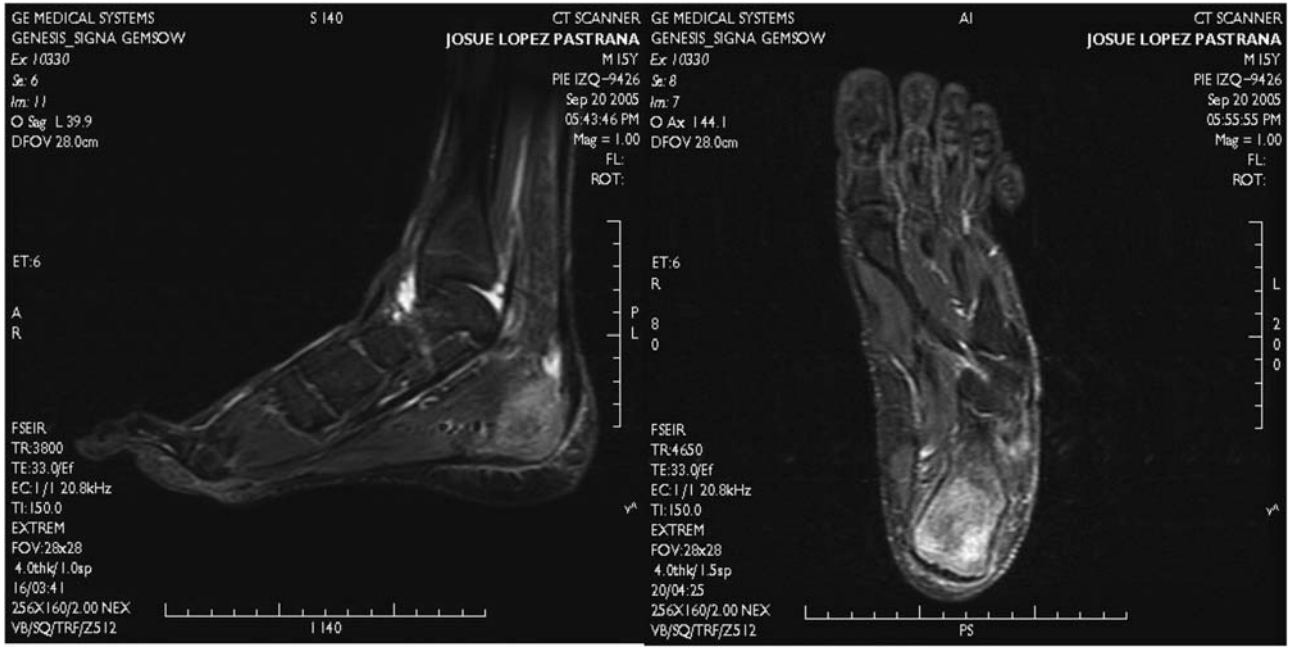

Figure 5. T2 fat suppressed lateral and coronal views of the feet of a patient with enthesitis at the attachment of the plantar fascia and Achilles tendon. There is extensive edema of the calcaneus, retrocalcaneal bursitis, and arthritis of the ankle.

Table 4
Medications used in the treatment of juvenile-onset SpA

Drug category	Major indication	Effect
NSAIDS	Pain and swelling	Symptomatic relief
	Peripheral and axial arthritis and enthesitis	
Sulfasalazine	Pain and swelling	Symptomatic relief
	Peripheral arthritis and enthesitis	
	Psoriasis, uveitis, intestinal bowel disease	
Glucocorticoids	Pain and swelling	Symptomatic relief
	Peripheral and axial arthritis and enthesitis	
	Uveitis, psoriasis	
Methotrexate	Pain and swelling	Symptomatic relief
	Peripheral arthritis	
	Uveitis, psoriasis	
Etanercept	Pain and swelling	Symptomatic relief
	Peripheral and axial arthritis and enthesitis	Remission, probably
Infliximab	Pain and swelling	Symptomatic relief
	Peripheral and axial arthritis and enthesitis	Remission, probably

Sulfasalazine provides symptomatic relief, methotrexate appears to improve peripheral symptoms in some patients, and both drugs might have some effect on skin and ocular manifestations. Nevertheless, none of these drugs appear to prevent disease progression.

In contrast, reports on the efficacy of tumor necrosis factor alpha (TNF-α) blockers in juvenile and adult-onset patients with SpA indicate that these molecules may occupy a prominent role in the treatment of patients with juvenile-onset SpA. Significant response to etanercept and infliximab have been noted very early during the course of treatment with no significant adverse events (Henrickson and Reiff, 2004; Tse et al., 2005).

Physical and occupational therapy should be mandatory in patients with juvenile-onset SpA (Hebestreit et al., 1998). In addition to physical measures to alleviate pain and swelling, it is important to prevent joint contractures and preserve physical functioning. Rest, dynamic splints, and exercise programs should be individualized. Special emphasis should be given to exercises that lessen the degree of hip contractures, lower limb muscle weakness, and stiff back.

Surgical modalities such as soft tissue release, synovectomy, tendon repair, arthroplasty, and joint replacement may be indicated in some forms of hip, knee, and MTP disease (Sochart and Porter, 1997).

Juvenile-onset SpA may profoundly harm the quality of life of children and adolescents, and, therefore, their transition to adulthood. Therefore, it is important to consider a number of issues including the psychological, educational, and socioeconomic aspects of life. Disease activity and later, disease damage, may affect these individuals' social life, including personal and family activities, education, and jobs.

Key points:

- Juvenile-onset SpA may be regarded as a group of HLA-B27-associated disorders characterized by enthesitis and arthritis affecting the lower extremities, and, in a variable proportion of cases, the sacroiliac and spinal joints. In some cases, extra-articular manifestations occur and in some other bacterial infections may trigger the disease.
- The clinical spectrum spans from undifferentiated conditions to syndromes or diseases that either fulfill specific diagnostic criteria or correspond with the clinical picture of diseases described in adults.

- The etiology of SpA, including the juvenile-onset forms is still unknown. In contrast to most autoimmune diseases, the pathogenesis of SpA is not linked to B lymphocytes hyperactivity, auto-antibody production, or to HLA-DR mediated genetic susceptibility. Nevertheless, two major factors—genetic susceptibility and bacterial infections—have been implicated in the pathogenesis of the disease.
- The therapeutic approach of children and adolescents with juvenile-onset SpA is aimed to reduce the intensity and duration of signs and symptoms that particularly relate to inflammation. Ideally, therapeutic measures should also reduce the structural consequences of the disease, yet there is no evidence thus far that any treatment may do so.

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Handbook of Systemic Autoimmune Diseases, Volume 6
Pediatrics in Systemic Autoimmune Diseases
Rolando Cimaz and Thomas Lehman, editors

CHAPTER 3

Systemic Juvenile Idiopathic Arthritis

Rayfel Schneider*, Ronald M. Laxer

The Hospital for Sick Children, University Avenue, and University of Toronto, Toronto, Ont., Canada

1. Introduction

The unique systemic features of systemic juvenile idiopathic arthritis (S-JIA), the association with macrophage activation syndrome, the relatively poor response to traditional treatment modalities and poor outcome for a significant proportion of patients have always intrigued investigators and clinicians. Some have questioned whether S-JIA should really be classified as a form of JIA at all. Over the past decade there has been considerable progress in determining disease course, outcome and early prognostic indicators of poor outcome. Increased attention to the disease pathogenesis over the past decade has finally started to yield tangible results with the introduction of novel treatments with biologic agents targeting IL-1 and IL-6 that hold great promise.

The International League of Associations for Rheumatology (ILAR) classification criteria for systemic arthritis have been widely accepted. In addition to arthritis in any number of joints, these criteria include fever for at least 2 weeks (documented to be quotidian for 3 days) and at least one of the following features: evanescent, erythematous rash, generalized lymphadenopathy, serositis and hepatomegaly or splenomegaly (Petty et al., 2004).

*Corresponding author.
Tel.: +4168136117; Fax: +4168134989
E-mail address: Rayfel.schneider@sickkkids.on.ca (R. Schneider).

DOI: 10.1016/S1571-5078(07)06007-2

2. Prevalence and epidemiology

S-JIA makes up 10–20% of most North American and European series of children with JIA, though in parts of Asia it may account for a greater proportion. Although the disease may begin at any age, about 50% of affected children have their onset prior to 6 years of age and it rarely occurs under the age of 1year. Boys and girls appear to be affected equally.

Several investigators have looked at seasonal onset, with some suggesting that onset in the winter months might be less common (Lindsley, 1987), but no consistent seasonal pattern has been found (Feldman et al., 1996). Although the clinical features may suggest potential infectious causes of the disease, this hypothesis has not been supported in the literature.

3. Pathogenesis of S-JIA

The characteristic clinical and laboratory features of S-JIA are associated with a distinctive cytokine profile and an increasing body of evidence implicating cytokine dysregulation in the pathogenesis of the disease. There is now particularly convincing evidence for a central role of IL-1β and IL-6 in the perpetuation of the inflammatory process in S-JIA, on the basis of recent studies which demonstrate that specific blockade of these cytokines in vivo result in rapid abrogation of the major clinical and laboratory features of the disease (Pascual et al., 2005; Yokota et al., 2005).

A number of studies support the role of IL-6 in producing both the extra-articular systemic manifestations of the disease as well as synovial inflammation (de Benedetti and Martini, 2005). Circulating IL-6 levels are markedly elevated in S-JIA, rise with the peak of fever and fall with its defervescence, a temporal association that has not been demonstrated with IL-1β or TNFα. IL-6 levels are also markedly elevated in synovial fluid and circulating levels are highly correlated with the extent and severity of arthritis. IL-6 combined with the IL-6 receptor (IL-6R) is a hepatocyte-stimulating factor and induces production of a variety of acute phase proteins including C-reactive protein (CRP), serum amyloid A and fibrinogen. Circulating IL-6 levels are significantly correlated with high CRP levels and with the elevated platelet counts typically seen with active disease. IL-6 increases ferritin expression and hepatic uptake of iron, resulting in a reticuloendothelial block with impaired availability of iron for effective erythropoiesis and the characteristic hypochromic, microcytic anemia.

Data from animal studies further support the role of IL-6 in the pathogenesis of chronic synovial inflammation, impaired growth and osteoporosis. IL-6 deficient mice appear to be protected from developing antigen-induced chronic arthritis, suggesting that IL-6 has an important role in inducing and sustaining chronic synovial inflammation. IL-6 transgenic mice, which have chronic overproduction of IL-6, show significantly impaired growth associated with low levels of insulin-like growth factor 1 (IGF-1) and IGF binding protein 3, which is also markedly reduced in patients with S-JIA (de Benedetti et al., 2001). These mice also show features of osteoporosis and increased osteoclastic activity.

Genetic studies suggest that a single nucleotide polymorphism in the promoter region of the IL-6 gene may be associated with overproduction of IL-6 in S-JIA (Fishman et al., 1998). Of the two genotypes identified, the –174GG genotype is associated with higher levels of IL-6 production and the –174CC genotype with lower IL-6 production. The low responder genotype is less commonly seen in S-JIA, especially in those children whose disease began before 6 years of age. A subsequent study confirmed that the –174G allele of the IL-6 gene confers susceptibility to S-JIA (Ogilvie et al., 2003).

In contrast to other soluble cytokine receptors, such as the soluble TNF receptor, which antagonize the actions of the cytokine, the soluble IL-6R (SIL-6R) acts as an agonist, potentiating the effects of IL-6. The SIL-6R binds IL6 and forms an IL-6-SIL-6R complex that binds to a transmembrane subunit, gp130, which then leads to signal transduction. A humanized monoclonal antibody to IL-6R, tocilizumab, binds with high affinity to both membrane-bound and SIL-6R, thereby neutralizing the activity of IL-6. The rapid resolution of fever, reduction of CRP and erythrocyte sedimentation rate (ESR) and reversal of thrombocytosis and anemia in patients treated with tocilizumab provide strong evidence for the pivotal role of IL-6 in the pathogenesis of S-JIA (Yokota et al., 2005).

Although IL-1β levels have not been shown to parallel the fever peaks in S-JIA, it is a highly active cytokine that can cause fever, elevated neutrophil and platelet counts, and an increase in circulating IL-6 which may then induce hepatic production of acute phase proteins and thrombocytosis (Dinarello, 2005). Circulating levels of this cytokine may not be highly correlated with disease manifestations. Furthermore, IL-1 receptor levels have been demonstrated to peak within an hour of the fever peak and may also account for relatively low circulating IL-1. A recent series of experiments has suggested that IL-1 dysregulation is central to the pathogenesis of S-JIA (Pascual et al., 2005). Serum from patients with S-JIA added to peripheral blood mononuclear cells (PBMCs) of healthy donors resulted in upregulated expression of a variety of cytokine genes, including IL-1α and IL-1β. Activation of systemic patients' PBMCs resulted in increased production of IL-1β. Finally, blocking IL-1 activity by administration of an IL-1 receptor antagonist (anakinra) resulted in the rapid resolution of fever, neutrophilia and thrombocytosis and rapid improvement in ESR, anemia and arthritis in most patients. Similarly dramatic improvements in clinical and laboratory features have been reported in patients with adult-onset Still's disease treated with anakinra (Fitzgerald et al., 2005). Future studies with more potent inhibitors of IL-1 activity will be of great interest.

Tumor necrosis factor-α (TNF-α) levels in the circulation and in synovial fluid are elevated in all subtypes of JIA but circulating levels do not rise and fall in association with fever spikes in S-JIA. Soluble TNF receptors are also elevated in all JIA subtypes, but are particularly high in S-JIA and correlate with fever and systemic disease activity rather than joint inflammation (Muzaffer et al., 2002). Administration of a chimeric monoclonal antibody to a patient with refractory S-JIA resulted in a rapid, short-term improvement in fever and systemic symptoms but no improvement in the patient's arthritis (Elliott et al., 1997). Subsequent reports of TNF inhibition with etanercept and infliximab have not convincingly shown improvement in systemic symptoms or arthritis, and a significant proportion of responders have disease flares (Russo et al., 2002). Elevated soluble TNF receptor levels have been associated with prolongation of the partial thromboplastin time and reduced prothrombin activity in S-JIA (de Benedetti et al., 1997). Polymorphisms in the 5′ flanking promoter/enhancer region of the TNF-α gene may be associated with the development of S-JIA (Datey et al., 1999).

Aberrant induction or regulation of other cytokines has also been reported in S-JIA. IL-12 levels have been reported to be elevated in both active and inactive S-JIA (Yilmaz et al., 2001). IL-18 is potent stimulator of production of pro-inflammatory cytokines by T lymphocytes, NK cells and macrophages, and extremely high levels of IL-18 have been reported in adult-onset Still's disease (Kawashima et al., 2001) and S-JIA (Maeno et al., 2002). Moreover, elevated serum IL-18 levels, which likely originate from the bone marrow (Maeno et al., 2004), are significantly associated with hyperferritinemia, hepatosplenomegaly and serositis, and may be seen in macrophage activation syndrome (MAS).

Macrophage migration inhibitory factor (MIF) is a pluripotent protein that has pro-inflammatory properties and significantly elevated levels have been found in the serum and synovial fluid of patients with S-JIA (Meazza et al., 2002). A MIF polymorphism (MIF-173*C allele) is associated with S-JIA (Donn et al., 2001) and is a predictor of poor outcome in S-JIA (De Benedetti et al., 2003).

Endothelial activation is an important component of the inflammatory response and elevated markers of endothelial activation have been found in patients with JIA, but these are especially elevated in S-JIA. Endothelial activation by pro-inflammatory cytokines results in elevated levels of von Willebrand factor antigen (Bowyer et al., 1989), activated Factor VII (Inamo et al., 1995) and elevated tissue plasminogen activator (Mussoni et al., 1990). More specific markers of endothelial activation such as soluble ICAM-1 and E-selectin are particularly elevated in S-JIA (Bloom et al., 2005). Skin biopsies of the rash of patients with S-JIA have also shown endothelial activation with upregulation of ICAM-1, VCAM-1 and especially E-selectin. It is noteworthy that even non-affected skin has increased expression of E-selectin by endothelial cells (Frosch et al., 2005). Myeloid-related protein 8 (MRP-8) and MRP-14 are proteins secreted by phagocytes at local sites of inflammation and promote adhesion of phagocytes to endothelial cells, and have a role in modulating migration of leukocytes. Biopsies of the rash of patients with active disease have demonstrated MRP-8 and MRP-14 expression by leukocytes and keratinocytes. However, expression of these proteins was not seen on skin biopsies of patients in remission (Frosch et al., 2003). These data suggest that activation of cutaneous endothelial and epithelial cells may be involved in the pathogenesis of S-JIA.

The striking association of MAS with S-JIA may provide some insights into the disease pathogenesis. Profoundly depressed natural killer (NK) cell function has been reported in both hemophagocytic lymphohistiocytosis (HLH) and in MAS. A similarly marked depression of NK cell activity has been observed in patients with S-JIA in the absence of overt MAS (Villanueva et al., 2005). A reduction in circulating NK cells associated with active disease has also been reported (Wouters et al., 2002).

4. Common clinical manifestations

When all the common clinical manifestations of S-JIA are present, the diagnosis is relatively straightforward. However, frequently, only some are present at onset, so that the differential diagnosis

becomes very broad and challenges even the most experienced clinicians.

The onset may at times be so abrupt that families can actually remember the date and time that the disease began. However, as the earliest manifestation is usually fever, the time of onset may not be recalled since the early symptoms would have been assumed to be part of a non-specific or viral illness. The fever has a unique pattern: quotidian or double quotidian, a daily or double daily rapid spike to 39°C or above, usually occurring late in the day (Fig. 1). This fever is often associated with chills and rigors and such children can appear extremely ill and "toxic" only to improve dramatically with defervescence. Initially, the fever pattern may be more hectic and less predictable, making diagnosis more difficult. With time and initiation of treatment, the classic daily fever pattern often develops. Another feature of the fever is that the temperature often returns to below the baseline early in the morning. Examination of a well-documented fever chart is a very important part of making a diagnosis. Fever must be present to make the diagnosis, and therefore is present in 100% of patients.

The other characteristic feature of S-JIA is the rash. Present in about 90% of patients, the rash is diagnostic when it occurs together with the fever spike. Therefore, if the diagnosis is uncertain, it is critically important that the patient is examined at the time of a fever spike in order to look for the rash. Rash may precede the development of other features of S-JIA by weeks or even months. The rash is typically a pink, salmon-colored macular rash (Fig. 2), characteristically concentrated in the warmer areas of the body (thigh, axilla and trunk). Occasionally the rash occurs on the face and hands and feet. Macules may have areas of central clearing and sometimes coalesce to form larger lesions. The rash may appear as linear streaks in areas of pressure and may be elicited by stroking the skin (Koebner phenomenon). Because of its light color, it may be extremely difficult to discern in patients with dark skin. Sometimes the rash appears as a very striking urticarial and pruritic eruption (Fig. 3). It may persist even in the absence of fever.

Involvement of the reticuloendothelial system is seen in about 75% of patients with diffuse lymphadenopathy, hepatomegaly and splenomegaly, usually all occurring together. Although these features may suggest lymphoreticular malignancy, the nodes and organs are typically soft and non-tender, and the nodes mobile. Liver function tests are frequently mildly abnormal with elevation in the levels of serum transaminases. These may worsen with the institution of non-steroidal anti-inflammatory treatment.

Serositis is another important clinical manifestation and typically presents with chest pain with or without shortness of breath, demonstrating

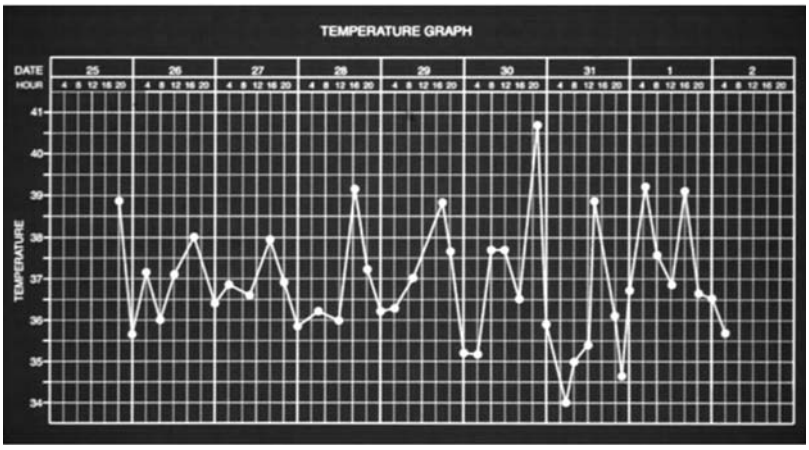

Figure 1. Typical once or twice daily fever pattern in a child with S-JIA. Note the temperature sometimes drops to subnormal levels when the fever defervesces.

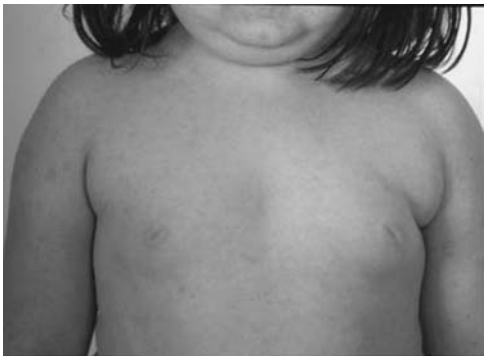

Figure 2. Typical salmon-pink macular rash on the trunk and proximal upper limbs of a girl with S-JIA. (See Colour Plate Section.)

Figure 3. Patient with S-JIA with an extensive urticarial, pruritic rash. (See Colour Plate Section.)

involvement of the pleural and pericardial membranes. Some patients with pericarditis will refuse to lie supine because this exacerbates the chest pain. Careful examination for pleural and pericardial friction rubs should be undertaken and a chest x-ray done to look for pleural effusion and widening of the cardiothoracic silhouette. During active systemic disease 2D-echocardiography reveals small pericardial effusions in >80% of patients, who are usually asymptomatic (Brewer, 1977). It is unusual for patients to have symptomatic serositis in the absence of other features of active systemic disease such as fever and rash. Rarely peritoneal involvement results in severe abdominal pain. Occasionally, the pleuropericardial inflammation may lead to cardio-respiratory compromise and even cardiac tamponade, requiring pericardial drainage. This is especially so if the serositis is a component of disease presentation and a firm diagnosis has not yet been made. Some patients have recurrent episodes of fever and pericarditis as the major manifestations of their disease.

The arthritis of S-JIA may take several forms, either oligoarticular or polyarticular, transient with the systemic attacks or persistent. Arthritis is not necessarily present at onset but the vast majority of patients will have arthritis within the first three months of the disease. Rarely, arthritis only develops after more than 1 year of systemic symptoms and has been reported to develop as long as 9 years after disease onset (Calabro et al., 1976). If it is not present at onset the diagnosis becomes even more difficult. Joints may be damaged rapidly, particularly hips and wrists with cartilage loss, erosions and ankylosis (Fig. 4). Cervical spine involvement also occurs early with ankylosis of the C2-3 facet joints that may progress to ankylosis of virtually the entire cervical spine. Chronic persistent arthritis develops in approximately 50% of patients.

5. Growth

Growth failure is a common and important morbidity in S-JIA. It is a predictable and almost inevitable outcome of patients who follow a severe, persistent disease course, particularly when the disease begins in the pre-pubertal period. The major determinants of growth failure are the duration and severity of active disease and the duration and cumulative dose of systemic corticosteroid treatment, although other factors such as hypercatabolism and suboptimal nutrition may also play a role.

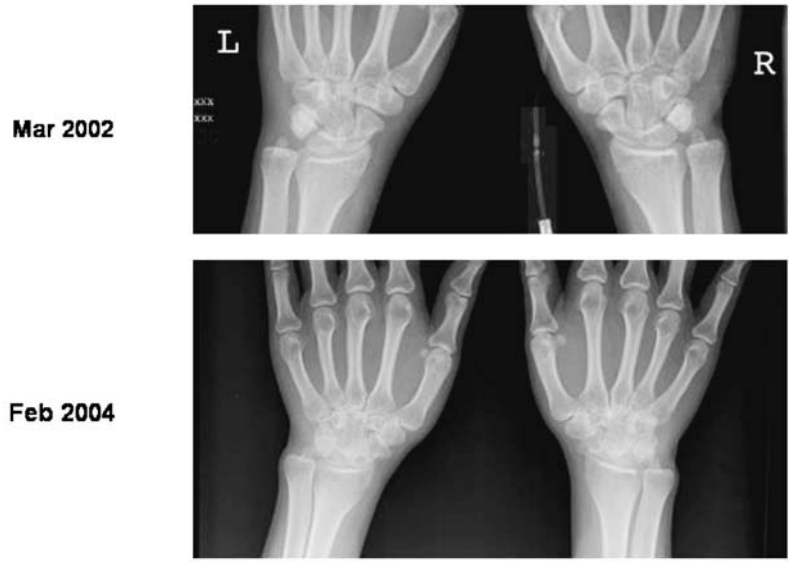

Figure 4. Rapid progression of joint space loss, erosions and ankylosis of both wrists in a 15-year old girl with systemic JIA, despite treatment with prednisone, intra-articular corticosteroids, methotrexate and etanercept.

A study of prepubertal S-JIA patients with persistent chronic inflammation requiring treatment with prolonged daily oral prednisone, showed a significant reduction in height velocity of more than 2 standard deviations during the first 4 years of follow up (Simon et al., 2002). Linear growth retardation was associated with the duration of prednisone therapy. Although most patients demonstrated at least partial catch up growth after prednisone was discontinued, some had further loss of height velocity. Final adult height was below their predicted target height in 87% and decreased by more than 2 standard deviations in 41%. Daily prednisone doses of more than 5 mg/m^2 (Blodgett et al., 1956) or more than 0.25 mg/kg/day (Potter et al., 1975) have been reported to impair linear growth.

Impaired linear growth in S-JIA has been shown to be related to disease activity independent of corticosteroid treatment (Allen et al., 1991), and has been demonstrated even in the absence of systemic corticosteroid therapy (Polito et al., 1997). The majority of patients with active S-JIA have normal growth hormone (GH) production but levels of IGF-1, a major mediator of GH activity and its primary binding protein, IGF binding protein 3 (IGFBP-3) are low (Allen et al., 1991; Tsatsoulis et al., 1999). Studies of IL-6 transgenic mice support a pathogenetic role for chronic IL-6 overproduction in the growth impairment seen in S-JIA. These mice have a 50% reduction in growth and have similarly normal GH secretions and low IGF-1 and IGFBP-3 levels, as seen in S-JIA (de Benedetti and Martini, 2005). Furthermore, circulating levels of IL-6 are inversely correlated with levels of IGF-1 and IGFBP-3 in patients with S-JIA, and treatment with anti-IL-6R antibody may result in an increase in height velocity.

A number of observational studies have suggested that GH therapy results in a significant improvement in linear growth in patients with S-JIA but no long-term studies have demonstrated an improvement in final adult height. A controlled study of GH therapy in corticosteroid-dependent JIA, most of whom had S-JIA, showed a sustained improvement in linear growth over a 4-year period (Bechtold et al., 2003). There was an inverse relationship between growth velocity and ESR, CRP and prednisolone dose in both treatment and control groups, but these predictors of growth velocity were less important in the group receiving GH. Although there are anecdotal reports of disease

flares that have been associated with initiation of GH therapy, most reports do not suggest that this is a significant association.

The role of GH for growth failure in S-JIA will ultimately depend on the results of long-term studies that evaluate its efficacy in improving final adult height. In the interim, controlling active disease and minimizing the dose of systemic corticosteroids should be the most important strategies for promoting optimum growth.

6. Less common clinical manifestations

The less common manifestations of S-JIA are listed in Table 1.

Although neurological complications are not common, they are potentially fatal events (Schneider et al., 2000) and therefore deserve special attention. Encephalopathy and cerebrospinal fluid pleocytosis are well-described manifestations of MAS and usually require more aggressive therapy. Non-infectious meningitis has been reported in adult-onset Still's disease (Blockmans et al., 2000), and we have observed this in a small number of children as well. We have seen the rapid development of severe hyponatremia resulting in cerebral edema in patients with S-JIA who have fever and vomiting. This is most likely a consequence of inappropriate ADH secretion. We urge particular vigilance for this complication in S-JIA patients who present with fever and vomiting, with close attention to fluid balance, regular monitoring of electrolytes and avoidance of hypotonic intravenous solutions.

Uveitis occurs in $<2\%$ of S-JIA patients. We therefore recommend ophthalmological assessment at the time of diagnosis and annually thereafter. However, patients who require long-term systemic corticosteroids should be monitored more frequently (we suggest every 6 months) for the development of cataracts and glaucoma. Superior oblique muscle tenosynovitis resulting in Brown's syndrome has been reported (Wang et al., 1984).

We have recently reported nasal septal perforation in three S-JIA patients. All had severe, refractory disease and one had associated leukocytoclastic vasculitis of the skin (Avcin et al., 2005). Vasculitis has also been reported following intravenous immunoglobulin administration (Uziel et al., 1996).

Pleuritis occurs less frequently than pericarditis and severe pulmonary complications are infrequent but may be serious. Interstitial pneumonitis (Athreya et al., 1980) and pulmonary fibrosis have been reported. Lipoid pneumonia is a rare

Table 1
Less common and rare manifestations of S-JIA

Organ system	Manifestations	References
Central nervous system	Encephalopathy with MAS, non-infectious meningitis, cerebral edema with SIADH, epidural lipomatosis	Blockmans et al., 2000; Tabak et al., 2003; Arroyo et al., 1988
Eye	Uveitis, tenosynovitis of superior oblique muscle (Brown's syndrome)	Wang et al., 1984
ENT	Nasal septal perforation, cricoarytenoid arthritis	Avcin et al., 2005; Pathan et al., 2001
Skin/subcutaneous tissue	Vasculitis, lymphedema	Avcin et al., 2005; Bardare et al., 1997
Lung	Interstitial pneumonitis, lipoid pneumonia, pulmonary hypertension	Athreya et al., 1980; Schultz et al., 2001
Heart	Cardiac tamponade, myocarditis, valvular abnormalities	Goldenberg et al., 1992
Muscle	Myositis	Miller et al., 1995
Hematological	Isolated thrombocytopenia	Lin and Jaing, 1999
Renal	Calculi, hematuria and proteinuria, glomerulonephritis	Foster et al., 1998

Note: SIADH—Inappropriate anti-diuretic hormone secretion; ENT—ear, nose, throat.

complication of severe, refractory disease with the development of progressive pulmonary cholesterol granulomas, which may result in respiratory failure (Schultz et al., 2001).

Although myalgias are common, documented myositis is rare but may be associated with typical inflammatory findings on MRI scanning of muscles (Miller et al., 1995). Myocarditis is similarly rare and usually accompanies symptomatic pericarditis (Goldenberg et al., 1992).

7. Macrophage activation syndrome

MAS is an important complication of S-JIA, occurring in approximately 7% of patients (Sawhney et al., 2001) but patients may also manifest some of the clinical and laboratory features without developing the complete syndrome. MAS can evolve rapidly with significant morbidity and mortality, making prompt diagnosis and treatment imperative.

The most common clinical features of MAS are sustained fever and hepatosplenomegaly, while lymphadenopathy, bruising, petechiae and mucosal bleeding are also characteristic features. These features may be accompanied by an unexpected improvement in the patient's arthritis. More severely affected patients can have multiorgan involvement with depressed level of consciousness, seizures, disorientation and even coma, respiratory distress with pulmonary infiltrates and cardiovascular instability with hypotension and shock. MAS has been reported in association with Kikuchi's disease, a necrotizing lymphadenitis, in S-JIA (Ramanan et al., 2003).

Typical laboratory features include pancytopenia, elevated transaminases and sometimes bilirubin, elevated LDH and triglyceride levels. Serum ferritin levels are often extremely high. A dramatic and sharp drop in ESR, despite an ongoing febrile illness, is an important laboratory clue to the diagnosis. Coagulopathy with prolongation of the prothrombin time and partial thromboplastin time, marked elevation of d-dimers, and low levels of fibrinogen are seen. Renal involvement may range from mild hematuria and proteinuria to acute renal failure requiring dialysis. Cerebrospinal fluid analysis may reveal pleocytosis and elevated protein. Other features include hyponatremia, hypoalbuminemia, elevated VLDLs and decreased HDLs.

Active systemic disease, infections and medication toxicities may mimic the clinical and laboratory manifestations of MAS, and can also occur in association with MAS. MAS has been associated with viral, bacterial and fungal infections, but has particularly been related to infections with the herpes viruses, especially with Epstein-Barr virus infection. Non-steroidal anti-inflammatory drugs, gold injections, sulfasalazine, methotrexate and more recently etanercept have all been reported to be associated with the initiation of MAS (Ramanan and Schneider, 2003).

It has been suggested that MAS should be classified as a histiocytic disorder—a form of HLH, secondary to rheumatic diseases. Both HLH and MAS are characterized by excessive activation of monocytes and macrophages and high levels of pro-inflammatory cytokines, including TNF-α, IL-6 and interferon-γ. Although 20–40% of patients with the primary form of HLH have defects in perforin genes, similar defects have not been found in MAS. However, patients with HLH and MAS do have similar immunological abnormalities. Low levels of perforin expression have been found in MAS associated with S-JIA and, interestingly, these levels can be restored to normal after autologous stem cell transplantation (Wulffraat et al., 2003). NK cell function is also markedly reduced in patients with HLH and MAS (Grom, 2004). Although these abnormalities suggest a common pathogenetic mechanism in HLH and MAS, the pathogenesis of MAS remains uncertain and it is unclear why some patients with S-JIA seem predisposed to develop MAS while others are not, even when exposed to the same triggers.

There are no validated diagnostic criteria for MAS associated with S-JIA. Stringent application of the proposed diagnostic criteria for HLH, revised by Henter et al for the Histiocyte Society in 2004 (Table 2) is not appropriate for several reasons. Firstly, the clinical criteria of fever and splenomegaly are not specific and can also be seen with active S-JIA. A persistent fever as opposed to

Table 2
Proposed diagnostic guidelines for hemophagocytic histiocytosis (HLH)

Clinical criteria
1 Fever
2 Splenomegaly
Laboratory criteria
1 Cytopenias, including at least 2 of the following:
a. Hemoglobin <90 g/l
b. Platelets $<100 \times 10\ l^{-1}$
c. Neutrophils $<1.0 \times 10\ l^{-1}$
2 Elevated fasting triglyceride ($>/=3.0$ mml/l) or low fibrinogen ($</=1.5$ g/l)
Pathologic criteria
1 Hemophagocytosis in bone marrow, spleen or lymph nodes (in the absence of malignancy)
New criteria
1 Low or absent NK cell activity
2 Elevated ferritin ($\geqslant 500$ μg/l)
3 Elevated soluble CD 25 ($\geqslant 2400$ U/ml)

Note: These guidelines suggest that the diagnosis of HLH requires 5 of the above 8 criteria (modified from Henter et al., 2007).

the typical quotidian pattern of fever in S-JIA is more suggestive of MAS or infection. Secondly, the hematological profile is problematic. Anemia with hemoglobin <90 g/l can also be seen in active systemic disease. More importantly, the requirement of a drop in platelet count to $<100 \times 10^9\ l^{-1}$ and neutrophil count $<1.0 \times 10^9\ l^{-1}$ may result in an unnecessary delay in diagnosis. Since both platelet and neutrophil counts are characteristically high in active systemic disease, a significant and sudden drop in these counts may be more important than the absolute number. Similarly, a substantial drop in fibrinogen levels may be more important than a level <1.5 g/l since fibrinogen is also elevated along with other acute phase proteins in S-JIA. Thirdly, it is well known that hemophagocytic changes may not be demonstrable pathologically. Tissue hemophagocytosis may be missed in the bone marrow early on, and biopsies of liver, spleen or lymph nodes are often not possible because of severe coagulopathy. On the other hand, mild hemophagocytic changes are not specific and may be seen in the absence of MAS. The inclusion of new criteria of low NK-cell function, elevated ferritin and elevated levels of soluble CD25 may be helpful in establishing a diagnosis but have not been evaluated. Ferritin is also an acute phase protein and levels >500 μg/l are frequently seen in active S-JIA without other features of MAS. Extreme hyperferritinemia may be more helpful but is not specific, and ferritin levels may only rise later in the course of MAS. Furthermore, elevated levels of LDH appear to be very helpful in the diagnosis of MAS but are not included in the proposed diagnostic criteria. It is critical to carefully follow the trend of laboratory features and to be vigilant for a pattern that suggests evolving MAS.

In an attempt to address some of the above issues, Ravelli et al. (2005) have proposed preliminary diagnostic criteria for MAS in S-JIA. The clinical criteria are central nervous system dysfunction, hemorrhages and hepatomegaly. The laboratory criteria include a reduction in platelet count to $\leqslant 262 \times 10^9\ l^{-1}$ (rather than true thrombocytopenia), elevated aspartate aminotransaminase (>59 U/l), white blood cell count $\leqslant 4 \times 10^9\ l^{-1}$ and fibrinogen $\leqslant 2.5$ g/l. It is important to point out that these criteria have not been validated.

The initial treatment of MAS requires the prompt administration of high dose corticosteroids. Our preference is to use intravenous pulse methylprednisolone 30 mg/kg/dose up to a maximum of 1000 mg/dose for 3–5 days, followed by high dose oral or intravenous corticosteroids. If there is central nervous system involvement, dexamethasone may be preferable to prednisone. We frequently add intravenous immunoglobulin to this regimen, which has been reported to be effective in MAS (Emmenegger et al., 2001). Approximately half the patients with MAS reported in the two largest pediatric series responded to corticosteroids alone. If there is an inadequate response to corticosteroids or if there is more severe multiorgan involvement, adding cyclosporin to the regimen may result in rapid and dramatic improvement (Mouy et al., 1996; Sawhney et al., 2001; Stephan et al., 2001). Since MAS can follow a course of rapid progression and deterioration, some authors feel that cyclosporin should be added to corticosteroids as first-line therapy

(Kounami et al., 2005). If there is rapidly evolving multiorgan failure, one should not hesitate to use corticosteroids, cyclosporin as well as etoposide. We have found the addition of etoposide to be very helpful in reversing the manifestations of severe MAS. We have successfully used a shorter duration etoposide treatment than that recommended in the HLH-94 protocol (Henter et al., 2002) in an attempt to reduce the risk of serious long-term toxicity, especially the risk of malignancy. Markedly elevated levels of TNF-α in MAS have prompted some to use TNF inhibitors (Prahalad et al., 2001), though it is quite clear that MAS can develop in patients being treated with TNF inhibitors and etanercept may even be one of the triggers of MAS (Ramanan et al., 2003). Other modalities used to treat refractory MAS include cyclophosphamide, antithymocyte globulin and exchange transfusion.

Although multiorgan involvement may be associated with a poor outcome, severe renal disease may fully recover if treatment is initiated promptly (Ramanan et al., 2004). The reported recurrence risk of MAS is 17% and the reported mortality 8–22% (Sawhney et al., 2001; Stephan et al., 2001).

8. Laboratory investigations

While there is a pattern of laboratory abnormalities that is characteristic of patients with S-JIA, there are no specific tests that allow the diagnosis to be made with certainty. There is a marked elevation of the acute phase response, consisting of anemia, typically hypochromic, microcytic, with leukocytosis and left shift, and thrombocytosis. With time, iron deficiency may also contribute to the anemia as result of poor nutrition.

The ESR and CRP are both markedly elevated and a persistently raised CRP may correlate with ongoing damage, a poor outcome, and the development of systemic amyloidosis. Other features of the acute phase response include hypergammaglobulinemia, hypoalbuminemia and raised levels of fibrinogen. The elevated immunoglobulin levels may result in confusion if specific antibodies are searched for. For instance, approximately 1/4–1/3 of patients will have an elevated antistreptolysin-o titer; however, this should not necessarily be assumed to be a result of a streptococcal infection. Raised serum ferritin may also be seen with elevation of other acute phase proteins, such as serum amyloid A. The raised ferritin in this case is a poor reflection of iron stores and iron deficiency may best be determined by the measurement of serum soluble transferrin receptor levels, which are not affected by chronic inflammation.

Both the rheumatoid factor and antinuclear antibody tests are typically negative helping to differentiate S-JIA from other autoimmune connective tissue diseases. Genetic testing for the autoinflammatory syndromes has not identified a specific gene mutation associated with S-JIA; and while there may be some very loose HLA associations, these are not at all useful for diagnosis at this stage.

Liver function abnormalities with transaminitis are common, particularly with active systemic disease. There may be a mild underlying coagulopathy with elevation of d-dimers without other evidence of overt MAS.

Synovial fluid analysis during active systemic disease may resemble the findings in infectious synovitis, with high white cell counts of a predominantly polymorphonuclear type.

9. Radiologic investigations

X-ray abnormalities in children with S-JIA include soft tissue swelling, reduced bone density, loss of joint space, advanced maturation, erosions and deformity. The early changes of soft tissue swelling and osteopenia are reversible. Radiographic damage occurs early, within 2 years of disease onset in about 1/3 of patients, who develop joint space loss and erosions (Lang et al., 1995). Destructive changes can occur rapidly over the course of 1–2 years, especially in the hips and wrists. The Poznanski score can be used as valid measure of joint space loss, and radiographic progression during the first year of disease correlates with the Poznanski score at the final visit, CHAQ and yearly progression (Magni-Manzoni et al., 2003). In univariate analysis, systemic disease also correlated

with yearly radiographic progression and the final Poznanski score.

Radiographic damage at 2 years, measured by erosions with or without joint space narrowing, correlates with thrombocytosis and active systemic disease in children with S-JIA. The most commonly involved joints are the wrist followed in frequency by the ankle, knee, tarsal, hip and metacarpophalangeal joints (Lang et al., 1995).

Joint ankylosis is also common in unresponsive disease, and usually involves the carpus and apophyseal joints of the cervical spine especially 2^{nd}–3^{rd} facet joints.

Growth disturbances are also common leading to micrognathia and retrognathia, shortened digits and reduced height of vertebral bodies.

Diagnostic imaging is also helpful for some of the complications of S-JIA. Growth delay is common and x-rays of the hand may be useful in determining bone age and the potential for future growth (this may be difficult if there is arthritis involving the carpus). Osteoporosis resulting from active disease, treatment with corticosteroids, reduced exercise and poor diet is common. Bone densitometry studies should be done to establish a baseline and to follow and determine the need for specific treatment. Patients with severe osteoporosis are at risk for spontaneous fractures, particularly those involving the vertebral bodies. Murray et al (Murray et al., 2000) reported that almost 1/4 of patients with S-JIA had at least one fracture and the majority of these were vertebral. Those with severe erosive disease, growth failure and high cumulative corticosteroid doses seem to be at highest risk of this complication. However, vertebral compression fractures can occur in the absence of significantly reduced bone mineral density measurements (Makitie et al., 2005). Synovial cysts are more common in S-JIA than other types, and ultrasound and magnetic resonance imaging studies may help detect and define these cysts.

10. Differential diagnosis

The differential diagnosis of S-JIA is one of the widest in pediatrics (Table 3), given the broad array of signs and symptoms that may develop. Furthermore, as there is no diagnostic test it often remains a diagnosis of exclusion. Broad categories that must be considered include infection, malignancy, systemic autoimmune disease and vasculitis, and the newly described autoinflammatory syndromes. However, careful attention to the signs and symptoms, and appropriate diagnostic testing should allow one to arrive at a diagnosis.

In approaching these patients, it is always imperative to rule out potentially treatable and life-threatening diseases. Thus malignancy and infection should be considered first. Lymphoreticular malignancies (leukemia, lymphoma) and neuroblastoma are suggested by the presence of

Table 3
Differential diagnosis of S-JIA

Malignancy
Leukemia, lymphoma, neuroblastoma
Infection
Viral: Epstein-Barr virus, cytomegalovirus, hepatitis, HIV
Bacterial: systemic—infective endocarditis, tuberculosis, Bartonella, Mycoplasma, Lyme
Localized: abscess, osteomyelitis
Inflammatory connective tissue diseases
Systemic lupus erythematosus
Mixed connective tissue disease/overlap syndrome
Juvenile dermatomyositis
Reactive arthritis
Acute rheumatic fever
Post-salmonella/shigella/yersinia arthritis
Periodic fever syndromes
Familial Mediterranean fever
Hyperimmunoglobulin D syndrome
TNF receptor-associated periodic fever syndrome (TRAPS)
Autoinflammatory syndromes
Familial cold autoinflammatory syndrome
Muckle-Wells syndrome
Chronic infantile neurologic cutaneous and articular syndrome (CINCA)
Systemic inflammatory syndromes
Crohn's disease
Sarcoidosis
Vasculitides
Cutaneous polyarteritis nodosa
Kawasaki disease

lymphadenopathy and splenomegaly, and supported by the systemic and constitutional features. The marked elevation of the acute phase response with leukocytosis and thrombocytosis would go against leukemia, but may be seen in lymphoma and neuroblastoma. Bone marrow aspirates and appropriate use of diagnostic imaging (ultrasound and CT scan of chest and abdomen) are often performed looking for signs of lymphoreticular malignancy. A lymph node biopsy may also be performed. Signs more suggestive of S-JIA would be the evanescent rash and typical periodicity of the fevers.

Infections must be strongly considered in view of the fever, constitutional symptoms, leukocytosis and elevated ESR. Bacterial infections to be considered include those associated with "fever of unknown origin" such as subacute bacterial endocarditis, abscess, osteomyelitis and even tuberculosis. Bartonella infections have been reported to produce a similar constellation of symptoms and signs to S-JIA. Mycoplasma pneumoniae can also cause serositis, rash and arthritis. Appropriate cultures, polymerase chain reaction tests, erological tests and radiographic investigations should be able to exclude these. Systemic viral infections such as Epstein-Barr virus (EBV) and cytomegalovirus are suggested by the fever and reticuloendothelial involvement and occasionally the rash. Sore throat, a common manifestation of EBV infection is frequent in adult-onset Still's disease and also occurs in S-JIA. However, leucopenia or lymphocytosis and thrombocytopenia would be more likely in these viral infections. HIV infection and Lyme disease should also be considered with the appropriate epidemiologic history.

Reactive arthritis should be excluded especially when it occurs with fever and rash. Acute rheumatic fever occurs within 10 days–3 weeks of an untreated streptococcal throat infection and has many features in common with S-JIA. However, the characteristic features of arthritis such as flitting arthritis, severe pain and exquisite response to aspirin or naproxen, persistent fever pattern, erythema marginatum rash and typical electrocardiographic abnormalities would not support the diagnosis of S-JIA.

Autoimmune connective tissue diseases to be ruled out include systemic lupus erythematosus (SLE), juvenile dermatomyositis (JDM) and mixed connective tissue disease (MCTD). SLE and MCTD in particular are associated with characteristic autoantibodies that are not present in S-JIA (ANA, anti-dsDNA, anti-Ro, anti-La, anti-Sm, anti-RNP). They frequently have reduced white blood cell and platelet counts and low levels of serum complement. Renal abnormalities, common in lupus are infrequent in S-JIA. Patients with S-JIA often have severe myalgias associated with the fever spikes, muscle strength may be difficult to evaluate in the presence of painful polyarthritis and transaminases may be elevated. However, they do not usually have elevated creatine kinase levels or the characteristic rashes seen in JDM.

Serum sickness and adverse drug reactions can also mimic S-JIA with fever, rash, arthritis and elevated inflammatory markers. A history of exposure to a drug, erythema multiforme rash and low serum complement (usually elevated in S-JIA) should help to make these diagnoses.

The autoinflammatory syndromes include familial Mediterranean fever, hyperimmunoglobulin D syndrome and tumor necrosis factor receptor-associated periodic syndrome (TRAPS) as well as the cold-induced autoinflammatory syndromes. They frequently have an earlier age of onset, positive family history, and episodes that are shorter in duration than flares of S-JIA. Persistent arthritis is not characteristic except in CINCA syndrome, which has its onset in the neonatal period. Other inflammatory disorders to be considered include Crohn's disease, sarcoidosis and systemic vasculitides such as polyarteritis nodosa (PAN), Wegener's granulomatosis and Kawasaki disease, especially when these diseases are associated with arthritis. Cutaneous PAN has many clinical features in common with S-JIA including fever, arthritis, splenomegaly and a very similar laboratory profile. A careful examination for tender subcutaneous nodules should exclude this diagnosis. Atypical Kawasaki disease may initially be confused with S-JIA and there are some recent reports of S-JIA that has followed classical Kawasaki disease.

11. Treatment

The treatment of patients with S-JIA remains one of pediatric rheumatology's greatest challenges. Recent studies showing that joint damage occurs early and permanent long-term remissions are uncommon reinforce the need for early aggressive treatment in those with a high risk of poor outcome. The therapeutic results seen with newer treatments in patients with polyarticular (non-systemic) disease have unfortunately not been nearly as successful for patients with S-JIA, but more recent advances in the understanding of the pathophysiology of S-JIA have lead to new approaches to treatment, which may improve the long term outcome of this disease.

Initially, treatment is directed at improving the systemic manifestations of disease including the fever and constitutional symptoms. A trial of nonsteroidal anti-inflammatory drugs (NSAIDs) for 1–2 weeks is appropriate. It appears that indomethacin (1–3 mg/kg/day in three divided doses) and ibuprofen (30–40 mg/kg/day in four divided doses) may be more effective than other NSAIDs. Since these drugs are protein bound within the circulation, care must be taken with dosing in patients who have hypoalbuminemia. In addition, attention must be paid to liver transaminases, as mild elevations of these can worsen with NSAID treatment. Acetaminophen may be administered for fever breakthroughs.

The severity of systemic manifestations determines whether it is appropriate to move beyond NSAIDs to systemic corticosteroids. It may be appropriate to "wait it out" with full dose NSAIDs and intermittent acetaminophen if the patient is otherwise not too troubled by the fever. However, if there is debilitation, weight loss, systemic toxicity, severe anemia or significant symptomatic serositis, corticosteroids at a dose of 1–2 mg/kg/day (maximum 60 mg) in two divided doses should be instituted. Consolidating to a daily dose and reducing to as low a dose as possible should be instituted early as the long-term course does not seem to be affected by corticosteroids. Pulse corticosteroid treatment is reserved for more severe or life-threatening manifestations such as severe anemia, severe pericarditis with risk of tamponade, or the development of MAS. Some patients may respond to treatment with intravenous immunoglobulin, at a dose of 2 g/kg every 4 weeks, which may be effective as a steroid-sparing agent but does not have much efficacy for the arthritis (Uziel et al., 1996).

Treatment of persistent synovitis has traditionally followed a similar algorithm as for patients with oligoarticular or polyarticular disease (Hashkes and Laxer, 2005), but the efficacy of this approach has been generally disappointing. Intra-articular triamcinolone hexacetonide for particularly symptomatic joints may be of benefit, but there is a shorter duration of response in patients with active systemic disease. In addition, the response to methotrexate (Woo et al., 2000) and the TNF antagonists etanercept (Kimura et al., 2005; Quartier et al., 2003) and infliximab (Katsicas and Russo, 2005) does not appear to be as robust as in children with other forms of polyarthritis, even when doses used are higher than the usual ones recommended. Thalidomide at a dose of 3–5 mg/kg/day may be successful in combination with other immunosuppressive agents, even in children who have failed treatment with etanercept (Lehman et al., 2004). Patients treated with thalidomide should be carefully monitored for symptoms of peripheral neuropathy, a rare adverse event that could be irreversible.

Both IL-1 and IL-6 have been shown to be important mediators of the inflammatory process in S-JIA. Case reports and small case series have documented significant benefit of anakinra, the IL-1 receptor antagonist (Reiff, 2005; Verbsky and White, 2004). Responses usually occur early, and if inadequate one can consider doubling the dose from 1 to 2 mg/kg/day. In responders, systemic symptoms seem to resolve within about a week of treatment, and the laboratory abnormalities improve quickly as well. Anakinra appears to be of benefit for some patients with long-standing refractory disease, but we have certainly had treatment failures at doses of 2 mg/kg/day. The drug must be administered subcutaneously on a daily basis, making this difficult to tolerate, especially in young children. Subcutaneous injections are often

painful and commonly cause local skin reactions, which can be treated with topical corticosteroids.

The monoclonal antibody to the IL-6R tocilizumab, has also recently been studied, and preliminary results are very encouraging. It has been administered intravenously at doses varying from 2–8 mg/kg, every 2 weeks. Clinical and laboratory improvements can be seen as early as 2–4 days post-infusion with resolution of fever and normalization of ESR and CRP. Efficacy may be best with the higher dose of 8 mg/kg which may be required in some patients to maintain a normal CRP, which in turn correlates particularly well with IL-6 levels and with disease activity (Woo et al., 2005; Yokota et al., 2005). However, tocilizumab is not yet available for clinical use.

Despite the advent of new agents, some patients continue to manifest severe polyarthritis and/or steroid dependency. For a very small subgroup of patients, autologous stem cell transplantation (ASCT) may be considered. While initial results showed a mortality of almost 15%, changes in the preparation protocol seem to have reduced the mortality risk (Wulffraat et al., 2005). Some patients have been able to discontinue all other forms of treatment and achieve a greatly improved quality of life. The risks of serious infections and the development of MAS remain major concerns.

Occasionally, surgical intervention is required to correct deformities. This may include soft tissue release for severe joint contractures, especially around the hip, arthrodesis of the foot or ankle, and joint replacement surgery. Indications for joint arthroplasty include intractable pain and severe loss of mobility. Recent experience with hip arthroplasty suggests that the outcomes with a cementless arthroplasty are excellent (Odent et al., 2005), but more long-term data are awaited.

12. Disease course, outcome and prognosis

Patients with S-JIA can have widely disparate disease courses and outcomes. These range from a monocyclic course followed by complete remission with no disability to a persistently active disease course often well into adult life, characterized by destructive polyarticular arthritis, markedly impaired growth, prominent corticosteroid toxicity, osteoporotic fractures and severe disability.

Despite advances in the treatment of JIA, most of the larger studies suggest that more than 50% of S-JIA patients have a persistently active disease course with only one third of patients achieving remission without medication 10 years after disease onset (Lomater et al., 2000; Oen et al., 2002; Fantini et al., 2003) The articular disease is more often persistent than the systemic symptoms, although these can also persist for longer than 10 years in 25–30% (Prieur et al., 1984; Hafner and Truckenbrodt, 1986). The proportion of patients reported to follow monocyclic, polycyclic or persistent disease courses depends on the definitions of remission used. In a recent study, we found that persistent disease occurred in more than 50%, monocyclic disease in over 40% and a polycyclic course with recurrent episodes of active disease following remission without medications for 1 year was least common, occurring in less than 5% of patients (Singh-Grewal et al., 2006). A similarly low rate of polycyclic disease has been reported by Fantini et al. (Fantini et al., 2003). Disease flares may occasionally occur after prolonged remissions.

Studies of functional outcome in S-JIA have consistently shown that a substantial proportion of patients have severe functional impairments. In studies from the 1970s and 1980s 29–50% patients were in Steinbrocker functional class III or IV (Ansell and Wood, 1976; Hafner and Truckenbrodt, 1986). Packham and Hall (Packham and Hall, 2002) reported that almost two-thirds of patients with S-JIA who were followed for a mean of almost 30 years, were classified as Steinbrocker class III or IV, 62% had HAQ scores reflecting severe disability and 75% had undergone arthroplasty. Although patients with milder disease are underrepresented in this study, it clearly demonstrates that patients with persistently active disease develop severe functional impairment. More recent studies of functional outcome, which may reflect more modern treatment approaches (but not the impact of biologic agents), have been

summarized by Adib (Adib et al., 2005). These studies report a wide range in the proportion of patients in Steinbrocker class III and IV (0–30%). The Steinbrocker classification of functional ability may result in an underestimation of disease severity, since in several of these studies reporting less severe impairment, a high proportion of patients had arthroplasties (David et al., 1994; Oen et al., 2002). In one study, 30% of patients were classified as Steinbrocker class III or IV within 5 years of disease onset compared to 12% of patients with polyarticular onset arthritis (Bowyer et al., 2003). Functional impairment in S-JIA as measured by the CHAQ or HAQ remains more severe than in the other JIA subtypes. In a study of 111 patients with systemic JRA, 22% had moderate-to-severe disability with a CHAQ score of >0.75, 7 years after disease onset (Spiegel et al., 2000).

The identification of reliable predictors of disease course and outcome within the first few months of disease onset is invaluable in determining which patients might benefit from early aggressive therapy. Three studies have evaluated early predictors of poor outcome in S-JIA. In a retrospective study, we determined that persistent systemic symptoms together with thrombocytosis (platelet count $> 600 \times 10^9\ l^{-1}$) at 6 months after disease onset predicted poor outcome, defined as polyarticular arthritis with joint space narrowing and erosions at 2 years. Additional predictors included polyarticular arthritis, WBC $>12 \times 10^9\ l^{-1}$ and hemoglobin <100 g/l (Schneider et al., 1992). In a subsequent study of 104 patients, persistent systemic symptoms (characterized by fever or the use or systemic corticosteroids) and thrombocytosis at 6 months were strongly predictive of poor functional outcome (CHAQ $\geqslant 0.75$) (Spiegel et al., 2000). Modesto et al. (Modesto et al., 2001) identified young age (<8 years), lymphadenopathy and high articular index at onset and polyarticular disease with hip involvement at 6 months as predictors of poor outcome.

As might be expected, the disease course can be correlated with outcome. Persistently active disease is associated with worse clinical, radiological and functional outcomes. Moreover, the cumulative duration of active disease correlates with outcome (Lomater et al., 2000). In a recent study evaluating predictors of disease course in S-JIA, we found that polyarticular disease at onset, fever and active arthritis at 3 months, and use of systemic corticosteroids, active arthritis and elevated ESR (>26 mm/hr) at 6 months were associated with a persistent disease course or a longer time to remission (Singh-Grewal et al., 2006). It has been suggested that males have a worse outcome than females (Oen et al., 2002) but this has not been consistent.

The first genetic predictor or poor outcome in S-JIA has been identified. De Benedetti et al. (De Benedetti et al., 2003) evaluated the functional and prognostic significance of a polymorphism of the MIF gene. The MIF-173*C allele has been associated with higher serum and synovial fluid levels of MIF, poor response to glucocorticoid therapy, persistence of active disease and poor functional outcome. It is likely that the future identification of combinations of clinical, laboratory and genetic predictors will improve the sensitivity and specificity of predicting disease outcome in S-JIA.

Despite bearing the burden of a severe systemic disease, children with S-JIA typically have normal cognitive development and performance, including normal performance on tests of IQ, memory, learning, attention and fine motor activities. Although these patients report fewer social activities than their peers, they may not have a significant increase in social or emotional problems (Feldmann et al., 2005).

13. Mortality

Although the mortality rate in JIA is considerably less than 1% (Wallace and Levinson, 1991), S-JIA accounts for a disproportionate two-thirds of deaths in JIA. The most important causes of mortality are infections and macrophage activation syndrome. Since symptoms of infection and MAS can be confused with active systemic disease, it is essential to promptly and rigorously exclude these entities in patients with fever. Immunosuppressive regimens result in an increased risk of infections

and a number of therapies, in particular ASCT, have been associated with the development of MAS. Patients with S-JIA should receive routine childhood immunizations with special attention to meningococcal, pneumococcal and annual influenza vaccines. Live virus vaccines including the varicella vaccine may be administered prior to initiation of immunosuppressive therapy. Children requiring long-term immunosuppressive therapy should be considered candidates for antibiotic prophylaxis for Pneumocystis carinii, depending on the particular immunosuppressive regimen followed.

The mortality in earlier European series of patients with S-JIA was reported to be as high as 14% with the majority of deaths resulting from amyloidosis (Ansell and Wood, 1976; Prieur, 1984; Hafner and Truckenbrodt, 1986). However, with the declining incidence of amyloidosis in S-JIA, lower mortality rates of $<5\%$ have been reported (Kobayashi et al., 1993; Lomater et al., 2000). The causes of mortality in S-JIA are listed in Table 4. Severe cardiac involvement may result in myocarditis, cardiac tamponade or arrhythmias (Goldenberg et al., 1992). Neurological complications include aseptic meningitis and we have observed a syndrome of inappropriate ADH secretion in association with active systemic disease resulting in hyponatremia and cerebral edema (Schneider et al., 2000). There are a few reports of the development of fatal lipoid pneumonia in patients with active, refractory disease (Schultz et al., 2001). Patients on cytotoxic chemotherapy protocols such as chlorambucil or etoposide, have an increased risk of developing malignancies.

Table 4
Causes of death in S-JIA

Macrophage activation syndrome
Infection
Neurological complications
Amyloidosis
Cardiac complications
Lipoid pneumonia
Treatment-related malignancy

Key points

- The diagnosis of S-JIA requires the rigorous exclusion of a broad range of conditions, particularly infections, malignancies and in the younger infants, the autoinflammatory syndromes.
- The clinician should be vigilant for both the common and less common systemic manifestations of the disease
- Macrophage Activation Syndrome is a potentially fatal complication that requires prompt diagnosis and treatment. Diagnosis of MAS by strict application of the proposed criteria for HLH may result in a delay in the diagnosis.
- Patients with S-JIA generally do not respond as well as other subtypes of JIA to standard therapies.
- The identification of clinical, laboratory and more recently genetic predictors of disease course, outcome and response to treatment may help to identify patients who may benefit from early aggressive treatment.
- An improved understanding of the roles of IL-1 and IL-6 in the pathogenesis of S-JIA has resulted in new and potentially highly effective therapies aimed at neutralizing the actions of these cytokines.

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Handbook of Systemic Autoimmune Diseases, Volume 6
Pediatrics in Systemic Autoimmune Diseases
Rolando Cimaz and Thomas Lehman, editors

CHAPTER 4

Macrophage Activation Syndrome

Angelo Ravelli*, Alberto Martini

Dipartimento di Pediatria, Università di Genova and Pediatria II, Istituto G. Gaslini, Genova, Italy

1. Introduction

Macrophage activation syndrome (MAS) is a life-threatening complication of rheumatic diseases that, for unknown reasons, occurs much more frequently in systemic juvenile idiopathic arthritis (S-JIA) and in its adult equivalent, adult-onset Still disease. It is characterized by pancytopenia, liver insufficiency, coagulopathy, and neurologic symptoms and is thought to be caused by the uncontrolled activation and proliferation of T lymphocytes and well-differentiated macrophages, leading to widespread hemophagocytosis and cytokine overproduction (Prieur and Stéphan, 1994; Grom and Passo, 1996; Sawhney et al., 2001; Ravelli et al., 2000).

2. Clinical features

The clinical presentation of MAS is generally acute and occasionally dramatic. Typically, patients become acutely ill with the sudden onset of non-remitting high fever, profound depression of all three blood cell lines (leukopenia, anemia, and thrombocytopenia), hepatosplenomegaly, lymphoadenopathy, and elevated serum liver enzymes. High concentrations of triglycerides and lactic dehydrogenase, and low sodium levels are observed consistently. There is often an abnormal coagulation profile, with prolongation of prothrombin and partial thromboplastin time, hypofibrinogenemia, and detectable fibrin degradation products. As a consequence, patients may have purpura, easy bruising, and mucosal bleeding. Central nervous system dysfunction occurs frequently and may cause lethargy, irritability, disorientation, headache, seizures, or coma. Renal, pulmonary, and cardiac involvement have been reported (Stéphan et al., 2001; Ramanan et al., 2004). In children with S-JIA, the clinical picture may mimic a sepsis or an exacerbation of the underlying disease. However, the pattern of non-remitting fever is different from the remitting high-spiking fever seen in S-JIA. Moreover, patients may show a paradoxical improvement in the underlying inflammatory disease at the onset of MAS, with disappearance of signs and symptoms of arthritis and precipitous fall in the erythrocyte sedimentation rate. The latter phenomenon probably reflects the degree of hypofibrinogenemia secondary to fibrinogen consumption and liver dysfunction. The pathognomonic feature of the syndrome is seen on bone marrow examination, which reveals numerous well-differentiated macrophages actively phagocytosing hematopoietic cells (Fig. 1). Such cells may be found in various organs and may account for many of the systemic manifestations. It is still unclear whether MAS is a discrete clinical event or whether it simply represents the most severe end of the spectrum of disease activity in S-JIA.

Hyperferritinemia is an important laboratory hallmark of MAS that has received increasing

*Corresponding author.
Tel.: +39-010-5636386; Fax: +39-010-5636211
E-mail address: angeloravelli@ospedale-gaslini.ge.it (A. Ravelli).

DOI: 10.1016/S1571-5078(07)06008-4

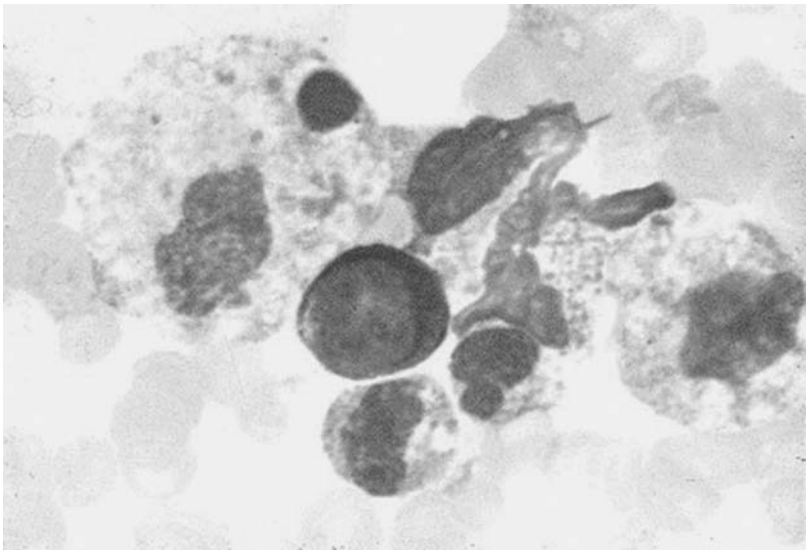

Figure 1. Bone marrow aspirate showing macrophage hemophagocytosis in a patient with S-JIA and MAS. (See Colour Plate Section.)

attention in recent years. Phagocytic macrophages are considered an important source of serum ferritin (Finch et al., 1984). In vitro studies have shown that intracellular ferritin accumulates markedly during the maturation of monocytes into macrophages, and that cultured monocytes in iron-containing medium or in the phagocytic process of erythrocytes produce ferritin quickly (Andreesen, 1984; Worwood et al., 1984). Very high ferritin levels are commonly seen in disorders characterized by histiocytic proliferation and active phagocytosis of erythrocytes, such as malignant histiocytosis and virus-associated hemophagocytic syndrome (Esumi et al., 1988). A sharp rise of ferritin, often above 10,000 ng/ml, has been reported in the acute phase of MAS (Ravelli et al., 2001; Prahalad et al., 2001; Cuende et al., 2001). Furthermore, a good correlation between ferritin level and response to therapy was observed, with the decrease of ferritin being associated with a favorable course of MAS (Ravelli et al., 2001). These findings indicate that measurement of serum ferritin level may assist in the diagnosis of MAS and represent a useful indicator of disease activity, therapy response, and prognosis.

Table 1 illustrates the main clinical and laboratory features of MAS occurring in the context of S-JIA.

Table 1
Main features of the macrophage activation syndrome

Clinical features
Non-remitting high fever
Hepatomegaly
Splenomegaly
Lymphoadenopathy
Hemorrhages
Central nervous system dysfunction
Laboratory features
Cytopenia
Abnormal liver function tests
Coagulopathy
Decreased erythrocyte sedimentation rate
Hypertriglyceridemia
Hyponatremia
Hypoalbuminemia
Hyperferritinemia
Histopathological features
Macrophage hemophagocytosis in the bone marrow

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3. Epidemiology

The incidence of MAS in childhood rheumatic disorders is unknown. Although it is considered a rare complication, it is probably more common

than previously thought. In a retrospective study from a tertiary care center, 7 of the 103 children diagnosed with S-JIA over a 20-year period developed MAS (6.7%) (Sawhney et al., 2001). To date, approximately 100 cases have been reported in the literature (Ravelli et al., 2005). MAS affects most commonly children with S-JIA, but has been observed in other rheumatic diseases, such as juvenile systemic lupus erythematosus (SLE) (Ravelli et al., 2000; McCann et al., 2006) and Kawasaki disease (Muise et al., 2003) and occasionally also in polyarticular JIA (Stéphan et al., 2001). It generally develops in the earlier phases of the underlying disease or may be the presenting manifestation, but occurrence up to 14 years after diagnosis has been reported (Stéphan et al., 2001). In most patients, the primary disease is clinically active at the onset of MAS, but the syndrome may occasionally occur in a quiescent phase.

Although many instances of MAS lack an identifiable precipitating factor, the syndrome has been related to a number of triggers, including a flare of the underlying disease, toxicity of aspirin or other non-steroidal anti-inflammatory drugs, viral infections, a second injection of gold salts, and sulfasalazine therapy (Ravelli, 2002). A young girl with S-JIA was described who developed a MAS shortly after the first methotrexate (MTX) administration in the apparent absence of any inciting factor, suggesting that MAS could have been a direct consequence of MTX toxicity (Ravelli et al., 2001). The shortness of the time interval (24 h) between MTX dosing and onset of MAS and the characteristics of clinical symptoms, particularly the intense and generalized itching, argued for a hypersensitivity or idiosyncratic reaction, a mechanism similar to that hypothesized in the pathogenesis of MAS secondary to gold salt injections.

In the recent years, instances of MAS in S-JIA patients during treatment with biologic medications, including TNF-α inhibitors and IL-1 receptor antagonists, have been described. However, the responsibility of these drugs in the induction of MAS is controversial (see below).

Serious episodes of MAS have been observed among patients who underwent autologous bone marrow transplantation for S-JIA refractory to conventional therapy (ten Cate et al., 2002; Wulffraat et al., 2005; De Kleer et al., 2004; Sreedharan et al., 2006). Although in most of these cases an infectious trigger for MAS was identified, it was hypothesized that the complication was favored by stringent T cell depletion, with resultant inadequate control of macrophage activation (De Kleer et al., 2004; Wedderburn et al., 2003). After an adaptation of the protocol, consisting in less profound T cell depletion, better control of systemic disease before transplantation and slow tapering of corticosteroids after the procedure, no further cases of MAS have occurred (De Kleer et al., 2004). The development of hemophagocytosis in three patients with S-JIA who received fludarabine as part of the conditioning regimen has been reported recently (Wulffraat et al., 2005).

4. Nomenclature and classification

The clinical syndrome of acute hemorrhagic, hepatic, and neurological abnormalities in patients with S-JIA was first described by Hadchouel et al. (1985). The term MAS, which subsequently gained increasing popularity in the pediatric rheumatology community, was proposed in 1993 by the same investigators, who found evidence of activation of the monocyte–macrophage system in patients with the syndrome and noted that its clinical features were very similar to those observed in other hemophagocytic syndromes that are now collectively referred to as hemophagocytic lymphohistiocytosis (HLH) (Janka and Zur Stadt, 2005).

HLH is not a single disease but a hyper-inflammatory syndrome that can occur in association with a variety of underlying conditions, both genetic and acquired (Table 2). Genetic HLH can be divided into two subgroups: familial HLH and the immune deficiencies Chèdiak-Higashi syndrome, Griscelli syndrome, and X-linked lymphoproliferative syndrome (XLP). Acquired HLH can be observed following infections (herpes viruses in particular), during the course of rheumatic disorders, of malignant diseases (especially lymphomas) and of some metabolic diseases.

Recently, the increasing recognition that MAS belongs to HLH has led to propose to rename MAS according to the contemporary

Table 2
Hemophagocytic lymphohistiocytosis (reproduced with permission from Janka and Zur Stadt, 2005)

Genetic HLH
Familial HLH (Farquhar disease)
Known genetic defects (perforin, munc 13-4, syntaxin 11)
Unknown gene defects
Immune deficiency syndromes
Chèdiak-Higashi syndrome
Griscelli syndrome
X-linked lymphoproliferative syndrome (XLP)
Acquired HLH
Exogenous agents (infections, toxins)
Infection-associated hemophagocytic syndrome (IAHS)
Endogenous products (tissue damage, inborn error of metabolism such as lysinuric protein intolerance and multiple sulfates deficiency)
Rheumatic diseases
Macrophage activation syndrome (MAS)
Malignant diseases (especially lymphoma-associated HS or LAHS)

classifications of HLH (Athreya, 2002; Ramanan and Schneider, 2003a, b). A suitable name could be, as suggested by Athreya (2002), ''rheumatic disease-associated hemophagocytic syndrome''. Indeed, uniform nomenclature would facilitate communication between pediatric rheumatologists and specialists in other fields, such as hematology, clinical immunology, and infectious diseases, who are very familiar with this syndrome but often unaware of the rheumatology literature on this subject.

5. Pathogenesis

MAS is characterized by a highly stimulated but ineffective immune response. Its pathogenesis, although still poorly understood, presents many similarities with that of the other forms of HLH. The best known of these is familial HLH (FHLH) which is characterized by a severe impairment of lymphocyte cytotoxicity.

The cytotoxic activity of NK and CD8+T lymphocytes is mediated by the release of cytolytic granules (containing perforin, granzymes, and other serine-like proteases) to the target cells. Several independent genetic loci related to the release of cytolytic granules have been associated with FHLH: perforin mutations have been observed in ~40% of patients. These mutations cause a severe impairment of cytotoxic function of NK cells and cytolytic T lymphocytes in patients with FHLH. Through mechanisms that have not yet been well elucidated this impairment in cytotoxic function leads to an excessive expansion and activation of cytotoxic cells with hypersecretion of pro-inflammatory cytokines such as IFN-γ, TNF-α, IL-6, IL-10, and macrophage-colony-stimulating factor (M-CSF). These cytokines are produced by activated T cells and histiocytes that infiltrate all tissue and lead to tissue necrosis and organ failure.

In perforin deficient mice, the animal model of HLH, infection with certain microorganisms initiates a similar uncontrolled immune response characterized by fever, splenomegaly, hemophagocytosis, hypertrygliceridemia, and hypofibrinogenemia resulting in death (Jordan et al., 2004). Multiple cytokines, including IL-6, IL-18, IL-10, M-CSF, IFN-α, and IFN-γ, are elevated but only antibody to IFN-γ, and not to other cytokines, prolongs survival and prevents the development of histiocytic infiltrates and cytopenia. The elevated IFN-γ is thought to be secondary to the increased antigen stimulation of CD8+ cells; neutralizing antibodies against the infectious agent (LCMV) lowers IFN-γ levels and prolongs survival.

In support to these findings in animals, a recent study of hepatic biopsies in patients with various types of HLH including MAS has revealed extensive infiltration of the liver by IFN-γ-producing CD8+ T lymphocytes and hemophagocytic macrophages secreting TNF-α and IL-6 (Billiau et al., 2005). It has also been suggested recently that the hyperproduction of IL-18 (which strongly induces Th-1 responses and IFN-γ production and enhances NK-cells cytotoxicity) and an imbalance between levels of biologically active free IL-18 and those of its natural inhibitor (the IL-18 binding protein), may also play a role in secondary hemophagocytic syndromes, including MAS (Mazodier et al., 2005). Moreover, very high levels of IL-18 have been reported in two patients with S-JIA and MAS (Maeno et al., 2002) and in a study of autopsy specimens of a child with S-JIA-associated MAS, the bone marrow was identified as the origin of increased serum IL-18 (Maeno et al., 2004).

The mechanisms leading to cytolytic defects in immune competent patients with acquired HLH are less clear. Patients with virus-associated HLH also have very low or absent cytolytic NK cell activity. However, in contrast to FHLH, this phenomenon appears to be related to profoundly decreased number of NK cells rather than to impaired perforin expression. Notably, NK function has been found to recover completely in some patients after the resolution of the acute phase (Grom, 2004).

There is evidence to suggest that depressed NK activity, with or without abnormal perforin expression, may be involved in the pathogenesis of S-JIA-associated MAS as well. Patients with active S-JIA were found to have reduced perforin expression in NK cells and in cytotoxic CD8+ T lymphocytes compared with other subtypes of JIA and healthy controls. In four patients, perforin expression returned to normal levels after autologous bone hematopoietic stem cell transplantation (Wulffraat et al., 2003). In another study, NK activity was found to be profoundly depressed in all patients with MAS during the acute stage or after resolution. In some patients, decreased NK activity was associated with very low number of NK cells but mildly increased levels of perforin expression in NK cells and cytotoxic CD8+ T lymphocytes, a pattern somewhat similar to that seen in virus-associated HLH. In other patients, very low NK activity was associated with only mildly decreased numbers of NK cells but very low levels of perforin expression in all cytotoxic cell types, a pattern indistinguishable from that seen in primary HLH. Remarkably, most of the patients with low perforin expression had a history of multiple episodes of MAS (Grom et al., 2003). It has also been suggested that decreased absolute numbers of NK cells and/or depressed NK cell cytolytic activity might be a feature that distinguishes patients with S-JIA from those with other forms of JIA (Villanueva et al., 2005; Wouters et al., 2002). It remains to be established whether these abnormalities may help to identify early in the disease course the patients who are more prone to the occurrence of this dreadful complication.

6. Diagnostic guidelines

Because MAS is a serious condition that can follow a rapidly fatal course, prompt recognition of its clinical and laboratory features and immediate therapeutic intervention are critical. However, because it lacks a single distinguishing manifestation and since it is clinically heterogeneous, early diagnosis can be difficult. The diagnostic challenges posed by MAS in S-JIA are compounded by the fact that it may mimic a flare of the underlying disease. Other important differential diagnoses would include intercurrent infections and side effects of medications. The recognition of MAS can be difficult also in patients with SLE because it may mimic the clinical features of the underlying disease. In a young patient reported recently, this complication presented as unexplained fever and cytopenia, thus suggesting a lupus flare. The diagnosis was facilitated by the absence of other clinical or serologic indicators of lupus exacerbation or signs of infection (Ravelli et al., 2000). The difficulties in making the diagnosis and the recent therapeutic advances (see below) emphasize the need of diagnostic tools and well-established diagnostic guidelines. Diagnostic criteria would be also important for research purposes and use in literature reports.

The recognition that MAS is clinically similar to HLH has led many clinicians to use the diagnostic guidelines for this disease (Henter et al., 1991). There are, however, several problems with the use of HLH criteria in patients with MAS, the main one being the requirement of tissue confirmation. It is well known that in patients with HLH (Janka, 1983) and MAS, bone marrow aspirate does not always show hemophagocytosis: furthermore, hemophagocytosis is not always demonstrable at onset. Although in HLH hemophagocytosis may be detected more frequently in liver, lymph node, or splenic biopsies than in the bone marrow, biopsies of these organs are contraindicated in children with MAS in the presence of intravascular coagulopathy. Of note, the failure to document hemophagocytosis does not exclude the diagnosis of HLH. These problems emphasize the need to identify criteria to try to obviate the need for tissue diagnosis. Another important limitation of HLH

Table 3
Preliminary diagnostic guidelines for MAS complicating S-JIA

Laboratory criteria
1. Decreased platelet count ($\leq 262 \times 10^9$/L)
2. Elevated levels of aspartate aminotransferase (>59 U/L)
3. Decreased white blood cell count ($\leq 4.0 \times 10^9$/L)
4. Hypofibrinogenemia (≤ 2.5 g/L)

Clinical criteria
1. Central nervous system dysfunction (irritability, disorientation, lethargy, headache, seizures, coma)
2. Hemorrhages (purpura, easy bruising, mucosal bleeding)
3. Hepatomegaly (≥ 3 cm below the costal arch)

Histopathologic criterion
Evidence of macrophage hemophagocytosis in the bone marrow aspirate

Diagnostic rule
The diagnosis of MAS requires the presence of any two or more laboratory criteria or of any two or three or more clinical and/or laboratory criteria; a bone marrow aspirate for the demonstration of hemophagocytosis may be required only in doubtful cases

Recommendations
The above criteria are of value only in patients with active S-JIA; the thresholds of laboratory criteria are provided by way of example only

criteria in MAS is the lack of applicability of certain criteria to patients with S-JIA. Due to the prominent inflammatory nature of the latter disease, the relative decrease in white blood cell count, platelets, or fibrinogen rather than the absolute decrease required by HLH criteria may be more appropriate to make an early diagnosis.

To identify criteria for MAS complicating systemic JIA, the diagnostic sensitivity and specificity of the clinical and laboratory features of the syndrome were recently scrutinized (Ravelli et al., 2005). The features of 74 patients with S-JIA-associated MAS reported in the literature or seen by the authors were compared with those of a control group of patients with a confusable condition, constituted by 37 S-JIA patients with 51 instances of ''high disease activity''. The relative power of clinical, laboratory, and histopathologic variables in discriminating patients with MAS from those with high disease activity was evaluated by calculating sensitivity, specificity, area under the receiver operating characteristic curve, and diagnostic odds ratio (DOR). The combinations of variables that led to best separation between patients and controls were identified through ''the number of criteria present'' approach. The strongest clinical discriminators were hemorrhages (DOR = 67) and central nervous system dysfunction (DOR = 63); the strongest laboratory discriminators were decreased platelet count (DOR = 1092), increased aspartate aminotransferase (DOR = 247), leukopenia (DOR = 70), and hypofibrinogenemia (DOR = 165). Best separation between patients and controls occurred when any two or more laboratory criteria (DOR = 1309) were simultaneously present. Based on these results, preliminary diagnostic guidelines for MAS complicating S-JIA were set up (Table 3). Before these guidelines gain widespread acceptation, prospective validation is needed. In particular, it would be important to further explore the diagnostic role of some important indicators of MAS, such as ferritin, which could be tested in only a small number of the study patients.

7. Management

The treatment of MAS is traditionally based on the parenteral administration of high doses of corticosteroids. However, there have been some fatalities in reported series, even among patients treated with massive doses of corticosteroids

(Prieur and Stéphan, 1994; Sawhney et al., 2001; Stéphan et al., 2001). The administration of high-dose intravenous immunoglobulins, cyclophosphamide, plasma-exchange, and etoposide has provided conflicting results. The use of cyclosporine A (CyA) was considered, based on its proven benefit in the management of FHLH (Stéphan et al., 1993). CyA was found to be effective in severe or corticosteroid-resistant MAS (Mouy et al., 1996; Ravelli et al., 1996, 2000, 2001). In some patients, this drug exerted a "switch-off" effect on the disease process, leading to quick disappearance of fever and improvement of laboratory abnormalities within 12–24 h (Ravelli et al., 2000). The demonstration of the distinctive efficacy of CyA has led some authors to propose using this drug as first line treatment in MAS occurring in childhood systemic inflammatory disorders (Ravelli et al., 2000; Mouy et al., 1996).

The demonstration of increased production of TNF in the acute phase of MAS (Stéphan et al., 1993) has provided the rationale for proposing inhibitors of TNF-α as potential therapeutic agents. However, although Prahalad et al. (2001) reported the efficacy of etanercept in a boy who developed a MAS other investigators (Grom et al., 2003; Ramanan and Schneider, 2003) have observed the onset of MAS in patients with S-JIA who were being treated with etanercept. Similarly, Lurati et al. (2005) reported the onset of MAS in a patient with S-JIA during treatment with the recombinant interleukin-1 receptor antagonist anakinra. The onset of MAS has also been reported in a patient with adult-onset Still disease who was receiving anakinra (Fitzgerald et al., 2005). Although the association between the development of MAS and the treatment with etanercept or anakinra may well be coincidental and not causal, the above-mentioned observations show that inhibition of TNF or IL-1 is not able to prevent the onset of MAS. In this respect it should be reminded that in perforin deficient mice, the animal model of HLH, while MAS-like symptoms are almost completely prevented by elimination of CD8+ T cells or by neutralization of INF-γ, inhibition of IL-1 or TNF provides only mild alleviation of the symptoms.

Key points

- Macrophage activation syndrome (MAS) is a life-threatening complication of systemic inflammatory disorders, which is seen most commonly in systemic juvenile idiopathic arthritis and is though to be caused by the activation and uncontrolled proliferation of T lymphocytes and macrophages, leading to widespread hemophagocytosis and cytokine overproduction.
- Recent findings in hemophagocytic lymphohistiocytosis, a disease that is clinically very similar to MAS, highlight the possible pathogenetic role of a defective function of cytotoxic lymphocytes.
- Prompt diagnosis is important and, recently, preliminary diagnostic guidelines for the syndrome have been proposed.
- The recognition that MAS belongs to the secondary or reactive hemophagocytic syndromes has led to propose to rename it according to the contemporary classification of histiocytic disorders.
- Cyclosporine A has been found to be effective in patients with corticosteroid resistant MAS. It is still unclear whether biologic agents have a role in the treatment of MAS.

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Handbook of Systemic Autoimmune Diseases, Volume 6
Pediatrics in Systemic Autoimmune Diseases
Rolando Cimaz and Thomas Lehman, editors

CHAPTER 5

Systemic Lupus Erythematosus: Etiology, Pathogenesis, Clinical Manifestations, and Management

Alexa Adams, Emma J. Macdermott, Thomas J.A. Lehman*
Division of Pediatric Rheumatology, Cornell University Hospital for Special Surgery, New York, NY, USA

1. Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by widespread inflammation and resultant end-organ damage. Flares of SLE are often episodic and characterized by variability in their severity and clinical manifestations. Because of the potentially varied clinical manifestations, children with SLE are likely to present to primary care physicians with non-specific symptoms resulting in delayed diagnosis. Childhood onset occurs in approximately 15% of cases (Harvey et al., 1954; Cassidy and Petty, 2005). Although SLE is typically considered a disease of young adult women, children with SLE may be of any age and either sex (Lehman et al., 1989a).

The etiology of SLE remains unknown. Although great strides are being made toward clarifying the immune dysregulation seen in SLE, clinical disease expression is undoubtedly the end result of varied environmental and immunologic stimuli acting on a genetically predisposed individual. Abnormalities of T cells, B cells, dendritic cells, Fcγ receptors, pro-inflammatory cytokines, the complement pathway, and apoptosis have all been found to play a role in the pathogenesis of SLE.

1.1. Clinical manifestations

Renal involvement is common and is a major cause of morbidity and mortality (Cameron, 1994). However, recent advances in the treatment of lupus nephritis (LN) are such that neuropsychiatric (NP) lupus, musculoskeletal, cardiopulmonary, hematologic, and dermatologic manifestations are becoming increasingly important factors in limiting quality of life. Additionally, children with long-standing SLE are at risk for premature arteriosclerosis, osteoporosis, and sequelae of hypertension. While no "cure" exists for SLE, the treatment options continue to broaden with improved disease control and survival. Corticosteroids remain the first line of treatment, but long-term reliance upon steroids, and steroid-related morbidity remain a major concern (Spahn and Kamada, 1995; Satel, 1990; Hyams and Carey, 1988; Loeb 1976; McCarthy et al., 1990). Fortunately, it appears that such treatment-related morbidity and mortality are on the decline with increased use of alternative immunosuppressive agents. The use of cyclophosphamide (CYC), mycophenolate mofetil (MMF), rituximab (RTX), and various combination therapies allows for a more rapid reduction in corticosteroid dosages and a decrease in the associated morbidities.

2. Definition/classification

The diagnosis of SLE is clinical. For the purposes of classifying a patient with definite SLE to allow

*Corresponding author.
Tel.: +1-212-6061151; Fax: +1-212-6061938
E-mail address: LehmanT@HSS.EDU (T.J.A. Lehman).

DOI: 10.1016/S1571-5078(07)06009-6

for entry into research studies, he or she must meet 4 of the 11 criteria as determined by the American College of Rheumatology in 1982, and revised in 1997 (Tan et al., 1982; Ferraz et al., 1994). However, 4 of the 11 criteria need not always be met to establish the clinical diagnosis. Over time, a patient may evolve to meet fewer or greater than 4 criteria. Each patient's clinical picture must be considered on an individual basis, and alternate causes of disease excluded before treatment for SLE is undertaken. SLE is a multi-system, episodic disease characterized by clinical disease flares and remissions in the presence of antinuclear and other auto-antibodies. Widespread inflammation results from immune dysregulation and formation of auto-antibodies with tissue deposition of antigen–antibody complexes. While no single specific test exists at this time for the diagnosis of SLE, the constellation of clinical symptoms with supporting laboratory values often provide strong support for the diagnosis.

3. Epidemiology

While in adults the annual incidence of SLE is estimated at 2–7.6 cases/100,000/year, the annual incidence in children in the US is estimated at 0.53–0.60/100,000/year (Cassidy and Petty, 2005). One study of children suggested a prevalence of 4.4/100,000 in Caucasian females with much higher rates in Black, Hispanic, and Asian females. Males were affected at a much lower rate (1–1.6/100,000) with too few affected males to allow estimation of prevalence by race (Lehman et al., 1989a). The high incidence of female as compared to male and African–American as compared to white patients has also been seen in other studies (McCarty et al., 1995). The increased frequency of female patients with SLE even in the youngest age groups suggests that sex hormones are not the single factor responsible for the difference (Cassidy and Petty, 2005). A retrospective review of 135 pediatric SLE patients in Taiwan indicated no difference in age at diagnosis or mortality for affected Oriental children (Lo et al., 1999).

4. Genetics

SLE clusters with other autoimmune diseases in some families suggesting common genetic and/or environmental predisposition (Priori et al., 2003) A 1992 study of 107 twin pairs indicates a 24% concordance rate for monozygotic twins, though other studies have suggested the incidence to be higher (Deapen et al., 1992). The inheritance of a predisposition to SLE is most likely multifactorial. Various HLA haplotypes, Fcγ receptor polymorphisms, and deficiencies in early components of the complement pathway (C1q, C2, and C4) have been associated with the development of SLE in a variety of studies (Tsao, 2003; Wakeland, 2001; Kelly et al., 2002). The genetic factors predisposing children to SLE may differ with varied ethnicity. Caucasians with SLE appear to have a twofold increase in the expression of the DR-B1 alleles DR2 and DR3, but this association is not seen in non-Caucasians (Schur, 1995). Similarly, specific Fcγ receptor polymorphisms occur more often in African–American women with SLE and nephritis (Salmon et al., 1996).

5. Etiology/pathogenesis

The etiology of SLE remains unknown. Immune dysregulation with polyclonal B-cell activation appears to drive the production of self-reactive auto-antibodies. The production of auto-antibodies seems to be the sentinel event in the pathogenesis of SLE, the development of which may precede the clinical manifestations of SLE by years (Arbuckle et al., 2003). Immune complexes are then formed with subsequent tissue deposition and complement activation. Although the exact stimulus for B-cell activation and auto-antibody production is unknown, the role of interferon-α (IFN-α) is receiving increasing attention. IFN-α is known to be elevated in the serum of patients with SLE, and its therapeutic administration for the treatment of hepatitis has been linked to the development of auto-antibodies and lupus-like syndromes (Hooks et al., 1979; Crow, 2003). It is believed that IFN-α promotes B-cell responses and immunoglobulin class switching, which may in turn increase IgG and IgA antibody production (Crow, 2003). Recent

studies have implicated defective apoptosis in the pathogenesis of SLE. Failure of normal apoptosis, or programmed cell death, may result in increased availability of immunogenic self-antigens, another potential driving force behind the production of auto-antibodies. In addition to IFN-α, a number of other cytokines have been implicated in the pathogenesis of SLE. Interleukins (IL)-6, 10, 12, and 18 are all elevated in the serum of SLE patients, and may correlate with disease activity (Robak et al., 1997; Grondal et al., 2000; Lauwerys et al., 2002; Park et al., 1998). In addition to genetics and immune dysregulation, the role of environmental factors such as sunlight and viral infections has been investigated with no evidence for direct causality.

6. Clinical manifestations and treatment

As with any chronic medical condition, the treatment of SLE in children is a particular challenge. As children enter adolescence and early adulthood, the desire for a seemingly "normal" life with a sense of independence from parents and medical authority figures may dominate, and compliance may wane. This is particularly true for teenage patients for whom body image issues come to the forefront when faced with the effects of corticosteroid therapy. Multi-disciplinary care with the participation of social workers, psychologists, nutritionists, and physical and occupational therapists can be of tremendous benefit to these patients. Children should be educated as to the nature and severity of SLE as early as possible and should be encouraged to participate actively in their own medical care. They should be made aware of the potentially life-threatening consequences of treatment noncompliance or abrupt treatment withdrawal. Preventive measures such as the use of sunscreen, physical activity, maintenance of a healthy body mass index (BMI) through diet and exercise, infection avoidance, and compliance with medications and medical follow-up should be reinforced. In our experience, medical compliance is the single best predictor of disease outcome in children with SLE.

Treatment of SLE must be individually tailored to each patient's clinical manifestations. Corticosteroids remain the first line of treatment for SLE. However, depending upon the extent and severity of internal organ involvement, medication regimens can range from low-dose corticosteroids and anti-malarials to inpatient treatment with pulse methylprednisolone and cytotoxic medications such as CYC and RTX. Treatment of SLE nephritis, one of the most common and immediately life-threatening disease manifestations, has been well studied in children. At this time, however, there is no true consensus as to the management of other clinical manifestations.

6.1. Lupus nephritis

LN may be present at some time and to some extent in the majority of patients. Treating physicians should routinely screen for hematuria and proteinuria as well as for clinical and laboratory signs of evolving nephrotic syndrome and hypertension. A high index of suspicion should be maintained, and symptoms such as headache, vision changes, weight gain, and swelling of the extremities should raise a red flag for possible renal involvement. Typically, microscopic hematuria and proteinuria precede more overt clinical signs of nephritis. Extent of renal involvement can be determined only by biopsy. The WHO classification system uses histologic appearance (on light and electron microscopy as well as immunofluoresence) to determine the type of renal involvement, while chronicity and activity scores measure cumulative damage and continuing inflammation and disease activity, respectively.

The treatment of new or worsening LN invariably requires corticosteroid therapy. Corticosteroids are useful for their immunosuppressive and anti-inflammatory effects. These effects are rapid, nonspecific, and may provide immediate disease control. However, the immediately beneficial effects must be weighed against the well-known adverse effects of corticosteroid use (Spahn and Kamada, 1995; Satel, 1990; Hyams and Carey, 1988; Loeb, 1996; McCarthy et al., 1990). The use of corticosteroids for SLE, while immediately effective and even lifesaving, is associated with significant adverse long-term effects and continues to contribute to the morbidity and mortality of SLE in children. Corticosteroids may not only predispose patients to,

but may also mask early signs of infection. Treating physicians must, therefore, maintain a high index of suspicion for infection in any patient receiving corticosteroid therapy. High doses of corticosteroids may be required for remission induction. This, however, cannot be viewed as a long-term treatment option. It is crucial in severe or refractory disease that steroid-sparing agents and aggressive use of alternate immunosuppressive therapies be instituted early in the disease course. There is no clear consensus as to the optimal dose and route of corticosteroid therapy.

Mild, class II or III LN with low activity scores on renal biopsy, normal renal function, blood pressure, and proteinuria below the nephrotic range may respond to low-dose corticosteroids (up to 0.5 mg/kg/day) and anti-malarials (hydroxychloroquine 7 mg/kd/day up to 200 mg/day). The exact mechanism of anti-malarial drugs such as hydroxychloroquine in LN remains unknown, although withdrawal of these drugs has been associated with disease flares (The Canadian hydroxychloroquine study group, 1991). More severely affected patients with highly active WHO Class III or IV LN require higher steroid doses as well as the addition of a second line immunosuppressive or cytotoxic agent. Oral prednisone doses of 1–2 mg/kg/day are used. In patients with severe nephrotic syndrome, hypertension, or deteriorating renal function, we advocate the use of pulse methylprednisolone (in addition to daily oral prednisone therapy) in conjunction with cytotoxic medications such as CYC or RTX. ACE-inhibitors and angiotensin-II inhibitors are useful for decreasing renal protein excretion and controlling blood pressure. Albumin infusions and diuretics are often needed for severe nephrotic syndrome.

CYC is a cytotoxic agent that has been shown to improve the course of LN in children by cross-linking DNA strands thus interfering with cell-division (Lehman et al., 1989b; Lehman and Onel, 2000). CYC is considered the standard of care for treatment of Class IV LN, and has been well studied in children. A multi-center study conducted in 1989 examined the efficacy and safety of intravenous pulse CYC in 16 children with LN. Patients were treated monthly for 6 months, and spaced to quarterly dosing. At one year, significant improvements were seen in several laboratory parameters, including hemoglobin, C4, renal protein excretion, and creatinine clearance, and prednisone reduction was tolerated (Lehman et al., 1989b). A prospective study of a 36-month course of treatment was performed in 2000. Sixteen children were treated as above, for a total of 36 months, and renal biopsies repeated. Again, significant improvements were seen in several parameters. No progression of chronicity was seen, nor were any adverse events (Lehman and Onel, 2000). It is therefore possible that CYC may prevent the irreversible renal scarring seen with severe LN. In severely ill LN patients with declining renal function or nephrotic syndrome, it is our practice to treat with three daily methylprednisolone pulses (30 mg/kg/day to a maximum dose of 1 g/day) in conjunction with CYC and daily oral prednisone (which is weaned as tolerated). A randomized, controlled trial of combination therapy with intravenous CYC and methylprednisolone pulses for rapid control of DPGN versus either CYC or pulse methylprednisolone alone showed improved outcome for those treated with the combination therapy, with no increase in adverse events (Ilei et al., 2001). We begin CYC at a dose between 500 and 750 mg/m^2, and increase to a maximum of 1g/m^2 with subsequent infusions. Laboratory testing is performed 2 wk after each infusion, and the dose lowered for persistent leukopenia below 2500/mm^3.

The use of CYC is not without risks, although serious adverse events can generally be avoided by intravenous administration in a monitored, inpatient setting. Laboratory parameters, fluid status, and infections are screened for prior to and following the administration of CYC. CYC is withheld in any patient with a suspected infection, and appropriate anti-microbial treatment promptly initiated. Nausea, vomiting, alopecia, and leukopenia are frequently seen. Hemorrhagic cystitis is a known risk with the use of CYC; however, this has been more commonly seen with daily oral CYC. The use of pre and post-CYC intravenous hydration and close monitoring of fluid status decreases the risk of both hemorrhagic cystitis and the syndrome of inappropriate anti-diuretic hormone secretion (SIADH). Gonadal toxicity and premature ovarian failure remain a concern. In our

experience, those patients who have received a cumulative dose of greater than 17 g/m^2 are at the highest risk for infertility. Lupron is an option for females, and sperm banking for male patients concerned about future fertility. All post-pubertal females are screened for pregnancy prior to CYC administration to avoid potential teratogenic effects. While the use of CYC may decrease corticosteroid dependence, we look to the use of combination therapies to minimize the lifetime cumulative CYC dose.

For cases of refractory or relapsed LN, who have already received a full 3-year course of CYC therapy, there is no consensus for further treatment. Combination therapy with CYC and methotrexate (MTX) has been used for a small number of pediatric LN patients, all of whom experienced long-term improvement with respect to SLEDAI scores, creatinine, C3, albumin, and steroid dosages (Lehman et al., 2004). Only five patients were treated in this study, however, and such measures should be reserved only for the most severe, refractory cases. This approach is likely to be replaced by the use of combination therapy with CYC and RTX.

The use of RTX in addition to CYC for severe or relapsed LN is an aggressive alternative regimen, which may allow for a lower cumulative CYC dose. RTX is a chimeric mouse/human monoclonal antibody against the B-cell surface antigen CD-20. CD-20 is expressed on the surface of pre and mature B-cells, but not on the surface of plasma cells. RTX targets the CD-20 antigen, causing cell death. Initial studies of RTX for SLE report dosing of 375 mg/m^2 weekly for 4 wk, as used for the treatment of idiopathic thrombocytopenic purpura. Larger doses of up to 1 g/dose, similar to those used for lymphoma, have since been used, with clinical improvement persisting for up to one year (Looney et al., 2004). Interestingly, no consistent correlation between B-cell depletion and clinical response has been seen. This may be the result of persistent, immeasurable CD-20 + cells in the tissues (Sfikakis et al., 2005). Marks et al. (2005) in a small study of seven children with refractory SLE, showed clinical improvement in all patients treated with combination therapy. All had failed CYC prior to combination therapy (Marks et al., 2005). At this time, we advocate the use of RTX in conjunction with CYC for severe LN, although the dosing regimen, interval, and parameters for re-treatment remain to be determined. Based upon our own preliminary experience, RTX alone is less effective than combination CYC and RTX. Our current clinical practice for newly diagnosed, or severe or CYC-refractory LN consists of a similar dosing regimen of two doses, 2 wk apart, of RTX 600 mg/m^2 (up to a maximum dose of 1 g, using methylprednisolone 60 mg/m^2 and diphenhydramine 25–50 mg/dose as pre-medications) in combination with CYC 750 mg/m^2. For particularly severe cases, we combine this with 3 days of pulse methylprednisolone therapy for more rapid disease control. At this point, we re-treat with another two doses of CYC/RTX at 6 months, and two more at 12 months, but only longer-term follow-up will determine the need for repeat doses. It remains to be seen if the use of CYC/RTX early in the disease course may halt progression thus obviating the need for lifelong immunosuppressive therapy. At this time, larger, longer-term studies are needed for the use of RTX in children with LN, although it does appear to be a promising alternative.

Infusion reactions are the most commonly seen adverse event associated with the use of RTX in children. Mild pruritus, rash, and hypotension are not uncommon, however more severe reactions including serum sickness have been reported (Bennett et al., 2006). In our experience, infusion reactions resolve with slowing of the infusion rate, and are often avoided altogether with the use of pre-medications. We have seen no cases of serum sickness using either low- or high-dose regimen. Development of human anti-chimeric antibodies (HACAs) is a concern as this may place patients at risk for allergic reactions and loss of efficacy over time. It is possible that the co-administration of RTX with CYC may prevent the formation of HACAs, but this remains to be determined. With the use of combination immunosuppressive therapy, infection is again of particular concern.

Class V LN with heavy proteinuria often responds to high-dose oral corticosteroids, which should be tapered as quickly as possible. There does not appear to be a role for cytotoxic therapy in Class V LN patients at this time. Class V LN is one of the few instances in which azathioprine (AZA)

may be useful in the treatment of LN in children (Fu et al., 1998). MMF is a penicillium-derivative with known immunosuppressive and anti-inflammatory properties which has been used for the treatment of psoriasis and renal transplant rejection (Kimball et al., 1995; Raab et al., 2002; Lui et al., 2002; Shimizu et al., 2004). Adult SLE patients have shown good response to 3 g/day of MMF when compared with monthly pulse CYC therapy (Ginzler et al., 2003). In children, however, the experience with MMF is less encouraging. A 2001 study indicated better renal response to MMF in Class V LN children than in those with Class IV (Buratti et al., 2001). Poor responses may be related to the large doses of MMF needed to achieve therapeutic effect. Many children are intolerant of large doses of MMF due to gastrointestinal upset, diarrhea, and leukopenia. The result is often noncompliance, which may complicate interpretation of medication response. In our experience to date, no patient with active LN has sustained an MMF-induced renal remission, and no patient has maintained a CYC-induced remission with MMF.

Cyclosporine (CsA) and AZA are among the immunosuppressant, steroid-sparing agents used to treat LN. CsA bears a risk of renal toxicity and hypertension in patients already at risk for both. While in adults, there is evidence to suggest a role for CsA, it is not widely used in children with SLE. AZA is a purine analog, which interferes with DNA synthesis. No formal studies have been conducted comparing AZA with CYC in children with SLE, and a retrospective study observed a beneficial effect largely among Caucasian patients (Hagelberg et al., 2002). Thus, CsA and AZA are used infrequently for children with SLE, in favor of newer, more promising therapies with improved toxicity profiles.

6.2. Neuropsychiatric lupus

CNS involvement is another major cause of morbidity and mortality in SLE (Sargent et al., 1975; Yancey et al., 1981). While overt NP involvement may be seen in approximately one-third of patients, subtle manifestations with cumulative cognitive dysfunction may only be appreciated with specialized NP testing (Meslin AG, Rothfield N; King, 2002; Caeiro et al., 2006; Glidden et al., 1983). Migraine headaches are commonly seen in lupus patients; however, other causes must be excluded (Isenberg et al., 1982). Seizure, psychosis, hallucinations, and chorea can be seen early or late in the disease course (Steinlin et al., 1995). Additionally, stroke or hemorrhage with neurologic manifestations can be seen related to other underlying disease manifestations or as a result of therapy. In patients displaying symptoms of depression, poor concentration, school difficulty, or adjustment disorder, it is difficult to distinguish subtle NP manifestations from medication side effect or mood disorder related to coping with a chronic illness. Treating physicians must be attuned to these issues when caring for children and adolescents with lupus.

To date, few trials exist for the treatment of NP SLE in either adults or children, and current data exist largely in case report form. In children with SLE and new onset CNS symptoms, infectious etiologies (bacterial, fungal, and obscure opportunistic infections seen in immunocompromised patients) as well as vascular phenomena including thrombi or hemorrhage (secondary to anti-phospholipid syndrome) must always be excluded with CNS imaging, and where appropriate, cerebrospinal fluid analysis and culture. Only after this has been accomplished should corticosteroid therapy be instituted. In severe cases, pulse intravenous methylprednisolone is given for three consecutive days (dosing as above) followed by oral corticosteroids (1–2 mg/kg/day). Milder cases not requiring hospitalization deserve an initial trial of oral corticosteroids. Often, a rapid and significant improvement in mental status and neurologic symptoms is seen with the use of high-dose steroids alone. The successful use of CYC for severe cases has been described for adults and children with NP SLE (Neuwelt et al., 1995; Bacca et al., 1999). Additionally, plasmapheresis has been used in adults and children both independently of, and in addition to CYC (Neuwelt, 2003). A single case report from 2005 describes the successful use of MMF to maintain remission in one patient with NP SLE (Jose et al., 2005). The use of IVIG has also been reported (Milstone et al., 2005). In all cases, NP symptoms should be optimally treated with such agents as anti-convulsants and anti-psychotics. To date, there have been no studies of the use of RTX for NP SLE in children. While

there may be a role for RTX, we have no experience with its use in such cases.

6.3. Pulmonary manifestations

Pleuritis and pleural effusions are commonly seen in children with SLE (Caeiro et al., 2006; Glidden et al., 1983; Schaller, 1982). These typically respond to low-dose corticosteroids. In patients who fail to respond, the possibility of pneumonia must always be excluded and treated with appropriate imaging, cultures, and anti-microbial therapy. Occasionally, severe, treatment-refractory cases of pericardial effusion are seen which require pericardial window placement. SLE-related pulmonary hemorrhage, although rare in children, may be more common than in adults. This rare condition is acutely life threatening, and typically presents with acute respiratory failure and a falling hematocrit (Schwab et al., 1993). Such cases must be treated quickly and aggressively with the support of a pediatric critical care unit. At this time, we advocate for the immediate use of intravenous methylprednisolone pulses in addition to intravenous CYC. CYC is continued for the full 3-year course for adequate treatment of the underlying inflammatory component, the nature of that can be delineated only on lung biopsy. Once stabilized, patients are treated with oral corticosteroids at high doses, and weaned as tolerated. At this time, there is little evidence to suggest a role for alternate immunosuppressive agents.

6.4. Hematologic manifestations

The hematologic manifestations of SLE are varied, and each of the cell lines can be affected. Leukopenia, thrombocytopenia, and anemia are commonly seen in children with SLE. Leukopenia and anemia are particularly common in poorly controlled disease and may be a marker of disease activity. Anemia tends to be microcytic, as related to chronic disease. Thrombocytopenia may be the presenting symptom of SLE in children, and, in our experience, may pre-date the development of other signs and symptoms of SLE by many years. All children with suspected immune thrombocytopenia (ITP) should have periodic lupus serologies performed, as well as monitoring of renal function and urinary sediment. Symptoms of fatigue, infection related to leukopenia, petechiae, easy bruisability, pallor, or epistaxis should be worked up thoroughly in any lupus patient. Autoimmune hemolytic anemia is not uncommon and may be severe with profound hemolysis requiring transfusion. Coagulation abnormalities related to the lupus anti-coagulant may be seen as well, often presenting with menorrhagia in adolescent females. Anti-phospholipid antibody syndrome (APS) and the presence of anti-cardiolipin antibodies (ACLA) put patients at risk for thrombotic events. At this time, it is our practice to treat ACLA positive patients with a daily dose of baby aspirin (81 mg daily) as prophlyaxis for thrombosis.

Treatment of lupus-related cytopenias consists, initially, of the use of oral corticosteroids. Mild to moderate anemia, leukopenia, and thrombocyto penia may respond quickly to oral corticosteroid therapy. In more severe cases, pulse methylprednisolone may be used. Once treatment with CYC is initiated, typically for other accompanying disease manifestations, an improvement in hematologic manifestations is generally seen. Thrombocytopenia deserves particular mention. Recent reports of the use of RTX for severe ITP and autoimmune hemolytic anemia are promising (Wang et al., 2005; Quartier et al., 2001). These studies report regimens of four weekly doses of 375 mg/m^2. We advocate for the use of larger doses in combination with CYC as described for the treatment of LN. Our own recent experience in treating two cases of SLE-associated thrombocytopenia with the LN regimen described above has been very successful. In the setting of secondary APS, thrombosis must be treated aggressively. IVIG, plasmapheresis, and CYC have all been used for ongoing thrombus formation and hemorrhage. In general, chronic management of APS is much the same in children as in adults. Long-term anti-coagulation must be instituted with coumadin or low-dose molecular weight heparin, and should only be stopped in the face of active bleeding. The role of RTX is currently under investigation.

6.5. SLE-related musculoskeletal disease

Arthritis, myositis, and avascular necrosis are frequently seen in children with SLE. Arthritis tends to be non-deforming, involving the small joints of the hands and feet. Myositis can be seen, and

is difficult to distinguish from steroid or other drug-related myopathies. The presence of proximal muscle weakness with elevations of the muscle enzymes and acute phase reactants suggests myositis related to SLE activity. In cases of steroid myopathy, muscle enzymes tend to be normal with little laboratory evidence to suggest worsening disease activity. Avascular necrosis is a known complication of corticosteroid therapy, and is unpredictable in relation to dosing or duration of corticosteroid treatment.

Treatment of SLE-related arthritis, arthralgias, and tenosynovitis can be accomplished with low-dose corticosteroids. Physical and occupational therapy is very effective in maximizing function, particularly when small joints of the hands are affected. The judicious use of non-steroidal anti-inflammatory drugs can be undertaken; however, extreme care must be exercised with the use of these medications, as side effects including transaminitis and interstitial nephritis are difficult to differentiate from SLE-related organ involvement. Ibuprofen is generally avoided because of reports of ibuprofen-related aseptic meningitis in SLE patients (Samuelson and Williams, 1979). Myositis can be treated with the use of corticosteroids, antimalarials, and non-steroidal anti-inflammatories. Medication-related myopathies may be severe, and long-term intensive rehabilitation may be required in order to restore strength.

6.6. *Cutaneous involvement*

Rashes are very common in SLE, and can vary tremendously from patient to patient. The classically described malar, or "butterfly" rash, with sparing of the nasolabial folds is seen in approximately one-third of patients at the time of presentation (King, 2002). This rash is typically photosensitive but non-scarring. Vasculitic lesions of the palms, soles, and hard palate are common, as are urticarial rashes. Vasculitic lesions may evolve to gangrene in the case of superinfection or interrupted blood supply. Discoid lupus is a separate entity, which is described later in this chapter. In our experience, the cutaneous manifestations of SLE are more responsive to systemic than topical corticosteroids. For severe gangrenous vasculitis with a threatened digit or limb, antimicrobial coverage in conjunction with pulse solumedrol and consideration of CYC may be reasonable. For all SLE patients, and particularly those with cutaneous involvement and a history of photosensitivity, the use of sunscreen should be advised. The use of long sleeves, long pants, and sun hats should be encouraged, as should the avoidance of midday sun. This is particularly important for patients living in warm climates. Flares of disease activity can be seen in photosensitive SLE patients following sun exposure. Such flares may be severe and may involve any organ system.

7. General aspects of management

While early disease control is crucial for the treatment of children with SLE, a comprehensive approach to care may reduce long-term morbidity and mortality as well. In all patients, blood pressure should be as tightly controlled as possible with the use of anti-hypertensive agents. Good blood pressure control is essential for maximal long-term renal, cardiac, and cognitive outcome. Additionally, as lupus patients appear to have an increased risk of early atherosclerotic disease, cardiac risk factors should be minimized with diet, exercise, and maintenance of a healthy BMI. All patients should be counseled as to the dangers of tobacco, alcohol, and illicit drug use. The Lupus APPLE (Atherosclerosis Prevention in Pediatric Lupus Erythematosus) study is ongoing at this time to investigate the effects of statin use in these children. We await the results of this study, as there is evidence to suggest that these drugs may have an anti-inflammatory effect in addition to cholesterol-lowering properties. Osteopenia and osteoporosis are known complications of long-term corticosteroid use. Peak bone mass is achieved in childhood, and the effects of corticosteroids on bone health in children are a particular concern. We advocate the use of calcium and vitamin D supplementation where appropriate. At this time, the use of bisphosphonates in children remains controversial with inadequate data as to long-term safety and future teratogenicity.

8. Course and prognosis

SLE is a chronic condition, and is manifested by intermittent flares in disease activity. No cure currently exists for SLE, a concept that is difficult for many families to accept. The long-term prognosis for children with SLE continues to improve with advances in our understanding of the immune system, improved therapies, and improved pediatric intensive care. With early, aggressive treatment, it is our hope that the incidence of renal failure, perhaps the greatest cause of morbidity and mortality, may continue to decrease (Wang et al., 2003). Vigilant control of infection and health maintenance, as described above, will likely play an increasing role as SLE patients live longer into late adulthood. Patients of non-Caucasian and African–American descent with early disease onset appear to have the poorest long-term prognosis (Hagelberg et al., 2002; Tejani et al., 1983). It is our hope that the coming decades will see as many advances in the understanding and treatment of SLE as have the last two.

9. Alternate forms of lupus: neonatal, discoid, drug-induced

SLE is distinct from, and should not be confused with, other sub-types of "lupus": neonatal, discoid, and drug-induced. Neonatal lupus is seen predominantly in the infants of SSA/Ro and SSB/La positive mothers (who themselves may or may not fulfill criteria for the diagnosis of SLE, Sjogren's Syndrome, or other rheumatologic disorders). These babies are at risk for congenital heart block requiring pacing. Affected infants present in the first days of life with heart block, rash, transaminitis, and thrombocytopenia. All or one of these manifestations may be present. The exact etiology of this condition is unknown, but evidence suggests that apoptosis of fetal cardiocytes is followed by exposure of Ro and La antigens which are in turn bound by maternal auto-antibodies with ensuant inflammation and fibrosis (Buyon et al., 2004). At this time, affected babies do not appear to have an increased risk of SLE later in life. Discoid lupus (DL) lesions are localized to the skin, and may cause significant pain and scarring. DL patients do not fulfill criteria for SLE, although they are at increased risk of developing systemic involvement, particularly in the face of early-onset disease (Moises-Alfarro et al., 2003). Drug-induced lupus (DIL) is diagnosed when clinical and serologic manifestations of SLE appear in patients taking certain medications. Anti-histone antibodies are seen more frequently than anti-dsDNA. In true DIL, all clinical and serologic manifestations disappear when the offending drug is removed. Drugs implicated in DIL include anti-epileptics, tetracyclines, and most recently, anti-TNFα drugs.

Key points

- The etiology of SLE remains unknown. Although great strides are being made toward clarifying the immune dysregulation seen in SLE, clinical disease expression is undoubtedly the end-result of varied environmental and immunologic stimuli acting on a genetically predisposed individual. Abnormalities of T cells, B cells, dendritic cells, Fcγ receptors, pro-inflammatory cytokines, the complement pathway, and apoptosis have all been found to play a role in the pathogenesis of SLE.
- As with any chronic medical condition, the treatment of SLE in children is a particular challenge. As children enter adolescence and early adulthood, the desire for a seemingly "normal" life with a sense of independence from parents and medical authority figures may dominate, and compliance may wane. This is particularly true for teenage patients for whom body image issues come to the forefront when faced with the effects of corticosteroid therapy.
- Treatment of SLE must be individually tailored to each patient's clinical manifestations. Corticosteroids remain the first line of treatment for SLE. However, depending upon the extent and severity of internal organ involvement, medication regimens can range from low-dose corticosteroids and anti-malarials to inpatient treatment with pulse methylprednisolone and cytotoxic medications such as cyclophosphamide and rituximab.

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Handbook of Systemic Autoimmune Diseases, Volume 6
Pediatrics in Systemic Autoimmune Diseases
Rolando Cimaz and Thomas Lehman, editors

CHAPTER 6

Neonatal Lupus Syndromes

Rolando Cimaz[a], Antonio Brucato[b,*]

[a]*Department of Pediatrics, Hopital Edouard Herriot, Lyon, France*
[b]*Department of Internal Medicine, Ospedali Riuniti, Bergamo, Italia*

1. Introduction

Neonatal lupus is an in vivo model of acquired autoimmune disease in which autoantibodies are transmitted through the placental barrier from a mother to her fetus (Watson et al., 1984; Buyon and Winchester, 1990; Silverman, 1993; McCauliffe, 1995; Chung and Buyon, 1997; Buyon et al., 2004; Buyon and Clancy, 2005a, b). There is substantial evidence that autoantibodies directed against the extractable nuclear antigens SSA/Ro and SSB/La are pathogenetically linked to the clinical manifestations of the so-called Neonatal Lupus Syndromes. The term neonatal lupus is in fact misleading, in that most of the mothers are not affected by systemic lupus erythematosus (SLE), but by other autoimmune disorders such as Sjogren's syndrome (SS) and undifferentiated connective tissue disorders (UCTD), and a significant proportion are completely healthy.

The most important clinical feature of neonatal lupus is congenital heart block (CHB), which is usually complete (i.e., third degree). Additional abnormalities affecting the skin, liver, and blood elements have been reported. We have reported other transient electrocardiographic abnormalities such as unexplained bradycardia (Cimaz et al., 1997; Brucato et al., 2000) and QT interval prolongation (Cimaz et al., 2000), but these findings have not been confirmed by other authors.

*Corresponding author.
Tel.: + 39 0264442211; Fax: + 39 0264442615
E-mail address: albrucato@ospedaliriuniti.bergamo.it
(A. Brucato).

DOI: 10.1016/S1571-5078(07)06010-2

2. Clinical features

2.1. Cardiac manifestations

Complete CHB (CCHB) is the most severe manifestation of neonatal lupus, since it is irreversible and carries a high morbidity and mortality rate. The presence of signs or symptoms is mainly related to the ventricular rate, which usually ranges between 30 and 80 beats/min; the lower the rate, the higher the possibility of fetal hydrops and neonatal cardiac failure (Vignati et al., 1999).

CCHB is most frequently detected in utero by prenatal ultrasound, between 18 and 24 wk of gestational age. This "window" is related to the timing of transplacental passage of autoantibodies (that does not start before the third month of gestation) and of the ontogenic development of the cardiac conduction system that is not fully developed until ~22 wk. In the majority of cases CCHB requires a pace-maker implantation, frequently but not necessarily in the neonatal period. In utero death is usually related to intractable heart failure.

Other cardiological manifestations have been reported, such as incomplete atrioventricular (AV) blocks, and sinus bradycardia (Cimaz et al., 1997; Brucato et al., 2000). This last finding is of importance, since it suggests that not only the AV node but also the sinus node can be affected. Our group has shown QT prolongation in infants from mothers with anti-SSA/Ro antibodies (Cimaz et al., 2000). Since a prolonged corrected QT is associated with increased risk of sudden death in

the first year of life, some of these infants were subsequently treated with a beta-blocker in order to prevent arrhythmia. Interestingly, such an electrocardiographic abnormality disappears as soon as the maternal autoantibodies are cleared from the baby's blood (Cimaz et al., 2003a, b). A French group has not confirmed this finding in a large controlled study of 152 consecutive pregnancies in 96 anti-SSA positive women (Costedoat-Chalumeau et al., 2004). On the other hand a QT interval prolongation has been reported also in adults positive for anti-SSA/Ro antibodies (Lazzerini et al., 2004; Gordon et al., 2001); therefore this topic and its clinical relevance are still a matter of debate.

A subset of patients with CCHB may develop dilated cardiomyopathy, even if the risk seems low (Eronen et al., 2000; Moak et al., 2001; Udink ten Cate et al., 2001). Myocardial biopsy revealed hypertrophy, interstitial fibrosis in most patients, and myocyte degeneration in few. The majority of affected children die from congestive heart failure or require cardiac transplantation, while a recovery was reported in few cases (Moak et al., 2001).

2.2. Skin rash

A skin rash can be present in the neonatal period, but more frequently it appears between the second and third month of life (Lee and Weston, 1997; Neiman et al., 2000). Unlike CCHB, it is transient since it disappears with the clearance of maternal autoantibodies from the baby's circulation, usually without any residua. The rash is erythematous and scaly, similar to subacute cutaneous lupus erythematosus (SCLE). It is frequently annular in shape, and mostly located in sun-exposed area with a characteristic predilection for the periorbital area. Ultraviolet exposure may be an initiating factor and can exacerbate an existing rash. Histologically the lesions are similar to subacute cutaneous lupus, with hyperkeratosis, epidermal atrophy, basal degeneration, interstitial edema, and perivascular mononuclear infiltrate. Immunoglobulin and complement deposition have been demonstrated by direct immunofluorescence at the dermo–epidermal junction. Since these lesions are self-limiting, usually no treatment is required.

2.3. Laboratory abnormalities

Hematologic abnormalities have been described, usually consisting in anemia, thrombocytopenia (Watson et al., 1988), and neutropenia (Kanagasegar et al., 2002). Hepatic involvement has also been described (Laxer et al., 1990; Lee et al., 1993): it can vary from asymptomatic increase in serum transaminases to severe cholestasis. This has been noted to be present at birth in some cases but has not been clinically evident until several weeks in others. We observed hematologic abnormalities in 27% of the babies from anti-SSA/Ro positive mothers and elevation of liver enzymes in 26% (Cimaz et al., 2003). As for skin rash and unlike CCHB, these manifestations are transient and usually do not need medical treatment.

3. Epidemiology

Neonatal lupus is a rare disease, which affects equally males and females. According to Michaelsson and Engle (1972), CCHB has an incidence of 1:20,000 live births; however these numbers include also CCHB associated with congenital anatomical malformations, and exclude in utero deaths. Exact figures are very difficult to obtain because of the rarity of the disease and because of the lack of national epidemiological registries. Confusion exists regarding congenital versus acquired AV block; for these reasons we propose a new definition of congenital complete AV block which might be acceptable to cardiologists, rheumatologists, pediatricians, and obstetricians: "an AV block is defined as congenital if it is diagnosed in utero, at birth or within the neonatal period (0–27 days after birth)" (Brucato et al., 2003).

3.1. Evaluation of the fine specificities of the maternal autoantibody profile

Anti-SSA/Ro and SSB/La are found in a high percentage of patients with SLE and SS. SSA/Ro is a complex antigen system, associated with RNA, the function of which is not completely known,

that comprises at least two polypeptides of molecular weight respectively of 52 and 60 kDa. There are some suggestions that anti-52-kDa Ro/SSA and anti-La/SSB antibodies are more strongly associated with CHB than anti-60-kDa Ro/SSA alone, at least when tested by immunoblot (Gordon et al., 2004).

A Swedish study has suggested that reactivity against a specific peptide of Ro 52 (p200) is associated with a higher risk of CHB (Salomonsson et al., 2002), but another group has not confirmed this finding, since they observed that reactivity to p200 is a dominant but not uniform anti-Ro 52 response in women whose children have CHB, and this antibody specificity was observed with a similar frequency in children with and without CHB born to mothers with anti-Ro 52 kDa antibodies (Clancy et al., 2005).

4. Pathogenesis

Current evidence suggests that the clinical manifestations of neonatal lupus are not only associated but causally related with the presence of autoantibodies, in particular those directed against the extractable nuclear antigens SSA/Ro and SSB/La (Horsfall et al., 1991; Lee et al., 1994; Silverman et al., 1995; Julkunen et al., 1998; Viana et al., 1998). These antibodies, in fact, cross the placenta beginning at approximately 16 wk of gestation and reach the fetal tissues (Reichlin et al., 1994; Tseng et al., 1996). Their pathogenicity is supported by the fact that, with the only exception of CCHB, clinical manifestations disappear in temporal relationship with clearance of antibodies from the baby's circulation.

The recovery from the manifestations is also the consequence of the replacement of damaged tissues by new cells, as in the case for the skin, hemopoietic and hepatic cell populations. The situation is different for the fetal cardiac tissues, where the antibodies may display at least three effects: (a) they may induce a *myocarditis*; (b) they might be *arrhythmogenic*; (c) and they can interfere with *apoptosis*. The immune-mediated damage of the cardiac conduction system ultimately ends with its substitution with fibrotic tissue.

4.1. Myocarditis

An inflammatory component in the development of CHB is supported by the mononuclear cell infiltration in the myocardial tissues as well as by the deposition of IgG, complement (including C1q, C4, C3d, C6, and C9), and fibrin (Herreman and Galezowski, 1985; Litsey et al., 1985; Lee et al., 1987). The first cardiac lesion may be a global pancarditis resulting in subsequent fibrosis of the conducting system. The immunohistological picture might vary from a clear inflammatory state to the presence of calcifications only, depending on the time when the pathological evaluation is performed. A generalized myocarditis/cardiomyopathy may rarely occur after birth. Serial echocardiographic evaluations have supported the hypothesis that a myocarditic process can be the initial event, as shown in a report case report from our group (Fesslova et al., 2003), but pathological or echocardiographic evidence of myocarditis remains extremely rare (Buyon and Clancy, 2005a).

4.2. Arrhythmogenesis and electrophysiological effects

Several publications have shown arrhythmogenic effects of anti-Ro/SSA antibodies in experimental models that used animal or human myocardial tissues (Alexander et al., 1992; Garcia et al., 1994; Boutjdir et al., 1997; Mazel et al., 1999). In particular, an interference of anti-Ro/SSA IgG with L-type calcium channel has been suggested by some experimental models (Boutjdir et al., 1998; Xiao et al., 2001).

Furthermore, animal models have shown that active immunization with the Ro antigen or passive infusion of anti-Ro/SSA IgG into pregnant animals generated varying degrees of AV conduction abnormalities, including complete AV block, in the pups (Boutjdir et al., 1998; Mazel et al., 1999). A recent study also showed that pups born to rats immunized with the p200 peptide developed AV block (Salomonsson et al., 2005). The same authors showed that anti-SSA/Ro antibodies disturb calcium homeostasis of cultured human fetal cardiocytes; in particular they observed that

p200-specific autoantibodies cloned from patients bound cultured cardiomyocytes and severely affected Ca^{2+} oscillations, leading to accumulating levels and overload of intracellular Ca^{2+} levels with subsequent loss of contractility and ultimately apoptosis; these findings suggest that passive transfer of maternal p200 autoantibodies causes CHB by dysregulating Ca^{2+} homeostasis and inducing death in affected cells. These important findings might be the link between reaction with calcium receptors, arrhythmogenesis, apoptosis, and fibrosis (Salomonsson et al., 2005).

Other intriguing interferences of anti-Ro/SSA antibodies have been demonstrated with different cell receptors: muscarinic receptors (Waterman et al., 2000) and serotoninergic receptors (Kamel et al., 2005). Furthermore, the observation that the QT interval may be prolonged in children from anti-Ro/SSA positive mothers (Cimaz et al., 2000) raises the possibility that other ionic channels might be affected as well.

4.3. Apoptosis: TGF-beta and the road to scar

Apoptosis is a selective process of physiological cell deletion in embryogenesis and normal tissue turnover. Ro and La antigen may be expressed on the surface blebs of apoptotic cells including human fetal myocytes and can be recognized by specific autoantibodies (Casciola-Rosen et al., 1994; Miranda et al., 1998). This observation supports the hypothesis that subcellular redistribution of La in the normally developing heart facilitates the binding of cognate maternal antibodies and subsequent tissue damage. Tran et al. (2002a, b) demonstrated in vivo the subcellular translocation of La autoantigen during apoptosis in the fetal heart and the conduction system under physiologic conditions in mice, and they also showed that transplacental anti-La autoantibodies bind specifically to apoptotic cells in selected fetal organs in mice.

Recently it has been demonstrated that anti-La antibodies bind to immunodominant epitopes of La within the NH(2)-terminus and the RNA recognition motif (RRM) region of apoptotic human cells, in both xenografts and fetal cardiocytes; in contrast, human antibodies affinity purified against the COOH-terminal La epitope did not bind apoptotic cells in either model. The potential importance of anti-La NH(2)-terminal and anti-La RRM specificity was confirmed by detection of these reactivities in mothers of children with CHB (Neufing et al., 2005).

Apoptotic cells per se do not evoke an inflammatory response; however, if sensitized by antibodies, they can be engulfed by professional phagocytes with the induction of inflammation. Accordingly, it has been reported that anti-SSA/Ro and anti-SSB/La autoantibodies, once bound to apoptotic fetal cardiocytes might promote phagocytosis by macrophages and the secretion of TNF-alpha and TGF-beta. TNF-alpha may induce an inflammatory process, but TGF-beta induces a pro-fibrotic activation of myofibroblast, leading to fibrosis of the conduction tissue. This might be one of the "fetal factors", since it has been demonstrated that CCHB babies carry a particular (pro-fibrotic) allele of the TGF gene more frequently than controls. Accordingly, babies displaying such pro-fibrotic phenotype should be more susceptible to a permanent damage at the level of the conduction tissue (Clancy et al., 2002). Accordingly, we have recently detected the pro-fibrotic TGF-beta genotype in a twin with CCHB but not in his healthy twin (Cimaz et al., 2006).

4.4. Other pathogenetic mechanisms

Several issues still have to be explained, such as why only a minority (1–2%) of mothers with anti-Ro and anti-La antibodies deliver an affected child, and why heart block affects almost always only the fetus and not the mother. Also, intriguing is the discordance of the disease in monozygotic twins (Watson et al., 1994; Cooley et al., 1997).

It has been suggested that anti-Ro/La antibodies do represent a condition necessary but not sufficient for the development of NLS. Additional maternal, fetal, and environmental factors have all been hypothesized.

Among the maternal factors, the persistent presence of maternal cells in the fetal heart (microchimerism) is an attractive hypothesis to explain

the occurrence of a local immune-mediated response of the maternal cells against the baby's tissues (graft versus host reaction) or alternatively of the baby's immune effector cells against the infiltrating maternal cells (allograft response) (Stevens et al., 2005).

5. Prognosis

5.1. Fetal

CCHB is a severe disease. Mortality, usually in utero or in the first 3 months of life, can reach 30% even after intensive and supportive care. Prophylactic pace-maker treatment might be considered even in asymptomatic patients because of high incidence of unpredictable Stokes-Adams attacks and significant morbidity and mortality.

After birth and pace-maker implantation, children can live an almost normal life. The possibility for these children to develop SLE or another connective tissue disease in later life seems to be extremely rare (Brucato et al., 1995a, b; Martin et al., 2002). The risk is apparently not higher than in asymptomatic children of mothers with autoimmune diseases (Cimaz, 2004; Martin et al., 2002).

5.2. Maternal

Long-term follow-up studies have shown that the long-term prognosis of mothers of babies with NLS is quite good, since only half of them eventually develop a connective tissue disease, mild, and non-life-threatening in most cases (Julkunen et al., 1993; Waltuck and Buyon, 1994; Brucato et al., 1995a; Press et al., 1996).

5.3. Risk of delivering a child with CCHB

Mothers known to have autoimmune disease are at risk of delivering an affected infant, and for preconceptional counseling it would be useful to have precise figures about the risk of delivering a child with CCHB. In a prospective study we found that the prevalence of CCHB in newborns of 100 women already known to be anti-Ro/SSA positive and with known connective tissue disease was 2% (95% confidence interval 0.2–7%) (Brucato et al., 2001). We only studied mothers who had been found to be anti-Ro/SSA positive by counter-immunoelectrophoresis (CIE), a method with high specificity and rather low sensitivity, to exclude women with low or dubious titers of anti-Ro/SSA. Our results therefore cannot be extrapolated for instance to those with a low-positive reaction for anti-Ro/SSA antibodies by ELISA, for which the risk, if any, should be even lower. This finding has been now confirmed by other groups: Gladman et al. (2002) reported no cases of CHB in 100 live births in 96 women with anti-SSA/Ro and/or anti-SSB/La antibodies and no history of a previous child with NLS; Cimaz et al. (2003) observed two cases of CCHB out of 128 infants (1.6%), and Costedoat-Chalumeau et al. (2004) one case out of 99 infants (1%). This risk might be further refined taking into account the presence or absence of anti-La antibodies: from a theoretical risk of 2%, the risk increases to 3.1% if the woman is also anti-La antibody-positive, and decreases to 0.9% if anti-La-negative (Gordon et al., 2004).

5.3.1. Risk of recurrence

The mothers have higher probabilities of delivering a second affected child. Few prospective studies exist on this issue, however the percentage value seems to be comprised between 15 and 20% (Buyon et al., 1998; Julkunen and Eronen, 2001; Buyon et al., 2004; Buyon and Clancy, 2005b).

5.4. Obstetric management of pregnancy at risk of developing CCHB

A woman is at risk of delivering a baby affected by CCHB if she is definitely anti-Ro/SSA positive. There are some suggestions that anti-52-kDa Ro/SSA and anti-La/SSB antibodies are more strongly associated with CHB than anti-60-kDa Ro/SSA alone (Julkunen et al., 1993; Buyon et al., 1993; Dorner et al., 1995; Colombo et al., 1999). If the positivity is uncertain or the titer is very low,

we advise to confirm the positivity with standard methods or in reference laboratories.

Serial echocardiograms and obstetric sonograms, performed at least every 2 wk starting from the 16 wk gestation are recommended in this setting. The goal is to detect early fetal abnormalities, that might precede complete AV block and that might be a target of preventive therapy (Rosenthal et al., 1998). Systematic prophylactic therapy with dexamethasone or betamethasone is not recommended, because of the low risk of CCHB and the potential side effects. Other steroids are not useful since they do not cross the placenta in active form.

6. Treatment

6.1. In utero therapy and the problem of neuropsychological development

There is no known effective therapy for CCHB. Prenatal interventions are substantially related to drug therapy to the mother, in order to diminish the autoimmune response and/or the cardiac inflammatory injury, and also in order to increase fetal heart rate.

Corticosteroids have been used, particularly dexamethasone and bethametasone, since they are not metabolized by the placenta and are available to the fetus in an active form. Steroid therapy has been reported as effective in the resolution of inflammatory signs (pleural effusions, ascites, and hydrops fetalis) in few case reports (Saleeb et al., 1999; Theander et al., 2001). However, it is still a matter of debate whether treatment is able to revert third degree heart block once established (presumably fibrosis of conducting system). Because of possible maternal side effects similar to any glucocorticoid therapy and specific fetal risks (oligohydramnios and adrenal suppression), fluorinated steroids should be promptly instituted only if the block is incomplete or of recent onset, or if a complete block is accompanied by signs of fetal distress such as hydrops, effusions, ascites, or heart failure. Corticosteroids should anyway be discontinued after several weeks if no benefit is obtained.

Evidence has accumulated on the potential harm of repeated course of steroids for the mother and the fetus. Animal models suggest that repeated antenatal steroid doses can interfere with the growth and development of the immature brain (Huang et al., 2000; Matthews, 2000; Jobe et al., 1998), and human observations suggest that antenatal and post-natal dexamethasone may negatively affect the child's neuropsychological development (French et al., 1999; Abbasi et al., 2000; Spinillo et al., 2004). The possible negative effects seem more linked to dexamethasone than betamethasone, and it has been suggested that betamethasone should be preferred when available (Jobe and Soll, 2004; Urban et al., 2005). Moreover, separate meta-analysis of the data in the Cochrane review show that only betamethasone and not dexamethasone significantly reduces neonatal mortality (Crowley, 1999). For these two reasons we are now moving to use bethametasone instead of dexamethasone in the context of CCHB, in agreement with the French group (Costedoat-Chalumeau et al., 2005, 2006).

The presence of maternal anti-Ro/SSA antibodies per se may be associated with learning disabilities in the offspring (Ross et al., 2003). In light of these findings CHB babies who are both treated in utero with high-dose dexamethasone and exposed to maternal anti-Ro/SSA antibodies could be at risk for neurodevelopmental defects. We have therefore formally tested our CCHB patients for neuropsychological development, IQ and learning disabilities: 16 children were enrolled in this study and all had normal IQ (Brucato et al., 2006). Although it is quite possible that repeated course of dexamethasone may be detrimental to the newborn's neurodevelopment, a child's final intellectual maturation remains an extremely complex process, involving the interplay of many biological, social, and cultural factors. We observed no negative effects on the neurodevelopment of our patients, many of them exposed to very high dosages of dexamethasone (much higher than those used to enhance fetal lung maturity) and to maternal anti-Ro/SSA antibodies. CHB is a rare

disease, but these reassuring findings might be clinically relevant also for the large number of newborns treated with repeated courses of antenatal fluorinated steroids to induce fetal lung maturity.

Therefore, possible beneficial effects need to be balanced against adverse effects, and only a randomized controlled trial will define the role of fluorinated steroids in the treatment of CCHB. We presently suggest the following schema. If the block is incomplete (e.g., 2nd degree), bethametasone 4 mg once or twice daily to the mother is started, with a note of caution: to differentiate incomplete from complete AV block may be difficult in utero, requiring a particular expertise. If the block is recent (the more common clinical situation) bethamethasone is recommended as well; the dose is tapered and betamethasone is discontinued if no change occurs after several weeks. If the block is associated with signs of myocarditis, heart failure, or hydropic changes, betamethasone is recommended. If the block is complete and present for more than 2–4 wk, with no effusions and no signs of hydrops, only serial echograms should be performed, with no therapy. We have recently treated with IVIG a mother whose fetus had CCHB and clear clinical and echocardiographic evidence of myocarditis: the myocarditis quickly resolved, but the complete AV block persisted. A possible therapeutic windows for IVIG in the early treatment of complete or incomplete AV block, or even in its prevention for high-risk cases, is under discussion (Kaaja et al., 1991; Kaaja and Julkunen, 2003; Tran et al., 2004).

On the cardiological side, salbutamol, a selective beta-2 adrenergic agonist, may be useful to increase the fetal heart rate, to improve ventricular function and fetal hydrops. This may be useful particularly as a bridge to reach a more advanced gestational age (Groves et al., 1995). It can be given orally to the mother, at a dosage of 2 mg 6–10 times daily, according to maternal compliance.

6.2. Post-natal treatment

Post-natal treatment of CCHB is based on pace-maker implantation. Frequently a pace-maker is implanted in the neonatal period; due to the very low weight of these subjects (often <2.5 kg) the pace-maker is implanted by thoracotomic or sternotomic route, with an electrode on the epicardial surface which is connected to an impulse generator placed in an abdominal subfascial pouch. In the presence of extreme bradycardia isoproterenol (0.1–0.3 mcg/kg/min) needs to be administered as well.

Non-cardiac manifestations such as skin rash or hematology abnormalities do not require any treatment, since they are reversible and spontaneously disappear, usually during the second semester of life.

Key points:

- Congenital heart block is a rare disorder closely linked to transplacental transport of maternal antibodies anti-Ro/SSA and anti-La/SSB. The prevalence of complete CHB in newborns of prospectively followed women already known to be anti-Ro/SSA positive and with known connective tissue disease is ~2%.
- Depending on the severity of the process the fetus may die in utero or a few days after birth or survive to the perinatal period and have a near normal life; in most survivors a pace-maker must be implanted. Skin lesions, hematological disorders, and hepatic cholestasis are other transient clinical features of the syndrome.
- Sinus bradycardia and QT interval prolongation may be observed as well in babies born from anti-Ro/SSA positive mothers. The risk of recurrence of complete block (CHB) ranges from 10 to 17%.
- Most of the mothers are asymptomatic at delivery and are identified only by the birth of an affected child. Their long-term outcome is generally more reassuring than previously assumed and arthralgias and dry eyes are the commonest symptoms.

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Handbook of Systemic Autoimmune Diseases, Volume 6
Pediatrics in Systemic Autoimmune Diseases
Rolando Cimaz and Thomas Lehman, editors

CHAPTER 7

Juvenile Dermatomyositis

Clarissa Pilkington*

Great Ormond Street and University College Hospitals and Juvenile Dermatomyositis Research Centre, Institute of Child Health, UCL, London, UK

1. Introduction

Dermatomyositis (DM) in children is a rare inflammatory disease that predominantly affects muscles and skin, but it can also be a multi-organ systemic disease. It has a variable disease course with a spectrum of severity. The disease needs to be diagnosed early and treated aggressively to improve outcome, especially if there are features present that are associated with a poor prognosis. Adequate disease control is dependant on careful monitoring to prevent long-term morbidity. Over the last few years, international collaborations have fostered research and improved knowledge about the disease, as well as developing tools for disease assessment.

2. Incidence of JDM

There are between two and five cases of juvenile dermatomyositis (JDM) per million children per year: this is a rare disease. The incidence of JDM is based on publications from different groups worldwide: these give different incidence rates for different age groups and have a variable sex ratio. A paper from the USA reported an incidence of 3.7 cases/million/year in 5–9 years old, and an incidence of 4.3 cases/million/year in 10–14 year olds (Medsger et al., 1970). The sex ratio was 1 girl:1.3 boys in 5–9 years old, and 4.7 girls:1 boy in 10–14 years olds.

In 1992, the UK British Paediatric Surveillance Unit undertook a prospective survey of all new cases of JDM seen by paediatricians (rheumatologists, neurologists and dermatologists) in the UK for a year. They found 1.9 new cases/million children in 1992–1993 with a sex ratio of 5 girls:1 boy (Symmons et al., 1995).

The low incidence of JDM has prompted various groups to collect data from several centres to be able to study larger cohorts of patients, and allow physicians to build up expertise in this area. One such centre is in the UK, which has set up a JDM registry for the UK and Ireland, allowing data from 10 centres within the UK to be collated centrally. So far, over 200 patients have been recruited: it is the largest European cohort to date. The data from 151 of these patients has been analysed and published (McCann et al., 2006). In this series the sex ratio of female:male was 2.2:1, with the ethnicity of the patients reflecting the UK population groups: the majority of the patients were Caucasian (90%), with possibly a higher incidence than might be expected of 2.4% in the Black ethnic group.

3. JDM epidemiology

Unlike adult DM, paediatric cases of DM are not associated with malignancy. However, many

*Corresponding author.
Tel.: +44 (0) 20 7905 2667; Fax +44 (0) 20 7905 2672
E-mail address: c.pilkington@ich.ucl.ac.uk (C. Pilkington).

DOI: 10.1016/S1571-5078(07)06011-4

physicians will screen older teenagers for malignancies such as lymphoma. There has been speculation that JDM has a seasonal variation, perhaps reflecting viral triggers, but this is not borne out by the literature. The series from the USA found that 55% of their cases had an onset between February and April (Medsger et al., 1970). The UK survey found several clusters, which varied with the year. The largest cluster was seen in April–May 1992 (Symmons et al., 1995).

4. Pathogenesis

The cause of JDM is unknown and its pathogenesis is poorly understood. It is an inflammatory condition that responds to immunosuppressive treatment and is felt to be an autoimmune disease. The underlying pathology appears to be vasculopathic rather than a true vasculitis: inflammatory cells are rarely found within the vessel wall, though some researchers believe that the endothelium may be the primary target. In children, more than in adults, there are cases that are clinically termed 'vasculitic', where there appears to be more widespread inflammation affecting blood vessels throughout the skin, muscles and other organs.

Early in the disease, the muscle biopsy can have normal histopathology, with only up-regulation of MHC class I molecules on immunological staining. Later on, the typical muscle biopsy findings will show variation in muscle fibre size with perifascicular atrophy and a perivascular inflammatory cell infiltrate. There may be increased fibrotic connective tissue between muscle bundles.

5. Clinical manifestations

5.1. Symptoms at diagnosis

There are now several studies of JDM that have been published from centres caring for large numbers of these patients: Chicago in the USA (Pachman, 1998), Toronto in Canada (Ramanan and Feldman, 2002) and London in the UK (McCann et al., 2006). Most patients have a characteristic skin rash at presentation, though it can be mild and short-lived, or can occur later in the disease course. The earlier series from Chicago reported all the patients presenting with a skin rash and muscle weakness, whereas 84% of the patients in the series from Toronto and 88% from the UK series had a skin rash.

The muscle weakness is proximal and symmetrical (100% in USA, 82% in UK). The proximal muscle weakness may present as tiredness initially with younger patients asking to be carried by their parents rather than walking, especially as they may have difficulty walking up and down the stairs. Not many parents notice that the children have weakness of the neck flexors, though it is usually present early on, until the children have difficulty lifting their heads off the pillow. In school-age children, they may start to complain that they cannot get up from the floor after sitting cross-legged on the floor, or are having difficulties in their sporting activities. In severe cases, the muscle weakness progresses to involve the distal muscles too, though children may still be able to move their fingers and toes even when they are unable to move the rest of the body spontaneously.

Proximal muscles include the muscles of the larynx and pharynx, resulting in a nasal voice (17%) and swallowing difficulties (29%). This has to be carefully checked for, as many parents do not notice these symptoms until after repeated questioning. The dysphagia is associated with a significant risk of aspiration, and patients may need to have naso-gastric tube feeding until the dysphagia has recovered.

Pain is a common symptom: often it is myalgia (68% in UK series), or arthralgia (66%) and a third of the cases have arthritis (36%). Children with JDM are irritable (51% in UK series) and this is more pronounced than in many other inflammatory conditions, especially in the younger children. It is a useful symptom to document as it may precede a flare in disease. Other symptoms include more generalised problems such as fatigue (78%), weight loss (43%), fevers (30%), headaches (18%), and abdominal pain (18%).

5.2. Clinical signs: rash

A careful assessment of the skin needs to be made. The rash can be the classical heliotrope (purple–pink in colour) rash over the eyelids, with or without peri-orbital edema. Common are Gottron's papules over the extensor surfaces (any of the small joints of the hands, as well as the elbows and the knees) or periungual erythema. The periungual erythema may be accompanied by periungual swelling, and capillary loop dilation in the nailbeds. There can also be dilation of the vessels in the eyelids, often along the margins of the eyelids. Less commonly there can be a facial rash that is around the eyes and nose, which classically does not spare the naso-labial folds (as opposed to SLE), and often affects the ears. A less common rash is found over the shoulders and chest (Shawl sign), or on the trunk. A poor prognostic sign is the development of skin ulcers, and these were present at diagnosis in 23% of the UK series. The ulcers can start off as small areas on the sides of the chest walls under the arms, and may be easily missed. Patients may have small ulcers near the inner canthus of the eye, which often heal leaving a small-pitted scar.

Periorbital edema can be slight swelling of the upper eyelid, or more extensive edema around the eyes. More generalised edema is associated with severe disease and was present in 32% of the UK series. The edema may be secondary to leaky blood vessels as the serum albumin is often normal. There may be livido reticularis or a widespread vasculitic rash.

5.3. Clinical signs: calcinosis

Calcinosis is due to the deposition of calcium as subcutaneous plaques or nodules, deeper flecks that can become plaques within the muscles (see Fig. 1), or sheets within the fascia around the muscles. It can be present at diagnosis (32% in the UK series, but only 3% in the Toronto series). Careful palpation of the skin for calcinotic nodules allows the superficial calcinosis to be charted. Later on in the disease, even after resolution of the myositis, the calcinosis can progress to sheet-type calcification (Miyamae et al., 2003; Ostrov et al., 1991). The calcium can extrude through the skin, or can discharge as a milky looking fluid. These deposits are a prominent source of discomfort and disability.

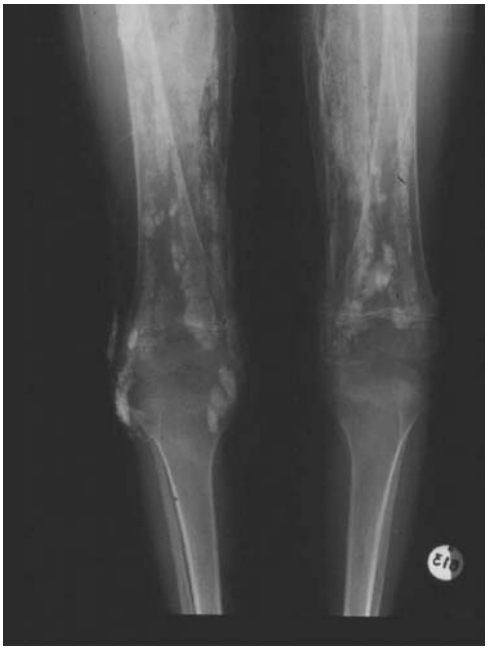

Figure 1. Calcinosis.

5.4. Clinical signs: muscle weakness

Muscle strength needs to be tested thoroughly. The manual muscle testing of 8 muscles (MMT8) has been validated in different centres (Bode et al., 2003; Rider, 1996). It tests the muscle power of individual muscles that are commonly affected in JDM. The muscle power is graded for each muscle out of 10, giving an overall score out of 80. The muscles that are tested are: neck flexors, shoulder abductor, elbow flexor, wrist extensor, hip abductor, hip extensor, knee extensor, ankle dorsiflexor and abdominal muscles, and Gower's sign where children are observed getting up the floor.

Muscle function and endurance is measured using the Childhood Myositis Assessment Score (CMAS) (Lovell et al., 1999). This involves asking the child to do some set manoeuvres, including

timed ones such as lifting the head up for 2 min. This assesses a different aspect of muscle function, not simply muscle power. It is correlated less directly with the MMT8, and more closely with the Childhood Health Assessment Questionnaire (CHAQ) that asks parents about functional difficulties with performing tasks associated with activities of daily living (Huber et al., 2001, 2004). Both the CMAS and the CHAQ are affected by muscle weakness, but they are also affected by synovitis and contractures.

5.5. General assessment at onset

Patients need to have their joints assessed for active synovitis (found in 36% of UK series) and for contractures (27%). Lipoatrophy (10%) can be localised over the face or limbs, or more generalised with marked loss of subcutaneous fat (see Fig. 2) and association with hypertriglyceridaemia and insulin resistance. Though it is rare for the heart to be involved, patients need a full cardiovascular examination. The respiratory system needs to be assessed for effects secondary to aspiration, for respiratory muscle weakness and for signs of interstitial lung disease (ILD). The gastrointestinal and neurological systems need to be examined to exclude vasculitis.

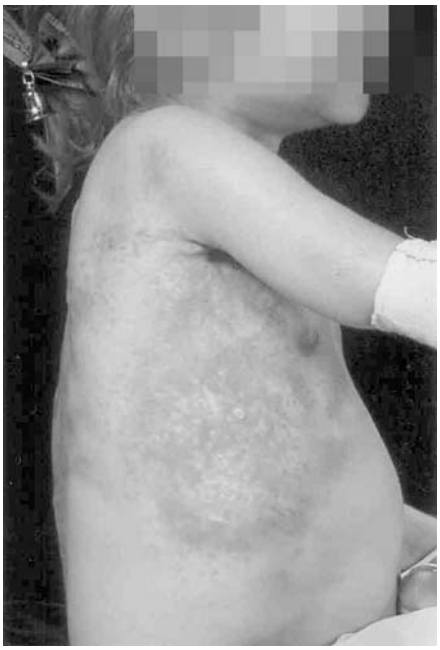

Figure 2. Lipoatrophy. (See Colour Plate Section.)

5.6. Disease course

The natural history of JDM falls into three groups: a monocyclic group with one episode of JDM, a polycyclic group with cycles of disease relapse, and a chronic persistent group who often have severe disease that is difficult to control and can be fatal. A retrospective study of 65 JDM patients in Canada reported that 37% of the patients had a monocyclic course and 63% a chronic or polycyclic course (median follow-up time of 7.2 years). Steroids had been used in 95% of this cohort, but 40% still had a rash and 23% were still weak at time of follow-up (Huber et al. 2000).

Poor prognosis is associated with skin ulceration, severe muscle weakness that has also involved more distal muscles, dysphagia or dysphonia, severe nailfold capillary abnormalities, severe gut involvement (which may lead to perforation), lung involvement with ILD, CNS involvement, generalised edema, and persistent severe disease activity. Another poor prognostic indicator is the presence of calcinosis (see Table 1).

The disease can remit within 2–3 years, or may persist for 10–15 years. Management is aimed at controlling disease activity, preventing fatalities and preventing the functional disability that results from disease damage.

Table 1
Poor prognostic factors

Skin ulceration
Severe muscle weakness that has also involved more distal muscles
Dysphagia or dysphonia
Severe nailfold capillary abnormalities
Severe gut involvement
Interstitial lung disease
CNS involvement
Generalised edema
Persistent severe disease activity
Calcinosis

6. Diagnostic investigations

6.1. Laboratory tests

Markers of inflammation (such as anemia and elevated ESR) need to be assessed using blood tests. Muscle enzymes (creatinine kinase, aspartate alanine transferase, alkaline phosphatase, lactate dehydrogenase, aldolase) are often (but not invariably) raised at onset. Anti-nuclear antibody and rheumatoid factor can be positive in JDM but are not diagnostic. Investigations for infections (viral, streptococcal, mycoplasma) need to be sent to exclude post-infectious myositis. In adult DM, there are specific myositis associated antibodies (MSA) found that correlate with different disease courses (such as anti-Jo1 and lung disease). The adult correlations do not hold true in JDM, but different MSAs may be important in children (Wedderburn and Li, 2004).

6.2. Radiological

In some centres, MRI scans have replaced muscle biopsies to document myositis. However, there is no consensus on a protocol for MRI imaging, or on the reporting of scan images. Changes can be mild and may need the appropriate images to be taken, as well as radiologists used to looking for the more subtle signs of myositis or edema of the muscle fascia (Chapman et al., 1994; Maillard et al., 2004). In some centres, MRI is used as a way of ensuring that the muscle biopsy is taken from an affected muscle. Ultrasound scans can be used to look for muscle inflammation, but it is dependent on operator expertise. Electromyogram (EMG) can be used, but many children find the procedure painful. Speech therapy assessment of swallowing can be valuable, but as symptoms can be silent, video fluoroscopy is a more definitive investigation of swallowing problems.

A chest X-ray can ensure there are no signs of infection secondary to aspiration. If the videofluoroscopy shows swallowing problems, a high resolution CT scan of the chest should be done.

Calcinosis is difficult to chart objectively and X-rays can help document its extent. CNS vasculitis, if suspected, requires a brain MRI to delineate its extent.

6.3. Muscle biopsy

A typical muscle biopsy will show variation in the muscle fiber sizes with perifascicular atrophy and a perivascular inflammatory cell infiltrate. There is often an increased connective between muscle bundles with fibrotic tissue. Early in disease, there can be normal histopathology, with only up-regulation of MHC class I molecules on immunological staining (Li et al., 2004). This is missed in laboratories that do not routinely do this staining on their muscle biopsies.

An open muscle biopsy has to be done under general anaesthesia and leaves a scar that can be painful. Some centers do not use open muscle biopsies but needle biopsies under local anaesthesia. This can only be done in centers that routinely do these procedures, as an inadequate biopsy sample does not allow the diagnosis to be confirmed. Recently there has been an attempt of bringing together some of the international experts in order to develop an assessment tool for scoring the features found on muscle biopsies that will allow biopsies done at different centres to be compared. Most expert histopathologists can agree on the severity of an abnormal muscle biopsy, but so far individual pathological signs have not been compared to clinical outcomes to see which ones are predictive (in the early stages of the disease) of a poor outcome, such as the development of calcinosis.

6.4. Functional tests

Lung function tests are needed if there is respiratory muscle weakness or if there are any signs of dysphagia. A restrictive pattern on lung function tests can be due to muscle weakness or ILD, and a diffusion factor (DLCO) can help differentiate the two. If there are any clinical signs of cardiac involvement, further investigations should include an ECHO and an ECG.

7. Diagnosis

7.1. Diagnostic criteria

The diagnostic criteria remain those published by Bohan and Peter in 1975 (Bohan and Peter, 1975a, b) (see Table 2) and are the same for paediatric as well as adult cases of DM. Cases need to have a typical rash such as the heliotrope rash with periorbital edema or Gottron's papules. This needs to be associated with three out of the following four:

1. progressive muscle weakness which is symmetrical and affects the proximal limb girdle muscles and neck flexors;
2. raised muscle enzymes such as creatinine kinase, lactate dehydrogenase, or AST transaminase;
3. a muscle biopsy consistent with the diagnosis of DM;
4. an EMG consistent with dermatomyositis. If these criteria are not fulfilled, then the patient can be classed as probable JDM, polymyositis (absent skin rash) that is very rare in children, or amyopathic JDM (typical skin rash without myositis).

7.2. Diagnostic problems

Many paediatricians feel that a typical case of DM does not need a muscle biopsy or an EMG to confirm the diagnosis. This is compounded by published reports of patients with a diagnosis of JDM having normal muscle biopsies or EMGs: the myositis can be patchy within individual muscles as well as within muscle groups. A survey of international paediatric rheumatologists reported that only 61.3% used muscle biopsy and 55.5% used EMG routinely. Many paediatricians use an MRI scan instead: 59% used MRI scans routinely (Brown et al., 2006). This leaves many paediatric cases in the probable category with a typical rash, muscle weakness and elevated muscle enzymes.

There are several international efforts underway to suggest up-to-date diagnostic criteria. One of these efforts is including classification criteria for myositis in children and in adults. This working group has included paediatric and adult rheumatologists, neurologists and dermatologists.

Table 2
Diagnostic criteria

Typical rash (Heliotrope, Gottron's)
Plus 3 of
Progressive muscle weakness: symmetrical
Proximal limb–girdle + neck flexor
↑ Muscle enzymes in serum
+ ve muscle biopsy
+ ve EMG

Source: Adapted from Bohan and Peter, 1975a, b.

7.3. Differential diagnosis

The diagnosis of a typical case of JDM is straightforward. However, some cases present without a typical rash. These patients may have had a short-lived mild heliotrope rash that parents ascribed to sunburn or they may have polymyositis. Polymyositis is extremely rare in children. Patients have normal capillary nailfolds and muscle biopsy is mandatory to make the diagnosis.

Myositis can occur as a post-infectious complication following a number of infections including viral, streptococcal or mycoplasma infections. The myositis can be severe enough to need steroids, but patients usually do not need a prolonged course of steroids, and only relapse if the infection recurs.

Myositis may occur as part of a connective tissue disease such as systemic lupus erythematosus (SLE), scleroderma, mixed connective tissue disease (MCTD) or a systemic vasculitis such as polyarteritis nodosa (PAN). In some cases, patients may have characteristics of both diagnoses and may be termed as having an overlap syndrome. This is a confusing area, and further work needs to be done to clarify the definition of the overlap syndromes.

Neuromuscular diseases are a differential diagnosis for cases lacking a skin rash. However, patients with a muscular dystrophy such as Duchenne's or Becker's can be distinguished on history (insidious onset, no systemic features, no myalgia) and

confirmed with a biopsy. Myasthenia gravis is rare and can usually be distinguished from JDM by the element of fatigability and confirmed by finding anti-acetylcholine receptor antibodies.

8. Treatment

8.1. Evidence-base for drug treatment

In the days before steroids, one-third of the patients died, one-third recovered and one-third recovered with severe disabilities (Bitnum et al., 1964). Oral steroids are effective in treating cases of JDM, but they do not prevent calcinosis; they do not keep severe disease controlled and there is little evidence about doses and the most effective route of administration. Most physicians used to treating JDM agree that all patients need steroids, and that they should not be tapered too early and they need to be tapered slowly. There is evidence that IV steroids help patients improve more rapidly (Pachman and Cooke, 1980) because of poor gut absorption with oral administration, but they do not affect long-term outcome. Some physicians prefer to give steroids orally at 2 mg/kg/day for at least a month before starting to taper.

There is evidence that adding a disease-modifying drug (DMARD) early in the disease course, such as methotrexate, appears to help prevent calcinosis (Fisler et al., 2002) and may shorten the length of time on steroids. The evidence for the effectiveness of the individual DMARDS is based on case series and clinician's experience: there are no good trials. In the UK, paediatric rheumatologists favour methotrexate, whereas paediatric neurologists favour cyclosporin A as the first-line DMARD of choice.

The difficulty arises with patients whose disease is not fully controlled on these medications. Some groups have felt that continuing skin disease is unimportant if the myositis is quiescent. However, whereas calcinosis in adult DM is felt to be due to damage and is reversible, calcinosis in children is felt to be due to ongoing disease, even if the myositis has resolved. Increasing calcinosis warrants stepping-up the immunosuppressive treatment. This can halt the progress of the calcinosis and can allow it to regress. Patients can respond to changing the DMARD (i.e. cyclosporin to methotrexate), changing the route of administration of the DMARD (i.e. oral to subcutaneous or IM methotrexate), or adding a second DMARD such as azathioprine to methotrexate (personal practice, see Figs. 3 and 4). However, some calcinosis is extremely resistant to treatment, and many medications have been tried with case reports of success, but sometimes more powerful immunosuppressive treatment may be needed (drug treatment review in Pilkington and Wedderburn (2005)).

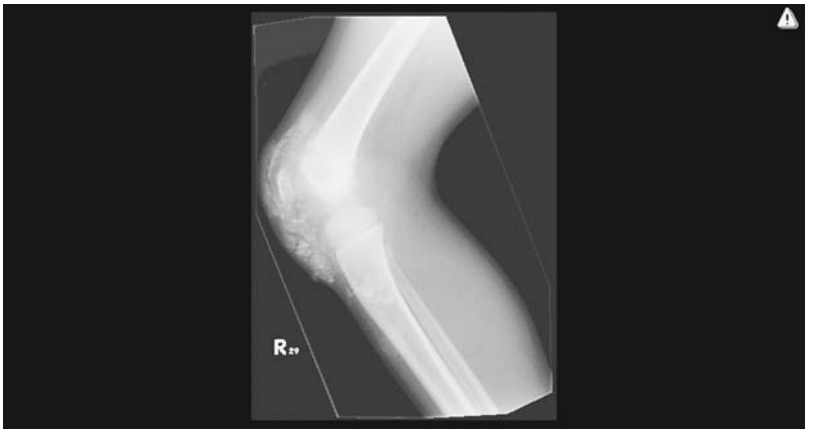

Figure 3. New calcinosis on treatment: steroids from onset for 16 months, developed calcinosis, methotrexate added for 6 months, increasing calcinosis so azathioprine added.

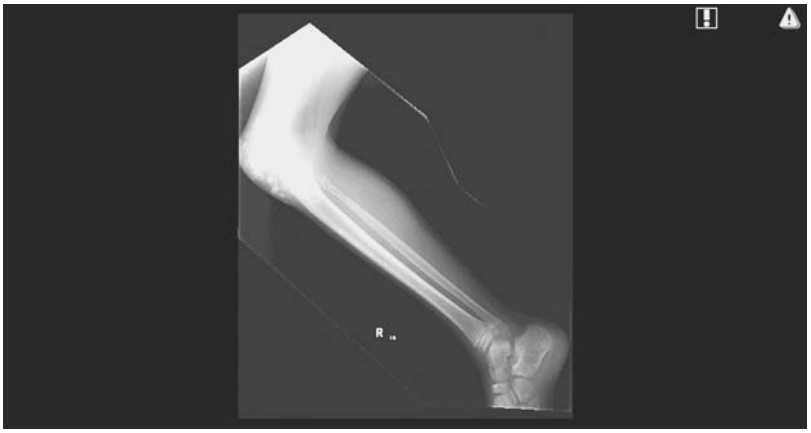

Figure 4. Calcinosis: 1 year later, on methotrexate + azathioprine, off steroids for 2 months.

There is evidence that IVIG is effective (Dalakas and Hohlfeld, 2003), as well as cyclophosphamide (Riley et al., 2004). This tends to be reserved for severe cases with poor prognostic signs. There are reports of biologics such as anti-TNF (Maillard et al., 2002; Miller et al., 2002) and rituximab (Levine, 2002) being effective.

8.2. Non-medical treatment

Treatment of JDM needs to be multi-disciplinary and involves therapists. Historically, active physiotherapy early on was felt to cause calcinosis through increasing muscle inflammation. There is little evidence to support this. A small study of JDM patients has demonstrated that there is no increase in muscle enzymes or MRI signal immediately after a supervised exercise session (Maillard et al., 2004). Long-term disability has been found to correlate with the presence of contractures (Espadaa et al., 2002): it is important for physiotherapists to be involved in early treatment to prevent contractures, and if they are present, to treat them (see chapter on physiotherapy). Physiotherapists also need to be involved in helping patients to rebuild their muscle strength. Aerobic exercise testing on a treadmill in patients with JDM has revealed an impairment in their maximal aerobic exercise capacity, stressing the importance of a supervised exercise programme to rebuild strength (Takken et al., 2003). The interventions of an occupational therapist will help with the activities of daily living, and there needs to be liaison with the patient's school to help the child appropriately during their illness.

8.3. Recent developments

International collaborative efforts have led to the development of new disease activity and damage assessment tools (Isenberg et al., 2004; Pilkington et al., 2001). This work was done by the International Myositis and Clinical Studies Group (IMACS), which brought together experts in the field of myositis in adults and children from around the world. The assessment tools are needed to allow standardised assessments to be done for patients in many centers and so allow multi-center drug trials and long-term outcome studies to be done in big enough groups to produce valid data (reviewed in Pilkington, 2004).

A slightly different approach was undertaken by a different group: the Paediatric Rheumatology International Trials Organisation (PRINTO) in collaboration with the Paediatric Rheumatology Collaborative Study Group (PRCSG, an American/Canadian group). Their work involved a questionnaire survey followed by a consensus conference to produce the domains and variables to be included in the preliminary disease activity

and damage core sets for JDM (Ruperto et al., 2003), as well as definitions of disease remission and flare. These were remarkably similar to the ones produced by the IMACS group.

At present, various groups are working on producing up-to-date diagnostic and classification criteria for patients with myositis. This will allow clarification of the definitions of subgroups so that further research can be based on homogenous groups. This will improve understanding of the disease and allow clinicians to tailor their treatments more effectively.

Key points

- Rare disease.
- Typical JDM is easy to diagnose, atypical cases are not.
- Diagnostic criteria are outdated.
- Disease treated late has a poorer prognosis.
- Disease severity is variable.
- Increasing calcinosis is a sign of disease activity.
- Assessments need to be detailed and standardised.
- International collaboration needed for treatment trials.

Acknowledgements

The author thanks Sue Maillard and Simon Arscott for their careful reading of the manuscript, Virginia Brown for her help in preparing this manuscript and the Cathal Hayes Research Foundation for funding the UK Registry and Repository for JDM.

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Handbook of Systemic Autoimmune Diseases, Volume 6
Pediatrics in Systemic Autoimmune Diseases
Rolando Cimaz and Thomas Lehman, editors

CHAPTER 8

Localized Scleroderma in Children

Francesco Zulian*

Rheumatology Unit, Department of Pediatrics, University of Padova, Padova, Italy

1. Introduction

Localized scleroderma (LS), also know as morphea, comprises a group of distinct conditions which involve the skin and subcutaneous tissues. They range from very small plaques involving only the skin, to full thickness lesions which may cause significant functional and cosmetic deformity, with a variety of extracutaneous features. Our understanding of the epidemiologic features of this group of disorders and the range of extracutaneous manifestations have expanded rapidly over the past few years.

2. Epidemiology

Although relatively uncommon, LS is far more common than systemic sclerosis (SSc) in childhood (10:1) (Peterson et al., 1997). Few studies have addressed (up to 1 per 100,000 of the population) (Uziel et al., 1994).

As with many other connective tissue diseases, juvenile localized scleroderma (JLS) mainly involves females with a F:M ratio of 2–3:1 (Vancheeswaran et al., 1996; Marzano et al., 2003; Zulian et al., 2006a). In children there are no differences in age at onset in the various JLS subtypes (Vancheeswaran et al., 1996; Marzano et al., 2003; Zulian et al., 2006a). A recent study described six patients with congenital LS. The linear subtype is the only manifestation of the disease at this age and, due to its unusual onset, it is often misdiagnosed as a skin infection, nevus, or salmon patch. This often leads to a delay of 2–4 years before the disease is recognized and properly diagnosed (Zulian et al., 2006b).

3. Etiology and pathogenesis

The etiology and pathogenesis of JLS are unknown. As in SSc, the focus of much investigation is on abnormalities of fibroblast proliferation, collagen production, and/or immunologic abnormalities. It seems certain that autoimmunity is important, given the frequent presence of abnormal serum antibodies (see Section 5.2).

Trauma has been implicated in initiation of lesions in 2.6–12.7% of the patients (Christianson et al., 1956; Falanga et al., 1986; Vancheeswaran et al., 1996; Zulian et al., 2006a). Although interesting, the mechanism by which a physical trauma may contribute to the development of linear scleroderma is still unclear.

A positive family history for rheumatic or autoimmune diseases was reported in around 12% of patients, underlying the importance of a genetic predisposition to the disease at least in a minority of patients (Vancheeswaran et al., 1996; Zulian et al., 2006a). The proposed association with *Borrelia burgdorferi* has been disproven (Aberer et al., 1985).

*Corresponding author.
Tel.: +39049-8213583; Fax: +39049-8218088
E-mail address: zulian@pediatria.unipd.it (F. Zulian).

DOI: 10.1016/S1571-5078(07)06012-6

In adults, a significant number of cases of morphea have been reported after irradiation for breast cancer, and the risk is estimated to be in the order of 1/500 (Reddy et al., 2005).

4. Clinical manifestations

4.1. Classification

JLS is a distinct entity, different from SSc. There is almost exclusive cutaneous involvement and absence of internal organ involvement. There is no uniformly accepted terminology; dermatologists typically use the term ''morphea'' and pediatricians and rheumatologists use the term ''localized scleroderma'' to refer to the same group of conditions. The most widely used classification divides LS into five general types: plaque morphea (PM), generalized morphea (GM), bullous morphea, linear scleroderma, and deep morphea (Peterson et al., 1995). Atrophoderma of Pasini Pierini, eosinophilic fasciitis, and lichen sclerosus et atrophicus are sometimes classified among the subtypes of LS but this is the subject of controversy. This classification system does not accommodate the mixed forms of LS where different types of lesions occur in the same individual. Mixed forms are more common than previously recognized, accounting for 15% of the whole (Zulian et al., 2006a).

4.2. Clinical subtypes

PM is characterized by oval or round circumscribed areas of induration with a central waxy, ivory color surrounded by a violaceous halo (Fig. 1). It is primarily confined to the dermis with only occasional involvement of the superficial panniculus. Atrophoderma of Pasini and Pierini is characterized by hyperpigmented atrophic patches with well-demarcated borders, which may coexist with other sclerotic lesions.

When there are four or more individual plaques larger than 3 cm involving at least two out of seven anatomic sites (head-neck, right upper extremity, left upper extremity, right lower extremity, left lower extremity, anterior trunk, posterior trunk) it is called GM (Fig. 2). Unilateral GM has been proposed as an extreme variant, usually beginning in childhood (Appelhans et al., 2006).

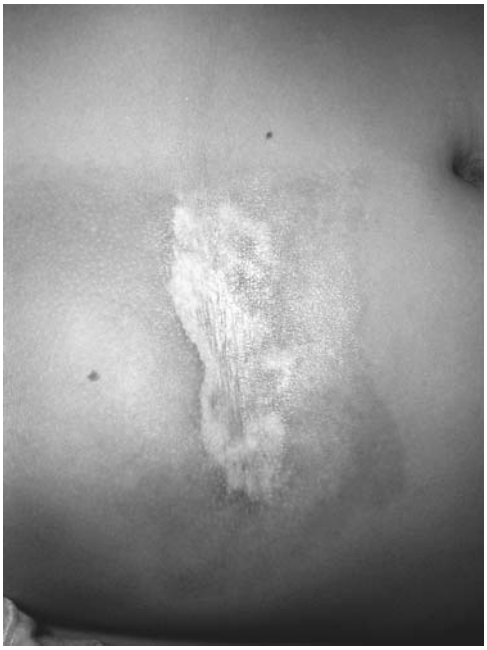

Figure 1. Plaque morphea of the abdomen. (See Colour Plate Section.)

Linear scleroderma, the most common subtype in children and adolescents, is characterized by one or more linear streaks that may extend through the dermis, subcutaneous tissue, and muscle to the underlying bone (Fig. 3). The upper or lower extremities can be affected (Fig. 4) as can the face or scalp, as in the en coup de sabre variant (ECDS) (so called because the lesion is reminiscent of the depression caused by a stroke from a sword) (Figs. 4 and 5).

The Parry Romberg syndrome (known also as progressive facial hemiatrophy) is characterized by atrophy of the skin extending through the dermis, subcutaneous tissue, and underlying bone, with mild or absent involvement of the superficial skin. This condition is actually considered the severe end of the spectrum of ECDS (Jablonska

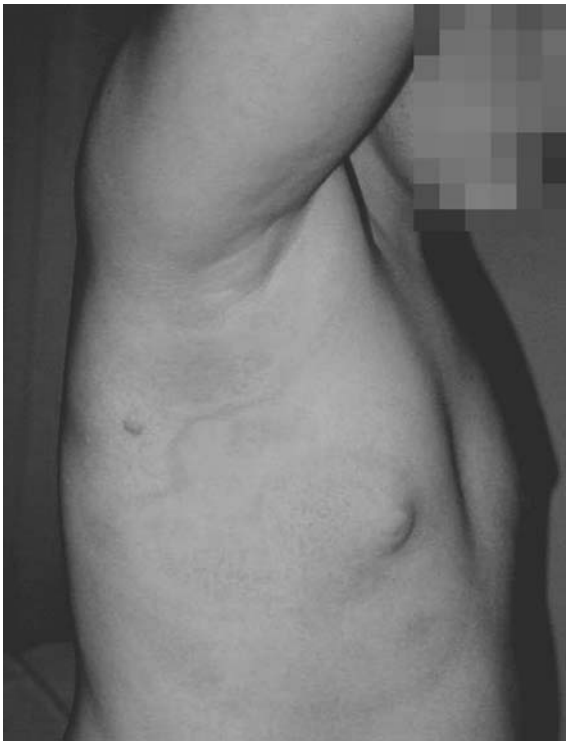

Figure 2. Generalized morphea involving the trunk. (See Colour Plate Section.)

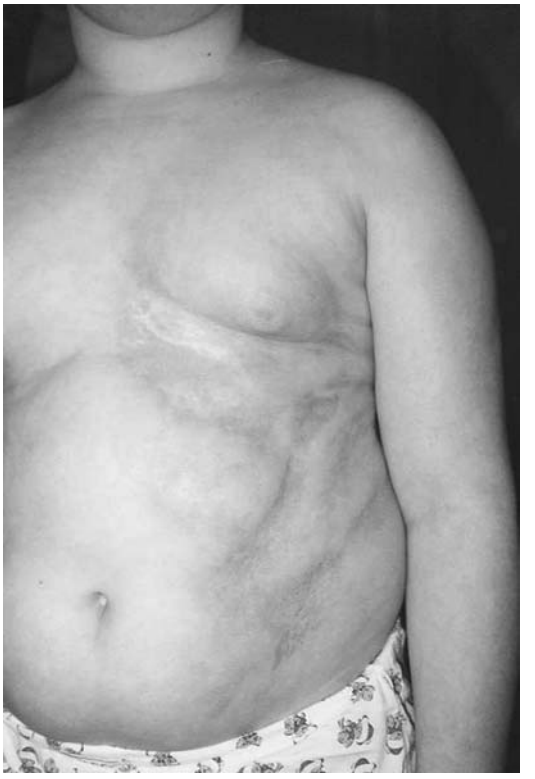

Figure 3. Linear scleroderma of the trunk. (See Colour Plate Section.)

and Blaszczyk, 2005). Evidence for this close relationship is the similar prevalence in both conditions of associated disorders, including seizures, dental, and ocular abnormalities (Menni et al., 1997; Blaszczyk and Jablonska, 1999; Sommer et al., 2006).

Bullous morphea is a rare subtype, probably related to lymphatic obstruction secondary to the sclerodermatous process.

In *deep morphea* the entire skin feels thickened, taut, and bound down sometimes with the appearance of a solitary, indurated plaque (Su and Person, 1981). *Pansclerotic morphea* is characterized by generalized full-thickness involvement of the skin of the trunk, extremities, face and scalp with sparing of the fingertips and toes. It is more common in children than adults. The involvement of the entire body without internal organ involvement helps differentiate this from SSc.

Chronic ulcers, complicating pansclerotic morphea may evolve into squamous cell carcinoma (Wollina et al., 2002; Parodi et al., 2001; Maragh et al., 2005).

4.3. Extracutaneous involvement

Articular involvement is the most frequent finding, and is especially prevalent in patients with linear scleroderma. The arthritic joint involved may be distant from the site of the skin lesion. Children with LS who develop arthritis often have a positive rheumatoid factor (RF), and sometimes an elevated erythrocyte sedimentation rate (ESR) and circulating autoantibodies (Dehen et al., 1994; Zulian et al., 2005). These children tend to have an accelerated course of disease, including rapid development of contractures.

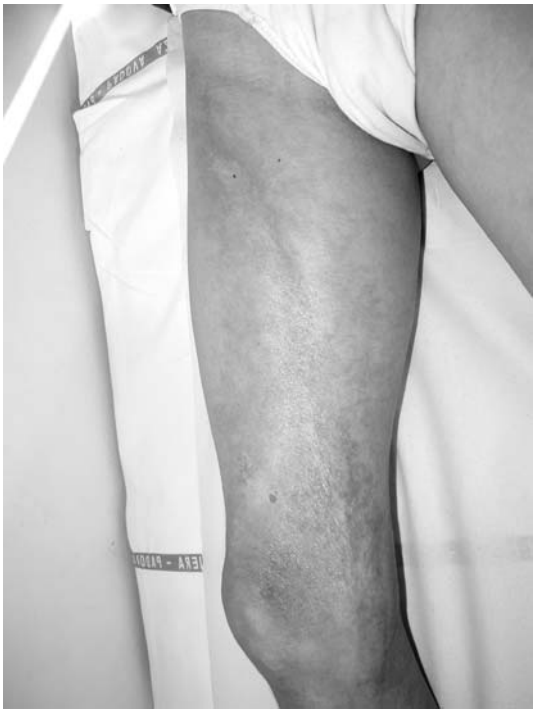

Figure 4. Linear scleroderma of the right thigh (early lesion) extending down to the leg. (See Colour Plate Section.)

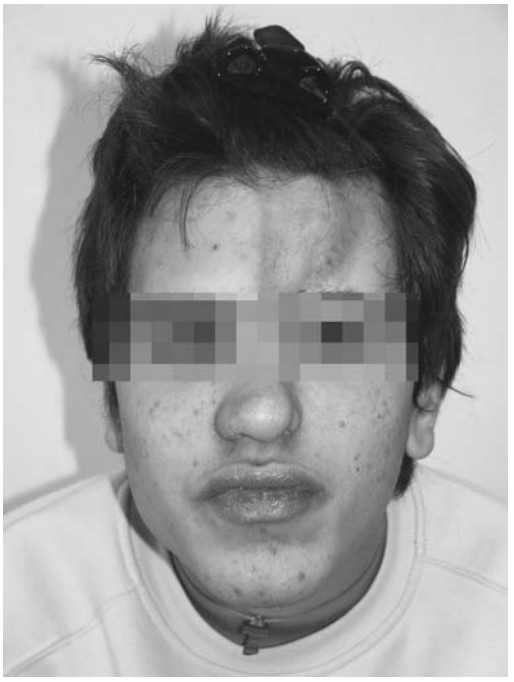

Figure 5. Scleroderma en coup de sabre associated with facial hemiatrophy in a teenager. (See Colour Plate Section.)

The most frequent neurologic complication are seizures and headaches, but behavioral changes and learning disabilities also have been described (Blaszczyk et al., 2003; Zulian et al., 2005). Abnormalities on magnetic resonance imaging (MRI) include: calcifications, white matter changes, and vascular malformations. Evidence of central nervous system (CNS) vasculitis has also been reported (DeFelipe et al., 2001; Flores-Alvarado et al., 2003). Biopsy findings include: sclerosis, fibrosis, gliosis, as well as vasculitis (Holland, 2006).

In a multicenter study of 750 children with JLS (Zulian et al., 2005), there was at least one extracutaneous manifestation present in 22% of children and 4% had multiple manifestations. The overall distribution of extracutaneous manifestations was as follows: arthritis 19%, neurological findings 4%, other autoimmune conditions (e.g., Raynaud's phenomenon) 3%, vascular findings (vasculitic rash and deep vein thrombosis) 2%, ocular involvement (uveitis, glaucoma) 2%, gastrointestinal findings 2% (gastro-esophageal reflux (GER) is the only gastrointestinal complication reported so far (Weber et al., 2000; Zulian et al., 2005)), respiratory findings (restrictive lung disease) 1%. SSc developed in only one patient.

JLS patients with extracutaneous manifestations represent a newly described subset with peculiar clinical and laboratory features. In these patients the organ impairment is milder and not life-threatening when compared with SSc.

5. Diagnostic investigations

5.1. Laboratory parameters

The diagnosis of JLS is established on the basis of the clinical picture, aided by biopsy of skin or subcutaneous tissues if necessary. The ESR may be increased with active inflammation, as in

eosinophilic fasciitis. Eosinophilia and hyper-gammaglobulinemia are hallmarks of this disorder but also may occur in other subtypes.

5.2. Autoantibodies

In a large cohort of patients, antinuclear antibodies (ANA) were found in 42.3% but did not correlate with the various subtypes or the disease course (Zulian et al., 2006a).

Of interest, anti-topoisomerase I antibodies (anti-Scl 70), a marker of SSc in adults, were found in 2–3% of children with LS (Zulian et al., 2006a; Blaszczyk and Jarzabek-Chorleska, 2000; Takehara and Sato, 2005).

Conversely, anti-centromere antibodies (ACA) were found in 12% of adults with LS but only in 1.7% of children (Ruffatti et al., 1986; Zulian et al., 2006a). Whether these antibodies reflect an immunological component of the disease process or can have a prognostic significance is unclear.

RF is detected, at low titer, in 16% of JLS patients. Its presence is significantly correlated with the occurrence of arthritis (Zulian et al., 2006a).

Anti-histone antibodies (AHA) have been detected in 47% of patients, mainly adults, with LS with a different prevalence in the various subtypes, higher in GM, lower in PM (Takehara and Sato, 2005). Monitoring AHA titers may be helpful in assessing disease activity (el Azhary et al., 2004).

A recent study underlined the role of anti-DNA topoisomerase IIα (anti-topo IIα) autoantibodies in LS (Hayakawa et al., 2004). These autoantibodies were detected in 76% of patients with LS and in 85% of those with GM. Immunoblotting showed no cross-reactivity of anti-topo IIα with anti-topo I autoantibody. Anti-topo IIα, however, is not specific for LS. It was present in 14% of the patients with SSc, in 8% of those with SLE, and even 10% in dermatomyositis.

Anti-phospholipid antibodies (aPL) have recently been shown to be present in adults with LS with an overall prevalence of 46% that increases to 70% in patients with generalized forms (Sato et al., 2003). In children this prevalence falls down to 13% and, in contrast to adults, presence of aPL is not associated with thromboembolic events or clotting abnormalities in children (Zulian et al., 2006a).

5.3. Thermography

To date, no validated tools have been developed for the assessment of disease extension in JLS. Infrared thermography (IRT) has been shown to be of value in the detection of active JLS lesions in children (Martini et al., 2002). Skin surface temperature is influenced not just by dermal blood flow, but also by the morphological skin changes that can occur in JLS. This technique has shown to have a very high reproducibility but it remains to be seen whether it will truly predict progression of disease.

5.4. Imaging techniques

The application of imaging techniques such as MRI and ultrasound (US) shows promise in supporting clinical management and greater understanding of JLS. MRI is useful when CNS or eye involvement is suspected and is able to demonstrate the true depth of soft tissue lesions and tissue involvement at other sites (Liu et al., 1994). A recent study described five characteristic US signs in LS: flattened ''yo-yo'', undulation of the dermis, disorganization, loss of thickness, and thickened hyperechoic bands in the hypodermis. A 92% sensitivity and 100% specificity for LS were found if four of these five signs were present (Cosnes et al., 2003).

6. Treatment

Over the years, many treatments have been utilized for LS. These have included topical, intra-lesional and systemic corticosteroids, topical and systemic calcitriol, topical tacrolimus, hydroxychloroquine, sulfasalazine, penicillamine, gamma-interferon, and methotrexate (MTX).

PM generally is primarily of cosmetic concern, and treatments with potentially significant toxicity are not justified. In general, the lesions will spontaneously remit with residual pigmentation.

Treatment should be topical therapies such as moisturizing agents, or topical glucocorticoids or calcipotriene (Cunningham et al., 1998). Good results were reported in a uncontrolled study with Imiquimod, a novel immunomodulator (Dytoc et al., 2005). This agent up-regulates a variety of cytokines including interferon α and γ, inhibiting collagen production by fibroblasts, by a down-regulation of TGFβ. The side effects were minimal and limited to local irritation which resolved with a reduced frequency of use.

For linear and deep subtypes of JLS, systemic treatment should be considered. MTX in combination with corticosteroids has been successfully used in children with LS (Walsh et al., 1999; Uziel et al., 2000; Fitch et al., 2006). The efficacy of MTX has been recently confirmed by an additional study in adults with LS (Kreuter et al., 2005).

The treatment protocol usually consists in a combination of oral prednisone or intravenous methylprednisolone (IVMP, 20–30 mg/kg/day for 3 days) and MTX (10–15 mg/m^2/wk). Most patients show a response within 2–4 months and the side effects are usually mild and associated more with corticosteroid than with MTX treatment.

Since the mid 1990s, phototherapy with ultraviolet (UV) light has been used to treat patients with LS. UVA1 at low, medium, and high doses, with or without psoralens (PUVA) seems to be effective. There are a variety of mechanisms of action by which UV phototherapy may work such as increased MMP1-collagenase activity, increased expression of INFγ, and decrease in TGFβ (El-Mofty et al., 2004). UV therapy may be effective for localized or superficial lesions (Kerscher et al., 1998; De Rie and Bos, 2000). An open randomized control trial comparing low and medium dose UVA1 and narrow band UVB therapy in adult patients showed that the more readily accessible UVB phototherapy was almost as effective as UVA1 in treating morphea (Kreuter et al., 2006).

However, UV treatment in children should be considered with caution. The rate of relapse after UV phototherapy is not known, and the need for prolonged maintenance therapy, leading to a high cumulative dosage of irradiation, increases the risk for potential long-term side effects including carcinogenesis (Staberg et al., 1983; Setlow et al., 1993).

The use of vitamin D or its analogs (topically and systemically) has been reported in several case series (Caca-Biljanovska et al., 1999; Hulshof et al., 1994); however, in the only controlled trial, it was no more effective than placebo (Hulshof et al., 2000).

The efficacy of topical tacrolimus was recently reported in seven adult patients with LS (Mancuso and Berdondini, 2005). Softening of the lesions was seen in all patients, with reduced erythema of inflammatory lesions within 1 month of treatment. The clinical improvement was supported by improvement in histologic findings as well.

Overall there is no uniform agreement on therapy for children with LS. Unless there is significant risk of structural or psychological damage, interventions should be minimal. MTX appears most successful amongst the proposed therapies for those children with more severe disease.

Key points

- Juvenile localized scleroderma (JLS), also known as morphea, has a variety of clinical manifestations. They range from very small plaques involving only the skin, to manifestations which may cause significant functional and cosmetic deformity.
- Important contributions over the past few years have included the descriptions of clinical manifestations of JLS in children, highlighting the possibility of extracutaneous manifestations.
- Although pathogenesis is unknown, the focus of much investigation is on disregulation of fibroblast production of collagen and immunologic abnormalities.
- The role of autoantibodies and correlation with various subtypes and disease manifestations may shed important light on disease pathogenesis.
- New approaches to the treatment of JLS, including methotrexate, corticosteroids, phototherapy, and other immunosuppressive agents have been recently developed. However, multicenter randomized controlled trials are needed to evaluate their real efficacy by using uniform classification criteria and validated outcome measures.

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Handbook of Systemic Autoimmune Diseases, Volume 6
Pediatrics in Systemic Autoimmune Diseases
Rolando Cimaz and Thomas Lehman, editors

CHAPTER 9

Juvenile Systemic Sclerosis

Ivan Foeldvari*

Association-Hamburger Zentrum für Kinder- und Jugendrheumatologie, Klinikum Eilbek, Hamburg, Germany

1. Introduction

Juvenile systemic sclerosis (jSSc) is a rare potentially life-threatening autoimmune disease of childhood, currently incurable and of unknown cause. JSSc is characterized by cutaneous and visceral fibrosis. The disease shows a progressive course with a long-term fatal outcome. It is classified according to the preliminary classification criteria of the American College of Rheumatology (ACR) (Masi et al., 1980), but currently new proposed pediatric classification criteria (Zulian et al., 2007) are emerging. The organ involvement pattern differs from the adult form. Survival seems to be better in the pediatric patients with a 5-year survival of 90–95%. The validation of the outcome measures for children with jSSc is currently under evaluation. Regarding effective treatment, there is no pediatric data and the pediatric rheumatologist need to rely on the experiences in adult disease.

2. Incidence and prevalence

There is no exact epidemiologic data regarding prevalence and incidence. It is suspected that 10% of all systemic sclerosis patients develop the disease before the age of 18. The incidence of the systemic sclerosis (SSc) in the adult population is two to ten per 1,000,000/year.

3. Classification and epidemiology

The disease is currently classified according to the preliminary classification criteria of the ACR (Masi et al., 1980), where the main criterion is skin thickening proximal from metacarpophalangeal joints, and minor criterion are sclerodactily, digital pitting scars and bibasilar pulmonary fibrosis (X-ray). This classification system is validated only in adult patients. LeRoy et al defined two subtypes of SSc: diffuse and limited (LeRoy et al., 1988). In the diffuse subtype, the skin involvement extends proximal from elbow and it may involve the trunk. In the limited involvement the skin changes are restricted to hands, forearms, face and feet. The CREST syndrome (calcinosis, Raynaud, esophageal dysmotility, sclerodactily, teleangiectasia) is a subgroup of the limited form.

Recently preliminary classification criteria for jSSc has been developed (Zulian et al., 2007) by a group of pediatric and adult rheumatologists together with dermatologists. The subsequently proposed criteria include (Zulian et al., 2007)—one major criterion, which is sclerosis and/or skin indurations specific for SSc, and eight minor criteria reflecting each involved organ system (e.g. pulmonary, cardiac, gastrointestinal, renal, vascular, musculoskeletal, neurological and serologic involvement, each characteristic for SSc). Using this set of criteria, the pediatric patient can be classified

*Corresponding author.
Tel.: +494020923694; Fax: +494020923693
E-mail address: sprechstunde@kinderrheumatologie.de
(I. Foeldvari).

DOI: 10.1016/S1571-5078(07)06013-8

as jSSc, when one major and two minor criteria are fulfilled. The validation of this proposed classification is under way, with the specific goal that this classification system facilitates an earlier diagnosis of the pediatric patients than the currently used preliminary adult criteria.

Most data on jSSc patients are published as single case reports or as small case series, but there are two larger retrospective case collections too. In the first published multinational survey of pediatric rheumatologic centers from all over the world (with a 14% response rate) 135 patients from 34 centers were collected (Foeldvari et al., 2000). Another data set was created during the classification project for jSSc. This set has been published only in abstract form (Martini et al., 2006), in which data from 153 patients from 55 centers were collected. The patient population of the two surveys overlaps. In the first survey most patients were Caucasian. The mean time of the follow-up was 5.0 years ($\pm$3.3 years). The ratio of female to male patients in the first study was 100 females to 35 males and in the second study 120 females to 33 males. The proportion of female patients is lower in the pediatric than in the adult population with SSc. The disease seems to be rare all over the world. The mortality data will be discussed at the end of the section of the clinical presentation.

4. Etiology/pathogenesis

SSc is a disease of unknown cause, and the pathogenesis remains incompletely understood. Most data regarding possible causes and pathogenetic changes are gained from the adult disease, and it is presumed that the pathogenesis of jSSc is similar to the adult form.

The pathologic changes in systemic sclerosis encompass a spectrum reflecting variable stages of development and progression of three major processes in the affected tissues: (1) severe tissue fibrosis with exaggerated deposition of collagen and connective tissue components in the extracellular matrix; (2) chronic inflammation, occurring predominantly in the early stages of disease and characterized by infiltration with mononuclear cells; (3) microvascular disease, characterized by intimal proliferation and concentric subendothelial deposition of collagen and mucinous material and narrowing and thrombosis of the vessel lumen. The theories, which try to explain the pathogenesis of SSc, must consider the three main components of the disease (Jimenez and Derk, 2004) and the immunological abnormalities (Senecal et al., 2005). As in other autoimmune diseases, an activation of the immune system from an unknown trigger/antigen occurs in a presumably genetically predisposed host, followed by a cascade of autoimmune phenomenon, which is partially reflected by the measurable autoantibodies (Senecal et al., 2005). One of the main options for the primary trigger point of the disease process is the activation of the endothelial cells; this is currently considered the prime mechanism of the disease. Other theories point to the persistence of maternal microchimeric cells (Jimenez and Aetlett, 2004), which persist into adulthood. This theory would explain the similarities to graft-versus-host disease (GVHD). Environmental and genetic factors play an important role too, and this is reflected in the high rate of other autoimmune diseases in household contacts and relatives (Jimenez and Aetlett, 2004; Assassi and Mayes, 2003). Interestingly, the frequency of SSc in twins is no different in monozygotic compared to dizygotic twins (Zhou et al., 2005).

5. Clinical manifestations

Regarding distribution of the organ involvement in children with jSSc, the best source is the two existing multinational multicenter surveys of patients with jSSc (Foeldvari et al., 2000; Martini et al., 2006). The pattern of organ involvement is presented in Table 1. In both studies, the participating centers were asked to describe the organ involvement, without requesting a standardized assessment algorithm to define the extent of the organ involvement, which makes the data less sound. A third source of data is a yet unpublished summary of case reports by the author of this chapter, this is presented in Table 1 too, in which

Table 1
Pattern of organ involvement of juvenile systemic sclerosis patients

Organ involvement	Foeldvari et al. (2000) $n = 135$ (%) (Ref 4)	Martini et al. $n = 153$ (%) (Ref 5)	Published case reports (1961–1997) $n = 51$ (%)
Skin	135 (100)	116 (75.8)[a]	51 (100)
Joints	106 (79)	97 (63.5)	23 (45)
GI tract	88 (65)	106 (69)	30 (58)
Only esophagus	63 (47)	47 (31)	17 (33)
Pulmonary	68 (50)	64 (41.8)	27 (53)
Cardiovascular	60 (44)	44 (28.8)	15 (29)
CNS	21 (16)	4 (3)	–
Renal	17 (13)	15 (9.8)	7 (14)
Muscular	13 (10)	37 (24.2)	7 (14)
Raynaud's	97 (72)	128 (83.7)	31 (56)
Calcinosis	36 (27)	28 (18.3)	2 (4)
Sjögren's syndrome	7 (5)	?	3 (6)
CREST	1	?	1 (2)

[a] 75.8% skin induration; 66% sclerodactyly; 44.1% edema.

17 published case reports of jSSc patients in English literature were collected with the prerequisite that sufficient data regarding organ involvement, outcome and demographic data of the patients were present. The pattern of organ involvement and distribution of ethnicity in the latter series were found to be similar when compared to the two above-mentioned surveys: 39 of the 51 patients were female, the mean age at diagnosis was 9.4 years, and the mean follow-up period was 3.25 years. In both surveys the mean age of disease onset was 8.8 years, with the youngest patient having onset at 3 months of age.

In 90% of the patients with jSSc Raynaud phenomenon occurs, and in around 70% of jSSc patients it is the first sign of the disease. Raynaud phenomenon is one of the minor defining criteria of jSSc according to the newly proposed criteria. The classical Raynaud's (Kahaleh, 2004) attack has three phases, the first presents with vasoconstriction, where the finger turns white, then comes bluish discoloration and then with the reperfusion a reddish discoloration occurs. It mostly occurs distally from the proximal interphalangeal joint on the fingers, mostly the thumbs are spared. In the severe course of the attacks, a "rat bite" necrosis/loss of tissue on the fingertips with or without ulceration can occur (Fig. 1). Microvasculature changes of the nailfolds are pathognomic for the secondary

Figure 1. Rat bite necrosis.

Raynaud associated to connective tissue disease (Nigrovic et al., 2003) and some patterns are suggestive of SSc-"Scleroderma-Pattern" (Cutolo et al., 2005). It has to be mentioned that some

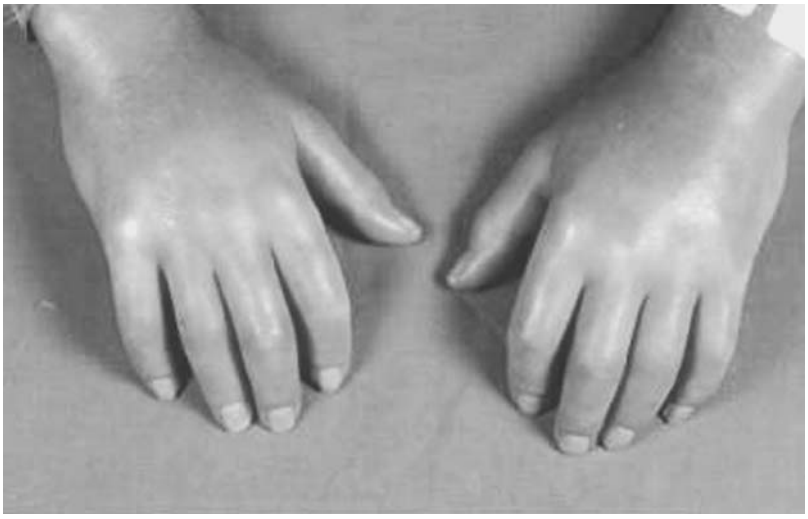

Figure 2. Early edematous phase of the skin.

changes are age dependent and that has to be considered in the interpretation of the changes (Dolezalova et al., 2003; Herrick et al., 2000).

After the occurrence of the Raynaud's phenomenon, a diffuse edematous swelling of the fingers occurs (Fig. 2); this is painless, but it often causes a decreased range of movements in the fingers. The skin involvement spreads from distal to proximal. The dynamic of the progress is individual. In the following months the fibrosis replaces the edematous changes, and causes the typical skin changes of jSSc. These changes lead to loss of the possibility to make skin folds; this can be quantitatively measured with the modified Rodnan skin score (Clements et al., 1995). The fibrosis can lead to loss of the mimic in the face. In the diffuse subtype, the spread of the skin involvement is faster and reaches a plateau mostly after 1–3 years. In some patients extensive subcutaneous calcifications can occur. The subtype of skin involvement was not assessed in the first study (Foeldvari et al., 2000), but in the study by Martini et al. (2006), 138 of the 153 patients had a diffuse pattern of skin involvement. In the first survey only one patient with CREST syndrome was reported, while in the second survey no CREST syndrome was reported. This pattern of distribution of the subsets between diffuse and limited involvement differs from the pattern of distribution in adult SSc patients.

Musculoskeletal involvement is often secondary to the skin involvement. Joint swelling is a rare presentation of the disease, but joint contractures caused by the fibrosis of the skin, are described in 79% of the cases. Subcutaneous calcifications can also lead to joint contractures. The so-called tendon friction rub is a hallmark of SSc; it can be felt during physical examination and eventually even heard. Myopathy can occur in 10% of the patients; it is caused by fibrosis on the muscular tissue or through secondary muscle atrophy or microvascular changes.

According to the current concept cardiac and pulmonary involvements are not viewed as separate organ involvements, but considered as one complex of organ involvement, where changes in one interfere with changes in the other. Cardiopulmonary involvement occurs in around 50% of the patients, and since the renal crisis is a treatable condition, this is the organ involvement-complex with the highest mortality. It can occur before the occurrence of the skin involvement. The two typical manifestations are pulmonary interstitial fibrosis and pulmonary hypertension. The interstitial fibrosis (Highland and Silver, 2005) (Fig. 3) occurs early in the diffuse subtype. The first clinical symptoms occur late in the disease course and are dyspnoea, fatigue and dry cough. To prevent the long-term deleterious effects of the progressive

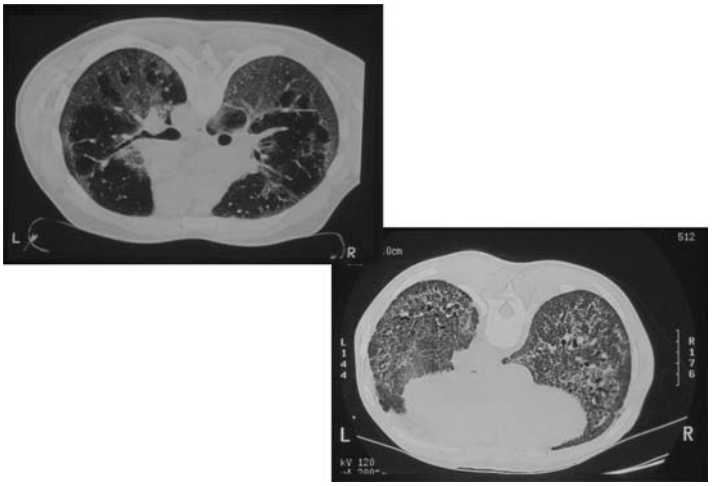

Figure 3. High Resolution Computer Tomography of the lungs, showing honeycombing and ground-glass appearance.

interstitial fibrosis, it is important to make the diagnosis early in the disease course. The interstitial fibrosis leads to increased pulmonary pressure too and this leads to secondary right heart changes.

The other typical complication is pulmonary hypertension, which is a hallmark of the limited subtype and occurs mostly later in the disease course. It is defined as a mean pulmonary artery pressure >25 mmHg at rest or >30 mmHg during exercise, with normal pulmonary artery edge wedge pressure, i.e. ≤ 15 mmHg, and an increased pulmonary vascular resistance index ≥ 3 Wood units $\times$ m^2 (Rosenzweig et al., 2004). It is caused by the imbalance between vasoconstrictive, thrombogenic, mitogenic and proinflammatory factors as opposed to anticoagulant, anti-mitotic and vasodilating mechanism, thus leading to endothelial dysfunction. Regarding the prevalence of this complication in the pediatric population there is currently no existing data, but the limited subtype represents just around 10% of the patients (Martini et al., 2006). The pulmonary hypertension leads to an elevated right ventricular systolic pressure including a loud single P2, murmur of tricuspid insufficiency and a murmur of pulmonary insufficiency; in addition there may be an S3 or S4 right ventricular gallop.

A myocardial dysfunction (Ferri et al., 2005) can also occur; it is often not recognized, and decreases myocardial contractility (Meune et al., 2004, 2005). In 10% of the cases, asymptomatic pericardial effusion can occur as well. Cardiac arrhythmia may also occur.

The gastrointestinal system is the third most commonly involved organ system. In 48% of the pediatric patients it is represented by involvement of the esophagus with disturbance of the esophageal motility (Roberts et al., 2006) (Fig. 4), often associated with gastro-esophageal reflux. In 17% of the patients an involvement of the distal part of the gastrointestinal system occurs with associated decreased motility, malabsorption, intestinal pseudo-obstruction, and in severe cases with pneumatosis intestinalis.

Only 10% of the pediatric cases have renal involvement. The renal crisis (Rhew and Barr, 2004), the main presentation of renal involvement, is characterized by a sudden onset of high blood pressures; 90% of the patients have blood pressure levels above 150/90 mmHg, and 30% have diastolic recordings >120 mmHg and/or a rapidly progressive oliguric renal failure during the course of SSc. It is a better treatable condition since the introduction of the angiotensin converting enzyme inhibitors. It mostly occurs in the first 5 years of the disease.

Sjögren's syndrome occurs only in 4% of the pediatric cases, it is often under-recognized (Heijstek et al., 2005; Houghton et al., 2005). The patients feel as if they have "sand" in their

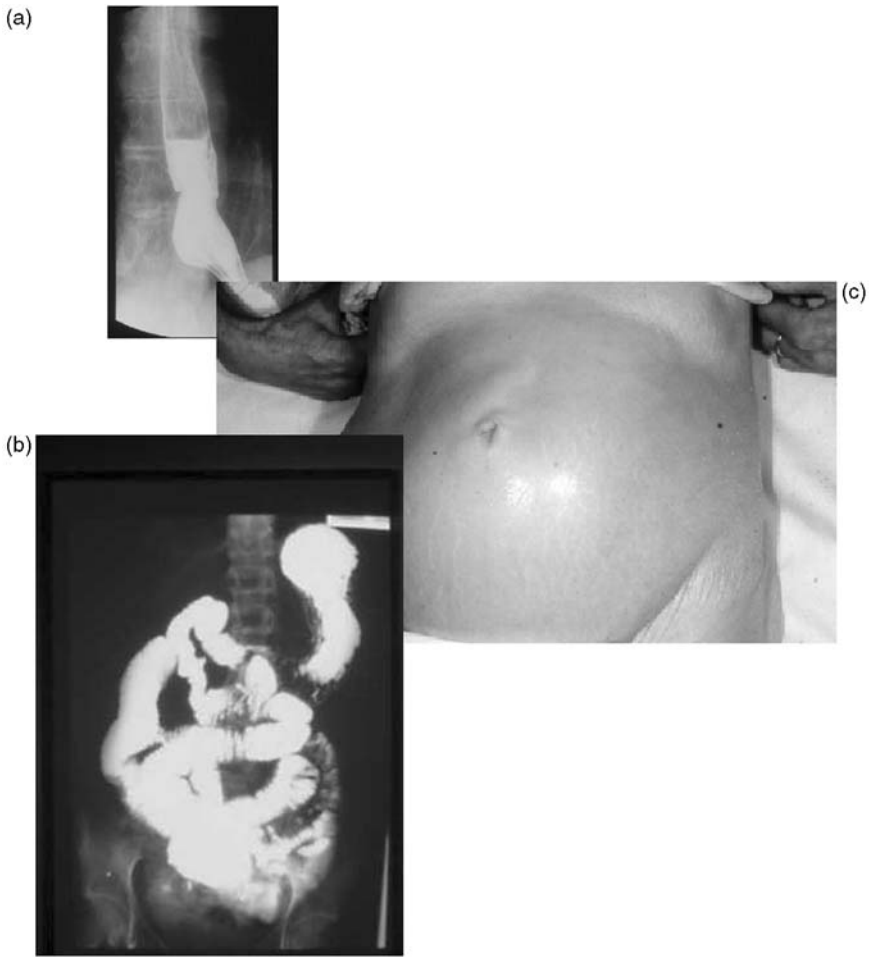

Figure 4. Gastrointestinal involvement with (a) dilated esophagus and (b) colon (barium swallow). (c) The dilated colon causes bloated abdomen.

eyes, need to drink a lot of fluid to be able to swallow, and have the feeling of dryness in the mouth. It presents as recurrent swelling of the parotids. Sjögren's syndrome as a secondary phenomenon to SSc is characterized by fibrosis of the parotid and lacrimal glands, and the dominating picture is not the lymphocitic infiltration as in the classical Sjögren's syndrome.

Surprisingly in one of the cohorts (Foeldvari et al., 2000), 14% of the patients had an involvement of the central nervous system judged by the physician who filled out the survey. In some of these cases a vasculitis of the central nervous system was described.

As for laboratory values, erythrocyte sedimentation rate is mostly in the normal range. An increased level of gamma globulins is observed. In the case of increased vasculitic activity the Factor VIII related antigen could be elevated—120 of 150 patients were antinuclear antibodies (ANA) positive, and 51 of the 120 ANA positive patients were ENA positive (Zulian et al., 2005). In addition, 36 of the 106 tested patients were anti-Scl 70 positive (Martini et al., 2006).

Anticentromere antibodies (Cepeda and Reveille, 2004) are specific for the limited subtype of the disease, which is rarely observed in the pediatric population. Anticardiolipin antibodies occur in

one-third of the patients, but the clinical relevance of this finding is still unclear. A new parameter is emerging, which should correlate with the degree of pulmonary hypertension, this is the brain natriuretic peptide (McLaughlin et al., 2004; Nasser et al., 2005). Another interesting marker is endothelin-1, which correlates well with pulmonary hypertension, but it is difficult to measure.

Mortality was relatively low in the cohort of 135 jSSc patients, only 8 of the 135 patients died (Foeldvari et al., 2000). These patients died after a mean disease duration of 24 months (12–96 months). The patients with fatal outcome had a higher rate of pulmonary (75%/49%), cardiovascular (100%/41%), renal (50%/10%) and central nervous system (38%/14%) involvement when compared to patients with a non-fatal outcome. In the case series, 12 of the 53 patients died. In this collection of cases, the mean duration from disease onset to death was 22.5 months (4–120 months) showing a similar outcome when compared to the survey. The patients with fatal outcome also showed a higher proportion of pulmonary (75%/46%), cardiovascular (75%/15%) and renal (42%/5%) involvement as well as Raynaud's syndrome (83%/54%) when compared to the non-fatal group. If the data regarding mortality are summarized, it can be revealed that most patients died in the first 4 years of their disease, and 12 of the 20 deaths occurred even within the first 24 months. In the other cohort (Martini et al., 2006) the outcome of 127 of the 153 patients was known, with 15 patients (11.8%) deceased, 10 of them for cardiac failure. Death occurred at a mean of 4.6 years after disease onset (range 0.3–18.8 years).

6. Diagnostic investigations

The diagnosis of jSSc is primarily clinical. To reach the diagnosis it is important to carefully examine the patients and to ascertain a good medical history. There are specific examination methods to evaluate the single organ involvements (Ong et al., 2005).

6.1. Radiological

6.1.1. Cardio-pulmonary involvement

The gold standard to evaluate the pulmonary fibrosis is the high resolution CT (Seely et al., 1998), where even scoring method exists for the radiological changes.

To evaluate pulmonary hypertension, cardiac echography is a screening tool; and to define patients with pulmonary hypertension, before start specific treatment (antiendothelinantagonist, phosphodiesterase inhibitor) for this complication, right-heart catheterization is still needed (Rosenzweig et al., 2004).

6.1.2. Gastrointestinal involvement

Gastrointestinal involvement frequently causes esophageal dysmotility, which can be visualized on a barium swallow or with scintigraphy. The distal changes on the gastrointestinal system are visualized with barium swallow as with gastroscopy and colonoscopy (Jaovisidha et al., 2005). Abdominal ultrasonography is a helpful noninvasive method to gain some information on gastrointestinal involvement.

6.1.3. Renal involvement

Abdominal ultrasound with Doppler can visualize the renal blood flow.

6.2. Functional

6.2.1. Raynaud's phenomenon

Nailfold capillaroscopy with an othoscope can be done in every medical office, a more sophisticated method is to examine the changes with a cold light microscope, and eventually with the video microscopy, with qualitative and quantitative evaluation of the pattern of the capillary nailfolds changes (Cutolo et al., 2005). The changes are age specific (Dolezalova et al., 2003; Herrick et al., 2000). Thermography is a fancy method to demonstrate the vasoconstriction after cold stimulation, but it is not routinely used in the clinical practice (Schuhfried et al., 2000; Caramaschi et al., 2006).

6.2.2. Skin

The Modified Rodnan Skin Score (MRSS) is the method to evaluate the skin thickening (not the tethering), it has a significant intra-observer variation (Clements et al., 1995). The skin thickening is scored from 0–3, with 3 as the highest score. It evaluates 17 body areas. A current study, which evaluated the applicability of this method in healthy children, suggested some modification of the scoring, when applied to children (Foeldvari and Wierk, 2006).

6.2.3. Musculoskeletal involvement

The evaluation of the swollen and limited joints is part of the clinical examination, as the evaluation of the presence of the tendon friction rub. To assess the muscle strength the Childhood Myositis Assessment Scale (CMAS) (Huber et al., 2004) is available, and has been validated for dermatomyositis.

6.2.4. Cardiopulmonary involvement

A noninvasive method to evaluate the cardiopulmonary fitness (Garofano and Barst, 1999) of the patients is the 6-min walk test, which has been evaluated in children with arthritis (Lelieveld et al., 2005) and in a small healthy cohort (Li et al., 2005). There is more experience with this evaluation in children with primary pulmonary hypertension, where the decreased mobility caused by the joint contractures and muscle weakness as a confounder does not exist.

The pulmonary function tests with the measurement of the obstructive and restrictive parameters and including the carbon monoxide diffusion capacity, which is especially sensitive for interstitial changes, are useful noninvasive methods for the evaluation of pulmonary involvement.

The bronchoalveolar lavage is used routinely in adults for the assessment of the inflammatory activity, with 3–4% polynucleates or any eosinophils defining the presence of alveolitis. At the present time, pediatricians should apply this method if the changes on HRCT do not clearly differentiate between infection and disease activity (agreement of the Juvenile Inceptions Cohort working group).

6.2.5. Renal involvement

Regular assessment of blood pressure, body weight and serum creatinine is the best screening tool for the renal involvement.

6.3. Biochemistry/serology/immunology

Laboratory tests can help to make the diagnosis, but not all patients have specific laboratory changes to support it. Erythrocyte sedimentation rate is mostly normal. The immunoglobulins may be elevated. In the case of active vasculitis Factor VIII antigen level is elevated. It is important to determine if the patient is ANA positive as well as anti-Scl-70 and anti-centromere antibody positive (Cepeda and Reveille, 2004), since the specific antibodies correlate with the subtype of jSSc. Anticardiolipin antibodies can be positive in 30% of the cases.

6.4. Evaluation of the severity of the disease

There is no validated measure to grade the severity of jSSc. There are validated measures for adults with SSc—the Medsger Disease Severity Scale (Medsger et al., 1999), which can be helpful to get a feeling of disease severity and the Disease Activity Criteria (Valentini et al., 2003a, b). Recently the evaluation of the quality of life is gaining importance to judge the severity of the disease (Johnson et al., 2005); for the pediatric population, the Child Health Questionnaire can be helpful. For the functional assessment, the disability score of the Child Health Assessment Questionnaire can be used, even though it was not specifically designed for jSSc. A special interest group at the OMERACT is in the process of developing measures of response to therapy (Furst et al., 2005).

7. Differential diagnosis

There is a large list of diseases, which can have components of systemic sclerosis. One, which can resemble SSc is sclerosis, which is a progressively

indurated edema on the neck, shoulder girdle, proximal parts of the extremities and face; the induration regress over 12–18 months, but unlike SSc the hands are not involved. Scleromyxedema is another SSc-like condition, characterized by aggregated lychenoid papules that form confluent plaques causing extensive thickening and hardening of the skin with accentuation of the skin folds. It involves the upper extremities, neck, upper trunk, and face, becoming progressively generalized. The main difference with SSc is that in this disorder the skin is not bound and tight to the underlying tissue. Some endocrine disorders such as hypothyroidism and juvenile insulin dependent diabetes and some metabolic disorders like phenylketonuria and porpyhria cutanea tarda can cause scleroderma-like changes. Rare disorders like Werner's syndrome and progeria, restrictive dermatopathy, congenital fascial dystrophy (''stiff skin syndrome'') resemble SSc. Pansclerotic morphea or generalized morphea, which is a subtype of localized scleroderma, can have a similar presentation to SSc. Patients after bone marrow transplantation can present GVHD, where the late changes are scleroderma-like, these patients show joint contractures in 60% of the cases, and some of them Sjögren's syndrome as well.

8. Treatment

There are unfortunately no therapeutic options that heal the disease. All controlled studies were conducted in adult patients. Treatment can be differentiated between immunosuppressive therapy, which aims to control and stop the disease globally, and supportive/palliative treatment, which aims to help for specific problems. Some therapies have global as well as organ-specific effects.

Regarding immunosuppressive therapy, there are not many controlled prospective studies. One of the studies demonstrated the ineffectiveness of D-Penicillamine (Clements et al., 1994) (evidence grade I). A recent controlled study could demonstrate the effectiveness of low-dose cyclophosphamide in early diffuse SSc over 12 months (Valentini et al., 2006) (evidence grade II). Several retrospective studies support the evidence for the effectiveness of cyclophosphamide on pulmonary interstitial disease (Pakas et al., 2002; Giacomelli et al., 2002) (evidence grade III). There is not sufficient data to judge if daily oral or pulse therapy is more effective. In a small pediatric cohort parenteral methotrexate showed a good efficacy (Foeldvari and Lehman, 1993) (evidence grade III). There is an impression that all immunosuppressive treatments are more effective, if they are started as early as possible in the disease, before real organ damage occurs. As a rescue therapy, autologous bone marrow transplantation seems to be successful, and has already been applied in some pediatric cases (Huber et al., 2004; Garofano and Barst, 1999; Farge et al., 2004; Martini et al., 1999) (evidence grade IIb, evidence grade IV).

In the treatment of pulmonary hypertension (Ong et al., 2005), a significant positive development occurred in the last years, owing to the availability of several new effective drugs (Humbert et al., 2004; Rashid and Ivy, 2005) such as the nonselective endothelin antagonist (Bosentan) (evidence grade I), the selective endothelin antagonist (Sitaxsentan) (evidence grade I), prostacyclines administered subcutaneously (Trepostinil) (evidence grade I) or intravenously (Epoprostenol) (evidence grade I) and a phosphodiesterase 5 inhibitor (Sildenafil) (evidence grade I). These medications are also effective to treat severe Raynaud's (Kahaleh, 2004; Fries et al., 2005; Milio et al., 2006) (evidence grade I), and small pediatric observational studies exist for severe Raynaud's and for pulmonary hypertension (Zulian et al., 2004; Barst et al., 2003). Calcium channel blockers can help in mild forms of Raynaud's syndrome, but nifedipine facilitates the gastroesophageal reflux. An important issue is to avoid cold exposure. Low dose aspirin (≤ 2 mg/kg body weight/day) helps protect against microthrombi in the small vessels in the digits. In the case of pulmonary hypertension, a prophylactic treatment with warfarin can help to prevent pulmonary thrombosis. In the case of arthritis a treatment with a nonsteroidal anti-inflammatory drug, like naproxen, can be helpful. Omeprazol is needed when gastroesophageal reflux occurs. To increase the motility of the gastrointestinal system (Ong et al., 2005), erythromycin,

cisapride or octreotide are suggested. Against constipation, a fiber-rich diet is helpful. The angiotensin-converting enzyme inhibitors are playing a primary role in the case of renal crises: an addition of angiotensin receptor blockers may have an additive effect (Rhew and Barr, 2004; Ong et al., 2005), while some patients still need hemodialysis in the acute phase.

Physiotherapy plays an important role to decrease joint contracture, to keep up stamina. Occupational therapy support can help to handle the daily problems of life caused by the disease.

Key points

- Juvenile systemic sclerosis (jSSc) is a rare autoimmune disease of childhood, with a progressive course, and with a potentially fatal outcome. We have a new proposed classification system for jSSc, which will hopefully help to make the diagnosis earlier in the disease course.
- The clinical presentation of jSSc differs from the adult disease; limited subtype and CREST syndrome are rare. It is important to evaluate the patients regularly for internal organ involvement, in order to introduce the therapy as early as possible.
- There is no causal therapy for jSSc, but there is a large progress in the treatment of pulmonary hypertension. A medication to control the disease globally is not yet available: cyclophosphamide seems to be partially effective and autologous bone marrow transplantation seems to offer an effective rescue, if it is done before significant organ damage occurrs.
- The survival of jSSc patients after 5 years (90–95%) is significantly better than for adult patients.

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Handbook of Systemic Autoimmune Diseases, Volume 6
Pediatrics in Systemic Autoimmune Diseases
Rolando Cimaz and Thomas Lehman, editors

CHAPTER 10

Episodic Autoinflammatory Disorders in Children

Loes M. Kuijk[a], Hal M. Hoffman[b], Bénédicte Neven[c], Joost Frenkel[d,*]

[a]*Department of Paediatric Immunology, University Medical Centre Utrecht, Utrecht, The Netherlands*
[b]*Division of Rheumatology, Allergy, and Immunology, University of California, San Diego School of Medicine, San Diego, CA, USA*
[c]*INSERM U429, Department of Paediatric hemato-immunology and rheumatology, Hopital Necker-Enfants Malades, Paris, France*
[d]*Department of Paediatrics, Division of Rheumatology, Allergy, Immunology, University Medical Centre Utrecht, Utrecht, The Netherlands*

1. Introduction

The autoinflammatory diseases are a newly recognized and expanding class of inflammatory disorders that share many features with autoimmune diseases (Stojanov and Kastner, 2005). They differ significantly, however, in that autoinflammatory syndromes are characterized by an absence, not only of pathogens, but also of high titre autoantibodies and pathogenic autoreactive T cells (McDermott and Aksentijevich, 2002).

Chronic autoinflammatory diseases in childhood include systemic onset juvenile idiopathic arthritis, sarcoidosis and Blau syndrome, which fall beyond the scope of this chapter. The intermittent autoinflammatory disorders, known as periodic fever syndromes, lead to recurrent episodes of fever alternating with more or less prolonged periods of disease remission. The fever episodes are usually accompanied by additional systemic and localized inflammatory symptoms involving joints, skin, eyes or abdomen (Drenth and van der Meer, 2001).

Each of these disorders has unique symptoms, as well as a unique pathophysiology and treatment. Many are inherited, which has allowed for determination of the responsible genes. In the last decade, an increasing number of patients has been appropriately recognized, diagnosed and treated due to advances in the understanding of the clinical characteristics and molecular basis of these diseases. In this chapter the clinical presentation and recent progress in elucidating the underlying pathophysiology will be described for each of these disorders (Brydges and Kastner, 2006). The chapter will be concluded by a paragraph on diagnosis.

2. Familial Mediterranean Fever (FMF)

2.1. Prevalence/epidemiology

Familial Mediterranean Fever (FMF; MIM# 249100) is the most prevalent of the hereditary autoinflammatory diseases, probably affecting more than 100,000 patients worldwide. It is an autosomal recessive disease, affecting mostly people from the Mediterranean area, including Armenians, Arabs, Turks and Sephardic Jews. By migration it has now also spread to Northern and Western Europe, Australia and the Americas.

*Corresponding author.
Tel.: 0031-30-250-4001; Fax: 0031-30-250-5349
E-mail address: j.frenkel@umcutrecht.nl (J. Frenkel).

DOI: 10.1016/S1571-5078(07)06014-X

2.2. Etiology/pathogenesis

The gene affected in FMF, *MEFV*, encodes the protein pyrin or marenostrin (The French FMF Consortium, 1997; The International FMF Consortium, 1997). Since its discovery in 1997, more than 100 exon mutations have been described for the *MEFV* gene (http://fmf.igh.cnrs.fr/infevers/). The most common mutations: M680I, M694V, M694I and V726A (Touitou, 2001) are situated within exon 10, which encodes the C-terminal B30.2 domain of the protein. The functional role of this domain is unknown. The protein further consists of a B-Box-type zinc finger, a coiled-coil domain and an N-terminal PYRIN domain. Pyrin is mainly expressed as a cytoplasmic protein in mature neutrophils and monocytes (Tidow et al., 2000), and it associates with actin (Mansfield et al., 2001). The exact role of pyrin in the clinical manifestations of FMF has not been elucidated thus far, but the N-terminal PYRIN domain was shown to interact with a protein called apoptosis-associated speck-like protein containing a CARD (ASC), whereas the carboxyterminal B30.2 can bind to caspase-1. This interaction places pyrin upstream in a pathway regulating caspase-1 and IL-1β processing, linking it to inflammation (Chae et al., 2003, 2006; Richards et al., 2001).

2.3. Clinical manifestations

Most patients suffer from recurrent fever attacks, with acute monoarthritis and/or serositis, affecting the peritoneum, pleura, pericardium or scrotum. Some patients display an erysipelas-like rash (Fig. 1) and a few develop chronic erosive arthritis (Grateau, 2004; Majeed et al., 1999; Samuels et al., 1998; Sohar et al., 1967; Tunca et al., 2005). However, in the rare case, recurrent abdominal pain during childhood can be the only manifestation of FMF (Brik et al., 2001).

Disease onset is usually in childhood, with 75–89% of patients having their first attack before the age of 20 years (Barakat et al., 1986; Majeed et al., 1999). Frequency of attacks can vary from several times per week to once every few months or even years. The attacks usually last 1–3 days.

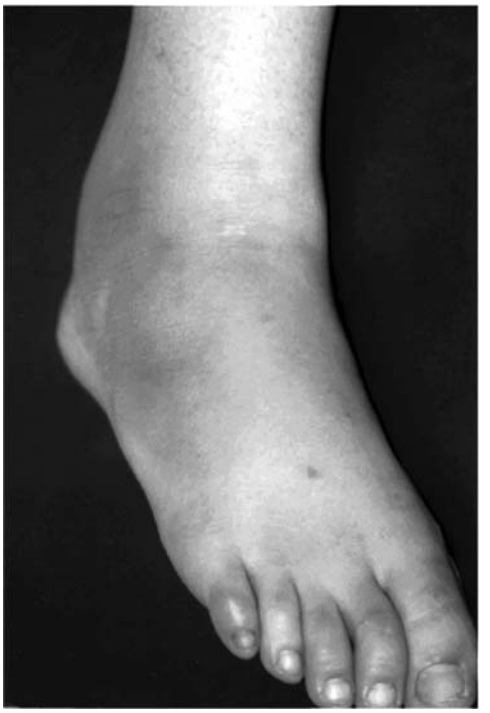

Figure 1. Characteristic erysipelas-like erythema in FMF. (See Colour Plate Section.)

2.4. Diagnostic investigations

During fever episodes serum markers of acute phase response: serum amyloid A (SAA) protein, C-reactive protein (CRP), complement and plasma fibrinogen are elevated and there is granulocytosis (Livneh and Langevitz, 2000; Schwabe and Peters, 1974; Tunca et al., 1999). Often, erythrocyte sedimentation rate (ESR) is increased. Between attacks patients are well, even though they may continue to have increased acute phase reactants. However, the prolonged elevation of SAA protein predisposes to AA systemic amyloidosis in which SAA deposition occurs in several organs leading to organ failure (de Beer et al., 1982; Gillmore et al., 2001; Sohar et al., 1967).

The diagnosis can be made on clinical grounds (Table 1), provided that the patient is from a population with a high prevalence of FMF (Livneh et al., 1997). The response to colchicine therapy is so characteristic that it is considered a major diagnostic criterion. Genetic testing may support the

Table 1
Diagnostic criteria for FMF in a population with high prevalence of the disease (Livneh et al., 1997)

Tel Hashomer criteria for diagnosis Familial Mediterranean Fever	
Major criteria	Minor criteria
Recurrent fever with arthritis and/or serositis	Recurrent fever attacks
AA-amyloidosis in the absence of a predisposing illness	Erysipela-like erythema
Favourable effect of colchicine	FMF in first degree relatives
Definite diagnosis: two major or one major and two minor criteria	
Probable diagnosis: one major and one minor criteria	

diagnosis, but in up to one-third of patients one or both *MEFV* alleles are normal (Grateau, 2004; Tunca et al., 2005). There are no clinical diagnostic criteria validated for populations with intermediate prevalence (Greeks, Italians, Spanish) and in these, genetic testing might offer an advantage. The value of *MEFV*-testing in populations with a low prevalence of FMF is limited at best (Tchernitchko et al., 2005).

2.5. Treatment

The usual treatment of FMF is colchicine, which prevents inflammatory attacks in ~60% of the patients and significantly reduces the number of attacks in another 20–30% (Ben-Chetrit and Levy, 1998; Goldfinger, 1972). The favourable response to colchicine is very characteristic for FMF, so much that it can be used as a diagnostic criterion. Its mode of action in FMF is poorly understood. The usual colchicine dose in young children is 0.5 mg/day, 1 mg/day in children 7–12 years of age and 1.5 mg (rarely 2 mg) in 2–3 doses in patients of 12 years and older. In order to minimize gastro-intestinal side effects, a 50% lower starting dose may be given. For pain relief during attacks nonsteroidal anti-inflammatory drugs (NSAIDS) can be used.

Long-term prognosis depends on the development of amyloidosis, which can result in organ damage, notably renal failure. The risk of amyloidosis is variable, depending on ethnic background, sex, *MEFV* mutation, disease modifying genes and especially on where the patient has lived (Touitou et al., 2007). However, even in high-risk populations, colchicine treatment reduced the incidence from over 60% to less than 5% (Grateau, 2000).

3. TNF-Receptor Associated Periodic Syndrome (TRAPS)

3.1. Prevalence/epidemiology

TNF-receptor associated periodic syndrome (TRAPS; MIM#142680) was first reported as Familial Hibernian Fever in 1982 in a large family of Irish and Scottish descent (Williamson et al., 1982), but it has now been described in more than 20 families from a wide variety of ethnic groups (Aksentijevich et al., 2001; Hull et al., 2002). Although more than 100 patients with TRAPS have been described, the exact prevalence is unknown. TRAPS has an autosomal dominant inheritance mode. The mutations described to date have variable penetrance. Mutations with a low penetrance may lead to rather atypical inflammatory disorders, not diagnosed as TRAPS (Aganna et al., 2001; Aksentijevich et al., 2001).

3.2. Etiology/pathogenesis

TRAPS results from mutations in the *TNFRSF1A* gene (McDermott et al., 1999). It encodes TNFRSF1A, the 55 kDa receptor for tumour necrosis factor (TNF), also termed CD120a. The *TNFRSF1A* gene consists of 10 exons. Most mutations are present in exons 2, 3 and 4 (http://fmf.igh.cnrs.fr/infevers/), which encode the extracellular cysteine-rich TNFR domains of the protein, thereby disrupting the tertiary structure. No mutations have been described for the intracellular domains. The mutations found in the extracellular TNFR domains can cause an impaired receptor shedding, leading to increased or prolonged signalling through the TNF receptor and to a reduced

generation of soluble TNF-receptor (sTNFRSF1A), the natural antagonist of TNF-α (McDermott et al., 1999). However, not all patients show defective receptor shedding suggesting that there are additional mechanisms behind the fever attacks in TRAPS, such as altered receptor trafficking or impaired neutrophil apoptosis (D'Osualdo et al., 2006; Siebert et al., 2005; Todd et al., 2004; Yousaf et al., 2005).

3.3. Clinical manifestations

The clinical presentation of TRAPS varies widely. The age of onset is between a few weeks and 53 years of age, but most patients have their first symptoms in childhood (Hull et al., 2002). Like FMF, TRAPS is characterized by periodic fever attacks, but they last days to weeks and recur two to six times a year. There is, however, a large variation between individuals. Fever attacks may start unprovoked, but can also be set off by emotional stress, minor infections or vigorous exercise.

Clinical features during attacks include conjunctivitis, pericarditis, migratory rash (Fig. 2), prominent myalgias, monoarthritis, mostly of the lower limbs, abdominal pain and erythematous swelling of eyelids, limbs, fingers and/or ears. The abdominal pain may be due to serositis, which can also involve other serosal surfaces, including the testicular tunica vaginalis. Focal neurological signs are a rare feature of the disease (Stojanov and McDermott, 2005; Minden et al., 2004).

3.4. Diagnostic investigations

During episodes of fever there is a clear acute phase response: leukocytosis, elevation of CRP, SAA and ESR (Stojanov and McDermott, 2005) and even in symptom-free intervals such inflammatory responses may be detected. Between attacks, many patients have reduced serum levels of sTNFRSF1A (McDermott et al., 1999), indicative of impaired receptor trafficking or shedding. However, diagnosis depends on the identification of *TNFRSF1A* mutations on DNA-analysis.

3.5. Treatment

TRAPS can be treated with NSAIDs and glucocorticoids to alleviate the symptoms, but these drugs do not affect the frequency of attacks, or the development of amyloidosis. Clinical trials with etanercept, a fusion protein of TNFRSF1B with the Fc portion of human IgG1, have been more successful. Frequency, duration and/or severity of attacks were reduced in the majority of patients (Hull et al., 2002). The use of etanercept has even been shown to reverse a case of amyloidosis in one TRAPS patient (Drewe et al., 2004). The usual dose

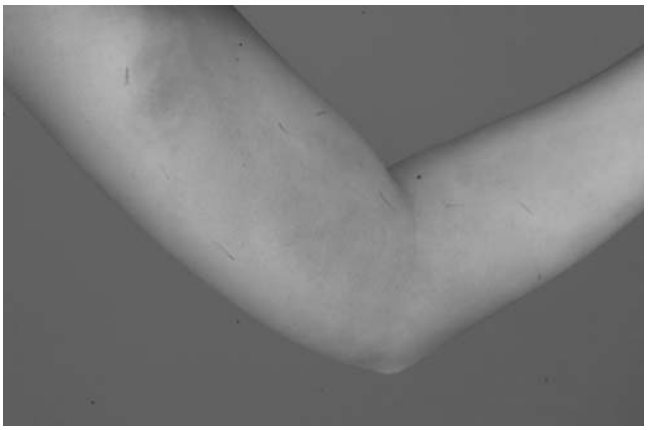

Figure 2. Migratory rash in TRAPS patient. (Courtesy of Dr. E. Hoppenreys.) (See Colour Plate Section.)

of etanercept is 0.4 mg/kg (maximum 25 mg) twice weekly.

Development of amyloidosis is the main determinant for prognosis. Remarkably, this risk is associated with the type of mutation: up to 24% of patients with mutations affecting cysteine residues develop amyloidosis, versus 2% of patients with noncysteine mutations (Hull et al., 2002).

4. Hyper IgD Syndrome (HIDS)

4.1. Prevalence/epidemiology

The Hyper IgD Syndrome (HIDS; MIM#260920) is an autosomal recessive disease, mostly affecting people from Caucasian origin (van der Meer et al., 1984). It is a rare disorder; the international Hyper IgD syndrome Registry (www.hids.net) currently has clinical data on approximately 200 patients worldwide. The disease is relatively common in the Netherlands, where carrier frequency approaches 1:350 (Houten et al., 2003).

4.2. Etiology/pathogenesis

In 1999, mutations in the gene which codes for mevalonate kinase (*MVK*) were found to be the cause of HIDS (Drenth et al., 1999; Houten et al., 1999). So far, approximately 70 mutations have been described that lead to documented HIDS or to the more severe phenotype of *MVK* deficiency, known as mevalonic aciduria (http://fmf.igh.cnrs.fr/infevers/). Two missense mutations are most prevalent: I268T and V377I, accounting for the vast majority of patients (Cuisset et al., 2001; Houten et al., 2000a,b). Mevalonate kinase (MK) is an enzyme in the cholesterol biosynthesis pathway. Besides cholesterol, this pathway produces a number of other, nonsterol, end products such as farnesyl and geranylgeranyl groups, which can be covalently attached to specific proteins, including proteins of the Ras superfamily. Although patients with HIDS have only 1–7% residual activity of MK (Houten et al., 1999), plasma cholesterol levels in these patients are within the normal range. How the metabolic defect leads to the clinical manifestations of hyper IgD is unclear, but evidence is now emerging that the shortage of specific isoprenylated proteins can induce interleukin-1β-mediated inflammation (Frenkel et al., 2002).

4.3. Clinical manifestations

The recurrent fever attacks that are characteristic of HIDS usually return every 3–6 wk and last for 3–5 days. They are almost always accompanied by painful cervical lymphadenopathy and often by abdominal pain, vomiting and diarrhoea (Drenth et al., 1994; Frenkel et al., 2001). A variety of other symptoms including headache, skin rashes, mucosal ulcers, myalgia and arthralgia may also occur. A profound MK deficiency, known as mevalonic aciduria, can, in addition, be accompanied by developmental delay, dysmorphic features, tapetoretinal degeneration, ataxia, cerebellar atrophy and psychomotor retardation (Figs. 3 and 4) (Balgobind et al., 2005; Hoffmann et al., 1993).

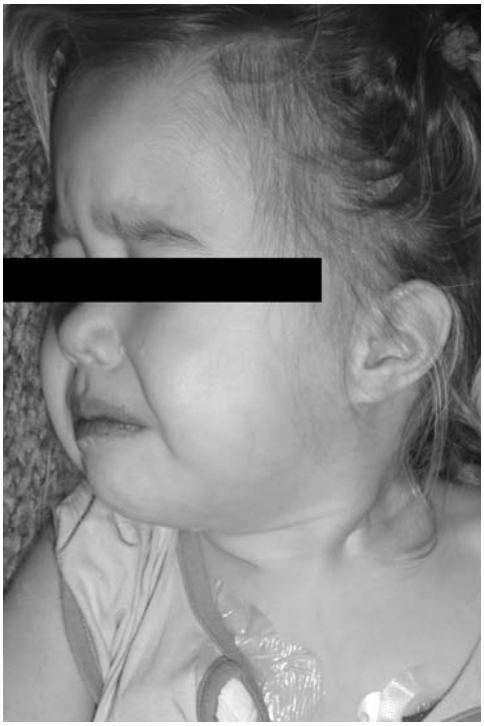

Figure 3. Facial dysmorphia in mevalonate kinase deficiency.

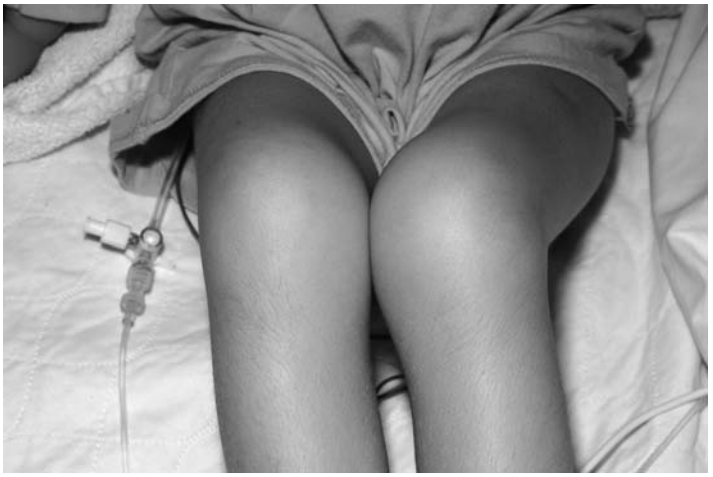

Figure 4. Monoarthritis in mevalonate kinase deficiency.

In reality, a phenotypic continuum exists between these extreme phenotypes (Simon et al., 2004b).

Ninety percent of HIDS patients will experience their first fever attack within the first year of life, but the fever episodes tend to become less frequent and less severe with age. Fever episodes can be provoked by a variety of triggers, including vaccinations, infections or minor trauma, but most often such a trigger cannot be identified (Drenth et al., 1994). When fever has subsided, malaise and arthritis may take days longer to resolve. Between attacks, patients are well and thrive normally.

4.4. Diagnostic investigations

As the name implies, most patients have elevated serum immunoglobulin D levels, but how this relates to the clinical disease is poorly understood. Since some patients with *MVK* mutations have normal levels of IgD it is likely that elevated IgD may be an epiphenomenon. Patients may also have elevated serum IgA (Klasen et al., 2001). Urine mevalonic acid concentrations are consistently raised during fever episodes. In addition, patients exhibit an acute phase response with leukocytosis, high levels of SAA and CRP and the presence of pro-inflammatory cytokines (Drenth et al., 1994, 1995).

4.5. Treatment

Therapy is problematic. Colchicine, thalidomide and immunosuppressive agents seem largely ineffective (Dios Garcia-Diaz and Alvarez-Blanco, 2001; Drenth et al., 1994, 2001). Treatment with simvastatin may induce a modest improvement (Simon et al., 2004a) and there have been case reports on successful treatment with etanercept (Takada et al., 2003). Studies with the recombinant interleukin-1 receptor antagonist, anakinra (Kineret®), are underway and look promising (Bodar et al., 2005). Long-term prognosis of hyper IgD is usually good: amyloidosis occurs in less than 3% of patients and no excess mortality has been reported among the patients currently registered at the HIDS registry.

5. Cryopyrin Associated Periodic Syndromes (CAPS)

5.1. Prevalence/epidemiology

Cryopyrin associated periodic inflammatory diseases include Familial Cold Autoinflammatory Syndrome (FCAS; MIM#120100), Muckle-Wells Syndrome (MWS; MIM#191900) and Neonatal Onset Multisystem Inflammatory Disease

(NOMID; MIM#607115), also known as Chronic Infantile Onset Neurologic Cutaneous Articular (CINCA) Syndrome. They are all dominantly inherited. Previously considered as distinct disorders, they are now thought as a spectrum of one systemic inflammatory disease with varying severity, FCAS being the mildest condition and CINCA/NOMID the most severe. The exact prevalence of these rare autoinflammatory diseases is unknown, but over 200 patients with FCAS live in North America, and more than 20 families with MWS and $\approx$100 patients with CINCA/NOMID have been reported worldwide.

5.2. Etiology/pathogenesis

FCAS, MWS and CINCA/NOMID are all associated with missense mutation of the *CIAS1* gene (Feldmann et al., 2002; Hoffman et al., 2001a). This gene encodes cryopyrin, also known as NALP3, PYPAF1, CATERPILLER1.1 or NLRP3. Its expression is limited to immune cells and chondrocytes. Cryopyrin contains an N-terminal PYRIN domain, a central NACHT domain with a nucleotide-binding site and a carboxyterminal leucine-rich repeat. The function of this protein is incompletely understood. Probably, it plays a central role in control of inflammation, cytokine processing and cell death (Aganna et al., 2002; Tschopp et al., 2003). After activation, cryopyrin interacts with other molecules to form a macrocomplex called inflammasome. This interaction mediates procaspase-1 activation, thus caspase-1 activates pro-IL-1β in its pro-inflammatory active form, IL-1β. It has also been suggested that the interaction of cryopyrin with ASC mediates activation of NF-κB (Manji et al., 2002).

All but one of the mutations identified to date in FCAS, MWS and CINCA/NOMID are missense mutations. They are almost all localized in exon 3, irrespective of disease severity (Aksentijevich et al., 2002; Dode et al., 2002; Hoffman et al., 2001b; Neven et al., 2004). This exon encodes for the NACHT domain and its flanking protein regions. Rare mutations have been described in the leucine-rich repeat region (Frenkel et al., 2004a). Mutations are believed to confer a gain of function resulting in increased cytokine-mediated inflammation (Agostini et al., 2004). There appears to be some genotype-phenotype correlation (Neven et al., 2004). Only 60% of patients with clinical findings of FCAS, MWS or CINCA/NOMID have mutations in the *CIAS1* gene. This suggests genetic heterogeneity.

5.3. Clinical manifestations

Cryopyrin associated periodic inflammatory syndromes are all characterized by early onset of recurrent episodes of fever with remarkable systemic inflammation, a characteristic nonpruritic urticaria-like skin rash with perivascular polymorphonuclear cells infiltrates in skin biopsy and a broad spectrum of joint manifestations ranging from arthralgia in the mild forms to recurrent arthritis and permanent arthropathies in severe diseases. Sensorineural hearing loss can develop with increasing age in MWS and CINCA/NOMID. Neurological involvement is observed in CINCA/NOMID and is due to chronic aseptic meningitis with neutrophilic granulocytosis in the CSF.

5.4. Familial Cold Autoinflammatory Syndrome (FCAS)

Patients with FCAS, previously known as familial cold urticaria (FCU), experience recurrent episodes of urticaria-like rash, fever and arthralgia precipitated by generalized cold exposure. Additional symptoms suffered during attacks include conjunctivitis, sweating, drowsiness, headache, extreme thirst and nausea. The symptoms usually develop 1–2 h after cold exposure, peak approximately 6–8 h later, and resolve in less than 24 h. Most of the patients describe a correlation between the severity of the crisis and the intensity of cold exposure. Attacks are more frequent in winter, in damp and windy days. Relatively mild exposures such as air-conditioned rooms can precipitate episodes. Many patients have daily rash and fatigue that peak in the evening and resolve by morning, regardless of cold exposure. Disease onset is often

at birth with neonatal rash and 95% of patients experience symptoms by 6 months of age. Amyloidosis is rare in FCAS (Hoffman et al., 2001b).

5.5. Muckle-Wells Syndrome (MWS)

The course of the disease varies from typical recurrent attacks of inflammation very similar to those observed in FCAS but without defined trigger to more permanent symptoms with periods of exacerbation. Attacks may be precipated by cold exposure, but also heat, stress, exercise, tiredness. Fever is not always present. Joint manifestations can be mild with short episodes of arthralgia but recurrent episodes of synovitis affecting predominantly large joints can also be observed. Conjunctivitis is frequently noticed. Sensorineural deafness, one of the hallmark features of MWS, develops in up to two-thirds of patients in late childhood. AA amyloidosis, due to chronic inflammation, is the main complication and develops in adulthood in 20–40% of patients. Focal neurological involvement has not been reported in MWS. Headache and papilledema have been reported in some cases (Hawkins et al., 2004). Mild forms of MWS are close to FCAS and more severe phenotypes overlap with CINCA/NOMID. The age of onset is variable from childhood to adulthood (Muckle and Wells, 1962).

5.6. CINCA/NOMID

CINCA/NOMID is the more severe phenotype in this spectrum of diseases. Urticaria (Fig. 5) is usually present at birth or during the first months of life. Fever is intermittent, can be absent or very mild in some cases. Bone and joint involvement vary in severity. In approximately two-thirds of the patients, joint manifestations are limited to arthralgia or transient nonerosive arthritis during flare-ups. In one third, however, joint abnormalities are severe. The metaphyses and epiphyses of long bones are affected, resulting in marked bony overgrowth, deformity of the joints, chronic pain and loss of function. The knees, ankles, wrists and elbows are most commonly affected in a symmetric pattern. Abnormalities of the CNS are present in almost all patients and are due to chronic aseptic meningitis. Chronic headaches, sometimes with vomiting and papilledema are frequently noted. Spastic diplegia and epilepsia may develop. Progressive cognitive impairment occurs in severely affected patients. Chronic increased intracranial pressure often leads to late closure of the anterior fontanelle, macrocephaly, frontal bossing and saddle back nose. Ocular disease consists of anterior uveitis in half and posterior uveitis in another 20% of affected patients. Optic atrophy can develop. Ocular manifestations can progress to blindness

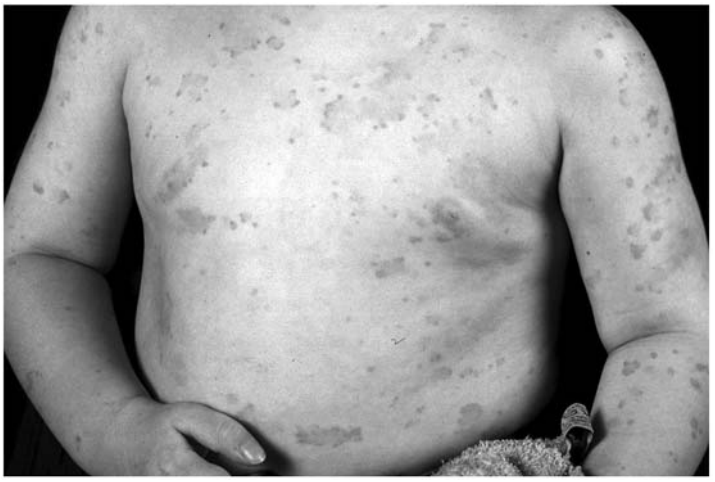

Figure 5. Urticaria-like rash in NOMID patient. (See Colour Plate Section.)

(Dollfus et al., 2000). Perceptive deafness is frequently observed in older patients (Prieur, 2001).

5.7. Diagnostic investigations

Patients suffering from the cryopyrin associated periodic fever syndromes have elevated acute phase reactants and leukocytosis during attacks. In MWS and NOMID patients acute phase reactants may be chronically elevated and anaemia of chronic illness is common. Cerebrospinal fluid examination in NOMID usually reveals a raised opening pressure pleiocytosis and elevation of CSF protein. Radiological manifestations in CINCA/NOMID patients with hypertrophic arthropathies are distinctive with overgrowth and irregular ossification of metaphysis and epiphysis of long bones (Fig. 6).

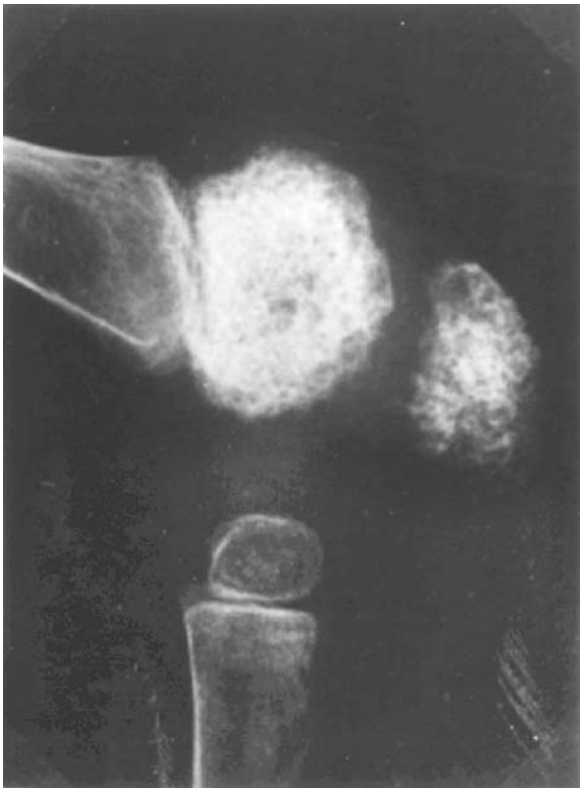

Figure 6. Radiographic appearance of arthropathy in NOMID/CINCA syndrome. (Courtesy of Dr. A.M. Prieur.)

5.8. Treatment

Treatment, until recently, has been limited to avoidance of cold exposure and to nonsteroidal anti-inflammatory medications for FCAS patients, and high dose steroids for more severe FCAS, MWS and NOMID patients. Recently, numerous case reports have demonstrated the IL-1 receptor antagonist, anakinra (Kineret®), to be highly effective in all three diseases (Frenkel et al., 2004b; Hawkins et al., 2004; Hoffman et al., 2004). The usual dose was 1 mg/kg subcutaneously once daily. These observations were confirmed in a large series by Goldbach-Mansky et al. (2006). Drug withdrawal led to prompt relapse in all prospectively studied patients. Therefore, a placebo-controlled trial will not be ethically acceptable. Additional therapies targeting IL-1 are under investigation. Prognosis ranges from excellent for FCAS patients, except in rare instances where amyloidosis develops, to fair in MWS, where the risk of amyloidosis is up to 25–40%, to poor in untreated NOMID patients with severe neurologic disease.

6. Pyogenic sterile Arthritis, Pyoderma gangrenosum, and Acne syndrome (PAPA)

6.1. Prevalence/epidemiology

The PAPA Syndrome (MIM#604416), previously described as the streaking leukocyte factor disease (Jacobs and Goetzl, 1975), was recognized and re-described by Lindor et al. (1997). Families described thus far are of European descent, but the number of documented cases is still very small. PAPA syndrome is an autosomal dominant disease, with a presumed complete penetrance.

6.2. Etiology/pathogenesis

The affected gene, *PSTPIP1*, encodes CD2 antigen-binding protein 1 (CD2BP1), also known as proline/serine/threonine phosphatase-interacting protein 1, PSTPIP1 (Wise et al., 2002; Yeon et al., 2000). This gene contains 15 exons, with only two

mutations described thus far. The function of PSTPIP1 is still unclear, but it has been shown to bind to pyrin, the protein that is mutated in FMF, suggesting it may also be involved in IL-1β regulation (Shoham et al., 2003).

6.3. Clinical manifestations

The PAPA syndrome is characterized by recurrent inflammation of joints, skin and muscle. During episodes of arthritis patients may present with fever. Ulcerative lesions (pyoderma gangrenosum) occur in the skin, often on the lower limbs or at sites of minor trauma or surgery. Patients also suffer from severe cystic acne starting in adolescence and persisting into adulthood, and from destructive arthritis (Lindor et al., 1997; Wise et al., 2000, 2002). Onset of the disease is in early childhood, but additional symptoms, like insulin-dependent diabetes mellitus, can develop at older ages.

6.4. Diagnostic investigations

During episodes patients may have elevated white blood cell counts and ESR (Cortis et al., 2004; Wise et al., 2000). Biopsies and joint aspirates usually show massive neutrophil influx.

6.5. Treatment

Treatment of the PAPA syndrome can consist of isotretinoin, for treatment of acne, usually in combination with steroids. Intra-articular steroids or surgical drainage of infiltrates in joints can be used to relieve severe arthritis. Alternative therapies include anti-TNF-α therapy with either infliximab or etanercept, which proved successful in several patients (Cortis et al., 2004). Recently, several members of one affected kindred were successfully treated with the interleukin-1 receptor antagonist anakinra during attacks (Dierselhuis et al., 2005).

The PAPA syndrome can lead to pronounced disfigurement. In addition, the severe acne and the scarring resulting from it can cause psychological damage like anxiety and depression. Prognosis is mostly determined by the development of diabetes mellitus and/or renal failure (Lindor et al., 1997).

7. Periodic Fever with Aphthous stomatitis, Pharyngitis and Adenitis (PFAPA)

7.1. Prevalence/epidemiology

Most children who present with recurrent fevers to paediatricians and specialists do not have one of the known hereditary autoinflammatory diseases discussed previously. A significant number of these children can be assigned a diagnosis of Periodic Fever with Aphthous stomatitis, Pharyngitis and Adenitis (PFAPA), an autoinflammatory disease characterized by recurrent episodes of fever for which no genetic cause has been identified thus far. The PFAPA syndrome, also known as Marshall's syndrome, was described on 1987 and is a relatively benign and common condition that has been reported in several areas of the world (Berlucchi et al., 2003).

7.2. Etiology/pathogenesis

The pathophysiology is unknown.

7.3. Clinical manifestations

The PFAPA syndrome is usually accompanied by one or more inflammatory findings including pharyngitis, cervical adenitis or adenopathy and aphthous stomatitis. Additional symptoms are similar to those seen in many of the hereditary disorders, including headache, malaise, abdominal pain, arthralgia and myalgia. Onset is usually between 2 and 5 years of age and attacks last between 3 and 6 days. Episodes are often quite predictable occurring every 3–8 wk and are separated by completely asymptomatic periods with normal growth and development. Unlike the hereditary disorders, this condition is self-limited and most children with PFAPA have a complete remission after 2–6 years of symptoms.

Table 2
Characteristics of the autoinflammatory syndromes

	FMF	HIDS	TRAPS	CAPS	PAPA	PFAPA
Inheritance	AR	AR	AD	AD	AD	Unknown
Gene	*MEFV*	*MVK*	*TNFRSF1A*	*CIAS1*	*PTSTPIP1*	
Protein	Pyrin	Mevalonate kinase	TNFRSF1A	Cryopyrin	PTSTPIP1	
Function	Regulation of apoptosis and inflammation	Isoprenoid biosynthesis	TNF-α-receptor	Regulation of apoptosis and inflammation	Regulation of apoptosis and inflammation	
Ethnic background	Armenian, Turkish, Jewish, Arabs	Dutch, French, German among others	Worldwide (more frequent in Scottish/Irish)	Worldwide	Worldwide	Worldwide
Onset	Childhood (>90%)	Infancy	Variable	Neonatal	Variable	2–5 years
Duration of attacks	12–72 h	3–5 days	Days to weeks	<24 h		3–6 days
Symptoms						
Vomiting		+				+
Diarrhoea		+	+			+
Abdominal pain	++	+	++	+/−		+
Peritonitis	++		++	+/−		
Pleuritis	+		++			
Acute scrotum	+		++			
Rash	+ (Erysipela-like, Henoch-Schonlein purpura)	++ (Pleiomorphic)	++ (Migrating erythematous plaques)	++ (Nonpruritic urticaria)	++ (Acne conglobata, pyoderma gangrenosum)	
Aphtosis		+				++
Pharyngitis		+				++
Eye signs			Periorbital oedema, conjunctivitis	Conjunctivitis, uveitis, papillitis		
Sensorineural hearing loss				++		
Joint symptoms	Mainly monoarthritis	Arthralgia, arthritis	Arthralgia	Varying from mild arthralgia to destructive arthropathy large joints	Destructive purulent monoarthritis	Arthralgia (rare)
Headache		+	++	++		+
Muscle aches	+	Rare	++	+		
Lymphadenopathy		++	+	+		++
Splenomegaly	+	+	+	+		
Amyloidosis	+	Rare	+	+		
Suggestive test results	Favourable response to colchicine	Raised serum IgD, IgA, elevated urinary mevalonic acid		CSF pleiocytosis, elevated CSF pressure	Sterile purulent joint aspirate	
Confirmation test	*MEFV* analysis	*MVK* analysis, *MK* activity	*TNFRSF1A* analysis	*CIAS1* analysis	*PTSTPIP1* analysis	

Notes: Symptoms encountered in the respective diseases are marked with +, or if very characteristic for the disorder with ++. AD, autosomal dominant; AR, autosomal recessive.

7.4. Diagnostic investigations

The only laboratory abnormalities are leukocytosis and increased acute phase proteins during attacks, and these abnormalities completely resolve between episodes. Increased serum levels of interferon-γ, TNF-α and IL-6 have been observed with fevers (Thomas et al., 1999). It may be necessary to exclude other periodic fever syndromes, notably MK deficiency, by genetic analysis, before making the diagnosis of PFAPA syndrome.

7.5. Treatment

Symptoms are very sensitive to systemic corticosteroid therapy. Additional reported effective therapies include prophylactic use of cimetidine and

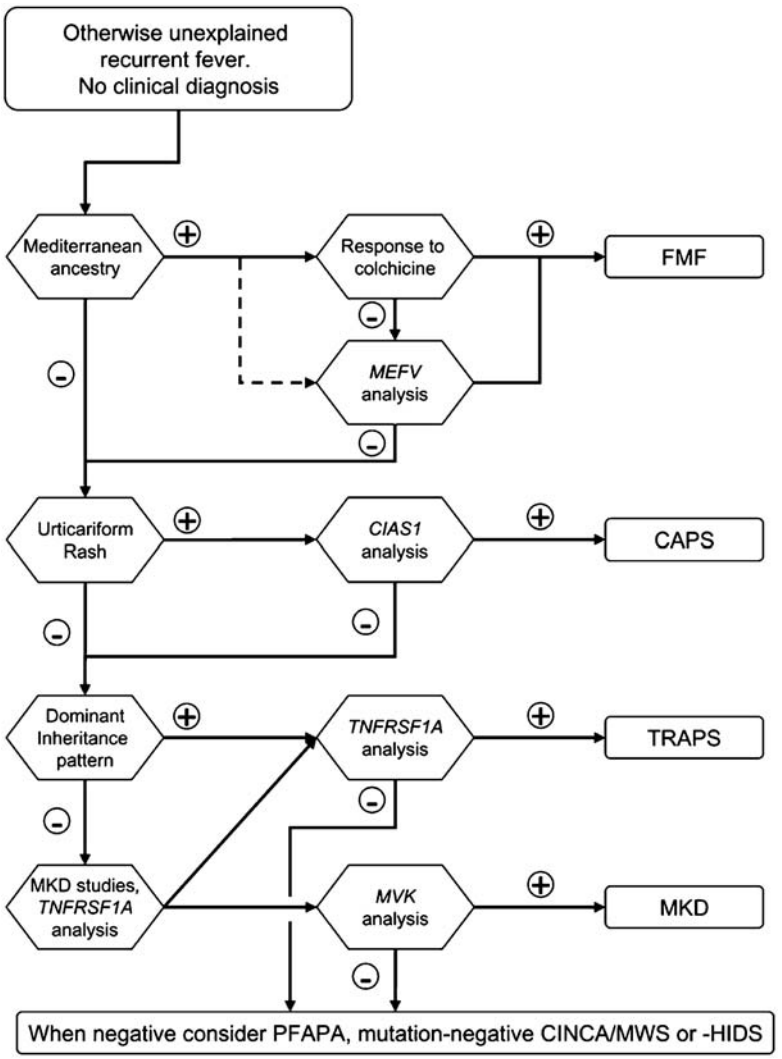

Figure 7. Proposed sequence of genetic analysis in patients with proven recurrent inflammation in whom no definitive clinical diagnosis could be established.

tonsillectomy (Feder, 2000). Prognosis is good; symptoms tend to become less intense and less frequent with time. There is no known long-term morbidity associated with PFAPA.

8. Differential diagnosis

Recurrent inflammation is the hallmark of the autoinflammatory syndromes. The first diagnostic step, therefore, is to examine the patient during an attack and to document an acute phase response (leukocytosis, ESR, CRP). Thus, factitious fever, autonomic dysregulation and most recurrent viral infections may be excluded. A careful evaluation should be performed for occult infection, such as urinary tract infections or otitis/sinusitis. A complete blood count with differential should be included to rule out cyclic neutropenia as the cause for periodic fever. Another characteristic of most of the autoinflammatory disorders is recovery between attacks. When the patient no longer fully recovers, chronic recurrent infections, autoimmune diseases and malignancies, notably lymphoma and leukaemia, must be ruled out.

If a patient has true autoinflammatory episodes, one of the periodic fever syndromes should be considered. In some cases findings at history taking, such as age of onset, length of attacks, precipitating factors, associated symptoms and family history are adequate to distinguish a known periodic fever syndrome (Table 2). This is true for many cases of CAPS and PFAPA. In patients with clinical findings consistent with HIDS, serum IgD and urine mevalonate during an episode may provide additional support for this diagnosis. However, in many patients there is no straightforward diagnostic work-up. Rather the combination of epidemiology, signs, symptoms and disease course should lead to a tentative diagnosis, which may then be supported by genetic testing (Fig. 7). Appropriate genetic testing for these genes is available at several commercial laboratories internationally, but in some cases comprehensive testing of certain genes can only be performed in specialized research laboratories.

A major factor for diagnosis in many centres is ethnic background. In patients of Armenian, Turkish, Arab or Sephardic Jewish extraction, FMF is so prevalent, that a clinical diagnosis will suffice. When the presentation is not typical of FMF, initial *MEFV* testing may be warranted. However, in Western Europeans and their descendants, disease-causing *MEFV* mutations are exceedingly rare and *MEFV* testing is of little benefit (Tchernitchko et al., 2005).

A problem arises when no tentative clinical diagnosis can be made, or when the tentative diagnosis is not supported by genetic testing. In such cases one might analyze other periodic fever genes. In cases where only the identified patient is affected, it is important to consider recessive as well as dominant (possibly *de novo*) diseases. If consecutive generations are affected, autosomal dominant disease genes should be tested initially. The yield of genetic testing, other than to confirm a tentative diagnosis, is usually very low (Simon et al., 2006). Unfortunately, there are also cases for each of the known disorders in which a patient has classic presentation, but exhaustive genetic screens are negative (between 20 and 50% of patients with NOMID, FMF or HIDS). With the identification of targeted therapies for many of these disorders, a therapeutic trial might become another diagnostic approach for these patients.

Key points

- The autoinflammatory syndromes are a distinct group of disorders characterized by generalized inflammation in the absence of microbial pathogens, autoreactive T cells or autoantibodies.
- Clinically, these syndromes can be recognized by the presence of periodic fever episodes, accompanied by systemic inflammatory symptoms involving joints, skin, eyes or abdomen.
- Since many of the autoinflammatory syndromes are hereditary, genetic testing can aid toward the diagnosis. However, in many patients a genetic diagnosis cannot be established.
- To diagnose a patient presenting with periodic fever, a combination of clinical characteristics such as age of onset, length of attacks, precipitating factors, associated symptoms and family history should be documented as well as genetic screening of the appropriate genes.

Acknowledgements

L. Kuijk is supported by a grant of the Wilhelmina Children's Hospital Research Fund.

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Handbook of Systemic Autoimmune Diseases, Volume 6
Pediatrics in Systemic Autoimmune Diseases
Rolando Cimaz and Thomas Lehman, editors

CHAPTER 11

Kawasaki Disease

Fernanda Falcini[a,*], Rolando Cimaz[a,b]

[a]*Department of Pediatrics, Anna Meyer Children's Hospital, University of Florence, Firenze, Italy*
[b]*Department of Pediatrics, Hopital Edouard Herriot and Universitè Lyon 1, Lyon, France*

1. Introduction

Kawasaki disease (KD) is an acute febrile systemic vasculitis usually occurring in children younger than 5 years, and rarely reported in neonates and adults (Kawasaki, 1967). The etiology still remains unknown, although epidemiological and clinical features strongly suggest an infectious cause. Immunological abnormalities in the acute phase of the disease reflect activation of immune system and marked production of cytokines by activated cells (Burns et al., 2004; Sundel et al., 2005).

The disease is self-limited but when coronary arteries are involved, sudden death in the acute phase and myocardial ischemia are life-threatening complications. Timely administration of intravenous immunoglobulins (IVIG) and aspirin (ASA) has significantly reduced the risk of cardiac damage up to 5% conversely to 20–35% of untreated patients, and the mortality rate is reduced to approximately 0.1% in the United States and Japan. Since coronary damage also develops in about 5% of the children who have received timely IVIG treatment, KD is reported as the leading cause of acquired heart disease in children in North America, Europe, and in Japan (Newburger et al., 2004). There is evidence that KD is a potential risk factor for adult ischemic heart disease and sudden death in early adulthood (Kato et al., 1992; Nakamura et al., 1998; Silva et al., 2001). Given that KD is a systemic vasculitis, all blood vessels may eventually be involved, and aneurysms and thrombotic occlusion may develop in axillary, brachial, celiac, mesenteric, iliac, femoral, and renal arteries (Tomita et al., 1992; Foster et al., 2000; Cura et al., 2004). Lacking specific laboratory tests the diagnosis is based only upon clinical criteria. In the acute phase, high-dose IVIG (2 g/kg) and ASA (50–80 mg/kg) have been proven to prevent coronary artery aneurysms (CAA) when given within 10 days from the onset of fever. However, 10–20% of KD patients do not respond to IVIG and require additional treatment. In refractory cases, following 1–3 IVIG infusions, corticosteroids either pulsed or orally may be given (Newburger et al., 2004; Burns et al., 2004). Recently, patients with persistent fever and severe CAA had successfully responded to anti-Tumor necrosis factor (anti-TNF-α) therapy (Weiss et al., 2004). The current main concerns are represented by infants younger than 6 months often displaying an atypical or incomplete disease and misdiagnosed with other infantile febrile illnesses with rash (Chang et al., 2006a, b).

2. Epidemiology

KD mainly affects children aged 1–5 years (85%) with an average age of approximately 2 years. It is more common in boys than in girls with a

*Corresponding author.
Tel.: +39 055 5662913; Fax: +39 055 5662916
E-mail address: falcini@unifi.it (F. Falcini).

DOI: 10.1016/S1571-5078(07)06015-1

male/female ratio of 1.3–1.8:1. The peak incidence age is lower in Japanese (9–11 months) than in North American children (2 years) with a few cases at the extreme ages of childhood, and in adulthood. Infants younger than 6 months are rarely encountered but they possibly are at high risk of CAA (Chang et al., 2006a, b). Although KD has been reported all over the world, it is most highly expressed among Asian populations. In Japan, the annual incidence is reported as 90–130 cases per 100,000 children per year, significantly greater than in Europe (3.6–6.9 cases per 100,000), and in the United States (6–9 per 100,000 children under age 5) (Taubert, 1997; Harnden et al., 2002; Gardner-Medwin et al., 2002; Nakamura et al., 2004). In Hawaii, where most people are of Asian ancestry, the incidence, though higher than in US, is lower than in Japan supporting the assumption that both genetic predisposition and environmental factors are critical in KD.

The recurrence rate in Japanese children is reported as 1–2% while in Caucasians it is less than 1%. The second episode of KD carries a higher risk of coronary damage, thus requiring appropriate treatment as at the first attack (Nakamura et al., 1998). Siblings of patients with KD have a significantly greater chance of acquiring the disease than do children in the general population (Fujita et al., 1989). Furthermore, patients with parental KD are prone to develop a more aggressive disease with higher incidence of CAA (Uehara et al., 2005). Therefore, a family history of KD may be a risk for increased severity and recurrence of the disease. The seasonal incidence varies in the different countries with most cases in winter and spring months, even though KD may spread at any time over the year.

3. Etiology

The etiology of KD remains uncertain despite roughly four decades have passed since its first report (Kawasaki, 1967), and more than 200,000 patients have been recorded in Japan. Although an infectious origin is deeply suspected and previous studies have proposed several viral or bacterial candidates, no one has been settled as the proper cause of the disease (Rowley, 2004). Besides, no correlation has been found among the presence or absence of any specific agent at disease onset and either the response to treatment or the outcome of coronary disease. (Benseler et al., 2005). The peak incidence in early childhood and the virtual absence in adulthood suggest that a microbe causing an asymptomatic infection in most individuals could be a possible trigger, with acquired immunity by adulthood. The rarity of illness in infants in the first months of life supports passive protection by maternal antibodies. The clinical pattern of KD (fever, exanthema, conjunctivitis, lymph node enlargement, and mucositis) closely resembles a bacterial or viral infection of childhood such as scarlet fever. Among other common infantile febrile diseases, adenoviral infection is characterized by prolonged fever, conjunctivitis, lymphoadenopathy, and mucous membrane changes, high erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) and may closely mimic KD, especially in infants (Rocholl et al., 2004; Shike et al., 2005). Recently, an association between KD and a novel coronavirus has been reported (Esper et al., 2005), even though the results have not been confirmed by a further study (Chang et al., 2006a, b). Mycoplasma infection (fever, rash, conjunctivitis, and lymphoadenopathy) has also been proposed as one of the potential triggers of KD (Wang et al., 2001; Leen and Ling, 1996; Merlin et al., 2004).

KD has some similarities to toxin-mediated diseases, both from a clinical and an immunological point of view. The role of one or more superantigens competent of stimulating large numbers of T cells produced by certain strains of *Staphylococcus* or *Streptococcus* has been discussed in the etiology of KD, but no general agreement has been achieved (Leung et al., 2002). After the first reports (Abe et al., 1992, 1993; Pietra et al., 1994) describing selective expansion of Vβ2+ and Vβ8.1+ T cells in patients with acute KD, but not in the convalescent phase, a plethora of other similar studies have been published, both with positive and with negative evidence for a

superantigen-mediated process (Choi et al., 1997; Leung et al., 2002).

4. Pathogenesis

A complex immune response followed by a significant overproduction of different cytokines and activation of endothelial cells has a pivotal role in the pathogenesis of KD. Pro-inflammatory cytokines have been shown to be critical in the disease pathogenesis (Matsuhara et al., 1990), and a recent study has provided preliminary evidence for an increased frequency of alleles associated with elevated TNF-α levels (Quasney et al., 2001).

Despite a polyclonal B-cell activation, autoantibodies in KD have not been found consistently. An exception is represented by anti-endothelial cell antibodies (AECA) that have also been implicated in the disease pathogenesis, as reported in a study showing endothelial dysfunction in mice immunized with AECA from a KD patient (Grunebaum et al., 2002). Other markers of immune and endothelial activation that have been described in KD patients include Von Willebrandt factor and angiotensin converting enzyme (Falcini et al., 1999), circulating intercellular adhesion molecules, CD30, and soluble CD23.

Systemic inflammation in many organs including myocardium, central nervous system, liver, lungs, kidneys, and lymph nodes in addition to artery involvement has been well documented in KD. The pattern of vessel inflammation is characterized by edema and infiltration of neutrophils, CD8+ T cells, and macrophages. The role of IgA immune response in KD has also been investigated, suggesting that a viral agent entering the respiratory tract provokes an oligoclonal IgA response; indeed, IgA-secreting plasma cells have been found in the inflammatory infiltrate of tissues and vascular walls of KD patients (Rowley et al., 2001; Shulman et al., 2004). In addition, vascular endothelial cell growth factor may play part in vessel wall edema, leading to subendothelial accumulation of monocytes and macrophages; the inflammatory infiltrate then migrates to the media, causing its destruction and the development of aneurysms (Kariyazono et al., 2004).

5. Clinical manifestations

The typical clinical manifestations of KD are high fever lasting more than 5 days without reasonable explanation and unresponsive to antibiotics *plus* (a) bilateral nonexudative conjunctivitis; (b) polymorphous exanthemata, (c) bilateral nonsuppurative cervical lymphoadenopathy (at least one lymph node larger than 1.5 cm), (d) mucous membrane changes (i.e. injected or fissured lips, redness of pharynx, strawberry-like tongue) and (e) extremity changes (e.g. erythema of palms and soles, edema of the hands and feet, periungueal digital peeling). Figs. 1–5 are representative examples of such manifestations. All symptoms are not present at onset and evolve over the first 10 days, then gradually resolving in most children even in absence of the specific treatment. Besides the characteristic clinical manifestations other less common symptoms include uretritis, aseptic meningitis, pneumonia, otitis, and gastroenteritis (Newburger et al., 2004; Royle et al., 2005). Arthritis is included in the clinical spectrum of KD, usually developing both in the acute and in convalescent phase, and involving one or more large joints (Gong et al., 2006). Fever of 5 days duration plus four of the five remaining criteria or the presence of fever and CAA detected on two-dimensional (2D)-echocardiogram with three additional criteria are needed for the diagnosis of complete KD (Table 1) (Japan Kawasaki Disease Research Committee, 2002; Ayusawa et al., 2005). In the recent proposal of new classification criteria for KD fever is mandatory, in addition to four of the five remaining typical clinical manifestations. It has been suggested that the presence of desquamation in the perineal area should be added in the diagnostic criteria to changes in peripheral extremities (Ozen et al., 2006). Recurrence of skin peeling after the disease recovery does not mean recurrence of the disease and does not require IVIG re-treatment, as it may be also observed in a number of other conditions

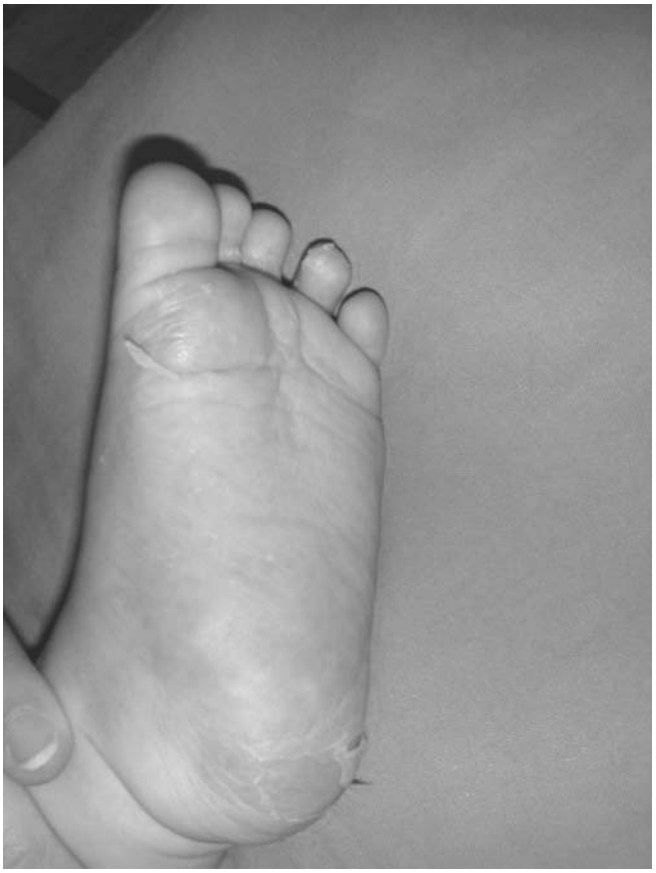

Figure 1. Esfoliative desquamation of foot.

caused by infectious agents and their toxins (Michie et al., 2000).

6. Laboratory findings

Laboratory findings are not specific for KD, as they are shared by other acute inflammatory febrile diseases. Early in the course of illness all parameters of inflammation are increased, namely ESR, CRP, white blood cell (WBC), and neutrophil counts. Platelet count is normal in the acute phase and markedly increases at the end of the second week, reaching 1,000,000 mmc^{-1} in the most severe cases. A low platelet count may be detected in approximately 10% of patients in the acute phase and may correlate with a poor prognosis. Approximately 50% of patients develop anemia with hemoglobin concentrations <2 SD below the mean for age. Urinalysis may show leukocytes and erythrocytes but no bacteria. Cerebral fluid contains increased numbers of WBC, mainly lymphocytes, as expression of aseptic meningitis. Hyponatremia frequently occurs in patients displaying a more aggressive disease; however its pathogenesis remains uncertain (Muta et al., 2005; Watanabe et al., 2006). In several patients liver enzymes and bilirubinemia are significantly elevated; jaundice and hydrops of gallbladder are relatively uncommon, and abdominal ultrasound may be helpful in detecting this complication that may support in the acute phase the diagnosis of atypical or incomplete KD (Falcini et al., 2000). An interesting finding, possibly related to a cross-reactivity between T cells and epitopes of mycobacterial and human heat

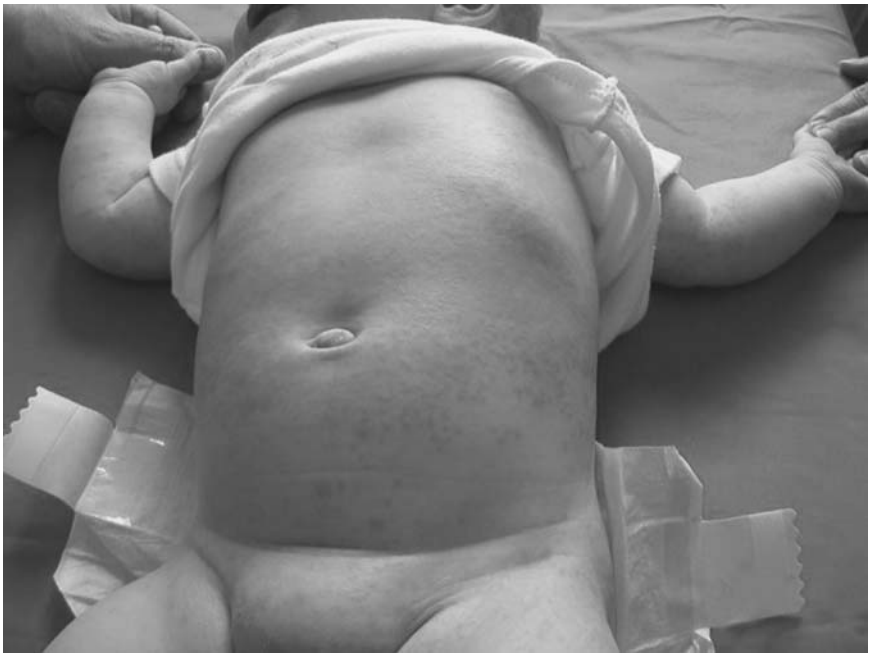

Figure 2. Macular morbilliform rash of trunk in an infant. (See Colour Plate Section.)

shock proteins, is the development of erythema and induration at sites of BCG immunization (Hsu et al., 1987; Wenstein, 2006**).** In the subacute phase changes of serum lipid profiles are detected, with increased levels of triglycerides and low-density lipoproteins, and reduced high-density lipoproteins that usually normalize within a few weeks after IVIG therapy. A correlation among abnormal serum lipid profile and intima-media thickness and arterial stiffness after KD has been reported (Cheung et al., 2004).

7. Atypical and incomplete KD

In children with the characteristic clinical findings, KD should be diagnosed within the first 5 days from the onset of fever and IVIG timely given to reduce the risk of coronary disease. Conversely, the diagnosis is a challenge in atypical and incomplete cases, as other common febrile infantile illnesses with rash closely resemble KD. Lacking specific and sensitive diagnostic test, an increasing number of children, particularly infants, are undiagnosed and develop CAA, raising concerns about the suitability of diagnosis based upon clinical criteria (Witt et al., 1999).

In atypical forms, along with fever lasting 5 or more days, acute surgical symptoms (e.g. appendicitis, acute pancreatitis) or neurological manifestations (e.g. seizures, facial palsy) can be the presenting signs, while the characteristic clinical findings may neither develop or develop over time (Fukushige et al., 1994; Zulian et al., 2003). The term ''incomplete'' should be reserved for patients with fever for at least 5 days, at least two of the clinical criteria for KD, in absence of other reasonable explanation of the disease, and laboratory data consistent with systemic inflammation. The presence of coronary alterations detected by 2D-echocardiogram helps to confirm the diagnosis. Recently, there have been proposals to add laboratory tests and minor clinical signs in diagnosing children with KD (Burns et al., 2004; Simonini et al., 2005).

An algorithm recently published by American Hearth Association (Newburger et al., 2004) suggests measuring CRP and ESR on day 5 of fever in

Figure 3. Edema and erythema of the palm in an infant.

children with 2 or 3 of the clinical criteria. Children with CRP $\geqslant$ 3 mg/dL and/or an ESR $\geqslant$ 40 mm/h should be also evaluated for additional tests. Albumin $\leqslant$ 3.0 g/dL, anemia, increased amino transferase levels, platelet count after 7 days $\geqslant$ 450,000 mmc^{-1}, WBC $\geqslant$ 15,000 mmc^{-1}, and sterile pyuria can all contribute to the correct diagnosis, which can be confirmed by the presence of echocardiographic alterations. The presence of uveitis can provide additional support to the diagnosis in patients with incomplete KD, and ocular evaluation with slit-lamp examination should be included as a part of the work-up of any suspected patient (Burns et al., 1985; Blatt et al., 1996). Another sign not included in the diagnostic criteria, but helpful in recognizing KD, is the disproportionate irritability of most children with KD that can be related to aseptic meningitis.

8. Infants and adolescents

Currently, there are few reports of patients with KD aged less than 6 months. Unfortunately, this small group seems to be at higher risk for CAA as

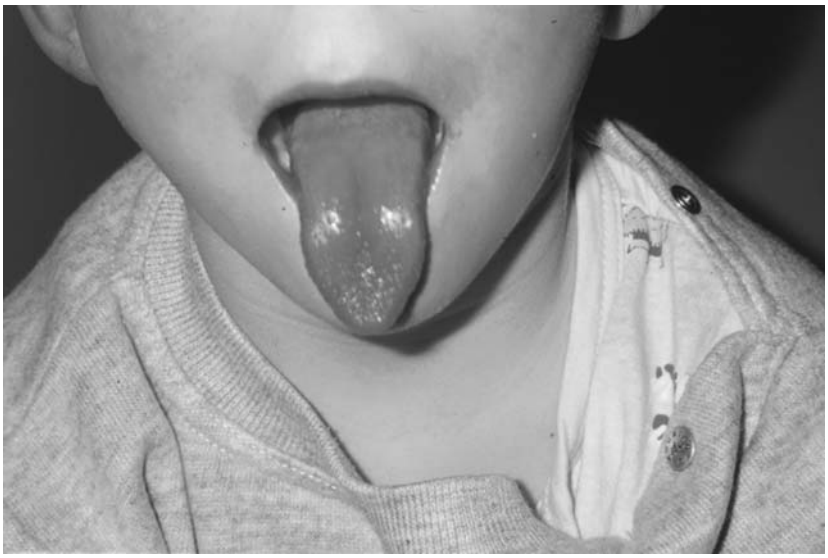

Figure 4. Strawberry-like tongue in an infant. (See Colour Plate Section.)

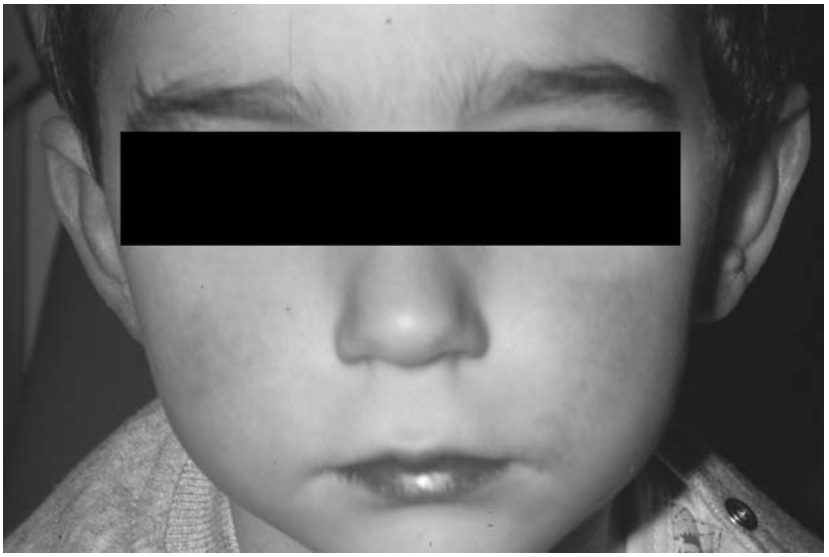

Figure 5. Reddening and cracking of the lips in an infant. (See Colour Plate Section.)

Table 1
Kawasaki disease: diagnostic criteria

Fever	Duration of 5 days or more plus 4 of the following
1. Conjunctivitis	Bulbar, non-suppurative, bilateral
2. Lymphadenopathy	Cervical >1.5 cm
3. Rash	Polymorphous, non vesicles or crusts
4. Changes of lips or oral mucosa	Red cracked lips; "strawberry tongue"; diffuse erythema of oropharynx
5. Changes of extremities	Initial stage: erythema and edema of palms and soles. Convalescent stage: peeling of skin from fingertips

Notes: Kawasaki disease may be diagnosed with fewer than 4 of these features if coronary artery aneurysms are detected by 2D-Echocardiography; fever is mandatory.

the disease displays an atypical course (45% vs. 12% in children >1 year) with persistence of inflammation leading to rapid and severe coronary damage, and treatment delay (Joffe et al., 1995; Mason and Takahashi, 1985; Chang et al., 2006a,b). The incidence of CAA is reported as high as 45% in this age group. Fatal outcome has been reported despite aggressive treatment with IVIG, aspirin, corticosteroids, and antithrombotics (Heaton et al., 2002).

On the other end of the age ranges, older children with KD are also at higher risk to develop cardiac complications (Muta et al., 2004). A recent study carried out in children aged 6 or more years showed that age resulted an independent risk factor for coronary sequelae (Pannaraj et al., 2004). This seems to be due to the delayed diagnosis and treatment in the older group when compared to the younger one. A survey involving general pediatricians and pediatric infectious disease specialists faced with children with a high fever reports that KD is rarely suspected at the extremes of pediatric age (Muta et al., 2004; Pannaraj et al., 2004). In adults, KD is seldom observed and usually has an atypical onset (Rozo et al., 2004; Seve et al., 2005).

9. Therapy

The current treatment regimen in any patient with definite or suspected KD includes IVIG (2 g/Kg) as a single infusion over 8–12 h and ASA (50–100 mg/Kg in four divided doses); the prevalence of coronary artery abnormalities is dependent on IVIG dose but independent from that of ASA (Durongpisitkul et al., 1995; Terai, 1997; Yanagawa et al., 1999).

Only for infants with cardiac compromise who may not tolerate the fluid challenge associated with a single infusion, divided doses over several days may be appropriate. IVIG should be administered as soon as the disease is suspected, and possibly within the first 10 days from the onset of fever. However, in presence of persistent signs of inflammation IVIG have to be given even in patients who are diagnosed later than 10 days from onset. Possible mechanisms of action of IVIG include the effect of specific antibodies to infectious agents or toxins, anti-idiotypic antibodies, or nonspecific effects such as blockage of Fc receptors and accelerated clearance of complement fragments. After the acute phase has resolved and platelet count rises, the dose of ASA is reduced to 3–5 mg/Kg/day as inhibitor of platelet function. In the absence of cardiac complications, low-dose aspirin is maintained for at least 6–8 wk. Long-term treatment is required in children with coronary alterations up to normalization of aneurysms, and long-life therapy is needed if they persist (Newburger et al., 2004). In children with aspirin intolerance another antiplatelet agent is suggested (dypiridamole 2–3mg/Kg) to prevent thrombi formation. In patients with giant aneurysms (GA) the addition of warfarin to aspirin is suggested, but there is no general agreement on this subject.

No specific guidelines are available for the management of patients refractory to this treatment (10–20%) in whom parameters of inflammation do not subside and fever persists or recurs, resulting in the risk of coronary artery sequelae. While a second infusion of IVIG (2 g/Kg) in addition to high dose ASA is strongly recommended in all children with persistent or recurrent fever, no consistent proposals have been made about how to treat the small group (3–4%) still remaining febrile (Hashino et al., 2001; Freeman et al., 2004; Nachiappan et al., 2004).

Since previous studies reported a high rate of coronary alterations in patients treated with corticosteroids, there has been some reluctance to use this therapy either as first-line treatment or as additional therapy in children who do not respond to IVIG (Wooditch et al., 2005). However, no association between corticosteroids and an zincreased incidence of CAA has been observed in recent reports, the use of corticosteroids as rescue therapy, either oral or pulsed (methylprednisolone 30 mg/Kg, 1–3 courses), in children refractory to IVIG has been suggested as an alternative and safe treatment (Newburger, 1999; Raman et al., 2001; Hung et al., 2004; Al-Mayouf, 2004; Jibiki et al., 2004; Takeshita et al., 2005; Lang et al., 2006).

Other therapies that have been tried in cases of aggressive disease recalcitrant to IVIG and corticosteroids, mainly published as single case reports or small series, include cyclophosphamide, cyclosporine, ulinastatin, and plasma exchange (Imagawa et al., 2004; Freeman et al., 2004).

Infliximab, a monoclonal antibody against TNF-α, has also been successfully given to IVIG- and corticosteroid-refractory children with severe coronary involvement, but results of different reports have been conflicting (Weiss et al., 2004; Stenboeg et al., 2005).

Although diagnostic criteria suggest that KD cannot be diagnosed before day 5 from fever onset, the presence of all typical symptoms may argue for earlier diagnosis and brings up the question of when to start IVIG therapy. It is still controversial whether IVIG have greater efficacy in preventing cardiac sequelae when given before or after day 4 from fever onset (Wanitkun, 2005). In addition, it is likely that early administration of IVIG may require additional infusions. Children treated before day 5 could have a different viral disease that did not respond to IVIG, thus requiring a supplementary infusion (Fong et al., 2004). Yet, the duration of fever in patients treated early is shorter than in the usual group, and since fever duration correlates with higher risk of CAA a timely treatment should prevent cardiac complications. The prevention of thrombosis and stenosis following myointimal proliferation is a great concern in children with KD. Up to now, low-dose aspirin (3–5 mg/Kg/day)

has proven to be effective in children with small to medium sized aneurysms, and there are only anecdotal reports of the association between aspirin and other antiplatelet agents (e.g. clopidrogel) (Newburger et al., 2004). Notwithstanding, long-term oral anticoagulation with warfarin is recommended in children with GA secondary to KD, although its efficacy and safety are not yet well defined. A recent study did not confirm a protective role of warfarin neither in the prevention against ischemia nor in the regression of aneurysms (Levy et al., 2005). The potential benefit, the risk of bleeding, and the difficulty in monitoring INR in children given long-term warfarin therapy require further large studies before inclusion of oral anticoagulation in the guidelines for GA treatment.

In children with severe cardiac sequelae surgical options (e.g. percutaneous transluminal coronary angioplasty, coronary bypass grafting, and cardiac transplantation) need also to be considered.

10. Cardiac follow-up

All patients with typical or suspected KD have to be closely monitored with electrocardiogram (ECG) and 2D-echocardiography. ECG can reveal arrhythmia, myocardial dysfunction, and ischemia. 2D-echocardiography is useful in detecting pericardial effusion, valvular inflammation and regurgitation, and coronary artery dilatation and aneurysms, which may be revealed by ultrasound also in peripheral arteries (Cura et al., 2004). Assessment by 2D-echocardiography is recommended at 10 days, and at 6–8 wk from the onset of fever as new aneurysms rarely occur later; in absence of CAA no further follow-up is suggested (Newburger et al., 2004). In children with transient coronary artery alterations that eventually restore, echographic control up to normalization is recommended. However, following the recent reports that marked thickening of the intima at the site of regressed aneurysms develop over time associated to endothelial dysfunction, stress testing to define myocardial function should be performed before starting sports. In all patients with GA at the risk of developing stenosis a close monitoring by a pediatric cardiologist over adolescence and early adulthood is warranted.

10.1. Coronary artery lesions

The long-term prognosis in KD has significantly improved in recent years due to a better knowledge of the disease and earlier appropriate treatment; however, coronary damage including dilatation, aneurysms, and GA remain a concern in approximately 5% of timely treated patients (Kato et al., 1996). Even after IVIG introduction KD is a disease at high morbidity, and in Japan the mortality among persons with a history of KD and cardiac sequelae is reported higher than in normal population (Oki et al., 2000; Nakamura et al., 2000). Risk factors for cardiac sequelae are male sex, age younger than 1 year or older than 5 years, high CRP, WBC $>30.000\,\mathrm{mmc}^{-1}$, and low serum albumin (Honkanen et al., 2003, Newburger et al., 2004) in addition to IVIG treatment after 6 days from the onset of fever (Zhang et al., 2002; Onouchi et al., 2005).

Although most of cardiac complications repair without further abnormalities, the coronary damage as firstly revealed by the wall brightness may progress to either ectasia or aneurysms (Tulloh et al., 2004). In contrast to aneurysms (diameter of coronary lumen $\geqslant 4$ mm) that may regress in size and restore over time, GA (diameter of coronary lumen $\geqslant 8$ mm) rarely improve, becoming stenotic in up one-third of patients. In these cases myocardial ischemia may develop, leading to myocardial infarction and sudden death even in early adulthood (Kato et al., 1992; Newburger et al., 2004). Therefore GA, a potential risk for rupture in the acute phase or subsequent thrombosis due to the stasis of blood flow and the procoagulant endothelial surface of inflamed vessels, are major concerns in KD and raise the dilemma of long-term anticoagulation in children, especially in infants (Levy et al., 2005).

Coronary arterial lesions are known to develop progressive intimal hyperplasia even many years after acute KD (Wilson et al., 2004). An immunohistochemical study performed on a child with history of KD without evidence of CAA who died of sudden infant death syndrome, showed a slightly thick intima, disruption of the lamina interna, and signs of persistent inflammation suggesting that even coronary arteries that appear normal on ultrasound may be damaged (Suzuki et al., 2004).

Furthermore, KD seems to predispose to premature atherosclerosis in adulthood (Cheung et al., 2004). An adverse cardiovascular risk profile (low HDL and apo-A1 but high apo-B1 levels, and increased peripheral arterial stiffness) after resolution of acute inflammation has been detected in KD children with CAA when compared to those without CAA, and controls. There is evidence of increased arterial stiffness related to the severity of inflammation in acute KD (Cheung et al., 2004). Ensuing regressed aneurismal lesions both myocardial flow reserve and endothelial function are impaired even in absence of artery stenosis (Dhillon et al., 1996).

10.2. Cardiac imaging

Even though 2D-echocardiography still remains the gold standard in the early cardiac assessment of KD children and in detecting CAA of proximal right and left coronary arteries, more invasive methods are needed in order to better visualize in detail the entire coronary artery system. To define the degree of cardiac damage, assessment of ventricular ischemia and myocardial blood flow is recommended. Dobutamine stress echocardiography has shown to be a safe and sensible tool in evaluating the outcome of CAA, comparable to cardiac catheterization (Zilberman et al., 2003).

Coronary magnetic resonance angiography (MRA) has proven to be equivalent to X-ray coronary angiography (XCA) and successful in the identification of CAA and in their follow-up (Mavrogeni et al., 2004). Electron beam computed tomography (EBT) is a noninvasive tool that enables the early detection of myocardial ischemia progressing from endocardial to central and epicardial region, thus allowing a prompt therapeutic approach (Endoh et al., 2004). Positron emission tomography (PET) has been reported useful in revealing flow reserve in children with normal epicardial coronary arteries, addressing the risk of residual coronary damage in absence of evident coronary involvement (Ohmocki et al., 1995; Furujama et al., 2002; Furujama et al., 2003; Hauser et al., 2004). Recently, multislice spiral computed tomography (MSCT) has proved to be a noninvasive sensitive tool comparable to coronary angiography in visualizing coronary artery stenosis in KD children. In the future MSCT could become the standard diagnostic tool and possibly replace angiography in patients with CAA (Sato et al., 2004).

11. Vaccinations

Live viral vaccines are an additional concern for children with KD, since IVIG therapy blocks an active immune response. Whereas an interval of 6–11 months is recommended in Japan and USA, there is not yet agreement about the nonresponders who had received a second IVIG pulse. A recent study (Miura et al., 2004) points to 9 months as the optimal time interval for measles vaccination and possibly for mumps, rubella, and varicella viruses in re-treated children.

Key points

- Kawasaki disease still remains a challenge for pediatric rheumatologists.
- Atypical cases are those with fever, acute surgical symptoms or neurological manifestations as presenting signs (the remaining typical clinical manifestations may or may not develop over time), while the term ''incomplete'' is reserved for patients who lack the classical diagnostic criteria but who present fever, at least two of the clinical criteria, and coronary alterations by echocardiography.
- Medical history, physical examination, and laboratory tests including elevated WBC count, ESR, CRP, and low hemoglobin, sodium and albumin levels may help to rule out illnesses mimicking KD.
- Treatment of refractory KD is still a dilemma. Oral or pulsed corticosteroids in children refractory to IVIG are an alternative and safe treatment. Infliximab, a monoclonal antibody against TNF-α, has been given to children with coronary aneurysms, refractory to IVIG and corticosteroids, but still with conflicting results.

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Handbook of Systemic Autoimmune Diseases, Volume 6
Pediatrics in Systemic Autoimmune Diseases
Rolando Cimaz and Thomas Lehman, editors

CHAPTER 12

Henoch-Schönlein Purpura, Polyarteritis Nodosa, Wegener's Granulomatosis, and Other Vasculitides

Seza Ozen*, Ali Duzova

Department of Pediatrics, Hacettepe University, Faculty of Medicine, Ankara, Turkey

1. Introduction

Vasculitis is the inflammation of blood vessels. This inflammation is characterized by the infiltration of the vessel wall with inflammatory cells. The vasculitis syndromes present their features according to the vessel size they affect. In some vasculitic syndromes only one vessel size is affected whereas all sizes can be affected in some, such as Behçet's disease. Focal lesions may cause aneurysm formation whereas segmental lesions may cause stenosis or occlusion (Scott and Watts, 2004). The consequence of the inflammation of the vessel leads to infarction, ischemia, or hemorrhage or dysfunction of the affected tissue. The inflammatory mediators induce further compromise.

Vasculitis may be primary or secondary to another associated disease or condition such as the vasculitis of systemic lupus erythematosus or a vasculitis secondary to meningococcemia. Primary vasculitides will be the primary focus of this chapter.

Vasculitis in children is overall more frequent than in adults. However, the most common vasculitic syndromes in children are the self-limited vasculitides such as Henoch-Schönlein purpura (HSP) and Kawasaki disease. The distribution of vasculitides may vary with geographical distribution, as is the case in adult cases. Evidence from the adult rheumatology literature suggests that an environmental factor(s) may be responsible for this distribution and that this reflects the interplay between environment and genes (Scott and Watts, 2000).

2. Classification

For more than 50 years now, rheumatologists have tried to decide on the best classification criteria for the vasculitic syndromes. The most widely used set of criteria used in adults have been the American College of Rheumatology (ACR) criteria for classification and the Chapel Hill Consensus Criteria for nomenclature of these diseases (Jennette et al., 1994). Neither of these criteria has been validated in children and they are based on adult experience only. In 2005, a pediatric set of criteria was suggested with the endorsement of European League against Rheumatism (EULAR) and Pediatric Rheumatology European Society (PRES) with the participation of members of the ACR and European Society of Pediatric Nephrology (ESPN) (Ozen et al., 2005). This paper defines a working classification of childhood vasculitides as well as a set of criteria for the common vasculitis syndromes seen in childhood (Table 1).

This chapter will discuss the common vasculitides of childhood in this context. Kawasaki Disease will be presented elsewhere.

3. Henoch-Schönlein purpura

HSP is the most common form of vasculitis of childhood in many geographical areas (Cassidy

*Corresponding author.
Tel.: +90-3123051863; Fax: +90-3123094232
E-mail address: sezaozen@hacettepe.edu.tr (S. Ozen).

DOI: 10.1016/S1571-5078(07)06016-3

Table 1
New classification of childhood vasculitis

I. Predominantly large vessel vasculitis
- Takayasu arteritis

II. Predominantly medium-sized vessel vasculitis
- Childhood polyarteritis nodosa
- Cutaneous polyarteritis
- Kawasaki disease

III. Predominantly small vessels vasculitis
A. Granulomatous
- Wegener granulomatosis
- Churg-Strauss syndrome

B. Non-granulomatous
- Microscopic polyangiitis
- Henoch-Schönlein purpura
- Isolated cutaneous leukocytoclastic vasculitis
- Hypocomplementic urticarial vasculitis

IV. Other vasculitides
- Behçet disease
- Vasculitis secondary to infection (including hepatitis B associated PAN), malignancies, and drugs, including hypersensitivity vasculitis
- Vasculitis associated with connective tissue diseases
- Isolated vasculitis of the CNS
- Cogan syndrome
- Unclassified

Source: From Ozen et al. (2005) (reproduced with permission from the BMJ publishing group).

and Petty, 2005). It is a syndrome characterized by palpable purpura, arthritis and/or arthralgia, abdominal pain, and glomerulonephritis. It is a small vessel vasculitis, mediated by immunoglobulin–A containing immune complexes.

3.1. Epidemiology

HSP is predominantly a disease of childhood. It has an incidence of 10.2–20.4 per 100,000 children (Gardner-Medwin et al., 2002; Yang et al., 2005; Dolezalova et al., 2004). In a study from United Kingdom the incidence was 70.3 per 100,000 in the 4- to 6-year age group (Gardner-Medwin et al., 2002). Although it is rare in children younger than 2 years, it has been reported in patients as young as 6 months (Allen et al., 1960; Al-Sheyyab et al., 1995; Gardner-Medwin et al., 2002). Ninety percent of patients are younger than 10 years of age (Allen et al., 1960). Male to female ratio was 1.5:1.0 in the series reported by Saulsbury (1999), and Calvino et al. (2001).

3.2. Etiology and pathogenesis

HSP is often preceded by an upper respiratory tract infection and a wide variety of pathogens including streptococci have been implicated in the etiology (Bagga and Dillon, 2001). Insect bites, exposure to drug and dietary allergens, subtle abnormalities in complement function and immune complex clearance may play a role in the pathogenesis of HSP (Stefansson Thors et al., 2005; Motoyama and Iitaka, 2005). Saulsbury (2001) has suggested that aberrantly glycosylated immunoglobulin A1 has a role in the pathogenesis of HSP. Patients who are predisposed to inflammation may well be more inclined to develop HSP. This was suggested in a study from Turkey where the incidence of HSP in patients with familial Mediterranean fever—an auto-inflammatory condition, was 2.7%, much higher than reported elsewhere (Turkish FMF Study Group, 2005).

3.3. Clinical manifestations

Diagnosis depends on the characteristic features of the disease: the typical non-thrombocytopenic palpable purpura (present in almost all), abdominal pain reflecting the gastrointestinal involvement (in 63–100% of the patients), arthralgia and/or arthritis (in 47–84% of the patients), and renal involvement (in 37–51% of the patients) (Saulsbury, 1993; Bagga and Dillon, 2001).

According to ACR criteria, a patient is said to have HSP if at least two of the following criteria are present: (1) age $\leqslant$20 years, (2) palpable purpura, (3) bowel angina, (4) wall granulocyte on biopsy; with a diagnostic sensitivity of 87.1% and specificity of 87.7% in adults (Mills et al., 1990). These criteria have been revised based on the experience in childhood cases (Table 2).

The rash is most manifest on pressure-bearing areas and extensor surfaces, especially the lower

Table 2
EULAR/PRES endorsed consensus criteria for classification of Henoch-Schönlein purpura

In the presence of *palpable purpura* (mandatory criterion) at least one of the following four should be present
1. Diffuse abdominal pain
2. Any biopsy showing predominant IgA deposition
3. Arthritis or arthralgia
4. Renal involvement (any hematuria and/or proteinuria)

Source: From Ozen et al. (2005) (reproduced with permission from the BMJ publishing group).

extremities and buttocks (Fig. 1). The typical skin finding is a palpable purpura. The lesions may range from petechiae to large echymoses to hemorrhagic bullae, progress in color from red to purple to brown. Cutaneous edema of the scalp and extremities is also quite typical.

Arthritis and arthralgia usually affect the large joints such as knees, ankles, elbows, and wrists. Gastrointestinal involvement may precede other manifestations, and may rarely lead to intussusception, perforation, and gangrene.

The spectrum of renal involvement ranges from microscopic hematuria and proteinuria to nephritic and/or nephritic syndrome, hypertension, and acute or chronic renal failure (see below).

Other rare manifestations are isolated CNS vasculitis, seizure (Lewis and Philpott, 1956), coma and hemorrhage (Bakkaloglu et al., 2000), ataxia (Bulun et al., 2001), neuropathy (Kaplan et al., 1970), pulmonary hemorrhage (Besbas et al., 2001), carditis (Imai and Matsumoto, 1970), and scrotal involvement (Mintzer et al., 1998).

3.4. Diagnostic investigations

There are no specific laboratory tests and the diagnosis is mainly a clinical one. There may be a moderate leukocytosis with a left shift. Acute phase reactants are usually mildly elevated. Serum IgA and IgM are increased in almost half of the patients and some may have circulating immune complexes (White et al., 1999). C1q, C3, and C4 levels, and ANCA are usually normal.

Renal involvement often manifests as hematuria and/or proteinuria. In 5–10% of the patients the involvement is severe resulting in hypoalbuminemia and abnormal renal function test, and necessitating immunosuppression (Szer, 1996). Renal biopsy is helpful in differentiating the severe renal disease from other causes: IgA deposition in the glomerular mesangium is the hallmark of HSP nephritis.

In patients with severe abdominal pain, an ultrasound is helpful to delineate whether there is an intussusception or perforation. Stool should be examined for occult or frank blood.

3.5. Differential diagnosis

HSP must be differentiated from immune thrombocytopenic purpura, systemic lupus erythematosus, hemolytic-uremic syndrome, poststreptococcal glomerulonephritis, disseminated intravascular coagulopathy, and other types of vasculitis.

3.6. Treatment

The optimal management of gastrointestinal and renal involvement has not yet been determined (Szer, 1996). Joint complaints respond well to nonsteroidal anti-inflammatory agents. Cutaneous manifestations are often self-limited; however they may have a relapsing pattern. Early morbidity is determined by the gastrointestinal vasculitis. The family should be cautioned against severe gastrointestinal involvement, such as frank bleeding that may be a sign of intussusception. For severe gastrointestinal involvement uncontrolled studies favor a short course of oral corticosteroids. In a randomized, double-blind, placebo controlled study the treatment group ($n = 21$) received oral prednisone, 2 mg/kg/day for 1 wk, with weaning over a 2nd wk, while the placebo group ($n = 19$) received an identical appearing placebo (Huber et al., 2004). There was no statistically significant difference in the rate of renal or gastrointestinal complications (2/21 in prednisone group vs. 3/19 in placebo group). However, two children in the placebo group did experience intussusceptions compared with none in the prednisone group. It is worth noting however, that steroids can also mask symptoms of such intestinal complications.

Urinary findings such as hematuria and mild proteinuria do not require immunosuppressive

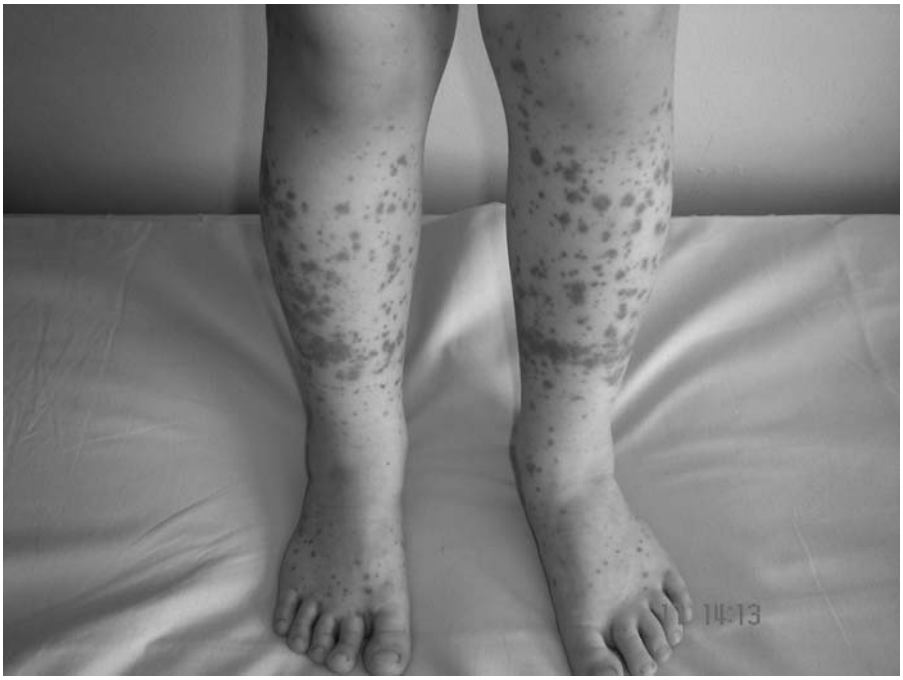

Figure 1. Typical purpura of Henoch-Schönlein purpura. (See Colour Plate Section.)

treatment but should be followed closely. Clinical features of rapidly progressive glomerulonephritis and/or nephrotic range proteinuria necessitate a biopsy: >50% crescentic glomerulonephritis leads to renal failure in 50% of patients with HSP (White et al., 1999). Thus in these patients an intensive approach with corticosteroids and oral cyclophosphamide (CYC) for 3 months has been suggested (Oner et al., 1995; Flynn et al., 2001).

We do not have evidence-based data on the use of steroids in this most common vasculitis. There are no studies proving the use of steroids for mild renal disease (White et al., 1999). The protective role of steroids is also debatable (Mollica et al., 1992; Saulsbury, 1993). In a prospective study by Mollica et al. (1992), patients without signs of nephropathy upon initial presentation entered into the study. A total of 84 patients received prednisone (1 mg/kg per day per os for 2 wk), and 84 patients did not receive steroids. The patients were followed for 24–36 months. None of the 84 patients treated with steroids and 10 (11.9%) of the 84 control patients developed nephropathy 2–6 wk after the acute episode. The difference in the prevalence of nephropathy between the two groups was highly significant ($p<0.001$). On the other hand, in the series reviewed by Saulsbury (1993) a total of 50 patients had no evidence of acute renal involvement; of these 50 patients, 20 were treated during the acute phase of the illness with corticosteroids, while 30 never received corticosteroid therapy. Delayed nephritis (>3 wk following an initial normal urinalysis) occurred in 4 of 20 (20%) patients who received prior corticosteroid treatment, and in 6 of 30 (20%) patients who were not treated, thus failing to show a benefit of steroid treatment.

We still need more data to decide on the role of therapy in this potentially ''self-limited'' disease. However, uncontrolled studies and expert-opinion may suggest the following algorithm:

- Oral steroids (short course) indicated for:
  - severe GI involvement,
  - less than 50% crescent in severe clinical renal involvement,
  - testis involvement.

- Steroids plus CYC indicated for:
  - more than 50% crescent in severe clinical renal involvement,
  - CNS, pulmonary vasculitis.

Early morbidity and mortality is associated with gastrointestinal, CNS, and pulmonary involvement, whereas late morbidity is associated with renal involvement (White et al., 1999). In a long-term study by Ronkainen et al. (2002) (mean follow-up, 24.1 years), patients with significant glomerulonephritis at onset had a 4.7-fold risk of developing a poor renal outcome as compared with patients with mild abnormalities. Women were at a 2.5-fold risk for a poor renal outcome. Seventy percent of women developed pregnancy complications of hypertension and decreased renal function.

4. Polyarteritis nodosa

Jennette et al. (1994) have defined PAN as necrotizing inflammation of medium- or small-sized arteries without glomerulonephritis or vasculitis in arterioles, capillaries, and venules. The criteria for PAN in childhood proposed by Brogan et al. (2002) and Ozen et al. (1992) were modifications of the ACR criteria (Lightfoot et al., 1990). Both criteria lack the presence of ANCA, which has emerged as an important marker for the disease and were not based on a large consensus. Pediatricians have recently suggested revised criteria, where a typical angiogram finding and/or a biopsy showing small-medium sized artery necrotizing vasculitis are mandatory criteria (Table 3).

The aforementioned group also defined cutaneous polyarteritis by the presence of subcutaneous nodular, painful, non-purpuric lesions with or without livedo reticularis, with no systemic involvement (except for myalgia, arthralgia, and non-erosive arthritis) and a skin biopsy shows necrotizing non-granulomatous vasculitis (Ozen et al., 2005). Tests for ANCA are negative. Cutaneous polyarteritis is often associated with serologic or microbiologic evidence of streptococcal infection. No formal classification criteria were proposed beyond this definition of a clinical syndrome.

Table 3
EULAR/PRES endorsed consensus criteria for classification of childhood PAN

A child is classified as having "childhood PAN" if he/she has a systemic illness and has the presence of (one of the below as a mandatory criterion)

- Biopsy showing small and mid-size artery necrotizing vasculitis and/or
- Angiographic abnormalities* (aneurysms or occlusions)

*Should include angiography if MRA is negative in the presence of at least two out of the following seven criteria

1. Skin involvement (livedo reticularis, tender subcutaneous nodules, other vasculitic lesions)
2. Myalgia or muscle tenderness
3. Systemic hypertension, relative to childhood normative data
4. Mononeuropathy or polyneuropathy
5. Abnormal urine analysis and/or impaired renal function
6. Testicular pain or tenderness
7. Signs or symptoms suggesting vasculitis of any other major organ system (gastrointestinal, cardiac, pulmonary, or central nervous system)

Source: From Ozen et al. (2005) (reproduced with permission from the BMJ publishing group).

Microscopic polyangiitis was defined separately as a necrotizing pauci-immune vasculitis affecting predominantly small vessels and is often associated with a high titer of myeloperoxidase antineutrophil cytoplasmic antibodies (MPO)-ANCA or positive perinuclear-ANCA (p-ANCA) staining (Ozen et al., 2005). Necrotizing glomerulonephritis was noted to be very common and pulmonary capillaritis as well, often in the absence of granulomatous lesions of the respiratory tract as was suggested by the Chapel Hill Consensus Criteria (Jennette et al., 1994; Ozen et al., 2005). The only modification of the Chapel Hill report is that ANCA was added to the description of microscopic polyangiitis.

4.1. Epidemiology

PAN is rare in childhood. It occurs with approximately equal frequency in boys and in girls. The average ages of patients were 9.3 and 7.5 years in two pediatric centers (Ozen et al., 1992; Dillon, 1990). A recent survey of 21 pediatric centers presented 110

patients classified as childhood PAN (Ozen et al., 2004). The F:M ratio was 56:54, and the mean age was 9.05±3.57 years. They were classified as systemic PAN (57.2%), cutaneous polyarteritis (30.0%), PAN-associated with HBsAg (4.6%), and ANCA-positive microscopic polyarteritis (8.1%).

4.2. Etiology and pathogenesis

The cause of PAN is unknown. Infectious agents have been associated especially with the "cutaneous" and "classic" form of the disease. Hepatitis B has been described in 10–54% of "classic PAN" cases resulting in an immune complex disease (Guillevin et al., 1995). PAN occurring after infection with hepatitis C (Cacoub et al., 1992), parvovirus B19 (Zulian et al., 1998), and cytomegalovirus (Fernandes, 1999) have also been reported. The association with streptococcal infection is a remarkable feature that has been described in various pediatric patients (David et al., 1993; Bont et al., 1998), this association is less common in adults (Dillon, 1998).

On the other hand microscopic PAN/polyangiitis is widely accepted as an ANCA-associated disease. In 2002 an animal model produced strong support for the direct pathogenic role of ANCA in microscopic PAN and ANCA-associated diseases (Xiao et al., 2002), showing that anti-MPO caused pauci-immune glomerular necrosis and crescentic glomerulonephritis in mice.

4.3. Clinical manifestations

Children almost always have constitutional symptoms such as malaise, fever, and/or weight loss. Severe myalgia and arthralgia were present in 56–81%, whereas renal involvement was present in 65–80% of cases in the series reported by Fink (1977) and Ozen et al. (1992). As discussed in the classification of PAN, a number of patients do not have typical presentations of microscopic or classic PAN, but have inflammation in varying sized arteries of skin, musculoskeletal, and other organ systems (Fig. 2) (Bakkaloglu et al., 2001; Watts et al., 1996).

Cutaneous PAN is characterized by crops of painful skin nodules and livedo reticularis and sometimes non-specific musculoskeletal findings such as myalgia, arthralgia (Dillon, 1998). There is often a history of preceding streptococcal infection (David et al., 1993; Bont et al., 1998).

Clinical manifestations of 110 patients classified as childhood PAN from 21 pediatric centers are shown in Fig. 3.

When it affects mid-size vessels, PAN frequently leads to aneurysm formation (Fig. 2). The main clinical feature is organ infarction occurring mostly in kidneys and gut. Hypertension due to renal artery aneurysms is a frequent manifestation in childhood patients.

Hepatitis B virus has been implicated in this disease. Guillevin et al. (1996) have shown that patients with abnormal angiograms had significantly more hypertension, more orchitis, more HBs antigenemia, and negative ANCA. This form of the disease has been suggested to be an immune-complex disease.

The predominant feature of microscopic poliangiitis is rapidly progressive renal involvement. Pulmonary vascular disease may accompany in some causing a "pulmonary-renal disease". The renal disease manifests as nephritic and/or nephrotic features often with renal insufficiency (Besbas et al., 2000). The hallmark of the disease is the necrotizing glomerulonephritis on renal biopsy, with no immune deposits and no granuloma formation. In a report of pediatric PAN patients from India six were classified as microscopic PAN and half of them had pulmonary-renal syndrome (Handa, 2001).

4.4. Diagnostic investigations

Patients with PAN frequently have anemia, leukocytosis, thrombocytosis, and almost always elevated ESR and C-reactive protein. On the other hand the acute phase reactants are often normal or mildly elevated in cutaneous PAN.

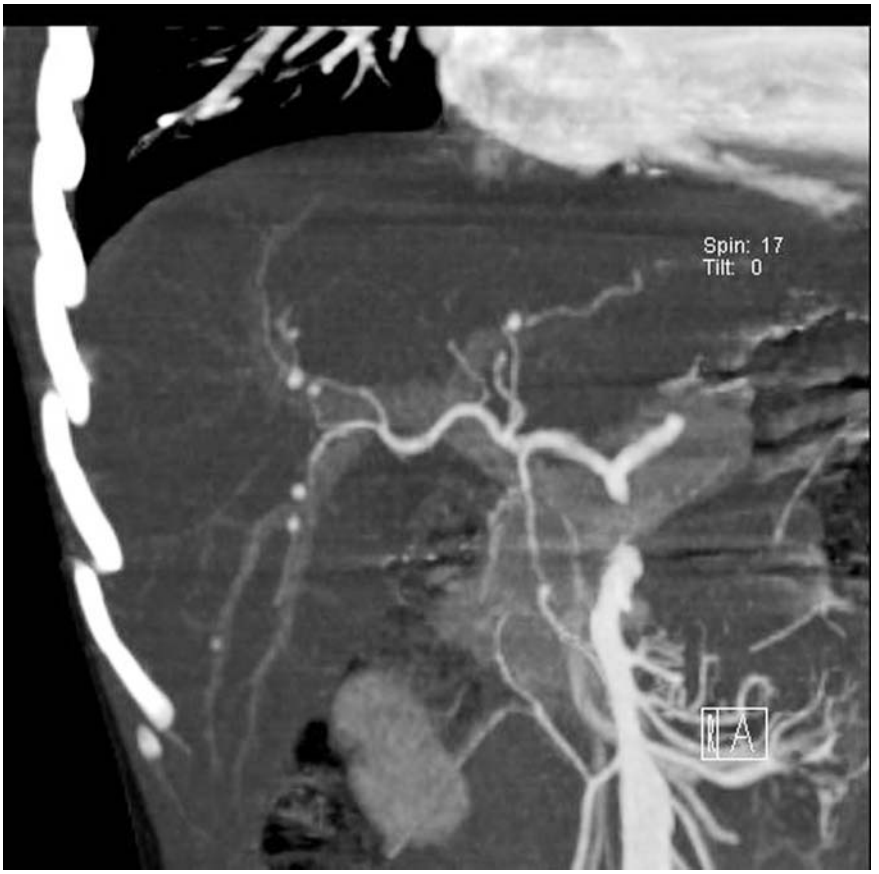

Figure 2. An angiogram showing aneurysms in systemic PAN.

A urinalysis must be obtained in all cases to look for hematuria, proteinuria, and casts. Blood urea nitrogen or creatinine may be elevated.

Diagnostic work-up of these patients should also include ANCA (Wong et al., 1998). In microscopic PAN, the ANCA predominantly shows a perinuclear pattern of antibody staining using the indirect immunofluorescence technique (Wong et al., 1998; Bakkaloglu et al., 2001). An ELISA test will frequently show that the auto-antibody is directed against myeloperoxidase. On the other hand ANCA is often not present in other forms of childhood PAN and if ANCA directed against myeloperoxidase is present, it is at low titer. Thus a negative ANCA would not exclude the diagnosis of childhood PAN.

A biopsy of the involved organ system showing necrotizing arteritis, or a conventional CT or magnetic resonance angiogram is indicated for definite diagnosis. Angiogram may show aneurysms or non-aneurismal changes: perfusion defects, the presence of collateral arteries, lack of crossing of peripheral renal arteries, and delayed emptying of small renal arteries (Brogan et al., 2002). The sensitivity and specificity of renal angiographic diagnosis of PAN by the finding of aneurysms was 43% (SE: 10%) and 69% (SE: 14%), respectively (Brogan et al., 2002). The sensitivity increased to 80%, and specificity fell to 50% for angiogram positivity defined as the presence of at least one of the above non-aneurismal signs irrespective of the presence of aneurysms. Aneurysms may also be demonstrated on hepatic and mesenteric angiography, and non-aneurismal signs can be found on hepatic, mesenteric, and splenic angiography.

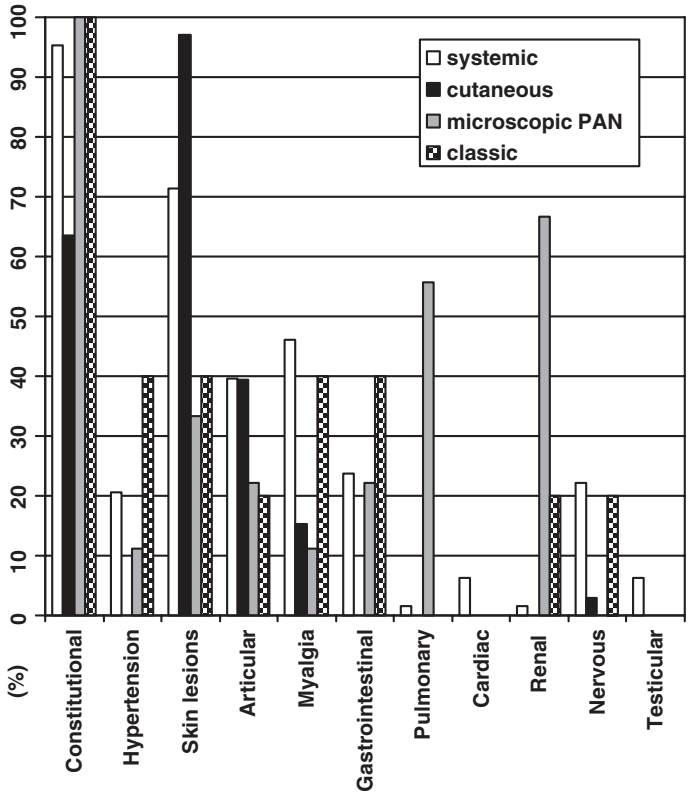

Figure 3. Clinical manifestations of 110 PAN patients (Ozen et al. (2004)).

4.5. Differential diagnosis

PAN should be suspected in any child with fever of unknown origin, skin rash, myalgia, unexplained pulmonary, cardiovascular, nervous system, or renal disease. It should be distinguished from other forms of vasculitis (HSP, Wegener granulomatosis), sarcoidosis, pulmonary-renal syndromes, relapsing polychonditis, and viral infections.

4.6. Treatment

Glucocorticoid therapy (prednisone 1–2 mg/kg/day) remains the basis of treatment. In severe organ involvement intravenous pulses of methylprednisolone are indicated. Systemic disease and renal involvement necessitate CYC for induction of remission (Besbas et al., 2000). In a child the cumulative dose of immunosuppressives remains a major concern. When data from large studies were analyzed, a cumulative dose of up to 200–250 mg/kg was considered safe for most children in terms of gonadal toxicity (Latta et al., 2001). This would be roughly equal to 3.5 months of oral CYC at a dose of 2 mg/kg/day. An intravenous route may also be employed. Thus, after 3 months, CYC is switched to azathioprine if remission is achieved. Switching to azathioprine has proved successful in adult studies as well. In the CYCAZAREM trial, patients received oral CYC and prednisolone until remission was achieved, between 3 and 6 months, and were then randomized to continue CYC or azathioprine. There was no difference in relapse rate during 18 months (Jayne, 2001). Uncontrolled studies have suggested the use of plasma exchange (Gianviti et al., 1996) in severe cases.

The efficacy and toxicity of i.v. pulse administration of CYC (0.75 g/m^2) versus daily oral CYC treatment (2 mg/kg/day) were investigated in a prospective, randomized, multicenter study in adult patients with ANCA-associated vasculitis and renal involvement (Haubitz et al., 1998). The cumulative CYC dose was reduced by 57% in patients with i.v. pulse treatment ($n = 22$) compared with patients treated with daily oral therapy ($n = 25$). Patient survival, remission rate, time of remission, relapse rate, and outcome of renal function were not different except for significantly less severe infections in the i.v. pulse group. On the other hand in another randomized prospective study (Guillevin et al., 1997) relapses were significantly more frequent in the i.v. pulse group as compared to the group on oral treatment.

In PAN that is associated with hepatitis B virus antiviral treatment is required.

Mortality has been reported to be as high as 20% in some older childhood series (Fink, 1977; Dillon, 1990). However, in more recent childhood series, the outcome has been substantially better; a good prognosis is especially seen in those cases associated with a streptococcal infection and in those who do not present the typical microscopic pattern defined in adult patients by the Chapel Hill report (Jennette et al., 1994; Ozen et al., 2004). In these patients the beneficial role of penicillin deserves controlled studies. This effect is especially striking in cutaneous PAN.

In cutaneous PAN non-steroidal anti-inflammatory drugs and short courses of low dose oral corticosteroids have been used. Relapses are frequent. Any constitutional symptom or organ involvement should alert the physician for the development of systemic PAN. We lack an evidence-based treatment for the management of these patients.

5. Wegener granulomatosis

WG is characterized by a granulomatous vasculitis affecting small-medium sized arteries. Glomerulonephritis accompanied by granulomatous lesions of the upper and lower respiratory tract is a common presentation.

5.1. Epidemiology

WG is rare in childhood. The 5 year incidence was 3.2 cases per 100,000 persons, in a large study (Cotch et al., 1996). In the pediatric age range, it occurs with approximately equal frequency in boys and in girls (Orlowski et al., 1978). On the other hand, in a British study, female to male ratio was 13:4 (Belostotsky et al., 2002). The mean age at onset of disease ranged from 6.3 years to 15.4 years (Rottem et al., 1993; Belostotsky et al., 2002). Fifteen percent of cases of WG are initially diagnosed in patients less than 19 years of age (Hoffman et al., 1992).

5.2. Etiology and pathogenesis

The cause of WG is unknown. It is a multifactorial disease as most of the other major vasculitides with a complex genetic predisposition. In a recent study an association has been defined with a region on chromosome 6p21.3, suggesting the need for extensive mapping of this region (Szyld et al., 2006). The pathogenic role of ANCA in the development of the disease suggests an autoimmune background of WG. Environmental factors have been highlighted in a number of reports especially those describing the geographic distribution and clusters of the disease. *Staphylococcus aureus* has been suggested to have a triggering role in its pathogenesis (Mayet et al., 1999). Autoimmune, hypersensitivity, allergic reactions, and nasal carriage for *Staphylococcus aureus* have been implicated. Recent studies have elegantly demonstrated the role of ANCA in the disease pathogenesis, and are well summarized in a review by Frosch and Foell (2004).

5.3. Clinical manifestations

Patients frequently present with malaise, fever, sinusitis, epistaxis, and hematuria. Diagnosis according to the ACR criteria requires two out of the four following criteria: (1) nasal-oral inflammation, (2) abnormal chest X-ray, (3) microscopic

hematuria or red blood cell casts, (4) granulomatous inflammation on biopsy (Leavitt et al., 1990). The triad of paranasal sinus involvement, pulmonary infiltration, and renal disease is characteristic of WG (Rottem et al., 1993). The EULAR/PRES Endorsed Consensus Criteria for Classification of Wegener's granulomatosis revised by pediatricians have introduced minor changes (Table 4); one of these was the inclusion of subglottic stenosis since this was a common pediatric feature.

Upper respiratory tract symptoms include rhinorrhea, nasal mucosal inflammation, epistaxis, persistent cough, hoarseness, and paranasal sinus pain.

Pulmonary involvement (cough, dyspnea, and hemoptysis) occurs in 74% of children (Rottem et al., 1993). It may be in the form of nodules, fixed infiltrates, or cavities (Leavitt et al., 1990). Multifocal infiltrates with or without small peripheral nodules were the commonest thoracic CT manifestations (McHugh et al., 1991). The skin disease may be in the form of palpable purpura, papules, vesicles, ulcers, and nodules (Rottem et al., 1993). Most features in children are similar to those of adults; however, some features such as subglottic stenosis and nasal deformity are more common in children (Rottem et al., 1993). Blurred vision, eye pain, conjunctivitis, episcleritis, persistent otitis media, myalgia, arthralgia are also common (Lindsley and Laxer, 2005). CNS and cardiac involvement are less common.

Table 4
EULAR/PRES endorsed consensus criteria for classification of Wegener granulomatosis

Three of the following six should be present
1. Abnormal urinalysis
2. Granulomatous inflammation on biopsy
3. Nasal-sinus inflammation
4. Subglottic, tracheal or endobronchial stenosis
5. Abnormal chest X-ray or CT
6. PR3 ANCA or C-ANCA staining

Source: From Ozen et al. (2005) (reproduced with permission from the BMJ publishing group).

In the pediatric series reported by Rottem et al. (1993, 23 patients), Stegmayr et al. (2000, 10 patients), and Belostotsky et al. (2002, 17 patients) upper airway involvement ranged from 58 to 91%, lung involvement from 74 to 87%, kidney involvement from 53 to 100%, eye involvement from 48 to 53%, CNS involvement from 10 to 17%, and skin involvement from 40 to 53%.

In patients with kidney involvement the findings range from proteinuria and/or hematuria to impairment of renal function. If kidney biopsy is performed it characteristically shows necrotizing pauci-immune glomerulonephritis.

5.4. Diagnostic investigations

Anemia, thrombocytosis, and marked elevation of ESR or CRP are prominent features. WBC counts are usually normal or moderately elevated. Urinalysis reveals hematuria and proteinuria, and renal function test may be abnormal.

Chest CT is often indicated. ANCAs may be cytoplasmic or perinuclear, but usually display a cytoplasmic-staining pattern by immunofluorescence, and is directed against serine proteinase 3 in more than 90% of cases (Specks et al., 1989; Nolle et al., 1989).

5.5. Differential diagnosis

Churg-Strauss syndrome, lymphomatoid granulomatosis, and primary angiitis of the central nervous system are other granulomatous vasculitides. Differential diagnosis includes the other graulomatous vasculitides as well as relapsing polychondritis, chronic granulomatous disease, the pulmonary-renal syndromes such as PAN, Churg-Strauss syndrome, Goodpasture syndrome, and SLE.

5.6. Treatment

Adult rheumatologists have included patients with WG along with microscopic PAN cases, in

European Vasculitis trials such as the CYCAZAREM study (Jayne, 2001). Treatment is similar to that for patients with microscopic PAN. In children with systemic disease steroids and CYC are used. The number of patients reported so far is too small to establish a standard recommendation for oral versus intravenous pulse CYC (Rottem et al., 1993; Stegmayr et al., 2000). Methotrexate may be used in non-renal less severe cases (Gottlieb et al., 1996). Whether trimethoprim-sulfamethoxazole is able to reduce disease relapse is controversial (de Groot et al., 1996; Stegeman et al., 1996). In an adult series etanercept was not effective for the maintenance of remission in patients with WG (WGET Research Group, 2005). Ten patients with WG resistant to conventional therapy were able to achieve stable condition with rituximab (Keogh et al., 2006). Leflunomide (Metzler et al., 2004) and mycophenolate mofetil (Langford et al., 2004) were found to be useful in the maintenance of remission. Plasmapheresis and immunoabsorption have been applied as adjunctive therapy in cases not responding to drug therapy (Guillevin and Pagnoux, 2003; Matic et al., 2001). Intratracheal dilation with an intratracheal injection of a long-acting glucocorticoid provides a safe and effective treatment for WG-associated subglottic stenosis (Langford et al., 1996; Staepperts et al., 2000).

Prognosis has been dramatically improved with immunosuppressive therapy. However, a significant proportion of patients are still subject to permanent morbidity and mortality from both the disease and treatment (Rottem et al., 1993). The course is complicated with relapses. Stegmayr et al. (2000) have reported that 80% of their young patients relapsed within a period of 4–120 months.

6. Takayasu arteritis

Takayasu arteritis (TA) is a segmental inflammatory arteritis leading to stenosis and aneurysms of large muscular arteries, mainly the aorta and its major branches (Hall et al., 1985). Females are affected more than males. Many reports have drawn attention to the association of TA with tuberculosis.

Table 5
EULAR/PRES endorsed consensus criteria for classification of Takayasu arteritis

At least one of the following four should be present
1. Decreased peripheral artery pulse(s) and/or claudication of extremities
2. Blood pressure difference >10 mmHg between the two sides
3. Bruits over aorta and/or its major branches
4. Hypertension (related to childhood normative data)
In the presence of angiographic abnormalities (conventional, CT or MR) of aorta or its main branches (a mandatory criterion)

Source: From Ozen et al. (2005) (reproduced with permission from the BMJ publishing group).

According to ACR classification based on adult experience, a patient is classified as having TA if three of the following six are present: (1) age <40 years, (2) claudication of extremities, (3) decreased brachial artery pulse, (4) blood pressure difference between the two sides >10 mmHg, (5) bruit over subclavian arteries or aorta, (6) arteriogram abnormality (Arend et al., 1990).

These criteria have also been revised along with the other pediatric vasculitides (Table 5) (Ozen et al., 2005).

6.1. Epidemiology

Although TA is rare in children, it follows HSP and Kawasaki disease in frequency (Lindsley and Laxer, 2005). Twenty percent of cases are younger than 19 years (Ishikawa, 1981). Female/male ratio varies from 4:1 to 2:1 in different series (Hall et al., 1985; Jain et al., 2000). The type of vascular involvement seems to differ according to the geographic area: obstructive lesions seem to be more common in the US and Western Europe and Japan, whereas aneurysms appear to be more common in south East Asia and Africa (Lindsley and Laxer, 2005).

6.2. Clinical and laboratory features

The presenting symptoms are fever, night sweats, anorexia, weight loss, and musculoskeletal

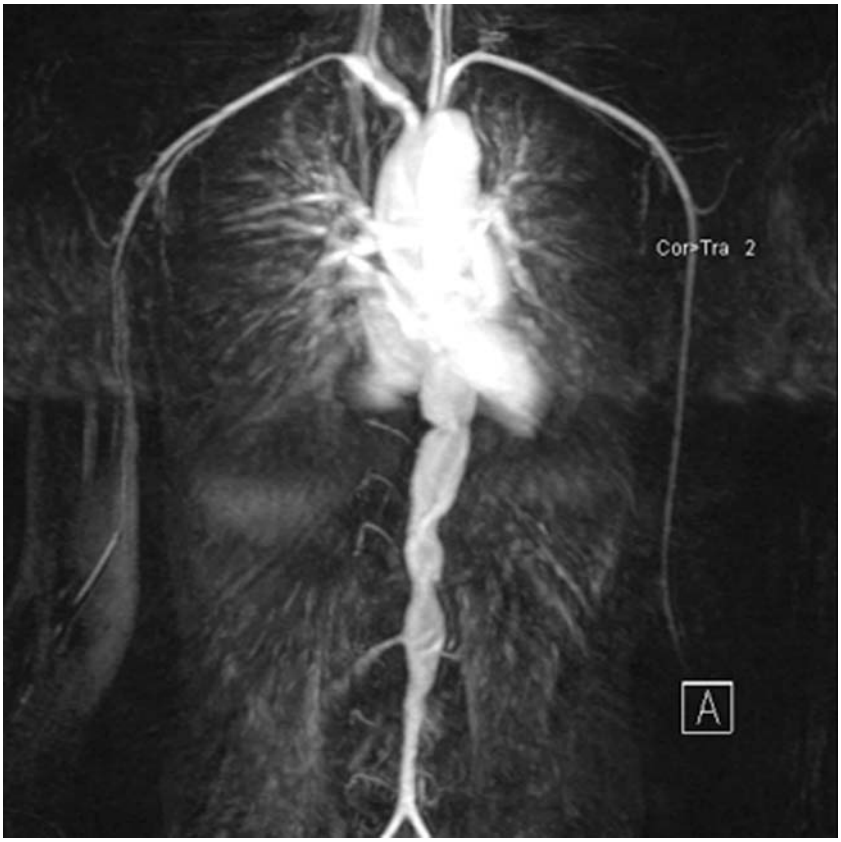

Figure 4. Takayasu arteritis demonstrating involvement of aorta.

symptoms. Symptoms related to hypertension and pulse deficits are common (Hall et al., 1985). In the series reported by Jain et al. (2000) hypertension was the most common mode of presentation, seen in 83% of patients. Sixteen percent of patients had congestive heart failure. Left ventricular hypertrophy was present in 54% of patients.

Acute phase reactants are elevated. Although plain radiographs may be helpful, diagnosis requires the demonstration of the arteritis and typical findings by magnetic resonance or conventional angiography (Fig. 4).

6.3. Treatment

Corticosteroids are used in acute disease (Hoffman et al., 1994). As in other vasculitides CYC is an effective alternative. Recent adult and childhood reports have emphasized the use of methotrexate as a steroid sparing agent (Hoffman et al., 1994).

A positive tuberculin test would justify antituberculous therapy. Subsequent reconstructive surgery and transluminal angioplasty may be employed for the vascular complications.

7. Other vasculitides

7.1. Churg-Strauss syndrome (allergic granulomatosis)

Churg-Strauss syndrome is a small vessel vasculitis defined by: allergic rhinitis, asthma, peripheral esoinophilia, peripheral neuropathy, pulmonary infiltrations, chronic sinusitis, and biopsy proven eosinophilic vasculitis. It is very rare in childhood. All childhood-onset patients had peripheral

eosinophilia and almost all had asthma (Louthrenoo et al., 1999). Cardiac, renal, and nervous involvement may also occur. Corticosteroids are the main therapy. Immunosuppressives were added in most reported cases. Mortality is very high.

7.2. Isolated cutaneous leukocytoclastic vasculitis

This is small vessel vasculitis confined to the skin. Histologically the lesion is a leukocytoclastic angiitis (Jennette and Falk, 1997). The definition requires the exclusion of any systemic feature.

Treatment is often symptomatic; however, steroids may be indicated although they have not been proven to alter the course of the disease.

7.3. Hypocomplementemic urticarial vasculitis

In this rare syndrome, children, usually girls, have recurrent episodes of urticaria associated with pruritus and burning. Purpura, papules, vesicles, fever, nausea, vomiting, arthralgia, arthritis, chest and abdominal pain are other manifestations. It may be associated with SLE, Sjögren's syndrome, hepatitis B and C, drugs and sun exposure (Cassidy and Petty, 2005). The pathogenesis is unknown. Complement levels (C1q, C3, C4) may be decreased. Antihistamines, colchicine, hydroxychloroquine, indomethacin, and dapsone have all been used (Mehregan et al., 1992). Glucocorticoids and other immunosuppressive drugs are required in severe cases.

7.4. Isolated CNS vasculitis

The true incidence of primary CNS vasculitis is not known. Acute severe headache (80%), focal neurologic deficits (78%), motor deficiencies (62%), cranial nerve involvement (59%), and cognitive dysfunction (54%) are the leading presenting features of primary CNS vasculitis in children (Benseler and Schneider, 2003). Infections, systemic vasculitis, collagen vascular disease, inflammatory bowel disease, sarcoidosis, vascular injury, drugs, and neoplasms are secondary causes of CNS vasculitis in children.

CSF fluid opening pressure may be elevated. In small pediatric series reported by Gallagher et al. (2001), Lanthier et al. (2001), Benseler and Schneider (2003) 9 out of 11 patients had had either pleocytosis or elevated protein CSF levels.

MRI is more sensitive than CT for the diagnosis of CNS vasculitis (Stone et al., 1994). The combination of normal CSF analysis and a normal brain MRI has a high negative predictive value. The most common angiographic feature of pediatric primary CNS vasculitis is arterial vessel stenosis (Gallagher et al., 2001). MR angiography is an alternative diagnostic tool. SPECT and PET may demonstrate perfusion abnormalities.

The gold standard for primary CNS vasculitis is a biopsy of the brain and leptomeninges. However large vessel vasculitis confirmed by angiography may not be associated with small vessel involvement seen on biopsy.

Corticosteroids $\pm$ CYC or other immunosuppressives may be useful in children with primary CNS vasculitis. Thromboembolic phenomena, prothrombotic conditions, and post-stenotic low-flow conditions may require prophylactic anticoagulation.

7.5. Cogan syndrome

Cogan syndrome is a rare disease that most frequently affects young adults. Major clinical features are inflammatory eye disease, vestibuloauditory dysfunction, systemic vasculitis, and constitutional symptoms. Eye disease and vestibuloauditory dysfunction are required to make the diagnosis (St. Clair and McCallum, 1999). Steroids and methotrexate are beneficial.

7.6. Secondary vasculitides

Since vasculitis is defined as inflammation of the blood vessels, practically any process accompanied by this feature may be termed as secondary vasculitis. Infectious agents may act as triggering

factors through various mechanisms such as molecular mimicry, or through direct damage, or by immune-mediated damage to the vessel by immune complex deposition or bystander damage to the blood vessel (Ozen, 1999). Among viral causes hepatitis-B and HIV-associated vasculitis have been described in children (Athreya, 1995).

The other causes of secondary vasculitides include malignancy, cryoglobulinemia and other rheumatic diseases such as systemic lupus erythematosus, or dermatomyositis.

Key points

- In 2005, a pediatric set of criteria was suggested with the endorsement of European League against Rheumatism (EULAR) and Pediatric Rheumatology European Society (PRES) with the participation of members of the American College of Rheumatology (ACR) and European Society of Pediatric Nephrology (ESPN). This paper defines a working classification of childhood vasculitides as well as a set of criteria for the common vasculitis syndromes seen in childhood.
- Henoch-Schönlein purpura (HSP) is the most common form of vasculitis of childhood in many geographical areas. It is a syndrome characterized by palpable purpura, arthritis and/or arthralgia, abdominal pain, and glomerulonephritis. It is a small vessel vasculitis, mediated by immunoglobulin-A containing immune complexes.
- Polyarteritis nodosa occurs with approximately equal frequency in boys and in girls. A recent survey classified childhood PAN as systemic PAN (57.2%), cutaneous polyarteritis (30.0%), PAN-associated with HBsAg (4.6%), and ANCA-positive microscopic polyarteritis (8.1%).
- Wegener's granulomatosis (WG) is characterized by a granulomatous vasculitis affecting small-medium sized arteries. Glomerulonephritis accompanied by granulomatous lesions of the upper and lower respiratory tract is a common presentation. Other kinds of vasculitides are rare in childhood.

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Handbook of Systemic Autoimmune Diseases, Volume 6
Pediatrics in Systemic Autoimmune Diseases
Rolando Cimaz and Thomas Lehman, editors

CHAPTER 13

Pediatric Antiphospholipid Syndrome

Tadej Avčin[a,*], Rolando Cimaz[b]

[a]*Department of Allergology, Rheumatology and Clinical Immunology, University Children's Hospital Ljubljana, University Medical Centre, Ljubljana, Slovenia*
[b]*Department of Pediatrics, Hopital Edouard Herriot, Lyon, France*

1. Introduction

Antiphospholipid syndrome (APS) is a multisystem autoimmune disease characterized by vascular thrombosis, recurrent fetal loss, thrombocytopenia and other clinical manifestations in the presence of persistent circulating antiphospholipid antibodies (aPL) (Levine et al., 2002). APS is considered as the most common acquired hypercoagulation state of autoimmune etiology and may occur as an isolated clinical entity (primary APS) or in association with an underlying systemic disease, particularly systemic lupus erythematosus (SLE). The features of APS have been increasingly recognized in children and since aPL-related thrombosis can affect any organ, pediatricians of different subspecialties must be aware of this syndrome and associated complications (Avcin et al., 2002b; Ravelli and Martini, 2005).

2. Prevalence of aPL

"Antiphospholipid antibodies" is an umbrella term used to describe a heterogeneous group of autoantibodies directed against negatively charged phospholipids or phospholipid-binding plasma proteins. The most useful aPL for identifying patients with APS are anticardiolipin antibodies (aCL), anti-β_2 glycoprotein I antibodies (anti-β_2GPI) and lupus anticoagulant (LA).

2.1. Healthy children

aPL can be found in a high percentage of children without any underlying disorder. Such naturally occurring aPL are usually present at low levels and could be the result of previous infections or vaccinations that are common in the pediatric population. Published study designs in healthy children have been primarily cross-sectional, with one ascertainment of aPL; therefore, fluctuations over time cannot be accurately assessed and the true prevalence of persistent aPL in healthy population is not known. The estimated frequency of aCL in healthy children ranges from 3% to 28%, which is higher than in normal adult population (Rapizzi et al., 2000; Avcin et al., 2001; Cabiedes et al., 2002). The frequency of anti-β_2GPI in healthy children ranges from 3% to 7% and high levels of anti-β_2GPI seems to be relatively more frequent in preschool children than in adolescents and healthy adults (Avcin et al., 2001; Cabiedes et al., 2002). There are insufficient data to determine the clinical risk associated with incidental finding of positive aCL or anti-β_2GPI in otherwise healthy children. It has generally been assumed that naturally occurring aCL are not associated with thrombotic events, but it is prudent

*Corresponding author.
Tel.: +386 1 522 90 90; Fax: +386 1 522 93 57
E-mail address: tadej.avcin@kclj.si (T. Avčin).

DOI: 10.1016/S1571-5078(07)06017-5

to perform a follow-up determination after a time interval of at least 12 wk to exclude persistent positive test. LA have also been described in apparently healthy children and are usually found incidentally in pre-operative coagulation screening as prolonged activated partial thromboplastin time (aPTT). Male et al. (1999) reported that none of 80 asymptomatic children with incidentally found positive LA experienced clinically relevant complications during a mean follow-up of 2.9 years, and that over half had normalization of aPTT values.

2.2. Systemic lupus erythematosus

SLE is the autoimmune disease where aPL occurs in highest percentage. The reported frequencies of aCL and LA in juvenile SLE have ranged from 19% to 87% and from 10% to 62%, respectively (Shergy et al., 1988; Ravelli et al., 1994; Gattorno et al., 1995; Seaman et al., 1995; Berube et al., 1998). This wide variability in the frequency of aPL reported in pediatric lupus may be due to differing sensitivities of assays and heterogeneity in the patient population regarding the disease duration, clinical features and disease activity. A meta-analysis of nine reported series of aPL in children with SLE yielded a global prevalence of 45% for aCL and 22% for LA (Avcin et al., 2002b).

A variety of clinical features have been reported to be present in aPL positive children with SLE including arterial and venous thromboses, different neurological manifestations and autoimmune cytopenias. In a retrospective cohort study of 149 children with SLE, Levy et al. (2003) identified 13 patients with thromboembolic events who were all positive for LA. The reported incidence of thrombosis was 54% in LA positive children with SLE (Levy et al., 2003). Additionally, Male et al. (2005) found that LA was the strongest predictor of the risk of thrombotic events in a non-selected group of 58 children with SLE, and that a single positive test for anti-β_2GPI and persistent aCL positivity were also significantly associated with thrombosis. Von Scheven et al. (2002) demonstrated elevated anti-β_2GPI in 48% of 57 children with SLE and found positive correlation with stroke, but not with other APS manifestations. The same group also reported association between β_2GPI gene polymorphism and the development of both aPL and aPL-related clinical manifestations in pediatric SLE (von Scheven and Elder, 2005).

2.3. Juvenile idiopathic arthritis

The presence of aCL in children with juvenile idiopathic arthritis (JIA) has been investigated in several cross-sectional studies, which reported a frequency ranging from 7% to 53% (Caporali et al., 1991; Serra et al., 1999). A prospective study of 28 children with JIA demonstrated persistently positive aCL in 21%, anti-β_2GPI in 4% and no patient with persistently positive LA (Avcin et al., 2002a). Most studies in JIA found no association between the presence of aPL and disease activity, and no clinical manifestations of APS were observed. There were only two reports of aPL-associated thrombosis in children with JIA (Caporali et al., 1992; Andrews and Hickling, 1997). Von Landenberg et al. (2003) found a high incidence of persistent parvovirus B19 infection in aPL positive children with JIA.

2.4. Other diseases

The presence of circulating aPL has been demonstrated in a variety of other pediatric autoimmune and non-autoimmune diseases, including juvenile dermatomyositis, Henoch-Schönlein purpura, Kawasaki syndrome, Wegener's granulomatosis, rheumatic fever, insulin-dependent diabetes mellitus, atopic dermatitis and malignancies (Avcin et al., 2002b; Ravelli and Martini, 2005). In most of these conditions aPL-related clinical manifestations are unusual, and the significance of aPL needs further confirmation.

2.5. Infections

There is growing evidence that various infections can induce aPL, which are usually transient and

not associated with thrombotic events. aPL has been described in adult patients with a broad range of infections, including varicella, cytomegalovirus, parvovirus B19, hepatitis C virus, human immunodeficiency virus, streptococcus, Mycoplasma pneumoniae and leprosy (Cervera and Asherson, 2005). The majority of post-infectious aPL differ immunochemically from those seen in patients with autoimmune diseases, and do not require the presence of β_2GPI for their binding to cardiolipin (Hunt et al., 1992; McNally et al., 1995); however, this distinction has been found not to be absolute (Blank et al., 2002). Kratz et al. (1998) described positive aCL in 30% of 88 children with upper airway infections without any thromboembolic complications. Additionally, Frauenknecht et al. (2005) detected at least one subtype of aPL in 89% of 37 children with infection and prolonged aPTT. Because most children suffer from frequent viral and bacterial infections, a high percentage of incidental aPL positivity might be expected in pediatric populations. Since post-infectious aPL tend to be transient, all positive aPL values should be verified on at least two occasions, preferably at a time when the child has not had a recent infection. The risk of APS manifestations with post-infectious aPL is not completely absent, however, and several case reports do describe thromboses following chickenpox infection linked to the presence of LA and reduced plasma level of protein S (Josephson et al., 2001).

3. Epidemiology of APS

The actual prevalence of APS in pediatric population is difficult to estimate since there are no validated criteria and diagnosis rests on extension of adult guidelines and clinical judgment. Current consensus criteria for the classification of APS in adult population designate patients who suffered from vascular thrombosis or recurrent fetal losses, accompanied by elevated titers of aCL, anti-β_2GPI or LA (Miyakis et al., 2006) (Table 1). APS in children has been largely reported in patients with thromboses and less frequently in association with neurological or hematological manifestations. Recurrent fetal losses, which represent one of the most important clinical criteria in adults, are obviously not a pediatric problem and it is possible that current consensus criteria may fail to recognize significant groups of pediatric patients with APS.

Table 1
Preliminary criteria for the classification of APS (Miyakis et al., 2006)

Clinical criteria	
1.	Vascular thrombosis One or more clinical episodes of arterial, venous or small vessel thrombosis, in any tissue or organ.
2.	Pregnancy morbidity One or more unexplained deaths of a morphologically normal fetus at or beyond the 10th wk of gestation. One or more premature births of a morphologically normal neonate at or before the 34th wk of gestation because of severe pre-eclampsia or eclampsia, or placental insufficiency. Three or more unexplained consecutive spontaneous abortions before the 10th wk of gestation.
Laboratory criteria	
1.	Anticardiolipin antibody of IgG and/or IgM isotype in serum or plasma Must be present in medium or high titer (i.e., >40 GPL or MPL, or >99th percentile) on two or more occasions, at least 12 wk apart, measured by a standardized enzyme-linked immunosorbent assay.
2.	Anti-β2 glycoprotein-I antibody of IgG and/or IgM isotype in serum or plasma Must be present in titer >99th percentile, on two or more occasions, at least 12 wk apart, measured by a standardized enzyme-linked immunosorbent assay.
3.	Lupus anticoagulant in plasma Must be present on two or more occasions at least 12 wk apart, detected according to the guidelines of the International Society on Thrombosis and Hemostasis.

Note: APS is considered to be present if at least one of the clinical criteria and one of the laboratory criteria are met.

Although the incidence of thrombosis in children is significantly less than in adults, the proportion of aPL-related thrombosis in children may be higher than previously thought. Manco-Johnson and Nuss (1995) identified LA in 25% of 78 consecutive children who were diagnosed with thromboses in their institution.

4. Etiology and pathogenesis

There is good evidence that aPL can be pathogenic rather than a simple serological marker for APS (Meroni and Riboldi, 2001; Mackworth-Young, 2004). These antibodies possess different pathogenic properties and it has become apparent that aPL found in patients with APS generally require the presence of β_2GPI for binding to cardiolipin, while aPL associated with infections bind to phospholipids directly (Hunt et al., 1992; McNally et al., 1995).

Several mechanisms have been proposed to explain the prothrombotic nature of aPL. The first implicates interference of aPL with the function of phospholipid-binding proteins involved in the regulation of the coagulation cascade. It has been shown that aPL can interfere with anticoagulant effects of protein C and protein S systems in two main different ways, including inhibition of the activation of protein C mediated by interference with thrombin and thrombomodulin, and acquisition of activated protein C resistance and protein C and/or S deficiency (Male et al., 2001). Because of the physiological role of the protein C and protein S systems, this finding can only explain the higher risk for venous but not for arterial thrombosis. A second theory focuses on the relationship between aPL and endothelial cells. It is now accepted that aPL, and particularly anti-β_2GPI antibodies, are able to react with the molecule expressed on the endothelial surface membrane and to induce a cell activation that ends in the expression of a proinflammatory and a procoagulant phenotype (Meroni et al., 2001). A third theory implicates an oxidant-mediated injury of the vascular endothelium. It has been demonstrated that the oxidation of phospholipids may be necessary for aPL recognition and autoantibodies to oxidized low-density lipoprotein (oxLDL)/β_2GPI complexes were detected in APS patients (Matsuura et al., 2005). Elevated levels of anti-oxLDL/β_2GPI complexes antibodies have been proposed to be markers for arterial thrombosis in the APS. An alternative theory by which aPL might promote thrombosis is by activating monocytes and platelets, resulting in production of tissue factor or thromboxane (Yasuda et al., 2005).

The triggering event for the development of APS is not known, nor is it known why in some patients this disorder behaves in such an aggressive fashion as catastrophic APS. It has been suggested that aPL per se are unable to trigger the coagulation cascade but that they can do it when a concomitant "second" thrombophilic condition does occur (the so-called "two-hit hypothesis") (Meroni and Riboldi, 2001).

The pathogenic mechanisms of pediatric APS have not been thoroughly investigated and remain largely unexplained. The most obvious factors that have particular relevance in pediatric population include increased incidence of infections, routine immunizations and immaturity of the immune and other organ systems. The frequency of infectious processes in childhood is likely responsible for the higher prevalence of non-pathogenic and transient aPL. There is increasing evidence concerning a possible association of aPL with immunizations. Blank et al. (2002) convincingly demonstrated induction of pathogenic anti-β_2GPI antibodies in mice immunized with Haemophilus influenzae or tetanus toxoid. Moreover, it has been reported that vaccination with recombinant hepatitis B vaccine may rarely induce production of anti-β_2GPI in healthy young adults (Martinuc-Porobic et al., 2005). Finally, age-dependent differences in immune responses are particularly important consideration in pediatric population and suggest a broader association of aPL with specific immunological mechanisms. For example, high frequency of non-thrombogenic IgG anti-β_2GPI with unique epitope specificity was found in infants with atopic dermatitis, presumably due to exaggerated immune response to nutritional antigens (Ambrozic et al., 2002).

5. Clinical manifestations

Classical clinical features of APS in adult population include vascular thromboses and recurrent fetal losses. Besides these classical features, the clinical spectrum has broadened considerably over the last years, and thrombocytopenia, hemolytic anemia, transverse myelitis, livedo reticularis, cardiac valve disease, multiple-sclerosis-like syndrome, chorea and migraine have been reported as well (Cervera et al., 2002). Most of the clinical features which can occur in adults with aPL have also been described in children, but there clearly are differences in the frequency of specific clinical events, since children generally do not have prothrombotic risk factors present in adults (such as atherosclerosis, cigarette smoking, hypertension, oral contraceptives, pregnancy etc.). Among the 29 children with APS currently enrolled in the international Register of Pediatric APS, venous thromboses were more frequent in female adolescents with SLE and arterial ischemic cerebral events in younger children (unpublished data).

5.1. Thromboses

Vascular occlusion in APS may involve arteries and veins at any level of the vascular tree and in all organ systems. The most frequently reported association with aPL is deep and superficial venous thrombosis in the lower extremities, which may be complicated by pulmonary embolism in some cases. Venous thrombosis can also affect vessels such as superior and inferior vena cava, renal, mesenteric, adrenal, hepatic, retinal and cerebral veins (Table 2).

Arterial thrombosis most often involves the cerebrovascular circulation, with most patients presenting with stroke or transient ischemic attacks. Other reported sites of arterial thrombosis include coronary, renal, mesenteric, hepatic, retinal and peripheral arteries (Table 3) (Levy et al., 2003; Gattorno et al., 2003; Ravelli and Martini, 2005).

The APS may occasionally be manifested with small vessel occlusions causing thrombotic microangiopathic hemolytic anemia, consumptive thrombocytopenia and varying degrees of organ involvement (Espinosa et al., 2004). The presence of aPL has been demonstrated in the classic pediatric hemolytic-uremic syndrome with acute renal failure due to widespread glomerular thrombosis (Ardiles et al., 1998; te Loo et al., 2002). aPL-associated nephropathy with renal small-artery vasculopathy and chronic renal ischemia has been reported in adult APS patients (Tektonidou et al., 2004).

Catastrophic APS is an uncommon, potential life-threatening variant of APS characterized by aggressive microvascular occlusive disease involving multiple organs, mainly kidney, lung, central nervous system, heart and skin (Falcini et al.,

Table 2
Venous thrombosis manifestations associated with aPL in children

Vessel involved (organ)	Clinical manifestations
Limbs	Deep vein thrombosis
Skin	Livedo reticularis, chronic leg ulcers, superficial thrombophlebitis
Large veins	Superior or inferior vena cava thrombosis
Lungs	Pulmonary thromboembolism, pulmonary hypertension
Brain	Cerebral venous sinus thrombosis
Eyes	Retinal vein thrombosis
Liver	Budd-Chiari syndrome, enzyme elevations
Adrenal glands	Hypoadrenalism, Addison's disease

Table 3
Arterial thrombosis manifestations associated with aPL in children

Vessel involved (organ)	Clinical manifestations
Limbs	Ischemia, gangrene
Brain	Stroke, transient ischemic attack, acute ischemic encephalopathy
Eyes	Retinal artery thrombosis
Kidney	Renal artery thrombosis, renal thrombotic microangiopathy
Heart	Myocardial infarction
Liver	Hepatic infarction
Gut	Mesenteric artery thrombosis
Bone	Infarction

1997; Orsino et al., 2004; Cervera et al., 2005). Diagnosis of catastrophic APS is based on clinical involvement of at least three organ systems over a short period of time (less than 1 wk) with histopathological evidence of small vessels occlusion and serological confirmation of the presence of aPL (Asherson et al., 2003).

5.2. Neurological manifestations

The most common neurological complications of APS are ischemic stroke and cerebral venous sinus thrombosis, both caused by thrombotic occlusion of cerebral vessels. aPL were found to be a significant prothrombotic risk factor for arterial and venous ischemic cerebral events (deVeber et al., 1998; Kenet et al., 2000; deVeber et al., 2001), and screening of all children with ischemic stroke for aPL seems to be justified. The association between aPL and recurrent stroke risk is more controversial. In a prospective observational study including 185 children with arterial ischemic stroke or transient ischemic attack, Lanthier et al. (2004) found no difference in recurrence rates between the aCL-positive and aCL-negative groups, but the aCL-positive children in their cohort were more likely to receive antithrombotic treatment which might decrease their recurrence risk.

Several other neurological manifestations have been linked to aPL such as chorea, seizures, transverse myelopathy, migraine, cerebral ataxia, transient global amnesia, psychosis and peripheral neuropathy (Angelini et al., 1996). These manifestations are not fully explained by the procoagulant effect of aPL and there are some experimental data that support possibility of a non-thrombotic, immune-mediated mechanisms of neurological impairment associated with aPL (Caronti et al., 1998; Chapman et al., 1999; Steens et al., 2006). Chorea has been described as an isolated clinical manifestation in children with aPL or in association with SLE (Angelini et al., 1996; Kiechl-Kohlendorfer et al., 1999; Watanabe and Onda, 2004). The association between childhood seizure disorder and aPL has been reported in two prospective studies (Eriksson et al., 2001; Cimaz et al., 2002). There has been controversy concerning a possible association of aPL and migraine, and recent prospective study has failed to demonstrate an association of aPL in an unselected group of children with migraine compared to tension-type headaches and healthy children (Avcin et al., 2004).

5.3. Hematological manifestations

There are well-documented associations between aPL and hematological abnormalities, such as thrombocytopenia, autoimmune hemolytic anemia and, less commonly, leukopenia (Cuadrado et al., 1997; Guzman et al., 1994; Cervera et al., 2002). Thrombocytopenia is usually mild (with platelet counts greater than $50 \times 10^9\,L^{-1}$) and clinically benign; however, there are a few reports of children with severe aPL-related thrombocytopenia causing major bleeding (Avcin et al., 2003). Thrombocytopenia may appear as an isolated clinical manifestation, associated with autoimmune hemolytic anemia (Evans syndrome) or along with other APS manifestations. Children with aPL who present with isolated hematological manifestations needs closer follow-up because of risk for the development of future thrombosis or progression to overt SLE (Diz-Küçükkaya et al., 2001; Gattorno et al., 2003).

Although the presence of LA confers an increased risk for thrombosis, this antibody has been occasionally associated with a severe bleeding diathesis. This complication termed ''LA-hypoprothrombinemia syndrome'' is usually preceded by a viral infection and has been attributed to the presence of antiprothrombin antibodies that could cause rapid depletion of plasma prothrombin (Lee et al., 1996; Becton and Stine, 1997; Anderson et al., 2003).

5.4. Other manifestations

Dermatological manifestations of aPL have not been extensively investigated in childhood, but in clinical practice many aPL positive children present with chronically cold hands and livedo reticularis. aPL were found in 21% of children

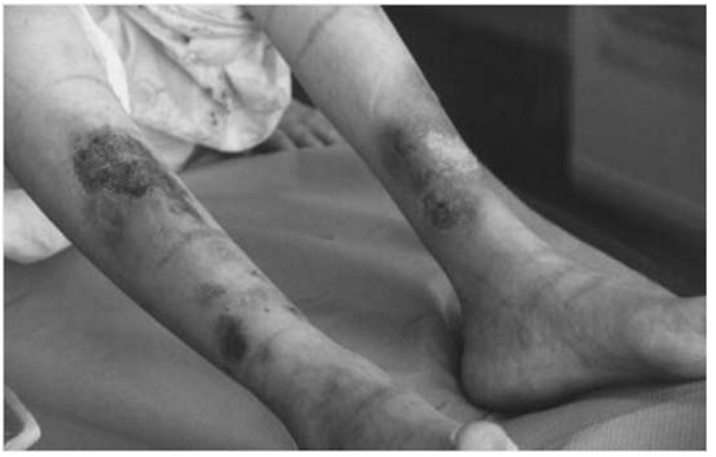

Figure 1. Chronic leg ulcers in a child with SLE and positive aPL. (See Colour Plate Section.)

with primary or secondary Raynaud's phenomenon (Nigrovic, et al., 2003). Several other dermatological manifestations have been associated with APS, including skin ulcers due to multiple small vessel occlusions (Fig. 1), cutaneous necrosis, digital gangrene and superficial thrombophlebitis (Cervera et al., 2002; Tomizawa et al., 2003).

An increased risk of developing avascular necrosis of bone in the absence of previous steroid administration has been reported in adult patients with aPL (Tektonidou et al., 2003). Association between aPL and Perthes disease has been suggested in pediatric population (Ura et al., 1992).

Echocardiographic studies have disclosed heart valve abnormalities resembling Libman-Sacks endocarditis in 11% of adult patients with APS (Cervera et al., 2002), but the frequency of this complication in pediatric APS is unknown.

5.5. Neonatal APS

Neonatal APS is a rare clinical entity characterized by neonatal thrombotic disease due to the transplacental passage of maternal aPL. While women with aPL show a high incidence of obstetric and fetal complications, the aPL-related thrombosis in their offspring seems to be exceedingly rare (Avcin et al., 2002b). The low frequency of neonatal thrombosis has been attributed to the lack of the most known "second hit" risk factors in infants, and to a low transplacental passage of IgG2 subclass of aPL, which are responsible for most clinical pathogenicity (Sammaritano et al., 1997).

Neonatal thromboses associated with transplacentally acquired aPL were most commonly described in cerebral vessels and abdominal organs (Navarro et al., 1997; Avcin et al., 2002b). Special concern is needed particularly when dealing with aPL-positive infants who are exposed to other acquired thrombotic risk factors (i.e, central vascular catheters, sepsis, prematurity, congenital heart disease), and possibly inherited prothrombotic disorders (i.e, deficiencies of antithrombin III, protein C, protein S, factor V Leiden mutation).

6. Diagnostic investigations

The presence of aPL should be investigated in every child presenting with thrombosis or clinical features that are very suggestive of APS, such as chorea, unexplained thrombocytopenia, hemolytic anemia and livedo reticularis. Determination of aPL may provide clinically relevant information also in children with other aPL-associated clinical features, including various neurological and dermatological manifestations (Avcin et al., 2002b; Ravelli and Martini, 2005). In a child with SLE, it is recommended to perform aPL testing at the time

of diagnosis and then at least once yearly as part of routine screening.

aPL are detected by a variety of laboratory tests and multiple tests should be used in diagnosing APS, because patients may be negative according to one test but positive according to another. Persistent positivity of aPL is of major importance for diagnosing APS and a time interval of at least 12 wk between tests was suggested to demonstrate persistence (Miyakis et al., 2006).

The most sensitive test for aPL is the aCL test, which uses enzyme-linked immunosorbent assay to determine antibody binding to solid plates coated either with cardiolipin or other phospholipids. The specificity of aCL for APS increases with titer and is higher for the IgG than for the IgM isotype. The observation that many aCL are directed against an epitope on β_2GPI led to the development of anti-β_2GPI immunoassays, which have improved specificities over the aCL test. The LA test is a functional assay measuring the ability of aPL to prolong in vitro phospholipid dependent clotting reactions such as the aPTT, the Russell viper venom time or the kaolin clotting time. In vivo, however, the presence of LA is paradoxically associated with thrombotic events rather than with bleeding. Inadequate data exist as to the clinical utility of other aPL assays for antibodies to prothrombin, phosphatidylserine and phosphatidylethanolamine.

Thrombosis must be confirmed by objective validated criteria. Imaging studies are aimed to detect thrombosis in target organ with the use of ultrasound, lung scanning, magnetic resonance arteriography/venography or conventional angiography. For histopathologic confirmation of small vessels occlusions, thrombosis should be present without significant evidence of inflammation in the vessel wall.

7. Differential diagnosis

Given the spectrum of clinical manifestations, differential diagnosis of APS is very broad and depends on target organ involvement. Characteristic of pediatric thrombosis is the requirement to have multiple risk factors that lead to abnormal clotting (Richardson et al., 2002), therefore, all children presenting with aPL-related thrombotic event should receive a broad investigation for congenital prothrombotic states (protein S, protein C, antithrombin III, total cholesterol, triglycerides, homocystein, factor V Leiden, prothrombin G20210A mutation) and acquired prothrombotic risks (infection, malignancy, heart disease, nephrotic syndrome, systemic vasculitis, central venous line, surgery, immobilization).

Differentiation of isolated aPL-related thrombocytopenia from classic idiopathic thrombocytopenic purpura is important to indicate closer follow-up because of risk for the development of future thrombosis or progression to SLE (Gattorno et al., 2003).

Catastrophic APS should be distinguished from severe lupus vasculitis, sepsis, thrombotic thrombocytopenic purpura, macrophage activation syndrome and disseminated intravascular coagulation (Ravelli and Martini, 2005).

8. Treatment

Asymptomatic children, in whom aPL were incidentally found, only rarely develop thrombotic complications. Because of the low thrombosis risk, it is generally assumed that these children do not need any prophylactic treatment.

There is considerable controversy as to whether prophylactic treatment is indicated in children who have never had thrombosis but have persistently positive aCL in moderate to high titers and/or persistently positive LA. An expert panel has recommended the use of low-dose aspirin (75–100 mg) for prevention of thrombosis in asymptomatic adult patients with a persistently positive aPL (Alarcon-Segovia et al., 2003), although there is no evidence yet that aspirin may provide protection against deep venous thrombosis or pulmonary embolism. Prophylaxis with heparin administered subcutaneous should be considered to cover high-risk situations, such as prolonged immobilization or surgery. Hydroxychloroquine, which has modest anticoagulant

properties, may be protective against the development of thrombosis in aPL positive patients with SLE (Petri, 1996). The optimal management of adolescents with aPL should include also the avoidance or reduction of other risk factors for thrombosis such as smoking, obesity, high-blood pressure and use of oral contraceptives.

Treatment of the acute thrombotic event in children with APS is no different from that of thrombosis arising from other causes. Patients are anticoagulated with unfractionated or low-molecular weight heparin followed by oral anticoagulants. There is general agreement that long-term anticoagulation is needed in children who experienced an aPL-related thrombosis to prevent recurrences, but there is no consensus about the duration and intensity of this therapy. Recommendations for a high level of anticoagulation producing an INR of 3.0 or higher were based on a large retrospective cohort study of adults with APS (Khamashta et al., 1995). These recommendations were challenged by two prospective, randomized, controlled studies which showed that moderate intensity warfarin (target INR, 2.0–3.0) was as effective as high-intensity warfarin (target INR, 3.0–4.0) for the prevention of recurrent thrombosis in patients with APS (Crowther et al., 2003; Finazzi et al., 2005). Given that the risk of recurrence might be lower in aPL positive children compared with adults, and considering the higher risk of hemorrhage during play and sports, it was suggested to perform moderate intensity anticoagulation therapy targeted at an INR of 2.0–3.0 in pediatric patients who have experienced an aPL-related thrombosis (Ravelli and Martini, 2005). Another recent large study has suggested that either aspirin or moderate intensity warfarin is acceptable for patients with aPL and a first episode of ischemic stroke (Levine et al., 2004). In the absence of controlled trials, the optimal type and duration of treatment cannot be determined.

Treatment of catastrophic APS needs to be aggressive with a combination of immunosuppressive therapy, anticoagulation with full doses of heparin and attempts to achieve a rapid reduction of aPL titers by intravenous immunoglobulin or, alternatively, plasma exchange (Asherson et al., 2003; Cervera and Asherson, 2005).

Key points

- Antiphospholipid syndrome is rare in the pediatric age, but it represents an interesting phenomenon since most of the known ''second hit'' risk factors such as atherosclerosis, smoking, hypertension, contraceptive hormonal treatment and pregnancy are not present in childhood.
- The increased frequency of infectious processes in the childhood age is likely responsible for the relatively high prevalence of non-pathogenic and transient aPL.
- Of particular interest is the special entity of neonatal APS, which represents an in vivo model of acquired autoimmune disease, in which transplacentally acquired aPL cause thrombosis in the newborn.
- Treatment is less aggressive overall in pediatric APS, given the reluctance to anticoagulate children over the long term. Studies on the outcome of pediatric APS and the relative risks of prolonged anticoagulation in children are necessary to determine the type and duration of anticoagulation therapy.
- International registries for pediatric and neonatal APS are currently in place; epidemiological, clinical and laboratory research will help to shed light on all the still obscure aspects of this fascinating but rare disorder in the very young.

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Handbook of Systemic Autoimmune Diseases, Volume 6
Pediatrics in Systemic Autoimmune Diseases
Rolando Cimaz and Thomas Lehman, editors

CHAPTER 14

Behçet's Disease

Isabelle Koné-Paut*

Department of Pediatrics and Pediatric Rheumatology, Bicêtre University Hospital, Le Kremlin Bicêtre, France

1. Introduction

Behçet's disease (BD) is a multisystem inflammatory disorder considered to be one of the vasculitic syndromes. It was initially reported as the association of bipolar aphthous lesions with uveitis. The vasculitic lesions consist of non-specific mononuclear cell infiltrates. Release of cytokines and expression of HLA class II antigens lead to ulceration easily identifiable in mucosae and skin. Involvement of medium and large vessels may lead to serious neurological or ocular damage and/or pulmonary or cardiac complications and death (Sakane et al., 1999). Although the normal age of onset is between the ages of 30 and 40, the disease may start before the age of 16 (Kim et al., 1994; Koné-Paut et al., 1998; Davatchi et al., 1993; Hamza, 1993).

The etiology of BD is unknown. Cases cluster from the islands of Japan to Mediterranean basin along the former Silk Road, suggesting genetic or environmental influences. For subgroups of patients, genetic factors may explain an earlier onset with a Mendelian pattern of inheritance (Molinari et al., 2003). The HLA B5101 antigen is closely associated with BD, especially in Mediterranean countries; however, it appears to exacerbate the severity of ocular manifestations, rather than be a causative factor (Mizuki and Inoko, 1993; Mizuki et al., 1997). The HLA-like antigen (MICA) and some mutations of the gene responsible for familial Mediterranean fever (MEFV) are also associated with BD, suggesting a multifactorial etiology (Touitou et al., 2000).

The clinical manifestations of BD are classically distinguished as major or minor based on their severity and frequency (Table 1). This diagnosis is based on a combination of major criteria, or major and minor criteria, since there are no pathognomonic clinical or biological features (Table 2). BD signs and symptoms overlap with those of several diseases: complex aphthoses, periodic fever syndromes, neutrophilic disorders, uveomeningitis, vasculitis, and seronegative spondyloarthropathies.

The prognosis of BD is unpredictable due to its insidious and recurrent nature. Eye and brain involvement may lead to chronic morbidity and severe disability (blindness, dementia, pseudobulbar syndrome). Steroids and immunosuppressive drugs are still the mainstays of treatment for severe manifestations. Specifically targeted biologic therapies against tumor necrosis factor-α (etanercept, infliximab) and interferon alpha (IFNα-2a) (Pipitone et al., 2006) have recently been used with success.

2. Epidemiology

The prevalence of BD is high in Eastern countries: Iran $16/10^5$, Japan $10–15/10^5$, Turkey $8–37/10^5$

*Corresponding author.
Tel.: +33-1-45-21-32-46; Fax: +33-1-45-21-33-43
E-mail address: isabelle.kone-paut@bct.aphp.fr (I. Koné-Paut).

DOI: 10.1016/S1571-5078(07)06018-7

Table 1
Manifestations of Behçet's disease from Barnes and Yazici (1999)

Major	Percentage of patients	Minor	Percentage of patients
Oral ulceration—recurrent	97–98	Arthritis and arthralgia	45–50
Genital ulceration	80–90	Neurological lesions	5–25
Inflammatory eye disease	50	Vasculitis	25
Iritis ± hypopyon		Aneurysm formation	
Retinal vasculitis		Arterial/venous thrombosis	
Skin lesions	80	Gastrointestinal lesions	0–25
Erythema nodosum	45	Cardiovascular lesions	
Folliculitis/acne	70	Pleuropulmonary lesions	
Pathergy test		Epididymitis	8

Table 2
Criteria of the International Study Group for BD

Positive diagnosis requires the major criterion plus two of the minor criterion
Major criterion
Recurrent oral aphtosis (major, minor, herpetiform) observed by a physician at least three times over a period of 12 months
Minor criterion
Genital ulceration
Eye lesion: retinal vasculitis or uveitis (ant., post.)
Skin lesion: erythema nodosum, acneiform nodules, papulo-pustular lesion (post adolescent, not receiving steroids)
Positive pathergy test: done by needle prick (oblique insertion of 20-gauge needle) or intradermal saline injection and read at 48 h by a physician, positive reactions include: papula, pustula, or papula with surrounding erythema

and lower in Western countries: $2/10^5$ in Germany and $2.5/10^5$ in Italy. Initial symptoms of BD are observed before age 16 in 4–26% of reported cases. The exact prevalence of pediatric BD is unknown (Zouboulis et al., 1997). French and Italian nationwide surveys reported a prevalence 1/600,000 in children before 16 years (Koné-Paut and Bernard, 1993; Picco et al., 2002). BD is reported more commonly in females in Japan and Korea, whereas males are more commonly affected in Middle Eastern countries. An equal sex ratio is observed in the European and the pediatric populations with reported BD. The familial aggregation (2–15%) is higher in endemic countries (Zouboulis et al., 1997; Gul et al., 2000; Fresko et al., 1998) and on the pediatric population (Koné-Paut et al., 1999). We had performed a first national epidemiologic survey of pediatric BD in 1992 and found 17 cases. During the year 2000 we updated our French pediatric series to 60 cases that fulfilled the international criteria, which increased the prevalence to 1/100,000 in this age group (Koné-Paut et al., 2002). We could also collect 86 cases from an international collaborative study involving 5 centers in 4 countries: Turkey, Iran, Saudi Arabia, and France (Koné-Paut et al., 1997). Several pediatric series are in the literature. Not all series distinguish patients meeting the criteria before age 16 and patients experiencing the first symptoms of BD before age 16 but subsequently meeting the criteria later (Hamza, 1993; Pivetti Pezzi et al., 1995; Kim et al., 1994; Bahabri et al., 1996). The gradual increase in reported cases may be related to greater awareness of the disease. Pediatric onset BD is characterized by more frequent familial aggregation and more frequent incomplete or atypical manifestations of the disease.

3. Etiology/pathogenesis

Both environmental (Herpes virus, *Streptococcus sanguis*, *Mycoplasma fermentans*, heat shock proteins) and genetic factors are involved in the etiology of BD pathogenesis (Lehner, 1997; Sakane et al., 1999). Genetic factors may be stronger in pediatric cases, while environmental factors may play a greater role in adult cases. Environmental factors may interact with immunological

mechanisms such as significant TH1 cell responses (Yamashita et al., 1997), by damaging oral mucosa. We recently conducted a familial segregation analysis which suggests an autosomal recessive pattern of inheritance in a subgroup of pediatric patients (Molinari et al., 2003).

4. Clinical manifestations

4.1. Main manifestations

4.1.1. Aphthosis

The aphthous stomatitis of BD is not strikingly different from other aphthoses, the lesions often last up to 2 wk, are frequently multiple, and may be scarring. They may occur on any part of the oral cavity including the palate and pharynx. Peculiar aspects include: punctiform, herpetiform, giant, necrotic, or malignant lesions but none of these are specific for BD. Oral aphthosis is the initial manifestation of 70–90% of pediatric BD. Lesions may appear as early as the first year of life. Careful follow-up is required since other BD symptoms may only appear several years later (Barnes and Yazici, 1999; Lee et al., 2003).

Genital lesions are generally painful, and located on the vulva or scrotum. Penile and perianal lesions occur more frequently in childhood. The presence and association with scarring strongly suggests the ultimate diagnosis will be BD.

4.1.2. Skin lesions

Acneiform, folliculitis-like, and papulo-pustular skin lesions often occur (Fig. 1). Unlike juvenile acne these lesions occur primarily over the lower extremities. Erythema nodosum (EN) and other vasculitic lesions often occur on the lower limbs in children with BD. Sweet's syndrome-like lesions, pyoderma gangrenosum, and necroziting vasculitis are less common in childhood.

Pathergy, the hyperreactivity of skin to intradermal injection or needle prick, was described by Blobner in 1937 and is the most unique feature of BD. Pathergy is defined as an erythemous induration with sterile pus at its center induced by needle prick or intradermal injection of normal saline. The reaction appears within 12–24 h. Pathergy occurs most commonly among Middle Eastern and Mediterranean patients. The prevalence of pathergy in children is low.

4.1.3. Eye lesions

The most common ocular involvement is posterior or pan uveitis. This is frequently bilateral and accompanied by retinal vasculitis, macular edema, and papillitis (Mason and Barnes, 1969). The

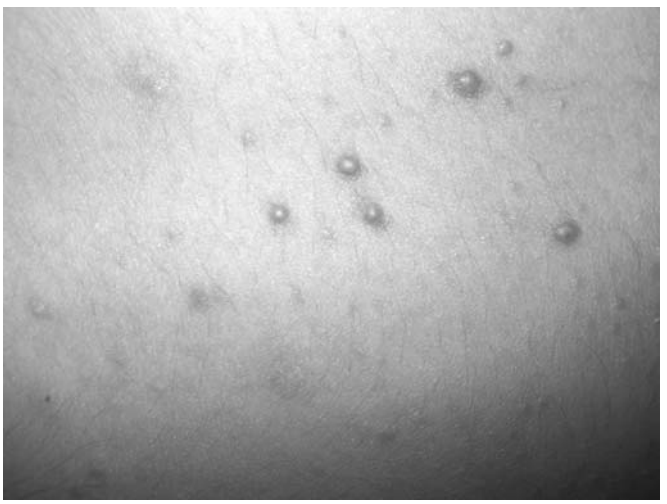

Figure 1. Papulo-pustular lesions in Behçet's disease. (See Colour Plate Section.)

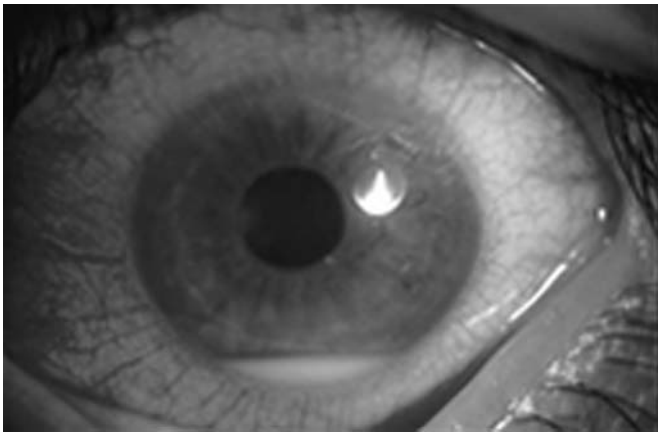

Figure 2. Ocular redness plus hypopion in a child with Behçet's disease. (See Colour Plate Section.)

course may be severe, with loss of visual acuity secondary to optic atrophy. Males are more frequently affected. Anterior uveitis with hypopion is rarely observed (Fig. 2). Many other minor ocular manifestations may occur (Matsuo et al., 2002).

4.2. Other manifestations

4.2.1. Neurological involvement

Neurologic manifestations of BD include encephalomyelitis, aseptic meningitis, and benign intracranial hypertension. These may lead to organic psychiatric disturbances, cerebellar signs, pyramidal and extrapyramidal syndromes, pseudobulbar syndrome, or epilepsy. These features are not specific to BD, and may also occur in multiple sclerosis (Koné-Paut et al., 1997). Multiple necrotizing lesions may develop in both white and gray matter. Both inflammation and venous thrombosis occur. Multiple high-density focal lesions in the brain stem, basal ganglia, and cerebral white matter are typical features on T2-weighted MRI. Aseptic meningitis with headaches and meningitic syndromes are common.

4.2.2. Arthralgia/arthritis

Articular manifestations of BD are usually minor. Large joints may have acute or chronic inflammation. The arthritis is not erosive and does not leave permanent deformity. Polyarthritis or involvement of small joints is uncommon (Mason and Barnes, 1969).

4.2.3. Vasculitis

Venous thrombosis is a predominant feature of BD. Involvement of the tibial, femoral, and iliac vessels is common. Pulmonary artery involvement may lead to aneurysm and thrombus formation.

4.2.4. Miscellaneous

Cardiac complications (pericarditis, myocardial infarction) are exceptional (especially in childhood). Recurrent epididymitis is more classical.

5. Diagnostic investigations

Because there is no specific clinical or biological test, the definite diagnosis of BD requires the combination of major and minor clinical manifestations described above (Mason and Barnes, 1969; Behçet Disease Research Committee in Japan, 1974; Barnes and Yazici, 1999). These diagnostic criteria were defined by the International Study Group for Behçet's Disease (1990). The fulfillment of diagnostic criteria appears mandatory for multicenter research studies; however, they may not be optimal for individual patients, especially for atypical cases in younger patients (<16 years).

5.1. Biochemistry

Conventional laboratory tests do not help for the diagnosis of BD. Leukocytosis and elevated ESR may be observed during disease flares, especially in case of vascular complications. The cerebrospinal fluid analysis may show pleiocytosis, elevated protein and IgG levels. Oligoclonal bands and antibodies against myelin basic proteins are not found. The HLA B5101 allele is not required for BD but occurs with increased frequency and may reflect high risk for severe uveitis, especially in males.

6. Differential diagnosis

6.1. Aphthosis

Recurrent aphthous stomatitis (RAS) is a common oral disorder that affects 20% of the general population with familial clustering. The lesions of RAS are not caused by single factor. Food hypersensitivity, trauma, stress, or infection may suggest RAS. Other causes include the syndrome of periodic fever, aphthous stomatitis, pharyngitis, and adenitis (PFAPA) initially described in 12 children (Marshall, 1987). This disease is characterized by high fevers lasting up to 5 days, recurring regularly every 3–6 wk, with symptom-free intervals. These episodes are often accompanied by abdominal pain, headaches, and nausea. PFAPA is benign since it responds to oral steroids or tonsillectomy.

The hyper IgD syndrome (HIDS) is infrequent, but has to be taken into consideration in young children with either oral or bipolar aphthosis. The main presentation is recurrent fevers lasting 5–7 days, accompanied by headaches, lethargy, cervical adenitis, abdominal distress, urticarial rash, and transient arthritis. First manifestations of HIDS start during the first year of life and are triggered by infections and immunizations. A high level of serum IgD was previously considered as a hallmark of HIDS. However increasing case reports have shown that this finding is neither constant nor specific. Conversely, detection of mevalonic aciduria in a febrile patient allows the diagnosis since HIDS is caused by a partial mevalonate kinase (MVK) deficiency. Genetic confirmation is available by identifying mutations in the MVK gene on chromosome 12p13 (Drenth, 1999; Houten, 1999).

Immunodeficiencies, especially neutrophil defects may present with recurrent aphthoses. Among them, cyclic neutropenia is the most frequent in young children (Palmer et al., 1996). It may be accompanied by mucosal ulceration, lymphadenoathy, infectious colitis, and life-threatening infections. A cyclic 21-day oscillation in the peripheral blood neutrophil count from low ($<2\times10^{6}\cdot L^{-1}$, often 0) to near-normal or normal levels is typical. Mutations in the gene coding for neutrophil elastase into chromosome 19p13.3 are present in 90% of cases. Other disorders characterized by oral ulceration include chronic granulomatous disease, severe combined immunodeficiency, leukemia, HIV infection, and Crohn's disease.

6.2. Recurrent fever syndromes

Well-defined entities causing fevers that should be distinguished from BD include PFAPA syndrome, HIDS (described above), and familial Mediterranean fever (FMF). FMF is the most common recurrent fever syndrome affecting people from Middle Eastern and Mediterranean countries. Mutations of the MEFV gene on chromosome 16p13.3 are responsible for FMF, and the presence of two mutations (one on each chromosome) is mandatory for the definite diagnosis of this autosomal recessive disease. FMF and BD affect the same populations and share common clinical symptoms. It is also important to note that MEFV mutations are more frequent in BD patients than in the general population, suggesting at least one common factor for auto-inflammation in these episodic diseases.

7. Treatment

Treatment in BD is dictated by the type and severity of organ involvement. Close communication among the various specialists is essential for successful management. Colchicine has beneficial effects on mucocutaneous lesions in 50% of cases, and is recommended to prevent flares of uveitis (Miyachi et al., 1981). Thalidomide is rapidly

effective in severe aphtosis and pseudofolliculitis with the caution of possibly neuropathy that has to be carefully monitored (Hamuryudan et al., 1998). High-dose steroids alone or in combination with immunosuppressants (azathioprine, cyclosporine, cyclophosphamide) remain a mainstay of therapy if severe clinical manifestations are present (ocular, neurological, gastrointestinal, or vascular). Biologic therapies have been effective in pilot studies. IFNα-2a was the first used in 1986. IFNα-2a is able to decrease the number of circulating $\gamma\delta$ cells (increased in active lesions of BD), to enhance HLA expression in peripheral monocytes of BD patients, and to decrease the adhesion of T-cells to the endothelium (Sakane et al., 1999). Several studies in adult patients have shown the efficacy of IFNα-2a at a mean dosage of 6,000,000 IU/three times a week for uveitis (Wechsler et al., 2004; Kötter et al., 2004). Complete or partial response was seen in ocular disease and in arthritis and mucocutaneous manifestations. Relapses after treatment discontinuation were observed. Anti-TNF agents have shown encouraging results in early studies. In a randomized trial etanercept was effective for mucocutaneous lesions (Melikoglu et al., 2005).

Key points

- Behçet's disease may be observed in 4–26% of cases before age 16. The diagnosis is difficult in this age group because only few patients present a complete and typical disease as defined by the international criteria.
- For a definite diagnosis, physicians need to confirm the presence of mucocutaneous lesions (by observation and, if necessary, by another specialist as well). The differential diagnosis includes many other inflammatory disorders, e.g., PFAPA syndrome, mevalonate kinase deficiency, and Crohn's disease.
- The course of BD in children is not known but may be worse in boys than girls. The visual outcome could gradually improve with the use of new biologic therapies, especially IFNα-2a and TNF blocking agents.

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Handbook of Systemic Autoimmune Diseases, Volume 6
Pediatrics in Systemic Autoimmune Diseases
Rolando Cimaz and Thomas Lehman, editors

CHAPTER 15

Childhood Sarcoidosis

Carine H. Wouters[a], Carlos D. Rose[b,*]

[a]*Pediatric Rheumatology Unit, University Hospital, Leuven, Belgium*
[b]*Department of Pediatrics, Thomas Jefferson University, Division of Rheumatology duPont Children's Hospital, Wilmington, DE, USA*

1. Introduction

1.1. Definition

The term childhood sarcoidosis has been used to designate a chronic inflammatory disease characterized by granulomatous "boggy" polyarthritis and tenosynovitis, uveitis and rash. Extension of the disease to involve large vessels (Gedalia et al., 1996; Rosé et al., 1990; Gross et al., 1986) as well as heart, lung, kidney and liver (Fink and Cimaz, 1997) in different stages of the disease is rare. Childhood sarcoidosis is seen typically in children younger than 5 years of age and, in contrast with the adult form, is associated with a paucity of constitutional symptoms, namely fever, lymphadenopathy and fatigue.

Since its earliest descriptions, it has been recognized that childhood sarcoidosis can present both in a familial form, reported by Edward Blau in 1985 (Blau, 1985), and a sporadic one, known as early onset sarcoidosis (EOS) described in 1970 by North (North et al., 1970). Additionally, it is worth remarking that both Blau syndrome (BS) and EOS are highly associated with mutations in the gene coding for CARD15 (Caspase Recruitment Domain 15), a highly conserved protein involved in the intracellular mechanisms of the innate immune system. This finding has placed EOS and BS in a select group of rheumatic diseases for which a specific mutation has been described. Interestingly these two are the most "rheumatic" of all suggesting a particular arthritogenic effect of this mutation.

1.2. Nomenclature

Despite the histopathologic similarities between adult sarcoidosis and EOS/BS, there is not much connection between these entities—neither clinically nor genetically. We follow the pioneering writings of Dr Miller and agree that the term "sarcoidosis" should be removed from these forms of pediatric arthritis. It has become clear in recent years that the differences between BS and EOS are probably artificial. Hence, these authors echoing Dr Miller's suggestion subscribe to the idea of renaming these conditions pediatric granulomatous arthritis (PGA) perhaps with the clarification of familial for those with a family history, and sporadic for those without. Even that latter distinction could possibly be eliminated since the mutation in the sporadic form can generate new familial (BS) pedigrees because the disease not necessarily decreases reproductive potential in affected individuals.

1.3. History

In 1985, two independent reports described families with an autosomal dominant form of

*Corresponding author.
Tel.: +1-202-651-5970; Fax: +1-302-651-5970
E-mail address: crose@nemours.org (C.D. Rose).

DOI: 10.1016/S1571-5078(07)06019-9

granulomatous arthritis. Douglas Jabs described a three-generation family with four affected members. Clinical manifestations included non-caseating granulomatous synovitis, uveitis, cranial neuropathies including sensory hearing loss and transient sixth nerve palsy, but no cutaneous involvement (Jabs et al., 1985). That same year, Edward Blau reported a four-generation family with 11 affected members. This family exhibited non-caseating granulomatous synovitis and tenosynovitis, granulomatous uveitis (clumpy precipitates) and papulo-squamous skin rash with associated dermal non-caseating granulomas (Blau, 1985). A third family, involving a mother and two daughters, was reported in 1990 with the "Blau triad" of polyarthritis, iritis and granulomatous papulo-squamous rash, and BS emerged as a distinct clinical entity (Pastores et al., 1990). Clinically indistinguishable from BS, however lacking the autosomal dominant transmission, EOS has been recognized in the 1960s but the first detailed description is owed to North and colleagues (North et al., 1970). Over the following years, the phenotype of the disease has been expanded significantly with multiple descriptions (Raphael et al., 1993; Rotenstein et al., 1982; Saini and Rosé, 1996; Ting et al., 1998; Gedalia et al., 1996; Rosé et al., 1990; Gross et al., 1986).

In the mid 1990s, a susceptibility locus was mapped on the original Blau kindred to chromosome 16 positioned at 16p12-21 (Tromp et al., 1996). In 2001, a mutation in CARD15, also termed "Nucleotide Oligomerization Domain protein 2" (NOD2), was found to increase the risk of Crohn's disease (CD). This locus fell within the susceptibility region mapped by Tromp for BS, and since CD is a granulomatous disease, Miceli-Richard and colleagues tested this "candidate gene" in four French Blau families (Miceli-Richard et al., 2001). Three distinct mutations within the nucleotide-binding domain (NBD) of CARD15, were found and proven different from the ones found for CD which are located in the leucin reach repeat (LRR) domain of the same protein (Ogura et al., 2000; Hugot et al., 2001). Recent molecular work by two independent research teams has demonstrated the BS mutation of *CARD15* in sporadic early onset granulomatous arthritis, confirming that BS and EOS are the same disease (Kanazawa et al., 2004; Rosé et al., 2005). Currently, PGA in its both forms (EOS and BS) is considered part of the group of hereditary autoinflammatory diseases as listed in Table 1, and their associated mutations are referenced in the Infevers Database (Touitou et al., 2004).

Table 1
Hereditary auto-inflammatory diseases listed with OMIM number, gene and protein involved

Disease	OMIM number	Inheritance/gene	Protein
Familial mediterranean fever (FMF)	294100	AR/MEFV (16p13)	Pyrin
Hyper IgD syndrome (HIDS)	260920	AR/MVK (12q24)	Mevalonate kinase
Tumour necrosis factor receptor associated periodic syndrome (TRAPS)	142680	AD/TNFRSF1A (12p13)	TNF receptor 1
Familial cold autoinflammatory syndrome (FCAS)	120100	AD/CIAS1 (1q44)	Cryopyrin
Muckle Well syndrome (MWS)	191900	AD/CIAS1 (1q44)	Cryopyrin
Chronic infantile neurologic cutaneous articular syndrome (CINCA)	607115	AD/CIAS1 (1q44)	Cryopyrin
Pyogenic arthritis pyoderma gangrenosum and acne (PAPA)	604416	AD/PSPTPIP1 (15q24)	Proline serine threonin phosphatase interacting protein
Crohn's disease (CD)	266600	Variable/CARD15 (16q12)	Caspase activating recruitment domain 15
Blau syndrome (BS)	186580	AD/CARD15 (16q12)	Caspase activating recruitment domain 15

2. Epidemiology

Few population-based studies of EOS are available. In the Danish Sarcoid Registry between 1979 and 1994, only 48 confirmed cases out of 5,536 reported had onset before age 15 and only 3 before age 5 (Byg et al., 2003). Of these three, two were twins; although family history is not provided, one could assume autosomal dominant inheritance in this case. According to this study the adult form of sarcoidosis presenting in the pediatric age has an incidence of 0.29/100,000 person-years, and PGA (familial and sporadic) an incidence of 0.06/100,000 person-years (Hoffmann et al., 2004). In an attempt to investigate the clinical features of BS/EOS a North American registry was initiated by Petty and Lindsley between 1991 and 1993 including 18 biopsy-confirmed patients from 7 countries. Of these, 17 had polyarthritis and 10 had uveitis. This registry was expanded to 53 in a consecutive report, and interestingly 11 of the reentries had a first-degree affected relative. Although prevalence figures cannot be extrapolated from this study, a ratio of 1:5 between familial and sporadic cases is suggested (Lindsley and Petty, 2000).

As expected from an autosomic dominant trait, the disease is equally distributed among genders with no phenotypic variability in relationship to sex. Most patients with a sporadic form develop symptoms before age 5 and over 2/3 of patients with a familial form present within the first 2 years of life. There is neither racial predominance nor phenotypic variation by race or ethnicity, and the disease seems to be distributed worldwide with cases reported throughout the Americas, Europe, Australia and Asia. To date there has been no relationship between phenotype and mutation variants but new mutations are being described raising the possibility of genotype/phenotype correlations to be found in the near future.

3. Etiology/pathogenesis

The *CARD15* gene encodes a 1,040 amino acid protein comprised of two N-terminal caspase recruitment domains (CARDs), one NACHT or nucleotide binding site (NBS) domain, and C-terminal LRRs. To date, nine different genetic mutations leading to amino acid substitutions in or near the NBS/NACHT domain of CARD15 have been documented in affected patients with either the familial or the sporadic presentations of the disease (Miceli-Richard et al., 2001; Kanazawa et al., 2005; van Duist et al., 2005) (Table 2). Of those, R334W (substitutes arginine to glutamine at position 334), and R334Q (arginine to tryptophan at position 334), are the most prevalent. The location of these mutations is different from the Crohn's disease mutations that have been found at or near the LRR region of CARD15 (Hugot et al., 2001). Conversely, work with adult sarcoidosis did not support a gene defect in *CARD15* (Rybicki et al., 1999; Schurmann et al., 2003) underlining the distinction between adult and EOS.

Table 2
Mutations in *CARD15/NOD2* gene associated with PGA (BS/EOS)

R334W (Arg334Trp)	Miceli-Richard et al., 2001
R334Q (Arg334Gln)	Miceli-Richard et al., 2001
D382E (Asp383Glu)	Kanazawa et al., 2005
E383 K (Glu383Lys)	van Duist et al., 2005
L469F (Leu469Phe)	Miceli-Richard et al., 2001
H496L (His496Leu)	Kanazawa et al., 2005
M513T (Met513Thr)	Kanazawa et al., 2005
T605P (Thr605Pro)	Kanazawa et al., 2005
N670 K (Asn670Lys)	Kanazawa et al., 2005

The CARD15/NOD2 protein and its homolog NOD1, are members of a growing family of nucleotide-binding oligomerization domain (NOD) cytosolic proteins implicated in inflammation and apoptosis. The NOD domain was first found in apoptotic protease activating factor-1 (APAF-1) and its nematode homologue CED-4, which are two essential regulators of programmed cell death. Most NOD-family members contain three distinct functional domains, an amino-terminal effector-binding domain, a centrally located NOD and a carboxy-terminal ligand-recognition domain. Within the family of NOD proteins, CARD15/NOD2 is mostly known for its major role in binding to RICK and NF-κB activation although a role in apoptosis has been shown as well

using often over-expression systems (Inohara and Nunez, 2003; Inohara et al., 2005) (Fig. 1).

The CARD domain structure is highly conserved across species, and has an important role in the mediation of NF-κB activation which results from CARD–CARD interactions between CARD15 and a pivotal downstream kinase protein RICK (receptor-interacting serine/threonine kinase, also known as RIP2 or CARDIAK) (Chin et al., 2002; Kobayashi et al., 2002). RICK mediates the activation of NF-κB through the common inhibitor of NF-κB kinase (IKK) complex and promotes caspase activation, leading to the secretion of pro-inflammatory cytokines. The NACHT domain, also referred to as NOD or nucleotide-binding site (NBS) domain, mediates self-oligomerization which is required for the activation of downstream effector molecules

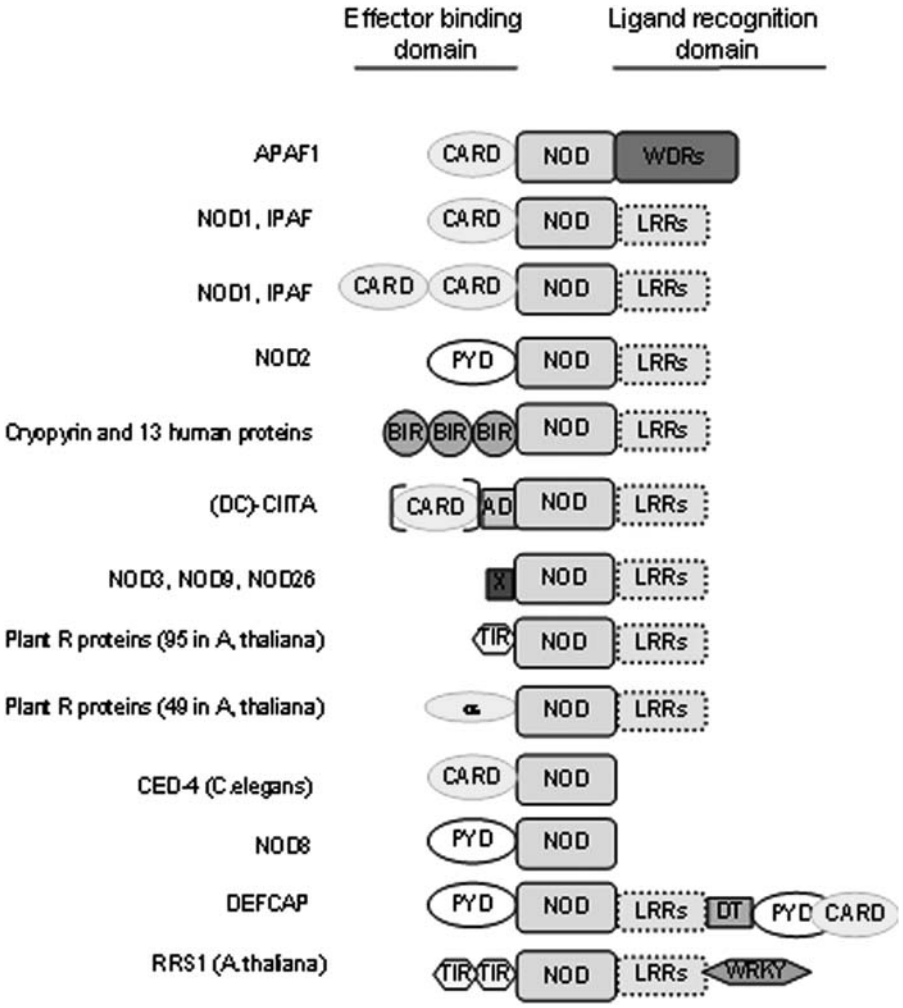

Figure 1. The majority of NOD proteins are composed of variable amino-terminal effector-binding domains, a centrally located NOD that mediates self-oligomerization, and a carboxyl-terminal ligand-recognition domain. WDRs, WD40 repeats; IPAF, ICE-protease activating factor; PYD, pyrin domain; NAIP, neuronal apoptosis inhibitory protein; BIR, baculovirus inhibitor-of-apoptosis factor; DC, dendritic cell; CIITA, MHC class II transactivator; AD, activation domain; X, putative effector-binding domains with no known homology; TIR, Toll/interleukin-1 receptor domains; α/c, α-helix/coiled-coil rich; DT, DEFCAP/TUCAN expanded homology domain; WRKY, zinc finger-like domain found in plant W-box-binding transcription factors (adapted with permission from Inohara et al. (2005).

(Inohara and Nunez, 2003; Inohara and Nunez, 2001). The LRR region is structurally related to the LRR regions of the Toll-like receptors (TLRs), which are molecules of the innate immune system indispensable for the "sensing" of molecular motifs specific to pathogens, such as lipopolysaccharide (LPS). Whereas the ligand for NOD1 is LPS, recent studies have shown that the moiety recognized by CARD15/NOD2 is actually muramyl dipeptide (MDP), a building block of peptidoglycan found in both Gram-positive and Gram-negative bacterial cell walls (Girardin et al., 2003; Inohara and Nunez, 2003) (Fig. 2).

CARD15 is expressed constitutively in monocytes, granulocytes and dendritic cells (Mechanic et al., 1997) as well as in Paneth cells in the villous crypts of the small intestine, which are of epithelial origin. Its expression can be induced by pro-inflammatory cytokines in cultured intestinal epithelial cells.

The mutations in CARD15 associated with Crohn's disease are found near or in the LRR region (Ogura et al., 2000; Hugot et al., 2001; Hampe et al., 2001). These mutations are loss-of-function variants since they result in a defective ability of CARD15 to sense peptidoglycan. Given that the response of CARD15 to peptidoglycan is

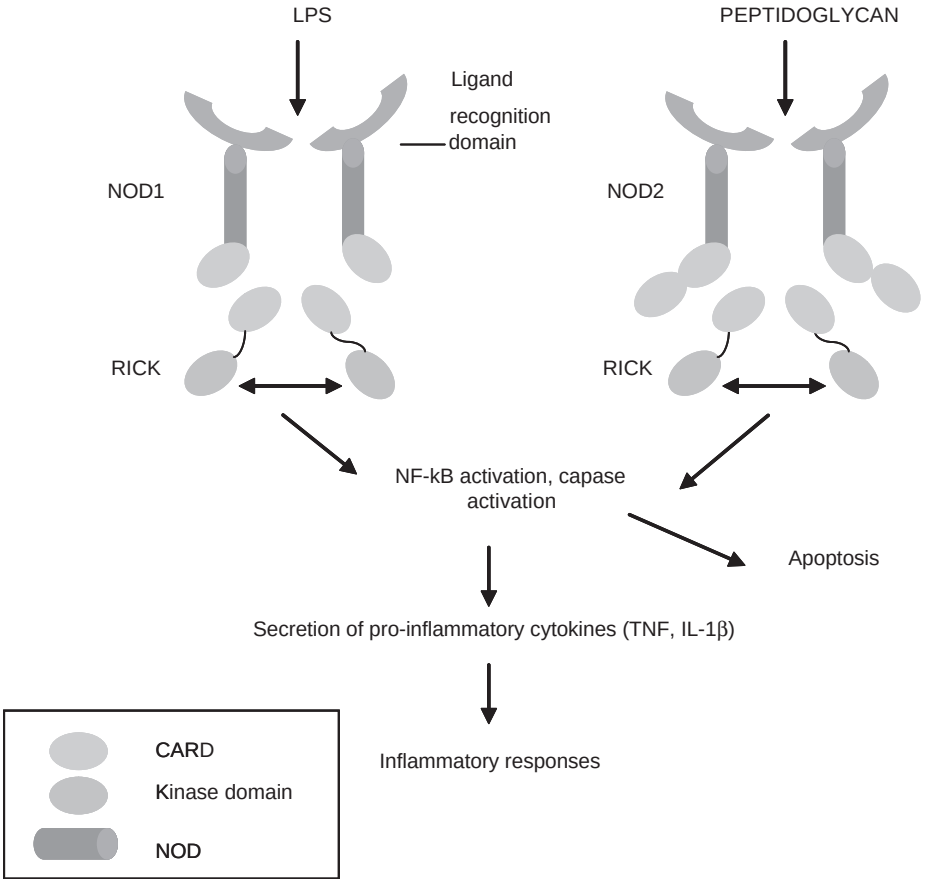

Figure 2. NOD1 and NOD2 proteins recognize bacterial derived LPS and peptidoglycan molecules through their LRR domains. Signaling through NOD1 and NOD2 is mediated through the kinase RICK, which interacts with NOD1 and NOD2 through CARD–CARD interactions. RICK mediates NF-κB activation through the common inhibitor of NF-κB kinase (IKK) complex (not shown) and promotes caspase activation that leads to the secretion of pro-inflammatory cytokines. (Adapted with permission from Inohara, Nature Reviews, 2003.) (See Colour Plate Section.)

the activation of an inflammatory cascade, the effect of these mutations in predisposing to inflammatory disease seems counter-intuitive although work in this area is evolving (Abbott et al., 2004; Watanabe et al., 2004). The gene variants associated with PGA involve residues located in the NOD domain and act as constitutively active CARD15/NOD2 mutants, that is gain-of-function variants. This is consistent with the autosomal-dominant nature of the disease. The NOD domain is critically involved in oligomerization and activation of CARD15/NOD2, suggesting that these mutations may increase function by stabilizing the active conformation of the protein (Kanazawa et al., 2005) although these findings have not been replicated yet (Fig. 3).

The pathologic hallmark of PGA is the presence of non-caseating epithelioid cell granulomata indistinguishable morphologically from those seen in sarcoidosis. This pathologic feature has not been biologically linked with CARD15. Experience in sarcoidosis led to the understanding that granulomas are the result of an exaggerated immune-inflammatory response against an undefined antigen. They consist of a central cluster of monocyte/macrophages in various states of activation, epithelioid cells and multinucleated giant cells, surrounded by a rim of CD4+ T cells and scattered CD8+ T cells and plasma cells (Agostini et al., 2000, 2002). Recent investigations in adult sarcoidosis have identified several cytokines and chemokines secreted in situ, and clarified mechanisms leading to recruitment and activity of lymphocytes and monocytes at sites of granuloma formation. In the early phase infiltrating CD4+ T cells show a dominant Th1-type profile with elevated mRNA and protein levels of IFN-γ and IL-2, which act as local growth factors. Sarcoid macrophages express IL-12, which is known to stimulate proliferation of activated T cells and

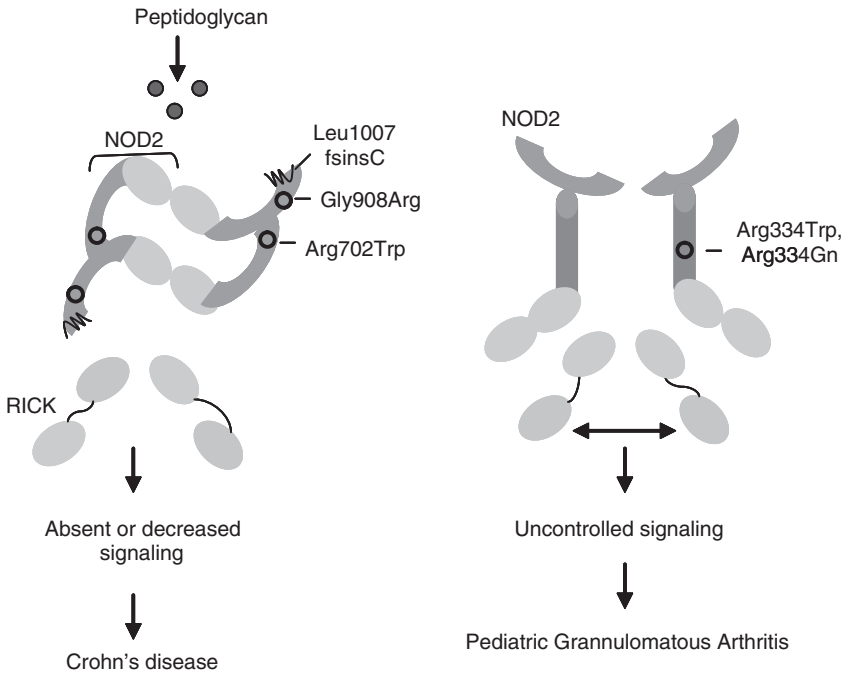

Figure 3. NOD variants that are associated with Crohn's disease (Leu1007fsinsC, Gly908Arg, Arg702Trp) are located near or in the leucine-rich repeats (LRRs). These variants are defective in their response to bacterial peptidoglycan, resulting in absent or decreased signaling. NOD2 mutations associated with Blau syndrome (Arg334Trp, Arg334Gln) are located in the nucleotide-binding oligomerization domain (NOD) and are activating mutations that lead to uncontrolled signaling in the absence of a ligand. (Adapted with permission from Inohara and Nunez (2003).)

differentiation of Th1 cells. Several chemotactic stimuli like IL-16 and IL-8 as well as monocyte chemoattractant protein-1 (MCP-1) and monocyte inflammatory protein-1α (MIP-1α) seem to cooperate with the recruitment of CD4+ T cells and monocytes (Agostini et al., 2000, 2002). A second mechanism responsible for the accumulation of inflammatory cells at the site of granuloma formation appears to be the in situ proliferation of both T cells and macrophages by the local release of cytokines and growth factors (Agostini et al., 2000). An increased expression of pro-inflammatory cytokine genes IL-1, TNF-α and IL-6 by cells inside granulomas was shown by in situ hybridization and immunohistologic techniques (Agostini et al., 2002). Finally, the continuous formation and persistence of immune granulomas may also reflect an abnormal regulation of apoptosis within the granulomatous structure through the chronic overexpression of TNF-α, IL-15 and IFN-γ (via the expression of $P21^{WAF1}$) and the up-regulation of a number of apoptosis-related gene products, including growth factors and the Bcl-2 family of genes (Agostini et al., 2002; Xaus et al., 2003).

Whereas the aforementioned data undoubtedly add to the understanding of cellular interactions governing the formation and maintenance of granuloma in adult sarcoidosis, the relationship between CARD15/NOD2 mutations and granulomatous inflammation remains to be elucidated. Apart from its major role in the mediation of NF-κB activation, CARD15 has been shown to enhance apoptosis and apoptotic caspase activation using only over-expression systems (Inohara and Nunez, 2003; Inohara et al., 2005). One is tempted to hypothesize that granuloma formation in PGA patients reflects both increased pro-inflammatory activity and defective monocyte apoptosis. Experiments to study this rather attractive theory are underway. Interestingly, altered neutrophil apoptosis was found to contribute to formation of granuloma in Chronic Granulomatous Disease (Kobayashi et al., 2004). The investigation of inflammatory and apoptotic events in PGA patients with *CARD15* mutations will be a major subject of future research in the field.

At last, due to the cytoplasmic localization of CARD15 and its potential participation in various signaling complexes it will be important to determine the array of proteins with which CARD15 interacts. One such study has identified a new binding partner of CARD15, GRIM-19, which may be an integral component of CARD15-mediated responses (Barnich et al., 2005).

4. Clinical manifestations

The description that follows encompasses the so-called "classic" form of the disease as described originally by Blau and Jabs (Jabs et al., 1985; Blau, 1985) for the familial form, by North (North et al., 1970) for the sporadic disease and expanded by later reports (Raphael et al., 1993; Rotenstein et al., 1982; Saini and Rosé, 1996; Ting et al., 1998; Gedalia et al., 1996; Rosé et al., 1990; Gross et al., 1986).

It should be noted that the spectrum of pediatric granulomatous diseases and of rheumatic conditions associated with granulomatous synovitis is much more complex. We will describe briefly the non-classical forms as disease variants since it appears that this group does not share the genetic mutations in CARD15 observed in the majority of individuals with the "classic" form.

4.1. Classic form: onset

The most common initial manifestation of the disease is the classical tan-colored cutaneous rash (vide infra) followed within 6 months by a symmetrical polyarthritis. Eye disease tends to appear in the second year of the illness. Slightly less commonly, the disease starts with polyarthritis and rash simultaneously and very rarely the three "core manifestations" (polyarthritis, dermatitis and uveitis) are present at onset. An International Registry of Pediatric Granulomatosous Arthritis coordinated by the authors of this chapter and incepted in 2005 had at 1 year 22 pedigrees entered. Of these 6 were non-classical and of the 16 classical pedigrees 10 belonged to EOS variant (simplex pedigrees) and 6 were BS families (multiplex pedigrees). Figure 4 shows distribution of

onset in individuals with classical phenotype in this the largest series existing to date (Martin et al., 2005). We have not seen individuals with isolated ocular onset. The average age of onset in the Registry was 26 months with one child presenting as early as 2 months of age and at the other end of the spectrum one female patient starting at 14 years of age. Both genders showed an almost equal representation, as it is expected in an autosomic dominant, single allele disease.

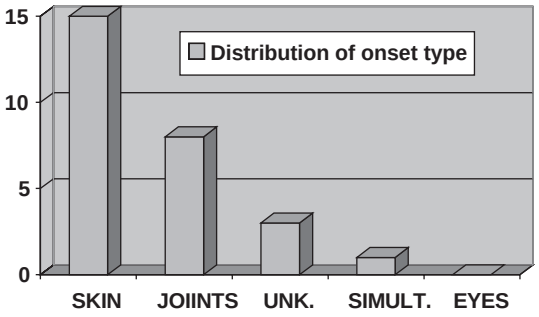

Figure 4. Type of onset among 27 affected individuals with the classic form of the disease (International Registry).

4.2. Classic form: articular involvement

The majority of patients present with polyarticular, symmetrical joint involvement either additive (within weeks) or generalized from onset. In the Registry 95% of the patients showed polyarticular onset and course. The disease affects large and small joints of hands and feet. Oligoarthritis has been observed as well. The most striking characteristic is the exuberant character of the synovitis which has been described as "boggy" or cystic; however, this pattern was seen in 75% of biopsy proven, mutation confirmed cases in the Registry. This bogginess is best exemplified in the carpus and tarsus where the physical appearance may resemble a synovial "cyst" (Fig. 5). Morning stiffness is less severe than in rheumatoid arthritis for an equivalent severity of joint inflammation. Similarly, the degree of contracture, pain and heat detected on the joint examinations tends to be less severe than what one would expect for the degree of swelling (Fig. 6). The joints feel spongy and range of motion is relatively preserved. An exception to such rule is the severe contracture in the PIP joints of the hands. It is common for those

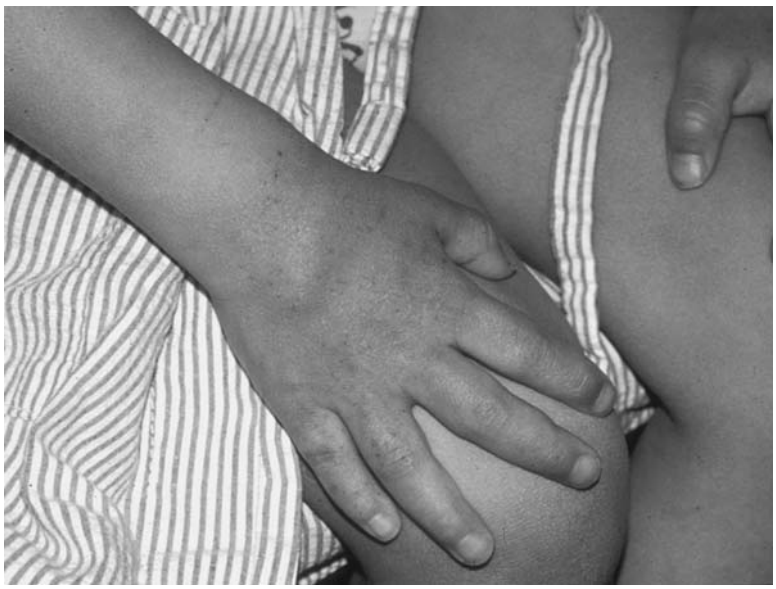

Figure 5. Cyst-like synovitis and ichtyosiform rash. (See Colour Plate Section.)

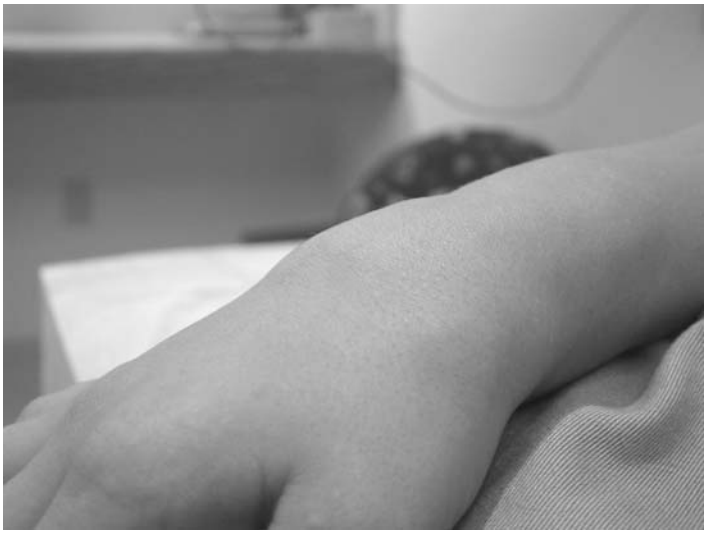

Figure 6. Boggy synovitis with relatively preserved range of motion.

presenting at early age that by late childhood they will exhibit sever PIP contracture of the finger joints (Fig. 7). Indeed, this finding earlier led authors to include camptodactily in the diagnostic triad (Raphael et al., 1993). Wrist subluxation and ulnar deviation can be seen in adults with long-standing disease (Fig. 8).

Involvement of tendon sheaths is characteristic. The involved tendons are thickened upon visual inspection and spongy on palpation. The most commonly affected are the extensor and flexor digitorum, anserinus, tibialis, peroneus and flexor pollicis longus (Fig. 9). Carpal tunnel symptoms from entrapment are exceptional.

4.3. Classic form: cutaneous manifestations

4.3.1. Tan-colored rash

The most common cutaneous manifestation is a characteristic scaly erythematous rash mainly located on trunk, mostly dorsum, arms and legs with a predilection for extensor surfaces in the latter two. It can be mildly itchy but is mostly asymptomatic. In itself it is more of a valuable diagnostic clue than an annoyance for the patient. The lesions tend to acquire a tan hue, they are round-shaped, barely palpable and small (5–7 mm). The rash is usually misdiagnosed as atopic dermatitis but it is more reminiscent of ichthyosis than of eczema (Fig. 10).

The natural history of the rash is that of exacerbation and quiescence persisting in some patients to adolescence and in other disappearing after a year or two. In the experience of the author, children with 6–10 years of disease will show some evidence of a scaly thickened rash which depicts no erythematous elements and is very reminiscent of mild *ichthyosis vulgaris* limited to small patches on extensor surfaces.

4.3.2. Erythema nodosum

A few patients with classical disease will develop short duration episodes of typical nodular rash in the lower extremities, clinically indistinguishable from erythema nodosum. There are no data with regard to the histological features of this particular manifestation.

4.4. Classic form: ocular manifestations

Very rarely, it will require more than 2 years from disease onset for these children to develop eye disease. PGA presents with chronic destructive uveitis while in adult sarcoidosis when uveitis occurs it is

Figure 7. Family with affected mother and two siblings, with development of camptodactily.

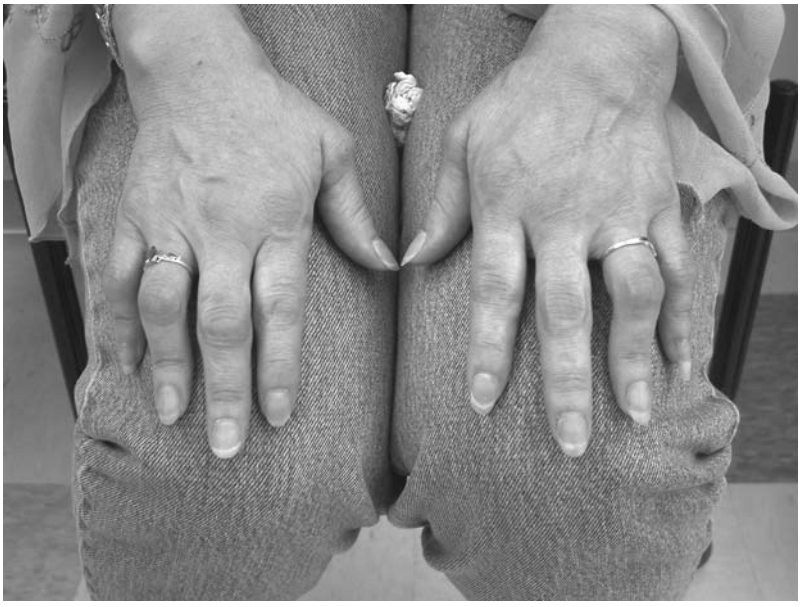

Figure 8. Long-standing wrist synovitis with ulnar deviation and camptodactyly.

in the setting of fever, parotitis and facial nerve palsy (Heerfordt-Waldenstrom syndrome). Usually presenting as bilateral asymmetrical anterior uveitis, it soon becomes a pan-uveitis, very difficult to control and persistent. Without a doubt it is the involvement of the eye, the single most important source of disability in this disease. Approximately 1/2 of the patients will develop secondary cataracts, and increased intraocular pressure is seen in 1/3. Posterior involvement with vitritis, retinal

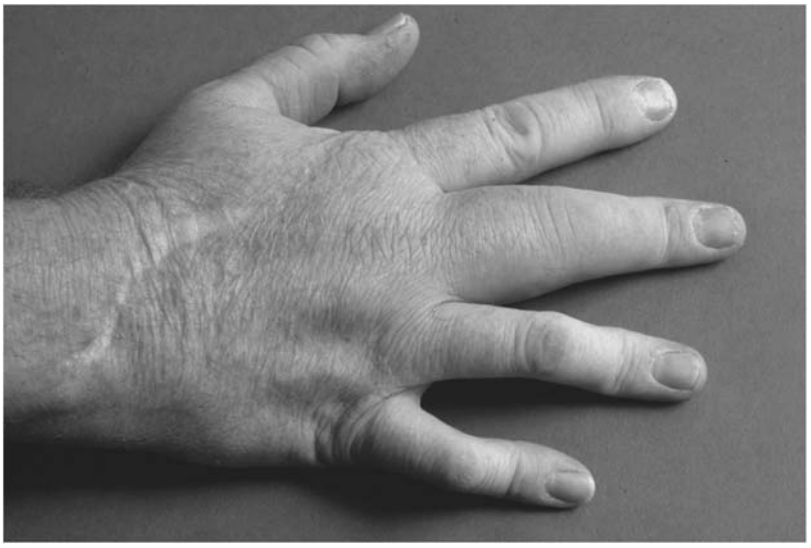

Figure 9. Wrist synovitis with camptodactyly and tenosynovitis of extensor digitorum longus.

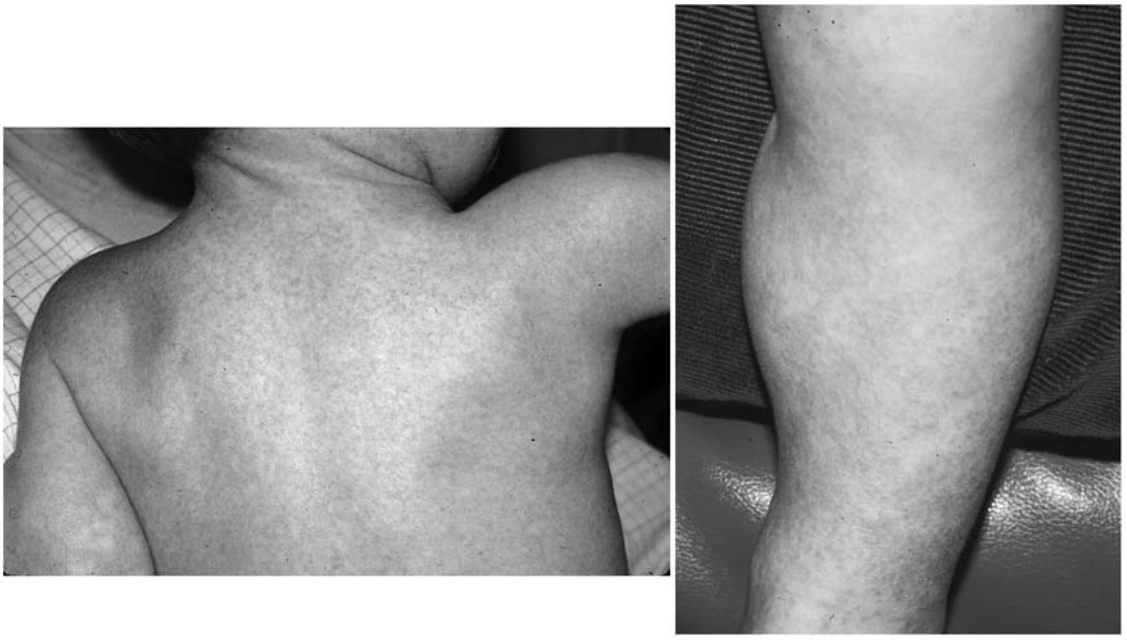

Figure 10. Ichthyosiform skin eruption. (See Colour Plate Section.)

vasculopathy and compromise of the optic nerve can be seen in ~20% with sometimes dismal visual outcome. The typical clumpy keratic precipitates will alert the experienced ophthalmologists into thinking in this disease. The reader is referred to Dr C. Lindsley description of the biomicroscopic ocular findings in PGA (Lindsley and Petty, 2000).

4.5. Classic form: internal organ disease

The triad of polyarticular arthritis/tenosynovitis, pan-uveitis and tan-colored rash (“core manifestations”) with onset before age 5 combined with the finding of non-caseating granulomatous inflammation in synovium, conjunctiva and dermis are the basis for the diagnosis of PGA. It should be noted however that over the years the spectrum of the disease has been expanding with visceral involvement documented in multiple case reports. Granulomatous infiltrates have been seen in the liver (Saini and Rosé, 1996), kidney (Ting et al., 1998), lung parenchyma (Fink and Cimaz, 1997) and myocardium (Fink and Cimaz, 1997). We have observed recently peripheral lymph node involvement in one patient as well. This rather widespread distribution seen in both familial and sporadic cases resembles primary adult sarcoidosis. Bilateral hilar adenopathy, however, has never been described in PGA. The significance of these histologic findings is unclear since at least in early stages of the disease they are associated with no morbidity. The hepatic granulomas, for example, were reported as asymptomatic with no clinical or biochemical manifestations; lung disease can be demonstrated by imaging techniques but is rarely associated with respiratory distress or cough. Myocardial granulomas were described in an autopsy case.

4.6. Classic form: vascular involvement

Early reports of large vessel involvement in PGA have been confirmed more recently and in at least one case with documented mutation in *CARD15* (Wang et al., 2002). Remarkably it is unknown if large vessel involvement is granulomatous as well. Reports of aortic arch and branches mimicking Takayasu’s arteritis (Rosé et al., 1990), abdominal aorta (Gedalia et al., 1996) and renal arteries (Gross et al., 1986; Rotenstein et al., 1982) with associated malignant hypertension have been documented. Small vessel and medium size vessel disease may occur but are uncommon. Hypertension without demonstrable large vessel involvement has been observed in patients with PGA (CDR, unpublished observation).

4.7. Classic form: late disease

A report of late disease (Fink and Cimaz, 1997) described widespread dissemination in autopsy-based studies. This report suggests that at least in some cases the disease is associated with mortality. Patients have died with cardiac failure and respiratory failure, and in some cases widespread granulomatous involvement was documented (Fink and Cimaz, 1997).

4.8. Other pediatric granulomatous inflammatory disease variants: systemic granulomatosis, granulomatous panniculitis and granulomatous osteitis

We have collected in the Registry a few children with very early onset of nodular panniculitis associated with granulomatous inflammation documented in the subcutaneous fat tissue biopsy or in other involved organs. These patients whose clinical course resembles a severe non-lipodystrophic form of Weber-Christian syndrome do not carry mutations in *CARD15*. Other children with granulomatous involvement of the reticulo-endothelial system mimicking systemic histiocytosis also show wild-type *CARD15*. Uveitis, synovitis but not tan-colored rash are seen in these children. Finally, monoostotic sarcoid-like osteitis with or without associated synovitis can occur and again in these children the wild-type *CARD15* has been seen.

4.9. “Adult-type” childhood sarcoid arthritis

Arthritis is not a common manifestation of adult sarcoidosis. Large series report around 5% frequency of true arthritis and 10% of articular symptoms among adults with sarcoidosis (Hoffmann et al., 2004; Byg et al., 2003). Clinicians have recognized two patterns of joint involvement. The most common is an acute arthritis (mainly ankles), associated with erythema nodosum and hilar adenopathy (Loefgren syndrome). These patients are

systemically ill, febrile and experience weight loss. The other rheumatic presentation is a more indolent form of oligoarthritis mainly affecting the knees. This chronic arthritis is similar to rheumatoid arthritis in its erosive potential but oligoarticular. The granulomatous character of the synovitis is unclear. In an early report by Sokoloff and Bunnin (1959) the disease was described as granulomatous with non-caseating granulomas in the synovial tissue. Palmer and Schumacher more recently performed a systematic investigation with needle biopsy on seven patients with sarcoidosis and arthritis and failed to show granuloma formation in the synovial samples (Palmer and Schumacher, 1984). Adolescents in particular those of African ancestry can present with any of these patterns-acute and rheumatoid-like. Occasionally this arthritis is associated with palpable purpura, and granulomata in the dermis can be found in association with otherwise classic leukocytoclastic vasculitis. These children are indistinguishable from adult sarcoidosis presenting all the features of that disease including hilar adenopathy, interstitial pneumonitis, myositis, aseptic meningitis and white matter disease. Detailed descriptions of adult-type sarcoidosis are beyond the scope of this review and excellent reviews are available in the literature (Newman et al., 1997).

5. Diagnostic investigations

5.1. Routine laboratory investigations

Peripheral blood counts are usually within normal limits except for mild anemia. Patients with systemic granulomatosis can present cytopenias but these are not seen in the classic form of the disease. Unless there is severe renal involvement as seen in the presence of interstitial nephritis the renal chemistries are normal. Despite granulomatous infiltration of the liver, hepatic chemistry is normal as well.

Antinuclear antibodies and rheumatoid factors are absent. Elevated angiotensin converting enzyme (ACE) is inconsistent and it lacks the diagnostic and monitoring value seen among adults with sarcoidosis. It should be noted that ACE levels in young children are not very well standardized. Hypercalcemia is only seen in the adult form of the disease. The sedimentation rate tends to be in the mid-fifties when disease is active but its value as a marker of disease activity has not been well studied in PGA.

5.2. Pathology

The diagnosis rests on the presence of non-caseating giant cell granulomas (Fig. 11). Typical skin lesions yield positive results in almost 100% of the cases. In the synovium however, sampling could affect the sensitivity of the test. In both synovial and cutaneous samples an associated chronic inflammatory infiltrate is characteristic. Involvement of the subcutaneous tissue is seen only in patients with clinical panniculitis, and in those involvement is lobular rather than septal and is of the non-vasculitic type. As noted before, patients with panniculitis have not shown mutations in CARD15. Conjunctival biopsy can yield granulomas when there is follicular/nodular involvement on clinical examination otherwise, but the sensitivity in asymptomatic or diffusely erythematous conjunctiva is low. The granulomas characteristically are those of non-caseating type. Each giant cell represents the fusion of 3–12 macrophages. When the nuclei are lined-up resembling epithelium the lesion is called epithelioid granuloma. There is scarce experience with the histology of the vessel wall in associated large vessel vasculitis except in autopsy-based cases.

5.3. Genetic testing

The published frequency of mutations in the CARD15 protein is 50% for the familial form (Wang et al., 2002) and 90% for the sporadic form of PGA (Kanazawa et al., 2004). In the experience of the authors all classic forms of the disease, either familial or sporadic, have shown mutations in CARD15 (Table 2). The diagnosis of the disease continues to be based on histologic confirmation

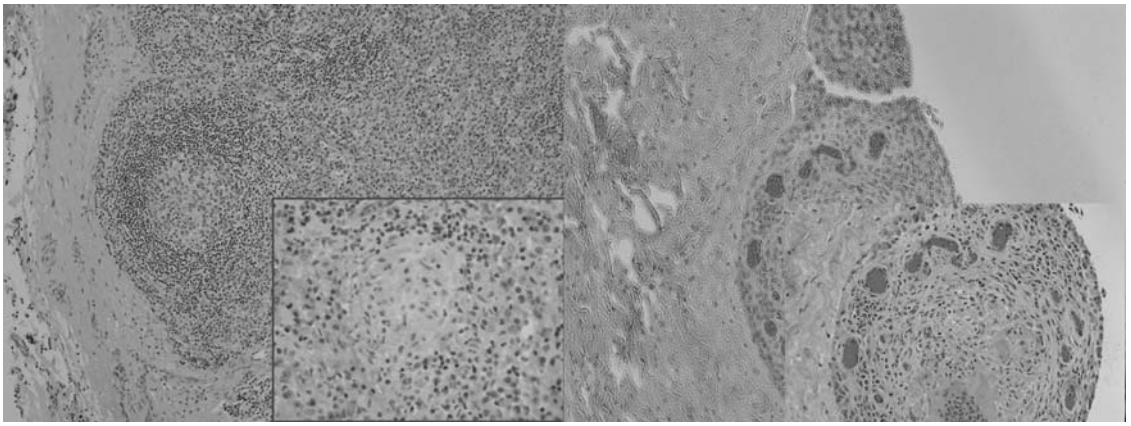

Figure 11. Non-caseating multinucleated giant cell granulomata.

of granulomata since genetic testing is still not a validated substitute. With more emerging information it may turn out to be in the future as an accurate diagnostic approach as it has been with other rheumatic disorders with defined mutations.

5.4. Imaging

Chest films may be necessary to establish the presence of interstitial lung disease. Although there are evidence-based current recommendations in order to detect mild parenchymal disease, high resolution CT may be necessary when patients become systemically ill. This technique should be used sparingly due to the high radiation exposure involved. Radiologic monitoring of joint involvement is usually not necessary, since the disease is not erosive and only after several years leads to contractures and limitation. Vascular imaging may be necessary when large vessel vasculitis is suspected. CT-angiogram, Doppler sonogram or magnetic resonance angiography (MRA) will be selected according to the territory under study and the preference of the center.

6. Differential diagnosis

The differential diagnosis of pediatric polyarthritis is vast. Here we include some of the most frequent conditions that can be a challenge for the clinician because of the combination of arthritis and uveitis. It is important to recall that in the familial forms of PGA, the index of suspicion will be raised by the presence of family history, albeit there are other causes of familial arthritis (Chalom et al., 1997) as well as occasional patients with JIA and a sibling or a parent with concordant phenotype. The consistent autosomic dominant pattern with high penetrance seen in familial PGA (Blau syndrome) is not seen in JIA. We organized the section by the main cardinal manifestations: arthritis, uveitis and rash.

6.1. Arthritis

The association of symmetrical polyarthritis with synovial and tenosynovial ''cysts'' and development of camptodactyly are the most important distinguishing features between PGA and polyarticular JIA. Furthermore, antinuclear antibodies and rheumatoid factor are typically absent in PGA. In familial forms of PGA, there is an observed element of ''anticipation'', or worsening of symptoms in succeeding generations (Raphael et al., 1993). A familial occurrence of arthritis and tendinitis can be seen in a subset of JIA called arthritis and enthesitis (previously also known as juvenile spondylarthropathy), however the arthritic pattern is most often oligoarticular and asymmetrical, and the strong association with HLA-B27 are distinguishing features.

Arthritis and rash with well-demarcated erythematous scaly lesions occurring at the extensor surfaces and with accompanying nail disease are typically seen in psoriatic arthritis. The arthritis in PsA is rarely polyarticular and the rash should not be confused with the ichthyosiform rash of PGA.

CD may be associated with an extensive list of extraintestinal manifestations including arthritis, uveitis, erythema nodosum, small and medium vessel vasculitis and pyoderma gangrenosum, sclerosing cholangitis and autoimmune hepatitis. The clinician should be aware that particularly in children the intestinal manifestations of the disease might occur years after the arthritis. As depicted in Table 3, the arthritis of CD is mostly oligoarticular and the only cutaneous manifestation that may be confusing is erythema nododsum. There is an axial pattern of the articular disease with involvement of sacroiliac joints and lower lumbar spine, however this distribution does not occur in PGA.

PGA and CD are granulomatous diseases but the finding of granulomas in the synovium while exceptional in CD is the rule in PGA. The reader should be reminded that CD and PGA share mutations in the CARD15 protein albeit in different domains. Additionally CD has shown associations with allelic variants in different genes, while in PGA, NOD2 is the only protein for which a mutation has been documented.

The adult form of sarcoidosis was discussed in detail in the clinical section. It is usually detected in older children by chest radiography, and the clinical manifestations are characterized by a classical triad of lung, lymph node and eye involvement, similar to those in adults. Constitutional symptoms, including fatigue, malaise and fever, are often present. Although visceral involvement has been reported in patients with PGA pulmonary involvement occurred very late if at all, and hilar adenopathy is almost never associated (Fink and Cimaz, 1997).

Although arthritis, uveitis and rash can occur in both PGA and sarcoidosis, the clinical pattern of these involvements is different. PGA is characterized by progressive polyarthritis causing severe joint deformities, whereas in sarcoidosis either acute arthritis (Loefgren's syndrome) or a chronic indolent oligoarthritis especially affecting the knees occurs. PGA is associated with a severe progressive uveitis that can be anterior, posterior, or both and is usually a significant source of morbidity, with long-term visual impairment. Conversely, in sarcoidosis, acute uveitis can be seen mostly in association with Heerfordt-Waldenstrom syndrome. Erythema nodosum has been reported in both conditions, but is typical of adult sarcoidosis. The tan-colored ichthyosiform rash characteristic of PGA has not been reported in patients with sarcoidosis. Whereas the adult form of sarcoidosis is seen mostly in black and Japanese children, PGA occurs worldwide and has no racial preference. Despite the striking similarity in pathology between the two conditions (non-caseating granuloma) no *CARD15* mutations have been published in studies of adult sarcoidosis (Rybicki et al., 1999; Hoffmann et al., 2004), or sarcoidosis-associated uveitis (Martin et al., 2003). Table 3 summarizes the differential characteristics of chronic inflammatory diseases with arthritis and uveitis in childhood.

6.2. Uveitis

Uveitis in PGA is chronic, can be anterior, posterior or panuveitis, and granulomatous or non-granulomatous. The association of chronic uveitis and arthritis can be seen in a number of inflammatory conditions including oligoarticular and polyarticular JIA, psoriatic arthritis, CD, Behçet's disease and CINCA. Uncommonly, chronic relapsing uveitis is seen in association with acute tubulointerstitial nephritis, known as TINU syndrome. Chronic uveitis also occurs in ~1/3 of children without additional evidence of other organ involvement. The characteristic biomicroscopic aspect of precipitates in a "clumpy", rather than diffuse distribution should alert the ophthalmologist of the possibility of PGA; characteristic granulomata may be revealed on a conjunctival biopsy, particularly in the areas of focal disease in the conjunctiva.

6.3. Cutaneous manifestations

A scaly erythematous rash may suggest atopic dermatitis (and frequently is diagnosed as such),

Table 3
Differential diagnosis of chronic pediatric arthritis with uveitis

	Joint disease pattern	Tendon involvement	Uveitis	ANA	HLA B27	Synovial granuloma	Extra-articular
PGA	Polyarticular, "boggy", camptodactily	Intense	Panuveitis can be severe	Neg.	Absent	Yes	Icthtyosiform rash, large vessel disease, hypertension
Polyarticular JIA	Polyarticular	Variable	Mostly anterior	40%	Absent	No	Subcutaneous nodules
Arthritis and enthesitis	Mostly oligoarticular	Typically at insertion (enthesitis)	Acute anterior, recurrent	Neg.	Present (not always)	No	Aortic ring, mucositis, E. nodosum[a]
Psoriatic arthritis	Poly or oligo-articular	Yes	Rare	40%	Only in axial forms	No	Psoriatic rash, nail disease
Crohn's arthritis	Oligoarticular (ankle frequent)	Variable	Rare	Neg.	Same as normal population	Can be found	Enteritis, pyoderma gangrenosum, E. nodosum
Adult sarcoid arthritis	Oligoarticular (ankle frequent)	No	Mostly acute (Loefgren)	Neg.	Absent	Can be found	Hilar adenopathy, systemic disease, alveolitis, E. nodosum

[a] Particularly in reactive arthritis (Reiter syndrome).

but the rash of PGA usually is non-itching and asymptomatic. The ichthyoses comprise a large number of scaling diseases mostly generalized and involving all skin layers. A review of the ichtyoses is beyond the scope of this chapter.

Erythema nodosum is characterized clinically by subcutaneous tender erythematous nodules. It is seen occasionally in PGA and is associated with a multitude of pediatric diseases, some of them also associated with arthritis (e.g. adult type sarcoidosis).

Although reported very rarely, patients with PGA may present with vasculitis (Rotenstein et al., 1982; North et al., 1970; Rosé et al., 1990), and the granulomatous vasculitides have to be considered in the differential diagnosis. Wegener's granulomatosis is characterized by a clinical triad of paranasal sinus involvement, pulmonary infiltration and renal disease with granulomatous involvement of medium size arteries and veins, and a necrotizing glomerulonephritis. Churg-Strauss syndrome, also called allergic granulomatosis is typically associated with severe asthma, fever, eosinophilia and vasculitis. Granulomatous extravascular and vascular changes may be found. Lymphomatoid granulomatosus is a very rare necrotizing pulmonary vasculitis that can be associated with immunodeficiencies (Wiskott Aldrich syndrome, X-linked lymphoproliferative syndrome), HIV infection and malignancy. Childhood primary central nervous system vasculitis (cPACNS), previously called granulomatous angiitis, presents as an acquired neurologic deficit and no systemic features. None of the above conditions are really challenging in the differential diagnosis with PGA. Takayasu's arteritis, although rare in children, is the most common giant cell arteritis of childhood, affecting the aorta and its major branches as well as the pulmonary artery. A Takayasu-like disease has been reported in association with PGA and so a form of abdominal aortitis (Gedalia et al., 1996; Rosé et al., 1990).

7. Treatment and prognosis

Compared with an asymptomatic and sometimes naturally disappearing course of the adult form of sarcoidosis in older children, PGA is progressive

and in many cases causes severe complications, such as blindness, joint destruction and visceral involvement (Fink and Cimaz, 1997).

There have been no controlled therapeutic studies for patients with granulomatous arthritis. Anecdotal experiences have shown poor response to NSAIDs for the rheumatic symptoms. These authors have reported excellent response to Infliximab (5–10 mg/Kg every 4–8 wk) particularly in the sporadic form; however, there is almost always some degree of detectable synovitis particularly in ankles and wrists (Brescia et al., 2002). The characteristic contractures of the PIP joints tend to be irreversible although radiologic changes are relatively mild. The only consistently effective measure to reduce synovial hypertrophy is the use of oral corticosteroids, but the side effects of their prolonged use limit their utility. Corticosteroid dependency for either eye or articular disease is common. Methotrexate has been ineffective in the author's experience. The sight-threatening panuveitis can be extremely severe and is usually managed with topical, sub-conjunctival or systemic corticosteroids. We have seen worsening of the uveitis while on Infliximab therapy although there is no experience with early intervention with TNF blockers for the uveitis. The authors have seen steroid-sparing effect with Cyclosporine A at usual doses (2–5 mg/kg/day).

Although formal functional studies in PGA are not yet available, most patients seem to handle activities of daily living quite well from the articular point of view. There are no reported cases of hip replacements, there is mild joint destruction on conventional imaging and reported pain is not very significant. Ocular disease on the other hand can be severe. In our Registry 46% of patients have moderate to severe disease based upon corrected visual acuity reports. We found no correlation with the type of amino-acid substitution on CARD15 or any other predictive feature, except perhaps for the type of inheritance with more ocular severity clustered among the multiplex (Blau syndrome) pedigrees.

Of some concern is the possibility of granulomatous dissemination in patients with PGA. An important report has dealt with the question of severity in advanced disease. In a series of sporadic cases (Fink and Cimaz, 1997) terminal involvement of vital organs was observed. We have in our series one mutation proven patient who had shown involvement of liver, lymph nodes and lung parenchyma after 16 years of disease so far responsive to corticosteroid therapy. The outcome of the atypical forms, including those with panniculitis and involvement of the reticulo-endothelial system, is associated with severe morbidity and mortality due to vital organ involvement.

Early intervention with TNF inhibitors and perhaps IL-1 inhibition may hold the key in the prevention of poor functional outcome.

Key points

- The term PGA is being proposed to include both the sporadic and familial forms of childhood granulomatous arthritis, uveitis and skin rash.
- PGA is highly associated with mutations in the NOD domain CARD15, a protein involved in inflammation and apoptosis.
- Both the classical clinical symptom triad of PGA and the association with a genetic mutation in CARD15 are major distinguishing features with adult sarcoidosis.
- Although with time expansion of granulomatous inflammation to other disease organs (liver, kidney, large vessels) has been described, the major causes of morbidity for patients with PGA is progressive polyarthritis and sight-threatening uveitis.
- In view of recent insights into the pathogenesis of PGA, biologic treatments directed at the inhibition of pro-inflammatory cytokines (TNF and IL-1) may become of great value.

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Handbook of Systemic Autoimmune Diseases, Volume 6
Pediatrics in Systemic Autoimmune Diseases
Rolando Cimaz and Thomas Lehman, editors

CHAPTER 16

Rheumatic Fever

Maria Odete Esteves Hilário*, Maria Teresa Ramos Ascensão Terreri
Pediatric Rheumatology Unit, Department of Pediatrics, Universidade Federal de São Paulo, Brazil

1. Introduction

Rheumatic fever (RF) is a late inflammatory, non-suppurative complication of an upper respiratory tract infection caused by Lancefield group A β-hemolytic streptococcus (GAS). It is characterized by involvement of the heart, joints, central nervous system, subcutaneous tissue and skin. RF and rheumatic heart disease (RHD) remain significant causes of cardiovascular diseases in the world. The most important effects are in children and young adults. The economic effects of the disability and premature death caused by RF are felt at both the individual and national levels through higher direct and indirect health-care costs (Terreri et al., 2001).

2. Prevalence

The RF distribution is worldwide. A few studies conducted in developing countries report incidence rates ranging from 1.0 to 150 per 100,000 school-age children (Joint WHO, 1994). The prevalence of RHD shows a wide variation between countries, ranging from 0.2 to 77.8 per 1000 (Anabwani and Bonhoeffer, 1996; Steer, 1999). The mortality rate for RHD vary from 0.5 to 8.2 per 100,000 population (World Health Statistical Annual, 1990–2000). In epidemics of streptococcal pharingotonsillitis, 3% of affected individuals develop RF, whereas in endemic situations, this decreases to 0.3% (Amigo et al., 1993).

3. Epidemiology

The highest incidence of RF is observed in children between 5 and 15 years old, and it is rare before 4 years old. Only 3–5% of first episodes arise in children younger than 5 years (Tani et al., 2003). There is a slight predominance of females and a higher frequency of chorea among girls. There is no racial predisposition, however it is a prevalent disease in developing countries (Ravisha et al., 2003; Özer et al., 2005). For the World Health Organization (WHO), RF remains a medical and public health problem even in industrialized countries.

4. Etiology/pathogenesis

There is strong evidence that an autoimmune response to streptococcal antigen mediates the development of RF in a susceptible host.

Although RF has been known to be consequent to a streptococcal infection, its pathogenesis is not completely understood. Some factors seem to be important in the disease frequency:

1. Genetic predisposition to the disease, with a higher frequency in some families.
2. Factors related to GAS: some serotypes like M1, M3, M5, M6, M14, M18, M19 and M24, are considered to be rheumatogenic.
3. Environmental factors: poor living conditions, overcrowding, bad access to health care and cold regions.

*Corresponding author.
Tel.:0055-11-5579-1590; Fax: 0055-11-5579-1590
E-mail address: odetehilario@terra.com.br (M.O.E. Hilário).

DOI: 10.1016/S1571-5078(07)06020-5

Major histocompatibility antigens, potential tissue-specific antigens and antibodies developed during and immediately after a streptococcal infection are being investigated as potential risk factors in the pathogenesis of the disease.

There is a well known theory of cross-reactivity of molecular mimicry by which the host would promote self-injury due to the presence of common antigenic sequences in their tissues and those of streptococcus (Khanna et al., 1997; Veasy and Hill, 1997; Asbahr et al., 2005).

Recent evidence suggests that T-cell lymphocytes play an important role in the pathogenesis of rheumatic carditis. It has also been postulated that particular M types of group A streptococci have rheumatogenic potential (Bhatnagar et al., 1999). In a very recent study Guilherme et al. (2005) reported that the streptococcal M5 (81-103) region, an immunodominant region, was recognized by both intralesional (valvular) and peripheral T-cell clones (62% vs. 38%, respectively).

Some studies suggested that abnormal regulation of TNF-alpha production may have a role in the pathogenesis of RF (Miller et al., 1989; Yegin et al., 1997; Guilherme et al., 2001; Guilherme and Kalil, 2002). Guilherme showed that T-cells from all RF patients produce significant amounts of TNF-alpha in response to streptococcal peptides with the highest production attained by the chronic RHD patients (Guilherme et al., 2001; Guilherme and Kalil, 2002). A study suggested that carrying a high responder TNF-alpha G-308A allele may be a genetic factor in increasing the susceptibility to develop RF disease (Sallakci et al., 2005).

The autoimmune reactions of RHD disease patients through an analysis of heart infiltrating T-cell repertoire, antigen recognition and cytokine production induced by specific antigens were described by Faé et al. (2005). Their results suggest that mimicry between streptococcal antigen and heart-tissue proteins, combined with high inflammatory cytokine and low interleukin (IL)-4 production, leads to the development of autoimmune reactions and cardiac tissue damage in the RHD patients.

Many studies have focused on the role of the superantigen-like activity of M-protein fragments, as well as of the streptococcal pyrogenic exotoxin, in the pathogenesis of RF (Kotb et al., 1993; Roberts et al., 2001). Superantigenic activation is not limited to the T-cell compartment alone but also to B-cell.

Aschoff's nodules represent the pathognomonic lesion of rheumatic carditis, characterized by infiltrate of macrophage, lymphocyte and complement C3 (Murphy, 1963).

Studies of different HLA-DR loci and ethnicity suggested that the link between susceptibility to RF and HLA was highly diverse and not linked to one particular allele, but to a susceptibility gene present at, or nearby, the HLA-DR locus (Ayoub et al., 1986). Subsequently, it was reported that a B-lymphocyte alloantigen, recognized by the monoclonal antibody, D8/17 and another 70 kDa molecule, may be genetically innate markers of an altered immune response to unidentified streptococcal antigens in susceptible subjects (Khanna et al., 1989). However, further studies carried out in different populations did not corroborate these findings (Hilário et al., 2003; Morer et al., 2005).

Concluding, initial streptococcal infection in a genetically predisposed host in a susceptible environment leads to the activation of T-cell and B-cell lymphocytes by streptococcal antigens and superantigens, which results in the production of cytokines and antibodies directed against streptococcal carbohydrate and myosin.

It is presumed that chronic streptococcal carrier states do not trigger the development of RF.

5. Clinical manifestations

In most cases the onset of clinical manifestations of RF occurs between the second or third week after the streptococcal infection. However, in a few cases it could be earlier.

5.1. Arthritis

Arthritis is the most frequent manifestation of RF, occurring in 60–80% of patients in the first attack. Usually it is the presenting complaint and the least specific manifestation. Although the arthritis is

typically migratory, transient and self-limited, polyarticular, with pain out of proportion to the inflammatory signs and present a satisfactory response to anti-inflammatory doses of salicylates, we have to be aware of atypical presentations that might lead to misdiagnosis. These include: relatively short latency period, mono or oligoarthritis, additive pattern, longer duration ($\geqslant$6 wk) and poor response to salicylates (Hilário et al., 1992).

Due to the high frequency of RF in our country and the lack of a clear distinction between post-streptococcal reactive arthritis and acute RF, we do not consider the diagnosis of post-streptococcal reactive arthritis as a different entity from RF.

5.2. Carditis

Carditis is the second most frequent manifestation of RF, occurring in 40–50% of the patients. Although the endocardium, myocardium and pericardium may be all affected characterizing a pancarditis, the endocarditis, isolated or not, is the most frequent feature. Nevertheless, the characteristic apical systolic murmur, clinical expression of mitral regurgitation, may be absent in a few patients. The most frequently affected valves are, in the following order: mitral, aortic, tricuspid and pulmonary. We have to be aware of carditis until the sixth week of acute phase.

In the last few years some authors have drawn attention to the existence of subclinical carditis, i.e., to the rheumatic carditis detected just by Doppler echocardiography (Wilson and Neutze, 1995; Hilário et al., 2000; Figueroa et al., 2001).

Murmurs present during the acute phase do not indicate a permanent valvular defect, and in the majority of cases (60%), they are transient.

Mitral stenosis is rare in the pediatric age group, and indicates previous cardiac involvement.

Myocarditis or pericarditis, by themselves, should not be labeled rheumatic in origin, when not associated with endocardial involvement, and other etiologies must be considered.

5.3. Sydenham's chorea

This manifestation of RF occurs primarily in children and adolescent females. It is rare in young adults or after the age of 20 years. Although its prevalence is reported between 15% and 20% in most series, we continue to diagnose chorea more frequently, in ~30–35% (Goldenberg et al., 1993; Ronchezel et al., 1998). Sydenham's chorea is characterized by emotional lability, muscle weakness and by uncoordinated abrupt and erratic movements. All muscle groups may be affected but movements of the hands, arms, feet and legs are most evident. Face, tongue and lips may also present involuntary movements. Other manifestations include handwriting and speech disturbance. Choreiform movements are usually bilateral, decrease with rest and always disappear during sleep.

Neuropsychiatric abnormalities such as obsessive–compulsive disorders have been associated with Sydenham's chorea (Swedo, 1994; Asbahr et al., 2005; Maia et al., 2005). Higher frequency of major depression, migraine, tics and hyperactivity with attention deficit in patients with chorea compared with RF patients without chorea and controls was described (Mercadante et al., 2000; Faustino et al., 2003; Al Teixeira et al., 2004; Maia et al., 2005).

Although Sydenham's chorea has been described as an isolated manifestation of RF, it is associated with carditis and/or arthritis in ~50% of our patients.

Recurrent attacks of acute RF in patients who presented chorea in the first episode are usually characterized clinically by chorea (Ronchezel et al., 1998).

5.4. Subcutaneous nodules

This is a very rare manifestation of RF, occurring in less than 3% of our patients. Characteristically they are round, firm, freely movable, painless varying in size and occurring on the extensor surfaces of the joints, particularly the elbows, knees, ankles and knuckles. In most cases they are associated with the presence of carditis, frequently severe carditis.

5.5. Erythema marginatum

This is also a rare manifestation of RF, which usually occurs early in the follow-up of a

rheumatic attack. This rash is nonpruritic and macular with a serpiginous erythematosous border usually on the trunk or proximal inner aspects of the limbs. It is usually associated with carditis.

5.6. Other manifestations

Fever and arthralgia are less frequent non-specific manifestations of RF. Fever may be a presenting manifestation of RF but usually lasts a few days. Abdominal pain and epistaxis may occur before major manifestations of RF, but they have not been considered a part of the Jones criteria due to the lack of specificity of the symptoms (Kula et al., 2005).

6. Diagnosis

6.1. Laboratory tests

Although not specific the laboratory tests are important to detect a recent infection caused by *Streptococcus pyogenes*, to determine the inflammatory process intensity and to exclude other causes of arthritis as leukemia and sickle cell anemia.

The hemogram can be normal or mild anemia (more intense in cases of carditis) and leukocytosis with neutrophilia can be found. Persistent lymphocytosis and severe anemia suggest a differential diagnosis with leukemia. Both erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are elevated at the onset of the acute phase and tend to normalize at the end of the second or third week. They are affected by anti-inflammatory medications. More elevated values of ESR are associated with carditis. Acid alpha-1-glycoprotein and alpha-2-globulin are elevated later in the acute phase of the disease and remain elevated for a prolonged time. Their levels are not influenced by anti-inflammatory medications and they have been used to monitor RF activity.

The gold standard for detecting *S. pyogenes* remains a culture of throat swab. However, in the context of RF it fails in sensitivity due to the latency period that usually lasts 2 or more weeks. On the other hand, neither culture nor rapid antigen detection tests can reliably distinguish between an acute streptococcal infection, and a streptococcal carrier with a concomitant viral infection (Ayoub, 1982). Therefore, serological tests for streptococcal antibodies (anti-streptolysin-O, anti-deoxyribonuclease B) are required and should be undertaken for all suspected cases of acute RF.

Although a single elevated antibody titer may be useful for documenting a previous streptococcal infection, it is recommended that an additional test be performed 2–3 wk after the first test in order to detect the rise of the titer.

The most commonly performed and commercially available test is the anti-streptolysin-O, however ~20–25% of the patients with acute RF do not present elevation of its titer. The range of normal values for this test is variable and depends on the geographical region.

Rapid antigen detection tests from throat swabs have the same limitations as cultures with specificity of 95% but lower sensitivity (Roddey et al., 1995).

6.2. Diagnosis of rheumatic carditis

Echocardiography became, in the last years, a key component in the diagnosis of heart disease. Doppler echocardiography is useful in evaluating myocardial function and in diagnosing valvular disease and pericarditis.

Echocardiographic findings of valvular lesions in the absence of clinical manifestations of carditis have been well described (Wilson and Neutze, 1995; Hilário et al., 2000; Figueroa et al., 2001).

In order to better characterize the subclinical carditis we performed two prospective and blind studies (Caldas et al., 2007a, b). Aiming to contribute to a better understanding of potential of Doppler echocardiography in establishing adequate diagnosis of pathologic valvular regurgitation in acute RF, we evaluated clinically and echocardiographically 56 patients with a first acute episode of the disease and followed them up to 60 months. The study revealed that regarding 29 patients with arthritis or chorea presentation without initial clinical

carditis, echocardiographic abnormalities were observed in 11 with persistence at late follow-up in 72% of the cases (Caldas et al., 2007b).

In an attempt to minimize the possibility of considering physiological regurgitation as pathological we studied the echocardiography in a semiquantitative way and such parameters like mitral variance, mitral flow convergence and aortic regurgitation were statistically more frequent in patients with clinical and subclinical carditis than in the control group. We also found that the mitral thickness of both groups of patients was larger than in controls (Caldas et al., 2007a).

It is important to emphasize that according to the American Society of Cardiology carditis is only considered in the presence of cardiac murmur (Dajani et al., 1992).

6.3. Diagnostic criteria

There is no symptom, clinical sign or laboratory test that is pathognomonic of RF. Definitive diagnosis may be difficult because of the variability of clinical manifestations. Fifty years ago Jones established criteria that are still an important guide for the diagnosis of RF (Jones, 1944). Since then Jones criteria have been revised five times by the American Heart Association; the most recent revision is from 2002 (Ferrieri, 2002). Since 1992 these criteria have been considered only for primary episode of RF (Table 1) (Dajani et al., 1992).

Diagnosis of RF is made in the presence of two major manifestations or of one major and two minor manifestations, if supported by evidence of preceding infection by GAS (Dajani et al., 1992). It is important to emphasize that not all patients with RF fulfill these criteria at onset of disease. In the presence of isolated chorea and indolent carditis a diagnosis of RF can be made without fulfilling other Jones criteria.

Unusual presentation of acute RF with a great range of clinical manifestations that do not fulfill the Jones criteria is responsible for mistakes and delay of diagnosis. It would be worthwhile changing the arthritis concept in an attempt to include the atypical forms; the echocardiography if utilized with strict criteria could be an accurate instrument to distinguish pathologic from physiologic valvular lesions and therefore to diagnosis subclinical carditis; the evidence of streptococcal infections is not always possible and for this reason it would be better to consider it as important evidence for the diagnosis and not as indispensable. Furthermore, the establishment of a score according to the frequency and importance of the manifestations of RF may improve the sensitivity and specificity of the Jones criteria.

Table 1
Guidelines for the diagnosis of an initial attack of rheumatic fever (modified Jones criteria, 1992)

Major manifestations	Minor manifestations
Carditis	Clinical
Polyarthritis	Fever
Sydenham's chorea	Arthralgia
Erythema marginatum	Laboratory
Subcutaneous nodules	Elevated acute phase reactants
	ESR
	CRP
	Prolonged P-R interval on ECG

Source: Dajani et al, (1992).

6.4. Differential diagnosis

Oligo or polyarthritis in the absence of other major manifestations of RF deserve differential diagnosis from many clinical entities. Septic arthritis, including gonococcal arthritis, other reactive arthritides, such as Lyme disease, connective tissue diseases, acute lymphoid leukemia and other tumors and sickle cell disease should be considered.

Viral or tuberculous pericarditis, viral myocarditis, bacterial endocarditis, innocent murmurs, congenital heart disease and connective tissue diseases as systemic lupus erythematosus or juvenile idiopathic arthritis, should be ruled out in the cases of carditis.

Although the presence of chorea is highly suggestive of RF, when it is isolated, other diseases need to be excluded like viral encephalitis, systemic lupus erythematosus and antiphospholipid syndrome.

7. Treatment

The management of acute RF consists of elimination of the *S. pyogenes* (primary prevention), treatment of carditis, arthritis and chorea and secondary prophylaxis against recurrent infection.

The primary prevention of RF is defined as the adequate antibiotic therapy of GAS upper respiratory tract infections to prevent an initial attack of acute RF. Streptococcus can be eliminated by a single intramuscular injection of benzathine penicillin G in a dose of 600,000 units for patients <25 kg or 1.2 million units for those $\geqslant 25$ kg. Patients with proven penicillin allergy should take erythromycin (30–40 mg/kg/day) in 4 divided doses for 10 days. Oral medications are less effective, mainly due to low compliance and potentially because of variable absorption. It is important to emphasize that sulfa drugs are not effective in eliminating streptococci. In Brazil, 24.6% of children presenting with sore throat were found to have GAS pharyngitis (Rimoin et al., 2005).

Antibiotics should not be administered to GAS carriers, because they are unlikely to spread the microorganism to contacts and they are at a low risk, if any, of developing RF.

Carditis is generally treated with corticosteroids in doses of 1–2 mg/kg/day, BID in the first week and given as a single daily dose thereafter. Its initial dose should be given for 4–6 wk until clinical and laboratory improvement and subsequently it should be tapered over 8–12 wk. Successive dose reductions should not exceed 20% of the previous dose. Diuretics, angiotensin converting enzyme inhibitors and digoxin are used for the treatment of heart failure. In patients with carditis, a rest period of at least 4 wk is recommended.

Acetyl salicylic acid (ASA) in doses of 80–100 mg/kg/day (maximum of 3 g/day) is recommended for the treatment of arthritis especially due to its efficacy and low cost. Once inflammatory parameters are brought under control, the dose should be reduced to complete 4–8 wk of treatment. For patients who are intolerant or allergic to ASA, naproxen or other non-steroidal anti-inflammatory may be used. For patients with associated carditis treatment with corticosteroids is sufficient.

For the treatment of Sydenham's chorea we recommend haloperidol (initial dose of 1–2 mg/day up to a maximum of 4–5 mg/day), valproic acid (30–40 mg/kg/day) or pimozide (1–6 mg/day) with gradual reduction over the months following disappearance of symptoms. Special attention should be given to side effects of these medications. Although there are no proven benefits of using corticosteroids to treat chorea, prednisone (1 mg/kg/day) may be useful in selected patients with very severe symptoms.

Secondary prophylaxis is carried out with benzathine penicillin G, in the same doses used for primary treatment. The recommended interval between doses is 4 wk, however for populations at high risk, penicillin should be given every 3 wk (Dajani et al., 1995). It is recommended that patients who develop RF without carditis should receive prophylaxis until 18 years of age, or for a minimum period of 5 years after the last attack (whichever is longer). Patients who develop mild carditis without sequelae should receive prophylaxis up to 25 years of age, or for a minimum period of 10 years. In the cases of involvement of both mitral and aortic valves, prophylaxis should be maintained indefinitely (Dajani et al., 1988; Taranta and Markowitz, 1989). Penicillin prophylaxis should be continued during pregnancy.

Penicillin allergy is a very rare condition, especially in children under 12 years of age (Wood et al., 1964; Lue et al., 1986; Dajani, 1996). In these cases alternative antibiotics can be used, as previously discussed.

Patients undergoing surgery or dental procedures should receive additional prophylaxis with amoxicillin. Tonsillectomy is not effective in reducing the incidence of RF, and is not recommended for the primary prevention of RF. It does not modify the course of the disease, and it does not alter the frequency of the first attack or recurrences.

Vaccines using streptococcal antigens are being developed for use in genetically susceptible individuals. The most promising approaches are M-protein-based, including those using multivalent type-specific vaccines, and those directed at non-type-specific, highly conserved portions of the molecule (Beachey et al., 1988; Dale, 1998). A new vaccine that contains N-terminal peptides from

streptococcal protective antigen and M proteins of 26 common pharyngitis, invasive and/or rheumatogenic serotypes was developed and it can have significant impact on the overall burden of streptococcal disease. No volunteer that received this vaccine developed evidence of rheumatogenicity (McNeil et al., 2005). Success in developing vaccines may be achieved in the next years, but this success would have to contend with important questions about the safest, most economical and most efficacious way in which to employ them, as well as their cost-effectiveness in a variety of epidemiologic and socio-economic conditions (World Health Organization Technical Report Series, 2004).

Key points

- Rheumatic fever is still a prevalent disease in developing countries, and rheumatic heart disease remains important cause of cardiovascular disease in the world.
- Atypical presentation of arthritis and carditis must be considered in the diagnosis of rheumatic fever.
- Adequate treatment of streptococcal infections in order to prevent rheumatic fever should be a priority for health politics specially in developing countries.

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Handbook of Systemic Autoimmune Diseases, Volume 6
Pediatrics in Systemic Autoimmune Diseases
Rolando Cimaz and Thomas Lehman, editors

CHAPTER 17

Lyme Borreliosis

Hans-Iko Huppertz[1,*], Hermann J. Girschick[2]

[1]*Prof.-Hess-Kinderklinik, Klinikum Bremen-Mitte, Sankt-Jürgen-Strasse, Bremen, Germany*
[2]*Universitäts-Kinderklinik Würzburg, Germany*

1. Introduction

Lyme disease or Lyme borreliosis (LB) is an infectious multi-system disease. LB is caused by *Borrelia burgdorferi*, a spirochete. *B. burgdorferi* organisms can be subdivided into several genotypes which have been associated with different though overlapping clinical syndromes. LB is transmitted by the vector *Ixodes ricinus*, a hard tick that is prevalent in many areas of the temperate Northern zones including most of Europe and parts of the USA. In some parts of Europe and the USA LB may be one of the most frequent infectious diseases with an incidence of 111 per 100,000 or more (Huppertz et al., 1999).

Up to 90% of patients with LB have erythema migrans, a mild reddening of the skin at the site of the tick bite that will disappear without intervention after a few days to weeks. The infection can affect the nervous system, joints, heart, eyes and other organs. Clinical manifestations are classified as early or late. Early manifestations occur a few days to several weeks after infection, while late occur months to years after infection (Huppertz and Dressler, 2005). Early manifestations are self-limiting and normally do not cause lasting damage. However, late manifestations may become chronic and lead to organ damage. Clinical manifestations differ in adults and children; in children radiculitis is rare while lymphocytic meningitis with or without cranial nerve palsy is more frequent. Acrodermatitis chronica atrophicans, chronic central nervous system disease and heart involvement are very rare in children.

Arthritis, called Lyme arthritis (LA) is the most frequent late manifestation in children. It is often episodic, but may become chronic and up to 15% of cases are resistant to antibiotic treatment (Bentas et al., 2000). Risk factors are female gender, age >10 years and treatment with systemic or intraarticular steroids prior to initiation of antibiotic treatment.

LB, and in particular LA, has attracted special interest by clinicians and researchers since arthritis due to infection with *B. burgdorferi* can become chronic.

Chronic arthritis following infection with *B. burgdorferi* has been attributed to several factors including persistent infection, immunopathological reactions to components of *B. burgdorferi* and autoimmunity (Girschick et al., 1996; Rittig et al., 1992).

2. Persistent infection

At the time of early manifestations, the presence of *B. burgdorferi* can be verified by isolation of the spirochete or by polymerase chain reaction (PCR) of borrelial genomic and/or plasmid-derived sequences, but this often proves impractical. In otherwise healthy patients with acrodermatitis chronica

*Corresponding author.
Tel.: +49-421-497-5411; Fax: +49-421-497-3311
E-mail address: huppertz.bremen@t-online.de (H.-I. Huppertz).

DOI: 10.1016/S1571-5078(07)06021-7

atrophicans *B. burgdorferi* could be grown from affected skin up to 10 years after the beginning of the disease showing the remarkable capability of the spirochete to persist in the human body in the presence of an apparently well functioning immune system. In contrast *B. burgdorferi* is rarely isolated from synovial fluid or tissue in patients with LA or from cerebrospinal fluid in patients with late neuroborreliosis. However PCR may be positive. The spirochete has been demonstrated in synovial tissue, by staining with silver salts or monoclonal antibodies (Priem et al., 1998). Interestingly, *B. burgdorferi* is found in a very low density.

3. Immunopathological reactions

B. burgdorferi may modulate the immune system. In patients with acrodermatitis chronica atrophicans decreased expression of the major histocompatability complex (MHC) has been observed on Langerhans cells in contact with *B. burgdorferi* (Silberer et al., 2000). Infection may increase or decrease the expression of adhesion molecules on a variety of cell types (Sellati et al., 1995; Girschick et al., 1999; Singh et al., 2005). *B. burgdorferi* specific CD4 positive T-cells can be isolated from peripheral blood or synovial fluid of patients with LA (Huppertz et al., 1996) and the response increases with prolonged disease. The lymphokines secreted by these cells have typical Th1 characteristics (Yssel et al., 1991). CD8 positive *B. burgdorferi* specific T-cells have been isolated from children with LA after resolution of arthritis suggesting that a regulatory deficiency may contribute to the development of chronic arthritis (Busch et al., 1996). *B. burgdorferi* does not produce toxins and does not harbour lipopolysaccharides, but it contains a variety of lipoproteins which may influence the development of arthritis (Infante-Duarte et al., 2000).

4. Autoimmunity

Patients with persistant LA have been shown to express MHC class II molecules associated with RA, including HLA-DRB1*0401 and *0101 (Steere and Baxter-Lowe, 1998). These patients showed high titers of antibodies against the outer surface protein A (OspA) which is a plasmid encoded virulence factor located in the outer envelope of the spirochete (Kalish et al., 1995). After phagocytosis borrelial antigens can be presented by MHC class II molecules to T-cells (Filgueiria et al., 1996). It was shown that the T-cell antigen LFA-1 can stimulate OspA-specific T-cells from patients with treatment resistant LA (Trollmo et al., 2001). Thus LFA-1 might serve as cross-reactive autoantigen by way of molecular mimicry in which initially an immune response is mounted against OspA; then the immune response also affects LFA-1 which leads to the stimulation of the T-cells; finally the immune response persists even in the absence of OspA and is directed against LFA-1. Unfortunately this hypothesis has not been confirmed.

In an animal model, B-cell tolerance was broken following chronic infection with *B. burgdorferi*. The immune complexes induced synergistic signaling between B-cell receptor, Toll-like receptors and T helper cell (Soulas et al., 2005).

Thus autoimmune reactions and not just molecular mimicry between bacterial and host antigens contribute to the chronic arthritis of LB (Kamradt and Volkmer-Engert, 2004).

5. Conclusions

LA is an intriguing disease; it is infectious, but the response rate to antibiotic treatment of ~85% is inferior to that found in other bacterial diseases. LA may also be considered a rheumatic disease, but with a very favourable outcome; there are few or no other rheumatic diseases that enter into remission in 85% after 1 or 2 short courses of antibiotics. Moreover the other 15% will follow a few months or years later after appropriate antirheumatic treatment including intraarticular steroids and/or methotrexate.

Although several not necessarily exclusive theories have been proposed, the mechanisms of the pathogenesis of antibiotic refractory LA remain

unknown. In addition, the hope to find clues for understanding the pathogenesis of RA or JIA by better understanding the pathogenesis of LA have not come true so far. Much more research is necessary to achieve that goal. However, a better understanding of the pathogenesis of treatment-refractory LA might not only help patients with LA to be treated more effectively. It might also increase our understanding of RA and JIA and thereby it might be possible to outline new options for treatment or even prevention that should counter the causative disease process rather than just suppress the inflammatory response as actual pharmacological treatment options do.

Key points

- LA is the most frequent bacterial infection associated arthritis.
- Chronic LA may be a human model of chronic inflammatory joint disease with a known etiology.
- Clarification of its pathogenesis may provide clues to the pathogenesis of other chronic inflammatory joint diseases including rheumatoid arthritis and juvenile idiopathic arthritis.

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Handbook of Systemic Autoimmune Diseases, Volume 6
Pediatrics in Systemic Autoimmune Diseases
Rolando Cimaz and Thomas Lehman, editors

CHAPTER 18

TNF-Inhibitors in Pediatric Rheumatology

Valeria Gerloni*, Irene Pontikaki, Flavio Fantini

Pediatric Rheumatology Unit, Chair and Department of Rheumatology, Gaetano Pini Institute of Milan, Milano, Italy

1. Introduction

The overproduction of the inflammatory cytokine tumor necrosis factor-alpha (TNFα) plays a key role in the maintenance of many chronic inflammatory rheumatic diseases, particularly those that depend on relationship between T-cells and macrophages (Beutler, 1995). TNFα has been shown to induce bone reabsorption, to inhibit proteoglycan (Bertolini et al., 1986; Saklatvala, 1986) and collagen synthesis (Maini, 1996; Feldmann et al., 1997), to induce prostaglandin E_2 and collagenase release from synovial cells and to stimulate fibroblast growth (Dayer et al., 1985). TNFα also plays a pivotal role in the enhancement of inflammatory cell trafficking into synovium, by regulating the expression of adhesion molecules on the endothelial cells (Cavender et al., 1987; Butcher, 1990). It also up-regulates the production of other proinflammatory cytokines, such as interleukin-1 (IL-1) and interleukin-6 (IL-6), and the expression of their respective receptors (Brennan et al., 1989).

TNFα blockade has been therapeutically achieved through the administration of monoclonal antibodies against TNFα or soluble TNFα receptors. Three anti-TNFα agents are approved in Europe and United States for use in adult onset rheumatoid arthritis (RA), spondyloarthritis (SpA) and psoriatic arthritis: a fusion protein combining two p75-TNFα receptors with a Fc fragment of human IgG1 (Etanercept [Enbrel® Wyeth-Ayerst and Immunex]); the chimeric, human and murine, monoclonal antibody against TNFα (Infliximab [Remicade® Centocor]); and the fully human TNFα monoclonal antibody (Adalimumab [Humira®Abbott]).

The monoclonal antibodies, in particular the chimeric antibody Infliximab, specifically and potently bind and neutralize not only the soluble TNFα but also its membrane-bound precursor inducing cell lysis by apoptosis; their action mechanism is different and more selective than that of the recombinant p75-TNFα receptor, which inhibits not only TNFα but also TNFβ (limphotoxin α) and does not cause the cell lysis binding to membrane TNFα.

Controlled trials in adults have shown that the TNFα inhibitors significantly reduce symptoms and signs, improve function and quality of life and reduce radiological damage in RA and related diseases. Concurrent treatment with methotrexate (MTX) appears to enhance the therapeutic response.

Since the end of the 1990s, this therapeutic approach was also extended to juvenile idiopathic arthritis (JIA) (Petty et al., 2004). The therapeutic approach to JIA is sometimes very troublesome. The progression to erosive chronic polyarthritis, that may occur in all JIA subsets, regardless of the type of onset, often results in extreme disability and very poor quality of life. In addition, it remains difficult to control the flares of systemic symptoms in systemic onset subtype (e.g., fever,

*Corresponding author.
Tel.: +39-02-58296793; Fax: +39-02-58296293
E-mail address: gerloni@gpini.it (V. Gerloni).

DOI: 10.1016/S1571-5078(07)06022-9

frequently associated with severe anemia). Many disease modifier anti-rheumatic drugs (DMARDs), commonly used in adult RA, have shown a lack of efficacy in several placebo-controlled trials and long-term prospective studies in children with JIA (Brewer et al., 1986; Giannini et al., 1988, 1990, 1991). The only treatment that has shown efficacy and safety in a large controlled clinical trial is MTX (Giannini et al., 1992). Nevertheless, in many cases the lack of efficacy of MTX or development of drug resistance or intolerance has led to try other therapeutic options, such as salazopyrine (Van Rossum et al., 1998), cyclosporine A (Gerloni et al., 2001), intravenous human immunoglobulins (Silverman et al., 1994) or, in rare cases, a more aggressive approach with autologous stem cell transplantation (Kuis et al., 1999). However, the beneficial effects of these therapeutic choices are debatable. Prior to the era of anti-TNFα therapies, more than 25% of children with polyarticular and nearly 50% with systemic JIA, at 5 years after onset, had functional limitations. Radiographically evident joint space damage was seen within 1 year of onset in polyarthritis and, by 5 years, 2/3 of polyarticular and systemic patients had damage (Bowyer et al., 2003). Therefore, there has been space in the last few years for the more specific and effective new biologic therapies that target specific cytokines, as the TNFα inhibitors.

2. TNF in the pathogenesis of JIA

Although the mechanisms causing the clinical features of JIA (high spiking fever, anemia, joint inflammation and destruction) are still unknown, indirect evidence suggest that cytokines, such as IL-1, IL-6 and TNFα, may play an important pathogenetic role (De Benedetti et al., 1997). Elevation of circulating TNFα was seen only occasionally and in small amounts in JIA (Prieur et al., 1987; Lepore et al., 1994; Madson et al., 1994), and no correlation was found between serum concentration of TNFα and parameters of disease activity (Lepore et al., 1994; Madson et al., 1994; Mangge et al., 1995). However, it is known that cytokines exert their effects mainly at the sites of inflammation (Cope and Maini, 1995). In fact, in JIA the TNFα levels are higher in synovial fluid than in the serum (Lepore et al., 1994) and the cytokine is expressed in synovial fluid mononuclear cells (Eberhard et al., 1994). Moreover, TNFα serum concentration does not differ significantly between the JIA patients and control group, but p55 and p75 soluble receptors (sTNFαR) are significantly elevated in serum from all JIA categories, particularly in those with systemic onset disease, and their levels correlate with disease activity (Prieur et al., 1987; Gattorno et al., 1996). TNFα itself is one of the best inducers of sTNFαR expression (Brennan et al., 1995) and their shedding from the cell surface is believed to be related to TNFα production (Fiers, 1991). Therefore the increased expression of sTNFαR in plasma and in synovial fluid may support the hypothesis that TNFα has a role in the pathogenesis of JIA. Elevations in IL-1, IL-6 and TNFα in patients with systemic episodes of disease, with a rise and fall in circulating TNFα out of phases with fever, were demonstrated (Rooney et al., 1995). Plasma and synovial fluid TNFα and IL-6 concentrations were found to be significantly increased in the active period of the disease (Kutukculer et al., 1998). An imbalance between TNFα and its naturally occurring inhibitors, the soluble receptors (lower sTNFαR/TNFα ratio), might be associated with the increased joint destruction observed in polyarticular disease (Rooney et al., 2000). Finally, in JIA, synovial tissue and synovial cells overexpress not only TNFα, but also TNFβ (limphotoxin α) (Grom et al., 1996; Eberhard et al., 1994). The mechanism of action of the chimeric and human monoclonal antibodies is more selective than that of the recombinant p75-TNFα receptor, which inhibits not only TNFα but also limphotoxin α.

2.1. Anti-TNFα therapy in JIA

The clinical experience on TNFα inhibition in JIA is mainly limited to Etanercept, the only TNFα inhibitor approved until now in the United States and in Europe for use in children with active

Table 1
TNFα inhibitors in JIA (the main published clinical studies)

Author	Nationality	Study design	Etanercept (no. of patients)	Infliximab (no. of patients)
Lovell et al., 2000	USA, multicenter	Randomized, controlled	69	
Takei et al., 2001	USA, Los Angeles, CA	Retrospective; high doses	8	
Schmeling et al., 2001	Germany, Halle-Wittnberg	Open, prospective; added to MTX	7	
Kietz et al., 2002	USA, St. Louis, MO	Open, prospective; added to MTX or MTX + chloroquine	22	
Russo et al., 2002	Argentina, Buenos Aires	Open, prospective	15	
Haapasaari et al., 2002	Finland, Heinola	Retrospective	31	
Quartier et al., 2003	France, multicenter	Open, prospective	61	
Lahdenne et al., 2003	Finland, Helsinki	Open, prospective	10	14
G Horneff et al., 2004	Germany	Registry	322	
Henrickson and Reiff, 2004	USA, Madera, CA	Open, prospective (ERA-ILAR category)	8	
Tse et al., 2005	Toronto, Ontario, Canada	Open, prospective (ERA-ILAR category)	2	8
Gerloni et al., 2005	Italy	Open, prospective; added to MTX		24
Nielsen et al., 2005	Italy	National registry	209	
Ruperto et al., 2007	International	Randomized, controlled added to MTX		122
Calvo et al., 2006, EULAR-PRES-2006	Spain	National registry	103	
Twilt et al., 2006, EULAR-PRES-2006	The Netherlands	National registry	93	
Giannini et al., 2006, EULAR-PRES-2006		National registry	403	

polyarticular JIA despite prior MTX therapy. The main published clinical trials are listed in Table 1.

Only one randomized placebo-controlled multicenter American trial on Etanercept has been published (Lovell et al., 2000), while the results of the international randomized placebo-controlled trial on Infliximab are in press (Ruperto et al., 2006, 2007), and the data from the Adalimumab randomized placebo-controlled study have been recently presented (Ruperto et al., 2007). Apart from this, the literature is limited to case reports (Elliott et al., 1997; Meddeb et al., 2002; Billiau et al., 2002; ten Cate et al., 2002; Cairns and Taggart, 2002; Barber et al., 2003; Mangge et al., 2003; Hung and Huang, 2005; Liang et al., 2005), retrospective studies (Takei et al., 2001; Haapasaari et al., 2002) or open prospective studies of small populations (Schmeling et al., 2001; Kietz et al., 2002; Russo et al., 2002; Quartier et al., 2003; Lahdenne et al., 2003; Gerloni et al., 2005), and to the results of some national registries: the German (Horneff et al., 2004), Italian (Nielsen et al., 2005), American (Giannini et al., 2006), Spanish (Calvo et al., 2006) and Dutch (Twilt et al., 2006) ones.

The first reported cases of TNFα blockade in JIA (Elliott et al., 1997; Meddeb et al., 2002; Billiau et al., 2002) were cases of systemic onset JIA (SoJIA) treated with Infliximab. However, most of the subsequent studies refer to experiences with Etanercept, with the exceptions of 14 patients treated with Infliximab reported in a Finnish study (Lahdenne et al., 2003), 24 patients of a recently published Italian study (Gerloni et al., 2005) and 122 patients of the international controlled study (Ruperto et al., 2007).

Both Etanercept (Lovell et al., 2000, 2003) and Infliximab (Lahdenne et al., 2003; Gerloni et al., 2005) have shown a dramatic clinical benefit in the

treatment of patients with active JIA with polyarticular course who did not tolerate or had an inadequate response to MTX. The TNF inhibitors not only control the symptoms and signs of arthritis but also improve the biochemical measurements of inflammation (ESR and CRP) and the quality of life. Moreover, the early introduction of anti-TNF agents in children with severe JIA, suppressing inflammation and providing a steroid sparing effect, could reduce the risk of osteoporosis (Simonini, 2005) and growth failure (Tynjala et al., 2006).

2.1.1. Etanercept

The open-label data from 69 patients of the Etanercept multicenter American trial (Lovell et al., 2000), showed that at the third month of therapy 74% of patients achieved the American College of Rheumatology Pediatric 30 Definition of Improvement (ACR-Pedi-30) (Giannini et al., 1997; Ruperto et al., 1998). In the subsequent, placebo-controlled, study of patients who had achieved the ACR-Pedi-30 response, the percentage of patients who withdrew because of disease flare was significantly higher in the group of patients who switched to placebo (81%), as compared with the group of the patients who continued with the active drug (28%). Etanercept is until now the only biologic agent registered for the treatment of polyarticular course JIA in patients who fail to respond to or do not tolerate MTX. The extended open-label phase of this study demonstrated a sustained clinical improvement with more than 4 years of continuous Etanercept treatment (Lovell et al., 2003, 2006).

The conventional pediatric dose of Etanercept is 0.4 mg/kg of body weight (maximum dose 25 mg) administered subcutaneously twice a week. However, a pharmacokinetic analysis and simulation of the time-concentration profile of Etanercept in pediatric patients with JIA showed that 0.8 mg/kg once-weekly and 0.4-mg/kg twice-weekly regimens generate comparable systemic exposure, likely leading to equivalent clinical outcomes. This has been the basis of the recent FDA approval of the 0.8 mg/kg once-weekly regimen in pediatric patients with JIA (Yim et al., 2005). In the case of lack of efficacy with the conventional dose, the dose can be increased up to 1 mg/kg twice a week (Takei et al., 2001).

The combination of TNFα antagonists with immunosuppressants generally seems to be beneficial in order to increase the efficacy of therapy. There is only a weak experience of the combination therapy of Etanercept with other DMARDs, but this seems to be feasible since tolerance so far seems not to be problematic. In small studies, Etanercept has been proven efficacious and safe when combined with MTX, MTX plus hydroxychloroquine, MTX plus salazopirine and leflunomide. (Kietz et al., 2001; Schmeling et al., 2001; Russo et al., 2002; Haapasaari et al., 2002; Horneff et al., 2006).

2.1.2. Infliximab

Since the first open prospective single center experiences (Lahdenne et al., 2003; Gerloni et al., 2005), TNFα blockade with the chimeric monoclonal antibody Infliximab added to MTX also resulted highly effective and safe in the treatment of patients with long lasting, active JIA despite previous therapy with MTX and one or more other DMARDs. This resulted in a clinically impressive and statistically significant reduction in disease activity, as assessed by a number of clinical end-points and biochemical markers, and was associated with an improvement in some aspects of the quality of life. Already after the first infusions the majority of the patients reported an improvement in pain and morning stiffness and a reduction of fatigue.

The international randomized controlled study (Ruperto et al., 2007) of Infliximab therapy in JIA showed that at week 14 of therapy, with the dose of 3 mg/kg, 63.8% of patients achieved the ACR-Pedi-30 response. By week 16, following crossover from placebo group to Infliximab 6 mg/kg (at which time all patients were receiving Infliximab), 73.2% of patients achieved an ACR-Pedi-30 response. Also with Infliximab, a sustained clinical improvement was demonstrated: by week 52, an ACR-Pedi-50 or ACR-Pedi-70 were reached by 69.6 and 51.8% of patients, respectively.

In the pilot clinical experiences in JIA, Infliximab was administered, as in adult RA, by i.v. infusions at the conventional dose of 3 mg/kg/infusion at weeks 0, 2, 6 and every 8 weeks thereafter and was usually added to MTX at the previous well-tolerated dosage. In fact, in the clinical trials in adult RA (Maini et al., 1998), the combined therapy was proven to be beneficial in order to increase the efficacy of therapy. Moreover, the combined therapy and higher doses of Infliximab, up to 10 mg/kg/infusion, seems to be safer reducing the rate of hyperergic infusion reactions (IRs). Similarly, in the controlled study in JIA (Ruperto et al., 2007), higher doses of Infliximab (6 mg/kg/infusion) proved to be safer than the 3 mg/kg dose in order to reduce the rate of IRs. For these reasons the recommended dose of Infliximab for the treatment of JIA is now 6 mg/kg/infusion and the association with MTX is the rule.

2.1.3. Adalimumab

The blockade of TNFα with the human monoclonal antibody Adalimumab, either alone or combined with MTX, was also shown to rapidly improve signs and symptoms of JIA. The open-label data from 171 patients of the international trial showed that after 16 wk of therapy, the response rates were 83% for ACR-Pedi-30, 74% for ACR-Pedi-50 and 52% for ACR-Pedi-70. In the subsequent, placebo-controlled, study of patients who had achieved the ACR-Pedi-30 response, significantly fewer patients receiving Adalimumab had disease flares than those who received placebo, regardless of concomitant MTX use (Ruperto et al., 2007).

2.2. TNFα blockade in the treatment of systemic onset JIA

The efficacy of TNFα blockade in patients with SoJIA appeared not to be as satisfactory as in the other non-systemic JIA ILAR categories (Lovell et al., 2000; Russo et al., 2002; Quartier et al., 2003; Horneff et al., 2004; Kimura et al., 2005). However, the rate of response appears to vary according to the presence or not of systemic activity (fever and rash) at the time of the treatment. In one study, Etanercept was efficacious in the 88% of patients with SoJIA in the first year of treatment, but in children with systemic symptoms at the time of therapy, improvement was short-lived or toxicity limited its continuous use. Patients with SoJIA but a non-systemic chronic polyarticular course, show a better response than children with a systemic activity, comparable with the one exhibited by patients with polyarticular JIA (Russo and Katsicas, 2006). In the patients with SoJIA in active phase, who fail to respond to Etanercept, the presence of fever/rash was not modified by the treatment when also switched to Infliximab (Katsicas and Russo, 2005). In a different experience (Pontikaki et al., 2006) TNFα blockade with either Etanercept or Infliximab resulted as effective in SoJIA as in the other JIA ILAR categories. In fact, most of the SoJIA patients in this study had a long lasting disease and were in a sustained polyarthritic phase without systemic symptoms.

2.3. TNFα blockade in the treatment of juvenile spondyloarthropathies

TNFα also plays an important role in the pathogenesis of enthesitis-related arthritis. Preliminary data from small populations show that anti-TNFα therapy, either with Infliximab or with Etanercept, is an efficacious treatment for refractory juvenile SpA (Henrickson and Reiff, 2004; Tse et al., 2005). The arthritis and enthesitis significantly improved, the markers of inflammation and the CHAQ scores normalized, and there was a reduction in requirements for anti-rheumatic drugs. Additionally, the patients noted increased mobility and overall well being. The improvement was sustained during the 1–2 year of follow-up.

Moreover, TNFα blockade seems to be also efficacious in the treatment of anterior acute uveitis. In fact, in adult patients affected by SpA, treatment with TNFα blockers is associated with a significant decrease in the number of anterior uveitis flares. This reduction is slightly more marked among patients treated with Infliximab (Braun et al., 2005).

3. Adverse events of TNFα blockade

Biologic drugs, such as TNF inhibitors, refer to genetically engineered drugs that have been designed to modulate a specific aspect of the underlying immune process, thus avoiding generalized immunosuppression, with the hope that such specificity will result in higher efficacy and fewer adverse events (AEs) than traditional cytotoxic DMARDs. However, as use of these agents has increased worldwide during the post-marketing period, infrequent AEs that were not apparent in controlled clinical trials required for registration have emerged (Quartier et al., 2003; Dekker et al., 2004; Gerloni et al., 2006). The neutralization of TNF is associated with an increased risk of certain serious but uncommon AEs, including serious bacterial infections such as tuberculosis (TB) and certain opportunistic infections, malignancy/lymphoma, congestive heart failure, demyelinating and neurological disorders, injection-site reactions or infusion-related systemic reactions, newly induced autoantibodies and lupus-like disease. However, several of these risks (e.g., lymphoma and serious infections) are associated with either the disease per se or the concomitant and previous immunosuppressive treatments (Hochberg et al., 2005).

These AEs may be related to blockade of TNF and may therefore represent class effects of these agents. However, the severity and degree of the risk may not be the same with all three agents.

Overall, tolerability of anti-TNF therapy in JIA is good. In 592 patient treatment-years of the German Etanercept registry (Horneff et al., 2004), there were 69 reports of AEs in 56 patients. In the USA registry (Giannini et al., 2006) a total of 601 patients (Etanercept 403 and MTX 198) were included and the rate of AEs observed with Etanercept was very low (21%), exactly the same as was observed with MTX treatment. The recent published data on safety after 4 years show that Etanercept also offers an acceptable safety profile in a long-term treatment: the rate of severe AEs was 0.13 per patient-year, and the rate of serious infections was 0.04 per patient-year, in a total Etanercept exposure of 225 patient-years (Lovell et al., 2006). The TNF blockade with either Etanercept or Infliximab was also safe and quite well tolerated in a large Italian prospective experience (Gerloni et al., 2006): less than 60% of treatments were complicated with one or more AEs, which contrasts with some adult studies where up to 95% of patients had at least one AE (Lipsky et al., 2000). The AEs observed in pediatric clinical experiences usually were not serious, led to discontinuation of treatment in ~20% of the whole population and all disappeared after discontinuation (Quartier et al., 2003; Gerloni et al., 2006). Overall, patients with SoJIA seem to be at greater risk for AEs than patients with non-systemic JIA.

3.1. Hyperergic reactions

The more frequent AE with Etanercept is a transient mild local allergic reaction to the s.c. injection recorded in up to 39% of JIA patients (Lovell et al., 2000), but ~10% of patients manifested a diffuse cutaneous reaction that required an antihistaminic treatment (Skytta et al., 2000; Lovell et al., 2000; Gerloni et al., 2006).

The most common AE with Infliximab is the IR which provokes sensations of thoracic constriction, dyspnea, flushing and urticaria. This AE can be prevented or attenuated by slowing the infusion velocity and by pre-treatment with antihistaminic and steroid drugs. Nevertheless, many patients (20%) failed treatment because of severe reactions, relapsing at each infusion despite this pre-treatment (Gerloni et al., 2006). In fact, one of the major concerns, limited to the TNFα blockade with the monoclonal-antibody Infliximab, is the potential formation of human anti-chimeric antibodies (HACA) that neutralize the therapeutic agent, limiting its long-term efficacy (silent inactivation) or causing allergic reactions during the infusions (Markham and Lamb, 2000).

In the randomized international controlled trial of Infliximab plus MTX in polyarticular JIA (Ruperto et al., 2007), antibodies to Infliximab developed more frequently (37.7% vs. 12.2%) with lower (3 mg/kg) rather than with higher (6 mg/kg) doses. Moreover, patients with antibodies to

Infliximab had a threefold incidence of IRs compared with patients who were negative for these antibodies. The same result was obtained in the first studies of Infliximab on adult RA where higher doses and combination with MTX significantly reduced the incidence of IRs to Infliximab treatment (Maini et al., 1998). The observation that in some cases the IR occurred despite previous medication with antihistamines and steroids, argues against the hypothesis that a true hyperergic mechanism could be responsible for these manifestations. A second hypothesis is that some IRs could be related to an aspecific release of prostaglandin D2, niacin-like effect, as described in the ''red man syndrome'' (Lobel et al., 2003; Becker et al., 2004).

3.2. Neuropsychiatric manifestations

The second more frequent AEs with both treatments are some aspecific signs of CNS involvement (Gerloni et al., 2006; Giannini et al., 2006). The neuropsychiatric manifestations observed with Etanercept ranged from aspecific signs such as headaches (in some cases severe and dose-dependent), vertigo, fatigue, hyperactivity and nervousness, to more rare cases of pain amplification syndromes, important behavioral alterations such as a severe unusual aggressiveness, or major neuropsychiatric syndromes such as panic, depression, anxiety, and finally to very rare neurological organic signs, such as the described cases of hypoglossal paralysis, optic neuritis and demyelinating syndromes (Lovell et al., 2000, 2003; Quartier et al., 2003; Horneff et al., 2004; Gerloni et al., 2006; Tauber et al., 2006).

Although exacerbations of multiple sclerosis and other neurological events suggestive of demyelinization have been reported for patients receiving treatment with the anti-TNFα agents Etanercept and Infliximab, it is not clear whether a causal relationship exists. In a recent study in adult RA, the rate of new cases of demyelinating neurological disease in exposed patients was not different from the rate of expected cases (Magnano et al., 2004).

The neuropsychiatric AEs observed with Infliximab are similar to those observed with Etanercept (Gerloni et al., 2006). In some cases these were aspecific and clinically less important, including symptoms such as sleepiness or insomnia, anxiety, transient paresthesia and fatigue. In other cases the AEs were represented by the classic major psychiatric manifestations: panic attacks, depressive syndromes and psychoses.

3.3. Infections

The major concern with the TNFα blockers is their potential pro-infective action. In fact, TNFα has immunostimulating functions in vitro (Havell, 1989) and its neutralization in experimental models may increment infections (Pfeffer et al., 1993).

Infections, particularly TB and less commonly fungal infections are among the most serious AEs. Infliximab appears to be associated with the greatest risk of infection, most likely because of its long half-life (Etanercept has a median half-life of 4.8 days, while Infliximab has a longer half-life of 8–9.5 days) and induction of monocyte apoptosis (Crum et al., 2005). The experiences in adult RA and in JIA also reported cases of death for sepsis (Elwood et al., 2003) and TB (Armbrust et al., 2004).

On the other hand, in adult RA the long-term exposure to the pro-inflammatory cytokine TNFα seems to impair T-cell responses in vitro and in vivo. This impairment seems to be reversed by anti-TNFα therapy (Cope et al., 1994). In fact, in patients with adult RA the incidence of serious infections associated with Etanercept and Infliximab was low, ~2–3% in Etanercept studies of up to 5 years duration, and 5% in a survey of more than 10 Infliximab trials (Moreland, 2004).

Infections can be minimized or prevented by screening and careful monitoring and follow-up; most infections respond to appropriate medical treatment. Most reported infections are mild infections of the upper respiratory (URI) or the urinary tract (UTI), which were easily managed with antimicrobial therapy. It is recommended that physicians and patients be alert to the development of any new infection so that the appropriate

treatment may be promptly started. These minor infections are mainly described in JIA patients treated with Etanercept, perhaps because of the younger age of these populations (monoclonal antibodies are not yet approved for patients younger than 18 years) and the higher baseline rate of these minor infections (URI and UTI) in school age children versus adolescents and young adults. Moreover, increased and closer observation, in the population enrolled in clinical trials, may be in part responsible for the reported increases in the rates of mild infections. A particular pediatric concern is the immunosuppressive action of biologics in children who are exposed to or develop varicella. In fact, in the multicenter controlled USA experience (Lovell et al., 2003), three children developed the varicella infection during Etanercept treatment and one of them needed hospitalization because of severe complications; nevertheless, both children completely recovered. At present it is suggested that, if possible, pediatric patients who are not immune should be vaccinated against varicella at least 3 months before the start of any anti-TNFα therapy. In the case of non-immune children who are exposed to or develop varicella while treated with TNFα blockers, the prophylaxis or an aggressive anti-varicella treatment should be promptly started. Administration of live vaccines to patients taking these drugs is not recommended, but patients should be brought up to date with all immunizations relevant to their age group before commencement of therapy.

Severe infections seem to be more frequent in adult RA than in JIA. Children affected by JIA have less therapeutic options (the only DMARD proven efficacious and safe in a large controlled trial is MTX). For this reason, children are usually treated earlier with anti-TNFα and are less exposed to previous long lasting immunosuppressant treatments and to immunosuppression due to the persistent uncontrolled disease activity.

One of the major concerns with the TNFα blockade is the potential reactivation of a silent TB infection. The TB infections are among the most serious AEs, especially given the delays in diagnosis due to their subtle or atypical presentation. This occurs mainly with Infliximab due to its capacity to bind to membrane TNFα and to induce cell lysis by apoptosis (Winthrop et al., 2005; Winthrop, 2005).

This AE, definitely related to the TNFα inhibition, was frequently observed in the first phase of clinical post-marketing experience in adult RA. It has now quite completely disappeared since the implementation of mandatory screening for TB silent infections and anti-TB prophylaxis in the case of positive Mantoux test, before the start of therapy with anti-TNFα. Two cases of TB arthritis in systemic JIA patients treated with Etanercept and Infliximab respectively have been described (Myers et al., 2002; Armbrust et al., 2004); one of them died for this reason.

3.4. TNF blockade and macrophage activation syndrome

Macrophage activation syndrome (MAS), which can be considered as secondary hemophagocytic lymphohistiocytosis, is a potentially life-threatening complication of SoJIA. Some case reports have suggested that Etanercept may be a useful adjunctive therapeutic agent in refractory MAS, non-responsive to corticosteroids and cyclosporine (Prahalad et al., 2001; Makay et al., 2006; Cortis and Insalaco, 2006). Nevertheless, cases of MAS in SoJIA during the treatment with both TNFα blockers are reported. In some cases the MAS was a complication of a bacterial or viral infection (Lahdenne et al., 2003; Ramanan and Schneider, 2003; Kimura et al., 2005; Gerloni et al., 2006).

3.5. New onset or worsening of autoantibody-mediated diseases

Another concern of TNFα blockade is its potential action to shift the pattern of the immune response from a Th1 to a Th2 response and thus the possibility of favoring antibody production and the new onset or worsening of autoantibody-mediated or allergic diseases. This is true mainly for Infliximab due to its long lasting Th1 suppression. In fact, the TNFα blockade with either Infliximab or Etanercept, in patients with RA as well as in those

with SpA and Crohn's disease, is clearly associated with the development of autoantibodies such as ANA and/or anti-dsDNA (De Rycke et al., 2005). The mechanism of this phenomenon is not well understood, but the development of these autoantibodies is rarely associated with the development of a lupus-like syndrome. Studies on adult RA have described cases of drug-induced SLE, discoid LE and cutaneous vasculitis. The anti-TNFα therapy with Infliximab, in the case of adult RA and SpA, seems to be more often responsible for the newly induced autoantibodies: newly induced ANA are observed in 60% of SpA and 40% of RA patients, newly induced anti-dsDNA in 70% of SpA and 50% of RA patients, while a lower rate of newly induced autoantibodies is observed with Etanercept: 2–13% (De Rycke et al., 2005). In the American multicenter controlled trial (Lovell et al., 2000) and in the subsequent experiences with Etanercept in the treatment of JIA, none of the treated patients developed de novo persistent ANA or anti-dsDNA, nor a second autoimmune disease with the exception of: one case of a new onset of insulin-dependent type I diabetes mellitus (Bloom, 2000), one case of juvenile SLE (Lepore et al., 2003) and one case of proliferative lupus nephritis and leukocytoclastic vasculitis (Mor et al., 2005). One case who newly developed anti-dsDNA and another whose autoimmune alopecia relapsed were described out of 14 JIA patients treated with Infliximab in Helsinki (Lahdenne et al., 2003). In our experience (Gerloni et al., 2006), two cases newly developed anti-dsDNA out of 127 Etanercept (1.6%) and 7 out of 81 Infliximab-treated patients (8.6%), without any clinical manifestation. In the Infliximab-treated population, one case with new onset of anti-ENA antibodies (anti-RNP) was also observed. Unexpected and surprising were some cases of new onset of an inflammatory bowel disease (IBD) with abdominal pain and chronic diarrhea (histologically confirmed Crohn's disease) observed during Etanercept treatment (Quartier et al., 2003; Ruemelle et al., 2004; Gerloni et al., 2006) in patients affected by long lasting JIA, who had never previously suffered from chronic abdominal complaints; nor did they present other signs that could rise the suspicion of a pre-existing subclinical IBD.

3.6. TNFα blockade and chronic anterior uveitis

Another concern with TNFα blockade, mainly with Etanercept, is the possible reactivation of chronic iridocyclitis (CIC) in the population at higher risk for this complication (oligoarticular ANA-positive JIA with previous episodes of CIC). In some experiences, such as a small controlled trial (Smith et al., 2005), a recent large survey (Schmeling and Horneff, 2005) and a large open prospective study (Gerloni et al., 2006), Etanercept seems inefficacious in preventing relapses of CIC in the population at risk. On the contrary, there are case reports, or retrospective review of small populations, in which Infliximab seems to be efficacious for refractory JIA uveitis. Infliximab resulted in better clinical responses with less ocular complications, such as new-onset or worsening of glaucoma or cataract, than Etanercept (Mangge et al., 2003; Richards et al., 2005; Saurenmann et al., 2006; Rajaraman et al., 2006; Kahn et al., 2006).

3.7. Bone marrow suppression

In contrast with the aspecific immunosuppression of traditional cytotoxic DMARDs, TNFα inhibition is a selective way to suppress a single key point of the immune response. In fact, bone marrow suppression, with leukopenia, thrombocytopenia or pancytopenia is only rarely described in JIA patients treated with TNFα blockers (Quartier et al., 2003; Gerloni et al., 2006).

3.8. Malignancies

The risk of malignancy and lymphoma such as for the case of infections, may also be associated with either the disease per se or the concomitant and previous immunosuppressive treatments. We observed one case of thyroid carcinoma in a JIA young adult treated with Etanercept, but also previously treated with Infliximab and many other DMARDs (Gerloni et al., 2006). Recently, some cases of hepatosplenic T-cell lymphoma have been

described in adolescents treated with Infliximab for Crohn's disease (Thayu et al., 2005). More studies are needed to evaluate the baseline occurrence of malignancies in patients with adult RA and JIA and to determine the potential adjunct risk posed by an anti-TNFα therapy.

4. TNFα-inhibitors in juvenile dermatomyositis

The idiopathic inflammatory myopathies (IIM) in childhood are diseases caused by muscle damage in association with an inflammatory infiltrate. Genetic causes, viral, parasitic or bacterial infections may play a part in the etiopathogenesis of the IIM. The most common of these autoimmune disorders is juvenile dermatomyositis (JDM). Proximal muscle weakness and skin rash are the basic clinical features in JDM; sometimes other organ systems can be involved (Pachman, 2004). Calcinosis is a complication of this disease which can be troublesome. It is associated with chronic inflammation (Ramanan and Feldman, 2002). Macrophages and pro-inflammatory cytokines, including IL-6, IL-1 and TNFα, have been found in the milk of calcium fluid examined from a patient (Mukamel et al., 2001). A long lasting active disease and the presence of pathologic calcifications have been associated with the A → G polymorphism in the TNFα-308 promoter region (TNFα 308A allele) and the increased TNFα production by peripheral blood mononuclear cells which may perpetuate the inflammatory response (Pachman et al., 2000). On this basis, TNFα blockade has being proposed to treat patients that are refractory to conventional immunosuppressive therapies such as corticosteroids, MTX, cyclosporine and i.v. immunoglobulins (Pilkington and Wedderburn, 2005). To date, there are some preliminary data concerning the use of TNFα blockers in children affected by chronic JDM: the use of Etanercept in the treatment of five children has been described (Miller et al., 2000) while three children were treated with Infliximab (Maillard et al., 2002). With Etanercept, there were not encouraging results, but the children treated were not selected on the basis of their TNFα 308A allele. In the three patients treated with Infliximab at the dose of 3–5 mg/kg/infusion a better result on calcinosis was observed: in the first patient there was a retarded progression, in the second and third there was a regression of calcinosis. Recently, the use of Etanercept, combined with the bisphosphonate pamidronate, was mentioned as to have benefit in patients with calcinotic skin disease (Maillard et al., 2003). However, further controlled studies are required to prove the effectiveness of TNFα blockade in JDM and to predict which patients will respond to this treatment and which will not.

5. TNFα-inhibitors in other pediatric rheumatic diseases

In adult patients, the TNFα inhibitors (Infliximab, Etanercept and Adalimumab) has been proven efficacious, by evidence-based data, in the autoimmune idiopathic uveitis, in the uveitis of Behcet's disease and sarcoidosis (Sfikakis et al., 2001; Munoz-Fernandez et al., 2001; Joseph et al., 2003; Markomichelakis et al., 2004; Suhler et al., 2005) and in the vasculitides (Samuels and Spiera, 2006). However, they still have a restricted use in these diseases in childhood. Infliximab is at present seemingly more effective than Etanercept in the treatment of refractory autoimmune uveitis. High-dose Infliximab has been proven to be a rapidly effective and well-tolerated therapeutic agent in children affected by autoimmune non-infectious refractory uveitis and uveitis of Behcet's disease and sarcoidosis (Kimura, 2003; Simonini et al., 2005; Kahn et al., 2006; Rajaraman et al., 2006). Moreover, Infliximab resulted in better clinical responses with less ocular complications than Etanercept (Saurenmann et al., 2006).

In the field of vasculitides, Etanercept or Infliximab have been successfully used in the treatment of one patient with childhood onset refractory polyarteritis nodosa (Feinstein and Arroyo, 2005), and in many cases of Kawasaki Syndrome (Weiss et al., 2004; Burns et al., 2005; Zulian et al., 2006).

Evidence-based data suggest that Etanercept may be effective in some autoinflammatory

diseases or hereditary periodic fever syndromes, where an abnormal uncontrolled production of TNFα, on genetic basis, seems to have a key pathogenetic role. In the TNF receptor associated periodic syndrome (TRAPS), Etanercept has been proven to decrease the severity, duration and frequency of symptoms and to provide a therapeutic alternative to glucocorticoid therapy (Hull et al., 2002). However there is variability in the treatment responses among different patients with TRAPS. A 2-year-old boy, of a Danish family with a new autosomal dominant mutation, was treated successfully with Etanercept (Weyhreter et al., 2003). In a Spanish child the autoinflammatory episodes disappeared with administration of Etanercept, but the levels of acute-phase reactants remained increased (Arostegui et al., 2005). In a series of seven patients affected by TRAPS, Etanercept did not abolish inflammatory attacks but improved disease activity allowing corticosteroid reduction (Drewe et al., 2003). On the contrary, the Hyper IgD with periodic fever syndrome (HIDS), caused by mutations in the mevalonate kinase (MVK) gene, has been reported, in case reports, to be not responsive (Marchetti et al., 2004) or only partially responsive to Etanercept treatment (Arkwright et al., 2002).

In the pyogenic sterile arthritis, pyoderma and acne syndrome (PAPA), the production of TNFα by mononuclear cells was also found abnormally elevated, and the efficacy of Etanercept has been reported in a child with several episodes of arthritis unresponsive to glucocorticoids (Cortis et al., 2004). Finally, Etanercept has been reported to induce a dramatic improvement of arthropathy in the chronic infantile neurological cutaneous articular (CINCA) syndrome (Federico et al., 2003).

6. Conclusions

The anti-TNFα agents have dramatically changed the treatment of JIA due to their efficacy and speed of onset. They allow better and faster disease control than was previously possible, the rate of response to TNFα inhibitors and the rapidity of response exceeding those of the other DMARDs studied including MTX.

The anti-TNFα agents are overall well tolerated and have demonstrated a favorable risk-benefit profile. Serious AEs on anti-TNFα therapy in JIA are rare. However, severe infections, including TB, have been reported. These can be largely prevented by appropriate screening. Clearly, comorbidities, long lasting persistently active disease and concurrent and previous immunosuppressive therapies all contribute to the risk of infection, malignancy and other serious AEs. The benefits of anti-TNFα

Table 2
TNFα-inhibitors in other autoimmune or autoinflammatory rheumatic diseases in childhood

Disease	Ref.
Juvenile dermatomyositis	Miller et al., 2000; Maillard et al., 2002
Autoimmune idiopathic uveitis	Kimura, 2003; Simonini et al., 2005; Kahn et al., 2006;
Uveitis in Behcet's disease	Rajaraman et al., 2006; Saurenmann et al., 2006
Uveitis in sarcoidosis	
Polyarteritis nodosa	Feinstein and Arroyo, 2005
Kawasaki syndrome	Weiss et al., 2004; Burns et al., 2005; Zulian et al., 2006
TNF receptor associated periodic syndrome (TRAPS)	Weyhreter et al., 2003; Arostegui et al., 2005; Drewe et al., 2003
Hyper IgD with periodic fever syndrome (HIDS)	Marchetti et al., 2004; Arkwright et al., 2002
Pyogenic sterile arthritis, pyoderma and acne syndrome (PAPA)	Cortis et al., 2004
Chronic infantile neurological cutaneous articular syndrome (CINCA)	Federico et al., 2003

therapy in JIA seem to outweigh these shortcomings, although long-term safety data still need to be established.

Given the evidence that TNFα has a primary role in the pathogenesis of JIA, particularly in joint destruction observed in polyarticular disease (Rooney et al., 2000), neutralizing this cytokine earlier in the course of the disease could halt or delay the progression of joint damage and the debilitating consequences of the disease (Nielsen et al., 2005). The early application of these drugs within the window of opportunity in combination with conventional DMARDs seems to produce the best outcomes. Thus, for JIA patients whose disease is not quickly controlled by MTX, therapy with TNFα blockers may be considered as a first-line treatment. Moreover, the therapeutic role of the anti-TNFα agent Etanercept in many other autoimmune or autoinflammatory rheumatic diseases in childhood (listed in Table 2) has been suggested by several case reports and needs to be evaluated and confirmed in further studies.

Key points

- Controlled trials in adults have shown that the TNFα inhibitors significantly reduce symptoms and signs, improve function and quality of life and reduce radiological damage in rheumatoid arthritis and related diseases.
- The clinical experience on TNFα inhibition in JIA is mainly limited to Etanercept, the only TNFα inhibitor approved until now in the United States and in Europe for use in children with active polyarticular JIA despite prior MTX therapy. Infliximab and adalimumab have however been used in the context of open label trials and in two large controlled studies. The anti-TNFα agents have dramatically changed the treatment of JIA due to their efficacy and speed of onset.
- The anti-TNFα agents are overall w ell tolerated and have demonstrated a favorable risk-benefit profile. However, long-term safety data still need to be established.

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Handbook of Systemic Autoimmune Diseases, Volume 6
Pediatrics in Systemic Autoimmune Diseases
Rolando Cimaz and Thomas Lehman, editors

CHAPTER 19

Autologous Stem Cell Transplantation (ASCT) for Drug Resistant Systemic Onset Juvenile Idiopathic Arthritis ☆

Nico M. Wulffraat*, Berent J. Prakken
Wilhelmina Children's Hospital University Medical Centre, Utrecht, The Netherlands

Estimates of the prevalence of autoimmune diseases in Western countries range from 3% to 7% of the population. The majority of autoimmune diseases are controlled, more or less satisfactorily, by conventional suppression of the immune system, but there is a minority of patients with refractory/relapsing, treatment resistant autoimmune diseases for which the term malignant autoimmunity has appropriately been proposed. In such cases, patients suffer considerable morbidity from the disease itself but also from serious adverse effects caused by the long-term treatment with immunosuppressive drugs. For this group of patients, intense immunosuppression (immunoablation), followed by allogeneic or autologous haemopoietic stem cell transplantation (autologous stem cell transplantation, ASCT) has emerged as an alternative treatment option.

1. Rational of autologous stem cell transplantation for autoimmune disease

The use of intensive immunosuppressive treatment coupled with stem cell transplantation (SCT) to treat human autoimmune diseases follows anecdotal observations of remissions of autoimmune disease in patients who have undergone allogeneic bone marrow transplantation because of coincidental haematologic malignancies (Snowden et al., 1998; Hough et al., 2005; McAllister et al., 1997). In addition, a great deal of prior research had already produced impressive results using transplant-based procedures in experimental animal models (Karussis et al., 1995; Knaan-Shanzer et al., 1991; van Gelder and van Bekkum, 1996). These studies showed that transplantation of normal allogeneic bone marrow, prevented and ameliorated or cured both spontaneous and induced autoimmune disease (Adachi et al., 1995; Ikehara et al., 1989; Levite et al., 1995). Furthermore, a high incidence of, often durable, remission was also observed following autologous bone marrow transplantation in adjuvant induced arthritis and myasthenia gravis (Knaan-Shanzer et al., 1991; van Gelder and van Bekkum, 1996).

The mechanism of efficacy in the allogeneic setting is presumed to reflect a reduction in the burden of self-reactive lymphocytes by the conditioning regimen with eradication of residual immune cells by a postulated graft-versus-autoimmune effect (Marmont and van Bekkum, 1995).

☆This research was originally published in *Blood*. Ismé de Kleer, Bas Vastert, Mark Klein, Gijs Teklenburg, Ger Arkesteijn, Gisella Puga Yung, Salvo Albani, Wietse Kuis, Nico Wulffraat, and Berent Prakken. Autologous stem cell transplantation for autoimmunity induces immunologic self-tolerance by reprogramming autoreactive T cells and restoring the $CD4^+CD25^+$ immune regulatory network. *Blood*. Feb 2006; Vol 107:1696-1702. © The American Society of Hematology.

*Corresponding author.
Tel.: +0031-30-250-4001; Fax: +0031-30-250-5349
E-mail address: n.wulffraat@umcutrecht.nl (N.M. Wulffraat).

DOI: 10.1016/S1571-5078(07)06023-0

The surprising efficacy of ASCT is thought to be the result of a similar ablation of self-reactive lymphocytes during conditioning followed by induction of self-tolerance by "re-education" of HSC-derived lymphocytes. Stem cell transplantation is applied in patients with autoimmune disease since 1995. By 2005, almost 800 patients had been transplanted (as registered in the European and North American databases) (Hough et al., 2005). The majority of the patients have received autologous rather than allogeneic stem cells, since autologous transplantation is associated with a lower mortality and avoids the problem of graft matching and graft versus host disease.

2. Autologous stem cell transplantation for juvenile idiopathic arthritis

In children ASCT has been applied in a large series of juvenile idiopathic arthritis (JIA) patients and incidental cases of other rheumatic diseases like systemic lupus erythematosus (SLE) and multiple sclerosis. JIA is the most common rheumatic disease in childhood and a major cause of disability. Although the overall prognosis for most children with chronic arthritis is good, in 5–10% of children with the systemic and polyarticular onset forms, the disease is refractory to conventional therapies, consisting of combinations of non-steroidal anti-inflammatory drugs (NSAID) and immunosuppressive drugs such as methotrexate (MTX), corticosteroids, and anti-TNFα therapy (Hough et al., 2005; Wallace and Sherry, 1997; Woo and Wedderburn, 1998; Lovell et al., 2000). The first results of a pilot study conducted in 1997 and 1998 to the clinical efficacy of ASCT for JIA were promising (Hough et al., 2005; Wulffraat et al., 1999b) and since then more than 52 cases have been reported and registered in the database of the European Group for Blood and Marrow Transplantation (EBMT).

2.1. In- and exclusion criteria

Since there is potential high morbidity and mortality associated with stem cell transplantations, it is imperative that children eligible for ASCT are carefully selected. The Pediatric Rheumatogy European Society (PRES), the European League Against Rheumatism (EULAR), and the EBMT therefore have published guidelines on inclusion criteria, as well as conditioning regimen and manipulation of the graft (Wulffraat et al., 1999a; Tyndall et al., 1999). The recommended inclusion criteria are failure to respond to high dose MTX (1 mg/kg/wk i.m. or s.c.), anti-TNF therapy and at least 1 other disease modifying anti-rheumatic drug (DMARD), corticosteroid dependency and/or unacceptable toxicity to DMARD's or corticosteroids. Recommended exclusion criteria are cardio-respiratory insufficiency, chronic active infection, persistent fever, and other signs of systemic disease activity despite corticosteroids at time of transplant, end stage disease (Steinbrocker IV) or poor compliance.

2.2. Mobilisation and stem cell preparation

Haematopoietic stem cells used in ASCT may be obtained either from bone marrow, or by inducing mobilisation into the peripheral blood using a single infusion of cyclophosphamide and granulocyte colony-stimulating factor (G-CSF). Subsequently, the graft can either be purged by T-cell depletion with CD2 and CD3 antibodies or by positive stem cell selection using CD34 selection devices. Once stem cells have been harvested they are purified, to remove mature lymphocytes. While full depletion of autoreactive T-cells may be desirable, profound depletion is also associated with a higher risk of opportunistic infection including EBV and CMV reactivation, post-transplantation. Furthermore, it is believed that macrophage-activating syndrome (MAS), one of the major complications of ASCT for JIA (see further in this chapter) is partly caused by uncontrolled activation by macrophages in the absence of T-cell regulation (Ferreira et al., 2006). A T-cell number of $1–5 \times 10^5$ T-cells/kg is therefore recommended (Barron et al., 2001).

2.3. Transplantation-protocol

Conditioning is performed immediately before stem cell reinfusion and is designed to remove the

cells mediating disease; many of the regimes used are highly immunosuppressive but not fully immunoablative or myeloablative. The most common combination used to condition JIA patients has been cyclophosphamide with antithymocyte globulin (ATG), and total body irradiation (TBI, 2 or 4 Gy). The use of TBI in children remains controversial because of concerns about long-term safety. Data recently published on the follow-up of 34 transplanted JIA patients suggested that children not given TBI have equally good outcome as those treated with irradiation (De Kleer et al., 2004a). This finding led to the recommendation to eliminate TBI from future conditioning regimens.

3. Clinical results

Since the first JIA patient was transplanted in 1997 more than 52 cases have been reported and registered in the EBMT database. One can find several case reports describing the clinical outcome of small groups of JIA patients treated with ASCT (Wulffraat et al., 1999b; Ferreira et al., 2006; De Kleer et al., 2004a; Kishimoto et al., 2003; Nakagawa et al., 2001). The largest study however is a report of 34 cases, transplanted in 9 different paediatric bone marrow transplantation units (De Kleer et al., 2004a). All 34 children described in this study showed before ASCT a polyarticular course of the disease complicated by erosions, osteoporosis, and stunted growth. In addition, all children with systemic JIA suffered from periods of spiking fever, exanthema, and severe steroid-related side effects. They were all corticosteroid-dependent and resistant to high dose parenteral MTX. Ten of the 34 children had failed treatment with anti-TNF therapy. The results were impressive with a prolonged drug-free follow-up of 6–60 months. ASCT induced a drug-free complete remission in 18 severely ill JIA patients (53%), even after prolonged withdrawal of anti-rheumatic drugs. Six patients (18%) achieved a partial response (30–70% improvement) and showed a remarkable improvement in most core-set criteria, indicating a profound increase in general well being. No response was noted in seven patients (21%) and four patients died of a transplant-related cause (12%). Altogether, using the preliminary definition of improvement in juvenile arthritis developed by Giannini et al. (1997), 50% of the patients showed a drug-free improvement of more than 50% after 4–60 months of follow-up, with a marked decrease in the scores of the Children Health Assessment Questionnaire, the physicians global assessment, and in swollen joint count. The measurement of limitation of movement did not change, illustrating that erosive joint destruction that existed prior to ASCT is not reversed by this treatment (during this follow up of 5 years). Younger children in particular had significant catch-up growth, while this was less notable in older children.

The recently introduced fludarabine-based protocol has been used in four patients with systemic onset JIA onset so far and has induced complete rheumatological remission in all four with a follow up of more than 2 years (Ferreira et al., 2006).

3.1. Transplant-related complications and mortality

All studies reported the development of chills, fever, and malaise during infusion of ATG. Infectious complications are common. In the above-described study 24 of the 34 children (71%) developed at least one infection. Especially varicella zoster virus, Epstein-Barr virus, and cytomegalovirus reactivations were seen frequently, mainly during the aplastic period (De Kleer et al., 2004a). Furthermore, 4 of the 34 children (12%) died 10 days to 16 months post-ASCT, which is an unexpected high mortality rate. Death was in all cases principally the result of infection consequent on bone marrow suppression. In three of the four fatal cases haemophagocytosis was present, also known as MAS. This complication was preceded by infections with Epstein-Barr virus, adenovirus, and disseminated toxoplasmosis. MAS is a well-recognized and frequently fatal complication of systemic JIA, described in various case reports over the past 30 years (Ravelli et al., 2001; Ramanan and Schneider, 2003; Stephan and

Galambrun, 2000). Of interest, often such an episode seemed to be induced by drugs such as salazopyrin, MTX, or intramuscular gold. Importantly, very recently we experienced mild episodes of haemophagocytosis/MAS in three patients with systemic JIA who received fludarabine as part of the conditioning protocol (Ferreira et al., 2006). MAS did not occur in all patients receiving fludarabine, and it is noteworthy that in one patient the features of MAS were CMV-induced and another occurred before start of fludarabine. Figures 1 and 2 show the typical bone marrow morphology and serum ferritin rise seen in one of these patients. In another patient, the MAS episode was induced by CMV, despite extensive viral screening pre-transplant. It was concluded that MAS in systemic JIA may more likely to occur as disease-specific than after the administration of a specific drug like fludarabine. Why especially patients with systemic JIA are at risk for episodes of reactive haemophagocytosis is unknown. The marked macrophage activation seems to reflect a loss of T-cell control and perhaps an underlying abnormality of macrophage function is also present (Grom et al., 2003; Grom, 2004; Wulffraat et al., 2003). Obviously, further research in this area is warranted.

Since MAS accounts for such a significant part of mortality in systemic JIA patients and is clearly the most dangerous complication after ASCT, careful monitoring for early signs of MAS (fever, hepatomegaly, cytopenias, clotting disorders, high ferritin values), early treatment with steroids and cyclosporin, and exclusion of patients with active disease just before the transplant (in particular with persistent fevers) has been added to current protocols to avoid MAS.

4. Mechanisms of tolerance induction by ASCT

While clinical experience with ASCT for autoimmunity is rapidly accumulating, still very little is known about which changes in the immune system induced by ASCT are responsible for the favourable effect. The initial temporary effect is likely to be attributable to the eradication of

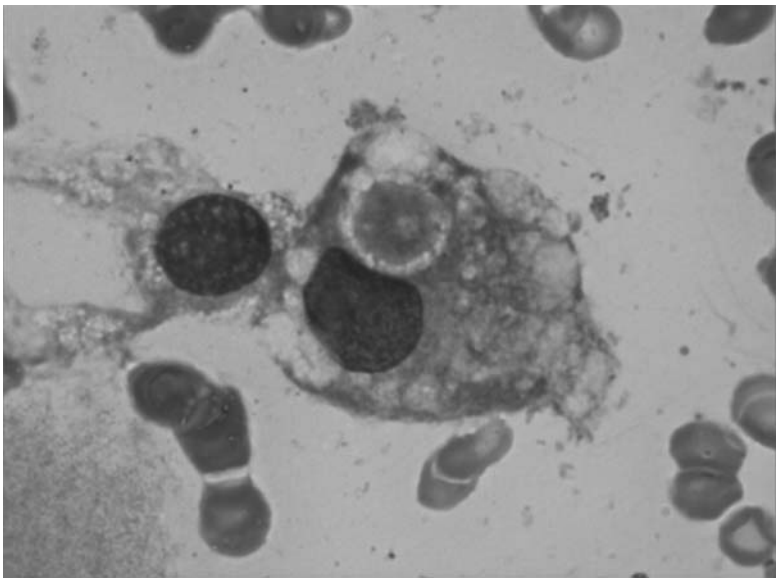

Figure 1. Bone marrow smear showing the typical haemophagocytosis in a patient 10 days after start of the fludarabine-based conditioning.

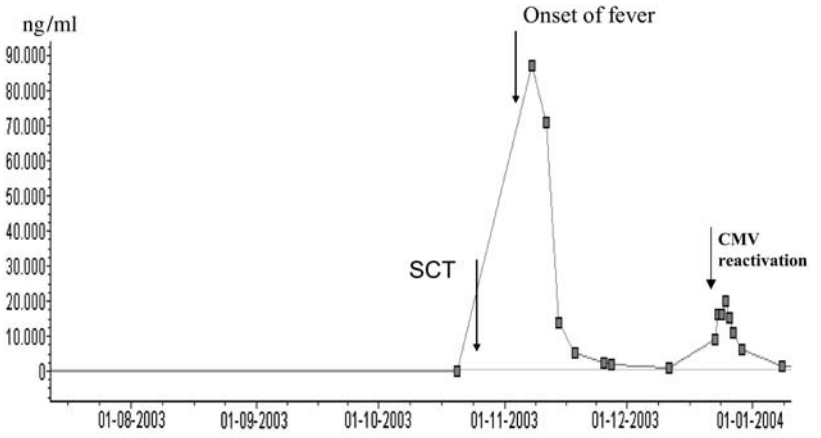

Figure 2. Increased serum ferritin values in a patient (same patient as in Fig. 1) 10 days after start of the fludarabine-based conditioning. Treatment with cyclosporin and high dose methylprednisolone induced a rapid remission of the symptoms related to MAS.

auto-reactive lymphocytes and memory cells due to the high-dose lymphoablative-conditioning regimen. However, although ASCT permits intense host immune suppression, elimination of every resting lymphocyte with high-dose chemotherapy and/or radiation is probably not feasible. In addition, there must be a significant contribution from altered immune reconstitution that occurs after autologous transplantation (Sykes and Nikolic, 2005). Isolated observations including alterations in CD4:CD8 ratios, decreased mitogenic responsiveness, restoration of reduced perforin expression, and changes in the T-cell repertoire have been made following autologous transplantation (Wulffraat et al., 2003; Roberts et al., 1993). Furthermore, foetal animal work is supportive of the hypothesis that exposure of the developing immune system to neoantigens, in a period when the immune system is developing its repertoire, leads to tolerance (Anderson and Matzinger, 2001; Chen et al., 2004; Touraine et al., 2005). These observations suggest that the success of ASCT is not only based on the loss of autoreactive T-cell clones, but also on the complete re-assignment of imbalanced cellular and soluble networks, including those that regulate the autoreactive T-cells. Indeed, analysis of the T-cell repertoire in multiple sclerosis patients treated with ASCT showed the reconstitution of an overall broader clonal diversity and an extensive renewal of clonal specificities compared with pre-therapy (Muraro et al., 2005). In addition, in JIA patients it has been shown that ASCT induces immunological self-tolerance by tolerising autoreactive T-cells and restoring the CD4+CD25+ regulatory network (De Kleer et al., 2006). In several experimental autoimmune models, T-cells responding to heat-shock proteins (HSPs) play an important role in the regulation of peripheral tolerance and the suppressing pathogenic immune responses. In the adjuvant-induced arthritis (AIA) model, it was shown that the protection resulted from the induction of self HSP60-cross-reactive T-cells capable of down-regulating inflammation. In the human situation, an increased expression of endogenously produced HSP60 in the membranes of synovial lining cells of patients with JIA was described. Subsequently, T-cell reactivity to mycobacterial and human HSP60 was documented in patients with JIA (Prakken et al., 1996). We recently published data showing that a decreased number of CD4+CD25+ Tregs in the synovial fluid of children with JIA is correlated with the development to a less favourable clinical course of the disease (De Kleer et al., 2004b). The most important group of Tregs is currently identified by the expression of CD25 and the

transcription factor FoxP3. Expression of Foxp3 distinguishes CD4+ cells Tregs from recently activated, non-regulatory CD4+CD25+ T-cells. In multiple experimental animal models it has been shown that, in the absence of these so-called CD4+CD25+ Tregs the risk of developing autoimmunity is significantly increased. Both conventionally treated and ASCT-treated patients before transplantation displayed significantly lower frequencies of CD4+CD25^{bright} T-cells (Fig. 3) than previously found in healthy children (De Kleer et al., 2006). The early-reconstituted CD4+CD25^{bright} T-cells expressed high amounts of mRNA FoxP3 and thus can be considered as professional regulatory T-cells. The levels of mRNA FoxP3 in these CD4+CD25+ T-cells were significantly higher than expressed by their counterparts obtained from time points before transplantation (Fig. 4). Furthermore, the early-reconstituted CD4+CD25^{bright} T-cells (1 month after ASCT) showed an increased expression of CTLA4, GITR, and CCR4 compared to their counterparts before ASCT (De Kleer et al., 2006).

Taken together, the increased expression of mRNA GATA-3 and IL-10 and a decreased expression of mRNA IFN-γ clearly indicated a more Th2 or regulatory phenotype of the human HSP60 specific T-cells present after ASCT. Thus, besides the recovery of the CD4+CD25+ regulatory network, ASCT also induces tolerising changes in the autoreactive T-cell clones.

More studies to the mechanistic basis of tolerance induction by ASCT are needed since this will provide a mechanistic basis for ongoing

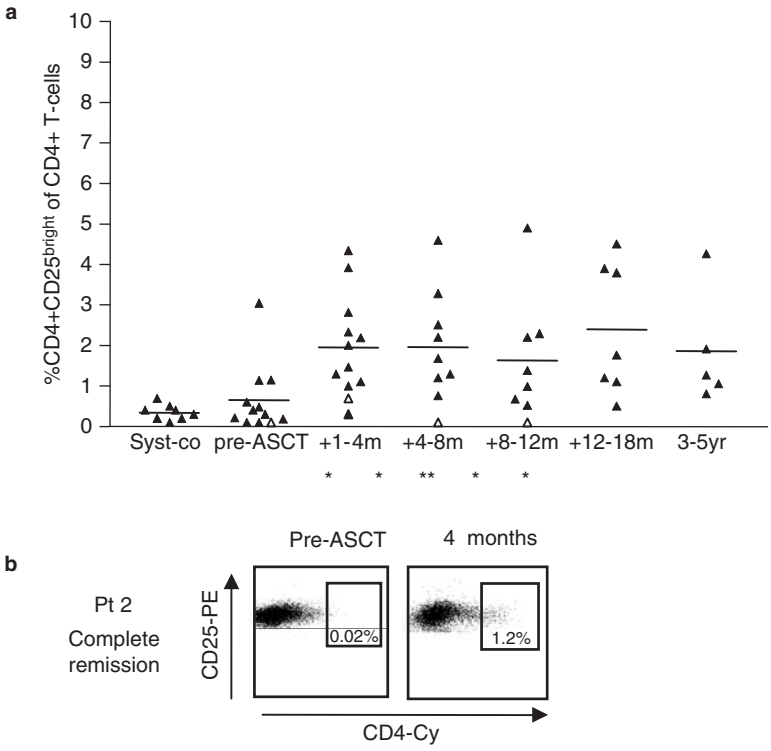

Figure 3. Recovery of CD4+CD25^{bright} T-cell frequency after ASCT. The relative number of CD4+CD25^{bright} T-cells in 8 systemic JIA patients on conventional therapy (syst-co) and in 12 children who received ASCT for refractory JIA was measured by FACS-staining. The patient represented by open triangles suffered a complete relapse 6 months post-ASCT. Since it has been shown that the regulatory CD4+ T-cells preferentially reside within the CD4+CD25^{bright} population, only the CD4+CD25^{bright} T-cells and not the CD4+CD25^{total} T-cells were analyzed. *$P<0.05$, **$P=0.06$.

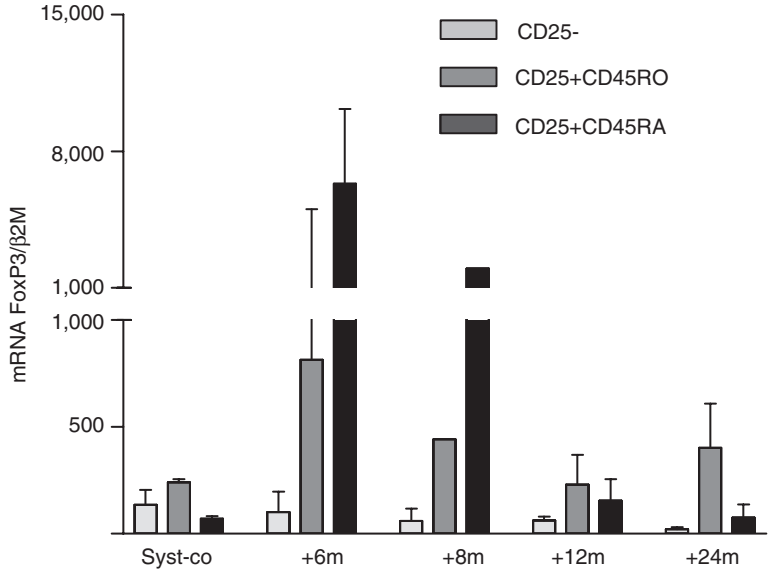

Figure 4. High expression of mRNA FoxP3 in thymus-derived CD4 + CD25 + T-cells. CD4 + CD25−, CD4 + CD25 + CD45RO, and CD4 + CD25 + CD45RA T-cells were isolated from the peripheral blood (PB) of three systemic JIA patients on conventional therapy and from three systemic JIA patients at different time points after ASCT by FACS sorting. mRNA FoxP3 was measured by quantitative PCR. Data are expressed as the mean normalized gene expression (±SEM) of the three patients.

and future clinical trials of this therapeutic strategy in autoimmune diseases.

Key points

- ASCT has become a generally accepted treatment option for severely ill systemic and polyarticular JIA patients for whom no other treatment options are left. It induces drug-free remission of the disease and profound improvement in general well being in a substantial proportion of the patients.
- However, the procedure carries a significant mortality risk, making it necessary to carefully weigh morbidity and mortality risks of the prolonged immunosuppression of ''conventional'' treatment against those of the short but intense immunosuppression of ASCT.
- Recently, the EBMT-working parties for autoimmune diseases and inborn errors officially decided to continue to explore the use of ASCT for these children.

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Handbook of Systemic Autoimmune Diseases, Volume 6
Pediatrics in Systemic Autoimmune Diseases
Rolando Cimaz and Thomas Lehman, editors

CHAPTER 20

Physical Therapy Management of Pediatric Rheumatology Conditions

Susan Maillard*

Great Ormond Street Hospital, NHS Trust, Institute of Child Health, University College London, London, UK

Pediatric rheumatology is a relatively new specialty for physical therapists and includes a variety of different conditions. Both inflammatory and non-inflammatory disease, have features of pain and loss of function of both the muscles and the joints. Inflammatory disease requires control of the inflammatory response. In contrast non-inflammatory disease is driven by biomechanical abnormality, and although pain may be controlled with medication, the correct realignment of the biomechanical structure through physical therapy is key to improvement (Fig. 1) (Tables 1 and 2).

1. Physical therapy management

The physical therapist's approach to rheumatology disease follows consistent principles as initially described. Disease specific information is provided in more detail where appropriate.

All assessments include both the subjective and objective elements. The assessment below is based on the expert consensus found in more detail through the British Society of Paediatric and Adolescent Rheumatology (BSPAR).

The assessment of children with a rheumatological condition should encompass the physical, psychological and social impact of the disease on the child and the family. Age appropriate milestones must be included in the assessments to ensure that the findings are properly interpreted.

2. Information to be gained from the subjective assessment

2.1. History of present condition

The history should include the symptoms, their progression and factors that precipitated them. This should include systemic features, e.g., fever, rash, appetite etc. This gives an indication of severity and speed of onset, chronicity and precipitating factors. Previous hospital admissions and investigations should be recorded chronologically to obtain a clear picture of previous investigations and treatments. It is important to have a clear diagnosis and recognize both the appropriateness of treatment and whether the disease has been untreated for a significant period.

2.2. Presenting problems and symptoms

It is important to establish the progression of the disease, because the longer the condition has been present the greater the resulting changes. Allow the family time to tell you what problems the child is experiencing and focus your questioning appropriately.

*Corresponding author.
Tel.: +44-(0)-20-7905-2665; Fax: +44-(0)-20-7905-2672
E-mail address: S.Maillard@ich.ucl.ac.uk (S. Maillard).

DOI: 10.1016/S1571-5078(07)06024-2

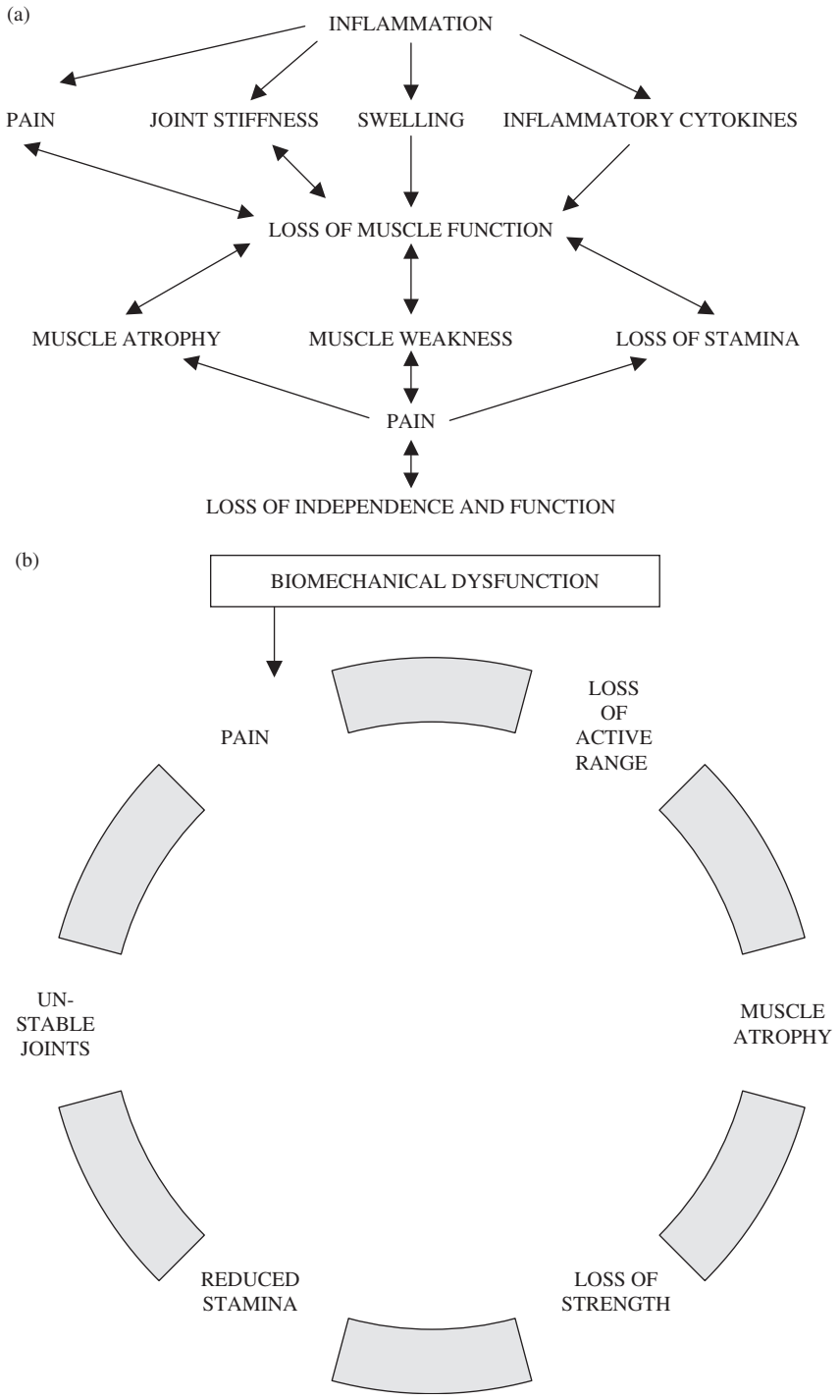

Figure 1. Pain cycling in inflammatory disease (a) and non-inflammatory disease (b).

Table 1
The most common rheumatic conditions seen in physical therapy

Inflammatory disease	Non-inflammatory disease
Juvenile idiopathic arthritis	Benign joint hypermobility syndrome
Juvenile dermatomyositis	Ehlers-Danlos syndrome
Scleroderma	Marfan syndrome
Systemic lupus erythematosus	Reflex sympathetic dystrophy
Vasculitis	Chondromalacia patellae
CRMO/SAPHO	Chronic pain syndromes
CINCA	Generalized musculoskeletal pains

Table 2
Reasons for muscle weakness and muscle atrophy in children with a rheumatological condition

Symptoms/signs	Muscle response
Pain in joint	Spasm of muscles that control that joint
Stiffness/loss of movement of specific joint	Muscles are unable to function through full range and therefore weaken
Joint swelling	Inhibits function of muscles that control the joint
Systemic illness	Generalized loss of strength and endurance
Deranged cytokine balance	The cytokines affect muscle function and may cause myositis and muscle weakness
Pain and fatigue	Global loss of strength and endurance

2.2.1. Pain
The areas affected, type, severity and intensity of the pain. Ask about when the pain is experienced (e.g., periodic) and the relieving and exacerbating factors. This will give a clear picture of where treatment is most appropriate. A pain scale is useful and a more objective measure of outcome (i.e., pain visual analog scale 0–10).

2.2.2. General functioning (in the context of developmental milestones)
Establish what activities are difficult, particularly functional tasks. Ask about walking distance and stair climbing. Fatigue is an important issue. It is important to gain a clear picture of functional problems to be addressed.

2.2.3. Early morning stiffness (EMS)
EMS is an indication of the severity and degree of activity of inflammatory disease. Know how severe the stiffness is, for how long it lasts and what areas of the body are affected. Establish whether there is stiffness at any other time. Evening stiffness is an indication of muscle fatigue, which may occur in both inflammatory and non-inflammatory conditions.

2.2.4. Child's and parents main concerns
Ask what they are most worried about, and what they think can be done as well as their understanding of the diagnosis and treatment. It is important that the family's main concerns are considered and that everyone is focused upon the same goals.

2.3. Past medical history

A developmental history is important to ensure there is not an underlying neurological condition alongside the rheumatological one. Children with hypermobility may be slightly slower in reaching milestones and often do not crawl.

Prior conditions may be relevant to the treatment. Enquire about operations in the past or planned for the future, injuries such as fractures, sprains or dislocations etc. This will also give information about previous hospital and pain experiences. Ask about all the investigations that the child has received, for this, and other conditions.

2.3.1. Medication
Medications taken previously, including dosage, dates started and finished should be recorded, with their effect on the disease and any side effects experienced. A complete list of current medications, including homeopathic medicines should also be recorded.

2.3.2. Social history and family history
Draw a tree of the relationships in the immediate family, including ages of other children. It is also necessary to ask who actually lives in the home as this may be different. Ask about the parent's occupation and indications of pressure on the family both with time and finances. Also ask who is the primary caregiver, as this may not be the mother. There may also be a friend or relative that needs to be involved. Ask about other diseases within the family. It is important to know the family's experience which may impact the child's coping mechanisms and perceptions.

2.3.3. Accommodation
Ask about types of accommodation if mobility is an issue.

2.3.4. Benefits
Ask about which benefits they are already receiving and if there is any that they are in the process of claiming. This is to ensure whether the appropriate support has been provided, and to highlight any shortfalls.

2.4. Home and school

2.4.1. Hygiene
Ask about mobility in and out of the bath/shower and whether the children are able to wash themselves, and whether they can wash their hair. Establish whether any equipment is required. Establish the level of age appropriate function. The goal of the treatment program is independent function. Are there any difficulties about using the toilet independently, i.e., flushing the toilet, undressing, wiping bottom, getting on and off the toilet etc?

2.4.2. Dressing and grooming
Ask about buttons, shoes and laces, socks, trousers and pullovers, teeth brushing and hair dressing. Establish whether aides are used or extra time is required.

2.4.3. Walking distance and mobility
How far is the child able to walk before rest is required, are they able to continue after a period of rest? Are they able to keep up with their peers/family? Walking distance and time may be used as an outcome measure. Are they able to manage stairs independently? Do they go up and down one leg at a time or alternate legs (correctly) and how many stairs are they able to do. Also establish whether any aides are used, i.e., banisters etc.

2.4.4. Eating and food preparation
Are they able to cut food independently, or prepare food, depending on age. Enquire about opening jars, turning taps and lifting kettles/pans/cups etc.

2.4.5. School
Obtain agreement from parents to contact the school if necessary.

2.4.6. Attendance
Explore the reasons why the child has missed any time from school. Check whether they are in the age appropriate class, what time they start and finish the school day, whether they have changed schools.

2.4.7. Transport
Ask how they get to and from school, and the distance traveled. Ask about stairs and distances around school, and any difficulties. Ask how books are carried, and issues about seating etc. Difficulties at school need to be addressed.

2.4.8. Statement of special needs
Check the amount and type of support that is required for the student. Establish what degree of support they receive from friends. It may be necessary to initiate a statement (individual education plan). Enquire about the support provided, i.e., laptop computer, scribe, ''in-school physical therapy program'', sloping desk etc.

2.4.9. Writing
How long can the child write for, and what are the limiting factors.

2.4.10. Physical education (PE)
Ask what the child is able to do, what they want to do and whether there are any alternatives available.

2.4.11. Rest facilities
Whether they have access to a medical/rest room rather than being sent home. Trips/outings/extra curricular activities: is the child able to attend and participate.

2.4.12. Play/break time
Where and with whom, do they play? Toileting: is it accessible and are they independent.

2.4.13. Other school subjects that provide some difficulties
Enquire as to whether there are any other subjects that cause difficulties physically, e.g., science, technology, home economics etc.

2.5. Other professional input

2.5.1. Physical therapy
Enquire whether they have had physical therapy before and what it consisted of and the effect that it had. It is important to know whether any other therapists are involved with their care. It is important that all treating professionals are providing consistent advice.

2.5.2. Splints and orthotics
Give details of any splints/orthoses that have been provided including fit and how they are used, also who provided them, and their contact details.

2.5.3. Wheelchairs and crutches
Enquire whether any mobility aids have been provided and where from and who is responsible for providing them/repairing them.

2.6. Hobbies, interests and socialization

These can be used as treatment goals or strategies to make interventions more relevant and fun.

2.6.1. Family hobbies
Enquire about hobbies that the family enjoys doing together, including any they are unable to do, due to the illness.

2.6.2. Individual hobbies
Hobbies that the child likes, any that he/she had to stop.

2.6.3. Swimming/sports
Details as to whether they are able to and enjoy swimming, and whether they play any other sports regularly, and it is also important to find out about any that they are now unable to play.

2.6.4. Socialization
Enquire about peer interaction, and whether they have stable friendships or not.

2.6.5. Drugs/alcohol/sexual activity
This needs to be age appropriate, and will often not be asked on the first visit.

2.7. Future career planning and development

Discussion is important from a relatively early age (i.e., 10–11) just to establish the child's ideas, and to ensure a holistic approach. This will help establish whether their career goals are realistic in the light of the arthritis and to provide goals for treatment.

2.8. Ethnic origin and cultural concerns

2.8.1. Religion

Some religions require a strict orthodoxy which may be physically difficult, i.e., kneeling on a prayer mat/diet/dress/gender appropriate activities etc.

2.8.2. First language

Ask about languages spoken by child and parents, and if an interpreter is required.

2.8.3. Level of understanding of disease

Discover what the child and their family understand about the diagnosis, its treatment and its implications. Establish the information they have already been provided with and where they obtained it from, and what else they may be interested in.

3. Objective assessment

Observe the family during the assessment to help gain an impression of family dynamics.

Visual analog scale (VAS) for pain completed by the child is a useful tool for the ongoing assessment of the level of pain. The *VAS Global assessment of disease and function* completed by the parents is one of the core outcome variables in the assessment of JIA. A *Physicians VAS* should also be completed (Lovell et al., 1999; Rider et al., 1997).

3.1. Assessment of each joint, including spinal movements

Active Range of Movement (AROM) is important; however small children may not tolerate a long assessment. It is recommended to assess the *Passive Range of Movement* (PROM) *as a priority.* (It is important to note the time of assessment, findings will often differ depending on time day.) As a physical therapist it is vital to assess specific ranges and not just to know that the joint is restricted. Increased range is an important outcome measure. Know whether range is restricted by pain, stiffness, muscle shortening or true joint contracture. This will then determine the treatment plan. When treatment is based around improving restricted range then an accurate recording of joint range is recommended.

Fluidity of movement gives information as does muscle spasm around the joint. Hypermobility is an important finding. It is important to assess all joints as the parents or the child may not recognize some joint involvement. Deformities are important to assess. Always evaluate the color and temperature around the joint and any pain associated with movement or palpation. Record any bony overgrowth affecting a joint.

Palpation is important to observe the stability of a joint including evidence of subluxation or dislocation, any swelling either of the joint (effusion), soft tissues or tendons. Feel for muscle spasm, which is often evident around the neck and spine.

3.2. Muscle strength and function

A variety of scales are used to assess of muscle strength. All have a slightly different focus. The most common testing system used is the MRC scale of 0–5 which is widely accepted despite its limitations (Barr et al., 1991; Burnett et al., 1990; Florence et al., 1992; McDonald et al., 1986; Medical Research Council, 1943; Young and Wright, 1995).

Muscle testing is an extremely important outcome measure and can be measured before and after intervention. It is also vital to assess muscle function to ensure that the physical therapy program is prescribed appropriately to address the weakness experienced by each child.

Specific measures of muscle strength and function have been developed for the assessment of juvenile dermatomyositis. These include a modified MRC scale to a 0–10 scale called the Kendall scale which is then applied to 8 muscle groups (MMT8) to give a score of 80 (or 160 if used bilaterally). The other important measure is that of the Childhood Myositis Assessment Scale (CMAS) which is a validated core-outcome assessment tool

for the management of JDM. This score is out of 52, with 52 indicating full function (Lovell et al., 1999).

Muscle strength can also be measured using a hand-held myometer. A myometer will give measurements of force that can be followed more accurately than the 0–5 scale, however this does have some limitations as it only measures anti-gravity strength (Lennon and Ashburn, 1993; Miller et al., 1988; Stratford and Balsor, 1994).

3.2.1. Posture

Observe posture in standing and sitting, note the position of neck, shoulders, elbows wrists, hand, spine, hips, knees and ankles.

3.2.2. Gait

This is very important in the assessment of any child with a physical difficulty as it provides a great deal of information about the function, independence, limitations and level of pain of the child. For example: loss of big toe extension limits the push-off phase. Fixed flexion deformities of hips and knees often causes continual loss of strength in hip abductors and extensors and inner range quadriceps often resulting in the development of a positive Trendelenberg gait pattern. Valgus knees and ankles alter the correct muscle function and observing the heel/toe action highlights difficulties in the feet and ankles.

Video may be a useful record of gait.

3.2.3. Observation of general movement and function

Look for any compensatory movements that may be performed both during the assessment and in the movement to get from the waiting area to the examination room.

3.2.4. Functional questionnaires and validated disease function measures

CHAQ Childhood Health Assessment Questionnaire (Huber et al., 2001; Nugent et al., 2001)

CHQ Childhood Health Questionnaire (Nugent et al., 2001; Ruperto et al., 2001)

These have all been validated in the assessment of inflammatory disease in children. The ones that are used most commonly are the CHAQ and the CHQ. In fact the CHAQ is one of the core set outcome measures in both JIA and JDM.

3.2.5. Stamina

Stamina is an important feature for all children. However there are no routinely used objective assessments. The 6 min walk test is a validated tool but is time consuming and so is not usually used in a clinic setting. Questionnaires regarding fatigue are being developed (Hamilton and Haennel, 2000; Paap et al., 2005; Pankoff et al., 2000; Takken et al., 2002, 2003a, b, d, 2005a, b).

3.3. Other important observations

3.3.1. Leg length

Leg length is important to measure as children with both inflammatory and non-inflammatory disease develop transient differences which if left unmanaged can cause permanent deformities to the spine. All leg length differences of greater than 1 cm should be treated with a complete shoe raise.

3.3.2. Muscle bulk

This is often a useful measure particularly when the condition only affects one side as it can give an objective measure for change in muscle size. Often measures are taken: 10 cm above knee joint line, the knee joint line and 10 cm below knee joint line. Ensure that this is consistent for each child.

3.3.3. Skin condition

Assess the condition of the skin and note any abnormalities. In juvenile dermatomyositis you might see the heliotropic rash over the eyelids, across the knuckles and across the extensor surfaces of the knees and elbows.

4. Physical therapy management

After assessment, the treatment program prescribed for each child will need to be reviewed and monitored regularly (Fig. 2).

4.1. Specific information for individual conditions

Physical therapy management of juvenile dermatomyositis has changed as it has been shown that exercise during active disease is no longer contraindicated. Physical therapy should be started at diagnosis and progress with the change in muscle strength. The ultimate goal remains full strength and stamina (Cassidy and Petty, 2001; Maillard et al., 2004b, 2005).

Many children have hypermobile joints, however, only a small percentage will have symptoms sufficient to be diagnosed as having benign joint hypermobility syndrome (Grahame, 1999). The symptoms and the severity may vary from child to child. Symptoms generally include muscle and joint pain after activity, at the end of the day and at night. Occasionally a joint becomes swollen briefly. The knee is often the main area of pain followed by the ankle.

The muscle weakness associated with benign hypermobile joint syndrome follows a specific pattern, usually involving quadriceps, hip abductors, extensors and plantar flexors. The management for this condition is physical therapy to improve the strength and function of the muscles in order to control the hypermobile joints, combined with a reduction in the activities causing pain (Sherry and Malleson, 2001; Maillard and Murray, 2003; Beighton, 1988; Jessee et al., 1980; Maillard et al., 2004c; Murray and Woo, 2001).

It is vital that the child understands that the pain will not resolve until the function has returned completely and nothing will remove the pain until normal function is regained (Maillard et al., 2004a).

4.2. Main goals of treatment

1. Full range of movement at each joint.
2. Full muscle strength throughout the whole range
   a. Including hypermobile range
3. Stable joints.
4. Excellent stamina
   a. Specific muscles
   b. General
5. Full physical function independent of pain.
6. Good balance and proprioception.
7. Age appropriate neuro-muscular co-ordination.
8. No pain.
9. Independent function.
10. Minimize loss of bone density.
11. Educated family and child.

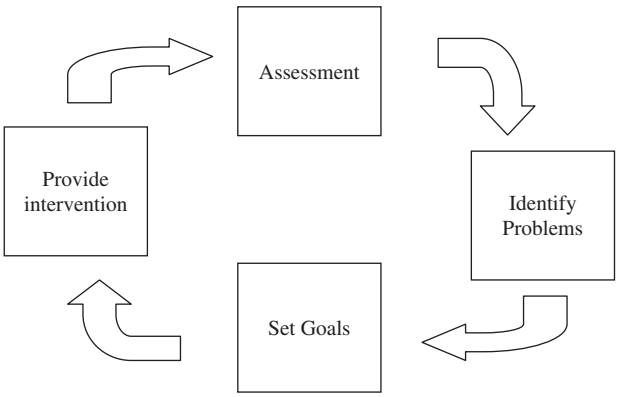

Figure 2. The basic cycle of physiotherapy assessment and treatment.

4.3. Osteoporosis

Immobilization causes increased bone resorption and decreased bone formation. Bone loss due to immobilization may be as much as 5% per month for the first 6 months; after which the rate of loss slows. Children who exercise regularly have stronger bones. It is vital that children exercise regularly at all stages of childhood to maximize bone density for adulthood. Ninety percent of bone mineral density accumulates by the end of adolescence. Differences in bone mineral density between children are primarily genetic with lesser variations due to level of calcium uptake, disease activity and up to 17% of the variation due to the amount of weight bearing activity being performed. Children with inflammatory disease taking medications which accelerate bone loss (such as steroids) who also experience immobility and loss of function as a result of their disease, are at high risk. Impact exercise should be encouraged at all times if possible (Bachrach, 2001; Cimaz, 2002; Davies et al., 2005; McDonagh, 2001; Tortolani et al., 2002).

A complete program may include a variety of interventions depending on the specific problems. The main principles of each intervention including hydrotherapy, stretching, splinting, pain relief, pacing, balance and proprioception re-education, gait re-education and muscle strengthening are described.

4.4. Hydrotherapy

Hydrotherapy has been a well-accepted technique for many years. Research into its effectiveness has shown that it is not as effective as "dry land" treatment. Hydrotherapy however is extremely effective when used in close conjunction with a land-based program and when the hydrotherapy treatments are employed effectively to use the specific effects of buoyancy to target the specific problems and make effective progress. Unfortunately it is all too easy to simply put a child into hydrotherapy each week without taking these factors into account. Therefore hydrotherapy should be provided with specific goals. The therapist and the child must remember that moving through water is much easier than walking on land, due to buoyancy, and that these exercises will not replace the need for exercise on land (Epps et al., 2005; Takken et al., 2003c).

4.4.1. Goals of hydrotherapy

These are attained with the combined effect of the warmth from the water and the effect of buoyancy supporting the body. Goals are:

- To reduce pain and muscle spasm.
- To increase joint range of movement and muscle strength by using buoyancy to stretch.
- To reduce joint stiffness by allowing more comfortable movement, especially first thing in the morning, encouraging joints to move through range and therefore improving circulation and reducing swelling.
- Increase muscle strength—when movement is completed against buoyancy and turbulence.
- Increase aerobic capacity by encouraging swimming and fast action games.
- Increase fun element to the treatment program.

4.5. Stretching

Stretching is an important part of the treatment program both for reducing contractures and preventing them while lengthening shortened muscles. In inflammatory disease the synovial fluid becomes thinner and full of inflammatory cells. These cells alter the effectiveness of the synovial fluid in its role as a lubricant. The surrounding soft tissues loose elasticity and become stiffer which may lead to contractures very quickly. Often children with inflammatory disease such as arthritis (but this also may occur in any of the other inflammatory diseases) experience stiffness in the joints after periods of immobilization—such as sitting in a classroom or after a long car ride. Therefore is it vital to stretch first thing in the morning through full range of movement to prevent the development of contractures (permanent loss of joint movement) and to reduce the pain and the stiffness. If the child has particularly active disease with many swollen

joints the stretches may be more effectively completed in a warm bath or hydrotherapy pool.

4.5.1. Goals of stretching

1. To reduce pain.
2. To reduce stiffness.
3. To maintain or increase joint range of movement in order to prevent contractures or to resolve them if necessary.
4. To increase muscle length.

4.5.2. Important rules for stretching joints

1. Stretch only one joint at a time.
2. Initially apply a slight traction to reduce any muscle spasm and to ensure that the joint is in a good alignment.
3. The stretch needs to be completed gently but also firmly to ensure that it is effective.
4. The stretch should be uncomfortable (not painful) and into new range that the child is not able to do actively.
5. Most stretches are into extension as that is the end of range that is most often lost and muscles also get weaker and find it difficult to maintain the range against gravity. However there are some exceptions as it is also important that range into flexion is not lost in the fingers and elbows and that plantar and dorsiflexion are maintained. Some joints will also need rotational stretches.
6. Stretches must be completed when the joint is inflamed. It is vital that stretches are done when the joint is swollen. This is the time when the most movement is lost.

4.5.3. Stretching shortened muscles

Due to the inflammatory nature of the muscle disease, muscles are very likely to shorten in conditions such as juvenile dermatomyositis. The muscles most commonly affected are gastrocnemius causing loss of dorsiflexion, hamstrings and the long flexors of the arm preventing full extension of all joints in the upper limbs. Muscle tightening and joint contractures may occur.

In children with hypermobility and pain syndromes muscle shortening also occurs, more often in the lower extremities. It is important to remember to stretch the whole muscle during therapy. This may include several joints at a time. Remember the anatomy of the joints and ensure that the stretch is maintaining normal alignment.

4.5.4. Stretch and cast (serial casting)

In some cases contractures are severe and are not able to be stretched on a daily basis. These contractures are typically associated with active disease and most common in the knees. Serial casting can be done using relaxation techniques. In the most severe case the child is taken to the operating theater and under general anesthesia the joint injected by the medical team and then the therapist can stretch very slowly into full extension and a cast is applied. This cast should remain on for a few days only and then it should be removed and intensive physical therapy provided. It is important that the cast is not kept on for too long—5 days maximum—in order to prevent stiffness into extension instead of flexion. It is vital that while the cast is on the child performs many static quadriceps contractions in order to start the process of gaining adequate inner range quadriceps strength, to maintain full range and to prevent a relapse of the contracture.

When the cast is removed then intensive physiotherapy is vital—twice a day minimum. The main focus of the program should be to regain full strength particularly in inner range quadriceps but also hip abductors and extensors and plantar flexors, which also become very weak. Subsequent casting may be done using relaxation techniques and should not require further injections.

4.5.5. Splinting

Splinting was one of the main interventions in the past. However with more effective medical management splints are now rarely required in rheumatic diseases. Splints are still useful as active wrist supports that support the wrist in extension

but allow full function of the fingers. These splints are used during activities such as writing to minimize fatiguing and pain while maintaining good functional position. Leg splints to keep the knee into extension and the ankle into dorsiflexion are required only when the disease is refractory to medical management.

Splinting should not be used in children with biomechanical problems such as hypermobility as they encourage muscle weakness which ultimately increases pain.

Splinting is completely contraindicated in pain syndromes such as reflex sympathetic dystrophy as immobilization always makes these conditions worse.

4.6. Pain relief

Techniques such as ice and heat are useful in the management of the pain in all these conditions. There is no reason to prefer ice or heat, either can be used and the best judge of which is most effective is the child. However cold is contraindicated when reflex sympathetic dystrophy is present.

Wax can be useful and will not only help with pain but can also be used as exercise.

Massage is also a useful technique to use. The child can be taught some self massage techniques and the family can also be taught. Massage is very useful as a desensitization technique for the management of the pain syndromes, but it is also useful for the reduction of muscle spasm and to help improve the circulation.

The main intervention for reducing pain in all these conditions is to regain normal movement and full muscle strength. This applies especially to the pain syndromes. Waiting for the pain to abate before physical therapy is started will mean that physical therapy is never started. Exercising and stretching are the most effective methods of reducing pain (Maillard et al., 2004a).

4.7. The amount of excercise

Children and young people naturally have lots of energy and want to keep going all day. However with rheumatic conditions the pain and symptoms may be made worse by doing too much resulting in pain and stiffness the next day. It is important to teach the child and their family not to overdo activities. It is useful to plan activities throughout the week, so that each day has similar challenges in it, and to avoid doing too much on one day.

After a flare it is important to start gradually to ensure that energy is conserved and that there is a paced approach back into full function. This may include reducing some activities initially so that the young person can manage school first, gradually adding in more activities as the child improves. When progressing back to full function, tasks should be set that will be achieved whether it is a good day or a bad day. Even on a good day the child should not do too much. This is important to avoid the ''roller-coaster'' effect.

4.8. Balance and proprioception

Balance and proprioception are altered by joint swelling, pain, muscle weakness and inactivity. Without balance/proprioception it is very difficult to complete tasks safely and the risk of injury is increased. The most simple and effective exercise to improve lower limb proprioception is practicing standing on one leg, progressing to doing this with eyes closed and then progressing to adding in plantar flexion on one leg (i.e., going up and down on tiptoes). Equipment, such as a wobble board, is useful for balance work and can be purchased for use at home (Hall et al., 1995; Mallik et al., 1994).

4.9. Gait re-education

Altered gait results from altered biomechanics, inflammation and muscle weakness. Additionally some children have ''learnt'' a pathologic gait pattern which has become their ''normal'' walk. It is important to correct the gait pattern; practicing walking in front of mirrors is useful. Often marching can help as it overcorrects most abnormal gaits

and encourages good use of range and muscle strength.

Supportive footwear is vital to normal gait. Shoes should be high and supportive around the heel, with a strap or laces/velcro to hold it firmly in place. However for children with unstable feet and ankles (hypermobile of inflamed joints) ankle boots; such as Timberlands/Kickers etc are useful as they support both the feet and the ankles and have effective shock-absorbing soles.

4.10. Advice about sporting activities

The aim of treatment is to give every child a normal and full life. For inflammatory disease medications and therapy are required. For non-inflammatory disease only physical therapy is required. Provided that each muscle group is doing its job properly and the young person is fit and strong, children are encouraged to join in any appropriate sporting activity. Nevertheless other sports require disproportionate strength (i.e., distance running, rugby and American football) and should be monitored carefully. A trampoline should also be used with care as sometimes the lands and jumps can be unpredictable.

4.11. Muscle strengthening and endurance exercises

There are many reasons for children to lose muscle strength and stamina, listed below (Fig. 3):

Pain inhibits muscle function.
Inflammation.
Biomechanical problems.
Loss of mobility.
Disease activity.
Muscle imbalance.

4.12. The role of cytokines in muscle function

Cytokines are small molecules produced by the body to send messages from one cell to another. Cytokines have become extremely important in the

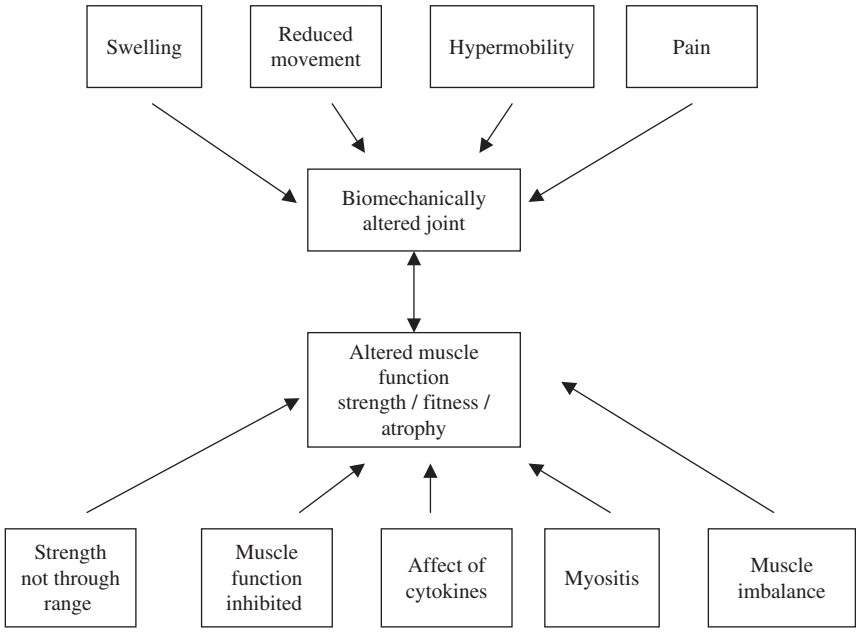

Figure 3. Cycle of muscle weakness in inflammatory disease.

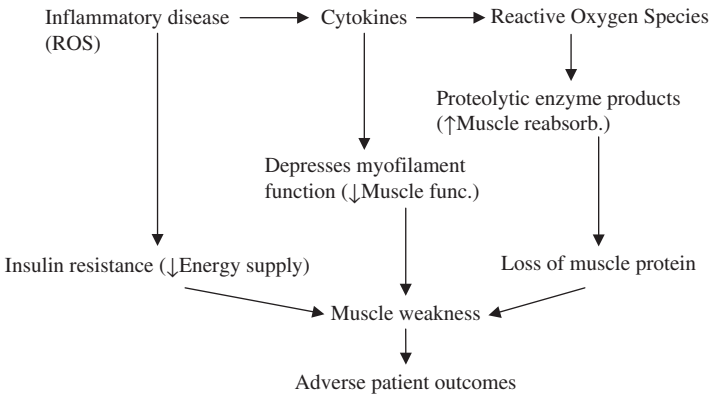

Figure 4. Diagram showing the simple relationship between cytokines and muscle function (Winkelman, 2004).

understanding of the nature of inflammatory disease and this knowledge has been used to produce a new group of medical therapies called the "biologics". Medicines such as "Etanercept" and "Infliximab" have been developed and these are "anti-TNFα" drugs. Other important anti-cytokine drugs are also being developed such as "anti-IL-6" and "anti-IL-1". However these cytokines also have an important physiological role in the function of muscle and may explain why children with inflammatory disease become so weak so quickly (Fig. 4) (Collins and Grounds, 2001; Fedczyna et al., 2001; Pachman et al., 2001; Spencer et al., 2000; De Bleecker et al., 2002; Feghali and Wright, 1997; Larsen et al., 2002; Lundberg et al., 1997; Lundberg, 2001; Malm, 2001; Nagaraju, 2001a, b; Nemet et al., 2002; Ostrowski et al., 1999; Pedersen, 2000; Pedersen et al., 2001a, b; Pedersen and Toft, 2000; Reid and Li, 2001a; Scheett et al., 1999, 2002; Toft et al., 2002).

4.12.1. TNFα function and muscles

TNFα's role in normal muscle is to increase the proliferation of new muscle cells and facilitate the apoptosis of old muscle cells. If the level of TNFα changes, abnormal muscle function occurs.

TNFα inhibits muscle contraction by reducing the contractile force and by blunting the response to calcium activation. TNFα increases proteolysis, inhibiting the insulin effect upon muscles and blocking the glycogen uptake by the muscles. A prolonged increase in TNFα inhibits skeletal muscle synthesis and accelerates skeletal muscle myopathy (Li and Reid, 2001; Reid et al., 2002, 2001a, b).

4.12.2. IL-6 and muscle function

IL-6 is a pro-inflammatory cytokine in the inflammatory diseases in childhood. IL-6 is vital for the homeostasis of muscle function. IL-6 causes glycogen levels to increase. IL-6 is produced normally by functioning muscles, not only to regulate the glycogen requirement but also as a pro-inflammatory cytokine. In order to increase the strength and size of muscle a small local inflammatory process is established causing local "damage" which can therefore be repaired by the function of the satellite cells.

4.12.3. Muscle repair and growth

Muscle repair and growth are dependent on satellite cells. These are undifferentiated cells which can then be stimulated to either replace damaged muscle cells or to add new muscle cells. These cells are stimulated by exercise. Daily exercise after damage encourages new growth and repair which is important in the healing process (Table 3).

4.13. Training children's muscles

Research shows that children do this best with a progressive resisted exercise program using high repetitions and low weights.

Table 3
Types of muscle work that should be included into a treatment program

Types of muscle work
Concentric
Eccentric
Isometric
Isokinetic
Closed chain
Open chain

Table 4
Advice as to how to develop a successful home exercise program for children with a rheumatological condition

Developing a successful home program:
The exercises need to be easy to do at home
Minimal equipment should be used
Use progressive and resisted exercises that can be done on the floor
Ensure that the program is not too long
Make the program specific to the muscle weakness found on assessment

Table 5
Example of a home exercise program for a child with a rheumatological condition

Muscle involved	Starting position
Inner range quadriceps	Lying supine Static quadriceps contraction Straight leg raise
Hip abductors	Straight side lying Lift straight leg up, keeping body still and slightly tilted forwards
Hip extensors	Prone lying Lift straight leg up, keeping hips still
Plantar flexors and balance	Standing On one leg going up and down slowly on to tiptoes

It is recommended to increase repetitions to a minimum of 15 before weights are added, however to regain full fitness of the muscles 30 repetitions are recommended. Low weights are also recommended with increases of 0.5 kg to a maximum of 2.5 kg in most children though increasing to 5 kg is safe for larger children.

The exercise program needs to be regular. Twice a week is more effective than once a week exercise, but four to five times a week is the most effective. The exercise program should be started slowly but constantly progress until full strength and fitness are regained. Progression on a daily or weekly basis is more effective than monthly progression (American Academy of Pediatrics Committee on Sports Medicine and Fitness, 2001; Baquet et al., 2001; Faigenbaum et al., 1999, 2001, 2002, 2003; Faigenbaum, 2000; Fowler et al., 2001; Helge and Kanstrup, 2002; Klepper, 2003; Obert et al., 2001; Purcell and Hergenroeder, 1994; Strong, 1990).

4.13.1. Specific exercise program

In developing a program for any child with a rheumatic disease regaining joint range of movement and regaining muscle strength and fitness are most important. Children often develop similar and specific muscle weakness patterns involving the hip abductors and extensors, inner range quadriceps and plantar flexors. A home management program should include a strengthening and stamina program for these muscles. It is important to provide a specific strengthening program to restore normal function.

It is extremely important that the child and the family also realize that for physical therapy to be effective it has to be completed regularly at home. The role of the physical therapist is to monitor the home program and to facilitate progression of the program. If the exercises are not completed regularly at home then no progress can be made.

For any specific prescribed exercise program to be effective in the management of these conditions these principles need to be followed:

1. Muscle strengthening and stamina of muscles is the most vital aspect of the program. This program should target the specific muscles that are weak and unfit and the program should be regularly progressed until 30 repetitions and 2.5 kg weights can be used for each exercise. (These guidelines should be modified for the smaller or larger child.)
2. If inflammatory disease is causing loss of joint movement then a daily stretching program should be included.

3. Balance and proprioception are also very important and can easily be included into a program (Tables 4 and 5).

Key points

In the management of children with rheumatological conditions there are several principles to always consider.

- At the assessment there is often underestimation as to the strength of children and so weakness is missed.
- With all the conditions involved the children usually have less muscle strength than normal.
- Loss of strength and stamina is very quick, especially in inflammatory disease and this is then exacerbated by
  - lack of activity
  - pain
  - loss of range of movement
- Strength and stamina of muscles can only be regained by exercise.
- Exercise should be progressed and resistance should be used to ensure maximum benefit.
- Muscles are the only dynamic control of joints and therefore need to be as strong and as fit as possible in order to protect the joints.
- Children with rheumatological conditions can regain full strength and function and then can be encouraged to join in with all activities as their peers would do.

So there are many reasons as to why children with rheumatological conditions are weak but with a regular progressive and resisted exercise program these children can be strong and fit and have an active and pain-free life.

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