Abstract Book

PReS Latin America Basic Pediatric Rheumatology Course

June 22 to 24, 2015

Aguas de Sao Pedro, Sao Paulo, Brazil

WELCOME

Dear Colleagues,

Welcome to Aguas de Sao Pedro, to the **PReS-Latin America Course in Pediatric Rheumatology**! This course was possible thanks to the collaboration of PReS and Sao Paulo State University - UNESP.

This is the first educational activity of its kind in the region, and we hope it will be the first in a series of similar initiatives in the future. The program was designed to get the best of in class state of the art in Pediatric Rheumatology.

A carefully selected team of speakers from Europe and Latin America will deliver firsthand knowledge and experience to the audience, while also carefully handpicked clinical cases will be presented by fellows from the region. We hope this will set the scenario for a highly interactive and enjoyable educational experience. You will have the chance to make long-lasting professional relationship among your colleagues from other countries in the region. We hope this course will start a new cornerstone in Latin America networking. You will receive digital contents of the course through the university telemedicine system.

Please, do not forget to use your mobile phones discreetly, be green-conscious and enjoy your stay in Aguas de São Pedro, Brazil!

Claudia Saad Magalhães

Department of Pediatrics
São Paulo State University
BRAZIL

Ricardo Russo

Hospital Prof. Garrahan
Buenos Aires
ARGENTINA

PReS / Latin America Basic Pediatric Rheumatology Course: An Update for Clinicians

June 22-24, 2015

Aguas de Sao Pedro – Sao Paulo, BRAZIL

Institution: Botucatu Medical School - Sao Paulo State University - UNESP

COURSE CO-ORDINATORS

Alberto Martini – PReS Chairman, IRCCS G Gaslini, Genoa - ITALY

Claudia Saad Magalhães – Sao Paulo State University, Botucatu, Sao Paulo - BRAZIL

Ricardo Russo – Hospital de Pediatria Prof. Dr Juan P Garrahan, Buenos Aires - ARGENTINA

FACULTY

Simone Appenzeller - University of Campinas, Sao Paulo - BRAZIL

Jorge López Benítez - Centro Médico La Costa, Assumpcion - PARAGUAY

Arturo Borzutzky - Universidad Católica, Santiago - CHILE

Paul Brogan - UCL Institute of Child Health and Great Ormond Street Hospital NHS Foundation Trust, London - UK

Carmen Laura de Cunto - Hospital Italiano, Buenos Aires - ARGENTINA

Claudia Saad Magalhães - Sao Paulo State University, Botucatu, Sao Paulo - BRAZIL

Alberto Martini - IRCCS G Gaslini, Genoa - ITALY

Sheila Knupp de Oliveira - Federal University of Rio de Janeiro - BRAZIL

Oscar Porras - National Children´s Hospital "Dr. Carlos Sáenz Herrera", San José, COSTA RICA

Angelo Ravelli - IRCCS G Gaslini, Genoa - ITALY

Carlos Daniel Rosé - Dupont Hospital, Delaware - USA

Carine Wouters - Leuven University Hospital, Leuven - BELGIUM

Nico Wulffraat - Utrecht Medical Center, Utrecht - NETHERLANDS

PROGRAM

Monday, June 22	
18:00-19:30	**Case Review Organizing Session**
20:00	**Welcome Dinner**

Tuesday, June 23	
Morning Session (8.00- 12.30)	
08.00-08.30	**Opening** *(Claudia Saad Magalhaes, Ricardo Russo and Alberto Martini)*
08.30-09.00	**pGALS - Paediatric Gait Arms Legs and Spine: a simple examination of the musculoskeletal system** *(Carine Wouters - Belgium)*
09.00-09.30	**Pathogenesis of rheumatic diseases: basic concepts** *(Nico Wulffraat - Netherlands)*
09.30-10.00	**Infectious arthritis. Post-infectious arthritis** *(Carlos Rosé- USA/Argentina)*
10.00-10.15	**Case Presentation:** *Renan Augusto Pereira – Hospital Infantil Pequeno Principe, Curitiba* **Discussion:** *Carlos Rosé - Nico Wulffraat*
10.15-10.45	coffee break
10.45-11.05	**Joint involvement in hematological diseases and cancer** *(Jorge Lopez Benitez- Paraguay)*
11.05-11.25	**Rheumatic manifestations of Immunodeficiency** *(Oscar Porras- Costa Rica)*
11.25-12.00	**Joint involvement in orthopedic diseases** *(Carmen de Cunto - Argentina)*
12.00-12.30	**Case Presentations:** **Case 1**- *Rafaela Wagner – Hospital Infantil Pequeno Principe – Curitiba* **Case 2**- *Yanina Suzana Ameruso, Universidade de Buenos Aires* **Discussion:** *Jorge Lopez Benitez - Carmen de Cunto - Oscar Porras*
Afternoon (14.00-18.30)	
14.00-14.30	**Rheumatic manifestations of Inflammatory bowel disease, psoriasis** *(Oscar Porras - Costa Rica)*
14.30-15.00	**Osteoporosis in children and adolescents** *(Sheila Knupp de Oliveira - Brazil)*
15.00-15.30	**Complex regional pain syndrome, and related entities** *(Jorge Lopez Benitez - Paraguay)*
15.30-16.00	**Case presentations:** **Case 1-** *Giuliana Pucarelli Lebreiro – Universidade Estadual do Rio de Janeiro* **Case 2-** *Ana Laura Tolin – Mendoza* **Discussion:** *Oscar Porras - Jorge Lopes Benitez*
16.00-16.15	coffee break
16.15-16.30	**Greetings from Prof. Silvana Artioli Schellini – Director of Botucatu Medical School, Sao Paulo State University (UNESP)**
16.30-17.00	**JIA: general clinical aspects** *(Alberto Martini - Italy)*
17.00-17.30	**JIA: complications (Uveitis, Macrophage Activation Syndrome)** *(Carine Wouters - Belgium)*
17.30-18.00	**JIA: treatment** *(Claudia Saad Magalhães - Brazil)*
18.00-18.30	**Case Presentations:** **Case 1-** *Beatriz H. Leòn Noguez - Universidad San Francisco de Quito Ecuador* **Case 2-** *Adolpho Pedro de Melo Medeiros, Mossoró, Rio Grande do Norte* **Discussion:** *Claudia Saad Magalhães - Alberto Martini - Carine Wouters*
Evening	
a cultural and social get together for all participants *Espaço da Figueira - Grande Hotel Aguas de São Pedro*	

Wednesday June 24	
Morning Session (8.00- 12.30)	
08.00-08.30	**Juvenile Spondyloarthropathies** *(Arturo Borzutzky - Chile)*
08.30-09.00	**Childhood Systemic Lupus Erythematosus and Neonatal Lupus** *(Paul Brogan - UK)*
09.00-09.30	**Antiphospholipid antibody syndrome** *(Sheila Knupp F de Oliveira - Brazil)*
09.30-10.00	**Case presentations:** **Case 1-** *Thaissa Amorin Nogueira - Universidade Estadual do Rio de Janeiro* **Case 2-** *Adriana Rodrigues Fonseca - Universidade Federal do Rio de Janeiro* **Discussion:** *Arturo Bortzuzky - Paul Brogan*
10.00-10.30	coffee break
10.30-11.00	**Juvenile Dermatomyositis** *(Carmen de Cunto - Argentina)*
11.00-11.30	**Small vessel vasculitides** *(Paul Brogan - UK)*
11.30-12.00	**Medium and large vessel vasculitides** *(Arturo Borzutzky- Chile)*
12.00-12.30	**Case Presentations**: **Case 1-** *André de Souza Cavalcanti - Universidade Federal de Pernambuco-Recife* **Case2-** *Catherine Gusman Anelli - Universidade Federal de São Paulo* **Discussion:** *Paul Brogan - Arturo Borzutzky*

Afternoon (14.00-19.00)	
14.00-14.30	**Juvenile scleroderma** *(Carine Wouters - Belgium)*
14.30-15.00	**Autoinflammatory diseases** *(Carlos Rosé - USA)*
15.00-15.30	**Vaccination policy for pediatric rheumatic diseases: biologics in the immunocompromised host** *(Nico Wulfraatt - Netherlands)*
15.30-16.00	**Case Presentations:** **Case 1-** *Paola Pinheiro Kahwage - Universidade de São Paulo- Ribeirão Preto* **Case 2-** *Priscila Beatriz de Souza Medeiros - Universidade de São Paulo- Ribeirão Preto* **Discussion:** *Nico Wulffraat - Carlos Rosé*
16.00-16.30	coffee break
16.30-17.00	**Imaging in pediatric rheumatic diseases** *(Angelo Ravelli-Italy)*
17.00-17.30	**Assessment of Disease Activity and Damage** *(Angelo Ravelli- Italy)*
17.30-18.00	**Transitional care for adolescents** *(Simone Appenzeller - Brazil)*
18.00-18.30	**Case presentation:** **Case 1-** *Gecilmara Salviato Pileggi - Universidade de São Paulo- Ribeirão Preto* **Discussion:** *Simone Appenzeller - Angelo Ravelli*
18.30	**Closing remarks** *(Ricardo Russo - Claudia Saad Magalhães)*

INTERACTIVE CASE-DISCUSSION Guided case-discussion and problem-solving sessions will take place after the lectures. Cases were selected according to the best interest to compose the case sessions and also for completeness of clinical approach, investigations and imaging. The audience will be elicited for opinion on diagnosis and management with the developed knowledge in previous lecture sessions. Faculty teams should provide the state of art on differential diagnosis and best practice for management according to the patient's environment.

MEETING AND ACCOMMODATION VENUE

Grande Hotel São Pedro – Aguas de Sao Pedro – Sao Paulo, Brazil

ADDRESS

Grande Hotel São Pedro, Pq. Dr. Otávio de Moura Andrade, s/n, Águas de São Pedro – SP

CEP: 13525-000, Brazil.

http://www.grandehotelsenac.com.br/Home.aspx?HotelId=1

High Speed Internet Access is available.

Hospitality and registration desk will be located in the conference centre from June 22 -24th .

A full information package and most of your meeting materials will be distributed on site electronically. We hope to be green, so that most of the digital contents of the course will be available

Águas de São Pedro is the smallest city in Brazil. It is included in reports from the United Nations as one of the resorts with the best quality of life index. This characteristic of offering good life makes that Águas de São Pedro attracts visitors searching for its welcoming atmosphere and pleasant, abundant green area and its famous medicinal waters, the Grande Hotel São Pedro adds peaceful and a relaxing scenario of the thermal spa.

The weather in Sao Paulo state is quite pleasant at this time of the year, with temperatures typically ranging from 12° to 23°C. It is winter time, so you may expect sunny days and cold nights. Be aware that the seasons in the southern hemisphere are exactly the opposite of those in the northern hemisphere.

Sao Paulo is located at time zone - 3:00 GMT. Typically 5 hours behind with respect to Western Europe and 1-2 hour ahead of the U.S. Eastern Time.

FACULTY PROFILE

Alberto Martini (Italy)

Alberto Martini is Professor of Pediatrics at the University of Genoa and Director of Pediatria II Reumatologia (EULAR Centre of Excellence in Rheumatology 2008-18) and the Department of Pediatrics in the G Gaslini Institute, Genoa, Italy. Prof Martini is President of the Pediatric Rheumatology European Society (PRES), Chairman of the Pediatric Rheumatology International Trial Organization (PRINTO), and Chairman of the EULAR Standing Committee on Pediatric Rheumatology, Past President of the Italian Council of Academic Professor of Pediatrics (2008-2012). He is Co-Editor of Clinical and Experimental Rheumatology and Pediatric Rheumatology and member of the Editorial Board of Annals of Rheumatic Diseases, being the author of more than 350 papers in peer reviewed journals related to pediatric rheumatic diseases, his H-index (Google scholar) is 67.

Angelo Ravelli (Italy)

Angelo Ravelli is Associate Professor of Pediatrics at the University of Genoa and Chief of the Center of Rheumatology at the Istituto Giannina Gaslini, Genoa, Italy. His research focus is on macrophage activation syndrome, metrics and outcome of pediatric rheumatic diseases. He was granted research award Gerolamo Gaslini Prize for Excellence in Research in 2004 and the American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) support to develop classification criteria for macrophage activation syndrome in systemic juvenile idiopathic arthritis. He is Associate Editor of Pediatric Rheumatology Online Journal, Assistant Editor of Clinical and Experimental Rheumatology and Editorial Board of The Journal of Rheumatology and Arthritis Care & Research. He is member of the Executive Committee of the Foundation for Research in Rheumatology (FOREUM), and Chairman of the International Consensus Conference for classification criteria of macrophage activation syndrome in systemic juvenile idiopathic arthritis in 2014.

Angelo Ravelli is Associate Editor of Pediatric Rheumatology Online Journal, Assistant Editor of Clinical and Experimental Rheumatology and serves or has served on the Editorial Board of The Journal of Rheumatology and Arthritis Care & Research. He is a member of the Executive

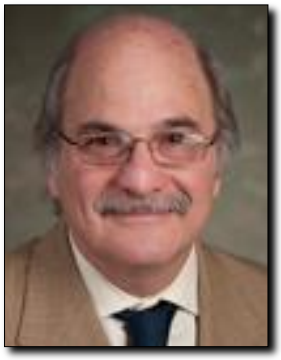
Committee of the Foundation for Research in Rheumatology (FOREUM). He was the chairman of the International Consensus Conference, which led to the development of the classification criteria for macrophage activation syndrome in systemic juvenile idiopathic arthritis (Genoa, Italy, 21-22 March 2014).

He was the speaker in more than 200 national and international meetings, and is author or co-author of more than 230 full-length articles in international scientific journals. His current Google Scholar h-index is 57. He has mentored a number of residents, post-doc students and international fellows.

Arturo Borzutzky (Chile)

Arturo Borzutzky is Chief of Pediatric Immunology and Rheumatology at the School of Medicine of Pontificia Universidad Católica de Chile in Santiago- Chile, where he graduated. He was a former fellow in Pediatric Rheumatology and Immunology at Boston Children's Hospital, Harvard Medical School. He is the principal investigator at the Translational Immunology Laboratory at his institution, where he performs research ranging from epidemiology to basic science on the pathogenesis of immune-mediated diseases, with special interest on vitamin D, atopic dermatitis, and Kawasaki disease. He is currently mentoring a fellow in Pediatric Rheumatology.

Carlos Daniel Rosé (USA)



Carlos Daniel Rosé is Professor of Pediatrics Professor of Pediatrics at Thomas Jefferson University, Philadelphia, USA and Chief of The Division of Rheumatology Nemours Children's Hospital, Wilmington, Delaware. His research line is mainly related to Lyme disease, Blau Syndrome natural history, biomarkers and downstream effects of NOD2 mutation.

The Pediatric Rheumatology Division at Nemours is American Board of Pediatrics approved for fellowship training. Professor Rosé mentored many pediatric rheumatology fellows in USA and overseas and also adult rheumatology fellows from Jefferson and Cooper Hospital Programs for the last ten years.

Carine H Wouters (Belgium)

Carine H Wouters is a pediatric rheumatologist working at Leuven University Hospital in Leuven, Belgium. She is head of the clinical department of pediatric rheumatology and immune-inflammatory diseases at the Leuven University Children's hospital, and is the chair for clinical affairs in the PReS council. Her major research interests comprise systemic juvenile idiopathic arthritis and macrophage activation syndrome (in collaboration with research group of Immunobiology, Patrick Matthys, Leuven) as well as granulomatous inflammatory diseases in children with a special interest to Blau syndrome (in collaboration with Carlos Rose, Wilmington, US).

Carmen Laura de Cunto (Argentina)

Carmen Laura de Cunto is a Pediatric Rheumatologist at the Pediatrics Department Hospital Italiano de Buenos Aires, Argentina. She was a former fellow from Baylor College of Medicine, Houston Texas, USA. Her main research interests are post-infectious arthritis, functional joint pain, hypermobility syndromes, autoinflammatory syndromes, health related quality of life, transitional care from pediatrics to adult medicine, progressive fybrodysplasia ossificans and narrative medicine. She is the Director of the Fellowship Program in Pediatric Rheumatology, Instituto Universitario Hospital Italiano de Buenos Aires.

Helen Foster (United Kingdom)

Helen Foster is Professor Paediatric Rheumatology at Newcastle University, UK and Honorary Consultant Paediatric Rheumatologist, Great North Children's Hospital, Newcastle Hospitals NHS Foundation Trust, Newcastle upon Tyne, UK. She trained intially in adult rheumatology and subsequently paediatric rheumatology with a Clinical Fellowship in Vancouver, Canada. Helen is academic head for the Newcastle paediatric rheumatology service, one of the largest in the UK with an active research programme and keen focus on undergraduate and postgraduate education. Her academic work, has always maintained a strong clinical focus and aims to improve access to care for children with arthritis. She leads an educational research programme to faciliate early recognition of childhood rheumatic disease and recent

work includes development of an evidence based paediatric musculoskeletal curriculum for medical students, the pGALS musculoskeletal examination which is now widely taught, pREMS as a detailed joint assessment along with e-resources to facilitate teaching and learning (paediatricmusculoskeletalmatters - www.pmmonline.org). She has published over 100 peer reviewed articles, book chapters and modules for the NHS e-Learning for Health programme. She was Chair of the Royal College for Paediatrics and Child Health Specialist Advisory Committee responsible for postgraduate training in paediatric rheumatology until 2014, is national lead NHS Specialist Commisioning and has contributed to national and international clinical guidelines and Standards of Care. She is Regional Speciality lead for the UK Clinical Research Network to promote clinical research and clinical trials in paediatrics.

Jorge Lopez Benitez (Paraguay)

Jorge Lopez Benitez is a Pediatric Rheumatologist at Centro Medico La Costa, Asunción, Paraguay. He is the Chief of Pediatrics at Centro Medico La Costa, Director of the Pediatric Rheumatology Program at the same Institution, and Head of the Research Section at the Pediatric Hematology and Oncology Department at the Universidad de Nacional de Asunción. He was a former Resident at Yale University, Waterbury CT, USA and a fellow at Tufts University Medical Center, Boston MA. He is the former Director of the Pediatric Rheumatology Fellowship Program at The Floating Hospital for Children at Tufts Medical Center in Boston, where he mentored USA and foreign fellows and also the Chief of the Division of Pediatric Rheumatology at the same Institution. He was appointed Assistant Professor of Pediatrics, Pediatric Rheumatology, at Tufts School of Medicine. His main research interest is on Vitamin D, Systemic Lupus Erythematosus and Pediatric Rheumatology access in underserved areas.

Nico Wulffraat (Netherlands)

Nico Wulffraat is Professor of Pediatric Rheumatology Utrecht Medical Centre, Netherlands. His research interests are on Systemic Juvenile Idiopathic Arthritis, Immunizations, Pharmacovigilance, Early treatment protocols for Juvenile Idiopathic Arthritis and biomarkers guided therapy. He is a member of the Executive Board of Pediatric Rheumatology European Society (PRES) and also a member of Pediatric Rheumatology International Trials Organization (PRINTO) Advisory Council leading worldwide Pharmachild and Share projects. He mentored national and overseas PRES fellows.

Oscar Porras (Costa Rica)

Oscar Porras is a Pediatric Immunologist , Head of the Pediatric Immunology and Rheumatology Division, National Children´s Hospital "Dr. Carlos Sáenz Herrera", San José, Costa Rica.

His main research interests are about Immunodeficiencies, Osteopetrosis, Systemic Lupus Erythematosus. He trainned and mentored Residents in Pediatrics and Clinical Immunology. Recent publications are about Pediatric Lupus, Genetics of Osteopetrosis and Vaccination in Primary Immunodefiencies.

Paul Brogan (United Kingdom)

Paul Brogan is Reader in Vasculitis and Consultant Paediatric Rheumatologist. UCL Institute of Child Health and Great Ormond Street Hospital NHS Foundation Trust. Dr Brogan runs a programme of translational research for vasculitis and autoinflammatory diseases. He has supervised 9 PhD. students, and his current projects include clinical trials for autoinflammatory diseases and vasculitis; discovery of novel monogenic autoinflammatory diseases; and discovery of novel therapeutic targets and biomarkers. He has published over 100 scientific papers, has co-authored 3 textbooks, and he is joint editor of the 2nd edition of the Oxford Handbook of Paediatric Rheumatology.

Sheila Knupp Feitosa de Oliveira (Brazil)

Sheila Knupp Feitosa de Oliveira is Associate Professor of Pediatrics at Rio de Janeiro Federal University, Chief of the Pediatric Rheumatology Unit at The Instituto de Puericultura e Pediatria Martagao Gesteira (UFRJ). She was a pioneer mentoring 15 board-certified fellows specialists in pediatric rheumatology since 1989, practicing in Rio de Janeiro and other states in Brazil. She is the Editor of 6 Pediatric Rheumatology Textbooks, Primers and a Practice Manual.

Simone Appenzeller (Brazil)

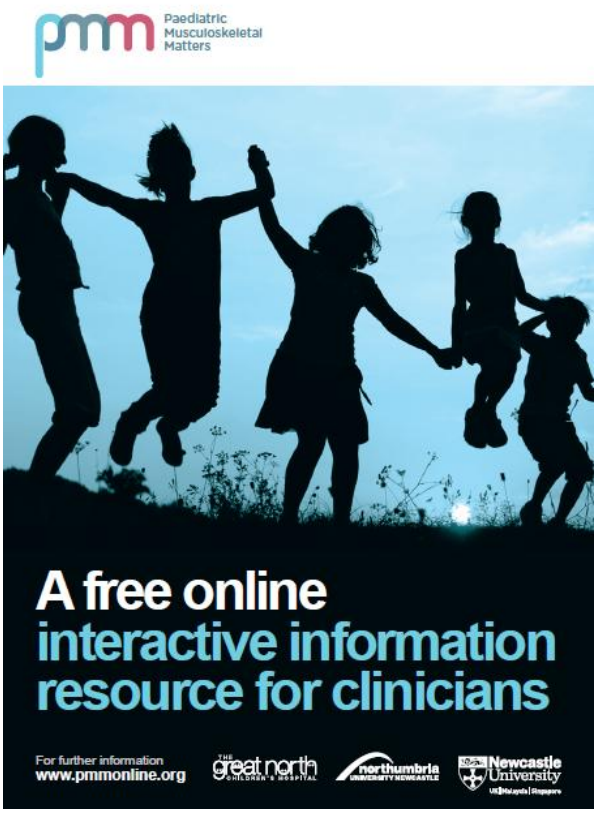
Simone Appenzeller is Associate Professor of Rheumatology at Campinas University UNICAMP, Brazil. She practices and conduct research in Pediatric Rheumatology with special interest on neuropsychiatric lupus, central nervous system imaging in autoimmune diseases caring for adolescents in transition to adult clinic. She is a member of the Executive Board of São Paulo Rheumatology Society. She mentored residents in rheumatology and pediatric rheumatology and PhD postgraduates students.

LECTURE ABSTRACTS

pGALS - Paediatric Gait Arms Legs and Spine: a simple examination of the musculoskeletal system

Helen Foster, UK

A description and demonstration of a simple and effective approach to joint examination using the principles of 'look, feel, move, function'. The history alone may not identify joint involvement and use of pGALS is an effective starting point to assess joints and help direct where to perform a more detailed joint examination (pREMS). Course attendees are encouraged to look at the Paediatric Musculoskeletal Matters website – a free online resource with demonstrations of pGALS, pREMS and a lot more ! Www.pmmonline.org. My session will include examples of joint examination in different clinical contexts and consider the approaches to differential diagnosis.



The pathogenesis of Juvenile Idiopathic Arthritis

NM Wulffraat and B Prakken, UMC Utrecht, the Netherlands.

The pathogenesis of Juvenile Idiopathic Arthritis is by definition unknown. The search for many biomarkers predicting onset, course or severity reflects our current thinking about this disorder. The nomenclature of the JIA subtypes is rather phenotypic than based on pathogenesis. All subtypes have chronic inflammation of the synovials tissues in the joints. Much of the research involves the balance of pro- and anti-inflammatory mechanisms. including T cell subsets such as the anti-inflammatory regulatory cells (such as FOXP3-positive regulatory T cells) Tregs, the proinflammatory effector cells (such as T-helper-17 cells), and a long list of cytokines produced by T cells, NK cells and macrophage/monocytes. Especially the studies on cytokine patterns seem to divide these subtypes into 2 major classes, i.e. ANA positive and ANA negative JIA.

An experiment of nature, the IPEX syndrome, shows the importance of Tregs in controlling autoimmunity. Further research has focused restoring this balance by the administration of FOXP3(+) regulatory T cells (Tregs) in the treatment of autoimmune disease. Interestingly Treg function (obtained from peripheral blood as well as the inflamed joints) in patients with JIA proved to be functional normal, despite the ongoing inflammation. The T effector cells from these patients seem resistant to suppression due to an enhanced activation of protein kinase B /c-akt pathway. Inhibition of this kinase restored responsiveness to suppression by Tregs. In addition epigenetic control of a hypomethylated region within the FOXP3 gene, is essential for stable FOXP3 expression and thus function of T regs.

The exact pathophysiology of systemic JIA (ANA negative by definition) involves the innate immune system. Profound dysregulation of innate pro- and anti-inflammatory cytokines, and rapid clinical response to cytokine blocking strategies in sJIA patients suggest impaired control mechanisms in innate immune cells contributing to sJIA pathogenesis. Endogenous TLR ligands, such as S100 protein complexes, enhance the pro-inflammatory phenotype. The research groups from Roth and Foell in Munster, Germany have provided us with assays measuring MRP/S100A12 capable of binding TLR4. Although this indicates an involvement of the inflammasome, no definite mutations in the genes involved in the inflammasome are found in SJIA, unlike the clinically related periodic fever syndromes.

Associations with polymorphisms in cytokine genes and their receptors suggest a genetic component. MicroRNAs (miRNAs) are non-coding RNAs that regulate gene expression of targeted mRNAs are found to correlate with ESR and matrix metalloproteinase-3, both in poly JIA and SJIA. Also, polymorphisms in the protein tyrosine phosphatase gene PTPN22 and STAT4 gene may be associated with the onset of JIA.

Ref :

Fan ZD. STAT4 rs7574865 G/T and PTPN22 rs2488457 G/C polymorphisms influence the risk of developing juvenile idiopathic arthritis in Han Chinese patients. Plos One 2015 Mar 17;10(3):e0117389. doi: 10.1371/journal.pone.0117389. eCollection 2015.

Joint involvement in hematological diseases and cancer

Jorge Lopez Benitez, Paraguay

Rheumatic manifestations of immunodeficiency

Oscar Porras, Costa Rica

The clinical manifestations of primary immunodeficiencies (PID) are associated with infection, autoimmune diseases (AID) and malignancy. The identification of a mutation in a gene that explains a PID, which is associated with symptoms and signs of autoimmunity, may allow to understand the pathophysiology of complex AID with similar clinical characteristics.

The patient with an AID must include an assessment for an associated PID. The onset of autoimmunity in IDP is explained by the concept of natural tolerance as a result of negative selection, which is paradoxical, because the disruption of the normal function of the immune system (needed to develop autoimmunity) leads to the production of autoimmunity.

The study of immune dysregulation, which occurs in PIDs, helps to identify immunologic mechanisms that are part of an AID. For example, mutations in the FOXP3 gene of the Immunedysregulation-Polyendocrinopathy-Enteropathy-X-linked syndrome (IPEX) have identified the importance of regulatory T cells in the generation of natural tolerance. Therefore, the presence of an AID associated with a PID is best explained by a lack of mechanisms that normally exist in the immune system (IS) to regulate autoreactivity. Other examples are the studies of inflammation mechanisms associated with genetic regulation, that have been done in monogenic autoinflammatory diseases, and the association between systemic lupus erythematosus and complement defects.

The spectrum of autoimmune manifestations (AIM) in PIDs is very broad. Ranges from the presence of an organ-specific AID, such as type 1 diabetes, hypothyroidism or cytopenias, to cytokine responses associated with syndromes that produce severe inflammation and inflammatory processes affecting liver, kidney, skin, digestive tract and central nervous system. Some AIM onset during the neonatal period, as is the case in those associated with IPEX, Omenn syndrome and NOMID. Others onset during infancy and childhood as in APECED, ALPS, C1q deficiency, HLH, DIRA, selective IgA deficiency (IGAD), chronic granulomatous disease and Wiskott-Aldrich syndrome. In some cases it occurs during adolescence and adulthood as in the Common Variable immunodeficiency (CVID) and selective IgA deficiency (IgAD).

A 25% prevalence of AIM in PID has been reported. However in some PID, autoimmune symptoms occur in all patients. Homozygous C2 Deficiency and SLE are associated in 10% of

cases. In ALPS, 50-70% of cases present AIM (autoimmune haemolytic anemia 29-38%, idiopathic thrombocytopenic purpura 23-43%, autoimmune neutropenia 29-38%). In 22-48% of CVID patients (mainly cytopenias, CVID with granulomas is associated with 50% AIM), in 25% of cases of HIGM with syndrome induced defect in the activation cytidine deaminase (AID) and in 40-72% of patients with Wiskott-Aldrich syndrome. In 57 symptomatic IgAD patients, AIM were documented in 29.8% of them (thyroiditis, vitiligo, hemolytic anemia). In cases with IgAD, a 34% frequency of IgM antibodies to native human collagen have been reported. A study of 72 cases with Juvenile Systemic Lupus Erythematosus showed a PID frequency of 22%, with complements defects and defects of immunoglobulins production in 6 and 10 cases, respectively.

Some IDPs have been associated with a low frequency of AIM (<10%). This is the case of deficiencies of C3, C5-9, Chronic Granulomatous Disease, Asplenia, Deletion Syndrome 22q11 with DiGeorge sequence (5-10%, ITP, JIA), MHC deficiency, factor D deficiency, IRAK-4 deficiency and IL-12 / IL-23, IFN and axis deficiencies.

However PID that compromise T-regulatory cells (IPEX, APECED, OS) lead to autoimmune disease with 100% penetrance. Congenital defects of the cell B and immunoglobulin production has a lower frequency of AIM.

It is important to consider the possibility of an associated immunodeficiency during the assessment of children with AIM (autoimmune cytopenias, organ-specific autoimmune diseases and chronic arthritis). In a study of 131 registered PID, arthritis was present as an initial symptom in 6.1% of them. It is important to search for CVID in adults with AIM, because a high prevalence (36-50%) of autoimmunity has been reported.

Ref :

Carneiro-Sampaio M, Coutinho A. Early-onset autoimmune disease as a manifestation of primary immunodeficiency. Front Immunol 2015; 6: 185: 1-7.

Bussone G, Mouthon L. Autoimmune manifestations in primary immune deficiencies. Autoimmun Rev 2009; 8: 332-336.

Seidel MG. Autoimmune and other cytopenias in primary immunodeficiencies: pathomechanisms, novel differential diagnoses, and treatment. Blood 2014; 124: 2337-2344.

Notarangelo LD. Primary immunodeficiencies (PIDs) presenting with cytopenias. Hematology Am Soc Hematol Educ Program 2009; 139-143

Verbsky JW, Routes JM. Management of autoimmunity and inflammation. In: Sullivan KE, Stiehm ER (eds): Stiehm´s immune deficiencies. Elsevier 2014, pp 931-942.

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Arason GJ, Jorgensen GH, Ludviksson BR. Primary immunodeficiency and autoimmunity: lessons from human diseases. Scan J Immunol 2010; 71: 317-328.

Jesus AA, Liphaus BL, Silva CA, et al. Complement and antibody primary immunodeficiency in juvenile systemic lupus erythematosus patients. Lupus 2011; 20: 1275-1284.

Ehlayel MS, Bener A, Abu Laban M. Primary immunodeficiency diseases in children: 15 year experience in tertiary care medical center in Qatar. J Clin Immunol 2013; 33: 317-324.

Joint involvement in orthopedic diseases

Carmen De Cunto, Argentina

Joint pain of non inflammatory origin is quite common in children and adolescents, and a frequent cause of referral to pediatric rheumatologists and orthopedic surgeons.Many of the orthopedic conditions associated with joint pain are related to mechanical causes, nevertheless, in same cases, as in osteochondritis , vascular supply mechanisms can be involved. The objective of the presentation will focus on the clinical features, the need of imaging assessment and therapy of different syndromes of joint pain. These will encompass joint pain associated with hypermobility, benign limb pain, common overuse injuries, osteochondritis and obesity.

Rheumatic manifestations of Inflammatory bowel disease (IBD) and psoriasis

Oscar Porras, Costa Rica

Inflammatory bowel disease (IBD) is a chronic inflammation disorder of unknown etiology. It consists of two different diseases: Crohn disease (CD)and ulcerative colitis (UC). An increase in the frequency of children with IBD has been reported. A study in Ontario showed an increase in incidence from 9.5 to 11.4/100 000 during a period of 10 years. The annual incidence reported for CD and UC is 0.2-8.5 and 0.5-4.3 cases/100 000, respectively.

Arthritis is the most common extraintestinal manifestation in IBD. Two patterns of joint inflammation have been described: peripheral polyarthritis (PA) and sacroiliac joints arthritis (SI). Children with IBD have a reported frequency, at presentation, of arthritis and artralgia of 7-12% and 7%, respectively. Other studies showed arthropathy in IBD with a frequency of 7-21%, with arthritis found in 9% in children with UC and 15.5% in CD. Artralgia is more frequent, with 32% and 22% of the cases in UC and CD, respectively. Other musculoskeletal symptoms reported are myalgia, skeletal pain and hypertrophic osteoarthropathy. Age at onset and sex are not different in children with and without arthropathy and IBD. SI arthritis is 30 times more frequent in patients with IBD than in people without IBD. HLA-B27 is frequently positive in children with IBD and SI arthritis, but it is not in cases with PA.

PA is the most frequent pattern of joint inflammation in IBD, ocurring mainly in ankles and knees. The involvement of small and temporomandibular joints is less frequent. Acute peripheral arthritis occurs in brief episodes of 1-2 weeks and are recurrent, they may be longer if the gastrointestinal (GI) disease is active. The SI arthritis is less related to GI activity and is usually characterized by pain and stiffness in the lower back, buttocks or thighs.

Erythema nodosum and pyoderma gangrenosum are skin complications associated with IBD. Vasculitis and Takayazu´s arteritis have been reported in children with IBD.

Uveitis is found accompanying IBD, it is usually bilateral, posterior and chronic. Uveitis is frequently complicated with cataract, glaucoma and cystoid macular edema of posterior synechiae. Other ocular manifestations are episcleritis and scleritis.

Very-early-onset IBD has been reported recently in children with gene mutations affecting IL-10 receptor, most of them developing symptoms within 1 year of age, but with no musculoskeletal symptoms.

Psoriasis is a papulosquamous skin disease that affects 1-3% of the population and represents 4% of the skin diseases in people aged less than 16 years of age. The term juvenile psoriatic arthritis (JPA) applies to the occurrence of arthritis before the age of 16 years associated with psoriasis. Classification criteria for JSA include arthritis, psoriasis, family history of psoriasis, dactylitis and nail pitting.

In patients with psoriasis, 20-30% are reported with arthritis. JPA represents 2-15% of children with chronic arthritis. The age of onset is bimodal, with a peak during preschool years and a second peak around 10 years. Psoriasis begins after arthritis in most of the affected children. Simultaneous onset is reported in less than 10% of the cases. It is more frequent in girls than in boys.

Arthritis usually begins in an oligoarticular form, symmetrical polyarthritis is rare at onset. Patients with JSA present more frequently small joint inflammation. The arthritis is asymmetrical, the most frequent affected joint is the knee, as well as small joints of the hands and feet. Interphalangeal joint arthritis is present in 29% of the cases and dactylitis in 49% of affected children. Asymptomatic anterior uveitis is diagnosed in 15-20% of patients.

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Osteoporosis

Sheila Knupp Feitosa de Oliveira, Brazil

The high morbidity of osteoporosis (OP) in adults has its roots in childhood. Pediatricians are responsible for prevention and should be aware of two important factors: the formation of peak bone mass (PBM) in the first two decades of life and the rate of bone loss that occurs later.

The purpose of this presentation will focus on preventive measures for osteoporosis in healthy children and how to identify and treat osteoporosis in pediatric patients.

The best preventive measures for osteoporosis should be early, started in the first decades of life, when the factors favoring formation of peak bone mass (PMB) are superior to the adverse factors that lead to bone loss.

Primary osteoporosis is rare in children. Secondary osteoporosis is much more common and arises as a complication of chronic diseases (rheumatic, endocrine, gastrointestinal, neoplastic, neurological and psychiatric) or its treatment, mainly glucocorticosteroids. The densitometry by DXA is considered the gold standard method for diagnosing low bone mass and evaluating therapeutic response. The control of the underlying disease is the most important part of treatment but sometimes medications as bisphosphonates are necessary.

Complex regional pain syndrome, and related entities

Jorge Lopez Benitez, Paraguay

Juvenile Idiopathic Arthritis (JIA): general clinical aspects.

Alberto Martini, Italy

Treatment in JIA

Helen Foster, UK

The outcome for children with JIA has improved radically with the emergence of new therapies and a more aggressive and proactive approach to management. My session will include an overview of the treatment options, their use in clinical practice and examples of recommendations for their use in different subtypes of JIA. Course attendees are encouraged to look at the Paediatric Musculoskeletal Matters website – a free online resource with information about JIA and treatment options and a lot more ! Www.pmmonline.org

Complications of JIA

Carine H Wouters, Belgium

Chronic uveitis (iridocyclitis) is an important, insidious and potentially sight-threatening complication of juvenile idiopathic oligoarthritis and polyarthritis. It is usually asymptomatic initially, effective screening is therefore essential to detect early disease and start treatment before the development of disabling consequences such as cataracts, glaucoma, and cystoid macular edema. In this presentation, the risk factors for uveitis, as well as for uveitis complications will be reviewed. A proposal for clinical assessment and follow-up, as well as outcomes for therapeutic trials will be discussed. Finally current therapeutic guidelines including treatment with biologics will be mentioned.

Macrophage activation syndrome is a stormy and potentially life-threatening complications of systemic juvenile idiopathic arthritis. The excessive activation and expansion of T cells and macrophages causes a hyperinflammatory state associated with a cytokine storm, cytopenias (as a consequence of hemophagocytosis), liver dysfunction and coagulopathy. MAS is associated with extreme hyperferritinemia and patients often manifest features of central nervous system dysfunction. In this presentation, the clinical and laboratory manifestations and diagnostic approach of MAS will be reviewed. Some pathophysiological aspects will be mentioned briefly, and current therapeutic approach will be discussed.

Juvenile Spondyloarthropathies

Arturo Borzutzky, Chile

The new term axial spondyloarthritis comprises both patients with early inflammation in the sacroiliac joints and patients with only radiographic evidence of sacroileitis. Active inflammation of subchondral bone marrow shown by MRI plays an important role for early diagnosis. HLA B27 is the strongest known pathogenic factor . Symptoms are present predominantly in the pelvis and spine , but extra-spinal manifestations are frequent . Besides regular physiotherapy there are only two types of drugs which have been proved to be effective. Non steroidal anti-inflammatory drugs and TNF blockers. Recommendation for the treatment of ankylosing spondylitis and axial spondyloarthropathies with anti-TNF have been developed.

Childhood Systemic Lupus Erythematosus and Neonatal Lupus

Paul A Brogan, UK

SLE is a multisystem autoimmune disorder characterized by widespread inflammation and organ damage. Approximately 15 to 20% of patients present before the age of 18 years, referred to as juvenile onset SLE (JSLE). The incidence of JSLE ranges from 0.36 to 0.8 /100,000 although this is probably an underestimate. JSLE is rare under the age of 5, and if it occurs should prompt consideration of monogenic disease, particularly in consanguineous families. Children are generally considered to have more severe disease onset than adults, with an overall more aggressive clinical course. In particular there is an increased incidence of renal, neurological, and haematological disease in the young. The incidence is higher in Black, Hispanic, and Asian children. The cause of SLE is unknown, although it is likely that there are genetic and environmental factors that result in immune dysfunction. Monogenic forms of the disease represent a minority of cases, although new genetic causes have recently been discovered. Regarding pathogenesis, a central theme is the production of autoantibodies that form immune complexes that activate dendritic cells to produce interferon-alpha, which further induces differentiation of B cells into antibody secreting plasma cells, thus perpetuating autoantibody production and immune complex production. B-cells further secrete cytokines and chemokines that enhance the inflammatory cascade. Impaired clearance of apoptotic cells may lead to increased presentation of nuclear antigens by dendritic cells to T cells. Other abnormalities of monocytes, NK cells, cytokines, and immunoglobulins are also identified. Important environmental triggers include ultraviolet light, viruses, hormones, and certain drugs. General principles of management include full engagement by a multidisciplinary team with experience in the various organ manifestations of SLE. Early and aggressive therapy is important to secure improved outcome. Late sequelae such as atherosclerosis, osteoporosis, neurocognitive impairment, and potentially increased risk of malignancy should be considered. There is scarce high quality data regarding the management of JSLE. Much of the evidence therefore comes from trials in adults. Corticosteroids, hydroxychloroquine, and increasingly mycophenolate mofetil (MMF) play an important role. MMF has largely replaced cyclophosphamide as the primary induction agent for JSLE. Biologic therapies such as rituximab are probably beneficial, although clinical trial data are thus far disappointing. Other

B-cell depleting therapies are increasingly available. These include ocrelizumab, belimumab, epratuzumab, and atacicept. Neonatal lupus syndrome is an autoimmune disease associated with transplacental passage of maternal autoantibodies to SSA/Ro and SSB/La antigens. The risk of an infant developing neonatal lupus in a positive mother is 2%; the risk to subsequent pregnancies is approximately 25%. Skin, cardiac, hepatic and haematological manifestations are the main features. Skin, hepatic, and haematological manifestations tend to resolve spontaneously as maternal autoantibodies disappear from the infant circulation. Complete heart block and cardiomyopathy can be life-threatening. Affected infants may be at increased risk of subsequent autoimmune disease.

Antiphospholipid antibody syndrome

Sheila Knupp Feitosa de Oliveira, Brazil

Antiphospholipid syndrome (APS) is a multisystem autoimmune disease characterized by vascular thromboses and/or pregnancy loss associated with persistently positive antiphospholipid antibodies. There is no validated classification criteria for diagnosing pediatric APS. The criteria used in adults have been adapted for pediatric population by excluding pregnancy morbidity as one of the clinical criteria. The presence of some common clinical and laboratorial manifestations not included as criteria may suggest the diagnosis in children.

The prevalence of pediatric APS is low. It may occur as: an isolated clinical entity (primary APS); in association with an underlying systemic disease, particularly systemic lupus erythematosus (secondary APS); or a very rare type of APS diagnosed in infants born to mothers with aPL - the neonatal APS.

It is important to know that clinical manifestations related to aPL positivity represent a spectrum: aPL positivity without clinical events, aPL positivity with nonthrombotic manifestations, APS with vascular thrombosis and, catastrophic APS.

If the patient had a thrombotic event, he should be treated acutely with heparin, followed by long-term anticoagulation as warfarin help to prevent new episodes. Hydroxychloroquine appears protective and may be considered a treatment option in patients with APS associated with SLE. In pediatric catastrophic APS (CAPS), anticoagulation and treatment with corticosteroids, plasma exchange, intravenous immunoglobulins, cyclophosphamide and rituximab have been reported.

Juvenile Dermatomyositis

Carmen De Cunto, Argentina

The juvenile idiopathic inflammatory myopathies are systemic autoimmune diseases characterized by skeletal muscle weakness, characteristic rashes, and other systemic features. Over the past years there has been considerable work that has contributed to a better understanding about the classification, clinical characteristics, diagnostic workup, outcome measurements, and therapy.

The objectives of this presentation are:

- to describe the different clinical phenotypes of idiopathic inflammatory myopathies in children, initial features, autoantibody profiles, prognostic factors, long term outcome, and update treatment guidelines.
- to discuss developments in the assessment of activity and damage in juvenile dermatomyositis, including definitions of improvement and inactive disease.
- to present an update on new therapies, and results of recent controlled drug trials.

The international registries have allowed to better understand the long term and prognostic factors of children with dermatomyositis in different populations, and highlighted the need for new treatment strategies to control disease activity over time, and to reduce damage.

Small vessel vasculitis

Paul A Brogan, UK

The paediatric small vessel vasculitides reviewed in this presentation are Henoch Schönlein purpura (HSP), and the ANCA associated vasculitides (AAV). New classification criteria for HSP and granulomatosis with polyangiitis (GPA, formerly Wegener's granulomatosis) are now validated and have facilitated the conduct of clinical trials in children. In acknowledgement of the important role of IgA in the pathogenesis of HSP, this entity is now referred to as IgA vasculitis in the most recent interation of the Chapel Hill vasculitis definitions (2012). Significant advances have been made in understanding the pathogenesis of AAV, particularly in relation to genome wide association studies and the role of HLA associations that determine ANCA generation. The clinical manifestations of small vessel vasculitis in children are described, and current approaches to treatment discussed. There is a lack of good clinical trial data on which to base therapy for HSP. Similarly, data based on randomized controlled trials (RCTs) for paediatric AAV are lacking, although children with AAV are for the first time now included in a soon to be published randomised controlled trial of mycophenolate mofetil versus cyclophosphamide for induction of remission (the "MYCYC" trial); and there is an ongoing open label trial of rituximab for paediatric AAV, currently still recruiting patients (the "PEPRS" trial). Significant challenges remain in the field of paediatric small vessel vasculitis, including development of validated disease outcome measures and biomarkers to be used in clinical trials. Lastly, long term outcome data are lacking in survivors of paediatric small vessel vasculitis, particularly in relation to late sequelae such as cancer, infertility and cardiovascular disease.

Medium and large vessels vasculitis

Arturo Borzutzky, Chile

Predominantly medium-sized vessel vascultis includes Childhood polyarteritis nodosa (PAN), Cutaneous Polyarteritis and Kawasaki disease with the common feature of necrotizing vasculitis associated with aneurysmal nodules along the walls of medium sized muscular arteries. PAN presents with skin nodules, myalgia or muscle tenderness, hypertension, renal involvement and peripheral neuropathy. The mechanism of vascular inflammation most often implicate is mediated by immunecomplex deposition. Infections (hepatitis B, parvovirus B19, cytomegalovirus and HIV) have been implicated.

Cutaneous polyarteritis nodosa is a form of vasculitis affecting small and medium –sized vessels limited to the skin. It is characterized by fever, sub-cutaneous nodules, purpuric lesions and livedo reticularis in lower extremities with little systemic involvement apart from arthritis an arthralgia. Clinical relapsing-remitting course may persist for years.

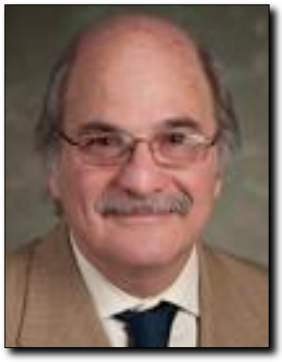
Kawasaki disease is an acute self-limited systemic vasculitis predominantly affecting young children with coronary artery predominant involvement. It is of worldwide distribution with male predominance and ethnic bias towards East Asian children occurring in occasional epidemics. It is the second most common vasculitis of childhood and the principal symptom is persistent fever , skin rash and mucosal changes. Criteria combining fever, rash, extremity signs, lip cracking and conjunctivitis have been established along other systemic manifestations like GI tract and urinary tract involvement as well as erythema of BCG inoculation sign. Routine 2-dimensional echocardiogram is the mean to identify coronary artery dilatation and aneurysma. And intravenous immunoglobulin is the main treatment in combination to salycilates.

Predominantly large-vessel vasculitis includes Takayasu arteritis involving aorta and main branches with the following angiographic abnormalities, pulse deficit or claudication, discrepancy in four-limb blood pressure measurements, bruits, hypertension, acute –phase response. An initial florid inflammatory vascultis phase is followed by a later fibrotic phase of the disease and progressive stenotic disease may be consequence of low grade inflammation along the years. Treatment usually involves steroid an cyclophosphamide for induction followed by methotrexate for maintenance treatment. Anti-TNF may be beneficial and anti-IL6 blockage in refractory cases.

Juvenile Scleroderma

Carine H Wouters, Belgium

Juvenile scleroderma encompasses both systemic sclerosis (SSc) characterized by skin, vascular and visceral organ fibrosis and localized scleroderma (LS) characterized by fibrosis of skin and underlying tissue. In recent years, specific classification criteria for juvenile systemic sclerosis and juvenile localized scleroderma have been developed, and will be discussed. Progress made in the assessment of juvenile scleroderma will be presented. Assessment of skin involvement, the main target organ of both jSSc and JLS, can be done using the modified Rodnan skin score, as well as using a recently described Localized Scleroderma Cutaneous Assessment Tool which is a composite index evaluating both skin disease activity and damage. A preliminary disease severity score for juvenile systemic sclerosis addressing skin, vascular and internal organ components will be mentioned as well. Current therapeutic approaches and supportive measures and some recent data on outcome will be briefly reviewed.



Monogenic auto-inflammatory diseases (MAD)

Carlos Daniel Rosé, USA

This group of diseases characterized by a spontaneous inflammatory phenotype and resulting mostly from mutations in innate immunity genes is one of the most interesting developments in pediatric rheumatology for the last 20 years. Although the approximately thirty diseases in this group are rare, the “lessons learned” from deciphering their mechanisms are leading to both effective targeted therapies and hypothesis generation applicable to the study of more common non-Mendelian diseases. Because of the large number of MADs the lecture will be focused on the basic principles guiding the clinician on when to suspect and how to plan the diagnostic work up. A practical approach to diagnosis and on how to select the candidates for genetic testing will be presented as well. Finally, an effort to classify them into broad phenotypic groups and by pathogenic mechanisms will be the main thrusts of the lecture.

Immunisation in children with rheumatic diseases

NM Wulffraat, N. Groot and M.W.Heijstek UMC Utrecht, Netherlands

Children with paediatric rheumatic diseases (PRD) have an increased risk of infection, which contributes to the mortality and morbidity of their disease. Effective and safe vaccination is key. Assessing efficacy of a vaccine in patients with PRDs is challenging. The ideal measure of efficacy, infection rates, is usually not studied as a primary endpoint because this requires large sample sizes. Surrogate measures such as immunogenicity are commonly used instead. Immunogenicity refers to the immune response induced by vaccination. This is usually measured by vaccine-specific geometric mean antibody titers (GMT) or concentrations (GMC), seroconversion rates and/or seroprotection rates. The measure for immunogenicity differs per vaccine, as the relation between the humoral and/or cellular immune response and protection differs per pathogen. Immunogenicity of a vaccine in patients with rheumatic diseases can differ from the healthy population, due to the disease or its immunosuppressive treatment. Besides short-term vaccine-induced immune responses, *persistence* of protective immunologic memory after vaccination is essential in preventing infections. Long-term effectiveness of most vaccines is unknown.The safety of vaccines in PRD can be addressed on different levels: adverse event rate in comparison to healthy controls, increased disease activity induced by vaccination and unintentional infections induced by live-attenuated pathogens in vaccines, especially in patients on immunosuppressive drugs. Another issue of vaccine safety is whether vaccines or their constituents can actually cause autoimmune disease (AID), which will be addressed briefly.Over the years, awareness of infection prevention by vaccination in rheumatic diseases has increased. Recently EULAR and Brazilian Society of Rheumatology published evidence-based recommendations regarding vaccination of adults and children with rheumatic diseases.Recent studies focus on safety and efficacy of the HPV vaccine. After initial studies in JIA, now a multicenter study in the Netherlands and Brasil is ongoing on the immunogenicity of the HPV vaccine in female adolescents with SLE.

Imaging in juvenile idiopathic arthritis

Angelo Ravelli, Italy

Until the past few years, most of the experience on joint imaging in JIA was based on conventional radiography. However, plain radiographs have poor sensitivity for the detection of active arthritis and rarely show erosive changes to the joint until late in the disease course. In the last decade, the interest in musculoskeletal ultrasonography and MRI has grown sharply. These newer imaging modalities enable better and earlier assessment of synovial, cartilage and bone abnormalities than conventional radiography. When dealing with imaging in JIA, it is important to emphasize that evaluation of children's joints is challenging owing to the unique features of the growing skeleton, which include age-related variations in the thickness of the articular cartilage and incomplete ossification. Furthermore, children with chronic arthritis can develop distinctive abnormalities, such as disturbance of bone growth and maturation. These issues make it difficult to reliably assess joint changes in pediatric patients without the availability of normal standards for comparison. Although conventional radiography is often regarded as an old-fashioned technique, it remains the gold standard for the demonstration of structural damage to joints in patients with chronic arthritis. Furthermore, plain radiographs remain best suited to visualize particular bone abnormalities seen in children with JIA, such as growth and maturation disturbances.

MRI is the only imaging tool that has the ability to simultaneously assess all relevant structures in inflammatory joint diseases. Moreover, it is superior to other methods in assessing disease activity in the temporomandibular, hip, sacroiliac and vertebral joints. The main advantage of MRI over conventional radiography is that it enables direct visualization and assessment of synovitis. Periarticular bone marrow edema seen on MRI images has been shown to be a key predictor of erosive joint damage and functional impairment in adults with RA. However, no information exists on its prognostic value in JIA. Advancement in imaging technologies and computer science permits the detection of molecular changes in the composition of cartilage matrix. MRI was found to detect twice as many joint erosions as conventional radiography and ultrasonography in patients with JIA who had wrist disease. These findings were challenged, however, by the finding in healthy children who underwent an MRI of the wrist that bony depressions mimicking joint erosions were present in all individuals and increased with age.

Ultrasonography has several advantages over other imaging modalities, including noninvasiveness, rapidity of performance, relatively low cost, ability to scan multiple joints at one time, repeatability, safety and high acceptability among patients. However, some challenges with itsuse do exist: it is the most operator-dependent imaging technique and its reliable application requires careful and long-lasting training. Ultrasonography is well suited for the diagnosis and assessment of synovitis and related abnormalities. Colour Doppler and power Doppler ultrasonographical techniques are considered superior to grey-scale ultrasonography in identifying active disease. Studies have shown that ultrasonography may be more accurate than clinical evaluation for detecting joint inflammation in children with JIA. Evidence of ongoing synovitis in one or more joints has been documented in a sizable proportion of patients with JIA classified has having inactive disease on clinical grounds. However, the clinical significance and prognostic value of this finding is unclear as the presence of abnormalities on ultrasonography, including power Doppler signal, did not predict subsequent synovitis flare. The capacity to assess joints dynamically, and in real time, in several focal planes makes ultrasonography a powerful tool to capture bone erosions. However, assessment of erosive changes in growing children is challenging as physiological irregularities in recently ossified bones can be misinterpreted as cortical erosions. Owing to its capacity to precisely identify inflammed areas, ultrasonography can guide intra-articular corticosteroid injections.

Assessment of disease activity and damage in pediatric rheumatic diseases

Angelo Ravelli

A vast array of instruments are available for measuring disease activity in juvenile idiopathic arthritis (JIA), including global rating scales, pain measures, joint counts, physical function questionnaires, acute phase reactants, and even more general measures, such as hemoglobin level, white blood cell count, platelet count, serum immunoglobulin level, body weight, and need for increasing medications. However, due to the high variability in the clinical presentation and course of JIA, no single measure can reliably capture disease activity in all patients. On the other hand, assessment of all measures individually may cause methodological and statistical problems, especially when these measures are employed as endpoints in clinical trials. Several approaches can be followed to achieve a more rational and standardized evaluation. One of these approaches is based on the so-called composite disease activity scores, which are made of a pool of individual measures and are aimed to quantify the absolute level of disease activity by providing one summary number on a continuous scale. These measures have the potential advantages of creating better consistency in disease activity evaluation across physicians, of allowing patients to better understand the meaning of disease activity by providing a single number, and of reducing the sample size requirement in clinical trials. Composite disease activity scores can be used in the assessment of therapeutic efficacy in clinical trials and in monitoring disease activity in individual patients in standard clinical practice. Recently, the first composite disease activity score for JIA, named Juvenile Arthritis Disease Activity Score (JADAS), has been developed. In validation analyses, it was found to have good metric properties, including the ability to predict the disease outcome. The cutoff values of the JADAS that corresponded with the states of inactive disease and minimal disease activity, or reflected the physician's, parent's or child's subjective rating of remission or the parent's or child's satisfaction with the outcome of the illness were established recently. These cutoffs represent an additional clinical tool that, if applied regularly in daily practice, may allow tighter control of therapy, support the optimization of treatment on an individual patient basis, and help prevent the development of joint damage and physical disability. Recently, a JADAS version with CRP instead of ESR and another version lacking an acute phase reactant (so-called clinical JADAS, cJADAS) were tested. The latter version is more feasible in everyday

clinical practice, because the physician does not need to wait for the results of laboratory tests to compute the score. Systemic lupus erythematosus (SLE) is a multisystem disease that may virtually affect all organ and systems. Although juvenile dermatomyositis (JDM) affects primarily the muscles and the skin, it may also involve the gastrointestinal tract, lungs and central nervous system. Any disease activity tool used in these diseases must, therefore, evaluate all organs/systems that can be affected by the illness. The most common global measures of disease activity used in SLE are the SLE Disease Activity Index (SLEDAI), the British Isles Lupus Assessment Group (BILAG), the Systemic Lupus Activity Measure (SLAM) and the European Consensus Lupus Activity Measurement (ECLAM). All indices are valid, reliable and comparable. Although their validation has been carried out in adult lupus settings, they are suitable for use in juvenile SLE. Recent revisions have been proposed that emphasize ongoing disease, not just new or recurrent activity (SELENA-SLEDAI and SLEDAI 2001). Two global disease activity assessment tools for JDM are currently available. The Juvenile Dermatomyositis Disease Activity Score (DAS) assesses the extent and distribution of cutaneous involvement, muscle weakness, functional status and vasculopathic manifestations. It yields a score from 0 to 20. The Myositis Disease Activity Assessment Tool combines two approaches: a series of visual analogue scales (VASs) that detect disease activity in each organ system (the Myositis Disease Activity Assessment Visual Analogue Scales) and a Myositis Intention to Treat Activity Index, which captures the intention-to-treat manifestations of active disease in several organ systems: constitutional, articular, cardiac, pulmonary, gastrointestinal, cutaneous and skeletal muscle.

JIA is characterized by prolonged synovial inflammation that may lead to permanent alterations in joint structures. Permanent changes may also develop in extra-articular organ/systems or result from side effects of medications. In order to provide a clinical measure that reflects the overall biological outcome of JIA, a clinical damage index, the Juvenile Arthritis Damage Index (JADI), was devised. This tool is comprises two parts: one devoted to the assessment of articular damage (JADI-A) and the other devoted to the assessment of extra-articular damage (JADI-E). In the JADI-A, 36 joints or joint groups are assessed for the presence of damage and the damage observed in each joint is scored on a three-point scale (0 = no damage; 1 = partial damage; 2 = severe damage, ankylosis, or prosthesis). The maximum total score is 72. The JADI-E includes 13 items in five different organ/systems. Each item is scored as 0 or 1 if damage is absent or present, respectively. Due to the relevant impact of ocular damage on the child's health, in each eye a score of 2 is given in case the patient has had ocular surgery and a score of 3 in case the patient has developed

legal blindness. The maximum total score is 17. The JADI was found to be feasible and to possess both face and content validities; furthermore, it exhibited good convergent construct validity, excellent reliability and strong discriminative validity in a large cohort of JIA patients with long-standing disease. In the past 10 years, there has been considerable interest in the development of appropriate instruments for measuring cumulative organ damage in patients with SLE. This effort has led to the development of the Systemic Lupus International Collaborative Clinics/American College of Rheumatology Damage Index (SLICC/ACR-DI). The SLICC/ACR-DI (SDI) measures the accumulated damage that has occurred since the onset of SLE, resulting from either the disease process or its treatment. Damage is defined as an irreversible change in an organ or system that has been present for at least 6 months. SDI records damage in 12 organ or systems and has a score range of 0 to 47. Although the SDI has been shown to be a valid and reliable instrument in patients with JSLE, it does not cover all forms of damage that children or adolescent with lupus may develop over time, particularly effects on growth and development. Furthermore, it does not incorporate the ability of children to recover and regenerate to a greater degree than adults. For these reasons, a modified (pediatric) version of the SDI, which includes assessment of growth retardation and pubertal delay and takes into account the potential reversibility of some damage items in children, has been proposed. A clinical instrument aimed at assessing damage in idiopathic inflammatory myopathies, named the Myositis Damage Index, has been developed. It assesses the extent of damage in several organ systems and includes a series of visual analog scale to quantify damage in each system. Organ systems assessed include muscle, skeletal, cutaneous, gastrointestinal, pulmonary, cardiac, peripheral vascular, endocrine, ocular, infectious, malignancy and others. Unlike the original SDI, the Myositis Damage Index includes estimation of linear growth and pubertal development.

Transitional care for adolescents

Simone Appenzeller, Brazil

Transition from pediatric to adult care is essential in adolescents with chronic rheumatic disease. Age at which transition occurs varies according to different services and ranges between 15-24 years. Previous studies have identified a significant gap in transition and around 75% of patients loose adequate follow-up. Identifying the reasons for this gap will increase adequate transition and maintain disease remission. In addition, adolescents have to be addressed regarding contraception and sexual transmitted diseases. An unplanned pregnancy with teratogenic medications could have negative impact in the adolescent development. Other issues that have to be addressed are vocational issues, university, health care during city/country changes, and work. We will discuss factors implicating in adequate transition and how to improve it.

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