RESÚMENES DE CONFERENCIAS

Autoinflammatory syndromes

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The monogenic autoinflammatory syndromes are conditions caused by mutations of genes coding for proteins that play a pivotal role in the regulation of the inflammatory response. Owing to their genetic nature, most of these disorders have an early onset. Clinically, they are characterized by recurrent flares of systemic inflammation, which present most frequently as sudden episodes of fever associated with increased levels of of acute phase reactants and a number of clinical manifestations, namely rash, serositis, lymphadenopathy and arthritis. Symptom-free intervals are characterized by complete well-being, normal growth and complete normalization of acute phase reactants. Familial Mediterranean fever (FMF), mevalonate-kinase deficiency (MKD) and tumour necrosis factor (TNF) receptor-associated periodic syndrome (TRAPS) are the 3 monogenic disorders comprised under the term periodic fevers, whereas the occurrence of systemic inflammation dominated by a characteristic urticarial rash associated with other clinical manifestations is typical of familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS) and chronic infantile neurological cutaneous and articular syndrome (CINCA). These diseases encompass the clinical spectrum of different mutations of a gene named cold-induced autoinflammatory syndrome 1 (CIAS-1, or NLRP3), coding for a protein called cryopyrin. For this reason, they are also known as cryopyrin-associated periodic syndromes (CAPS). Other conditions that are part of the autoinflammatory syndromes are characterized by typical granulomatous formations. Blau's syndrome (familial juvenile systemic granulomatosis) presents with non-caseating granulomatous inflammation affecting the joint, skin, and uveal tract (the triad of arthritis, dermatitis and uveitis) and is associated with mutations of the NACHT domain of the gene CARD15 (or NOD2).

Juvenile idiopathic arthritis - State of the art

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In recent years, there have been several important advances in the field of juvenile idiopathic arthritis (JIA). Some of the main progresses have taken place in the following 3 areas: 1) outcome measures; 2) macrophage activation syndrome (MAS) in systemic JIA; 3) biologic medications.

A vast array of instruments are available for measuring disease activity in JIA. 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. 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. 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 metrologic 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.

MAS is a serious, potentially life-threatening complication of rheumatic diseases, which is seen most frequently in systemic JIA. It is characterized clinically by unremitting high fever, pancytopenia, hepatosplenomegaly, hepatic dysfunction, encephalopathy, coagulation abnormalities, and sharply increased levels of ferritin. The pathognomonic feature of the syndrome is seen on bone marrow examination, which frequently, though not always, reveals numerous morphologically benign macrophages exhibiting hemophagocytic activity. MAS is overt in 10% of children with sJIA, but occurs subclinically in another 30–40%. Because MAS can follow a rapidly fatal course, prompt recognition of its clinical and laboratory features and immediate therapeutic intervention are imperative. However, it is difficult to distinguish sJIA disease flare, infectious complications or medication side effects from MAS. A multinational collaborative effort aimed at developing diagnostic criteria for MAS in sJIA is under way. The first-line therapy of MAS complicating sJIA is based on the parenteral administration of high doses of corticosteroids, with or without cyclosporine A. There is increasing evidence that biological therapies, particularly interleukin-1 inhibitors, represent a valuable adjunct to corticosteroids and cyclosporine A in treating MAS complicating sJIA.

Recent advances in understanding the pathophysiology of the inflammatory response have led to the development of a new class of medications that are capable of inhibiting selectively the principal mediators of inflammation and tissue damage. The introduction of these new molecules, which are collectively termed biologic agents, has opened a new era in the treatment of JIA. Biologic agents have been designed to target key cytokines implicated in JIA, including tumour necrosis factor (TNF)-α, interleukin (IL)-1 and IL-6 as well as signalling molecules involved in the regulation of B-cell and T-cell responses. The efficacy three anti-TNF agents (etanercept, infliximab, and adalimumab) and of the inhibitor of T-lymphocyte activation abatacept has been shown in the polyarticular form of the disease. Recently, IL-1 inhibitors (anakinra and canakinumab) and anti-IL-6 therapy with tocilizumab have been found to be efficacious in systemic JIA, a disease that responds less well to ant-TNF drugs. Although the experience gained so far has shown that biologic agents are overall safe in children with chronic arthritis, use of these medications in the pediatric population raises questions about risk of infections (particularly opportunistic infections and tuberculosis), response to vaccination, development of autoimmune phenomena and long-term effects on immune surveillance and possible risk of malignancy. Additional data concerning long-term safety of these drugs will be provided by the large-scale pharmacovigilance studies that are underway.

Lupus Eritematoso Sistémico Juvenil

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El Lupus Eritematoso Sistémico se reconoce ampliamente como una enfermedad crónica autoinmune órgano-inespecífica caracterizada por la producción de autoanticuerpos y cuya morbilidad y mortalidad se han reducido notoriamente con el uso de inmunosupresores más selectivos. Se reconoce que en la adolescencia es una enfermedad más heterogénea, más severa, con un curso clínico más agresivo y con recaídas más severas. Por la gran cantidad de cambios (físicos, emocionales, de crecimiento y desarrollo, incluidos los aspectos sexuales) que presenta el paciente en esta etapa de transición hacia la adultez, es necesario poner especial atención en los afectados con Lupus que se encuentren dentro de este grupo etario.

La incidencia y prevalencia de LES varían según la localización geográfica y etnias. Es más frecuente en

poblaciones afroamericanas, asiáticas e hispanas, grupos en los que las expresiones son más severas. La incidencia estimada es de 0,6 caso por 100.000 niños menores de 16 años. Se encuentra una mayor prevalencia en el género femenino, en todos los rangos de edad.

Su etiología es compleja y aún poco comprendida. Generalmente comprende una susceptibilidad genética individual, que regula la respuesta inmunológica normal al antígeno y que en los pacientes con LES estaría alterada.

Desde el punto de vista patogénico, esta enfermedad se caracteriza por la producción de anticuerpos contra los elementos celulares y nucleares propios, siendo el más destacado el anticuerpo antinuclear. El anticuerpo anti DNA doble cadena y anti nucleosomas tienen un rol central en la patogenia de LES. Entre los agentes potencialmente gatillantes de la respuesta anómala de producción de autoanticuerpos se incluyen factores ambientales como infecciones, luz ultravioleta y/o exposición a fármacos. Las alteraciones en el proceso de la apoptosis en conjunto con la defectuosa eliminación de los restos apoptóticos favorecen la exposición de los nucleosomas al sistema inmune, produciéndose un quiebre de la tolerancia por activación linfocitaria, formándose clones autorreactivos que producen anticuerpos antiantígenos nucleares; antihistonas, anti DNA, constituyendo el principal mecanismo de daño tisular al unirse a los antígenos nucleares, de membrana celular y otros como proteínas plasmáticas . Se presenta, entre otros, una respuesta inflamatoria local de daño, es decir, con destrucción tisular local y sistémica, órgano-inespecífica con liberación de citoquinas, como IL-12 e IFN-alfa, entre otras.

En LES Juvenil es importante considerar la forma de inicio de la enfermedad, la diversidad de manifestaciones clínicas basadas en los Criterios Diagnósticos ACR (American College of Rheumatology), evaluar la magnitud de la respuesta inflamatoria asociada, la evolución y el control de la actividad de la enfermedad. Otro aspecto importante a considerar está relacionado con la oportunidad de estudio de órganos y sistemas cuyo compromiso se relaciona con el pronóstico. En el LES infanto-juvenil el compromiso renal en el inicio de la enfermedad es más frecuente que en la población adulta, requiriendo la evaluación conjunta con el mefrólogo para programar la oportunidad de la biopsia renal.

Es fundamental cuantificar los índices de daño acumulado con objeto de otorgar las mejores terapias inmunosupresoras de que se dispone en la actualidad y evitar progresión del daño.

Las terapias inmunosupresoras para LES son cada vez más selectivas, con menos efectos no deseados y/o toxicidad. La elección y el protocolo de uso del inmunosupresor (s) dependerán de la situación en particular, recordando que por la gravedad en las formas infanto-juveniles las dosis de esteroides serán más elevadas y por más tiempo que en el adulto. En el caso de nefritis lúpica grave, el micofenolato mofetilo ha demostrado ser equivalente a ciclofosfamida endovenosa en pulsoterapia para la terapia de inducción, sin riesgos de infertilidad. Además, ha probado su efectividad en la fase de mantención, por lo que se ha propuesto en esta etapa como opción selectiva a la azatioprina. Las terapias inmunosupresoras actuales están siendo más promisorias en las fases de inducción cuando se han utilizado como terapia combinada, permitiendo que el esquema de mantención sea seguro al administrarse durante tres años. Por otra parte, el rituximab es otro fármaco que surge como opción en pacientes que presentan principalmente recaídas o que son refractarios a las terapias habituales. La eficacia de belimumab, que se encuentra en fase de estudio en adultos en LES sin nefritis importante, no ha sido suficientemente demostrada en la forma juvenil.

Se recomienda administrar hidroxicloroquina como inmunomodulador concomitante a la terapia inmunosupresora de base desde el inicio de la fase de inducción terapéutica, debido a que se ha demostrado una disminución en la frecuencia de recaída renal, en insuficiencia renal terminal y en la mortalidad. Este fármaco requiere evaluar periódicamente su posible toxicidad retiniana.

La terapia de apoyo en LES estará dirigida a reducir los factores de riesgo cardiovascular con modificaciones de estilo de vida, evitar la hipertensión arterial, control de proteinuria usando inhibidores de la angiotensina o bloqueadores de receptor de la angiotensina y manejo de dislipidemia en el caso de ser necesario. Otro aspecto importante es la reducción de riesgo de osteoporosis por esteroides con suplementación de calcio, vitamina D y administración de bifosfonatos en caso de ser requeridos. Los estudios de seguimiento han demostrado que el compromiso renal y neurológico continúan siendo relevantes para lograr buena calidad de vida del paciente; sin embargo, no hay que descuidar aspectos de adhesión terapéutica, el manejo oportuno de las infecciones intercurrentes, evaluación e intervención en el ambiente psicosocial y escolar. La elaboración de pautas de trabajo de autoestima y autocuidado responsable en el adolescente es un aspecto importante a considerar en el tratamiento de LES.

Advances and challenges in imaging in juvenile idiopathic arthritis

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Imaging evaluation of joints of children with juvenile idiopathic arthritis (JIA) is challenging, due to the unique features of the growing skeleton. Traditionally, imaging studies in childhood arthritis have been based on conventional radiography. However, in the past few years, interest in the use of MRI and ultrasonography has increased. As a result, imaging has become a main area of clinical and research investigation in pediatric rheumatology. The main progress in the field of conventional radiography has been the development and validation of pediatric scoring systems for the assessment of radiographic progression. Several studies have shown that MRI provides a precise quantification of synovitis in children with JIA. Furthermore, a high frequency of bone marrow edema and bone erosions has been found early in the disease course. However, a sizeable proportion of healthy children were found to have changes resembling bone marrow edema in the carpal bones, identical to those described in patients with JIA. Longitudinal studies are required to establish whether the presence of bone marrow edema predates the development of bone erosions in children with chronic arthritis. Ultrasonography has been proven to be superior to clinical examination in detecting synovitis, tenosynovitis and enthesitis. Furthermore, recent studies have documented the presence of US-detected synovial pathology in children with JIA in clinical remission. However, the clinical significance and prognostic value of this finding is unclear as the pres¬ence of abnormalities on ultrasonography, including power Doppler signal, did not predict subsequent syno¬vitis flare. Guidance to local injection therapy represents an important application of US in routine care. More information from healthy children is needed to enable differentiation of the bone and cartilage abnormalities that reflect damage from those that are part of normal development using MRI or ultrasonography.

New approaches in the diagnosis and treatment of patients with Spondyloarthritis

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The Spondyloarthritides (SpA) are a group of diseases that are comprised by different subtypes, which share similar clinical manifestations and are associated with HLA-B27. Ankylosing spondylitis (AS) represents the prototype of SpA and affects mostly young patients. AS can be diagnosed by using the modified New York criteria but the requirement of advanced signs of radiographic changes in the sacroiliac joints (SIJ), has led to a long diagnostic delay of 5-10 years. In early disease without definite radiographic changes, active SIJ inflammation can be visualized using magnetic resonance imaging (MRI). The overall impression of the published data is that the disease activity of patients with early SpA is similar to those with definite AS. The International Society for Research in AS (ASAS) has published new classification criteria for patients who are suspicious of SpA and might evolve to AS. These criteria are based on the main clinical symptom of chronic low back pain at an age of <45 years and include also sacroiliitis seen on MRI. Furthermore, patients with no imaging suspicion of SpA but with a genetic predisposition (positive for HLA-B27) can also be classified to SpA, if they fulfill further clinical criteria.

Tratamiento de la Osteoporosis: ¿A Quien Tratar? ¿Cómo y Cuándo?

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Cuando planificamos tratar a pacientes con osteoporosis debemos tener claro que no basta con el diagnóstico operacional de osteoporosis según la OMS y que debemos considerar conceptos tales como resistencia ósea, la que depende de la densidad y calidad óseas, esta última influenciada por mecanismos como recambio óseo, mineralización, grado de acumulación de daño y otros factores, como arquitectura ósea. En último término, lo que queremos evitar al tratar la osteoporosis es la fractura osteoporótica, complicación que implica menor calidad de vida e incluso aumento de la mortalidad.

Influye en la decisión de a quién tratar, cómo y cuándo la presencia de diversos factores de riesgo, entre los cuales el uso de glucocorticoides o la presencia de patologías crónicas como artritis reumatoide son determinantes.

Felizmente en la actualidad contamos con variadas posibilidades terapéuticas con capacidad de disminuir el riesgo de fractura.

Entre la terapia antirresortiva se cuenta: Terapia de reemplazo estrogénica, Bifosfonatos orales e inyectables, SERM, Denosumab.

Como terapia anabólica contamos con Teriparatide, y como combinación de ambas terapias tenemos el Ranelato de estroncio.

No debemos olvidar que como base de cualquier terapia es primordial la mantención de ingesta adecuada de calcio, la mantención de niveles apropiados de hormona D y la práctica necesaria de actividad física.

A continuación, la elección del agente terapéutico dependerá de la edad del paciente, de la magnitud del riesgo de fractura, de la eficacia del agente terapéutico, de la persistencia de sus efectos, del balance de beneficios vs riesgos, de la duración necesaria de la terapia, de las interacciones medicamentosas, de los costos y de la decisión consensuada con el paciente suficientemente bien informado.

Radiografic progression in Spondyloarthritides

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Treatment of patients with SpA is efficacious by using TNF-blockers. Inflammatory activity on MRI is significantly reduced under TNF-blockers and predicts the outcome of such treatment. Furthermore, short-term results can be used as predictors of the long-term outcome of these patients after at least 8 years. The radiographic data of patients who are being treated with TNF-blockers show a significant decrease of the radiographic progression only after long-term treatment (at least 4 years), as compared to patients on conventional treatment. Latest data have shed more light in the knowledge of whether and how anti-inflammatory treatment with non-steroidal anti-inflammatory drugs (NSAIDs) or TNF-blockers have a modifying effect on radiographic progression in those patients. So far, it seems that patients with increased CRP can benefit from NSAID treatment, showing decreased radiographic progression over time if treated continuously over at least 2 years. On the other hand, anti-TNF treatment is decreasing the rate of radiographic progression in all patients needed such treatment but only if treated for time periods of > 4 years. Latest data have shown that treatment with TNF-blockers at an early stage of the disease might be able to protect from future radiographic progression, while late treatment (detected as structural changes and fatty degeneration in the spine of patients with AS) has a positive effect only on clinical symptoms but not on radiographic progression.