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Juvenile Spondyloarthritis / Enthesitis Related Arthritis (SpA-ERA)

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1. WHAT IS JUVENILE SPONDYLOARTHRITIS/ENTHESITIS-RELATED ARTHRITIS (SpA-ERA)

1.1 What is it?

Juvenile SpA-ERA constitutes a group of chronic inflammatory diseases of the joints (arthritis), as well as tendon and ligament attachments to certain bones (enthesitis) and affects predominantly the lower limbs and in some cases the pelvic and spinal joints (sacroiliitis - buttock pain and spondylitis - back pain). Juvenile SpA-ERA is significantly more common in people that have a positive blood test for the genetic factor HLA-B27. HLA-B27 is a protein located on the surface of immune cells. Remarkably, only a fraction of people with HLA-B27 ever develops arthritis. Thus, the presence of HLA-B27 is not enough to explain the development of the disease. To date, the exact role of HLA-B27 in the origin of the disease remains unknown. However, it is known that in very few cases the onset of arthritis is preceded by gastrointestinal or urogenital infection (known as reactive arthritis). Juvenile SpA-ERA is closely related to the spondyloarthritis with onset in adulthood and most researchers believe these diseases share the same origin and characteristics. Most children and adolescents with juvenile spondyloarthritis would be diagnosed as affected by ERA and even psoriatic arthritis. It is important that the names "juvenile spondyloarthritis", "enthesitis-related arthritis" and in some cases "psoriatic arthritis" may be the same from a clinical and therapeutic point of view.

1.2 What diseases are called juvenile SpA-ERA?

As mentioned above, juvenile spondyloarthritis is the name for a group of diseases; the clinical features may overlap with each other, including axial and peripheral spondyloarthritis, ankylosing spondylitis, undifferentiated spondyloarthritis, psoriatic arthritis, reactive arthritis and arthritis associated with Crohn’s disease and ulcerative colitis. Enthesitis-related arthritis and psoriatic arthritis are two different conditions in the JIA classification and are related to juvenile SpA.

1.3 How common is it?

Juvenile SpA-ERA is one of the most frequent forms of chronic arthritis in childhood and it is more frequently seen in boys than in girls. Depending on the region of the world, it can account for about 30% of children with chronic arthritis. In most cases, the first symptom appears around the age of 6 years. Since a great proportion of patients (up to 85%) with juvenile SpA-ERA are HLA-B27 carriers, the frequency of adult SpA and juvenile SpA-ERA in the general population and even in certain families depends on the frequency of this marker in the normal population.

1.4 What are the causes of the disease?

The cause of juvenile SpA-ERA is unknown. However, there is a genetic predisposition, which in most patients relies on the presence of HLA-B27 and other genes. Today, it is thought that the HLA-B27 molecule associated with the disease (which is not the case for 99% of the population with HLA-B27) is not synthesized properly and when it interacts with cells and their products (mostly pro-inflammatory substances), it triggers the disease. Nonetheless, it is very important to emphasize that HLA-B27 is not the cause of the disease, but rather a susceptibility factor.

1.5 Is it inherited?

HLA-B27 and other genes predispose individuals to juvenile SpA-ERA. In addition, we know that up to 20% of patients with such diagnoses have first or second degree relatives with the disease. Thus, juvenile SpA-ERA

might have some family clustering. However, we cannot say that juvenile SpA-ERA is hereditary. The disease will affect only 1% of people with HLA-B27. In other words, 99% of people who have HLA-B27 will never develop SpA-ERA. Moreover, the genetic predisposition is different among ethnic groups.

1.6 Can it be prevented?

Prevention is not possible as the cause of the disease is still unknown. It is not useful to test other siblings or relatives for the HLA-B27 if they have no symptoms of juvenile SpA-ERA.

1.7 Is it infectious?

Juvenile SpA-ERA is not an infectious disease, not even in cases triggered by an infection. Moreover, not all people infected at the same time with the same bacteria develop juvenile SpA-ERA.

1.8 What are the main symptoms?

Juvenile SpA-ERA has common clinical characteristics.

Arthritis

The most common symptoms include joint pain and swelling, as well as limited mobility of the joints.
Many children have oligoarthritis of the lower limbs. Oligoarthritis means that the disease involves 4 or fewer joints. Patients developing chronic disease may have polyarthritis. Polyarthritis means that the articular involvement affects 5 or more joints. The joints most frequently affected are the knee, the ankle, the mid-foot and the hips; less frequently, arthritis involves the small joints of the foot.
Some children may have arthritis of any joint of the upper limbs, particularly the shoulders.

Enthesitis

Enthesitis, inflammation of the enthesis (the site where a tendon or ligament attaches to the bone), is the second most frequent manifestation in children with SpA-ERA. Commonly affected entheses are located at the heel, in the mid-foot and around the kneecap. Most

common symptoms include heel pain, mid-foot swelling and pain and kneecap pain. Chronic inflammation of the enthesis may lead to bony spurs (bony overgrowth) causing heel pain in many cases.

Sacroiliitis

Sacroiliitis refers to the inflammation of the sacroiliac joints, located in the rear of the pelvis. It is rare during childhood; it most frequently occurs 5 to 10 years after the onset of arthritis.
The most common symptom is alternating buttock pain.

Back pain; spondylitis

Involvement of the spine, very rare at onset, may occur later in the course of the disease in some children. The most common symptoms include back pain during the night, morning stiffness and reduced mobility. Back pain is frequently accompanied by neck and, in rare cases, also by chest pain. The disease may cause bony overgrowth and bridging joining the vertebral bodies many years after onset in a few patients. Therefore, it is almost never observed in children.

Eye involvement

Acute anterior uveitis is due to inflammation of the iris of the eye. Although it is an uncommon complication, up to one-third of patients may be affected once or several times during the course of their disease. Acute anterior uveitis presents with ocular pain, redness and blurred vision for several weeks. It usually affects one eye at a time but it may have a recurrent pattern. Immediate control by an ophthalmologist (an eye doctor) is necessary. This type of uveitis is different from the type found in girls with oligoarthritis and antinuclear antibodies.

Skin involvement

A small subset of children with juvenile SpA-ERA may already have or may develop psoriasis. In these patients, the classification as ERA is excluded and changed to psoriatic arthritis. Psoriasis is a chronic skin disease with patches of scaling skin mainly located on the elbows and the knees. The skin disease may precede the arthritis by years. In other patients, the arthritis can already exist several years before the first psoriasis rash occurs.

Bowel involvement

Some children with intestinal inflammatory disorders, such as Crohn's disease and ulcerative colitis, may develop spondyloarthritis. ERA does not include inflammatory bowel disease as one of its components. In some children, intestinal inflammation is subclinical (without gut symptoms) and the severity of articular symptoms is greater, requiring specific treatment.

1.9 Is the disease the same in every child?

The spectrum is wide. While some children have a mild and short-term disease, others have a severe, long-term and disabling disease. Thus, it is possible that many children might have just one joint involved (e.g. a knee) for several weeks and never present the same picture or additional features for the rest of their life, while others develop persistent symptoms extending to several joints, entheses and the spinal and sacroiliac joints.

1.10 Is the disease in children different from the disease in adults?

The initial symptoms of juvenile SpA-ERA are different from those of adult SpA, but most data suggest that they belong to the same spectrum of diseases. Peripheral (limbs) joint disease is more frequent at onset in children, in contrast to the more frequent axial (spinal and sacroiliac joints) involvement in adults. Disease severity is greater in children than in adults.

2. DIAGNOSIS AND THERAPY

2.1 How is it diagnosed?

Doctors diagnose juvenile SpA-ERA if the onset of the disease is before the age of 16 years, the arthritis lasts for more than 6 weeks and the characteristics fit into the clinical pattern described above (see definition and symptoms). The diagnosis of a specific SpA-ERA (i.e. ankylosing spondylitis, reactive arthritis, etc.) is based on specific clinical and radiographic features. It is clear that these patients should be treated and followed by a paediatric rheumatologist, or an adult

rheumatologist with experience in children´s rheumatic diseases.

2.2 What is the importance of tests?

A positive HLA-B27 test is useful in the diagnosis of juvenile SpA-ERA, particularly in mono-symptomatic children. It is very important to know that less than 1% of people with this marker develop spondyloarthritis and that the prevalence of HLA-B27 in the general population might be as high as 12%, depending on the region of the world. It is also important to note that most children and adolescents practice some kind of sport and that these activities might result in injuries somewhat similar to the initial symptoms of juvenile SpA-ERA. Therefore, it is not the presence of HLA-B27 by itself but rather its association with the characteristic signs and symptoms of SpA-ERA that has relevance.
Laboratory tests such as erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) provide information about general inflammation and therefore, indirectly, about inflammatory disease activity; they are useful in disease management, although this should be based much more on clinical manifestations. Laboratory tests are also used to monitor possible adverse events related to treatment (blood cell count, liver and kidney function).
X-ray examinations can be useful to follow disease evolution and assess any joint damage caused by the disease. However, the value of X-ray examinations is limited in children with SpA-ERA. Since X–ray results may be normal, ultrasonography and/or magnetic resonance imaging (MRI) of the joints and entheses is required to reveal the early inflammatory signs of the disease. With MRI, inflammation of the sacroiliac joints and/or the spine can be detected without the use of irradiation. Ultrasonography of the joints, including power Doppler signal, can provide a better idea of the occurrence and severity of a peripheral arthritis and enthesitis (limbs).

2.3 Can it be treated/cured?

Unfortunately, there is still no curative treatment for SpA-ERA since we do not know its cause. However, current therapy can be very useful to control disease activity and probably to prevent structural damage.

2.4 What are the treatments?

Treatment is based mainly on the use of drugs and physiotherapy/rehabilitation procedures that preserve joint function and contribute to preventing deformities. It is important that the use of medications depends on approval by local regulatory agencies.

Non-steroidal anti-inflammatory drugs (NSAIDs)

These drugs are symptomatic anti-inflammatory and antipyretic medications. Symptomatic means that they serve to control symptoms due to inflammation. The most widely used in children are naproxen, diclofenac and ibuprofen. They are usually well-tolerated and the most frequent adverse event, gastric discomfort, is in fact rare in children. A combination of NSAIDs is not recommended, although it may be necessary to switch from one NSAID to another in case of inefficacy or adverse events.

Corticosteroids

These drugs have a role in the short-term management of patients with more severe symptoms. Topical (eye drops) corticosteroids are used in the treatment of acute anterior uveitis. In more severe cases, periocular (around the eyeball) injections or systemic corticosteroid administration may be required. In prescribing corticosteroids for arthritis and enthesitis, it is important to bear in mind that there are no adequate studies about efficacy and safety in children with SpA-ERA; in some cases, expert opinion supports their use.

Other treatments (Disease Modifying Drugs)

Sulfasalazine

This drug is indicated in children with peripheral disease manifestations that persist despite adequate therapy with NSAIDs and/or intralesional corticosteroid injections. Sulfasalazine is added to previous NSAID therapy (which must be continued) and its effect might be evident only after several weeks or months of treatment. Nevertheless, there is only limited evidence of sulfasalazine efficacy in these children. At the same time, despite their widespread use, there is no clear evidence that methotrexate, leflunomide or anti-malarial drugs would be effective in juvenile SpA-ERA.

Biologics

Anti-tumour necrosis factor (TNF) agents are recommended in early stages of the disease because of their significant efficacy in treating inflammatory symptoms. There are studies on the efficacy and safety of these drugs that support their use in patients with severe juvenile SpA-ERA. These studies have been submitted to health authorities and are waiting for approval to start their use in SpA-ERA. In some European countries, anti-TNF agents are already approved for children.

Joint injections

Joint injections are used when one or very few joints are involved and when persistence of joint contracture may cause deformity. In general, long-acting corticosteroid preparations are injected. It is recommended that children are admitted to the ward and sedated to perform this procedure under the best conditions.

Orthopaedic surgery

The main indication for surgery is prosthetic joint replacement in the case of severe joint damage, particularly in the hip. Thanks to better drug treatment, the need for orthopaedic surgery is decreasing.

Physiotherapy

Physiotherapy is an essential component of treatment. It must be started early and should be performed routinely to maintain range of motion, muscle development and strength, and to prevent, limit or correct joint deformities. Moreover, if axial involvement is prominent, the spine must be mobilised and respiratory exercises should be performed.

2.5 What are the side effects of drug therapy?

The drugs used in the treatment of juvenile SpA-ERA are usually well-tolerated.

Gastric intolerance, the most frequent side effect of NSAIDs (which should therefore be taken with food), is less common in children than in adults. NSAIDs may cause an increase in the blood levels of some liver enzymes, but this is a rare event with drugs other than aspirin.

Sulfasalazine is reasonably well-tolerated; the most frequent side effects are stomach problems, elevated liver enzymes, low white blood cell counts and skin reactions. Repeated laboratory examinations are

needed to monitor its possible toxicity.
The long-term use of high dose corticosteroids is associated with moderate to severe adverse events, including stunted growth and osteoporosis. Corticosteroids at high doses cause a marked increase in appetite, which can in turn lead to marked obesity. It is therefore important to instruct children to eat foods that can satisfy their appetite without increasing caloric intake.
Treatment with biologic agents (TNF blocking agents) may be associated with a higher frequency of infections. Preventive screening for (latent) tuberculosis is mandatory. To date, there is no evidence of a higher frequency of malignancies (except for some forms of skin cancer in adults).

2.6 How long should the treatment last?

Symptomatic treatment should last as long as symptoms and disease activity persist. Disease duration is unpredictable. In some patients, arthritis responds very well to NSAIDs. In these patients, treatment can be stopped early on, within months. In other patients with a more prolonged or aggressive course of disease, sulfasalazine and other types of medications are needed for years. Total drug withdrawal may be considered after prolonged and complete disease remission on drugs.

2.7 What about unconventional/complementary therapies?

There are many complementary and alternative therapies available and this can be confusing for patients and their families. Think carefully about the risks and benefits of trying these therapies as there is little proven benefit and they can be costly both in terms of time, burden to the child and money. If you want to explore complementary and alternative therapies, please discuss these options with your paediatric rheumatologist. Some therapies can interact with conventional medications. Most doctors will not be opposed, provided you follow medical advice. It is very important not to stop taking your prescribed medications. When medications are needed to keep the disease under control, it can be very dangerous to stop taking them if the disease is still active. Please discuss medication concerns with your child’s doctor.

2.8 How long will the disease last? What is the long-term evolution (prognosis) of the disease?

The disease course can be different from one patient to another. In some patients, arthritis disappears quickly with treatment. In others, it is characterised by periodic remissions and recurrences. Finally, in other patients, arthritis may follow an unremitting course. In the vast majority of patients, symptoms are confined to peripheral joints and enthesis at the beginning of disease. As the disease progresses, some children and adolescents may develop sacroiliac and spinal joint involvement. Patients with persistent peripheral arthritis and axial symptoms have a higher risk of developing joint damage in adulthood. Nevertheless, at the beginning of the disease it is impossible to predict the long-term outcome. In contrast, adequate treatment can influence the course and prognosis of the disease.

3. EVERYDAY LIFE

3.1 How might the disease affect the child and their family's daily life?

During the periods of active arthritis, almost every child will experience limitations in his/her daily life. Since lower limbs are often affected, walking and sports are the activities most frequently affected by the disease. A positive attitude from parents who support and encourage the child to be independent and physically active is extremely valuable in overcoming the difficulties related to the disease, successfully coping with peers and developing an independent, well-balanced personality. If the family cannot cope with the burden of the disease, psychological support is needed. Parents must support their child in physical therapy exercises and encourage them to take their prescribed medications.

3.2 What about school?

There are a few factors that may cause problems for school attendance: difficulty walking, minor resistance to fatigue, pain or stiffness. It is therefore important to explain the child's possible needs to teachers: proper desks and regular movements during school hours to avoid articular stiffness. Whenever possible, patients should take part in gym

lessons; in this case, the same considerations discussed below, in terms of sports, should be taken into account. Once the disease is well-controlled, the child should have no problem participating in all the same activities as their healthy peers.
School for a child is what work is for an adult: a place where he/she learns how to become an independent and productive person. Parents and teachers should do whatever they can to allow the child to participate in school activities in a normal way, in order not only for the child to be successful academically but also to be accepted and appreciated by both peers and adults.

3.3 What about sports?

Playing sports is an essential aspect of the everyday life of any normal child. Sports in which mechanical stress to the joints is absent or minimal, such as swimming or riding a bike, are recommended.

3.4 What about diet?

There is no evidence that diet can influence the disease. In general the child should observe a balanced, normal diet for his/her age. Overeating should be avoided in patients taking corticosteroids because these drugs may increase appetite.

3.5 Can climate influence the course of the disease?

There is no evidence that climate can affect the disease manifestations.

3.6 Can the child be vaccinated?

Since most of patients are treated with either NSAIDs or sulfasalazine, a normal vaccination scheme can be followed. A patient being treated with high-dose corticosteroids or biologic agents should avoid vaccination with live attenuated viruses (such as anti-rubella, anti-measles, anti-parotitis, anti-polio Sabin). Otherwise, they should be postponed due to the potential risk of infections spreading as a consequence of reduced immune defences. Vaccines that do not contain living viruses but only infectious proteins (anti-tetanus, anti-diphtheria, anti-polio Salk, anti-hepatitis B, anti-pertussis,

pneumococcus, haemophilus, meningococcus) can be administered. Theoretically, immunosuppression may reduce or cancel the effect of a vaccination.

3.7 What about sexual life, pregnancy, birth control?

There are no restrictions on sexual activity or pregnancy due to the disease. Nevertheless, patients taking medications should always be very careful about the possible toxic effects of these drugs on a foetus. There is no reason to avoid having children, despite the genetic aspects of the disease. The disease is not lethal and even if the predisposing genetic factor could be inherited, there is a good chance that siblings will not develop any form of juvenile SpA-ERA.

3.8 Will the child have a normal adult life?

This is one of the main goals of therapy and it can be achieved in the majority of cases. Therapy for these kinds of diseases in childhood has improved dramatically over recent years. The combined use of pharmacological treatment and rehabilitation is now able to prevent joint damage in the vast majority of patients.