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## JUVENILE IDIOPATHIC ARTHRITIS

### **What is it?**

Juvenile idiopathic arthritis (JIA) is a chronic disease characterized by persistent joint inflammation; the typical signs of joint inflammation are pain, swelling and limitation of movement. “Idiopathic” means that we don’t know the cause of the disease and “juvenile”, in this case, means that symptoms appear before 16 years of age.

### **What does chronic disease mean?**

A disease is said to be chronic when the appropriate treatment does not lead to an immediate recovery, but only to an improvement of symptoms and laboratory test results. This also means that when the diagnosis is made, it is impossible to say for how long the child is going to be sick.

### **How frequent is it?**

JIA is a rare disease that affects about 80-90 per 100,000 children.

### **What are the causes of the disease?**

Our immune system protects us from infections (virus and bacteria). In doing so, it is able to distinguish what is harmless and part of our body and what is foreign and potentially dangerous, which it destroys.

It is believed that chronic arthritis is a consequence of an abnormal response of our immune system, which, due to unknown causes, loses part of its capacity to distinguish between dangerous and normal cells and attacks its own joint components.

For this reason, diseases such as JIA are called autoimmune, meaning that the immune system reacts against the organs of its own body.

However, the precise mechanisms that cause JIA, as with as most human chronic inflammatory diseases, are unknown.

### **Is it a hereditary disease?**

JIA is not a hereditary disease, since it cannot be transmitted directly from parents to their children. Nevertheless, there are some genetic factors, largely still to be discovered, that increase the chance of developing the disease. The agreement in the scientific community is that this disease is multifactorial, which means it is the result of a combination of genetic factors and exposure to environmental factors (probably infections). Even when there may be a genetic predisposition, it is very rare to have two children affected in the same family.

### **How is it diagnosed?**

Doctors diagnose someone as having JIA when the onset of the disease is before the age of 16, arthritis lasts for more than six weeks and the causes are unknown (which means that all other diseases responsible for arthritis have been ruled out). The arthritis must be

present for more than six weeks in order to exclude forms of temporary arthritis that may follow viral infections.

The diagnosis of JIA is, therefore, based on the presence and persistence of arthritis and the careful exclusion of any other disease by medical history, physical examination and laboratory tests.

### **What happens to the joints?**

The synovial membrane is the cellular lining surrounding the joint and is usually very thin. In JIA it becomes much thicker and filled with inflammatory cells, while the amount of the synovial fluid inside it increases. This causes swelling, pain and limitation of movement. A characteristic feature of joint inflammation is joint stiffness, which occurs after prolonged rest. It is, therefore, particularly pronounced in the morning (and referred to as morning stiffness).

Often the child attempts to reduce pain by keeping the joint in a position half-way between flexion (fully bent) and extension (straight), this position is called antalgic indicating the fact that it is maintained to reduce pain.

If not properly treated, joint inflammation may produce damage by two main mechanisms:

- a) The synovial membrane may get very thick and form what is called the synovial pannus, which, through the release of various substances, provokes the erosion of articular cartilage and bone.
- b) Keeping the joint in the antalgic position for a long time causes muscle atrophy, which is the wasting away of muscles and soft tissues, leading to flexion deformity.

### **Are there different types of the disease?**

There are several different forms of JIA. They are mainly distinguished on the presence or absence of systemic symptoms. Systemic symptoms are symptoms that affect many organs, such as fever or rash and on the number of joints involved. By convention, the different forms of JIA are defined according to the symptoms presented during the first six months of the disease. For this reason, they are often referred as onset forms.

**Systemic JIA.** This form is diagnosed because of the presence of systemic features, besides arthritis. The main systemic symptom is represented by high spiking fever, often accompanied by a salmon coloured rash that appears during fever spikes. Other symptoms may include muscle pain, enlargement of the liver, spleen or lymph nodes (groups of cells that filter out bacteria etc., as a critical part of the immune system), and inflammation of membranes around the heart (pericarditis) and lungs (pleuritis). Arthritis may be present at disease onset, or appear later on. The disease may affect children at any age.

About half of all patients are diagnosed with systemic features. These patients tend to have the best long-term prognosis (predicted outcome). In the other half of patients, systemic symptoms often tend to subside with time and joint involvement becomes more important. In a minority of these patients, systemic symptoms persist together with joint involvement.

Systemic JIA accounts for less than 10% of all JIA cases, but is seldom observed in adults.

**Polyarticular JIA.** This is diagnosed because of the involvement of five or more joints during the first six months of disease and in the absence of the above mentioned systemic symptoms. The presence or absence of an autoantibody in the blood called rheumatoid factor (RF) allows for polyarticular JIA to be distinguished into two subforms: RF negative and RF positive.

1) RF positive polyarticular JIA. This is rare in children (<5% of all JIA patients). It is considered the equivalent of adult RF positive rheumatoid arthritis (the major type of chronic arthritis in adults). It often causes symmetric arthritis affecting mainly the small joints of hands and feet, initially, extending to the other joints as disease progresses. It is much more common in females than in males and usually has its onset after 10 years of age. It is often a severe form of arthritis.

2) RF negative polyarticular JIA. This accounts for 15-20% of all JIA cases and can occur at any age. It is a complex form, which probably includes different diseases. The variable course and eventual outcome of the disease in different patients reflect this complexity.

**Oligoarticular JIA.** This is diagnosed when less than five joints are involved in the first six months of disease and there are no systemic symptoms. It affects large joints (such as knees and ankles) in an asymmetrical way. Sometimes, only one joint is affected (called the monoarticular form). In some patients the number of joints affected increases after the first six months of disease to five or more, this is called extended oligoarthritis.

Oligoarthritis usually has its onset before the age of six and is mainly observed in females. With appropriate treatment, there is a good chance of maintaining full joint use where the disease remains limited to a few joints. It is harder to predict the long term outcome for those patients who develop an extension of articular involvement.

A consistent proportion of patients can develop problems with their sight (anterior uveitis), the inflammation of the sheet enveloping the eye and containing its vascular supply (the vessels that provide blood). Since the iris and the ciliary body form this part of the eye, the complication is called chronic anterior uveitis, or **chronic iridocyclitis**.

If unrecognized and left untreated, anterior uveitis progresses and can cause very serious damage to the eye. Early recognition of this complication is, therefore, of utmost importance. Since anterior uveitis may not be noticed by parents or clinicians, as there are no obvious symptoms, it is imperative for children at high risk to have periodic eye check ups with an ophthalmologist every three months, using a particular instrument called a slit lamp.

Oligoarthritis is the most frequent form of JIA, accounting for 50% of cases. The ANA positive type (see Laboratory exams), combined with uveitis, is a disease typical of childhood, but is not observed in adults.

**Psoriatic arthritis.** This is diagnosed by the presence of arthritis, associated with psoriasis or psoriatic features. Psoriasis is a skin disease with patches of scaling skin, mainly located over the elbows and the knees. The skin disease may precede or follow the onset of arthritis.

This form is complex in clinical manifestations and prognosis.

**Arthritis associated with enthesitis.** The most common manifestation is an oligoarthritis, mainly affecting the large joints of the lower limbs and associated with enthesitis. Enthesitis is the inflammation of the enthesis, the point of insertion of tendons over bones. The most common site of pain in this form of arthritis is localized in the foot, behind or below the heel. Sometimes these patients may present with an acute anterior uveitis. Unlike the oligoarticular form, anterior uveitis associated with enthesitis may cause red eye, lachrymation (excessive watering of the eyes), or increased sensitivity to light. Most patients are positive for a laboratory test called HLA-B27. The disease affects predominantly males and usually begins after seven or eight years of age. The course of disease in this form is variable. In some patients the disease remits, while in others it extends to affect the spinal region. Initially, with the involvement of the sacroiliac joints (around the lower back). Indeed, this form belongs to a group of diseases that are more frequent in adults and are called spondyloarthropathies, since they can affect the spine.

**What causes chronic iridocyclitis? Is there a relationship with arthritis?**

As with arthritis, eye inflammation is caused by an abnormal immune response against the eye (an autoimmune response). The precise biological mechanisms involved are unknown.

This complication is mainly observed in patients with the oligoarticular type of arthritis. These patients tend to be of a younger age, with a positive laboratory test called antinuclear antibodies (ANA).

It is not known why iridocyclitis is linked with articular disease. It is important to remember that arthritis and iridocyclitis may follow independent courses, so periodic slit lamp examinations have to be continued even if arthritis goes into remission. Periodic flares, independent of the arthritis flares, characterize the course of iridocyclitis.

Iridocyclitis usually follows the onset of arthritis, or may be detected at the same time. It can precede arthritis, but this is rare. These are usually the most unfortunate cases, since the disease is asymptomatic, iridocyclitis is not discovered until it has already caused some symptomatic complications like visual disturbances.

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

Mostly, yes. The polyarticular RF positive form, which is responsible for about 70% of adult rheumatoid arthritis cases, accounts for less than 5% of cases of JIA. The oligoarticular form with early onset represents about 50 % of JIA cases and is not observed in adults at all. Systemic arthritis is characteristic of children and is seldom observed in adults.

**What laboratory exams are needed?**

At the time of diagnosis, some laboratory examinations help to better define the type of JIA a patient is suffering from. They can also help to identify patients at risk of developing some complications, such as chronic iridocyclitis.

**Rheumatoid factor (RF)** is an autoantibody that is positive and in high concentration only in the polyarticular form of JIA, which is the childhood equivalent of RF positive adult rheumatoid arthritis.

**Antinuclear antibodies (ANA)** are frequently positive in patients with oligoarticular early-onset JIA. This identifies JIA patients at high risk of developing chronic

iritidocyclitis and who have to have an ocular examination with a slit lamp every three months.

**HLA-B27** is a cellular marker that is positive in up to 80% of patients with enthesitis associated arthritis. Its frequency in the general, healthy population is much lower (5-8%).

**Other exams**, such as erythrocyte sedimentation rate (ESR), or C-reactive protein (CRP), measure the extent of general inflammation and are useful in disease management, along with clinical examinations.

Periodic X-ray examinations are useful to assess potential disease progression and, therefore, to ensure the therapeutic regimen remains appropriate.

Depending on the drug regimen, patients may need periodic laboratory examinations to assess potential drug toxicity.

### **How can we treat it?**

There is no specific therapy to cure JIA. The aim of treatment is to allow children to conduct a normal life and prevent joint and organ damage, while waiting for spontaneous disease remission. Treatment is based mainly on the use of drugs that inhibit inflammation and on rehabilitation procedures that preserve joint function and help to prevent deformities.

Therapy is complex and needs the cooperation of different specialists (e.g. paediatric rheumatologists, orthopaedic surgeons, physical and occupational therapists, ophthalmologists).

**1) Non-steroidal anti-inflammatory drugs (NSAIDs).** They are symptomatic anti-inflammatory and antipyretic (controls fever) medications. Symptomatic means that they cannot induce disease remission, but serve to control symptoms due to inflammation. The most widely used are naproxen and ibuprofen. Aspirin, although effective and cheap, is much less used nowadays, because of its risk of toxicity. NSAIDs are usually well tolerated and gastric discomfort, the most common side effect in adults, is uncommon in children. NSAIDs are not prescribed in association with one another, but one NSAID may be effective where another has failed. The optimal effect on joint inflammation occurs after several weeks of therapy.

**2) Joint injections.** These are used when few joints are involved and there is a risk of long term damage. The drug injected is a long-acting steroid preparation. Triamcinolone hexacetonide is preferred for its prolonged effect (frequently many months).

**3) Second level drugs.** These are prescribed for children that have a progressive polyarthritis, despite adequate therapy with NSAIDs and steroid injections. Second level drugs are added to previous NSAID therapy, which therefore, has to be continued. The effect of most second level drugs only becomes fully evident after several weeks or months of treatment.

The drug of first choice is low-dose weekly **methotrexate**, as it is effective in the majority of patients. It has an anti-inflammatory activity, but is also able, in some patients, to induce disease remission, although it is not yet understood how this happens. It is usually well tolerated, with gastric intolerance and an increase in transaminase levels (a type of enzyme), representing the most common side effects. Potential toxicity needs monitoring during treatment with periodic laboratory tests, as discussed above. Folic acid, a vitamin, diminishes the risk of side effects.

**Salazopyrine** has also been showed to be effective in JIA, but is usually not as well tolerated as methotrexate. The experience with salazopyrine is much more limited than with methotrexate.

So far, no proper studies have been conducted in JIA to assess the efficacy of other potentially useful drugs, such as **cyclosporin** or **leflunomide**. Cyclosporin is a valuable drug for the treatment of steroid-resistant macrophage activation syndrome (a serious complication in many childhood inflammatory disorders). This is a severe and potentially life-threatening complication of systemic JIA, which is secondary to a massive general activation of the inflammatory process. Very little information about the use of leflunomide on children is available.

In the last few years **anti-TNF drugs** have been introduced. Anti-TNF drugs selectively block tumor necrosis factor (TNF), an essential mediator of the inflammatory process. They are used alone, or in association with methotrexate, and are effective in most patients. Their effect is quite rapid and their safety has been shown to be good, so far, but follow-up studies are needed to establish potential long-term side effects. As with all second level drugs, they must be administered under strict medical control. Anti-TNF drugs are very expensive.

**4) Corticosteroids.** These are the most effective available anti-inflammatory drugs, but their use is limited because their long-term use is associated with several important side effects, including osteoporosis and stunted growth. They are, however, valuable for the treatment of systemic symptoms that are resistant to other therapies, for life threatening systemic complications and as a bridge drug to control acute disease while waiting for second level drugs to take effect.

Topical steroids (eye drops) are used in the treatment of iridocyclitis. In more severe cases, steroid injections around the eye, or systemic steroid administration, may be required.

**5) Orthopedic surgery.** The main procedures are prosthetic joint replacement in the case of articular destruction and surgical releasing of soft tissues in the case of permanent contractures.

**6) Rehabilitation.** This is an essential component of treatment. It includes appropriate exercises and, where necessary, wearing splints to correct posture. It must be started early and should be performed routinely to keep the range of movement, muscle trophism and strength and to prevent, limit or correct deformities.

### **What are the main side effects of therapy?**

The drugs used in the treatment of JIA 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 can cause increases in some liver enzymes in the blood, but this is a rare event with drugs other than aspirin.

Methotrexate is also well tolerated, but gastroenteric side effects, such as nausea and vomiting, are not uncommon. To monitor potential toxicity, it is important to perform periodic laboratory tests. The most frequent laboratory anomaly is an increase in liver enzymes, which normalizes with drug withdrawal or dose reduction. The administration of folinic or folic acid is effective in reducing the frequency of hepatic toxicity. Hypersensitivity reactions to methotrexate can occur, but are rare.

Salazopyrine is reasonably well tolerated. The most frequent side effects are cutaneous rash, gastrointestinal problems, hypertransaminasemia (liver toxicity) and leukopenia (lowering of white blood cells leading to risk for infections). For these reasons, as with methotrexate, periodic laboratory examinations are needed.

Anti-TN agents are usually well tolerated, but patients should be carefully monitored for severe infections.

The long-term use of steroids in significant dosage is associated with several side effects. These include stunting growth and osteoporosis. Steroids, at high doses, cause a marked increase in appetite, which leads to obesity. It is, therefore, important to instruct children to eat foods that can satisfy the appetite without increasing calorie intake.

### **How long should treatment last for?**

Treatment should last as long as the disease persists. Disease duration is unpredictable, but, in the majority of cases, JIA goes into spontaneous remission. The course of JIA often includes periods of remission and exacerbation, which require very different treatments. Treatment is only withdrawn completely after prolonged and complete disease remission.

### **Eye examination (Slit lamp examination). How often is it necessary and for how long?**

For patients at risk (those with an ANA positive laboratory test result), slit lamp examination has to be performed at least every three months. Those who have developed iridocyclitis should be submitted to more control tests, the frequency of which depends on the severity of eye involvement.

The risk of developing iridocyclitis decreases with time, but iridocyclitis can still develop many years after arthritis onset. It is, therefore, prudent to check the eyes for many years, even if arthritis is in remission.

Acute uveitis in patients with arthritis and enthesitis is symptomatic (red eye, pain and photophobia) and, therefore, there is no need of periodic slit lamp examinations for early diagnosis.

### **What is the long-term prognosis (predicted course of disease) of arthritis?**

The prognosis of arthritis depends on its severity, the clinical form of JIA, how early treatment begins and how adequate the course of treatment followed is. The prognosis for JIA has been considerably improved by the progresses in therapy that have occurred over the last ten years.

Systemic JIA has a variable prognosis. About half of patients have few signs of arthritis and the disease is mainly characterized by periodic disease flares. The ultimate prognosis is often good, as the disease frequently goes into spontaneous remission. In the other half of patients, the disease is characterized by persistent arthritis, while systemic symptoms tend to fade. Severe articular destruction can also develop in this subset of patients. In a tiny minority of this second group of patients, systemic symptoms persist together with articular involvement. These patients have the worst prognosis and may develop amyloidosis, a severe complication requiring aggressive therapy.

RF positive polyarticular JIA usually has a progressive, articular course that can lead to severe joint destruction.

RF negative Polyarticular JIA is complex, both in clinical manifestations and prognosis. The overall prognosis, however, is much better than that of RF positive polyarticular JIA, only about one quarter of patients develop articular damage.

Oligoarticular JIA has a good articular prognosis when the disease remains limited to a few joints. Patients in which the articular disease extends to involve several joints have a prognosis similar to that of patients with polyarticular RF negative JIA.

Most patients with psoriatic JIA have a disease similar to oligoarticular JIA, but have a somewhat higher tendency to become polyarticular with time.

JIA associated with enthesopathy also has a variable prognosis. In some patients the disease remits, while in others it progresses and may involve sacroiliac joints.

So far, no reliable clinical or laboratory features to predict which patient will have the worst prognosis are available during the early stages of disease. Such predictors would be of considerable clinical use, since they could allow the identification of patients who should be prescribed a more aggressive treatment from the beginning of the disease.

### **What is the long-term prognosis of iridocyclitis?**

Iridocyclitis, if left untreated, may have very serious consequences, including problems such as cloudiness of the lens of the eyes (cataract) and blindness. However, if treated in its early stages, it usually responds very well to therapy. Early diagnosis is, therefore, the major determinant of prognosis.

### **Are vaccinations allowed?**

If a patient is being treated with an immunosuppressive therapy (steroids, methotrexate, anti-TNF etc.) vaccinations with live, micro-organisms (such as anti-rubella, anti-measles, anti-parotitis, anti-polio Sabin and BCG) have to be postponed, because of the potential risk of infections spreading, due to the reduced immune defences. Vaccines that do not contain living micro-organisms, but only infectious proteins (anti-tetanus, anti-diphtheria, anti-polio Salk, anti-hepatitis B, anti-pertussis, pneumococcus, haemophilus, meningococcus) can be performed, the only theoretical risk is vaccination failure, due to the immunosuppressive treatment.

### **Can diet influence the course of the disease?**

There is no evidence that diet can influence the disease. In general the child has to take a balanced, normal diet. Overeating has to be avoided in patients taking steroids, since steroids increase the appetite.

### **Can climate influence the course of the disease?**

There is no evidence that climate can affect the disease.

### **Are sports allowed?**

Playing sports is an essential aspect of the everyday life of a normal child. One of the main aims of JIA therapy is to allow children to conduct a normal life and not to consider themselves different from their peers. Therefore, the general tendency is to leave patients to play the sports they want and to trust that they will stop if a joint hurts. Although mechanical stress is not beneficial in an inflamed joint, it is assumed that the little damage that could ensue, is much smaller than the psychological damage of being



prevented from playing sports with friends because of the disease. This choice is part of a more general attitude that tends to encourage the child to be autonomous and able to cope with the limits imposed by the disease.

As part of these considerations, it is better to favour sports in which mechanical stress to the joints is absent or minimal, such as swimming and riding a bike.

### **Can the child attend school regularly?**

It is extremely important that the child attends school regularly. There are a few factors that may cause problems with school attendance though, such as difficulty in walking, minor resistance to fatigue, pain or stiffness. It is, therefore, important to explain to the teachers the child's possible needs, which are likely to include proper tables, regular movements during school hours to avoid articular stiffness and difficulty in writing. Patients should take part in gym lessons wherever possible, but in this case the considerations discussed above in the issue of sports have to be taken into account.

School, for a child, is a place where he learns how to become an autonomous person, productive and independent. Parents and teachers have to do whatever they can to make the sick children participate in school activities in a normal way in order to have academic success. In addition to this, it is at school that the child develops the ability to communicate effectively with peers and adults and to be accepted and appreciated by his friends.

### **Will the child have a normal adult life?**

This is one of the main goals of therapy and it can be reached in the majority of cases. Therapy for JIA has improved dramatically in the last ten years and it is conceivable that several new drugs will be available in the near future. The combined use of pharmacological treatment and rehabilitation prevents joint damage in the majority of patients.

Major attention should also be paid to the psychological impact of the disease on the child and his family. A chronic disease like JIA is a difficult challenge for the whole family and, of course, the more serious the disease, the harder it is to cope with it. It will be difficult for the child to cope properly with his disease if the parents don't. The parents may develop a strong attachment towards their sick child and, in order to prevent him from any possible problem, can become-overprotective.

A positive attitude from parents who support and encourage the child to be as independent as possible, despite the disease, is extremely valuable in helping the child to overcome difficulties, to successfully cope with his peers and to develop an independent, well-balance personality.

The paediatric rheumatology team should offer psychosocial support when needed.