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Blau's Disease / Juvenile Sarcoidosis

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1. WHAT IS BLAU'S DISEASE/JUVENILE SARCOIDOSIS

1.1 What is it?

Blau syndrome is a genetic disease. Patients suffer from a combination of skin rash, arthritis and uveitis. Other organs may be affected and intermittent fever may be present as well. Blau syndrome is the term used for familial forms of the disease but sporadic forms can occur as well and are known as Early Onset Sarcoidosis (EOS).

1.2 How common is it?

The frequency is unknown. It is a very rare disease that affects patients in early childhood (mostly before 5 years of age) and becomes worse if left untreated. Since the discovery of the associated gene, it is being diagnosed more frequently, which will allow for a better estimate of prevalence and natural history.

1.3 What are the causes of the disease?

Blau syndrome is a genetic disease. The responsible gene is called NOD2 (synonymous with CARD15), which encodes a protein with a role in the immune-inflammatory response. If this gene carries a mutation, as in Blau syndrome, the protein does not function properly and patients experience chronic inflammation with granuloma formation in various tissues and organs of the body. Granulomas are characteristic long-lived clusters of inflammatory cells that are associated with inflammation and may disrupt the normal structure and functioning of various tissues and organs.

1.4 Is it inherited?

It is inherited as an autosomal dominant disease (which means that it is not linked to gender and that at least one parent must show symptoms of the disease). This type of transmission means that to have Blau syndrome, an individual needs only one mutated gene, either from the mother or the father. In EOS, the sporadic form of the disease, the mutation emerges in the patient him/herself and both parents are healthy. If a patient carries the gene, he or she will suffer from the disease. If one parent has Blau syndrome, there is a 50% chance that his/her child will suffer from it.

1.5 Why does my child have this disease? Can it be prevented?

The child has the disease because he/she carries genes that cause Blau syndrome. Currently, the disease cannot be prevented but the symptoms can be treated.

1.6 Is it infectious?

No, it is not.

1.7 What are the main symptoms?

The main symptoms of the disease are a clinical triad of arthritis, dermatitis and uveitis. The initial symptoms comprise a typical exanthema, with tiny round lesions that vary in colour from pale pink to tan or intense erythema. Over the course of years, the rash waxes and wanes. Arthritis is the most common manifestation, starting in the first decade of life. There is joint swelling with preserved mobility at onset. With time, limitation of movement, deformities and erosions may develop. Uveitis (inflammation of the iris) is the most threatening manifestation, since it is often associated with complications (cataract, increased intraocular pressure) and may cause decreased vision if left untreated.

In addition, granulomatous inflammation may affect a wide spectrum of other organs, causing other symptoms, as well such as decreased lung or kidney functioning, increased blood pressure or recurrent fever.

1.8 Is the disease the same in every child?

It is not the same in every child. Moreover, the type and severity of symptoms may change as the child grows older. The disease progresses if left untreated and the symptoms will evolve accordingly.

2. DIAGNOSIS AND THERAPY

2.1 How is it diagnosed?

Generally, the following approach is followed for the diagnosis of Blau syndrome:
Clinical suspicion: It is relevant to consider Blau syndrome when a child presents a combination of symptoms (joint, skin, eye) out of the typical clinical triad. A detailed investigation into the family history should be considered, because this disease is very rare and inherited in an autosomal dominant manner. Demonstration of granulomas: to make the diagnosis of Blau syndrome/EOS, the presence of typical granulomas in affected tissue is essential. Granulomas can be seen on a biopsy of a skin lesion or of an inflamed joint. Other causes of granulomatous inflammation (such as tuberculosis, immune deficiency or other inflammatory diseases such as some vasculitides) need to be excluded by thorough clinical examination and blood tests, imaging and other tests. Genetic analysis: in the last couple of years, it has been possible to perform a genetic analysis of patients to ascertain the presence of mutations that are thought to be responsible for the development of Blau syndrome/EOS.

2.2 What is the importance of tests?

Skin biopsy: a skin biopsy involves the removal of a tiny piece of tissue from the skin and it is very easy to perform. If the skin biopsy shows granulomas, the diagnosis of Blau syndrome is made after exclusion of all other diseases that are associated with granuloma formation. Blood test: blood tests are important to exclude other diseases that can be associated with granulomatous inflammation (such as immune deficiency or Crohn’s disease). They are also important to see the extent of inflammation and to evaluate the involvement of other organs (such as the kidney or liver). Genetic test: the only test that unambiguously confirms the diagnosis of Blau syndrome is a genetic

test that shows the presence of a mutation in the NOD2 gene.

2.3 Can it be treated or cured?

It cannot be cured but it can be treated with drugs that control inflammation in the joints, the eyes and any involved organ. The drug treatment aims to control symptoms and halt the progression of the disease.

2.4 What are the treatments?

At present, there is no evidence concerning the optimal treatment for Blau syndrome/EOS. Joint problems can often be treated with anti-inflammatory non-steroidal drugs and methotrexate. Methotrexate is known for its capacity to control arthritis in many children with juvenile idiopathic arthritis; its effectiveness in Blau syndrome may be less marked. Uveitis is very difficult to control; local therapies (steroid eye drops or local steroid injection) may not be sufficient for many patients. The efficacy of methotrexate to control uveitis is not always sufficient and patients may need to take oral corticosteroids in order to control severe eye inflammation.

In patients with difficult-to-control inflammation of the eyes and/or joints and in patients with involvement of internal organs, the use of cytokine-inhibitors such as TNF-α inhibitors (infliximab, adalimumab) may be effective.

2.5 What are the side effects of drug therapy?

The most frequent adverse effects seen with methotrexate are nausea and abdominal distress on the day of intake. Blood tests are needed to monitor liver function and the number of white blood cells.

Corticosteroids are associated with possible side effects such as weight gain, swelling of the face and mood swings. If the steroids are prescribed for a prolonged period, they can cause suppression of growth, osteoporosis, high blood pressure and diabetes.

TNF-α inhibitors are recent drugs; they can be associated with an increased risk of infection, activation of tuberculosis and possible development of neurological or other immune diseases. A potential risk of development of malignancies has been discussed; at present, there are no statistical data proving an increased risk of malignancies with these drugs.

2.6 How long should treatment last?

There are no data at present that support an optimal duration of treatment. It is essential to control inflammation in order to prevent joint damage, visual loss or damage to other organs.

2.7 What about unconventional or complementary therapies?

There is no evidence concerning this type of therapy for Blau syndrome/EOS.

2.8 What kind of periodic check-ups are necessary?

Children should be seen regularly (at least 3 times yearly) by their paediatric rheumatologist to monitor the control of the disease and adjust the medical treatment. It is also important to have regular visits with the ophthalmologist, at a frequency depending on the severity and evolution of eye inflammation. Children being treated should have blood and urine tests at least twice yearly.

2.9 How long will the disease last?

It is a life-long disease. However, the activity of the disease may fluctuate over time.

2.10 What is the long-term prognosis (predicted outcome and course) of the disease?

The available data concerning the prognosis in the long-term is limited. Some children have been followed for more than 20 years and have attained almost normal growth, normal psychomotor development and a good quality of life with well-adjusted medical treatment.

2.11 Is it possible to recover completely?

No, because it is a genetic disease. However, appropriate medical follow-up and treatment will give the majority of patients a good quality of life. There are differences in the severity and progression of the disease

among patients with Blau syndrome; at present, it is impossible to predict the disease course for the individual patient.

3. EVERYDAY LIFE

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

The child and the family may experience various problems before the disease is diagnosed. Once the diagnosis has been made, the child will need to visit doctors (a paediatric rheumatologist and an ophthalmologist) regularly to monitor disease activity and adjust the medical treatment. Children with difficult joint disease may need physiotherapy.

3.2 What about school?

The chronic course of the disease may interfere with school attendance and performance. A good control of the disease is essential to allow school attendance. Information about the disease at school may be useful, in particular to give advice on what to do in case of symptoms.

3.3 What about sports?

Patients with Blau syndrome should be encouraged to perform sports; limitations will depend on the control of the disease activity.

3.4 What about diet?

There is no specific diet advised. However, children taking corticosteroids should avoid extra sweet and salty food.

3.5 Can climate influence the course of the disease?

No, it cannot.

3.6 Can the child be vaccinated?

The child can be vaccinated except with live vaccines when under

treatment with corticosteroid, methotrexate or TNF-α inhibitors.

3.7 What about sexual life, pregnancy, birth control?

Patients with Blau syndrome do not have fertility problems due to the disease. If they are being treated with methotrexate, proper birth control should be used, since the drug may have side effects on a foetus. There are no safety data concerning TNF-α inhibitors and pregnancy, so patients must stop using these when they wish to become pregnant. As a general rule, it is better to plan a pregnancy and adapt treatment in advance and propose a follow-up adapted to the disease.