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Papa Syndrome (Piogenic Arthritis, Pioderma, Gancrenosum and Acne)

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1. WHAT IS PAPA

1.1 What is it?

The acronym PAPA stands for Pyogenic Arthritis, Pyoderma gangrenosum and Acne. It is a genetically determined disease. A triad of symptoms that includes recurrent arthritis, a type of skin ulcers known as pyoderma gangrenosum and a type of acne known as cystic acne characterises the syndrome.

1.2 How common is it?

PAPA syndrome appears to be very rare. Very few cases have been described. However, the frequency of the disease is not known exactly and may be underestimated. PAPA affects male and females equally. Usually, the disease appears during childhood.

1.3 What are the causes of the disease?

PAPA syndrome is a genetic disease caused by mutations in a gene called PSTPIP1. The mutations change the function of the protein for which the gene codes; this protein plays a role in the regulation of the inflammatory response.

1.4 Is it inherited?

PAPA syndrome is inherited as an autosomal dominant disease. This

means that it is not linked to gender. It also means that one parent shows at least some symptoms of the disease and usually more than one affected individual is be observed in a single family, with affected individuals in each generation. When someone with PAPA syndrome is planning to have children, there is a 50% chance of having a child with PAPA syndrome.

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

The child has inherited the disease from one of his/her parents who carries a mutation in the PSTPIP1 gene. The parent who carries the mutation may or may not exhibit all symptoms of the disease. The disease cannot be prevented but the symptoms can be treated.

1.6 Is it infectious?

PAPA syndrome is not infectious.

1.7 What are the main symptoms?

The most common symptoms of the disease are arthritis, pyoderma gangrenosum and cystic acne. Rarely are all three present in the same patient at the same time. Arthritis occurs usually early in childhood (the first episode occurs between 1 and 10 years of age); it usually involves one joint at a time. The affected joint becomes swollen, painful and red. The clinical appearance resembles septic arthritis (arthritis caused by presence of bacteria in the joint). Arthritis of PAPA syndrome may cause damage to articular cartilage and periarticular bone. The large ulcerative skin lesions, known as pyoderma gangrenosum, usually have a later onset and often involve the legs. Cystic acne usually appears during adolescence and may persist into adulthood, involving the face and trunk. Symptoms are often precipitated by minor injury to the skin or joint.

1.8 Is the disease the same in every child?

The disease is not the same in every child. An individual carrying a mutation in the gene may not exhibit all the symptoms of the disease or may exhibit only very mild symptoms (variable penetrance). Moreover,

the symptoms may change, usually improving, as a child grows older.

2. DIAGNOSIS AND TREATMENT

2.1 How is it diagnosed?

It is possible to consider PAPA syndrome in a child with repeated episodes of painful inflammatory arthritis that clinically resemble septic arthritis and do not respond to antibiotic treatment. Arthritis and skin manifestations may not appear at the same time and may not be present in all patients. A detailed evaluation of the family history should also be performed; since the disease is autosomal dominant, other family members are likely to exhibit at least some symptoms of the disease. The diagnosis can only be made by genetic analysis to ascertain the presence of mutations in the PSTPIP1 gene.

2.2 What is the importance of tests?

Blood tests: erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and blood cell counts are usually abnormal during the episodes of arthritis; these tests are used to demonstrate the presence of inflammation. Their abnormalities are not specific for the diagnosis of PAPA syndrome.
Joint fluid analysis: during episodes of arthritis, joint puncture to obtain joint fluid (known as synovial fluid) is usually performed. Synovial fluid from patients with PAPA syndrome is purulent (yellow and dense) and contains an elevated number of neutrophils, a type of white blood cell. This feature is similar to septic arthritis but bacterial cultures are negative. Genetic test: the only test that unambiguously confirms the diagnosis of PAPA syndrome is a genetic test that shows the presence of a mutation in the PSTPIP1 gene. This test is performed on a small amount of blood.

2.3 Can it be treated or cured?

Since it is a genetic disease, PAPA syndrome cannot be cured. However, it can be treated with drugs that control inflammation in joints, preventing joint damage. The same is true for skin lesions, although their response to treatment is slow.

2.4 What are the treatments?

The treatment of PAPA syndrome is different depending on the dominant manifestation. Arthritis episodes usually respond rather promptly to oral or intra-articular corticosteroids. Occasionally, their efficacy may not be satisfactory and arthritis may also recur very often, necessitating long-term corticosteroids that may cause to side effects. Pyoderma gangrenosum shows some response to oral corticosteroids and is also usually treated with local (cream) immunosuppressant and anti-inflammatory drugs. The response is slow and the lesions may be painful. Recently, in single cases, treatment with new biologic drugs that inhibit IL-1 or TNF have been reported to be efficacious for both pyoderma and for treating and preventing the recurrences of arthritis. Because of the rarity of the disease, no controlled studies are available.

2.5 What are the side effects of drug therapy?

Corticosteroid treatment is associated with weight gain, swelling of the face and mood changes. Long-term treatment with these drugs may cause suppression of growth and osteoporosis.

2.6 How long should treatment last?

Treatment is usually aimed at controlling recurrences of arthritis or of skin manifestations and usually it is not administered continuously.

2.7 What about unconventional or complementary therapies?

There are no published reports of effective complementary therapies.

2.8 How long will the disease last?

Affected individuals usually get better as they grow older and disease manifestations may disappear. However, this does not occur in all patients.

2.9 What is the long-term prognosis (predicted outcome and

course) of the disease?
Symptoms get milder with age. However, since PAPA syndrome is a very rare disease, the long-term prognosis is not known.

3. EVERYDAY LIFE

3.1 How might the disease affect the child and the family's daily life?
Acute episodes of arthritis impose limitations on daily activities. However, if treated appropriately, they respond rather promptly. Pyoderma gangrenosum may be painful and respond rather slowly to treatment. When skin involvement affects visible body parts (e.g. the face), this can be very distressing to patients and parents.

3.2 What about school?
It is essential to continue education in children with chronic diseases. There are a few factors that may cause problems for school attendance and it is therefore important to explain the child's possible needs to teachers. Parents and teachers should do whatever they can to allow the child 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. Future integration in the professional world is essential for a young patient and is one of the aims of the global care of chronically ill patients.

3.3 What about sports?
Activities can be performed as tolerated. Therefore, the general recommendation is to allow patients to participate in sports activities and to trust that they will stop if a joint hurts and to advise sports teachers to prevent sport injuries, in particular for adolescents. Although sports injuries may precipitate joint or skin inflammation, these can be treated promptly and the ensuing physical damage is much smaller that the psychological damage of being prevented from playing sports with friends because of the disease.

3.4 What about diet?

There is no specific dietary advice. In general, the child should observe a balanced, normal diet for his/her age. A healthy, well-balanced diet with sufficient protein, calcium and vitamins is recommended for a growing child. Overeating should be avoided in patients taking corticosteroids because these drugs may increase appetite.

3.5 Can climate influence the course of the disease?

No, it cannot.

3.6 Can the child be vaccinated?

Yes, the child can be and should be vaccinated; however, the treating physician should be informed before administering live attenuated vaccines to give proper advice on a case–by-case basis.

3.7 What about sexual life, pregnancy, birth control?

So far, no information on this aspect in patients is available in the literature. As a general rule, like for other autoinflammatory diseases, it is better to plan a pregnancy in order to adapt treatment in advance due to the possible side effect of biologic agents on a foetus.