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PAPA SYNDROME

What is it?

The acronym PAPA means **P**iogenic **A**rthritis, **P**ioderma gangrenosum and **A**cne. It is a genetically determined disease. The syndrome is characterized by a triad of symptoms that includes recurrent arthritis, a kind of skin ulcers, known as pyoderma gangrenosum, and a kind of acne, known as cystic acne.

How common is it?

PAPA syndrome appears to be very rare. Very few families (less than 10) have been described. However, the frequency of the disease is not known exactly, and may be underestimated. It affects male and females equally. Usually the disease appears during childhood.

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, which plays a role in the regulation of the inflammatory response.

Is it inherited?

PAPA syndrome is inherited as an autosomal dominant disease. It means that it is not linked to gender. It means also that one parent shows at least some symptoms of the disease and usually more than one affected individual may 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.

Why has my child got 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.

Is it contagious?

PAPA syndrome is not contagious.

What are the main symptoms?

The most common symptoms of the disease are arthritis, pyoderma gangrenosum and cystic acne. Rarely all three are present in the same patient at the same time. Arthritis occurs usually early in childhood (first episode between 1 and 10 year 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, have usually a later onset and involve the legs. Cystic acne usually appears during adolescence and may persist into adulthood involving face and trunk.

Is the disease the same in every child?

It is not the same in every child. An individual carrying the mutation in the gene may not exhibit all the symptoms of the disease, or even exhibit very mild symptoms (variable penetrance). Moreover, the symptoms may change, usually improving, as a child grows older.

How is it diagnosed?

Clinical suspicion: 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 investigation into the family history should also be performed: since the disease is autosomal dominant, other family members show at least some symptoms of the disease. Results from laboratory tests (see below) may support the clinical suspicion, but there is no laboratory test that provides the diagnosis.

Genetic analysis: for the last 5 years it has been possible to perform genetic analysis to ascertain the presence of mutations in the PSTPIP1 gene

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 (so called synovial fluid) is usually performed. Synovial fluid from patients with PAPA syndrome is purulent (yellow and dense) and contains an elevated number of neutrophils, similar to septic arthritis. However, bacteria are not found in synovial fluid and 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 mutation in the PSTPIP1 gene. This is performed on small amounts of blood.

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.

What are the treatments?

The treatment of PAPA syndrome is different depending on the dominant manifestation. Arthritis episodes usually respond rather promptly to oral corticosteroids, or intraarticular corticosteroids. Occasionally their efficacy may not be satisfactory and arthritis may also recur very often, necessitating long-term corticosteroids that may expose 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.

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.

How long should treatment last for?

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

What about unconventional or complementary therapies?

There are no published reports of effective complementary medicine

How long will the disease last for?

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

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

Everyday life

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

Acute episodes of arthritis impose limitation of daily activities. However, if treated appropriately they respond rather promptly. Pyoderma gangrenosum may be painful and respond rather slowly to treatment.