www.printo.it/pediatric-rheumatology/GB/intro

NLRP-12 Related Recurrent Fever

Version of 2016

1. WHAT IS NLRP-12-RELATED RECURRENT FEVER

1.1 What is it?

NLRP-12-related recurrent fever is a genetic disease. The responsible gene is called NLRP12 (or NALP12), which has a role in inflammatory signalling pathways. Patients suffer from recurrent bouts of fever accompanied by a variety of symptoms such as headache, joint paint or joint swelling and skin rash. Symptoms are probably triggered by cold exposure. Untreated, the disease could be very debilitating but it is not life-threatening.

1.2 How common is it?

The disease is very rare. Currently, fewer than 10 patients have been identified worldwide.

1.3 What are the causes of the disease?

NLRP-12 related recurrent fever is a genetic disease. The responsible gene is called NLRP12 (or NALP12). The genetically modified gene is responsible for a disturbance of the inflammatory response of the body. The exact mechanism of this disturbance is still under investigation.

1.4 Is it inherited?

NLRP-12 related recurrent fever is inherited as an autosomal dominant disease. This means that to have NLRP-12 related recurrent fever, an individual needs to have one affected parent. Sometimes, there is no

other member of the family suffering of recurrent fever: either the gene has been damaged at the child's conception (known as de novo mutation) or the parent who carries the mutation may not exhibit the clinical symptoms or exhibits only a very mild form of the disease (variable penetrance).

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

The child has the disease because he/she inherited the disease from one parent who carries a NLRP-12 gene mutation, unless a de novo mutation has occurred. The person who carries the mutation may or may not exhibit the clinical symptoms of NLRP-12-related recurrent fever. The disease cannot currently be prevented.

1.6 Is it infectious?

NLRP-12 related recurrent fever is not an infectious disease. Only genetically-affected subjects can develop the disease.

1.7 What are the main symptoms?

The main symptom is fever. Fever lasts about 5-10 days and recurs at irregular intervals (weeks to months). The bouts of fever are accompanied by a variety of symptoms. These may include headache, joint pain and joint swelling, urticarial rash and myalgia. Fever bouts are probably triggered by cold exposure. In one family only, sensorineural hearing loss was observed.

1.8 Is the disease the same in every child?

The disease is not the same in every child; the disease varies between a mild and a more severe form. Moreover, the type, duration and severity of attacks may be different each time, even in the same child.

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

As patients grow up, the fever attacks seem to become fewer and milder. However, some disease activity will remain in most if not all

affected individuals.

2. DIAGNOSIS AND TREATMENT

2.1 How is it diagnosed?

A medical expert will suspect this disease on the basis of clinical symptoms identified during a physical examination and from taking a family medical history.
Several blood analyses are useful to detect inflammation during the attacks. The diagnosis is confirmed only by genetic analysis providing evidence of mutations. Differential diagnoses are other conditions presenting with recurrent fever, especially cryopyrin-associated periodic syndromes.

2.2 What is the importance of tests?

As above, laboratory tests are important in diagnosing NLRP-12-related recurrent fever. Tests such as CRP, serum Amyloid A protein (SAA) and whole blood count are important during an attack to assess the extent of inflammation.
These tests are repeated after the child becomes symptom-free to observe if the results are back to or near normal. A small amount of blood is also needed for the genetic analysis.

2.3 Can it be treated or cured?

NLRP-12-related recurrent fever cannot be cured. There is no effective preventive treatment for attacks. Treating the symptoms can reduce inflammation and pain. Some new drugs to control inflammatory symptoms are currently under investigation.

2.4 What are the treatments?

The treatments for NLRP-12-related recurrent fever include non-steroidal anti-inflammatory drugs such as indomethacin, corticosteroids such as prednisolone and possibly biologic agents such as anakinra. None of these drugs appears to be uniformly effective, although all of them appear to help in some patients. Proof of their efficacy and safety

in NLRP-12-related recurrent fever is still lacking.

2.5 What are the side effects of drug therapy?

Side effects depend on the drug that is used. NSAIDs may cause headaches, stomach ulcers and kidney damage, corticosteroids and biologic agents may increase susceptibility to infections. In addition, corticosteroids may cause a wide variety of other side effects.

2.6 How long should treatment last?

There are no specific data to support life-long therapy. Given the normal tendency for improvement as patients grow up, it is probably wise to attempt drug withdrawal in patients whose disease appears to be quiescent.

2.7 What about unconventional or complementary therapies?

There are no published reports of effective complementary remedies.

2.8 What kind of periodic check-ups are necessary?

Children affected with NLRP-12-related recurrent fever should have blood and urine tests at least twice a year.

2.9 How long will the disease last?

The disease is life-long, although symptoms may get milder with age.

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

NLRP-12-related recurrent fever is a life-long disease, although symptoms may get milder with age. As the disease is very rare, the exact long-term prognosis is still unknown.

3. EVERYDAY LIFE

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

Quality of life can be affected by recurrent episodes of fever. There can often be considerable delay before the correct diagnosis is made, which may give rise to parental anxiety and sometimes to unnecessary medical procedures.

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 care of chronically ill patients.

3.3 What about sports?

Playing sports is an essential aspect of the everyday life for any child. One of the aims of therapy is to allow children to conduct a normal life as much as possible and to consider themselves not different from their peers. All activities can therefore be performed as tolerated. However, restricted physical activity or rest may be necessary during attacks.

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?

Cold temperatures may trigger symptoms.

3.6 Can the child be vaccinated?

Yes, the child can be and should be vaccinated; however, the treating physician should be informed before giving live attenuated vaccines as these may be incompatible with some therapies.

3.7 What about sexual life, pregnancy, birth control?

To date, 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 biologics agents on a foetus.