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Mevalonate Kinase Deficiency (MKD), or Hyper IGD Syndrome

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1. WHAT IS MKD

1.1 What is it?

Mevalonate kinase deficiency is a genetic disease. It is an inborn error of the body’s chemistry. Patients suffer from recurrent bouts of fever, accompanied by a variety of symptoms. These include painful swelling of lymph nodes (especially in the neck), skin rash, headache, sore throat, ulcers in the mouth, abdominal pain, vomiting, diarrhoea, joint pain and joint swelling. Severely affected individuals can develop life-threatening fever attacks in infancy, developmental delay, impaired vision and kidney damage. In many affected individuals, a blood component, immunoglobulin D (IgD), is elevated, giving rise to the alternative name of "hyper IgD periodic fever syndrome".

1.2 How common is it?

The disease is a rare entity; it affects people of all ethnic groups but is more common among the Dutch. The frequency of the disease, even in the Netherlands, is very low. Fever attacks start before the age of six years in the vast majority of patients, usually in infancy. Mevalonate kinase deficiency affects both boys and girls equally.

1.3 What are the causes of the disease?

Mevalonate kinase deficiency is a genetic disease. The responsible gene is called MKD. The gene produces a protein, mevalonate kinase.

Mevalonate kinase is an enzyme, a protein that enables a chemical reaction that is required for normal health; this reaction is the conversion of mevalonic acid to phosphomevalonic acid. In patients, both available copies of the MVK gene are damaged, resulting in insufficient activity of the mevalonate kinase enzyme. This results in accumulation of mevalonic acid, which will appear in the urine during fever flares. Clinically, the result is recurrent fever. The worse the mutation in the MVK-gene, the more severe the disease tends to be. Although the cause is genetic, fever attacks can sometimes be provoked by vaccinations, viral infections, injury or emotional stress.

1.4 Is it inherited?

Mevalonate kinase deficiency is inherited as an autosomal recessive disease. This means that to have mevalonate kinase deficiency, an individual needs two mutated genes, one from the mother and the other from the father. Hence, both parents are generally carriers (a carrier has only one mutated copy but not the disease) and not patients. For such a couple, the risk of having another child with mevalonate kinase deficiency is 1:4.

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

The child has the disease because it has mutations in both copies of the gene that produces mevalonate kinase. The disease cannot be prevented. In very severely affected families, antenatal diagnosis can be considered.

1.6 Is it infectious?

No, it is not.

1.7 What are the main symptoms?

The main symptom is fever, often starting with shaking chills. Fever lasts about 3-6 days and recurs at irregular intervals (weeks to months). The bouts of fever are accompanied by a variety of symptoms. These may include painful swelling of lymph nodes (especially in the neck), skin rash, headache, sore throat, ulcers in the mouth, abdominal pain,

vomiting, diarrhoea, joint pain and joint swelling. Severely affected individuals can develop life-threatening fever attacks in infancy, developmental delay, impaired vision and kidney damage.

1.8 Is the disease the same in every child?

The disease is not the same in every child. 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 tend to become fewer and milder. However, some disease activity remains in most if not all affected individuals. Some adult patients develop amyloidosis, which is organ damage due to abnormal protein deposition.

2. DIAGNOSIS AND TREATMENT

2.1 How is it diagnosed?

The diagnosis is based on chemical studies and genetic analysis. Chemically, abnormally high mevalonic acid can be detected in urine. Specialised laboratories can also measure the activity of mevalonate kinase enzyme in the blood or skin cells. Genetic analysis is performed on DNA of the patient, in which the mutations to the MVK genes can be identified.
Measurement of serum IgD concentration is no longer considered a diagnostic test for mevalonate kinase deficiency.

2.2 What is the importance of tests?

As mentioned above, laboratory tests are important in diagnosing mevalonate kinase deficiency.
Tests such as erythrocyte sedimentation rate (ESR), CRP, serum Amyloid-A-protein (SAA), whole blood count and fibrinogen 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 sample of urine is also tested for the presence of protein and red blood cells. There may be temporary changes during attacks. Patients with amyloidosis will have persistent levels of protein in urine tests.

2.3 Can it be treated or cured?

The disease cannot be cured, nor is there a proven effective treatment to control disease activity.

2.4 What are the treatments?

The treatments for mevalonate kinase deficiency include non-steroidal anti-inflammatory drugs such as indomethacin, corticosteroids such as prednisolone and biologic agents, such as etanercept or anakinra. None of these drugs appears to be uniformly effective but all of them appear to help in some patients. Proof of their efficacy and safety in mevalonate kinase deficiency 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 increase susceptibility to infections. In addition, corticosteroids may cause a wide variety of other side effects.

2.6 How long should treatment last?

There is no data to support life-long therapy. Given the normal tendency for improvement as patients grow older, 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 being treated should have blood and urine tests at least twice yearly.

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?

Mevalonate kinase deficiency is a life-long disease, although symptoms may get milder with age. Very rarely, patients develop organ damage, especially to the kidneys, due to amyloidosis. Very severely affected patients may develop mental impairment and night-blindness.

2.11 Is it possible to recover completely?

No, because it is a genetic disease.

3. EVERYDAY LIFE

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

Frequent attacks disrupt normal family life and may interfere with a parent's or patient's job. There is often 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?

Frequent attacks cause problems with school attendance. Teachers should be informed about the disease and what to do in the event that an attack starts at school.

3.3 What about sports?

There is no restriction in terms of sports. However, frequent absence from matches and training sessions may hamper participation in

competitive team sports.

3.4 What about diet?

There is no specific diet.

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, even though this may provoke fever attacks.
However, if the child is on treatment, the treating physician should be informed before administering live-attenuated vaccines.

3.7 What about sexual life, pregnancy, birth control?

Patients with mevalonate kinase deficiency can enjoy normal sexual activity and have children of their own. During pregnancy, attacks tend to decrease. The chance of a partner who carries mevalonate kinase deficiency is extremely small, except when the partner comes from the same extended family as the patient. When the partner is not a carrier of mevalonate kinase deficiency, their children cannot get mevalonate kinase deficiency.