



Mevalonate kinase Deficiency (MKD) (or Hyper IgD syndrome)

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, diarrhea, 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".

How common is it?

The disease affects people of all ethnic groups, but is relatively common among the Dutch. The frequency of the disease, even in The Netherlands, is very low. World-wide the disorder has been recognized in just ... people. Fever attacks start before the age of six years in the vast majority of patients, usually in infancy. Mevalonate kinase deficiency can affect both boys and girls equally.

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. That 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. Clinically, the result is recurrent fever. The worse the damage to 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.

Is it inherited?

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

Why has my child got this 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

Is it contagious?

No, it is not.

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

Is the disease the same in every child?

It 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.

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 will remain in most if not all affected individuals. Some adult patients develop amyloidosis, which is organ damage due to abnormal protein deposition.

How is it diagnosed?

The diagnosis can be made by chemical studies or by genetic analysis.

Chemically, the abnormally high mevalonic acid can be detected in urine. Specialized laboratories can also measure the activity of the mevalonate kinase enzyme in blood or skin cells.

Genetic analysis is performed on DNA from the patient, in which the damage to the MVK genes (mutations) can be identified.

Measurement of serum IgD concentration is no longer considered a diagnostic test for mevalonate kinase deficiency.

What is the importance of tests?

a) Blood tests: The laboratory tests, as mentioned before, are important in diagnosing mevalonate kinase deficiency. Tests like erythrocyte sedimentation rate (ESR), CRP, serum Amyloid-A-protein (SAA), whole blood count and fibrinogen are ordered during an attack to see the extent of inflammation.

These are repeated after the child becomes symptom-free, to observe if the results are back to normal, or near normal.

b) Urine test: 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.

Can it be treated or cured?

It cannot be cured and neither is there a proven effective treatment to control disease activity.

What are the treatments?

The treatments for mevalonate kinase deficiency include non steroidal anti-inflammatory drugs such as indomethacin, corticosteroids, such as prednisolone, statins, such as simvastatin, and biologicals, such as etanercept (Enbrel®) or anakinra (Kineret®). 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.

What are the side effects of drug therapy?

This depends on the drug that is used. NSAID's can give rise to headaches, stomach ulcers and kidney damage, corticosteroids and biologicals increase susceptibility to infections. In addition, corticosteroids may cause a wide variety of side effects.

How long should treatment last for?

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

What about unconventional or complementary therapies?

There are no published reports of effective complementary remedies

What kind of periodic check-ups are necessary?

Children being treated should have blood and urine tests for at least twice yearly.

How long will the disease last for?

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

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

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

Is it possible to recover completely?

No, because it is a genetic disease.

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

Frequent attacks disrupt normal family life and may interfere with the parents' or patient's job. There is often considerable delay before the correct diagnosis is made, which gives rise to parental anxiety and sometimes to unnecessary medical procedures.

What about school?

Frequent attacks cause problems with school attendance. With effective treatment, this is less of a problem.

The teachers should be informed about the disease and what to do in case an attack starts at school.

What about sports?

There is no restriction to sports. However, frequent absence from matches and training sessions may hamper participation in competitive team sports.

What about diet?

There is no specific diet.

Can climate influence the course of the disease?

No, it cannot.

Can the child be vaccinated?

Yes, the child can be and should be vaccinated, even though this may provoke fever attacks.

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 marrying 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 no carrier of mevalonate kinase deficiency, their children cannot get mevalonate kinase deficiency.