



Hyper-IgD syndrome (HIDS)

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1. Introduction

For whom is this information?

This information is meant primarily for people with the hyper-IgD syndrome (also abbreviated to HIDS). Here you'll find among other things general information on the disease, the tests that can be done, what is known about treatment and about heredity. You may come to some information which does not directly concerns you, but which applies to others with this disease. It might be useful for your partner, relatives and friends to read this brochure as well. That will make it easier to think about and discuss the disease.

HIDS is a rare disorder, which has only been appreciated for the last few years. Many doctors will therefore hardly know about this syndrome, if at all. At the department of General Internal Medicine of the University Medical Center St. Radboud, Nijmegen, in the Netherlands, there is a research interest in HIDS and other periodic fever syndromes. Physician-scientists involved in this research are drs. A. Simon, J.P.H. Drenth and prof.dr. J.W.M. van der Meer. This research group has also initiated a website with information on HIDS (hids.net).

If you have questions after reading this information, don't hesitate to get answers. You can contact us or of course your own specialist or family doctor. We would also like to hear any comments on or suggestions for improvement for this brochure.

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HIDS in brief

The hyper-IgD syndrome, which can yet be abbreviated to HIDS, is a rare disorder involving repeated episodes of high fever accompanied by other signs of inflammation, like swollen lymph nodes, fatigue, headache, muscle ache and stomach ache. Such a fever attack usually lasts a few days, after which it disappears spontaneously. In blood samples, high levels of a certain protein, the IgD, are found. It is a hereditary disease, and DNA-tests can be performed to diagnose the syndrome. No effective treatment is known.

2. Basic information

HIDS – what are the symptoms?

People with the disease HIDS suffer from ever-recurrent periods, “attacks”, of high fever. Such a fever attack often lasts about four to six days, but it can be shorter or longer. This is different from person to person, and also from attack to attack. Often, it is a high, spiking fever. In young children, the fever can get so high that it causes fever convulsions. Other symptoms that can occur during a fever attack:

- exhaustion
- swollen lymph nodes, especially in the neck
- stomachache, diarrhea, nausea, vomiting, loss of appetite
- pain in muscles and joints
- headache
- small ulcers (aphthous ulcers) in mouth or on genital organs
- red spots on the skin

After the end of an attack these symptoms will disappear, although it sometimes takes a few days longer before all symptoms have disappeared. The severity of symptoms can be very variable in different attacks. Generally, outside the fever episodes, a person with HIDS does not feel ill.

Most persons with HIDS experience their first fever attack at a very young age, often in the first year of life. However, it can be manifested for the first time later in life. How often these fever attacks occur varies from person to person. Some people have an attack every month, or even more often. Others have a fever episode for example about six times a year. This can also change in the course of life. Sometimes, a person does not have any symptoms of disease for months, and then he gets a few attacks in a row. Children often have very frequent fever attacks. In many people the pattern of the disease changes during puberty or just after, and often the attacks occur less often afterwards. But unfortunately this does not always happen.

Certain things seem able to provoke an attack. Many people with HIDS notice that a fever attack often starts at a time of physical or emotional stress. For example, often there will be an attack after an operation, or in an exam period. Women with HIDS sometimes notice a relation to the menstrual cycle, and for example no attacks during pregnancy, while delivery is followed by a major fever episode. Another often-implicated factor is vaccination – children with HIDS almost always get a fever attack after vaccination.

HIDS is a rare disorder. Worldwide, about 200 patients are known with this disease. It occurs in both men and women with the same frequency. It is a hereditary disease, it can occur in several brothers or sisters from one family. HIDS does not cause an early death; people with HIDS live a normal life span as far as we know. It does not have a direct influence on the growth and development of a child, although the frequent episodes of illness can of course have an influence, for example through missed time at school.

How is the diagnosis made?

A fever attack is an inflammatory process. The results of laboratory examinations and other tests during such an episode will all fit with inflammation. For example a raised sedimentation rate and a high white blood cell count. But these results are not typical only for HIDS.

There are numerous causes of fever and inflammation. Most of these occur much more often than the rare disorder HIDS. HIDS is so rare that many doctors know little about it, and will not think of this diagnosis. Often, a lot of tests are done to exclude many possible causes of fever and inflammation. Often, these tests do not yield a clear result in people with HIDS, unless of course they have some other disease as well. Most people with HIDS can recount a childhood with numerous hospital admissions and countless medical examinations.

To make the diagnosis HIDS the first step is that the physician considers this rare disease. A suspicion of HIDS is strengthened by a typical disease course: lifelong recurrent fever attacks without a clear cause, which last a few days and resolve spontaneously, and sometimes similar symptoms in a brother or sister. Sometimes, however, the course of the disease is less characteristic.

Immunoglobulin D (IgD)

An important test is the determination of the concentration of immunoglobulin D (IgD) in the blood. HIDS patients usually have a very high concentration of IgD. For this test a blood sample is drawn. To be sure about the result, this examination is often done twice at different times. The patient does not need to have a fever at the time of drawing the blood sample.

DNA-analysis

Because it is known in which part of the inherited information the faults that cause HIDS are located (in most cases), it is possible to prove the genetic disposition for this disorder by analysis of DNA. DNA is found in all cells of the body, which includes white blood cells. Most often a blood sample is used to perform the DNA analysis. Bear in mind that it can take some months before you get the results, because it is a time-consuming examination. The patient does not need to have a fever at the time of drawing the blood sample.

Mevalonic acid

It is also possible to measure the concentration of mevalonic acid in a urine sample to make a diagnosis. In HIDS patients, this concentration will be high during a fever attack. However, the concentration will be still too low for the routine assays; only specific assays will be able to detect the peak in mevalonic acid during the fever attack.

Some patients suffer from the typical fever attacks, but do not carry the expected defects in the specific bit of DNA. The DNA analysis in these persons will therefore not yield anything, and the mevalonic acid concentration in the urine during fever will not be high. These patients do have a form of HIDS, but it is not known what the exact cause of the disease is in those cases.

Treatment

HIDS cannot be cured. It is caused by a defect in the genes that cannot be corrected. To control the symptoms of fever and pain many patients benefit from the use of non-specific drugs like paracetamol (acetaminophen). A recent study in a group of adult HIDS patients showed that simvastatin will in most patients diminish the number of days of illness (although it did not stop all fever attacks). Simvastatin is a drug often used for other reasons, most often to lower cholesterol; it has relatively few side effects, and no side effects were observed in the HIDS patients. Simvastatin has not been formally tested in children with HIDS. Research into other forms of treatment, including treatment only used at times of fever, is being carried out.

A lot of people with HIDS who have suffered from fever attacks for a long time do not visit a doctor each time, because they know what is happening and how to deal with it. In case of a fever episode which is different from usual, more severe or with other symptoms, or which persists, we do recommend that you visit your family doctor or specialist. He or she can then determine whether there is not something else going on. For people with HIDS of course have as much chance to get another illness as others.

What is the cause of HIDS?

The exact answer to this question is not known yet. We know that a certain protein does not function properly in a person with HIDS because of a defect in the hereditary information (this protein is called mevalonate kinase, see also the background information in the next chapter). It is unknown what this protein has to do with inflammation and fever exactly.

It seems to be a defect in the control of inflammatory reactions. The body possesses a complicated inflammation and immune system. This system is so complicated that a lot of details are unexplained as of yet. One of its functions is to get rid quickly of substances that do not belong in the body. For example, imagine a splinter in your finger: if this remains in place, within a short time an inflammatory reaction will start at that spot to get rid of the splinter. You notice this because the spot will get hot and red, and will pulsate. If it gets worse, you can even get a fever. But as soon as the splinter drops out, the inflammation is not necessary any more and is only annoying. The body therefore has the ability to turn off an inflammatory reaction when it is not needed any more. Usually, this system is so well ordered that most problems, such as a small wound or bacteria, are resolved with a very small local inflammation, which you do not even notice yourself. This probably occurs every day. Only if the problem gets to big to deal with in such a manner, you start to notice it: you for example get symptoms of a cold because of a virus which you can not get rid of quickly enough or you get diarrhea after eating contaminated food.

It appears to be that in HIDS there is a defect of the turning off of the inflammatory system, which can more easily lead to an exaggerated inflammatory response. In a situation where another person will for example not even notice that his inflammatory system has got rid of a virus, in a person with HIDS the inflammation will get going and will keep on going, even after the virus has long since disappeared. This will lead to a severe inflammatory reaction with fever and for example pain in muscles and joints. Only after a longer period, the inflammation dies out. The exact reason for the attacks in HIDS is unclear yet.

To emphasize: patients with HIDS do not have an impaired immune system, they are not more prone than others to catch a bacteria or a virus. At the time of a fever attack there is an inflammatory reaction, but no bacteria. Antibiotics will therefore not help to dissolve all fever attacks. Of course, someone with HIDS can just as well as everyone be infected with a bacteria, but this does not happen more often than in healthy persons. Exposure to a bacteria can probably provoke a fever attack: the body tries to get rid of the bacteria by means of an inflammatory reaction, and that reaction is not stopped promptly, as explained in the previous paragraph. For example, many patients are sure to get a fever attack when there is flu going around: probably the flu virus is the triggering factor in that case.

Patients platform

Due to its incapacitating attacks that occur very frequently, HIDS has a great impact on social and cultural life. The recurrent periods of illness profoundly affects family life. In most families, life is centered on the patient with HIDS, which may have subsequent disadvantageous consequences. Patients with a chronic illness such as HIDS need support, acknowledgement and information.

On two occasions (Utrecht, 18-1-1996 and Nijmegen, 25-8-1999) Dutch HIDS patients convened. On the last occasion, four patients took the initiative to create a patients platform.

Goal of this platform is to create a knowledge center with information for (new) patients, to stimulate contact between patients, to keep patients informed about the latest developments and eventually to found an official association for HIDS patients which status can hopefully provide us with more possibilities.

For further details or suggestions you can contact one of the initiators of this platform. The email address can be found at the website: hids.net.

3. Background information

More on HIDS

What is the origin of the name?

This disorder is officially called “hyper-immunoglobulinemia D and periodic fever syndrome”. It was first described under this name in 1984. Within a short period of time, Prof. van der Meer and his colleagues saw a number of patients with strange, unexplained fever attacks, who all had high concentrations of IgD in their blood. It turned out that this had to be a disease that had not been described before. The disorder is often abbreviated to “hyper-IgD syndrome” or “HIDS”.

What is immunoglobulin D (IgD)?

Immunoglobulin D (IgD) is a protein produced by a certain type of white blood cells. A lot is known about other immunoglobulins (like IgG, IgA and IgM), they play an important role in the immune system. The function of IgD is still unclear. Patients with HIDS have a high concentration of this IgD in their blood.

There are a diversity of other diseases in which a high concentration of IgD can be found, which include tuberculosis, Pfeiffer’s disease and chronic bronchitis.

What is mevalonate kinase?

In 1999 it was discovered where exactly in the inherited information the fault lies in patients with HIDS. It turned out to be in a piece of DNA that contains information for the production of a specific protein called mevalonate kinase. This mevalonate kinase is a central enzyme in a number of metabolisms in the cell, which leads for example to cholesterol formation. In HIDS this mevalonate kinase does not function properly. Why this defect leads to fever attacks is not yet known.

Where is the predisposition located?

Our body is made up of little living units, which we call cells. Each cell has a nucleus in which are found 23 pairs of chromosomes. Chromosomes are largely made up out of DNA. This DNA contains all our inherited information, which determines all the characteristics of our body.

One pair of chromosomes contains one chromosome with inherited information from the mother and one from the father. Each separate chromosome of a pair contains information of identical characteristics. Everyone therefore has two copies for the predisposition of every characteristic.

Genes

A gene is a little piece of chromosome. It is built up out of DNA. One gene contains the information for one inherited predisposition. It is estimated that a human being has about 50.000 to 100.000 genes. Genes give a cell the information on what the function of that cell should be. Genes are for example responsible for blood types, color of the eyes, and the development of a cell into a muscle cell. There are also genes that control the production by the cell of substances that can inhibit or activate an inflammatory response.

Mutations

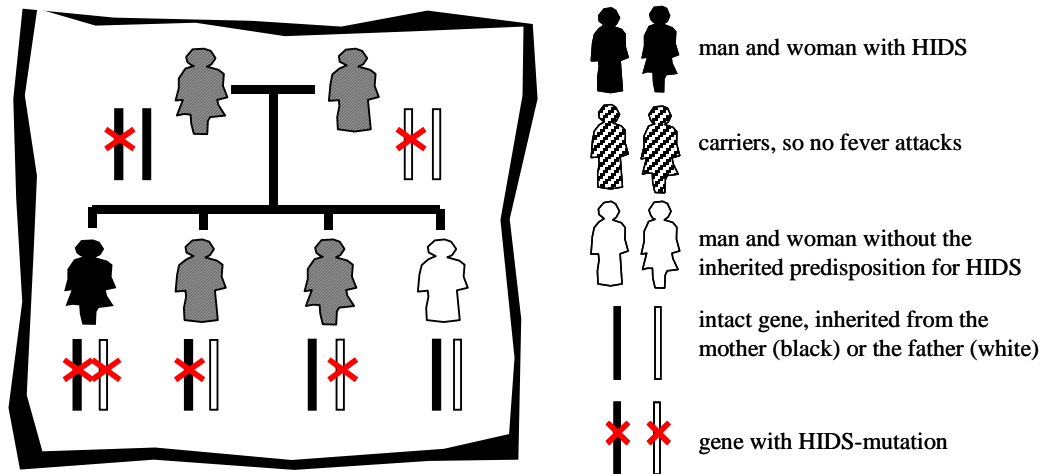
The DNA, that is, the inherited information, has to be copied a lot. This happens for example when reproductive cells are formed, but also when new cells for skin, blood or intestines are made. This copying can lead to mistakes. This happens very often. Some mistakes are recognized and corrected by mechanisms in the cell. Others remain. Most mistakes have no consequences, because they are located in a part of the DNA that is not used, or because the other chromosome of a pair, with the same information, compensates them. If such a mistake does have consequences, it is called a mutation. A gene containing a mutation often does not function properly.

From mutation to disease

HIDS is caused by mutations, that is small mistakes, in the inherited information, in one specific gene (called the mevalonate kinase gene). Both chromosomes of a pair with the gene must contain the mutation to get the disease. Someone who has a mutation in one copy of the gene and one copy without the mutation will not get fever attacks. Such a person is called a "carrier".

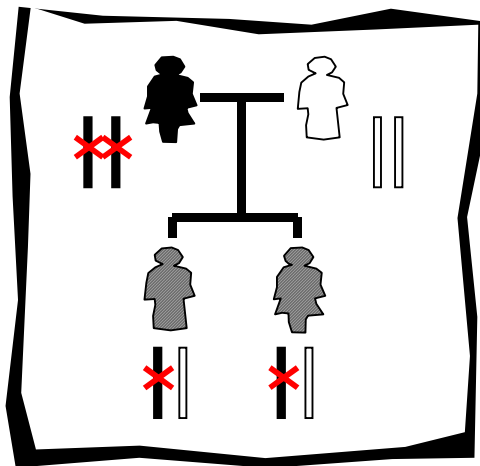
So how about the heredity?

Every child gets one copy of all his chromosomes from his father and one from his mother. A child will only get ill if both parents transmit a gene with the mutation to their child. Which copy of the gene is transmitted by the parent to his or her child is purely coincidental. In the next figures a few possibilities are discussed.



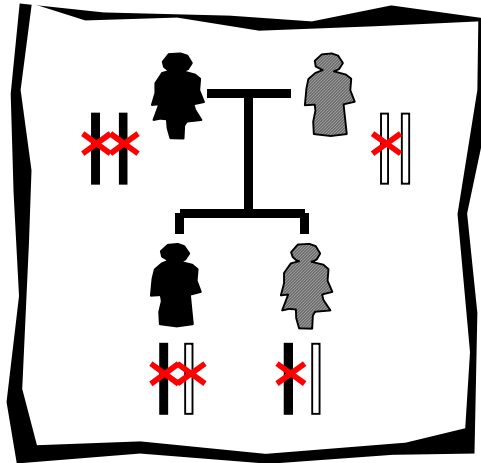
• Figure 1

Someone with HIDS has two HIDS-mutations. Both parents must therefore be a carrier of such a mutation – see figure 1. The risk of a child of parents who are both carriers to get the disease is 25% (1 in 4). In half of all cases, the child of such parents will be a carrier of the mutation. But a child does not always get the inherited predisposition. The inheritance of genes is purely coincidental – so it can also happen that for example 3 out of 4 children of such parents get the disease. Or none of the children.



• Figure 2

What happens to children of a person with HIDS? The most common situation is depicted in figure 2. Someone with HIDS, so who has 2 HIDS-mutations, has children together with someone without the inherited predisposition. These children will all be carriers of a HIDS-mutation. They will always get one gene with the mutation from the parent with HIDS and one normal gene of the healthy parents. The children in this case will therefore not be ill themselves.



• Figure 3

The only way in which it can happen that someone with HIDS gets a child who also suffers from HIDS is shown in figure 3. The partner of the HIDS-patient has to be, by coincidence, carrier of a HIDS-mutation. In such a case there is a 50% chance that their child will get the disease. However, this is a very exceptional situation. At this moment, no family with HIDS is known in which this has happened, because the disease is so rare. A rough estimate is that at most about 1 in 500 persons in the Netherlands (which has a higher prevalence than other countries) are carrier of a HIDS-mutation. So for a Dutch patient marrying a Dutch partner, the chances of a child with HIDS are at most 1 in 1000.