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RECURRENT FEVERS RELATED TO A GENETIC ANOMALY

General introduction

Recent progresses in research have clearly shown that some rare fever diseases are caused by a genetic anomaly. In many of them, other members of the family can also suffer from recurrent fevers.

What does genetic anomaly mean?

This means that a gene has been modified by an accident called a mutation. This mutation changes the function of the gene which gives wrong information to the body and results in the disease. In every cell, there are two copies of each gene. One copy is inherited from the mother and the other copy is inherited from the father. The mutation can be

a) present in the parents. The inheritance is of 2 different types:

-*recessive*: that means that both parents carry the mutation, on only one of their two genes. They are not ill because the disease occurs only if the two genes are affected. The risk for a child inheriting the mutation from each parent is one in four.

-*Dominant*: that means that one mutation is enough to express the disease. In that case, one of the parents is ill, and the risk for transmission to the child is one in two.

b) absent in the parents. The accident has occurred during the child's conception. It is called *de novo* mutation. There is theoretically no risk for another child (no more than random), but the affected child's offspring has the same risk of being affected as with the dominant mutation (i.e. one in two).

Hereditary recurrent fevers

Familial Mediterranean Fever is counted in this group, see separate section.

Familial hibernian fever or Tumor Necrosis Factor Receptor Associated Periodic Syndrome (TRAPS).

WHAT IS IT?

TRAPS is a dominantly inherited syndrome of recurrent high spiking fevers, usually of two to three weeks duration. The fever is typically accompanied by gastro-intestinal disturbances, painful red skin rashes, muscle pain and periorbital swelling. This disease is very newly recognized and understood.

How common is it?

TRAPS is thought to be a rare disease with less than 100 confirmed cases, however, its true prevalence is currently unknown. It affects males and females equally and the onset seems to be during late childhood, or adulthood.

The first cases were reported in patients from Irish-Scottish ancestry, however the disease has also been identified in other populations: French, Italians, Sephardic and Ashkenazi Jews, Armenians, Arabs and Kabylisians from Maghreb

The seasons and climate have not been demonstrated to influence the course of the disease.

What are the causes of the disease?

TRAPS is due to an inherited anomaly of a protein (Tumor Necrosis F Factor Receptor[TNFR]), which leads to an increase of the patient's normal acute inflammatory response.

An inflammatory hormone named tumor necrosis factor (TNF) overacts, because it is not controlled by the TNFR that normally binds to it and lowers the magnitude of inflammatory response.

Infection, trauma or psychological stress may induce attacks.

Is it inherited?

TRAPS has a dominant pattern of inheritance meaning that more than one case may be observed in a single family, every generation. The gradual reduction of family's intermarriages (sibships) has lowered the possibility of this.

Why has my child got the disease? Can it be prevented?

The child has inherited his disease from one of his parents that carries a TNFR gene mutations unless a *de novo* mutation has occurred.

The person who carries the mutation may, or may not, exhibit the clinical symptoms of TRAPS. The disease cannot currently be prevented.

Is it contagious?

TRAPS is not an infectious disease. Only genetically affected subjects develop the disease.

What are the main symptoms?

The main symptoms are recurrent attacks of fever lasting typically two or three weeks, associated with chills and intense muscle pain involving the trunk and the upper limbs. The typical rash is red and painful, corresponding with underlying inflammation of the skin and muscle area.

Most patients experience a sensation of deep cramping muscle pain at the onset of attacks that gradually increases in intensity and begins to migrate to other parts of the limbs, followed by the appearance of the rash. Diffuse abdominal pain with nausea and vomiting are common. Inflammation of the membrane covering the front of the eye (the conjunctiva), or periorbital swelling, is characteristic of TRAPS, although this symptom can be observed in other diseases.

TRAPS may present somewhat differently with attacks of shorter or longer duration. Chest pain is also reported due to inflammation of the pleural (the membrane surrounding the lungs), or the pericardium (the membrane surrounding a joint) inflammation.

Amyloidosis is the most severe complication of TRAPS, occurring in 14% of patients. It causes large amounts of proteins in the urine and progresses to renal failure.

The relationship between amyloidosis and TRAPS probably relies on both chronic inflammation and genetic factors.

Is the disease the same in every child?

TRAPS presentation varies from one patient to another in terms of the duration of each attack and the duration of symptom-free periods. The combination of the main symptoms is also variable. These differences may be explained, in part, by genetic factors.

How is it diagnosed?

An expert physician will suspect TRAPS 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 ascertained only by genetic analysis providing evidence of mutations.

Differential diagnoses are other conditions presenting with recurrent fever especially Familial Mediterranean fever and HyperIgD syndrome.

What are the treatments?

To date, no treatment exists to prevent or cure the disease. Non-specific anti-inflammatory agents help to relieve symptoms. High dose steroids are often effective but sustained usage leads to serious side effects. Specific TNF blockade has been shown to be an effective treatment in some patients when given at the beginning of an attack.

How long should treatments last for?

The duration of treatment is limited to relieving acute symptoms, since no drug is effective for the prevention of fever attacks.

How long will the disease last for?

TRAPS will manifest at repeated and irregular occasions throughout the life.

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

The prognosis is very variable, the worst prognosis affects only the minority of patients and these patients develop secondary amyloidosis. This risk is difficult to determine, because it depends on both genetic and environmental factors. Amyloidosis is a severe complication and frequently leads to renal failure.

At the present time no one knows if this complication can be avoided.

Is it possible to recover completely?

This possibility is currently unknown, but not excluded. Indeed, the genetic TNFR structural modification does not induce a functional defect in the bodies systems, making the discovery of a cure a perceivable possibility. Moreover, the eventual cessation of exposure to a potential triggering agent may induce sustained remission.

Mevalonate kinase Associated Periodic fever Syndrome (MAPS) (also called hyper IgD syndrome, HIDS)**What is it?**

Patients suffer repeated attacks of high fever with skin rash, swelling of lymph nodes in the neck (lymph nodes are a vital component of the immune system), vomiting,

abdominal pain and diarrhoea. The most severe form of MAPS is an exceptional disease, present at birth, and is also known as mevalonic aciduria.

Patients with this form suffer severe fever attacks as well as poor growth and neurological damage. The mildest form of MAPS, which is discussed here, is known as Hyper IgD and periodic fever Syndrome (HIDS). This name refers to the presence of high levels of a protein called IgD in the blood of the majority of affected patients.

How common is it?

MAPS is a rare disease. Some 200 patients have been described worldwide. Most of these have the mild (HIDS) form. This form is more common in Western Europe, especially in the Netherlands and in France.

MAPS has been described among all ethnicities. Boys and girls are equally affected. The symptoms usually starts in early childhood, most commonly in the first year of life.

What are the causes of the disease?

The cause of MAPS is genetic. The gene affected in MAPS is called *MVK*. *MVK* contains the specifications for the protein mevalonate kinase. Mevalonate kinase is a protein that facilitates a chemical reaction in the body.

Genetically defective enzymes affect our body's metabolism and diseases such as MAPS are, therefore, known as inborn errors of metabolism. In the mild form (HIDS) the enzyme activity is 1-10% of normal.

Despite ongoing research, we do not know how deficiency of mevalonate kinase leads to fever and inflammation, but it does. During the attacks there is generalised inflammation, i.e. the body behaves as if it were battling with a serious infection.

This is reflected in fever, loss of appetite and malaise as well as in the rise in white blood cell levels, sedimentation rate and C-Reactive Protein (CRP) levels in the blood. Since there is no infection that causes the inflammation, MAPS is known as an auto-inflammatory disease.

It is not known how a genetic defect, that is present all the time, leads to a disease that is manifest only during fever attacks. The fever attacks may come spontaneously or be provoked by emotional stress, minor infections and, very typically, by childhood vaccinations.

Women with MAPS may have attacks triggered by the menstrual cycle. When pregnant they tend to have less symptoms.

Is it inherited?

As with most human genes, two copies of *MVK* are present in every body cell. One copy is inherited from the mother, the other copy from the father. Periodic fever only arises when both *MVK* genes are damaged.

This is known as autosomal recessive inheritance (this means that the disease occurs in men and women and neither parent needs to show signs of the disease). The mother and father each carry one damaged *MVK*-gene. Since they also have one normal copy of the gene, they are healthy. Two healthy carriers can pass the damaged genes on to their children.

Every child born to the couple has a 50% chance to become a healthy carrier and a 25% chance to become a MAPS patient.

Unless the patient finds a partner who carries the damaged gene, his or her children will be healthy. The chance of both members of a couple carrying a damaged gene is increased when they are blood relatives.

Is it contagious?

MAPS is not contagious

What are the main symptoms?

Fever attacks, lasting three to seven days, recur every 2-12 weeks. The attacks begin suddenly, often with shaking chills, cold, pale, or even blue, fingers toes and lips and sometimes fever fits.

Headache, abdominal pain, loss of appetite and malaise are common. Most patients experience nausea, vomiting or diarrhea.

Skin rashes, painful ulcers in the mouth and joint pain all occur, but the most striking feature is swelling of the lymph nodes in the neck, or other parts of the body.

Is the disease the same in every child?

Depending on the mutation, the disease may be mild (HIDS) or very severe (Mevalonic Aciduria). Within one family the severity may differ somewhat between affected members

How is it diagnosed?

The disease is suspected on clinical grounds from the findings of a clinical investigation. Although also called Hyper IgD syndrome, IgD can be normal, particularly in young children.

The diagnosis can be suspected on a urine analysis, collected during a fever attack, called chromatography. In disease the chromatography shows an increased level of mevalonic acid. This leads to a special blood test being done to measure the mevalonate kinase activity on blood cells. For research purpose a genetic study may be performed.

What is the importance of tests?

Laboratory exams show a rise in blood markers for inflammation (such as erythrocyte sedimentation rate and C-reactive protein) during attacks. IgD (a circulating immunoglobulin) serum levels are often elevated, although they may be normal in the early stage of the disease.

Can it be treated or cured?

MAPS cannot be cured. An effective treatment to prevent attacks is not available. Research is being done to find a safe and effective therapy

What are the treatments?

Some patients have benefited from Non Steroidal Anti Inflammatory Drugs or prednisone. The effectiveness of TNF blockers and the cholesterol lowering drug Simvastatine is under investigation.

How long will the disease last for?

MAPS is a lifelong disorder.

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

The mild (HIDS) form tends to get less severe with age in many patients. Others may develop arthritis, but HIDS does not lead to irreversible organ damage.

Chronic Inflammatory Neurological Cutaneous Articular syndrome and related diseases

What is it?

Chronic Infantile Neurological Cutaneous Articular (CINCA) syndrome (also called Neonatal Onset Multisystemic Disease (NOMID) in North America) is a rare hereditary recurrent fever syndrome.

The most frequent symptom is a skin rash at birth, or observed within the first weeks of life. The disease is present in infants that there are neurological manifestations, such as chronic meningitis and that joint involvement is one of the most important symptoms.

Two other diseases more often recognised later in life are called Muckle-Wells syndrome (MWS) and Familial Cold Urticaria (FCU). They are related to CINCA as the genetic causes have been identified in the same gene.

How common is it?

CINCA is a very rare condition. Probably less than 100 cases have been recognised in the world.

What are the causes of the disease?

The cause of CINCA is genetic and in half of all cases, a mutation can be found. The genetically modified gene is responsible for a disturbance of the inflammatory response of the body. The exact mechanism of this disturbance is still unknown. No trigger is identified for CINCA flares.

The disease manifests as a skin rash present at birth in most cases. It occurs equally in males and females. It has been observed in all populations, Caucasian, black or Asiatic. There is no seasonal influence.

Is it inherited?

Most often there is no other member of the family suffering of CINCA. In CINCA, the gene has been damaged at the child's conception (called a *de novo* mutation). As there is no mutation in the parents, there is no more risk than random to have another child suffering from CINCA. When someone with CINCA is planning to have children, the risk is 50% of them having a child with CINCA. In cases where no mutation is found, the genetic risk must be considered as similar.

Why has my child got this disease? Can it be prevented?

Since CINCA is a genetic disease, the child born with CINCA will have the disease lifelong. If parents with a child suffering from CINCA want another child, it is justified that they look for genetic counselling. To that end, prenatal diagnosis is justified only

when the mutation has been identified in one parent. To date, there is no way of detecting CINCA anomaly during pregnancy with ultrasonic examination.

Is it contagious?

CINCA is not contagious.

What are the main symptoms?

At birth, half of babies with CINCA are premature. They often seem to have infection, but no germ is found. The first symptom is skin rash resembling non-itching urticaria. It varies in intensity during the day. The second symptom occurs in joints and pain is frequent.

Sometimes transient swelling can be observed without joint deformity. In severe cases (less than 50%), an overgrowth of cartilage, the epiphysis (extremity of the bone), or the knee cap, can be present, resulting in joint deformity. Bone anomalies show up on X-rays.

Chronic headaches result from a chronic meningeal inflammation. The skull is often slightly increased in size. In some children, there is delayed closure of the anterior fontanel.

Increased intracranial pressure is probably responsible for headaches. Eye abnormalities occur with time. Some children may develop visual impairment. Perceptive deafness (in various degrees) is present.

There is progressive growth retardation. In older children, the hands appear short and thick and there may be clubbing (thickening) of the extremity of fingers and toes.

Is the disease the same in every child?

No, the disease varies between a mild form, and very severe involvement. About 10% have no meningeal inflammation. Less than 50% have severe joint involvement.

How is it diagnosed?

CINCA is suspected on clinical grounds and confirmed by genetic analysis. A genetic abnormality is found in 50% of cases. Other cases are probably due to one or more unknown genetic anomalies.

Can it be treated or cured?

CINCA cannot be cured. There is no preventive treatment for attacks. Treating the symptoms can reduce inflammation and pain. Recent research has identified new drugs currently under investigation

What are the treatments?

Non steroidal anti-inflammatory drugs, corticosteroids and pain relieving drugs, are used. There is no curative treatment. Attempts at treating this disease with anti TNF drugs, such as Etanercept, had controversial effects.

Physical therapy is extremely important when joint deformity occurs. Splints and walking aids might be necessary.

Hearing aids must be adapted in children with deafness. In growing children, when eye involvement induces a visual loss due to corneal deposits, eye surgery with a cornea graft has been performed.

The orthopaedic surgeon must be involved in treatment, to reduce deformities, if necessary.

How long will the disease last for?

CINCA is a lifelong disorder.

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

Children with CINCA may have growth disturbances during the course of the disease. The functional prognosis of CINCA depends on the severity of joint involvement. The long term prognosis also depends on the severity of chronic meningitis. Some rare cases of fatalities seem to be related to brain damage.

Muckle-Wells syndrome and Familial Cold Urticaria.

Two other diseases, Muckle-Well syndrome (MWS) and Familial Cold Urticaria (FCU), described more often in older children, or adults, are related to mutations found in the same gene as MAPs. In half of all cases, there is no mutation.

In FCU, exposure to cold induces a flare.

Familial cases are frequently observed in MWS and in FCU. The later are autosomal, (ie occurring in females as well as in males), dominant (ie one of the parent is affected) inheritance.

RECURRENT FEVERS WITHOUT KNOWN GENETIC ANOMALY

Periodic fever with Aphthous Pharyngitis Adenitis (PFAPA)

What is it?

The patient suffers from recurrent attacks of fever and affects children in early childhood, two to four years). This disease has a chronic course, but is a benign disease with a tendency toward improvement over time. This disease was recognised for the first time in 1987 and called Marschalls' syndrome at that time.

How common is it?

The frequency of PFAPA is not known, but the disease appears to be more common than generally appreciated.

What are the causes of the disease?

The exact cause of the disease is currently unknown. During periods of fever, the immune system is activated. This activation leads to an inflammatory response with fever and inflammation of the mouth, or throat. This inflammation is self-limited as there are no signs of inflammation to be found between two episodes. There is no infectious agent present during attacks.

Is it inherited?

Familial cases have been described, but no genetic cause has been found so far.

Is it contagious?

Infectious agents may play a role in the PFAPA syndrome, but it is not an infectious disease and is not contagious.

What are the main symptoms?

The main symptom is a recurrent fever, accompanied by a sore throat, mouth ulcers, or enlarged cervical lymph nodes (an important part of the immune system). The episodes of fever start abruptly and last for three to six days. During episodes, the child looks very ill and complains about at least one of the three above-mentioned symptoms. The episodes of fever are recurring every few weeks. Between episodes, the child is asymptomatic and his activity is normal. There is no consequence at all on the development of the child, who looks perfectly healthy between attacks.

Is the disease the same in every child?

The main features described above are found in all affected children. However, some children may have a milder form of the disease, or may present additional symptoms, like malaise, joint pain, abdominal pain, headache, vomiting, diarrhoea or cough.

How is it diagnosed?

There are no laboratory tests, or imaging procedures, specific for diagnosing PFAPA. The disease will be diagnosed based on the results of a physical examination. Before the diagnosis is confirmed, it is mandatory to exclude all other diseases that may present with similar symptoms.

What type of laboratory exams are needed?

Values of tests, like the erythrocyte sedimentation rate (ESR) or the C-reactive protein (CRP) levels in the blood, are raised during attacks.

Can it be treated or cured?

There is no specific treatment to cure PFAPA syndrome. The aim of the treatment will be to control symptoms during the episodes of fever. In a large proportion of cases, the disease will spontaneously disappear with time.

What are the treatments?

Symptoms do not usually respond to paracetamol, or non-steroidal anti-inflammatory drugs. A single dose of prednisone, given when symptoms first appear, has been shown to shorten the length of an attack. However, the interval between the episodes may also be shortened with this treatment, and the next febrile episode may recur earlier than expected. In some patients a tonsillectomy can be considered.

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

The disease may last for a few years. With time, the intervals between the febrile attacks will increase and the symptoms will resolve spontaneously.

Is it possible to recover completely?

Over the long term PFAPA will spontaneously disappear, usually before adulthood. Patients with PFAPA do not develop damage. The growth and development of the child are usually not affected by this disease.