



## **Tumor Necrosis Factor Receptor Associated Periodic Syndrome (TRAPS) or familial Hibernian fever.**

### **What is it?**

TRAPS is an inflammatory disease characterized by recurrent attacks of high spiking fevers, usually of two to three weeks duration. The fever is typically accompanied by gastrointestinal disturbances (abdominal pain, vomiting, diarrhea), painful red skin rash, muscle pain and periorbital swelling. Renal impairment due to severe proteinuria can be observed in the late phase of the disease. It is possible to observe similar cases in the context of the same family.

### **How common is it?**

TRAPS is thought to be a rare disease with less than 200 confirmed cases, however, its true prevalence is currently unknown. It affects males and females equally and the onset is usually during childhood, even if patients with an adult onset have been described. 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 Kabylians 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 Factor Receptor I [TNFRI]), which leads to an increase of the patient's normal acute inflammatory response. TNFRI is one of the cellular receptors specific for a potent inflammatory circulating molecule, named tumor necrosis factor (TNF). The direct link between the structural and functional alteration of the TNFRI protein and the severe recurrent inflammatory state observed in TRAPS has not been completely identified yet. Infection, trauma or psychological stress may trigger the 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.

### **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. Some patients, specially in adulthood, have a fluctuating and sub-chronic disease course, characterized by flares of abdominal pain, arthro-myalgia, ocular manifestations with or without fever and by a persistent elevation of laboratory parameters of inflammation. Amyloidosis is the most severe long-term complication of TRAPS, occurring in 14% of patients. It is due to the tissue deposition of a circulating molecules produced during inflammation, called serum amyloid A. Renal deposition of amyloid A leads to the loss of a large amounts of proteins in the urine and progresses to renal failure.

### **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, including infections, malignancies and other inflammatory chronic diseases, including other autoinflammatory diseases, such are Familial Mediterranean fever (FMF) and Mevalonate kinase deficiency (MKD).

### **Which examination are needed?**

a) Blood tests: The laboratory tests, as mentioned before, are important in diagnosing TRAPS. 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.

c) molecular analysis of the TNFR1 gene is performed in specialized genetic laboratories

### **What are the treatments?**

To date, no treatment exists to prevent or cure the disease. Non-steroidal anti-inflammatory drugs help to relieve symptoms. High dose steroids are often effective but sustained usage leads to serious side effects. Specific TNF blockade with the type II TNF receptor-immunoglobulin fusion molecule (Etanercept) has been shown to be an effective treatment in some patients for the prevention of fever attacks. Conversely, the use of monoclonal antibodies against TNF has been associated with an exacerbation of the disease. Recently a good response to anti-IL-1 treatment (anakinra), has been reported in some children affected with TRAPS.

### **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 treatments last for?**

Due to the relative number of cases treated with anti-TNF and anti-IL-1 treatment it is not still clear if this treatment should be given continuously or at the moment of a new fever attack.

### **What about unconventional or complementary therapies?**

There are no published reports of effective complementary remedies

### **What kind of periodic check-ups are necessary?**

Patients being treated should have blood and urine tests for at least every 2-3 months.

### **How long will the disease last for?**

It is a life-long disease, although with age, fever attacks may decrease of intensity and a more chronic and fluctuating course can be observed. Unfortunately this evolution do not prevent from the possible development of amyloidosis.

### **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 and long-lasting 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 TRAPS can enjoy normal sexual activity and have children of their own. However they have to be aware that there is a probability of 50% of that their child could be affected.