www.printo.it/pediatric-rheumatology/GB/intro

TNF Receptor Associated Periodic Syndrome (TRAPS)

Version of 2016

1. WHAT IS TRAPS

1.1 What is it?

TRAPS is an inflammatory disease characterised 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, diarrhoea), painful red skin rash, muscle pain and swelling around the eyes. Impaired kidney function can be observed in the late phase of the disease. It is possible to observe similar cases in the same family.

1.2 How common is it?

TRAPS is thought to be a rare disease but the true prevalence is currently unknown. It affects males and females equally and the onset is usually during childhood, although patients with an adult onset have been described.
The first cases were reported in patients of 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.

1.3 What are the causes of the disease?

TRAPS is due to an inherited anomaly of a protein (Tumour 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 known as tumour necrosis factor (TNF). The direct link between the alteration of the TNFRI protein and the severe recurrent inflammatory state observed in TRAPS has not been completely identified yet. Infection, injury or psychological stress may trigger the attacks.

1.4 Is it inherited?

TRAPS is inherited as an autosomal dominant disease. This form of inheritance means the disease is transmitted by one of the parents who has the disease and carries an abnormal copy of TNFRI gene. All individuals have 2 copies of all genes; hence, the risk of an affected parent transmitting the mutated copy of the gene TNFRI to each child is 50%. De novo (new) mutation may also occur; in such cases, neither parent has the disease and neither carries a mutation of the TNFRI gene but disruption of TNFRI gene appears at the child's conception. In this case, the risk of another child developing TNFRI is random.

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

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

1.6 Is it infectious?

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

1.7 What are the main symptoms?

The main symptoms are recurrent attacks of fever typically lasting two or three weeks but sometimes of shorter or longer duration. These episodes are 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 a rash. Diffuse abdominal pain with nausea and vomiting are common. Inflammation of the membrane covering the front of the eye (the conjunctiva) or swelling around the eyes is characteristic of TRAPS, although this symptom can be observed in other diseases. Chest pain due to inflammation of the pleura (the membrane surrounding the lungs) or of the pericardium (the membrane surrounding a joint) is also reported.
Some patients, especially in adulthood, have a fluctuating and sub-chronic disease course, characterised by flares of abdominal pain, joint and muscle aches, ocular manifestations with or without fever and a persistent elevation of laboratory parameters of inflammation.
Amyloidosis is the most severe long-term complication of TRAPS, occurring in 14% of patients. Amyloidosis is due to tissue deposition of a circulating molecule produced during inflammation, called serum amyloid A. Renal deposition of amyloid A leads to the loss of a large amount of proteins in the urine and progresses to renal failure.

1.8 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.

2. DIAGNOSIS AND TREATMENT

2.1 How is it diagnosed?

An expert physician will suspect TRAPS on the basis of clinical symptoms identified during a physical examination and a family medical history.
Several blood analyses are useful for detecting inflammation during the attacks. The diagnosis is confirmed 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 as Familial Mediterranean Fever (FMF) and Mevalonate Kinase Deficiency (MKD).

2.2 Which examinations are needed?

Laboratory tests are important in diagnosing TRAPS. 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 exhibit persistent levels of protein in urine tests. Molecular analysis of the TNFRI gene is performed in specialised genetic laboratories.

2.3 What are the treatments?

To date, no treatment exists to prevent or cure the disease. Non-steroidal anti-inflammatory drugs (NSAIDs such as ibuprofen, naproxen or indomethacin) help to relieve symptoms. High dose corticosteroids are often effective but sustained use may lead to serious side effects. Specific blockade of the inflammatory cytokine TNF with the soluble TNF receptor (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 a drug blocking another cytokine (IL-1) has been reported in some children affected with TRAPS.

2.4 What are the side effects of drug therapy?

Side effects depend on the drug that is used. NSAIDs can give rise to headaches, stomach ulcers and kidney damage. Corticosteroids and biologic agents (TNF and IL-1 blockers) increase susceptibility to infections. In addition, corticosteroids may cause a wide variety of side effects.

2.5 How long should treatments last?

Due to the rather small number of patients treated with anti-TNF and anti-IL-1, it is not entirely clear whether it is better to treat each new fever attack as it occurs or to treat continuously and if so, for how long.

2.6 What about unconventional or complementary therapies?

There are no published reports of effective complementary remedies.

2.7 What kind of periodic check-ups are necessary?

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

2.8 How long will the disease last?

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

2.9 Is it possible to recover completely?

No, because TRAPS is a genetic disease.

3. EVERYDAY LIFE

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

Frequent and long-lasting 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 investigations.

3.2 What about school?

Frequent attacks cause problems with school attendance. With effective treatment, school absence becomes less frequent. 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 to 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. In particular, if your child will be treated with corticosteroids or biologic agents, vaccinations are essential to protect against possible infections.

3.7 What about sexual life, pregnancy, birth control?

Patients with TRAPS can enjoy normal sexual activity and have children of their own. However, they should be aware that there is a 50% probability that their child is affected. Genetic counselling should be offered to discuss this aspect with children and families.