Periodic Fever Syndromes

What are Periodic Fever Syndromes?

Periodic Fever Syndromes are a group of autoinflammatory diseases that cause disabling and recurrent fevers. They may be accompanied by joint pain and swelling, muscle pain and skin rashes – with complications that can be life-threatening[1-3]. Most patients present with symptoms in infancy or childhood[2]. Once the episode of fever is over, patients usually recover within a few days[2]. All types of Periodic Fever Syndromes can have severe long-term complications such as kidney failure[1]. Many of these syndromes are hereditary[1], hence also being referred to as Hereditary Fever syndromes.

What causes Periodic Fever Syndromes?

The underlying cause in all these syndromes is over-activity of the immune system, which leads to prolonged inflammation[3]. Inflammation is the body's protective response to injury or pathogens but in some diseases, such as Periodic Fever Syndromes, this inflammation stays switched on and drives further inflammation. This unwanted, prolonged inflammation is what causes the damage and symptoms seen in Periodic Fever Syndromes[3].

What links Periodic Fever Syndromes?

Interleukin-1 beta (IL-1 beta) is one of a group of proteins called cytokines produced by the body's immune response. Cytokines are a necessary part of the body's inflammatory response to injury or pathogen. Overproduction of IL-1 beta causes the symptoms and damage associated with all Periodic Fever Syndromes; this is why it is an interesting target for therapeutic intervention and prompted scientific investigation into whether blocking its action site could be a way of treating autoinflammatory diseases[4,5].

What are the different types of Periodic Fever Syndromes?

Eleven different syndromes have been identified[2]. There are similarities in the symptoms of the different syndromes, but major differences in relation to[2]:

- the genetic mutation that causes disease
- the particular immune pathway that is overactive and causes auto-inflammation
- the way in which the condition is inherited
- the clinical features:
  - age of onset
  - frequency of attacks
  - duration of attacks
  - symptoms during attacks
  - triggers for attacks

FMF, TRAPS and HIDS/MKD

Familial Mediterranean Fever (FMF), TNF Receptor Associated Periodic Syndrome (TRAPS) and Hyper Immunoglobulin D Syndrome/Mevalonate Kinase Deficiency (HIDS/MKD) cause periodic fevers that do not have an infectious cause; episodes of these syndromes are followed by periods of general wellbeing[1].

- FMF is the most common of these syndromes. It mainly affects people of Eastern Mediterranean ancestry: 1 in 250 to 1 in 1,000 individuals in these populations are affected[2]. It is far less common in other ethnic groups, but it can affect anyone[2]. The symptoms are recurrent fever, with abdominal, chest or joint pains – but not all patients have all symptoms and symptoms may change over time[1]. Episodes can resolve themselves without treatment, although some can be extremely painful and last 1-4 days[1]. Some children, however, have such frequent episodes they do not fully recover or do not grow properly[1].

- TRAPS is very rare and affects 1-2 per 1 million people[2] – with approximately 50 confirmed cases in the in the UK[6]. It is characterized by recurrent episodes of fever that last for 2-3 weeks that are associated with chills and intense muscle pain[1]. Patients also have a red and painful rash that moves around the body, as well as abdominal pain and eye problems[1].

- HIDS/MKD is also very rare affecting 1-2 per 1 million people[2]. In this condition, fever lasts 3 to 7 days and occurs every 2-12 weeks with no warning[1]. Other symptoms are skin rashes, painful mouth ulcers, joint pain and swelling of the lymph nodes[1].

CAPS

Cryopyrin-Associated Periodic Syndromes (CAPS) are very rare and affect 1-2 per 1 million people[2] – but are severe and life-limiting for many patients. The syndromes are characterized by flu-like symptoms including severe fatigue, fever and muscle pains, often starting in early infancy[6].

CAPS vary in terms of severity and duration of attack; in some people the fever may become continuous[7]. Associated problems include involvement of the skin, eyes, joints and brain; patients may develop long-term disabilities such as blindness, deafness and amyloidosis, in which protein deposits build up and damage organs[1,6,8]. Until relatively recently, there have been no effective therapies for CAPS[7].

CAPS includes three conditions:
- Familial Cold Urticaria (FCU) – FCU is the least severe CAPS. It causes attacks of itchy rash, red eyes and fever within hours of exposure to cold. The majority of affected patients are located in North America[1,2]
- Muckle Wells Syndrome (MWS) – MWS causes daily episodes of rash, red eyes and fever, which are worst in the evenings. About a quarter of patients will become deaf later in childhood[9]
- Chronic Infantile Neurological Cutaneous and Articular Syndrome (CINCA) (also known as Neonatal Onset Multisystem Inflammatory Disease [NOMID]) – CINCA/NOMID is the most severe CAPS. It causes chronic inflammation of the lining of the brain that results in loss of hearing, poor vision and learning difficulties. The condition is also associated with rash, fever and poor growth[1].

The remaining Periodic Fever Syndromes are: NALP12 associated periodic syndrome; Deficiency of IL-1ra (DIRA); Pyogenic Arthritis Pyoderma gangrenosum and Acne (PAPA); Blau Syndrome; Majeed Syndromes; Deficiency of the IL-36ra (DITRA); and Chronic Atypical Neutrophilic Dermatosis with Lipodystrophy and Elevated temperature/Joint contractures, Muscle atrophy, microcytic anaemia and Panniculitis-induced childhood-onset lipodystrophy syndrome (CANDLE/JMP).

What are the goals of treatment for Periodic Fever Syndromes?

The goal of treatment is the early, rapid and sustained control of disease activity to prevent the complications associated with unwanted prolonged inflammation that leads to life-threatening organ damage[3]. Treatment should enable patients to participate in day-to-day activities and improve their health-related quality of life[3].

What treatments are available for Periodic Fever Syndromes?

There is now a treatment that specifically targets the IL-1 beta cytokine, which triggers the prolonged inflammation that causes the symptoms and damage in Periodic Fever Syndromes. Ilaris® (canakinumab) – a high-affinity human monoclonal antibody has shown positive results in the treatment and management of CAPS, FMF, TRAPS and HIDS/MKD[10-12].

Before the approval of Ilaris for TRAPS, HIDS/MKD and CAPS, there was no treatment available to change the course of an episode of fever as related to these Periodic Fever Syndromes[11]. The mainstay of treatment has been non-specific anti-inflammatory agents, including steroids, but these were used only to help manage the symptoms. Long-term steroid use leads to serious side effects[3].

Before the approval of Ilaris for FMF, colchicine was the only FDA-approved treatment for FMF. Colchicine is not effective in 5% of patients with FMF[3].

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