

# INHERITED AUTOINFLAMMATORY RECURRENT FEVERS

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**SUMMARY :** Autoinflammatory diseases have a quite similar clinical picture and are characterised by recurrent episodes of fever, joint features, abdominal features and skin features.

Auto-inflammatory syndrome are related to mutations in genes implied in apoptosis or inflammation. FMF's gene is MEFV, present on the short arm of the chromosome 6, encoding the pyrin or marenostrie which is widely expressed in neutrophils and monocytes and implied in the control of the inflammation. Muckle wells syndrome and Familial cold urticaria are related to CIAS1 gene mutations which are located on the long arm of the chromosome 1 and encodes cryopyrine involved in apoptosis. TRAPS gene is present on the chromosome 12, the majority of mutations are located in the extra cellular region of the receptor.

**Key words:** Autoinflammatory Syndrome, Recurrent Episodes, Inflammation, Apoptosis,.

**F**ever represents the most common symptom in human pathology. In most cases, it is related to an infectious, neoplastic, autoimmune, and parasitic as well as an inflammatory mechanism of indeterminate nature without hereditary component. On the other hand, apart from any cause mentioned above, it is, in rare cases recurred by episodes and is primarily based upon a genetic substratum related to gene mutations implied in apoptosis and inflammation mechanisms [1]. Hull *et al.* [2] have recently proposed the inclusion of these types of fever that have a quite similar clinical picture and that are mainly characterized by recurrent episodes associated with at least five of the following symptoms: Fever, joint features, abdominal features, skin features and an inflammatory biological syndrome in the broad concept of the "auto-inflammatory syndromes".

Throughout the years, it is likely that the numbers of diseases that can be included in this concept will increase with the development of new molecular biology procedures and gene sequencing methods.

In this paper, we will particularly address the most characteristic auto-inflammatory diseases:

- The Familial Mediterranean Fever (FMF) previously referred to as periodic disease.
- Tumor Necrosis Factor Receptor-Associated Periodic Syndrome (TRAPS) characterized by recurrent episodes of periodic fever
- Familial Cold Urticaria (FCU) as well as Muckle wells syndrome (MWS)

Among these four diseases, three have been directly related to gene mutations. These genes express a set of proteins that contain a pyrin domain. Even more, this pyrin domain defines a family of proteins themselves involved in the apoptosis and the inflammatory processes.

- Pyrin (or Marenostrie) of the FMF
- Cryopyrin (expressed by CIAS1 cold-induced auto inflammatory syndrome 1), which basically owes its name to the fact that it appears while exposed to cold (cryo) and is responsible of fever (pyrin) in Familial Cold Urticaria and Muckle-Wells syndrome.

Actually, Pyrin and Cryopyrin belong to a super family, which contains mainly a pyrin domain as well as caspase death and activation domains. There are nine well-known super family members, in particular Pyrin, Cryopyrin, death effector-filament-forming-Ced4 like apoptosis protein D2FCAP, etc...that have an important role in inflammation and apoptosis mechanisms.

## HEREDITARY PERIODIC FEVERS RELATIVE TO PYRIN DOMAIN PROTEINS

### Familial Mediterranean Fever:

Inherited as an autosomal recessive, Familial Mediterranean Fever is much more common among Mediterranean peoples, Sephardic Jews, Arabic, Armenians, Turks, etc.

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It is mainly characterized by recurrent attacks that lasts in most cases for about 1 to 3 days and by the onset, which is usually before the age of 20.

The frequency of the diverse clinical features of the disease cited in the literature is mentioned in table 1. This attack is defined by an abrupt onset of fever reaching 39 to 40 degrees and lasting 2 to 3 days associated with joint signs in the form of oligo or monoarthritis affecting mostly knees, elbows and wrists. In many cases, the presence of mild abdominal pain located usually in the periumbilical area were also noticed, which can lead to misdiagnosis and thus to surgical intervention.

Very rarely, polyserositis with pleural effusion, pericarditis or mild ascites were seen (3,4). Erysipelas-like lesions can also be present.

The intensity of the episodes is variable ranging from very intense for some to somewhat mild for others. Each symptom mentioned above may be present alone, especially fever, which will regress by itself.

Throughout the time, the repetitive occurrence of the attacks and the association to many symptoms indicated above will suggest in a compatible epidemiological context the diagnosis of Familial Mediterranean Fever (5).

In case of the persistence of the episodes over the years, we look inevitably for amyloidosis, which is the most common complication of familial Mediterranean fever, mostly renal but also intestinal, hepatic or even endocrine or cutaneous amyloidosis(6).

The pathophysiology of Familial Mediterranean Fever is currently well known. The MFEV, the gene involved in this disease is present on the short arm of chromosome 16 and encodes a protein called marenostin or pyrin, which consists of 781 Amino Acids. Based on its primary structure, 10 coding regions or exons are present but the mutations were mainly found in the exons 2 and 10 and rarely other

codons are involved. The vast majority of mutations correspond as a matter of fact to the substitution of an amino acid by another in the structure of pyrin. Let us mention the M694V mutation where the amino acid methionine is substituted by the amino acid valine on the 694-codon region (Unfortunately, it is associated with the appearance of more severe phenotype of FMF) and the V726A or E148Q mutations (substitution of valine by alanine or glutamine by glutamic acid) (7,8).

The most frequent mutation, the M694V was detected in 20 to 60 % of cases, whereas the V726A was present in only 7 to 35 % of the population (8,9). The recessiveness of the disease explains that two mutations on the MFEV must be present in order for the disease to develop.

Pyrin is widely expressed in neutrophils and monocytes and is involved in the regulation of the inflammation. In these conditions, it is obvious to propose that any modification in regulation of this mechanism carried away by the existence of "harmful mutations" will trigger the appearance of the attacks.

Until today, up to 28 mutations on the MFEV have been reported (5).

The diagnostic is suggested clinically and the establishment of the molecular diagnosis is based upon the use of genetic procedures. However, DRENTH and VAN DER MEER (5) have reported that unusual mutations may be involved. In general, screening for these mutations is not realized during the habitual molecular diagnosis. Hence, it is very important to attract the attention of the genetists toward particular clinical cases. Therefore some patients may present a mutation only in one allele whereas, others may present two mutations on two alleles resulting from nonpenetrance, which, in this case no clinical syndrome is observed. In these difficult cases, it is beneficial to ask for a complete molecular study and to start a preventive treatment by colchicine until the molecular results are available.

■ **Treatment:** A preventive treatment during attacks relies on colchicine whose action on the motility, the phagocytosis as well as the inhibition of the lysosomal degradation of neutrophils, is well known. Controlled trials of ZEMER *et al* [10] and DINARELLO *et al* [11] have showed that it clearly reduces the number and the intensity of the attacks.

For the episode itself NSAID are widely used.

Despite its high costiveness and its difficulty of use, at a certain point interferon alpha was proposed. The double blind study of TUNCA *et al* (12) did not confirm its effectiveness on the fever and the symptoms of the attack. Till now, etanercept and anti TNF drugs have not demonstrated an efficacy to decrease amyloidosis complicating the FMF.

## FEATURES OF FAMILIAL MEDITERRANEAN FEVER (PERIODIC FEVER)

### Symptoms lors des attacks

- Autosomal recessive Transmission
- Mediterranean population
- In 90% of cases, onset before age 20
- Duration of episodes over 24 to 96 h
- Fever during attacks associated to other symptoms 90 % of cases
- Abdominal pain of 1 to 2 d in 95 % of cases
- Sometimes episodes of isolated mono ou oligoarticular in 75 % of cases
- Pleural effusion : 30 % of cases
- Pericarditis : less than 1 % of cases
- Erysipelas-like lesions (legs and feet) : 7 to 40 % of cases
- Myalgias : 10 % of cases
- Scrotal pain and edema : 5 % of cases
- Isolated fever : 5 a 10 % of cases
- Associated fever : 90 % of cases
- Complications of amyloidosis

### References

- BEH-CHETIT (Lancet 1996)
- SOHAR (Lancet 1998)
- SOHAR (Lancet 1998)
- ESHEL (Br J Surg 1994)
- MAJEED (QJM 1990)

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## **Muckle Wells syndrome and Familial Cold Urticaria:**

Recently, these two syndromes have been linked to auto-inflammatory syndrome. They are also related to CIAS1 gene mutations (cold-induced auto-inflammatory syndrome 1), which are found on the long arm of the chromosome 1 that encodes cryopyrin, itself containing one pyrin domain and two NACHT and LRR domains involved in apoptosis [1, 13, 14].

CIAS1 gene is primarily expressed on the leukocytes. KASTNER and O'SHEA [1] have proposed that pyrin and a set of related proteins are involved in the apoptosis mechanism of certain precursor of the leukocytes line. They play a role in the triggering as well as the amplification of the first steps of inflammation process.

The existence of genetic mutations will lead to an inhibition of the apoptosis of these cells and to the perennisation of the inflammatory cascade.

■ **Muckle-Wells syndrome**, inherited as an autosomal dominant, is characterized by episodes that are generally related to cold exposure, associated with fever, abdominal pain, joint involvement, conjunctivitis, urticarian rash; even more, throughout the years, most of these patients will progressively present sensorineural deafness and will develop renal failure due to amyloidosis [15].

■ **Familial Cold Urticaria (FCU)**: Recently, HOFFMAN *et al* [16] have reported their experience of 45 cases of FCU of 6 American families. Episodes during this disease are rather comparable to other auto-inflammatory syndromes, but, evidently, the cutaneous features, often of urticarian type, predominate during the attacks. The onset of this disease has been often reported to be during the first year particularly during the first days of life.

In variable conditions, in addition to fever and joint features, cutaneous symptoms triggered by cold exposure dominate the clinical picture of the disease. Usually, they consist mostly of maculo-papular rash affecting the extremities, rather than urticarian lesions. These cutaneous features will last from some hours to 3 days, occur in a variable period of time (15 minutes to 8 hours) following cold exposure and regress progressively in one to three days.

Rarely, the fever exceeds 38.5 degrees. It is readily accompanied by chills which can precede the appearance of rash. Cutaneous features are generally less apparent and are associated to bilateral or unilateral polyarthralgias affecting mainly hand joints, less often ankles, wrists and knees. Rarely, true arthritis was seen. On the other hand, myalgias are more common. Other symptoms have been reported such as,

profuse sweating, bilateral conjunctivitis and headaches. Like every disease compromised in the auto-inflammatory syndrome, the episode is marked by the presence of an inflammatory syndrome with net elevation of ESR and CRP as well as an increased number of leukocytes often exceeding 12000. FCU can be distinguished from acquired urticaria by its familial character, the negativity of the ice test, the onset of the symptoms, which require many hours of exposure to cold, the absence of histamine elevation during episodes and by its onset habitually seen in children. Amyloidosis does not seem to complicate this disease.

The insufficiency of our actual knowledge on the pathophysiology of these two diseases does not allow us to propose a preventive treatment. In this case, steroid therapy, colchicine and anaboli-steroids are less efficient [17]. The treatment during episodes is only symptomatic based on non-steroid anti-inflammatory drugs.

Recently, an overlap-syndrome (Muckle-wells, FCU) with a gene mutation (V262G) was improved by anakinra\*, an IL1 receptor antagonist.

## **DISEASES RELATED TO THE DYSFUNCTION OF TNF RECEPTOR OR TRAPS:**

Hereditary fever syndrome related to a dysfunction of TNF receptor or TRAPS (tumor necrosis factor receptor super family 1A-associated periodic syndrome) have emerged progressively from clinical cases close to Familial Mediterranean Fever but are distinguished by its mode of transmission, which is autosomal dominant, the appearance in diverse populations (Scandinavians, African-Americans, Europeans...), as well as its resistance to colchicine [18,19].

Like every disease described in this paper, the clinical picture of TRAPS relies, on the appearance of recurrent episodes associating fever, joint and dermatological signs as well as inflammatory syndrome related to the presence of gene mutations in TNF type 1A receptor.

The symptoms begin, or are generally recognized, in adolescents or young adults whereas, the patient questioning may reveal minor episodes occurring at younger age but that have not been detected if the familiar context has not been taken into consideration. These episodes are more or less frequent lasting often from few days to 2-3 weeks. The fever rarely reaches 39 degrees. Sometimes, simple febrile attacks, from 1 to 2 days, intersperse with more intense attacks.

According to the intensity of these episodes, joint features which are present in three quarter of times, are roughly symmetrical, mainly arthralgias (hands,

wrists, knees and ankles) and very rarely destructive arthritis. In 25 % of cases, during the episode, these joint signs as well as fever are the first symptoms to appear. Muscles pain (20) readily completes the picture. Histological involvement of myositis or fasciitis type may be found.

Regarding dermatological features, they readily inaugurate the episode and are found in 84% of TORO *et al.* [21] series: periorbital edema, sometimes associated with conjunctivitis, urticaria, erythematous and edematous lesions, round or more diffused, like cellulites.

The long-term evolution of TRAPS is primarily conditioned by the appearance or not of secondary AA amyloidosis, which in 25 % cases were found by HALL *et al.* [22]. Some mutations of TNFR1 gene seem to predispose to a high risk of amyloidosis, especially C30S.

■ **TRAPS genetics:** AKSENTIJEVICH *et al.* [3] and MacDERMOTT *et al.* [22] highlighted the role of the Gene coding for TNF type 1 receptor TNFSF1A (tumor necrosis factor receptor super family 1A) in the development of TRAPS. This gene is present on the chromosome 12 (12p13) [23]. Type 1A TNF receptor contains three parts. The first, extra membrane (in four CRD 1,2,3,4 units), the second, the transmembrane domain, the third corresponds to an intracellular domain (death domain). In our current estate of knowledge, the majority of mutations are located in the extra cellular region of the receptor and in CRD1 and CRD2 domains.

The vast majority of mutations correspond to the substitution of cysteine involved mainly in disulfide bounds, by another amino acid. According to the mechanisms considered presently, the resulting mutations (more than 20 known to this day) modify, more or less the function of TNF 1A receptor and /or its form (the relative part of the soluble structure with respect to the transmembrane unit), thus allowing the appearance of the inflammatory syndrome.

During episodes, the proinflammatory action of TNF (cytokines secretion, leukocytes activation) is responsible of fever and biological inflammatory syndrome: Increase of circulate TNF, hyperlympho-monocytosis, C-reactive protein and erythrocyte sedimentation rate.

■ **Treatment:** Unlike the FMF, the TRAPS involve less neutrophiles and no curative or preventive action of colchicine on the attacks or on the amyloidosis have been demonstrated. In a short trial of 7 patients [27], steroid therapy showed an improvement of symptoms and a regression of the episodes. Unfortunately, its effects seem to lessen with time.

Our knowledge of the role of TNF alpha in this disease has induced to propose TNF inhibitors, in particular etanercept (Enbrel®). This product is a competitive inhibitor of the binding of the TNF to its 55KD cell

membrane receptors or 75KD, thus inhibiting the TNF biological activity. Its mode of use is still discussed: either curative or preventive treatment of attacks or of amyloidosis.

The few published studies [22, 23, 24] suggest a decrease in the intensity and duration of episodes and the spacing of the attacks: 25 mg subcutaneous of etanercept, given twice weekly has led to a marked improvement in six of eight patients treated by GALON *et al.* [23]. The choice of a sequential or continuous use, like in rheumatoid arthritis, 2 subcutaneous injections every week in long term, is not yet a clear cut. DREWE *et al.* [24] noticed a partial remission of proteinuria in a patient with nephrotic syndrome during the use of etanercept.

Finally, it will be interesting to know the eventual effect of adalimumab, which is the first alpha Human anti TNF antibody.

## CONCLUSION :

These last years, our knowledge has particularly progressed in the determination of the processes involved in cellular birth, life and death. Far from being simple, these processes, in fact, rely on a set of activator or inhibitor events, which globally lead to a temporary equilibrium.

For instance, proteins that contain the pyrin domain are obviously involved in the inflammatory and apoptosis mechanisms, therefore, may be, exclusively in the innate immunity.

As already mentioned, pyrin and cryopyrin are primarily expressed in the peripheral blood leukocytes and, with time, new arguments suggest that leukocytes apoptosis is likely a common path leading to an auto inflammatory mechanism. Similarly, it was demonstrated that 55 KD TNF receptor (mutated in TRAPS) also plays a regulatory role in apoptosis.

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