New Pieces in the Puzzle of Autoinflammatory Disorders

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Familial Mediterranean fever is the prototype of a group of disorders classified as episodic febrile syndromes, an entity first brought to our attention in the 1940s [1]. These disorders are defined by four basic characteristics:

- attacks of painful manifestations, usually of short duration (1–30 days), repetitive, with either regular or irregular periodicity
- fever
- elevated levels of acute-phase reactants
- spontaneous remissions.

This group of disorders is large and includes infectious diseases (e.g., malaria), autoimmune syndromes (e.g., systemic lupus erythematosus) and malignancies (e.g., lymphoma).

The episodic febrile autoinflammatory diseases constitute a subgroup of episodic febrile syndromes encompassing a growing number of entities [Table 1]. The term autoinflammatory was coined to differentiate these conditions from autoimmune diseases. Autoinflammatory diseases are characterized by the existence of inflammation with no detectable autoantibodies or involvement of antigen specific T cells. The EFAIDs are long-known disorders, but it is only in the last 5 years that progress has been made in understanding them, particularly after cloning of the disease-associated genes and identification of the culprit mutations [2,3]. In comparing these different gene products of EFAIDs to other proteins with homologous domains, some light was shed on the possible pathophysiology of these diseases even though it was not completely resolved in any of them. There are many similarities in the clinical, laboratory and pathophysiologic aspects of the various EFAIDs [Table 2]. The purpose of this review is to present these aspects (excluding familial Mediterranean fever that has been previously discussed in length), in light of the progress that has been made in the field.

EFAID = episodic febrile autoinflammatory disease

Tumor necrosis factor receptor 1-associated periodic syndrome

TNF receptor 1-associated periodic syndrome (known as TRAPS) is a rare autosomal dominant disease, first described in families of Irish and Scottish ancestry (previously known as familial Hibernian fever)

TNF = tumor necrosis factor

Table 1. Episodic febrile autoinflammatory disorders

- Familial Mediterranean fever (FMF)
- Hyper-IgD syndrome (HIDS)
- TNF receptor-associated periodic fever syndrome (TRAPS)
- Muckle-Wells syndrome (MWS)
- Chronic infantile neurologic, cutaneous, and articular syndrome (CINCA)
- Periodic fever, aphthous stomatitis, pharyngitis and adenopathy (PFAPA)
- Behçet's disease (BD)
- Familial cold autoinflammatory syndrome (FCAS)
- Pyogenic arthritis with pyoderma gangrenosum and acne (PAPA)
- Chronic recurrent multifocal osteomyelitis (CRMO)

Table 2. Summary of system involvement in the different disorders

	Fever	Skin	Joints/bones	Muscle	Lymph nodes	Abdominal pain	Conjunctivitis	Headache	CNS	Amyloid	Duration
FMF	+	+	+	+		+				+	> 72 hours
TRAPS	+	+	+	+	+	+	+	+		+	7–21 days
HIDS	+	+	+	+		+	+	+			3–6 days
MWS	+	+	+					+	Deafness	+	>36 hours
FCAS	+	+	+				+	+		+	Varying
CINCA	+	+	Hyperostosis	+	+	+	+	+	Severe	+	Varying
PFAPA	+				+			+			4 days
CRMO	+		Osteomyelitis								Varying
PAPA	+	+	+								Varying

and later also in families from Western Europe, the United States, Puerto Rico, Australia and recently in an Arab child in Israel.

The disease manifests usually in the second decade of life. Its clinical picture includes attacks of fever with severe myalgia (affecting one muscle group) and an erythematous migratory rash. Attacks of peritonitis and peripheral lymphadenopathy were described in 90% of patients, arthralgias in 50–70% and headache with conjunctivitis in some 80%. The attacks last 7–21 days (but may persist longer) and resolve spontaneously. AA amyloidosis, appearing at a very early stage of the disease, can be seen in about 25% of patients [4]. The laboratory profile is characterized by dramatic elevations in acute phase reactants, with very high levels of pro-inflammatory cytokines (interleukins 1 and 6, TNFα and serum amyoid A).

The disease is caused by mutations in the *TNFRSF1* gene on chromosome 12q13, encoding for TNF receptor 1. More than 30 different mutations have been identified, with the most common one, C33Y, located in the extracellular cystein-rich region of the receptor. The different mutations were shown to modify cytoplasmic trafficking, surface expression, serum shedding and reduced TNF binding affinity of the mutated receptor, thus interfering with TNFα neutralization [5].

Some symptomatic relief can be achieved by using steroids and non-steroidal anti-inflammatory drugs during the attacks. Colchicine, methotrexate, azathioprine, cyclosporine, cyclophosphamide, tacrolimus and thalidomide were all tried but without success. Etanercept, a soluble TNF receptor, elicited a favorable clinical response and is currently being used to prevent attacks. It does not prevent the development of amyloidosis, nor does it normalize the levels of serum acute phase reactants such as serum amyoid A. Infliximab (a chimerical anti-TNF antibody) produced similar results in some patients but worsened the course in others. Sirolimus, a cell cycle-regulating medication with pro-apoptotic and anti-co-stimulatory effects, was tried on one patient with promising results [2].

Hyper-immunoglobulin D syndrome

Hyper-IgD syndrome is an autosomal recessive disease found in European families of Dutch, French, Swiss and English ancestry. Attacks may be provoked by vaccination; thus the disease manifests early, in the first year of life, and is characterized by attacks of fever, abdominal pain, skin rash (macules, papules, urticaria and vasculitis) and headaches in most patients. Lymphadenopathy (95%), arthralgias (70%), arthritis (mostly oligo- or polyarticular and affecting large joints), and hepatosplenomegaly (40%) are commonly seen. Some patients describe oral or genital ulcerations, pleuritis or myalgia. The attacks last 3–6 days and relapse every 4–8 weeks. Amyloidosis does not develop in spite of marked rises of serum APRs and neutrophils. Elevated (>100 u/ml) serum levels of IgD may be found during both attacks and remissions.

The mutation was identified in the *MVK* gene, encoding for the enzyme mevalonate kinase, catalyzing an important step in the metabolism of cholesterol. It was shown that a deficiency in downstream products, but not precursor abundance, is responsible for the disease phenotype. It is interesting to note that the same mutation can lead to mevalonic aciduria, a different disease but with a similar clinical spectrum manifesting as severe psychomotor retardation, failure to thrive, dysmorphism, ataxia and recurrent febrile episodes. It was shown that mevalonate kinase activity differs between these diseases (being about 8–10% in HIDS but less than 1% in mevalonic aciduria), explaining the difference in disease severity. High levels of mevalonic acid can be found in the serum and urine of patients with these two diseases – correlating clinically with disease bouts in HIDS [6,7]. Simvastatin, an HMG co-A reductase inhibitor (an enzyme upstream of mevalonate kinase), currently being evaluated for treatment of HIDS, has yielded promising results. Prolonged statin treatment may lead to up-regulation of all the enzymes involved in the pathway, including mevalonate kinase, thus enhancing its activity.

Cold-induced autoinflammatory syndrome 1 gene-associated syndromes

Cold-induced autoinflammatory syndrome 1 gene-associated syndromes include three different disorders with many overlapping clinical features, arising from mutations in the same *CIAS1* gene:

- Muckle-Wells syndrome
- Chronic infantile neurologic cutaneous and articular syndrome
- Familial cold autoinflammatory syndrome.

Families have been described in which two distinct syndromes appear in two individuals with the same mutations, while relatives of affected individuals may exhibit only isolated features of the syndrome repertoire, such as high serum APR.

The *CIAS1* gene encodes for the cryopyrin protein, a pyrin-like protein expressed predominantly in peripheral polymorphonuclear cells. The gene was cloned on chromosome 1q44 and several mutations were identified in the different syndromes.

Muckle-Wells syndrome

Muckle-Wells syndrome is a rare autosomal dominant disease. Families were reported in Western Europe, the U.S. and North Africa. The disease manifests in the second decade of life by attacks of fever, abdominal pain, urticarial or papular skin rash and arthralgias or arthritis lasting up to 36 hours. Less commonly, hepato- and splenomegaly, aphthosis, pleuritis and hyperostosis were reported. The hallmark of the disease is the development of progressive bilateral sensory-neural deafness [8]. AA amyloidosis develops in 35% of patients.

Familial cold autoinflammatory syndrome

Familial cold autoinflammatory syndrome, formerly called familial cold urticaria, is a rare autosomal dominant syndrome that has been described in families from Europe, Africa and India. The disease manifests shortly after birth, with attacks of painful urticarial rash in all patients, fever and arthralgias (90%), and headaches with conjunctivitis (60–80%). Attacks are induced by exposure to low ambient temperature and subside after removal to warm surroundings [9]. In 35% of patients AA amyloidosis may

Ig = immunoglobulin
APR = acute phase reactant
HIDS = hyper-IgD syndrome

develop. Most mutations were found in exon 3 (the most common being T1058C), a region encoding for the NACHT domain of the protein, an important transcription factor regulation domain (see below) [11,12].

Chronic infantile neurologic cutaneus and articular syndrome

Previously named NOMID – neonatal onset multi-system inflammatory disease – this severe autosomal dominant disease affects multi-organs and has a wide spectrum of clinical manifestations. Sporadic as well as familial cases have been reported in France and the U.S. Natal onset mental retardation, dysmorphysm and severely destructive and deforming arthritis, with pseudo-tumoral hyperostosis are prominent features. Attacks of fever, rash, arthralgias and lymphadenopathy occur in 90% of patients, and splenomegaly in 70%. The liver is enlarged in 40% of patients. Neurologic abnormalities include low IQ, convulsions, hemiplegia, headaches, episodic or chronic aseptic meningitis, visual disturbances with optic disk edema, uveitis and brain atrophy. In some individuals AA amyloidosis develops [13–15].

Laboratory tests are significant for eosinophilia, high levels of APR and cytokines (IL1, IL3, IL5, IL6, and TNFα). No medical therapy is currently available, including anti-TNFα medications. Currently, anakinra (an anti-IL1 antibody) is being tested as a potential therapy.

Periodic fever, aphthous stomatitis, pharyngitis, adenitis

This disease manifests in childhood with periodic episodes of high fever recurring at fixed 2–8 week intervals, lasting up to 4 days and subsiding spontaneously. In over 70% of patients the fever is accompanied by aphthous stomatitis, pharyngitis and cervical adenitis. Elevated erythrocyte sedimentation rate is the laboratory hallmark. The episodes are successfully treated with small doses of prednisone [16]. The course of the disease is generally non-progressive and remits after the age of 20. It is not a familial disease and whether it has a genetic background is currently unknown.

Chronic recurrent multifocal osteomyelitis

This is a poorly understood and rare disorder. Sporadic case reports and a single Jordanian family (with autosomal recessive inheritance) have so far been described. The clinical manifestations of the disease include attacks of fever, bone pain and multifocal aseptic osteomyelitis with spontaneous exacerbations and remissions, affecting predominantly the metaphyses of long bones [17]. Arthritis of adjacent or distal joints is also frequent. The disease may be accompanied by dyserythropoietic anemia. The gene has been mapped to chromosome 18.

Pyogenic arthritis, pyoderma gangrenosum and acne syndrome

Known as PAPA, this is a very rare autosomal dominant disease. Its manifestations are recurrent attacks of aseptic arthritis and skin inflammation. The skin lesions are rich with polymophonuclear infiltrates [18]. The gene *CD2BP1* has been mapped to chromosome 15 [18,19].

IL = interleukin

The pathophysiology of Pyrin domain-containing proteins and their role in apoptosis and inflammation

Pyrin protein, the *MEFV* gene product (mutations of which are associated with FMF), and cryopyrin, the *CIAS1* gene product (mutations of which are associated with MWS, FCAS, CINCA syndromes) share large structural similarities in some of their domains. These proteins are part of a growing group of proteins with homologous sites resembling the death domain of apoptotic proteins. The pyrin domain shared by pyrin, cryopyrin, ASC, POP1 and other proteins is a six α-helix structure made up of 90 amino acids and participating in protein-protein (via PyD-PyD) interactions. Pyrin interacts with ASC (apoptosis-associated speck-like protein with caspase recruitment domain) and appears in specks. These are round, hollow, highly positive immunofluorescence staining cytoplasmatic structures formed by ASC protein. All cells in which specks appear undergo apoptosis. Another aspect of Pyrin-ASC interaction is caspase-1 activation and through the production of the transcription factor NF kappa B transcription of ILβ. Thus, PyD-containing proteins may exert both pro-inflammatory and apoptotic features. It is not yet known how mutations in PyD-bearing proteins affect these cellular functions.

Conclusion

The periodic febrile disorders are a group of vary *rare* disorders characterized by recurrent episodes of self-limited inflammatory manifestations affecting multiple organs and systems. Familial Mediterranean fever, commonly diagnosed in Israel, is referred to as the prototype of these disorders, and is discussed elsewhere. All but PFAPA[1] are inherited, and all but HIDS and CINCA are transmitted in an autosomal dominant fashion. In recent years the culprit genes and their products have been cloned and identified. A vast effort in understanding the physiology and pathophysiology of PyD-containing proteins has been made but the mechanism leading to the episodic fevers inflammation remains a mystery.

References

1. Reimann HA. Periodic diseases probable syndrome including periodic fever, benign paroxysmal peritonitis, cyclic neutropenia and intermittent arthralgia. *JAMA* 1948;41:239–44.
2. Drenth JP, Van Der Meer JW. Hereditary periodic fever. *N Engl J Med* 2001;345:174–57
3. Drenth JP, Van Der Meer JW. Periodic fevers enter the era of molecular diagnosis. *Br Med J* 2000;320:1091–2.
4. McDermott M, Simille DM, Powell RJ. Clinical spectrum of familial Hibernian fever: a 14 year followup study. *Mayo Clinic Proc* 1997;72:806–17.
5. Galon J, Aksentijevich I, McDermott M, O'shea JJ, Kastner DL. TNFRSF1A mutations and autoinflammatory syndromes. *Curr Opin Immunol* 2000;12:479–86.

FMF = familial Mediterranean fever
MWS = Muckle-Well syndrome
FCAS = familial cold autroinflammatory syndrome
CINCA = chronic infantile neurologic, cutaneous and articular syndrome
PyD = pyrin domain
PFAPA = periodic fever, aphthous stomatitis, pharyngitis and adenopathy

6. Houten SM, Kuis W, Duran M, et al. Mutations in MVK encoding mevalonate kinase cause hyper immunoglobulinemia D and periodic fever syndrome. *Nat Genet* 1999;22:175–7.
7. Drenth JP, Cuisset L, Grateau G, et al. Mutations in the gene encoding mevalonate kinase cause hyper IgD and periodic fever syndrome. International hyper IgD study group. *Nat Genet* 1999;22:178–81.
8. Muckle TJ, Wells M. Urticaria deafness and amyloidosis: a new heredofamilial syndrome. *Q J Med* 1962;31:235–8.
9. Zip CM, Ross JB, Greaves MW, et al. Familial cold urticaria. *Clin Exp Dermatol* 1993;18:338–41.
10. Hoffman HM, Wanderer AA, Broide DH. Familial cold autoinflammatory syndrome: phenotype and genotype of an autosomal dominant periodic fever. *J Allergy Clin Immunol* 2001;108:615–20.
11. Hoffman HM, Mueller JL, Broide DH, et al. Mutation of a new gene encoding a putative pyrin-like protein cause: familial cold autoinflammatory syndrome and Muckle-Wells syndrome. *Nat Genet* 2001;29:301–5.
12. Dode C, Le Du N, Cuisset L, et al. New mutations of the CIAS1 gene that are responsible for Muckle-Wells syndrome and familial cold autoinflammatory syndrome: a novel mutation underlies both syndromes. *Am J Hum Genet* 2002;43:1535–42.
13. Cuisset l, Drenth JP, Berthelot JM, et al. Genetic linkage of the Muckle Wells syndrome to chromosome 1q44. *Am J Hum Genet* 1999;65:1054–9.
14. Prieur AM, Gricelli C, Lampert F, et al. A chronic infantile, neurological, cutaneus and articular syndrome. A specific entity analyzed in 30 patients. *Scand J Rheum Suppl* 1987;66:57–68.
15. Feldman J, Prieur M. Chronic infantile, neurological, cutaneus and articular syndrome is caused by mutations in CIAS1, a gene highly expressed in polynorphonuclear cells and chondrocytes. *Am J Hum Genet* 2002 (online)
16. Frederico G, Rigante D, Pugliese AL, et al. PFAPA syndrome. *Clin Exp Rheum* 2002;20:s-73
17. El-Shanti HI, Tayeh MK, Majeed HA, et al. Assignment of the gene responsible for recurrent multifocal osteomyelitis and congenital dyserythropoietic anemia to the short arm of chromosome 18 and the examination of TGIF as a candidate gene. *Clin Exp Rheum* 2002;20:s-74
18. Yeon HB, Lindor NM, Seidmen JG, et al. Pyogenic arthritis, pyoderma gangrenosum and acne syndrome maps to chromosome 15q. *Am J Hum Genet* 2000;66:1443–8.
19. Lindor NM, Arsenault TM, Solomon H, et al. A new autosomal dominant disorder of pyogenic sterile arthritis, pyoderma gangrenosum and acne: PAPA syndrome. *Mayo Clin Proc* 1997;72:611–15.

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