Editorial

Adult-onset autoinflammatory disorders: a still debated entity?

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Mutations in genes regulating the homeostasis of innate immunity lead to oversecretion of many proinflammatory cytokines, including interleukin (IL)-1β, and cause the so-called *autoinflammatory disorders* (AIDs), characterised by seemingly unprovoked inflammation recurring with variable rhythmicity and involving skin, serosal membranes, synovial membranes, or gastrointestinal tube, with reactive amyloidosis as a potential severe long-term consequence (1, 2). Recent findings have greatly modified our knowledge regarding the pathophysiology of hereditary monogenic AIDs, and showed that protean inflammatory symptoms can be variably associated with periodic fevers, depicting multiple specific conditions, which usually start in childhood (3). However, different case reports have provided insights into the principle that some patients may experience a delayed disease onset and receive a definite diagnosis during adulthood (4). Renal AA amyloidosis represents the ominous complication of misdiagnosed and neglected AIDs, with a prevalence ranging from 2 to 25% for the different clinical syndromes: in particular, renal amyloidosis might lead to severe deterioration of kidney function, resulting from the extracellular deposition of proteolytic cleavage products of the acute phase reactant serum amyloid-A, synthetised in the liver under the effect of IL-1β and other biologic mediators (5).

The most frequent monogenic disease among AIDs is familial Mediterranean fever (FMF), caused by homozygosity or compound heterozigosity in the MEditerranean FeVer (*MEFV*) gene encoding the pyrin protein, which is mainly expressed in inflammatory cells: the incidence of this pyrin-related autoinflammatory disease is higher in populations living around the Mediterranean basin, and main clinical features are represented by recurrent brief episodes of fever, serositis, joint symptoms, and erysipelas-like erythema in the lower limbs. Febrile attacks are typically prevented by long-term colchicine administration, which is also the mainstay for amyloidosis prevention in these patients (6). Meeting Tel Hashomer diagnostic criteria and being of Mediterranean origin should be considered clues for recommending *MEFV* genetic testing (7).

FMF onset age is reported between 30 and 50 years in only 2% of probands (8). In our centre we have tested 414 patients for *MEFV* mutations and 49 were genetically positive. We also found 17 genetically-negative FMF patients, and 15 were adults (9). Thirthy out of 49 genetically-positive patients were adults and they mostly carried low-penetrance *MEFV* mutations; their phenotype was similar to that of younger patients. Accordingly, it is known that adult onset-FMF might display clinical features similar to those presented by younger patients, except for a lower rate of arthritis and erysipelas-like eruption: these subjects with oligosymptomatic disease should not be overlooked, and genetic testing may be contributive to ascertain FMF diagnosis (10).

Tumour necrosis factor (TNF) receptor-associated periodic syndrome (TRAPS) is related to mutations in the soluble TNF receptor super family 1A gene (*TNFRSF1A*), and is the most common autosomal dominantly-inherited among AIDs, as well as the most heterogeneous in terms of clinical features (11). The disease starts with long-lasting inflammatory attacks which comprise migratory erythematous plaques, myalgia, joint and ocular signs, following a wide spectrum of *TNFRSF1A* mutations: mutated *TNFRS1A* variants induce cytoplasmic retention of the TNF receptor, defective TNF-induced apoptosis, production of reactive oxygen species, and dysregulation in the secretion of IL-1

Table I. Summary of the monogenic autoinflammatory disorders observed in childhood and adulthood.

	FMF	TRAPS	FCAS	MWS	CINCAs	NLRP12-AD	BS
Gene	*MEFV*	*TNFRSF1A*	*NLRP3*	*NLRP12*	*CARD15/NOD2*		
Locus	16p13.3	12p13	1q44	19q13	16q12.1-13		
Protein involved	Pyrin	TNFR	Cryopyrin	Monarch-1	NOD2		
Inheritance	AR	AD	AD	AD	AD		
Main clinical features							
Fever	+	+	+	+	+	+	+
Pleuritis	+	+	–	–	–	–	–
Pericarditis	+	+	–	–	–	–	–
Peritonitis	+	+	–	–	–	–	–
Skin rash	erysipelas-like eruption	migratory erythematous rash	cold-induced urticaria-like rash	evanescent urticaria-like rash	neonatal onset urticaria-like rash	urticaria-like rash	granulomatous dermatitis
Eye involvement	–	conjunctivitis, periorbital edema	–	–	uveitis, retinopathy, papilledema	-	recurrent granulomatous panuveitis
Joint involvement	monoarthritis	arthralgia or chronic arthritis	arthralgia	lifelong arthralgia	deforming arthritis; premature abnormal patella ossification	+	symmetrical granulomatous polyarthritis
Central nervous system involvement	demyelinating lesions, reversible leukoencephalopathy syndrome	inflammatory demyelinating disease	–	–	aseptic chronic meningitis	–	–
Hearing	–	–	–	sensorineural hearing loss	ensorineural s hearing loss	–	–
Amyloidosis	+	+	–	+	+	–	+

FMF: familial Mediterranean fever; TRAPS: tumour necrosis factor receptor-associated periodic syndrome; FCAS: familial cold autoinflammatory syndrome; MWS: Muckle-Wells syndrome; CINCAs: chronic infantile neurologic cutaneous articular syndrome; NLRP12-AD: NLRP12-associated autoinflammatory disorder; BS: Blau syndrome; AR: autosomal recessive; AD: autosomal dominant.

(12). Adult onset-TRAPS patients may display a clinical picture mimicking FMF and challenging a coherent differential diagnosis. We identified variables related to the probability of detecting *MEFV* and *TNFRSF1A* mutations in patients with thoracic or abdominal pain and positive family history for recurrent fevers (13-15). At our Centre the majority of TRAPS patients had a clinical onset in adulthood, even in the sixth decade (16). Late onset-TRAPS was mostly related to low-penetrance mutations and frequently started with atypical clinical sceneries, such as recurrent pericarditis, myocarditis, or sacroiliitis, no less than unique isolated manifestations (17-19). Accordingly, we also suggested that difficult-to-treat pericarditis and lack of spontaneous amelioration after the first year from the first attack of pericarditis may represent further clues to investigate *TNFRSF1A* genotype (20). The presence of pericarditis should also raise the diagnostic suspicion of TRAPS in the absence of a positive family history (21). In addition, we observed that R92Q, P46L, D12E, V95M, and R104Q variants are low-penetrance mutations, rather than benign polymorphisms, disclosed in adults with febrile episodes lacking the most typical TRAPS signs and showing a milder disease course. These subjects seem to have a lower risk of developing amyloidosis (22).

The group of cryopyrin associated periodic syndrome (CAPS), caused by mutations in the *NLRP3* gene, encoding the cryopyrin protein, which directly commands the release of bioactive IL-1β, includes familial cold urticaria syndrome (FCAS), Muckle-Wells syndrome (MWS) and chronic infantile neurological cutaneous articular syndrome (CINCAs), respectively ranging from the least to the most severe, and starting prevalently in paediatric age (23). In particular, FCAS is characterised by episodic fevers, skin rashes and arthralgias, mostly triggered by exposure to cold, MWS consists of similar symptoms associated with progressive neuro-sensorial deafness, while CINCAs is marked by neonatal onset-skin rash, severe deforming arthropathy, and chronic meningeal involvement (24). When the diagnosis of CINCAs is formulated in childhood the use of IL-1 antagonists can induce positive therapeutic effects even at a neurological level (25). At our Centre we tested 113 adults for *NLRP3* mutations, and recently described a case series of patients with FCAS-like symptoms, all carrying the low-penetrance Q703K mutation (26). The *NLRP12*-associated autoinflammatory disorder (*NLRP12*-AD) is very similar to CAPS, but rarer, and caused by mutations in the *NLRP12* gene, which encodes the monarch-1 protein: the disease is characterised by recurrent

bouts of fever, skin rash, mouth ulcers, and abdominal pain (27). We analysed 61 patients for *NLRP12*-AD at our Centre, and 44 of probands (11 positive) had a disease onset in adulthood. We also reported 5 patients carrying a heterozygous F402L mutation and 1 patient carrying a heterozygous G448A mutation in the *NLRP12* gene, all showing a late disease onset (28).

Blau syndrome (BS), an autosomal dominant granulomatous disease starting within the first 4 years of life with symmetrical polyarthritis, papular-nodular rash with tendency to lichenoid-like lesions, and panuveitis, is caused by mutations in the nucleotide-binding domain of caspase recruitment domain *CARD15/NOD2* gene (29): among 54 patients tested for BS at our Centre, 27 were adults.

Although inherited monogenic AIDs are generally encountered in children, all of these diseases have been frequently identified in adults too, with the exception of mevalonate kinase deficiency syndrome, heralded by multi-organ inflammatory attacks starting within the first 5 years of life in all cases and persisting throughout lifetime (30). Most cases of AIDs with onset in adulthood have been related to low-penetrance mutations, generating mild and non-specific phenotypes. Differential diagnosis of AIDs can be complicated by the high frequency of periodic fever, aphthosis, pharyngitis, adenitis (PFAPA) syndrome, a clinical entity included in the group of the multi-factorial polygenic AIDs, characterised by periodically-recurring fever attacks, which is largely recognised in children, though many adults with PFAPA syndrome have been reported as well, suggesting that this diagnosis should be taken into consideration at whatever age (31, 32).

During the last few years, different diagnostic scores have been proposed to improve the identification of people with AIDs and optimise their access to genetic testing (33). Although hereditary monogenic AIDs are rare diseases, the improved basics among physicians from different specialties is bringing about a sizeable increase in the identification of patients, even with non-canonical presentation: we have commonly encountered adult onset-AIDs with incomplete and atypical disease patterns in the clinical practice. However, we suggest caution in the interpretation of low-penetrance mutations in probands with suspected AIDs, given the high frequency of healthy carriers and the unknown influence of additional genetic and/or environmental modifying factors (34, 35). The increasing reports of adults with AIDs will help clarify the connection between innate immunity and environment, though a specific diagnosis will still require the integration of multiple information, both clinical and laboratory data, family history, ethnicity, and focused genetic analysis.

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