Childhood versus adulthood-onset autoinflammatory disorders: myths and truths intertwined

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SUMMARY

Autoinflammatory disorders are characterized by spontaneous episodes of systemic inflammation deriving from inherited defects of the innate immune system. Childhood is usually the lifetime involved in most inherited autoinflammatory disorders, but a moderate number of patients may experience disease onset during adulthood. Herein we report our experience in the clinical and genetic approach to the diagnosis of autoinflammatory disorders in regard of the first 500 pediatric and adult patients evaluated during the period 2007-2012 in our Center, due to histories of periodically-recurring inflammatory attacks, giving emphasis to the differences observed according to patients'age and to the most relevant data differentiating child and adult-onset autoinflammatory disorders in the medical literature.

Key words: *Autoinflammatory disorders, Child, Adult, Interleukin-1β.*

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INTRODUCTION

Autoinflammatory disorders (AID) are a newly recognized expanding group of hereditary monogenic diseases in which systemic inflammation recurs without any auto-reactive T-lymphocytes or auto-antibodies, caused by dysfunction of the *inflammasome* (1). The inflammasome, a multiprotein complex regulating the release of caspase activation-dependent cytokines, represents an alert sentry of the innate immune system and all AID are characterized by dysregulated production of proinflammatory cytokines, released by the inflammasome, such as interleukin (IL)-1β. The inflammatory flare, often triggered by an unknown stimulus, results in periodically-recurring symptoms with variable involvement of skin, joints, gastrointestinal tube, serosal membranes, or central nervous system: nevertheless each flare is separated by symptom-free intervals of variable duration (2). Understanding the genetics behind AID has led to the discovery of new molecules involved in the inflammatory response to different exogenous and endogenous signals, but no formal guidelines for the approach of patients with AID exist both for children and adults. To leave aside these patients might lead to renal AA amyloidosis, the best-known and ominous long-term complication of AID, with a prevalence ranging from 2 to 25% for the different clinical entities (3). Apart from lifelong recurrent flares, AID have distinctive features, such as age of onset, prognosis and ethnic origin of patients, but the differential diagnosis remains a challenge and genetic analysis might only in part contribute to diagnosis. A host of multi-factorial disorders, such as Behçet disease, gout, adult Still's disease, systemic-onset juvenile idiopathic arthritis, and periodic fever/aphthosis/pharyngitis/adenitis (PFAPA) syndrome, are nowadays deemed as acquired AID on a potential polygenic basis (4) and must be taken in consideration in the differential diagnosis of AID.

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The experience of our Center

The list of monogenic AID attended in our tertiary referral Center includes familial Mediterranean fever (FMF), tumor necrosis factor receptor-associated periodic syndrome (TRAPS), mevalonate kinase deficiency syndrome, also known as hyper-gammaglobulinemia-D syndrome (HIDS), the whole family of cryopyrin associated periodic syndromes (CAPS), which encompass familial cold urticaria syndrome (FCAS), Muckle-Wells syndrome and chronic infantile neurological cutaneous and articular syndrome (CINCAs), and also NLRP12-associated autoinflammatory disorder (NLRP12AD) and Blau syndrome (BS). Table I summarizes the main clinical characteristics of these AID.

The advent of genetic testing for AID has led to the identification of specific disea-

Table I - Brief summary of the monogenic autoinflammatory disorders diagnosed and managed in our Center.

Disease	Gene Locus	Protein	Inheritance	Prominent clinical features	Treatment
FMF	MEFV 16p13.3	Pyrin	AR	Fever, serositis, arthralgias or arthritides, erysipelas-like eruption on the legs, amyloidosis in untreated patients	Colchicine, anakinra
TRAPS	TNFRSF1A 12p13	Tumor necrosis factor receptor 1	AD	Fever, migrating muscle and joint involvement, conjunctivitis, periorbital edema, arthralgias or arthritis, serosal involvement, steroid responsiveness of febrile attacks, amyloidosis	Corticosteroids, etanercept, anakinra
HIDS	MVK 12q24	Mevalonate kinase	AR	Fever, polymorphous rash, arthralgias, abdominal pain, diarrhea, lymph node enlargement, splenomegaly, aphthosis	Anti-inflammatory drugs, anakinra, corticosteroids
FCAS	NLRP3 1q44	Cryopyrin	AD	Fever, cold-induced urticarial rash, conjunctivitis, arthralgias	Anakinra, rilonacept, canakinumab
MWS				Fever, urticarial rash, conjunctivitis, episcleritis, arthralgias, neurosensorial deafness, amyloidosis	
CINCAs				Fever, urticarial rash, uveitis, papilledema, deforming arthritis involving large joints, aseptic chronic meningopathy, neurosensorial deafness, amyloidosis	
NLRP12AD	NLRP12 19q13	Monarch-1	AD	Fever, arthralgia, cold-induced urticarial rash	Anakinra
BS	NOD2(CARD15) 16q12.1-13	NOD2	AD	Granulomatous dermatitis with ichthyosis-like changes, symmetrical granulomatous polyarthritis, camptodactyly, recurrent granulomatous panuveitis, intermittent fevers, cranial neuropathies	Corticosteroids, immunosuppressive agents, tumour necrosis factor inhibitors, anakinra

FMF, familial Mediterranean fever; AR, autosomal recessive; TRAPS, tumor necrosis factor receptor-associated periodic syndrome; AD, autosomal dominant; HIDS, hyper-gammaglobulinemia D syndrome; FCAS, familial cold autoinflammatory syndrome; MWS, Muckle-Wells syndrome; CINCAs, chronic infantile neurologic cutaneous articular syndrome; NLRP12AD, NLRP12-associated autoinflammatory disorder; BS, Blau syndrome.

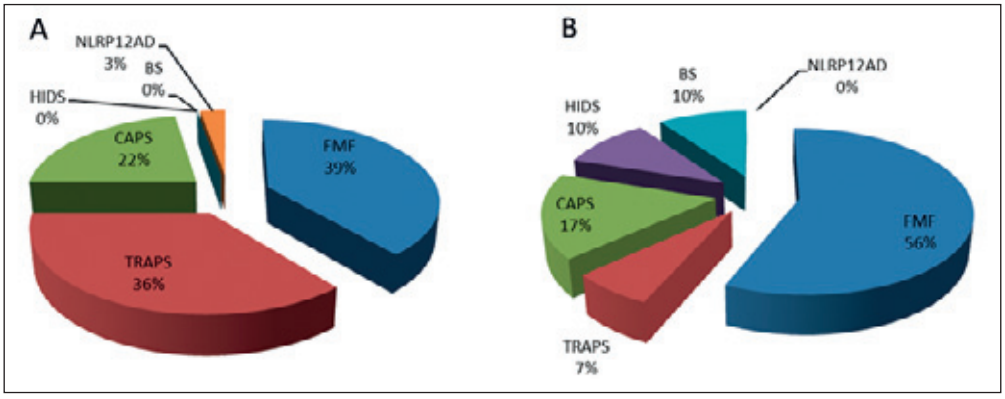

Figure 1 - Percentages of the autoinflammatory disorders diagnosed in our Center among patients older than 18 (A) and younger than 18 years (B).

ses for patients with peculiar clinical phenotypes and ethnic origin, but a number of patients with clear periodic febrile/inflammatory symptoms cannot be classified by genetic testing.

To date, the rate of detection of autoinflammatory gene mutations in patients suspected of having AID is very low, less than 20% in most case series. With the exception of HIDS, AID-related genes encode for proteins involved in the regulation and/or activation of the inflammasome. In our Center we have dedicated ourselves to the diagnosis and clinical management of different patients with AID and so much as 500 patients have been screened in the period September 2007 - September 2012. Figure 1 shows the percentages of AID diagnosed with differences between patients older and younger than 18 years. The histogram showed in Figure 2 describes the number of AID diagnoses made among patients with more or less than 18 years for each disease among all patients undergoing genetic analysis. The histogram showed in Figure 3 describes the number of patients with more or less than 18 years who un-

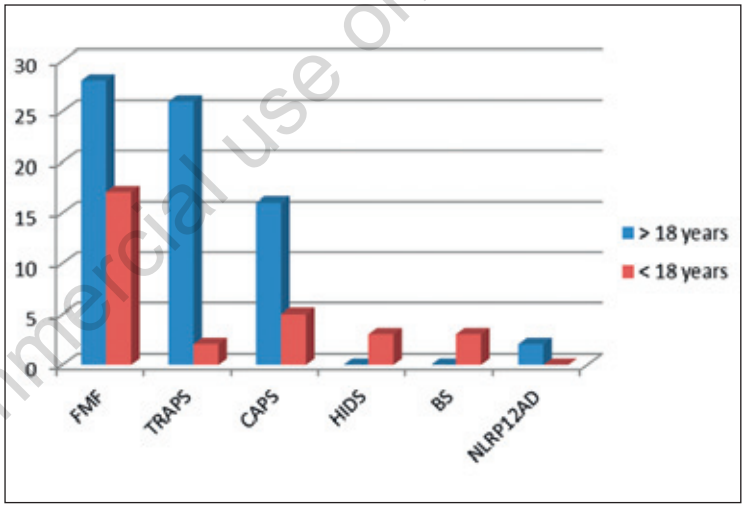

Figure 2 - Number of diagnoses of specific autoinflammatory disorders among all probands undergoing genetic analysis at our Center (differentiated for age).

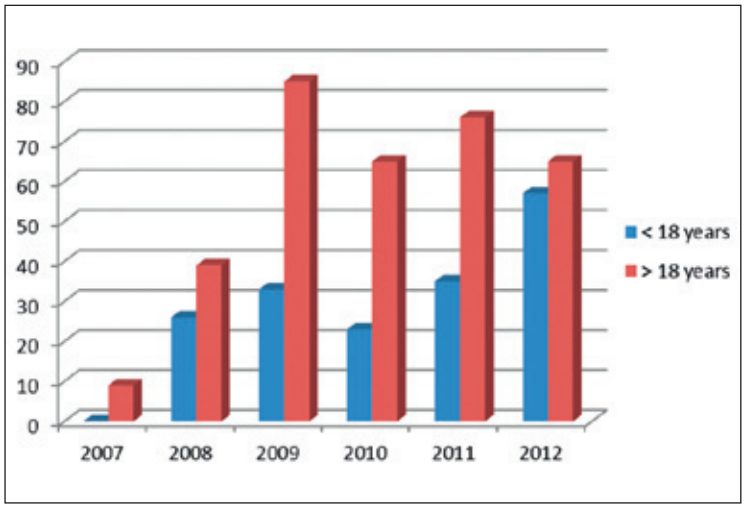

Figure 3 - Number of patients with more or less than 18 years undergoing genetic analysis at our Center in the period 2007-2012 subdivided per year (for the year 2007 the period was between September and December; for the year 2012 the period was between January and September).

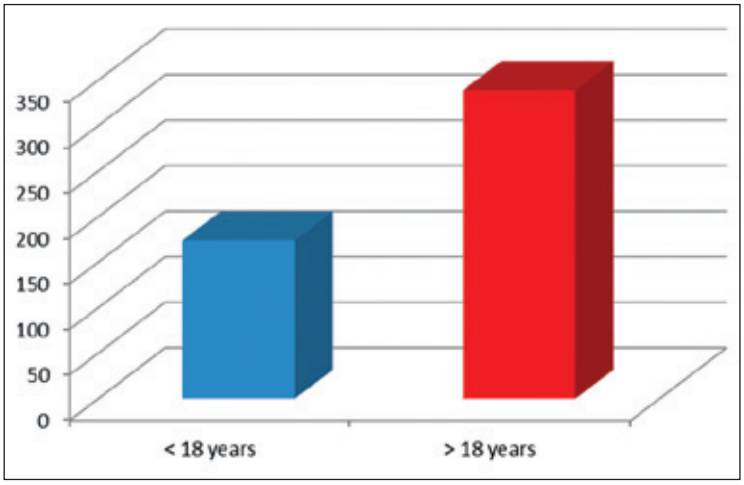

Figure 4 - Total number of patients undergoing genetic analysis at our Center in regard to age (more or less than 18 years) in the period September 2007 - September 2012.

derwent genetic analysis at our Center in the period 2007-2012, subdivided per year. Figure 4 shows the total number in regard to age of patients undergoing genetic analysis during the same 2007-2012 period. Figure 5 shows the annual percentages of genetically positive patients compared to the total number of subjects genetically evaluated per year. At last, Figure 6 depicts the number of genes evaluated in the period 2007-2012, among patients with more or less than 18 years for a total of 857 genes evaluated. The gene/patient ratio was 1.67. Many reflections can be drawn by reading these figures, combined with comparisons with data differentiating child and adult-onset AID in the medical literature.

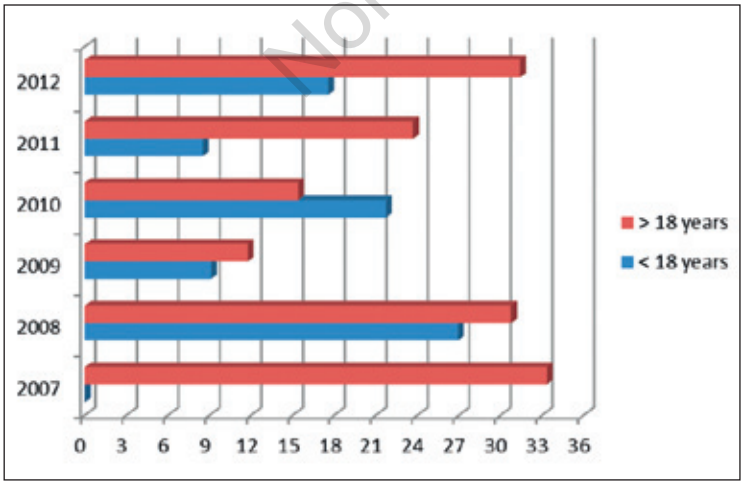

Figure 5 - Annual percentages of genetically positive patients compared to the total number of subjects genetically evaluated per year (for the year 2007 the period was between September and December; for the year 2012 the period was between January and September).

What we have found and what is known about child and adult-onset autoinflammatory disorders

With regard to FMF, more than 60% of patients have a disease onset before age 10, but onset occurs before age 30 in 98% of patients, and before age 50 in the remaining 2% (5). A delayed onset has frequently been reported in FMF (6, 7). Adult-onset FMF seems to be related to heterozigosity and low-penetrance mutations: although adults often experience a milder phenotype, clinical features might be similar to those found in younger patients, except for a lower rate of arthritides and erysipelas-like rash. Establishing promptly FMF diagnosis allows to set up its mainstream treatment, based on the oral administration of colchicine (8). Although the Tel Hashomer criteria are mostly useful in diagnosing adult patients with FMF, a new set of criteria studied in a cohort of Turkish children has showed a higher sensitivity and specificity for the diagnosis of FMF in childhood (9).

A clinical diagnosis can be confirmed by *MEFV* mutations, but adult-onset FMF patients may sometimes show an incomplete clinical picture and these subjects will never fulfil the currently used diagnostic criteria, requiring genetic testing as a crucial point to the diagnosis (10). Several mutations in the *MEFV* gene have been observed in different populations, mostly of Armenian, Turkish, Arabic and non-Ashkenazi Jewish ancestry, but the distribution of *MEFV* mutations across different countries is unfairly elucidated (11).

Federici et al. carried out a study on a large group of adults presenting with periodic fever episodes and suggested that meeting FMF diagnostic criteria and being of Mediterranean origin should recommend molecular analysis of the *MEFV* gene: the authors also underscored that, in the presence

of a negative *MEFV* test, a further genotype screening should be chosen on the basis of expert advice (12). In addition, patients living in the Eastern Mediterranean areas have a milder disease phenotype once they migrate to Europe, reflecting the effect of environment on FMF clinical expression (13). In our Center we have tested 304 patients for *MEFV* mutations, and 32 out of 304 were genetically positive. Seventeen out of 32 were younger than 18 years; of the remaining 15, 7 were adults with onset of symptoms during childhood and 8 had the onset of symptoms during adulthood (14-17). As we recently described, our adult-onset patients mainly carried low-penetrance *MEFV* mutations, however their clinical manifestations were similar to those of younger patients. Among the genetically positive FMF patients, 4 carried homozygous mutations, 9 were compound heterozygous and 19 carried heterozygous high penetrance mutations. In addition, 13 genetically-negative adult patients fulfilled the FMF diagnostic criteria and were diagnosed with FMF.

TRAPS is the most variable and protean entity among AID in terms of age of disease onset, frequency, duration and severity of inflammatory flares, and this heterogeneity is probably linked to the wide spectrum of *TNFRSF1A* mutations (18, 19). The average age of TRAPS onset is around 3 years, but adult-onset up to the sixth decade has been reported as well (18). As with FMF, it is frequently related to low-penetrance mutations. The majority of children with an R92Q *TNFRSFA1* mutation show a milder disease course than that in children with structural mutations and have a higher rate of spontaneous resolution or amelioration of the recurrent fever episodes (20). In addition, adult patients with TRAPS may present atypical clinical clues, such as recurrent pericarditis or myocarditis, as unique clinical manifestations (21-24). We recently investigated the possible involvement of *TNFRSF1A* gene mutations in 30 patients with colchicine-refractory recurrent pericarditis, finding that both a poor response to colchicine and/or familial clustering of pericarditis might indicate the need to investigate TRAPS mutations (25). Recently, we suggested that difficult-to-treat pericarditis and lack of spontaneous amelioration of symptoms after the first year from the first attack of pericarditis may represent further reasons to investigate for *TNFRSF1A* (26). We have more recently identified some variables strongly related to the probability of detecting mutations in the *MEFV* and *TNFRSF1A* genes (16), and also validated a diagnostic score for identifying patients at high risk to carry these mutations according to clinical manifestations, age of disease-onset, and family history (14, 15): the score may serve in the initial diagnostic evaluation of adults presenting with recurrent fever episodes, helping to identify those subjects who may be carriers of *MEFV* and *TNFRSF1A* mutations.

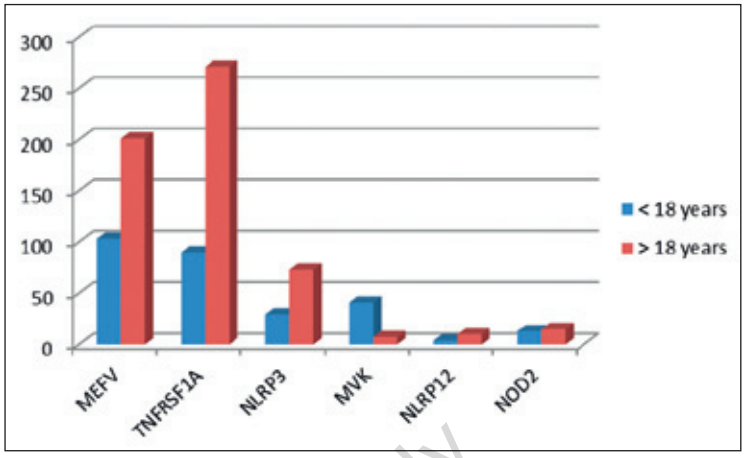

Figure 6 - Number of genes evaluated in the period September 2007 - September 2012, for a total of 857 genes, for patients differentiated per age.

However, before it can be recommended for a large application, further evaluation is needed by means of longitudinal studies on people of different ethnicities and living in non-Mediterranean areas.

HIDS is typically characterized by onset in the first year of life, and *MVK* genetic testing appears not indicated in patients who have their first fever attack after 5 years (27). All our patients tested for *MVK* had their first clinical manifestations starting in early childhood. Clinical data obtained from 103 patients of 18 different countries

showed that the median age of the first attack was 6 months, with a median period of 9.9 years from onset of disease to diagnosis, that the most frequent symptoms other than fever were lymphadenopathy, abdominal pain, arthralgia, diarrhea, vomiting, skin lesions, and aphthous ulcers, and that the frequency of attacks decreased with the patient's increasing age (28).

Also CAPS, based on elevated IL-1β overproduction, start in early childhood with most patients presenting periodic fever, skin rash, osteoarthropathy, and risk of aseptic meningitis, sensorineural hearing loss, and optic neuritis (29): even CINCAs, the most severe form of CAPS with neurologic involvement, if properly recognized in children, might show sensational responses to IL-1 antagonists (30). We have recently described a case series of patients presenting with FCAS-like symptoms, mainly worsened by cold exposure, and carrying the low-penetrance Q703K mutation in the *NLRP3* gene, most of whom were characterized by adult-onset disease (31). In agreement with these findings, we have recently diagnosed a Caucasian mother and her daughter with FCAS: both these patients carried the low-penetrance V198M mutation in the *NLRP3* gene and displayed the clinical onset during adulthood, with clinical manifestations triggered by generalized cold exposure (unpublished data).

Also patients with NLRP12AD suffer from early infancy-onset recurrent bouts of fever, joint symptoms, and skin rash triggered by cold exposure (32). However, Borghini *et al.* have recently described a 32-year-old woman as a carrier of the D294E mutation in the *NLRP12* gene, and this patient experienced FCAS-like symptoms since she was 20 (33). In agreement with this report, we recently diagnosed a 27-year-old Caucasian woman with NLRP12AD, carrying the F402L mutation, who presented a daily low-grade fever (<38°C) since the age 22, confirming that a subset of *NLRP12*-mutated patients might display onset-symptoms during adulthood (unpublished data).

BS is phenotypically characterized by granulomatous polyarthritis with boggy synovial effusions and cysts, uveitis and persistent dermatitis with scaly or lichenoid features, starting before 4 years, but its diagnosis is often overlooked or postponed due to the poor knowledge of the syndrome among clinicians (34). In our Center we have tested 28 patients for mutations in the gene responsible for BS. Thirteen out of 28 were children and 3 of them were genetically positive. Fifteen adults were suspected of being affected with a previously undiagnosed BS, but no mutations were found.

Differential diagnosis of AID can also be complicated by other challenging acquired entities, as PFAPA syndrome (35): to date, this disorder does not have a documented genetic basis, and spontaneous resolution of febrile flares is usually observed a few years later its onset, mostly in pediatric patients. Controversy exists about differentiation between patients with PFAPA syndrome and other established monogenic AID: a diagnostic score has been formulated on the basis of a statistical analysis in 173 children with periodic fevers and PFAPA-like symptoms, analyzed for *MEFV*, *TNFRSF1A*, and *MVK* genotypes, disclosing that age at onset, positive family history, thoracic or abdominal pain, diarrhea, and oral aphthosis were the variables predicting the probability of a positive genetic test result for hereditary AID with an overall accuracy of 66% (36, 37).

Recent medical literature has involved dozens of suspected cases of PFAPA syndrome also in adults of different age (38-40). As patients with PFAPA syndrome develop predictable and stereotypic febrile attacks occurring approximately every 4 weeks, with aphthous stomatitis, exudative or nonexudative pharyngitis, cervical lymph node enlargement, and even abdominal or skin signs, they pose diagnostic challenges with regards to FMF, as the clinical features might overlap between the two conditions. It has been established that the frequency of PFAPA syndrome-like findings tends to decrease from patients with FMF having a single low-penetrance mutation towards those with two high-penetrance mutations (41).

CONCLUSIONS

In conclusion, although AID are mostly characterized by onset occurring in childhood, both delayed diagnosis during adulthood and adult-onset symptoms are commonly encountered. Adulthood-onset AID might be related in most cases to the presence of low-penetrance mutations, generating a nonspecific and nuanced phenotype in comparison with children. Low-penetrance mutations may also be responsible for incomplete or mild disease patterns in some cases, and for the appearance of atypical manifestations in other cases.
The increasing reports of adult patients are shedding a new light on the protean clinical scenery, genotype-phenotype correlations, overall prognosis and therapeutic management of AID, but a specific diagnosis will still require a thorough clinical examination, family history, ethnic origin, and laboratory evaluation combined with focused genetic analysis.

Conflict of interests: the authors declare no potential conflict of interests.

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