Auto-inflammatory diseases register : data from the newest Reuma.pt protocol

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Introduction

Auto-inflammatory diseases (AIDs) are a newly understood group of conditions with expanding phenotypes and genetic markers. However, many AIDs are extremely rare and genotype-phenotype correlations, disease course, response to treatment and outcomes are difficult to characterize. Multicentre AIDs registries enable a better understanding of clinical features and outcomes of such diseases and are a valuable tool for clinical and translational research in this field.

Objectives

To assess clinical and genetic features of auto-inflammatory diseases registered at Reuma.pt AIDs protocol.

Methods

Since September 2013 Rheumatic Diseases Portuguese Register, Reuma .pt, has a build-in protocol specifically developed for AIDs.
Inclusion criteria in this protocol are monogenic AIDs or clinically confirmed AID with unknown genetic background. Monogenic AIDs includes familial mediterranean fever (FMF), mevalonate kinase deficiency (MKD), TNF receptor 1-associated periodic syndrome (TRAPS), cryopyrin-associated periodic syndrome (CAPS), chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE), Blau syndrome, pyogenic sterile arthritis, pyoderma gangrenosum and acne (PAPA), Majeed syndrome, deficiency of IL-1B receptor antagonist (DIRA), deficiency of IL-36 receptor antagonist (DITRA) and others like auto-inflammatory PLCG2-associated antibody deficiency and immune dysregulation (APLAID). Periodic fever, aphthous stomatitis, pharyngitis and adenopathy (PFAPA) syndrome and chronic recurrent multifocal osteomyelitis (CRMO) are included as AID with unknown genetic background. Undefined AID concerns clinically confirmed AID with more than three self-limited episodes of fever > 38,5ºC, increased inflammation markers and asymptomatic intervals between episodes in an otherwise healthy patient. Available data from this register were analyzed regarding genetic, epidemiological and clinical features.

Results

From the 74 patients currently included in Reuma.pt AID protocol, 72 patients (44 males and 28 females) registered by two centres (35 from HSM and 37 from HDE), were analysed. Of these, 10 (13.9%) have been documented only prospectively and for 56 (77.8%) patients retrospective and prospective data have been made available. Mean age was 8.6±8.2 years (2.2 to 19.2 years), mean age at disease onset was 2.5±2.2 years, disease duration was 5.7±3.9 years and mean time between symptoms onset and clinical diagnosis was 2.9±1.5 years.
The following diagnosis have been identified: FMF (n=2), MKD (n=2), TRAPS (n=1), PFAPA (n=47), CRMO (n=5), APLAID (n=1) and undefined AID (n=14).

Table 1. Diagnosis and treatment options

Dianosis	Number of cases	Treatments
FMF	2	Colchicine - 2
MKD	2	Corticosteroids on demand -2; Anakinra - 1
TRAPS	1	Corticosteroids on demand -1; Etanercept - 1
PFAPA	47	Corticosteroids on demand - 47
CRMO	5	Corticosteroids -5; Pamidronate – 4; Methotrexate – 1
APLAID	1	Corticosteroids on demand -1
Undefined AID	14	Corticosteroids on demand - 6; Canakinumab – 1

Table 2. Spectrum of mutations in monogenic AIDs

Gene mutations	Number of mutations
FMF	
***MEFV* pG304R**	1
MKD	
***MVK* pR277G**	1
***MVK* pVal377Ile**	1
***MVK* pCys152Tyr**	1
TRAPS	
***TNFRSF1A* pR92Q**	1
APLAID	
PLCG2	1
Total (n)	6

Pathogenic mutations for monogenic AID were found in 5 patients: *MEFV* PG304R in 1 patient with FMF, *MVK* pR277G (homozygous), *MVK* p.Val377Ile and *MVK* p.Cys152Tyr (compound heterozygous) in 2 patients with MKD, *TNFRSF1A* R92Q in 1 TRAPS patient and *PLCG2* gene mutation in 1 APLAID patient. Regarding treatment, 2 FMF patients were treated with colchicine, corticosteroids on demand were used in all PFAPA patients and also for MKD, TRAPS, APLAID and 6 undefined AID patients. Biological therapy was used in: MKD (1 patient partly controlled with anakinra), TRAPS (1 patient treated with etanercept) and undefined AID (canakinumab has been used in 1 patient). Of the 5 CRMO patients 4 were treated with prednisolone and pamidronate and 1 with prednisolone and methotrexate. Twenty seven blood samples from 3 patients have been collected at Biobanco-IMM. The collection of blood samples from the remaining patients is ongoing.

Conclusions

Through this register AIDs can be systematically investigated paving the way to a better understanding of disease course, treatment responses and prognosis. This tool could be also valuable in the future to enable genotype-phenotype correlations in order to identify new AIDs and new mutations.

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