Pedido de acesso a dados do Registo Nacional de Doentes Reumáticos (Reuma.pt) da Sociedade Portuguesa de Reumatologia

1. Title

Autoinflammatory Diseases: analysis based on The Rheumatic Diseases Portuguese Register.

2. Background

Autoinflammatory diseases (AIDs) are inborn disorders of the innate immune system characterized by episodes of systemic inflammation that are mediated largely by myeloid cells. The field of autoinflammatory diseases was established in 1997, following the identification of the first genes underlying periodic fever syndromes.[1] The incidence of autoinflammatory diseases is low, with diseases such as cryopyrin associated periodic syndromes (CAPS) that have an estimated frequency of 1 to 3 per million, and the most rare conditions have an estimated frequency of less than 10 reported families worlwide.[1]

Our knowledge of autoinflammatory diseases although expanding rapidly, is still very limited. The recent advent of next-generation sequencing allowed the discovery of new genes, unravelled different pathways and more complicated mechanisms of inheritance. As genomic sequencing becomes increasingly available, data sharing and the functional analysis of sequence variants is becoming even more critical. However, genotype-phenotype correlations and the potential influences of environmental and epigenetic factors are still largely unknown. This phenotypic variability along with the rarity of these diseases leads to delayed diagnosis.[2] Sometimes, even when a diagnosis is achieved, there is difficulty in providing definitive answers and the best treatments to these patients.

A major limitation to understand autoinflammatory diseases has been the fragmentation of clinical experience in these low incidence diseases. In order to avoid this, an international project named Eurofever Project was created in 2009, including an international registry of autoinflammatory diseases, which aims to promote awareness of these diseases among the medical community and to improve knowledge of the clinical presentation, response to treatment and long term complications of these disorders.[3]

Comparatively, in Portugal, the growing research dedicated to innate immunity and the variability of autoinflammatory diseases led to the creation, in 2013, of a protocol in the Rheumatic Diseases Portuguese Register (Reuma.pt) that allows the characterization of

Portuguese patients in each known group of autoinflammatory diseases. This electronic clinical record aims to improve the monitoring and clinical care of Portuguese patients from the different rheumatology departments across the country. This will permit a better understanding of these diseases and to follow over time their clinical course and response to treatment.

It is our goal to stimulate the Portuguese paediatric and rheumatology departments to register their patients and analyse this information, creating the first descriptive analysis of the autoinflammatory diseases in the Portuguese population. This will encourage the creation of a robust and clinically meaningful analysis of phenotype/genotype correlations and response to treatment, as well as the comparison of different cases of rare monogenic diseases and undefined autoinflammatory diseases.

3. Objectives

Primary goal

- Characterization of patients with the diagnosis of autoinflammatory syndromes registered in Reuma.pt/Autoinflammatory Syndromes protocol.

Secondary goal

- Analysis of each subgroup of autoinflammatory syndromes to evaluate clinical manifestations, laboratory and registered genetic mutations relevant for the diagnosis.

4. Methods

Cross-sectional analysis of the data collected up to the last visit of each patient registered in Reuma.pt/Autoinflammatory Syndromes protocol.

Study Population

We will analyse all patients registered in Reuma.pt/Autoinflammatory Syndromes protocol up to June 2018. 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; Pyogenic arthritis, pyoderma gangrenosum, acne, and hidradenitis suppurativa (PAPASH); pyoderma

gangrenosum, acne and suppurative hidradenitis (PASH); deficiency of IL-1B receptor antagonist (DIRA); deficiency of IL-36 receptor antagonist (DITRA); NALP12- associated periodic fever; familiar cold autoinflammatory syndrome (FCAS); Muckle–Wells Syndrome (MWS) and chronic infantile neurological cutaneous and articular syndrome (CINCA) and others like adenosine deaminase-2 (ADA2) deficiency; STING-associated vasculopathy and auto-inflammatory PLCG2-associated antibody deficiency and immune dysregulation (APLAID). Periodic fever, aphthous stomatitis, pharyngitis and adenopathy (PFAPA) syndrome; chronic recurrent multifocal osteomyelitis (CRMO); adult-onset Still's Disease and Schnitzler Syndrome 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 will be analysed regarding registered genetic information for diagnostic purposes, epidemiological and clinical features.

The expected size of the cohort based on a preliminary screening of Reuma.pt registry is 130 patients.

Analysis plan

Participating centres will be asked to complete the registered information regarding each patient and include in Reuma.pt\Autoinflammatory Syndromes protocol other cases of patients with Autoinflammatory diseases that might be missing in the register.

The main data categories considered will be:

- Baseline information: diagnosis, age (years), gender, country of birth and residence, ethnicity, age at disease onset and at diagnosis (years), date of first and last visits to the treating centre, education level, relevant family history and history of consanguinity will be recorded.
- Clinical manifestations: any clinical manifestation and organ involvement registered will be analysed.
- Laboratory analysis, imaging and others diagnostic procedures: namely laboratory results, imaging procedures, biopsies and other diagnostic procedures. Genetic tests are not mandatory for inclusion but, if made, information of the extent of analysis, mutations detected relevant for AID diagnosis and laboratory where such analysis was performed will be retrieved.
- Disease assessment: disease activity will be considered based on clinical manifestations, laboratory markers (namely complete blood count, erythrocyte sedimentation rate, c-reactive protein, serum amyloid A), visual analogic scale (from the physician and the

patient point of view) and Auto-Inflammatory Diseases Activity Index (AIDAI) in the four major hereditary recurrent fever syndromes in which it is validated: familial Mediterranean fever (FMF), mevalonate kinase deficiency (MKD), TNF receptor 1-associated periodic syndrome (TRAPS), cryopyrin-associated periodic syndrome (CAPS).[4] Functional evaluation will be assessed by the Child Health Assessment Questionnaire (CHAQ) in children or by Health Assessment Questionnaire (HAQ) score in adult patients.

- Treatment and response to treatment: drugs used (including dose and duration) will be analysed according to the register and its safety will be evaluated through side effects registry and reasons for discontinuation. Response to therapy will be considered based on the physician assessment of the disease regarding spontaneous remission, remission after medical or surgical therapy.

Statistical Analysis

Continuous variates will be expressed in terms of their mean and standard deviation (if normal distributed) or median and interquartile range (if not normal distributed). Categorical variates will be described by frequency distribution. All calculations will be performed using the statistics program SPSS. Data extracted will be analysed and then each subgroup will be considered separately.

5. Expected limitations

Expected limitations are the ones characteristic of retrospective studies, mainly underreporting or missing data and limitations related to the low prevalence of this group of diseases, namely a small number of national cases for most subgroups of Autoinflammatory Diseases.

6. Calendar of tasks

I. Data collection: May 2018 – July 2018.
II. Data analyse: July – November 2018.
III. Results publication starting first semester of 2019.

7. Team

Proponents: Joana da Silva Dinis, João Nascimento, Ana Margarida Garcia, Margarida Guedes, Marta Conde, Raquel Campanilho-Marques, Filipa Oliveira Ramos.

Centers involved: participation is open to all Portuguese centers interested in collaborating in this project. Co-authorship will be granted to a maximum of 2 coauthors per center, actively collaborating in the project. Co-authorship will be dependent on the number of patients enrolled (a minimum of 3 patients per participating center is required) and on the involvement of the authors in the work to collect data and write the manuscripts.

8. Disclosure statement

The authors have declared no conflicts of interest. This project has applied and has been approved to receive a grant from Novartis.

9. References

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