Web resources for rare auto-inflammatory diseases: towards a common patient registry

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Objectives. To review information resources on rare auto-inflammatory disorders (AIDs) for use by health care professionals, focusing particularly on patient registries.

Methods. Using relevant key words, we surveyed the websites of several scientific societies of immunology, paediatrics and rheumatology, as well as PubMed and specialized databases for AIDs.

Results. The Internet provides a wide variety of information related to AIDs. Moreover, several other initiatives have been undertaken to create new resources for professionals. We reviewed six patient registries for rare AIDs, taking a special interest in the submission questionnaire. We revealed a wide overlap between the items used in the questionnaires, whereas the currently available registries appeared inappropriate for AIDs patients with complex or undefined diagnosis.

Conclusions. AIDs share common clinical features, pathophysiological pathways and therapeutic approaches. Although several resources are now available for rare AIDs, a unique and dedicated site gathering all aspects of these diseases as a whole is still lacking, i.e. covering research as well as the needs of AIDs patients and health care professionals. Our study thus advocates a merging of existing patient registries or the creation of a common database.

INTRODUCTION

Hereditary auto-inflammatory diseases (AIDs) are recently recognized conditions caused by mutations in genes involved in the regulation of innate immunity [1]. These genes encode modulators of inflammatory signalling pathways and apoptosis [2]. They are also thought to act as susceptibility factors or modifiers in multifactorial AIDs, such as Behcet’s disease. Several non-inherited conditions [i.e. Behcet’s disease, the periodic fever, adenitis, pharyngitis and aphthosis (PFAPA) syndrome and chronic recurrent multifocal osteomyelitis], which are characterized by low auto-antibody titres and enhanced inflammatory response, which are compatible with the findings in other auto-inflammatory disorders. IL-1, a potent pyrogenic pro-inflammatory cytokine, is a common key factor found to be deregulated in AIDs [3]. Accordingly, fever and several types of clinical inflammation represent the main symptoms of these disorders, sometimes making a differential diagnosis challenging [4].

Soon after the cloning of the gene for the prototype disease FMF [5, 6], professionals interested in AIDs attempted to meet regularly and create web resources to facilitate communication. Since most AIDs are rare diseases, gathering material and patient data are essential in order to collect a sufficient mass of information for research purposes and patient care by rapid dissemination of educative papers. Several international websites mentioning our diseases of interest (Table 1) are available and can be classified into three different groups. The first group comprises generalist websites such as Orphanet [7], Online Mendelian Inheritance in Man (OMIM) [8] and Human Genome Mutation Database of Cardiff (HGMD) [9]. The second group of websites covers the medical specialities involved in AIDs, including European Society for Immunodeficiency (ESID) [10] and Paediatric Rheumatology IInternational Trials Organisation/Paediatric Rheumatology Society (PRINTO/PReS) [11]. The third group of websites encompass those specializing in AIDs, for example MetaFMF (FMF), HIDSnet (Hyper IgD Syndrome), PFAPA.net, International Society for Behcet’s Disease (ISBD), Infévers [12] and International Society for Auto-Inflammatory Diseases (ISSAID). Cumulatively, these websites provide a variety of informative combinations, including descriptions of symptoms and gene mutations, as well as information for patients and health care professionals. However, taken individually, only HIDSnet covers all fields of AIDs.

To assess the relevance of existing initiatives, we reviewed the web and other types of resources currently available for rare AIDs, focusing on patient registries. Indeed, online patient databases represent a valuable tool in the estimation of disease incidence and prevalence, delineation of disease criteria and/or natural history, identification of phenotype-genotype correlations and evaluation of patient outcome. Analysis of their submission questionnaires highlighted a wide range of overlap and missing data. Furthermore, large numbers of patients could either be matched to more than one registry or fitted to none of them.

METHODS

We undertook different steps in this study. We first conducted an Internet-based survey on rare AIDs to review existing websites focusing on patient registries using three complementary approaches: (i) we visited websites of immunology, rheumatology and paediatric societies; (ii) we carried out searches on PubMed and Google using key words corresponding to all hereditary AIDs, i.e. FMF, mevalonate kinase deficiencies (MKDs) consisting of two clinical components: HIDS and mevalonic aciduria (MA), cryopyrin-associated periodic syndrome (CAPS) consisting of three phenotypes: familial cold auto-inflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS) and chronic infantile neurological cutaneous and articular syndrome (CINCA), as well as AIDs with unknown aetiology, PFAPA syndrome and Behcet’s disease; and (iii) we also contacted members of ISSAID by e-mail to enquire whether they were aware of any existing registries for AIDs patients.

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Then, we reviewed the variables incorporated in the registry patient-inclusion forms. The questionnaire items, defined as questions with the same meaning (for example, ‘serositis in the joints’ and ‘arthritides’) were listed for each disease. The cross-overlap between registries was estimated as the number of common items divided by the number of total items of the concerned registries, including epidemiological features.

Finally, we examined the literature content and the patients’ medical charts recorded by the French Reference Centre for Auto-Inflammatory Diseases to identify patients eligible for more than one registry.

**Results**

Several initiatives have been undertaken over the last decade to create patient registries focused on specific AIDs or their subtypes. Our survey retrieved six disease-specific registries eligible for the purpose of our study, the earliest and most complete being the Hyper-IgD and periodic fever syndrome registry, HIDSnet, co-ordinated by Dr. A. Simon at http://www.hids.net/. This website contains everything about this rare disease with pages designed for physicians and scientists, as well as for patients, their families and others who may be interested. The professional page includes a definition of the disease, information on clinical, biochemical and genetic diagnosis, forms for inclusion of HIDS patients in the Nijmegen patient registry and links to research meetings and literature. The FMF registry created by the International Study Group for Phenotype-Genotype correlation in FMF (MetaFMF [13]) at http://fmf.igh.cnrs.fr/metaFMF/index.html and the PFAPA registry created by Dr. M. Hofer at http://www.pfapa.net/ also developed an online patient registry including a subgroup for AIDs patients, but their questionnaire only contains common items for immunodeficient patients, namely a core data set (epidemiological data), general diagnosis and quality of life items, medication, laboratory values and family history. As no AIDs-specific clinical form created by ESID existed at this time, we could not compare this registry to the others.

Since AIDs share many clinical and biological features, we analysed in detail all questions present in the submission questionnaires of these six registries in order to discriminate between those that were specific and common. We listed 130 items divisible into demographic, clinical and paraclinical categories. Five of the eight demographic items were common to all six questionnaires (Fig. 1). Among the 130 recorded, the number of items per disease ranged from 32 (25%, Blau syndrome) to 69 (53%, PFAPA syndrome) (Fig. 2). Surprisingly, the ‘mevalonate aciduria’ and ‘CARD15 mutation’ variables specific to the HIDS and Blau syndromes, respectively were lacking in their corresponding registries, while the PFAPA registry contained both items. Cross-examination revealed that the PFAPA and TRAPS registry disclosed 44% of the items in common (Table 3). The TRAPS and Blau syndrome registries showed the least congruence.

In order to evaluate the number of patients potentially matching more than one registry, we reviewed the literature and clinical charts from our reference centre for complex cases. We identified 39 patients [14–31] with two mutated genes or fulfilling criteria for at least two diseases (Table 3). These cases could be included into more than one of the six registries described above.

**Discussion**

This study revealed the availability of an increasing amount of information from various sources focused upon or supplying information on AIDs, in order to help clinicians, patients and health care individuals obtain the information, tools and support required to facilitate the effective management of these diseases. The resources analysed in this study demonstrated that each provided complementary information, but none centralized the entire specific details about rare AIDs to one single place. Most rare diseases are life-threatening and chronically debilitating, with the vast majority being genetically determined. Individually, their prevalences are low and so require specially combined efforts to allow disease analysis so as to improve diagnosis, care and prevention. Research in the field of rare AIDs would be significantly improved if a sufficient number of patients were accessible. Electronic patient registries can help provide the basis for this by collecting both retrospective and prospective data over a long period of time and integrating centres on a national or even international scale. We found six individual initiatives for patient registries entirely devoted to one AID, with three of them already available online. A thorough examination of their content demonstrated a particularly high rate of item overlap ranging from 18 to 44%, easily explained by the fact that AIDs belong to the same physiopathological group of diseases by definition. These databases proved very useful for preliminary studies on the clinical presentation of the patients [32], diagnostic value [21] and on risk factors for complications [33]. However, registries for several AIDs (e.g. CAPS) are still lacking, and patients with an undetermined phenotype or with multiple gene mutations would scarcely benefit from existing registries.

The very high overlap between the six registries analysed herein and the increasing number of unclassified patients advocates the
creation of a central database for all rare AIDs, especially those
with a paediatric onset. We feel that it is possible to have a
global rather than a piecemeal approach to the registration of
AIDs patients. Although incorporation of 130 variables is tech-
nically feasible, one may question the relevance of accumulat-
ing so many pieces of information for each disease. To circumvent this,
TABLE 3. Cases eligible for more than one AIDs patient registry

<table>
<thead>
<tr>
<th>Reference</th>
<th>Phenotype</th>
<th>Genotypea</th>
<th>Possible registries</th>
<th>Patient’s origin and clinical information</th>
</tr>
</thead>
<tbody>
<tr>
<td>[25]</td>
<td>Behçet’s</td>
<td>E148Q/M694V</td>
<td>Behçet’s or FMF</td>
<td>Non-Ashkenazi Jew, oral aphthosis, erythema nodosum, non-febrile arthralgia</td>
</tr>
<tr>
<td>[25]</td>
<td>Behçet’s</td>
<td>E148Q/M694V</td>
<td>Behçet’s or FMF</td>
<td>Non-Ashkenazi Jew, oral aphthosis, erythema nodosum, non-febrile arthralgia</td>
</tr>
<tr>
<td>[25]</td>
<td>Behçet’s</td>
<td>E148Q/M694V</td>
<td>Behçet’s or FMF</td>
<td>Non-Ashkenazi Jew, oral aphthosis, folliculitis, non-febrile arthralgia</td>
</tr>
<tr>
<td>[29]</td>
<td>Behçet’s</td>
<td>V377I/S135L</td>
<td>Behçet’s or HIDS</td>
<td>French, fever, 40°C, chills/monthly, headaches, bilateral aphthosis, erythema nodosum, severe acne, conjunctivitis, abdominal pain, diarrrhoea, transient arthralgia, arthritis, febrile and skin reaction after immunizations</td>
</tr>
<tr>
<td>[29]</td>
<td>Behçet’s</td>
<td>V377I/V377I</td>
<td>Behçet’s or HIDS</td>
<td>French, fever, bilateral aphthosis, macular rash, skin hypersensitivity, erythema nodosum, keratitis, transient arthralgia</td>
</tr>
<tr>
<td>[31]</td>
<td>Behçet’s</td>
<td>R92Q</td>
<td>Behçet’s or TRAPS</td>
<td>In a series of 74 unrelated European patients with Behçet’s disease, 5 (6.8%) carried R92Q</td>
</tr>
<tr>
<td>[29]</td>
<td>Behçet’s</td>
<td>V918M</td>
<td>Behçet’s or CAPS</td>
<td>French, buccal aphthosis, skin aphthosis, erythema nodosum, urtica, venous thrombosis, ulcerative colitis, transient arthralgia</td>
</tr>
<tr>
<td>[17]</td>
<td>CAPS</td>
<td>E148Q</td>
<td>R92Q, A439V</td>
<td>Caps or TRAPS</td>
</tr>
<tr>
<td>[15]</td>
<td>FMF</td>
<td>M694V/M680I</td>
<td>R92Q</td>
<td>FMF or TRAPS</td>
</tr>
<tr>
<td>[15]</td>
<td>PC</td>
<td>V726A</td>
<td>R92Q</td>
<td>FMF or TRAPS</td>
</tr>
<tr>
<td>[18]</td>
<td>FMF</td>
<td>M694V/M694V</td>
<td>V198M</td>
<td>FMF or CAPS</td>
</tr>
<tr>
<td>[23]</td>
<td>FMF/FMFF</td>
<td>E148Q/E148Q</td>
<td>V918M</td>
<td>FMF or HIDS</td>
</tr>
<tr>
<td>[23]</td>
<td>FMF/FMFF</td>
<td>E148Q/M694I</td>
<td>Behçet’s or FMF</td>
<td>Behçet’s criteria, episodic peritonitis with fever and arthritis</td>
</tr>
<tr>
<td>[24]</td>
<td>FMF/FMFF</td>
<td>E148Q/M694I</td>
<td>Behçet’s or FMF</td>
<td>Japanese, multiple buccal aphthoses, genital ulcers and iridovetits, attacks of fever and thoracoabdominal pain, lasting for 1–2 weeks, good response to colchicine</td>
</tr>
<tr>
<td>[30]</td>
<td>FMF/CAPS</td>
<td>E148Q; I692del/V726A</td>
<td>V918M</td>
<td>FMF or CAPS</td>
</tr>
<tr>
<td>[28]</td>
<td>FMF/TRAPS</td>
<td>M694V/M694V</td>
<td>R92Q</td>
<td>FMF or TRAPS</td>
</tr>
<tr>
<td>[21]</td>
<td>HIDS</td>
<td>E148Q</td>
<td>P167L/I268T</td>
<td>FMF or HIDS</td>
</tr>
<tr>
<td>[21]</td>
<td>HIDS</td>
<td>V726A</td>
<td>V377I/V377I</td>
<td>FMF or HIDS</td>
</tr>
<tr>
<td>[19]</td>
<td>HIDS</td>
<td>V377I/S378P</td>
<td>R92Q</td>
<td>HIDS or TRAPS</td>
</tr>
<tr>
<td>[20]</td>
<td>PFAPA</td>
<td>R92Q</td>
<td>PFAPA or TRAPS</td>
<td>German, chills, vomiting, arthralgia, cervical and inguinal adenopathy, fever, mild elevation of IgD</td>
</tr>
<tr>
<td>[20]</td>
<td>PC</td>
<td>R92Q</td>
<td>PFAPA or TRAPS</td>
<td>Periodic fever, recurrent pharyngitis, cervical adenopathy, apthous ulcers, severe flank pain, myalgia, conjunctivitis, abdominal pain and vomiting, prednisone effective</td>
</tr>
<tr>
<td>[21]</td>
<td>TRAPS</td>
<td>E148Q</td>
<td>D93E</td>
<td>TRAPS or FMF</td>
</tr>
<tr>
<td>[14]</td>
<td>Unclassified</td>
<td>E148Q</td>
<td>V918M</td>
<td>CAPS or FMF</td>
</tr>
</tbody>
</table>

PC: personal communications from R. Manna, V. Hentgen, I. Touitou, L. Federicci. aUsual names were used (as recorded in Infevers http://fmf.igh.cnrs.fr/ISSAID/infevers/; [12]).
Rheumatology key messages

- Valuable sources of information for rare AiDs were identified (websites, scientific societies).
- Efforts are still needed to optimize these new resources, e.g. a common patient registry.

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