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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.

Key words: Auto-inflammatory diseases, Web resources, Patient registry.

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 Behçet's disease. Several non-inherited conditions [i.e. Behçet's disease, the periodic fever, adenitis, pharyngitis and aphthosis (PFAPA) syndrome and chronic recurrent multifocal osteomyelitis], which are characterized by low autoantibody 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 improve 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 INternational 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 Behçet's Disease (ISBD), Infevers [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 Behçet'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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TABLE 1. Currently available international web resources treating AIDs and their information content

	Website	URL address	Description of mutations	Description of symptoms	Information for patients	Information for health professionals
Generalists	Orphanet	http://www.orpha.net/	No	All diseases	All diseases	All diseases
	OMIM	http://www.ncbi.nlm.nih.gov/sites/entrez?db=omim	All diseases	All diseases	No	No
	HGMD	http://www.hgmd.cf.ac.uk/	All diseases	No	No	No
Immunodeficiency (ID) and paediatric rheumatology (PR) specialties	ESID	http://www.esid.org/	ID diseases	ID diseases	No	ID diseases
	PReS	http://www.pres.org.uk/	No	No	No	PR diseases
	PRINTO	http://www.printo.it/	No	PR diseases	PR diseases	PR diseases
AIDs specialized	MetaFMF	http://fmf.igh.cnrs.fr/metaFMF/	FMF	FMF	No	No
	HIDSnet	http://www.hids.net/	HIDS	HIDS	HIDS	HIDS
	PFAPAnet	http://www.pfapa.net/	PFAPA	PFAPA	No	No
	ISBD	http://www.behcet.ws/	Not applicable	Behçet's disease	No	Behçet's disease
	Infevers	http://fmf.igh.cnrs.fr/ISSAID/infevers/	All hereditary AIDs	No	No	No
	ISSAID	http://fmf.igh.cnrs.fr/ISSAID/	No	No	No	All AIDs

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 'arthritis') 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, coordinated 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/ only contains clinical and biological data about patients. The Behçet's disease registry by Prof I. Koné-Paut, the TRAPS registry (EuroTRAPS) by Dr M. Gattorno and Dr H. Lachmann, and the Blau syndrome registry by Prof. C. Rose and Prof. C. Wouters are each to be posted on the Internet shortly. The ESID at http://www.esid.org/ 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 'mevalonic 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 2). 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

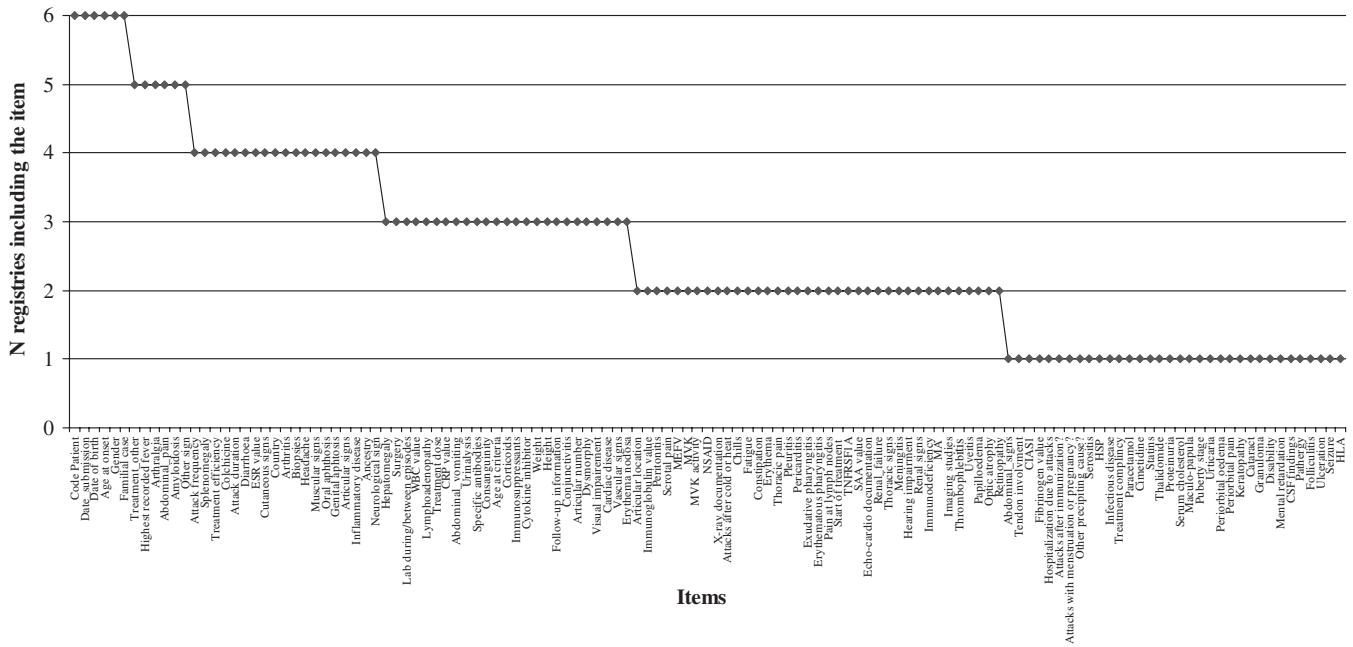

FIG. 1. Item frequency in six auto-inflammatory patient registries. The presence of each of the questionnaire items was searched for in each of the six registries evaluated in this study. Six of these items, such as patient date of birth, were found in all six questionnaires, while only 33 were found in a single registry.

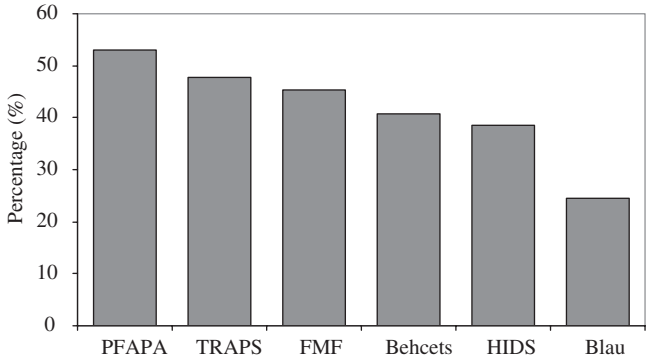

FIG. 2. Percentage of items present in each registry among the 130 recorded. The presence of each of the questionnaire items was searched for in each of the six registries evaluated in this study. The PFAPA registry included 53% ($n = 69$) of the 130 items, while the Blau registry included 25% ($n = 33$).

TABLE 2. Cross-overlap among the six registries

	PFAPA (%)	FMF (%)	TRAPS (%)	HIDS (%)	Behçet's disease (%)	Blau syndrome (%)
PFAPA	100					
FMF	35	100				
TRAPS	**44**	38	100			
HIDS	43	36	32	100		
Behçet's disease	34	26	26	21	100	
Blau syndrome	22	21	**18**	21	31	100

Values in bold indicate diseases with the two extreme percentages of overlap.

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 technically feasible, one may question the relevance of accumulating so many pieces of information for each disease. To circumvent this, we propose that this common patient registry would consist of a core data set including stable lifelong data, i.e. epidemiological and genetic data. This module would be connected to various specific disease forms according to the initial diagnosis. Several items in each form would be common to more than one disease. The editor of the disease initially diagnosed, e.g. the registry creators aforementioned, would validate each patient's data. Each physician would have secured access to the data she/he contributed.

One of the major problems related to a unique registry is the extremely wide spectrum of the clinical manifestations associated with the different AIDs. Is it therefore possible that the number of non-overlapping items significantly increases when other AIDs (*NLRP3*- and *NALRP12*-related conditions, PAPA syndrome, Majeed's syndrome and chronic recurrent multifocal osteomyelitis) are considered? Moreover, some of these conditions display a prevalent chronic course, whereas others have a recurrent or periodic behaviour. These issues may raise possible practical and technical implications; however, we believe that follow-up and specific projects could be integrated over time.

The advantages of a centralized database are substantial. Heavily solicited clinicians could be kept motivated with a single URL, a single questionnaire or a single submission, even if the diagnosis of the patient was to be later refined. A unique registry would not completely solve the problem of the correct classification of patients with multiple possible diagnoses, but we believe that it would help delineate phenotype–genotype correlations, identify oligogenic transmission and possibly provide better targeted therapeutics to patients. In order to obtain reliable statistics, homogeneous data must be longitudinaly (many items in a single disease) or transversely (a single item across different diseases) correlated. The prevalence of each disease among the AIDs group could then be compared accurately. Time and money could be saved. Such a project is under consideration by members of the ISSAID society. The PReS network and the reference centres for AIDs are a potential source of data for epidemiological and clinical research, and the PRINTO group has the facilities to collect data from established registries across countries with minimal additional infrastructure, using a web-based system.

TABLE 3. Cases eligible for more than one AIDs patient registry

Reference	Phenotype	Genotype[a]				Possible registries	Patient's origin and clinical information
		MEFV	*MVK*	*TNFRSF1A*	*NLRP3*		
[25]	Behçet's	E148Q/M694V				Behçet's or FMF	Non-Ashkenazi Jew, oral aphthosis, erythema nodosum, non-febrile arthralgia
[25]	Behçet's	E148Q/M694V				Behçet's or FMF	Non-Ashkenazi Jew, oral aphthosis, erythema nodosum, non-febrile arthralgia
[25]	Behçet's	E148Q/M694V				Behçet's or FMF	Non-Ashkenazi Jew, oral aphthosis, folliculitis, non-febrile arthralgia
[29]	Behçet's		V377I/S135L			Behçet's or HIDS	French, fever: 40°C, chills/monthly, headaches, bipolar aphthosis, erythema nodosum, severe acne, conjunctivitis, abdominal pain, diarrhoea, transient arthralgia, arthritis, febrile and skin reaction after immunizations
[29]	Behçet's		V377I/V377I			Behçet's or HIDS	French, fever, bipolar aphthosis, macular rash, skin hypersensitivity, erythema nodosum, keratitis, transient arthralgia
[31]	Behçet's			R92Q		Behçet's or TRAPS	In a series of 74 unrelated European patients with Behçet's disease, 5 (6.8%) carried R92Q
[29]	Behçet's				V198M	Behçet's or CAPS	French, buccal aphthosis, skin aphthosis, erythema nodosum, uveitis, venous thrombosis, ulcerative colitis, transient arthralgia
[17]	CAPS			R92Q	A439V	CAPS or TRAPS	French, recurrent fever, urticaria
[15]	FMF	E148Q		R92Q		FMF or TRAPS	Italian, recurrent fever, abdominal attacks lasting 2–3 days, poor response to colchicine, attacks controlled by steroids
PC	FMF	M694V/M680I		R92Q		FMF or TRAPS	Non-Ashkenazi Jewish. Fever, good response to colchicine
[15]	FMF	V726A		R92Q		FMF or TRAPS	Italian, atypical FMF but good response to colchicine
PC	FMF	M680I		R92Q		FMF or TRAPS	Italian, recurent fever, abdominal pain, erysipelas, since the age of 5 years
[18]	FMF	M694V/M694V			V198M	FMF or CAPS	Turkish, FMF patient with amyloidosis
PC	FMF	P283L	V377I			FMF or HIDS	Magrebhian, recurrent fever, abdominal pain
[23]	FMF/Behçet's	V726A/V726A				Behçet's or FMF	Arab, Behçet's criteria, episodic peritonitis with fever and arthritis
[23]	FMF/Behçet's	E148Q/E148Q				Behçet's or FMF	Arab, Behçet's criteria, episodic peritonitis with fever and arthritis
[24]	FMF/Behçet's	E148Q/M694I				Behçet's or FMF	Japanese, multiple buccal aphthoses, genital ulcers and iridouveitis, attacks of fever and thoracoabdominal pain, lasting for 1–2 weeks, good response to colchicine
[30]	FMF/CAPS	E148Q; I692del/V726A			V198M	FMF or CAPS	Anaemia, splenomegaly, bilateral sensorineural deafness, recurrent abdominal pain and fever, arthritis, renal amyloidosis
[28]	FMF/TRAPS	M694V/M694V		R92Q		FMF or TRAPS	Armenian/Italian, fever, arthritis, erysipela-like rash, conjunctivitis, peri-orbital oedema, flare duration 4–12 days, poor response to colchicine, good response to steroids
[21]	HIDS	E148Q	P167L/I268T			FMF or HIDS	Dutch, classical HIDS
[21]	HIDS	V726A	V377I/V377I			FMF or HIDS	Armenian, monthly attacks of fever, arthralgia, abdominal pain, oral ulcers, erythema rash which lasts for 4–6 days. No response to colchicine
[21]	HIDS		V377I/I268T	R92Q		HIDS or TRAPS	Dutch, classical HIDS
[19]	HIDS		V377I/S378P	R92Q		HIDS or TRAPS	Gerrman, chills, vomiting, arthralgia, cervical and inguinal adenopathy, fever, mild elevation of IgD
[20]	PFAPA			R92Q		PFAPA or TRAPS	Periodic fever, recurrent pharyngitis, cervical adenopathy, aphthous ulcers, severe flank pain, myalgia, conjunctivitis, abdominal pain and vomiting, prednisone effective
PC	PFAPA			R92Q		PFAPA or TRAPS	Magrebhian, recurrent fever, oral aphthosis, pharyngitis, cervical adenopathy, lasting 5–6 days, abdominal pain, cortisone responsive
[21]	TRAPS	E148Q		D93E		TRAPS or FMF	Dutch, clinical TRAPS
PC	Unclassified	E148Q	V377I			FMF or HIDS	Magrebhian/French, recurrent fever lasting 7 days, arthralgia, myalgia, aphthosis, oedema, urticaria, good response to cortisone
PC	Unclassified	K695R	V377I/V377I			FMF or HIDS	French, recurent fever, urticaria, abdominal pain, arthralgia, conjunctivitis, lasting 3 days
[27]	Unclassified	E148Q		R92Q		TRAPS or FMF	Asymptomatic apart from AA renal amyloidosis
PC	Unclassified	M694V		R92Q		TRAPS or FMF	Non-Ashkenazi Jewish. Fever, articular, thoracic and abdominal pain before the age of 10 years
PC	Unclassified	E148Q		R92Q		TRAPS or FMF	Magrebhian, fever with aphthosis, lasting 5 days, response to cortisone
[16]	Unclassified		V377I/G211A	P46L		HIDS or TRAPS	Caucasian, Afro-Caribbean, clinical signs of HIDS, severe abdominal pain, altered shedding of the TNFR, response to etanercept
[22]	Unclassified		V377I	R92Q		HIDS or TRAPS	English/German, mild symptoms of HIDS and good response to steroids
[26]	Unclassified			R92Q	V198M	CAPS or TRAPS	French, urticaria and oedema precipitated by heat and water, lasting a few hours, moderate fever, symmetric arthralgia, bipolar aphthosis, intense fatigue and conjunctivitis
[14]	Unclassified	E148Q			V198M	CAPS or FMF	British, unclassified systemic inflammatory disease

PC: personal communications from R. Manna, V. Hentgen, I. Touitou, L. Federicci. [a]Usual 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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