Editorial

Taxonomy of auto-inflammatory diseases: time to consider changing some names

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Taxonomy is the science of naming. It is as old as the language skills of mankind. It is relevant to all fields of biology in which we name plants and animals. In Medicine, the naming of diseases or clinical methods and procedures has a special significance. That is because naming can give some clues about the disease, its clinical features, etiology and sometimes even the approach to treatment. Furthermore, it can serve as a basic means of communication between the different groups of the health care community.

Taxonomy of diseases (technically called *nosology*) has been an important issue for a long time. In ancient Greece, Galen and other physicians had their own version (1). In the 17th century it was a "hot" topic as well. However, in the 18th century, Carolus Linnaeus was the first to develop a taxonomic system to classify diseases (*Genera Morborum*, 1763*)* (2). He divided diseases into three categories:

a. Exanthematic (feverish with skin eruptions);
b. Phlogistic (feverish with heavy pulse and topical pain);
c. Dolorous (painful).

In the 20th century, the International Classification of Diseases (ICD) became the most commonly used categorisation of diseases. It is used for statistical analyses and decision support, making it an integral part of health-care systems throughout the world. It is updated every 3 years and revised every 10 years.

How do we name objects, syndromes or diseases?

A simple approach to classification is using the name of the person who first developed the procedure or method or described the disease. Examples are Kocher's forceps, Gruntzig balloon, or Takayasu disease and Behçet's syndrome. Another way is to use a name which reflects the geographic spread of the disease such as West Nile fever, Japanese encephalitis or Familial Mediterranean fever (FMF). Some names present typical clinical features of the disease, *e.g.* systemic lupus erythematosus (SLE), cystic fibrosis or ulcerative colitis. The problems arising from these taxonomic methods are numerous. When a disease is named after the person who first described it, one should remember the exact association between this name and the clinical manifestations since there is no clue what the pathophysiology might be. When the name is related to the region of its spread it may be misleading. Physicians might not consider these possible diagnoses in regions which are not endemic for the disease. Using symptoms and signs for naming is problematic since they are often non-specific and rarely identify a disease unambiguously.

Furthermore, numerous diseases – including some of the most common ones such as cancer, cardiovascular disease, and chronic infection – are asymptomatic in the early stages. In addition, the lack of an adequate understanding of the biological background of a disease may lead to wrong concepts. For example, without a germ theory of disease, rabies was characterised as a psychiatric disorder because of the brain dysfunction that occurs in advanced cases.

To overcome the above-mentioned drawbacks, the President's Council on Advisors on Science and Technology (PCAST) of the NIH aims to promote "Precision Medicine" by "New Taxonomy for diseases and Personalized Medicine (tailoring treatment)" (3). One of the questions which may be raised is why we need to do it now. The reason is our new capability to compile molecu-

lar data on patients on a scale that was unimaginable 20 years ago. Moreover, advances in information technology, such as the advent of electronic health records, make it possible to acquire detailed clinical information about large numbers of patients and to search for unexpected correlations within huge data sets. Thus, the goal of the new taxonomy is to create a consistent terminology to permit clear communication about diseases. It should also ensure that the classification system properly reflects advances in our understanding of molecular pathways and environmental factors that contributes to the pathophysiology of diseases. Taxonomy should be dynamic, continuously evolving, integrative, and flexible. An ideal taxonomy should describe and define diseases based on their intrinsic biological mechanisms in addition to the traditional "signs and symptoms".

What is the current situation in naming the autoinflammatory syndromes?

Some syndromes are named for the underlying genetic pathophysiology. Examples are TRAPS: TNF-Receptor Associated Periodic Syndrome; DIRA: Deficiency of Interleukin-1 Receptor Antagonist. Some names describe the clinical features of the disease (phenotype) as in PFAPA: Periodic Fever, Aphthous stomatitis, Pharyngitis, Adenitis, or PAPA: Pyogenic Arthritis, Pyoderma gangrenosum and Acne. Some are named for the physicians who first described them. Examples are Muckle-Wells syndrome (MWS), Schnitzler's syndrome and Majeed's syndrome. Some are named for the geographic area of the disease's spread as in Familial Mediterranean Fever (FMF), Guadeloupean fever (NALP 12 associated disease), and Familial Hibernian fever (TRAPS). As mentioned above, the problems are that the name does not say anything about the disease (*e.g.* MWS), that the name is not accurate (*e.g.* Hyper IgD) or may be misleading (*e.g.* FMF). Furthermore, some diseases carry several names. For example, Chronic Atypical Neutrophilic Dermatosis with Lipodystrophy and Elevated Temperature Syndrome (CANDLE) is also called Nakajo - Nishimura syndrome and Joint arthritis, muscle atrophy, macrocytic anaemia and panniculitis (JMP). CAPS (cold association periodic fever syndrome) also has several names: MWS, Familial cold urticarial syndrome (FACS), neonatal onset multisystem inflammatory disease (NOMID), and chronic infantile neurological, cutaneous and articular syndrome (CINCA).

So what should we do?

There are several ways to cope with the problems associated with the current taxonomy of the autoinflammatory diseases. We could use names which provide some details or clues about their main clinical manifestations (phenotypes). Alternatively, we could use names describing the genetic mutation causing the disease (pathophysiology). Moreover, we can use them both in different clinical settings.

Our suggestions are as follows. As a rule of thumb, we should prefer names with clinical or pathogenic meanings and abolish names derived from the first reporter of the disease or related to its geographic spread, etc. Moreover, we should use a different approach in cases of monogenic diseases and polygenic autoinflammatory syndromes. In the former, the name should be based on the disease associated gene or protein (pathophysiology). When the gene or protein is not known or its name is too complicated we should prefer short phenotype descriptions. When a disease has two names, one of which is based on clinical features while the other on etiology and genetics, we should prefer the one which is simpler to remember yet still has clinical meaning as in the case of pyogenic arthritis, pyoderma gangrenosum and acne (PAPA) *vs*. Proline/Serine/Threonine Phosphatase-Interacting Protein 1(PSTPIP 1) associated disease.

What about the name FMF which may be found in sporadic cases in patients living in Armenia? In this case the disease is not *familial*, and not *Mediterranean*. In some rare cases the disease may also present without *fever*. When the disease was first described (1954) several names were suggested, such as Periodic fever, Maladie periodique, Recurrent polyserositis, Benign recurrent peritonitis and Familial recurrent polyserositis (4). The main drawback of these names is that they describe clinical features which may meet the criteria of almost all the classical periodic fever syndromes: MWS, TRAPS, Hyper IgD, etc. All of them are familial, may affect the joints and abdomen and present with periodic fever. Therefore, our suggestion for a new name for FMF is derived from its genetic etiology: *Pyrin-associated periodic fever syndrome* - PAPS. The main advantage of this name is that it can also include cases with atypical manifestations (different from FMF) and yet possess the *MEFV* mutations. This way of naming may also justify colchicine therapeutic trial in these situations. Several questions might be raised if we use PAPS instead of FMF. A first possible problem is that the diagnosis can be made only by genetic testing. The solution for this problem is that one should not mix nomenclature and diagnostic criteria. A diagnosis may still be made on clinical grounds. Genetic testing may provide additional support. A second question is how should we name the cases without *MEFV* mutations but with the typical clinical features? In such cases we should first try to exclude other diseases, and only then add "mutation negative" (since we never test for all the possible mutations). What about asymptomatic individuals carrying *MEFV* mutations found incidentally? We think that they should not be diagnosed as PAPS unless they become symptomatic. It is very rare to find an individual carrying two mutations without having either clinical symptoms or elevated inflammatory biomarkers. In such cases it seems that the risk of not diagnosing them or treating them is negligible. Finally, one should remember that Familial Hibernian (Ireland) Fever had a similar history of naming which became TNF-Receptor associated periodic syndrome – TRAPS, following the identification of the gene associated with the disease.

What about the name Schnitzler's syndrome? Since the disease contains a gammopathy, a question is raised

whether it should remain among the autoinflammatory diseases or join the family of plasma cell dyscrasias. If it remains among the autoinflammatory syndromes, the name FUPAP should be considered since its major manifestations are: *F*ever, *U*rticaria and *PAr*aprotein.

What about the polygenic autoinflammatory syndromes?

The current naming of the polygenic diseases was largely based on phenomenology or on their first reporters, such as Behçet's syndrome, Crohn's disease or Still's disease. Oligogenic disorders, in which just a few genes impact on the disease, are more likely to be classifiable by genetic polymorphism. True polygenic disorders, in which a multiplicity of small effects determines the risk of developing the disease, are not likely to be named after their genetic profile. Furthermore, it may well be that following such discoveries we will reale that what we considered to be a single disease is actually several different diseases. The case of diabetes mellitus may serve as an example. Less than 100 years ago, diabetes was considered to be a single disease with an excess of sugar in the urine (5). Later, it was recognised that diabetes was sometimes associated with an excess rather than a lack of insulin. Insulin excess was typically seen in adult-onset disease or non-insulin dependent diabetes (NIDDM) which is also known as type II diabetes. Juvenile onset disease was characterised by a lack of insulin (IDDM) and is known as type I diabetes. An additional rare variant of type II diabetes is maturity onset disease of the young (MODY), which appears in early middle age, tends not to present with ketoacidosis and segregates as an autosomal dominant disorder. MODY2 was linked to chromosome 7 (mutations in the glucokinase gene), MODY1 to chromosome 20, MODY3 to chromosome 12q. The latter two mutations involve transcription factors regulating the hepatic nuclear family of genes (HNF-1 for MODY3 and HNF-4 for MODY1) (6). While recent breakthroughs have focused on genomics as a consequence of the rapid development of technology in that area, the future may see comparable advances in our ability to understand epigenetic, environmental, microbial, and social contributions to the onset and course of the disease.

Thus, in polygenic diseases we have to expect dynamic changes in names and classifications. As more and more details will be discovered over time, our understanding of the pathophysiology of these diseases will improve and the name will be subject to modifications or changes.

What about naming diseases in paediatric patients?

Should we just call them (for example in BD) *Early-onset* Behçet's disease, *Paediatric* BD, or *Juvenile* BD? At first glance all the names look alike. Based upon a recent paper naming SLE in paediatric patients (7), our suggestion is as follows: If the disease in childhood is clinically identical to that in adults, we should use the term *Paediatric* or *early-onset* BD. If the disease is different clinically or by its pathophysiology from the variant in adults, we should use the term *Juvenile-onset* disease.

To further discuss these suggestions and problems of the current taxonomy of autoinflammatory conditions we suggest establishing an International Consensus Conference Nomenclature of Autoinflammatory Diseases (ICCNAD). We need to elect recognised experts in autoinflammatory diseases from different countries and different medical specialties – Rheumatologists, Geneticists, Paediatricians, Dermatologists, Nephrologists and Pathologists. Suggestions should then be submitted by e-mail among the members of the committee. Subsequently, a consensus conference should be organised to discuss these suggestions and decide on the new taxonomy.

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