New criteria and new methodological tools for devising criteria sets of inflammatory rheumatic diseases

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ABSTRACT

Rheumatologists use classification criteria to separate patients with inflammatory rheumatic diseases (IRD). They change over time, and the concepts of the diseases also change. The paradigm is currently moving as the goal of classification in the future will be more to select which patients may be relevant for a specific treatment rather than to describe their characteristics. Therefore, the challenge will be to reclassify multifactorial diseases on the basis of their biological mechanisms rather than their clinical phenotype. Currently, various projects are trying to reclassify diseases using bioinformatics approaches and in the near future the use of advanced machine learning algorithms with large omics datasets could lead to new classification models not only based on a clinical phenotype but also on complex biological profile and common sensitivity to targeted treatment. These models would highlight common biological pathways between patients classified in the same cluster and provide a deep understanding of the mechanisms involved in the patient's clinical phenotype. Such approaches would ultimately lead to classification models that rely more on biological causes than on symptoms. This overview on current classification of subgroups of IRD summarises the classification criteria that we use routinely, and how we will classify IRD in the future using bioinformatics and artificial intelligence techniques.

Introduction

The landscape of rheumatology is not only vast and varied, but also changing. Rheumatology manuals published in the early 20th century distinguished three categories of joint disease: acute rheumatism, chronic rheumatism, and gout (1). In 1942, Stone stated that inflammatory arthritis could be classified as pyogenic, tuberculous, rheumatoid, chronic traumatic, allergic, and of unknown mechanism (2). Current concepts of inflammatory rheumatic diseases (IRDs), whose emergence is largely ascribable to the identification of specific disease markers, seem to bear little relation to these early classifications. The pathogenesis of IRDs, however, remains a predominantly grey area, and concepts about IRDs change at a fast pace, in lockstep with the brisk tempo of rheumatology and immunology research. As a result, even for the same IRD, several classification systems are often available, with differences in the types of items used, such as clinical findings, genetic background, and aetiological factors. None of these systems is perfect. Continuous efforts are therefore made by the rheumatology community to improve them.

Each IRD has widely varying presentations, and most IRDs have no feature that could serve as a reference standard for the diagnosis. Consequently, although criteria sets are intended for classification, they are widely used as diagnostic aids. However, due to the persisting major disagreements regarding the concepts relevant to IRDs, the application of classification criteria to determine the distribution of diagnoses within patient cohorts can produce variable results, even when performed by highly experienced international experts (3). Some experts consider criteria cumulatively and others simultaneously (4). Furthermore, exclusion criteria may or may not be applied (5).

The performance of a classification system can be improved via two main types of advances. One is the discovery, testing, and inclusion of new criteria. The other is the introduction of new

methodological tools for devising criteria sets, such as bioinformatics and artificial intelligence. Active research is currently ongoing in both areas and can be expected to produce improved classification systems in the near future. An overview of the current state of IRD classification and discussion of probable future developments therefore seems timely.

Aetiology and pathogenesis

Aetiology and pathogenesis are major considerations when seeking to constitute clinically relevant groups, as they largely govern the therapeutic strategy. Two types of arthritis are due to clearly identifiable causes: septic arthritis and crystal deposition disease. Arthritis without infection or crystal deposition defines multifactorial IRD, whose aetiology is unclear but involves a combination of genetic and environmental factors. IRDs may be axial or peripheral; involve one, a few, or many joints; and/or produce systemic manifestations. In addition, IRDs can be classified according to their pathogenic mechanism (Fig. 1a).

In addition to autoimmunity, autoinflammation can cause arthritis. The concept of autoinflammation was introduced in 1999 to distinguish two monogenic hereditary periodic fever syndromes, familial Mediterranean fever (FMF) and TNF receptor-associated periodic syndrome (TRAPS), from classical autoimmune diseases (6). In contrast to autoimmune diseases, which are attributed to dysregulation of the adaptive immune responses, autoinflammatory diseases are not associated with pathogenic autoantibodies or autoreactive T cells and are thought to involve defects in innate immunity proteins (7). Research has established that interleukin (IL)-1 secretion in response to Toll-like receptor stimulation is mediated through co-operation with the nucleotide-binding domain and leucine-rich repeat-containing family, pyrin domain-containing 3 (NLRP3) inflammasome (8). Another recent finding is that the NLRP3/cold-induced autoinflammatory syndrome 1 (CIAS1)-containing NLRP3 inflammasome is an intracellular receptor that is triggered not only by exogenous microbial molecules, but also by endogenous stress molecules (9), and co-ordinates IL-1 processing and release via caspase-1 activation (10). These studies have provided insight into the molecular mechanism of IL-1-mediated inflammation and the episodic nature of the inflammatory response. The distinction between autoinflammatory and autoimmune diseases is not clear-cut. Some monogenic autoinflammatory conditions are characterised by complex phenotypes combining autoinflammation with defects in the adaptive and/or innate immune system that are responsible for infections, autoimmunity, and/or uncontrolled hyperinflammation in addition to autoinflammation. Furthermore, strong evidence points to adaptive immune response activation in patients with classical IL-1-driven autoinflammatory diseases (11). Thus, autoinflammatory diseases might now be viewed as immunological diseases defined by an overactive inflammatory response driven by dysregulation of molecules and cells of the innate immune system, combined with host susceptibility factors and often with activation of the adaptive immune system and with immune dysfunctions such as susceptibility to infections, autoimmunity, or uncontrolled hyperinflammation (12).

IRDs may be confined to the joints or produce systemic manifestations. Systemic autoimmune IRDs are characterised by the production of autoantibodies to a variety of intracellular targets, as a result of a specific adaptive immune response against self antigens. Adaptive immune responses are initiated by the activation of antigen-specific T cells, and autoimmunity may be triggered in the same way. T-cell responses to self antigens damage tissues via direct or indirect mechanisms. Cytotoxic T-cell responses and inappropriate macrophage activation by Th1 cells can cause extensive tissue injury, and help provided inappropriately by T-cells to self-reactive B cells can trigger deleterious autoantibody responses. Thus, autoimmune IRDs result from three distinct but interrelated components: loss of self tolerance; the development of chronic inflammation in one or more organs; and, if the disease is active, tissue destruction with the attendant detrimental effects (13).

Main classification criteria sets for arthritis

Infectious agents

Septic arthritis and discitis are not IRDs but infections, in which the tissue damage and symptoms are directly caused by infectious agents. Nevertheless, infectious agents can trigger autoimmunity and/or autoinflammation, thereby causing reactive IRD, which may be combined with systemic manifestations. An example is rheumatic fever, which is a systemic immune response to *Streptococcus pyogenes*. Reactive IRD and infection seem to occur concomitantly, however, in Whipple's disease, which is due to *Tropheryma whipplei* and usually resolves with long-term antibiotic therapy but may also have a reactive component, since the organism is not always detectable in the synovial membrane (14). Among the reactive arthritides, only rheumatic fever has internationally validated diagnostic criteria (online Supplementary Table S1) (15-21).

Microcrystal deposition diseases

Arthritis can be caused by the deposition of microcrystals of sodium urea in gout (22), calcium pyrophosphate in chondrocalcinosis (23, 24), or hydroxyapatite in calcinosis (Suppl. Table S2 (22, 25)). These three diseases involve autoinflammatory mechanisms. Gout has internationally validated criteria (22, 26). The identification of the relevant crystals in synovial fluid remains the key to the diagnosis. However, ultrasound, radiography, or computed tomography may also be helpful.

Systemic autoimmune inflammatory rheumatic diseases

Systemic autoimmune IRDs can affect all organs. They include connective tissue diseases, vasculitides, and a few rare diseases such as the inheritable periodic fevers (Suppl. Table S3) (18-20, 27-40). Autoantibodies are usually present (41-43). Internationally validated diagnostic criteria are available for all the systemic autoimmune IRDs except sarcoidosis.

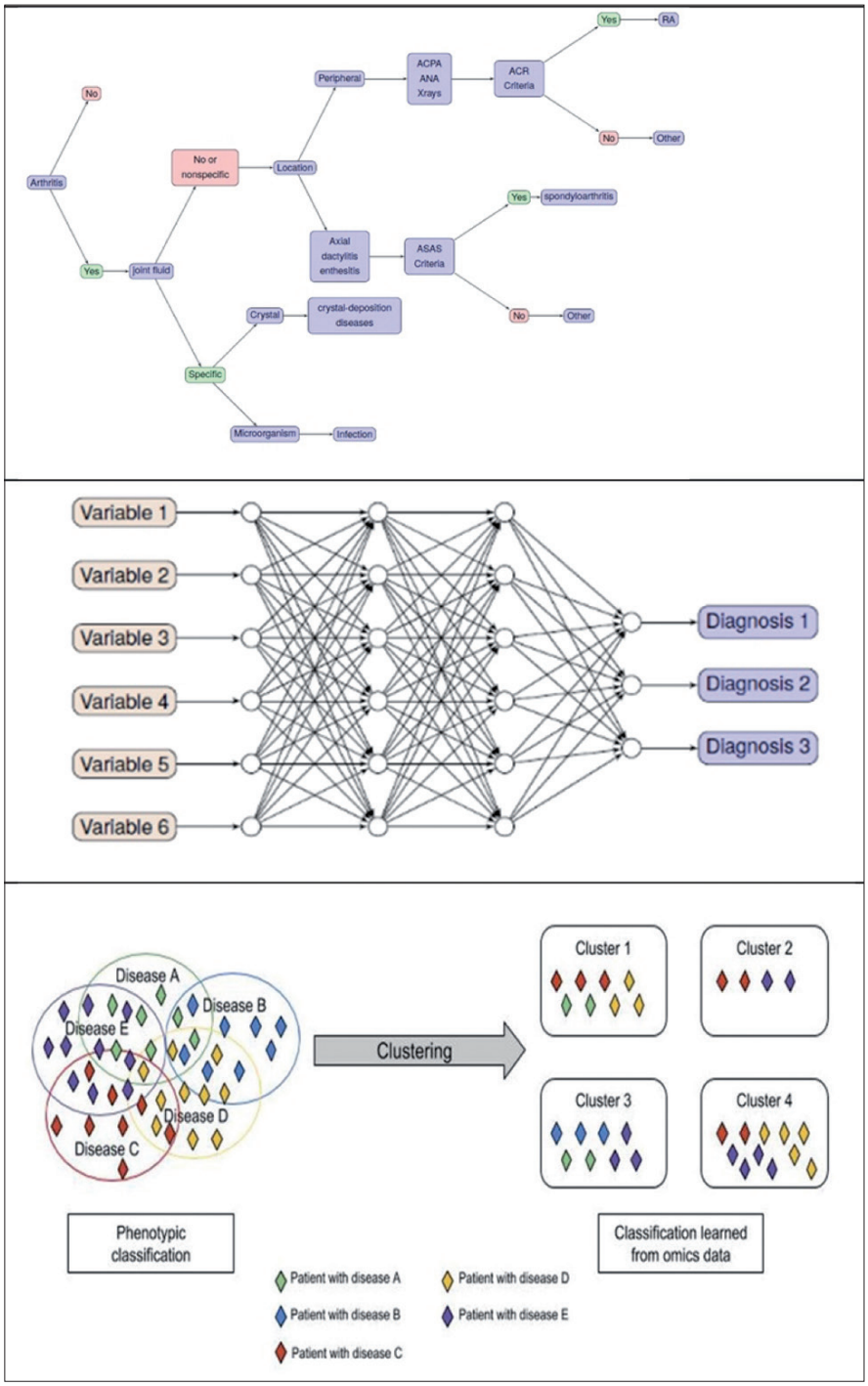

Fig. 1. Classification of rheumatic diseases.
1a. Classical diagnostic tree for early arthritis. This tree illustrates a common issue in the field of machine learning, which is the small number of patients compared to the number of variables available for describing them.
1b. Model currently use to define new classification criteria. Construction of the model can be helped by introducing established knowledge about the variables into the algorithm.
1c. In the future, cluster analysis will shift the basis of classification approaches from clinical phenotype to combinations of vast numbers of variables.

Among the connective tissue diseases, only Sharp's syndrome (29) and antiphospholipid syndrome (28) do not have validated ACR/EULAR classification criteria. The classification of vasculitides was revised in 2012 using a nomenclature system based on the affected vessels (44). Nevertheless, separate classification criteria exist for each type of vasculitis [*e.g.* giant cell arteritis (33)].

Joint-dominant inflammatory rheumatic diseases

The cause of these conditions is unknown. Examples include rheumatoid arthritis (RA) and spondyloarthritis in adults, polymyalgia rheumatica in older individuals, and juvenile idiopathic arthritis in children. Internationally validated diagnostic criteria are available for all these diseases (Suppl. Table S3) (45-50).

Why have international classification criteria been developed for most rheumatic diseases?

Classification criteria are needed when no sensitive and specific investigation exists to confirm the diagnosis, such as the detection of microcrystals in synovial fluid for the microcrystal deposition diseases (51, 52). Even then, some patients may not undergo synovial analysis, and some may not have visible crystals. Similarly, criteria are necessary for patients with suspected septic arthritis but negative microbiological tests (53). Validated classification criteria are needed when the diagnosis is challenging and must rely on a converging set of clinical, laboratory (41), and imaging study (54) findings. This is the case for IRDs. The American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) have expended huge efforts to develop uniform classification systems that can be applied worldwide. Most of the new classification systems have been endorsed by these two societies.

Why do disease concepts and classifications change over time?

For many diseases, several criteria sets are available, leading to confusion, as patients may meet some sets but not others. Thus, replacing multiple sets by a single set is an important goal. Furthermore, new criteria sets seek to improve the performance of earlier sets by adding newly identified criteria, introducing exclusion criteria, and using new methodological tools.

Technological advances result in the development of new tools that are capable of detecting new signs of disease. The performance of these new signs for

diagnosing and/or classifying disease must then be evaluated. If it proves good, then the new sign may deserve to be included within classification criteria sets. Examples include the addition of echocardiography to Jones' criteria for acute rheumatic fever (21) and of the ultrasound double-contour sign and dual-energy CT identification of sodium urate deposition for gout (22). Similarly, recently validated tools include shoulder and hip ultrasound for polymyalgia rheumatica, capillaroscopy for scleroderma, and sacroiliac magnetic resonance imaging for spondyloarthritis. A striking modification of classification criteria related to the introduction of a new tool occurred for the four autoinflammatory diseases FMF, mevalonate kinase deficiency (MKD), TRAPS, and cryopyrin-associated periodic syndrome (CAPS): the development of genetic testing strategies now allows the detection of the underlying gene abnormalities (32). Another important change was the introduction of newly identified autoantibodies to the criteria sets for several diseases, such as anti-citrullinated peptide antibodies (ACPA) for RA.

For some diseases, new epidemiological data (55) about at-risk populations have led to changes in the criteria sets. Acute rheumatic fever is an example (21). Also, when developing the new criteria for Behçet's disease (45), the differences in clinical presentations according to geographic origin were considered, with the goal of enabling classification without having to perform a pathergy test.

The introduction of new treatments that are effective but expensive and associated with side effects is an important reason for working to improve the sensitivity and specificity of classification systems, since these are widely used as diagnostic aids. The sensitivity of the criteria set for spondyloarthritis was increased by introducing the concept of nonradiographic forms. For systemic lupus erythematosus, sensitivity was improved by adding typical nephropathy without serum anti-DNA antibodies (56). In RA, the introduction of methotrexate (57) and biologics as major treatment options very early in the disease created a need for tools capable of confidently providing the early diagnosis, and the identification of ACPAs as an effective diagnostic marker (58) required a change in the 1987 ACR criteria (4). In 2010, the ACR and EULAR therefore issued a new criteria set (46). In addition to ACPAs, exclusion criteria were introduced, providing an example of how changes in strategy, in addition to items, can improve performance. Interestingly, when we applied these exclusion criteria to a cohort of patients with early arthritis, we found very few classification discrepancies across previous criteria sets (59). Changes in criteria sets over time have hindered attempts to determine the prevalence of RA, although a single criteria set can be applied retrospectively (60). Similarly, new ASAS criteria for spondyloarthritis were issued in in 2011 (47). There are also new criteria for vasculitis, which include recently identified antibodies (ANCA), introduce new categories, and provide new treatment guidance (61).

Difference between classification and diagnostic criteria

Criteria can be developed for a diagnostic situation to help the clinician (*i.e.* developed for diagnostic purposes in the clinic) or for classification when a patient with rheumatic disease must be classified among other patients in a rheumatology outpatient clinic for clinical research or epidemiologic studies (a patient with a rheumatic disease must be classified from a large population comprising healthy subjects) (62) The study design, choice of populations, and gold standard are completely different in terms of conception. Nevertheless, many sets of criteria were developed as classification criteria for clinical research but are widely used as diagnostic criteria.

The ACR has elected to focus on classification rather than on diagnosis. Most of the criteria sets currently endorsed by the ACR/EULAR were developed using a two-step methodology. First, data from patient cohorts were scrutinised to identify the factors most likely to be of interest as classification criteria and to assign weights to each of them. Then, based on the findings from this first step and on a literature review, a panel of experts developed and ranked clinical case scenarios using multiple combinations of clinical features, with the assistance of decision analysis software. A panel of specialists then determined which patients they would treat with a disease-modifying antirheumatic drug (such as methotrexate in rheumatoid arthritis) or enroll in a clinical trial of an investigational biologic therapy.

How will bioinformatics help classify multifactorial inflammatory rheumatoid diseases?

In everyday practice, rheumatologists use synovial fluid analysis when available as a diagnostic tool. Otherwise, a combination of clinical findings may be sufficient to determine the diagnosis (Fi.g 1a). If not, investigations are carried out.

The number of items – subjective symptoms, physical findings, and test results – needed to establish a diagnosis of IRD can be very high. In this situation, software based on classification criteria could be useful (Fig. 1b). Advances in research are considerably expanding the amount of information available on IRDs. Thus, when devising classification systems, the omics or big data approach is becoming relevant (63).

Bioinformatics techniques

Bioinformatics techniques can improve the performance of classification systems because they can simultaneously consider large numbers of items and the links between them (Fig. 1c). A bioinformatics technique highly relevant to the development of disease classification systems is cluster analysis, which is an unsupervised machine learning technique used in artificial intelligence. Unlabeled items are fed to an algorithm, which identifies clusters of items connected in some way to one another. When used to devise IRD classifications, the items are laboratory data. It is very important to evaluate the quality of these data. Data curation methods have been developed to tackle this problem for specific pathologies such as Sjögren's syndrome (64). Pa-

tients who have the same cluster of items are likely to share pathogenic biological pathways, irrespective of their diagnosis. Clustering analysis is at the heart of classification projects for complex diseases, such as the multicentre study PRECISEADS involving 12 European countries and investigating six systemic autoimmune IRDs (65).

The omics approach provides high-dimensional model representations of patients. Classical clustering techniques such as k-means algorithms are ill-suited to exploring high-dimensional models. Dimension reduction via selection of the most informative features is therefore required. An increasing number of algorithms is becoming available for dimension reduction (66-68) by selecting the most informative inhabitants of the dataset jungle and using them to build a more manageable model.

Injecting knowledge into the algorithms

Relying solely on big data to devise classification systems raises several challenges, notably when dealing with high-dimensional models. More specifically, overfitting is likely to occur when the number of item types in the dataset is considerably larger than the number of patients. Overfitting can be prevented by feeding well-established knowledge about the items into the algorithm. Such knowledge is available in online databases (*e.g.* KEGG Pathway, PubMed, and InnateDB). Application programming interfaces can be used to develop software that partially automates knowledge retrieval from the databases. Once established knowledge has been supplied, the algorithm can automatically assess whether a relationship it has detected between two dataset items is scientifically plausible, has been described previously, and/or has been validated experimentally. This approach was applied in a recent study to perform a systematic literature review by rapidly screening a very large number of publications using a list of keywords and the natural language processing approach (69).

Artificial intelligence (AI)

As advances in research produce ever larger data sets and uncovers ever more complex pathogenic mechanisms, attention is turning toward artificial intelligence as an analysis tool (70). AI techniques can identify highly complex links among variables within a huge dataset. Of the many available AI algorithms used for unsupervised learning, generative adversarial networks seem particularly promising as a tool for devising classification systems. In the generative adversarial network approach, two neural networks are made to compete against each other in a zero-sum game. One network generates new data instances, which are then evaluated as valid or not by the other network. This strategy increases the efficiency with which the algorithm can detect complex structures within a dataset (71). AI techniques applied to big data, combined with established knowledge, can be expected to become the reference standard for creating classification systems in the near future.

Conclusion

The clinical acumen of the physician remains the best guarantee of an accurate diagnosis. Nevertheless, classification criteria, although designed as tools to obtain uniform patient cohorts for research, are used as diagnostic adjuncts. Exclusion criteria designed to eliminate differential diagnoses have emerged as similarly or perhaps more useful compared to the presence of disease features. Both the criteria used in classification systems and the tools applied to analyse them are evolving rapidly in the wake of technological progress. In the near future, the use of advanced machine learning approaches can be expected to produce new classifications based not only on clinical phenotypes, but also on complex biological profiles and shared sensitivities to targeted treatments. Specific biological pathways defining patient clusters will no doubt be identified, supplying new insights into the mechanisms involved in each clinical phenotype and potentially providing information about which type of treatment is most likely to succeed. Thus, better classification systems should translate into better patient outcomes.

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Key messages

- Many reasons (new tests, new treatments...) explain modification of classification criteria over time.
- In the future, classification criteria could be built on the basis of treatment efficacy or target.
- An up-to-date summary of classification criteria may help clinicians, biologists and bioinformaticians working with clinicians in a context of early or unclassified arthritis.

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