Systemic rheumatic diseases: beyond classification criteria

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Systemic rheumatic diseases are clinically heterogeneous entities with no pathognomonic clinical features, laboratory, imaging, or other diagnostic tests. Many symptoms are non-specific and the overlapping organ manifestations often make the diagnosis challenging. Despite significant advances in the diagnostic tools available to the rheumatologist, the diagnosis of systemic rheumatic diseases still relies on a knowledgeable clinical judgment and expertise.

ADVANTAGES OF USING CLASSIFICATION CRITERIA

Categorizing clinical entities using classification criteria not only facilitates communication between clinicians, but also helps standardization of disease definitions across centers geographically distant, and provides a framework for both clinical practice and research. Criteria sets are not static concepts – on the contrary, they are rather permissive to updates as our knowledge advances. Indeed, since 2010 the European League Against Rheumatism and the American College of Rheumatology published new criteria for classification of rheumatoid arthritis, polymyalgia rheumatica, Sjögren's syndrome and candidate criteria for systemic sclerosis; the Systemic Lupus International Collaborative Clinics proposed new criteria for systemic lupus erythematosus and criteria for primary systemic vasculitis are currently underway.

The worldwide acceptance of these consensus relies on their validity, clinical relevance, applicability, and reproducibility. However, classification criteria are not perfect tools: the formulation of criteria largely relies on expert opinion – less so in light of current standards of methodological quality –, and the evaluation of their measurement properties has not always been the most appropriate, particularly in earlier years[1].

Classification criteria are mainly developed for use in research and surveillance. They facilitate the enrollment of similar patients into clinical trials by differentiating one rheumatic disease from another, and contribute, among others, to a better knowledge of disease epidemiology, natural history, and genetics. Although not intended for diagnosis, they are very popular among rheumatologists and frequently used at the individual patient level to help with the diagnosis of a particular rheumatic disease. It is well known, though, that meeting the criteria is not equivalent to making a diagnosis, and patients with a clinical diagnosis may not fulfill the criteria. These limitations were nicely demonstrated for the ACR 1990 vasculitis criteria[2].

LIMITATIONS AND CAVEATS

When using classification criteria in clinical practice it is important to have in mind that, while balancing sensitivity and specificity, many clinically relevant features are left behind. This might negatively impact the clinical awareness and recognition of such clinical manifestations. Moreover, the development of new drugs and new therapeutic strategies almost always neglect these clinical features.

In the particular case of antiphospholipid syndrome (APS), only vascular thrombosis and pregnancy morbidity are part of the classification criteria, although the association of APS with cardiac valve disease, *livedo reticularis*, thrombocytopenia, nephropathy, and neurological manifestations is well recognized[3]. The article by Pinto-Almeida *et al.*[4] highlights how common cutaneous involvement in APS is, ranging from *livedo reticularis* to necrotic skin ulcers and gangrene.

FILLING THE GAPS

Nevertheless, no formal studies have addressed their treatment, which remains empirical. This lack of in-

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formation is understandable, since clinical trials are unlikely to cover less frequent clinical conditions or include patients without fulfilling classification criteria. Nevertheless, we now have at our disposition clinical registries such as Reuma.pt that systematically collect information on demographic characteristics, clinical features, disease activity, co-morbid conditions, treatment, and outcome of various rheumatic diseases[5]. The wide use of registries on a routine basis will hopefully improve our knowledge about the unmet needs of less frequent rheumatic diseases and how they respond to empiric and off-label drug therapies.

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