

Evolution of paediatric-specific vasculitis classification criteria

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This issue of *Annals of the Rheumatic Diseases* includes two articles describing the proposed paediatric-specific classification criteria for childhood polyarteritis nodosa (c-PAN), Wegener granulomatosis (c-WG), Takayasu arteritis (c-TA) and Henoch-Schönlein purpura (HSP) which resulted from an ambitious multicentre, international collaborative project that was initiated in Vienna in 2005 and culminated in the 2008 Ankara Consensus Conference (see articles on pages 790 and 798).^{1,2}

The vasculitides are a heterogeneous collection of multisystem disorders that manifest as the inflammation of blood vessels and may occur as a primary process or may be secondary to another disorder, most commonly infection. Despite this commonality, the vasculitides differ significantly in their clinical, radiographic, laboratory and histopathological features. Much of this heterogeneity arises from the different sizes of the blood vessels that are primarily affected, the involvement of arteries, veins, or both, and from the varying patterns of organ involvement, all of which have important implications for the optimal medical treatment and prognosis of the disorders. Perhaps some of the most interesting and significant variations within the vasculitides are those associated with the age of onset. For example, the prevalence of certain vasculitides varies considerably by age of onset. Kawasaki disease (KD), one of the most common paediatric vasculitides, only rarely manifests in adulthood, while other vasculitides, such as giant cell arteritis, are seen only in adulthood. Other vasculitides have different patterns of organ involvement and differing prognoses depending on age of onset, such as in HSP, for which the prevalence of arthritis and the prognosis associated with kidney involvement both vary significantly according to the age of onset.^{3,4}

Development of classification criteria for the vasculitides has been particularly

challenging given these variable disease presentations and the evolution of laboratory and radiographic techniques that have changed the way in which the vasculitides are evaluated and diagnosed. Some of the most significant developments have been the development of the antinuclear cytoplasmic antibody (ANCA) assay and the increased use of techniques such as CT angiography and magnetic resonance angiography, which are increasingly used in diagnosing these disorders and in some cases are used in place of tissue biopsy.

In general, the goal of a set of classification criteria is to identify relatively homogeneous, non-overlapping groups of patients who share a common disorder, and they are generally defined as a group of clinical or other findings that predict the presence of the defining aspects of the disease.⁵ Diagnostic criteria, on the other hand, are derived to help clinicians distinguish vasculitis from non-vasculitis in their daily practice. In the case of the vasculitides, the classification criteria are based upon clinical, laboratory, histopathological and radiographic characteristics and are intended to differentiate patients who have been diagnosed with vasculitis into specific subtypes. The two sets of criteria therefore serve distinct purposes. Sensitive and specific classification criteria remain of key importance for defining cohorts for study in epidemiological, basic science and clinical research.

The classification criteria for vasculitis have undergone numerous iterations which reflect improvements in recognition and diagnosis of the disorders and the increased availability of published clinical reports describing case characteristics and outcomes. One of the initial significant developments in the study of vasculitis was the first formal scheme for the classification of vasculitis that was published in 1952 by Zeek.⁶ The criteria required the presence of necrotising angiitis and were based primarily on the size of the vessels affected and the pattern of organ involvement. The criteria defined classification criteria for five different types of vasculitis: (1) hypersensitivity angiitis; (2) allergic granulomatous angiitis; (3) rheumatic arteritis; (4) peri-

arteritis nodosa; (5) temporal arteritis. The emphasis on vessel size led the way for the development of additional sets of classification criteria and modifications centred upon this defining characteristic.

In the 1980s the American College of Rheumatology (ACR) established a subcommittee to derive classification criteria for seven specific categories of vasculitis: giant cell arteritis, TA, WG, Churg-Strauss syndrome (CSS), PAN, HSP and hypersensitivity vasculitis. These criteria, published in 1990, were derived from a prospectively developed cohort of 1000 patients with vasculitis from 48 centres in Mexico, Canada and the USA and provided classification criteria in both traditional and tree classification formats.⁷ The resultant criteria had sensitivities and specificities, ranging from 70% to 99%. However, these criteria were developed before the widespread use of ANCAs and did not include classification criteria for microscopic polyangiitis (MPA), which was being increasingly described in the literature, but had not yet been formally recognised as a separate entity.

Given concerns about the continued lack of standardised nomenclature and disease definitions, the Chapel Hill Consensus Conference on the Nomenclature of Systemic Vasculitis was convened in 1994 and included an international, multidisciplinary committee which used modified nominal group techniques to propose a set of definitions for the vasculitides (ie, the elements of each disease that are present in every case of the disease).⁸ The primary contributions of this conference were to include a definition for MPA and to acknowledge that, owing to the limitations in histological data such as the typically patchy involvement which may result in the biopsy not being representative, in some cases surrogate markers could be acceptable in place of tissue. Subsequent efforts have tried to derive classification criteria from these definitions with varying success.^{9,10}

It was recognised early on that these classification criteria, derived from adult cohorts, would not have acceptable sensitivity and/or specificity for use in paediatrics. In particular, the lack of classification criteria for KD and HSP, two of the most common paediatric vasculitides, and the lack of inclusion of ANCAs in the criteria were felt to be significant limitations. In response to these concerns, the Pediatric Rheumatology European Society along with the European League Against Rheumatism established

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a working group consisting of paediatric rheumatologists and nephrologists whose objective was to assess whether the 1990 ACR criteria were adequate for paediatrics, and, if not, to develop a preliminary set of paediatric-specific classification criteria that would adequately reflect the differences between paediatric and adult disease and would incorporate new diagnostic tools.¹¹ This conference was held in Vienna in 2005 and, after a review of the literature and expert consensus, as derived from a combination of Delphi and nominal group techniques, it was decided to base the criteria on vessel size, similar to the 1990 ACR criteria, and the small-vessel vasculitis subgroup was further divided into granulomatous and non-granulomatous vasculitis. The 'Other vasculitides' category was expanded to include such diagnoses as Behçet disease and Cogan syndrome. Preliminary criteria were subsequently proposed for c-PAN, WG, HSP, TA and KD and the planning for data collection for the prospective validation of these criteria was begun. The final examination of the data and consensus processes, as described in this issue of the *Annals*, subsequently occurred in 2008 at the Ankara Consensus Conference.

Some of the major changes proposed at the 2005 Vienna conference included the removal of the age criterion from the HSP criteria and the inclusion of the presence of IgA deposition on biopsy as a criterion. Palpable purpura was added as a mandatory criterion. Serological evidence of streptococcal infection was added to the criteria for PAN, recognising the frequent association between streptococcal infection and PAN in children. The WG criteria were augmented to include subglottic, endotracheal and/or endobronchial stenosis and the presence of anti-proteinase 3 or cANCA as detected by direct immunofluorescence. The use of a CT scan instead of plain radiographs was also added. Similarly, antimyeloperoxidase and pANCA were added to the criteria for MPA. For TA, angiographic abnormalities were added as a mandatory criterion, although the diagnostic modality for how these should be detected was not specified, and hypertension, as assessed in relation to age-specific norms, was added as an additional criterion. In the case of KD, perineal desquamation was added as a criterion and coronary artery involvement, as detected by echocardiography, was included.

The two papers included in this issue of *Annals* therefore describe the formal validation of these preliminary classification

criteria for childhood PAN, WG, HSP and TA and the classification criteria that resulted from the 2008 Ankara Consensus Conference. Other, rarer vasculitides such as MPA and CSS were excluded from this project owing to small case numbers. Validation of the KD criteria is the subject of a separate project.

These criteria were validated through a procedure similar to that used to derive the 1990 ACR criteria. Data on 1398 children with vasculitis were collected both retrospectively and prospectively via a web-based data entry system by 97 sites in 36 different countries. Data were entered on the patients at baseline and at approximately 3 months of follow-up. Included in these data was the diagnosis given by the treating physician, which subsequently served as the 'gold standard' against which the derived criteria were tested. The resultant criteria had sensitivities ranging from 90% to 100% and specificities ranging from 87% to 100%. In general, these criteria had similar sensitivities to the ACR criteria and higher specificities.

It should be recognised that these criteria will have different performance characteristics depending on the population to which they are applied, such as the somewhat lower sensitivities of the WG criteria when applied to a cohort of children with ANCA-positive vasculitis.¹² The sensitivities and specificities are also likely to differ when other modalities, such as magnetic resonance angiography or ANCAs performed by other techniques, are substituted for those included in the criteria. It is also unclear whether these new criteria will impact the inclusion criteria for vasculitis clinical trials that include both adults and children. Furthermore, it should also be recognised that the use of the treating physician's assessment as the 'gold standard' for diagnosis may have limited the project's ability to define entirely new criteria, as the physician diagnosis is informed by currently existing criteria.

This project provides a model for multicentre, international collaboration in paediatric rheumatology. These criteria provide a large step forward for the study of paediatric vasculitis, laying the groundwork for inclusion criteria for clinical trials, better-defined cohorts for genetic study and components for disease activity indices. The large number of cases submitted and their geographic diversity are invaluable strengths of this project, as is the multidisciplinary panel of physicians who were involved. It is hoped that this project will lay the groundwork for future such collaborations and will

be emulated as classification criteria are derived for other paediatric vasculitides, including MPA and central nervous system vasculitis, and paediatric rheumatic disease. Ideally, similar future collaborations should also include longer duration of patient follow-up and the collection and banking of biological specimens for further study. It should also be expected that these criteria are not final and will continue to evolve as these current classification criteria lead to further research into genotype-phenotype correlations in vasculitis and as diagnostic technologies continue to develop.

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