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VASCULITIS (LR ESPINOZA, SECTION EDITOR)

Critical Appraisal of Classification Criteria for Vasculitides

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Abstract The vasculitides are a group of protean diseases, some of which are caused by conditions including infections, other autoimmune diseases, or neoplasias. They are a challenge to the clinician, in terms of both diagnosis and therapy. No diagnostic criteria exist, although a multinational effort to develop them is in progress. However, many classification criteria have been proposed, and these have served as diagnostic surrogates and have made it possible to discriminate between many, although not all, of the vasculitides, mainly for epidemiological and therapeutic trial design purposes. In this review we recognise the difficulties of defining such criteria, but at the same time attempt to provide a critical overview of efforts to do so. The increasing knowledge regarding many of these diseases makes us confident that the time will come when their aetiology, or at least their main pathogenic features, is known, rendering proposed classification criteria obsolete.

Keywords Vasculitides · Vasculitis · Criteria · Classification · Diagnosis · ACR criteria · EMA algorithm

Introduction

Vasculitis implies the presence of vessel wall inflammation, induced by what can be generally termed as autoimmune mechanisms, and of its consequences, including obliteration, thrombosis, ischaemia, and parietal disruption and, ultimately, destruction, and its main microscopic and pathophysiological finding, necrosis. Vasculitis can have many aetiologies [1]. Some are known, as for vasculitides secondary to infections, whereas others produce the damage via different pathways, and their cause has yet to be determined. These last vasculitides are usually termed *primary*, whereas those for which an aetiology is proved, or at least strongly suspected, are called *secondary*.

The vasculitides, as a generic term, are one of the greatest challenges for physicians in any field, because the clinical manifestations of a vasculitis, regardless of its origin, can be puzzling. The vasculitides almost always need many specialists to work together for patient care and diagnosis, and they require the most important clinical exercise: differential diagnosis.

The vasculitides share with other poorly understood diseases the characteristic that diagnostic criteria (*criterion: something used as reason for making a judgement or decision*, as defined in the Merriam-Webster dictionary) [2] need to be proposed, developed, and brought to consensus. At present, there are none with sufficient strength and/or confidence to be satisfactory as a universal reference. However, the different criteria proposed have provided a working method for categorisation, mainly for epidemiological purposes and developing therapeutic trials. Certainly, diagnosis has come a long way since the first formally recognised proposal, a seminal work by Dr Pearl Zeek in 1952 [3]. This was followed by the criteria of Alarcón-Segovia, first published in 1964, with two subsequent modifications [4–6], and then by those most used: the ACR criteria [7] and the Chapel Hill Consensus Nomenclature of 1994 [8]. Other tools and more recent proposals have been added to these, including an update of the CHCC 1994, published last year [9••].

In this review, we discuss the evolution of the criteria proposed, including their advantages and limitations, and

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emphasise some of the main studies that have tested their usefulness. Although we provide a mostly clinical, critical overview of their practical applicability over time, we recognise the efforts made by experts in the field in their attempts to solve this difficult problem.

From the ACR Criteria to the EMA Algorithm

In the last years of the 1980s, the American College of Rheumatology decided to work on definitions for many of the rheumatic diseases. As part of this objective, a process was initiated to provide classification criteria enabling comparison of subjects who presented with similar manifestations at different treatment centres, and who were part of research projects. Although such criteria would discriminate one disease from the other, they would not consider all the manifestations that could be present at one time in a given individual. Therefore, it was known *a priori* that they would not be suitable for diagnostic purposes [7].

Regarding the vasculitides, the objective was to develop criteria that would make it possible to distinguish between many of them. Probably because of the magnitude of the task, only seven diseases were included: giant cell arteritis (GCA), Takayasu's arteritis (TA), polyarteritis nodosa (PAN), Churg–Strauss syndrome (CSS), Wegener's granulomatosis (WG), hypersensitivity vasculitis (HV), and Henoch–Schönlein purpura (HSP). Eight hundred and seven patients, all previously diagnosed as having any of these diseases, and selected from 48 centres in Mexico, Canada, and the USA, were analysed. A set of different clinical, laboratory, radiological and histological characteritics was used, in order to select discriminating features that would allow to best discern among the abovementioned selected diseases. This was done with two approaches: a conditional process termed "traditional format", which created a short-list of items that in combination provided the best possible differentiation, and a second process which developed "classification trees". This was based on grouping and subgrouping that, depending on the presence or quality of a variable, split patients into those with (case) or without (non-case) those variables that best allocated a subject to a given disease. Although either of the formats could be used, in the end the short-list gained widespread acceptance, mainly because of its ease of use [10]. Overall, these criteria provided 71–95.3 % sensitivity, and specificity in the range 78.7–99.7 %, for the seven diagnoses that were subject to this approach [11–17].

However, this method has many limitations. Probably most important is that the target diagnosis was the established diagnosis given by those who submitted the information: this introduced an important bias, reinforced by the fact that no individuals with other diseases that share manifestations with the seven vasculitides considered were included. Additionally, although some features of one disease can be most frequently associated with it and could thus be regarded as "typical", priority was given to those features which made most difference to the method used, thus excluding others that are clinically relevant. Also, comparison was not made afterward between each type of vasculitis chosen, but was instead restricted to a global comparison among the whole group of patients with a diagnosis of vasculitis; there was no standardisation of the tests that supported diagnosis of the different diseases considered, nor a definition of those tests; only rheumatologists took part in this project, despite the vasculitides having diverse organ manifestations; although already described as a useful tool for diagnosing these diseases, antineutrophil cytoplasm autoantibodies (ANCA) were not considered in this exercise (possibly because they were not, at the time, widely accessible) [18]; and, finally, many other diseases were excluded.

The usefulness of this classification method has been challenged. In 1998 Rao et al. analysed 198 patients with suspected vasculitis who had been sent to a referral centre by rheumatologists. Only 51 were thereafter diagnosed, by use of these criteria, with WG, PAN, GCA, or HV. The positive predictive value of the criteria ranged from 17–29 % when applied to the whole group, with an increase ranging from 29 % (for PAN) to 75 % (for GCA) when used for the vasculitides patients. These results proved that these criteria performed poorly when used for diagnostic purposes in an open context, something important to consider in daily practice [19].

Within our setting, a nationwide referral centre for respiratory diseases, we studied the performance of the ACR classification criteria as diagnostic criteria for granulomatosis with polyangiitis (GPA) (Wegener's) (published in abstract form). When applied to 93 consecutive patients with suspected GPA, 13 of which cases were eventually established by biopsy, the sensitivity of the criteria was 31 %, with a specificity of 56 % and an area under the curve of 50 %, reflecting poor performance [20].

The first CHCC on vasculitides nomenclature [8] differed from the ACR criteria in attempting to clearly define the characteristics of those diseases from which data had been extracted to develop the ACR criteria. Implicit in this attempt was the fact that those entities had not previously been defined, as mentioned above. Although the original purpose was different, the higher and more reliable sensitivity and specificity compared with the ACR criteria—especially for some entities, including HSP, PAN, and HV—resulted in the inclusion as defined entities of a microscopic polyangiitis (MPA) and of others excluded by the ACR criteria, namely Kawasaki disease and essential cryoglobulinaemic vasculitis. The combined opinion of an expert multidisciplinary team was used to aid in classifying, and even diagnosing, patients. This attempted definition, which gained widespread acceptance, emphasised the importance of biopsy for diagnosing

vasculitis, and recovered basic concepts previously stated by Zeek and in Alarcón-Segovia′s proposals [3–6]. Although not entirely based on fundamental characteristics, because some definitions were accompanied by clinical surrogates, the nomenclature relied heavily on histopathology, providing a framework into which to allocate specific diseases on the basis of the size of the affected vessels. It ultimately achieved its objective: its adoption was practically universal, with some of its major achievements related to the clear-cut separation of MPA and PAN, and to emphasising the ambiguity of the term "HV", which was not entirely overcome by the cutaneous leukocytoclastic angiitis definition they proposed.

When subjecting the CHCC criteria to further evaluation—similar to that performed for the ACR criteria, but with emphasis placed on the clinical surrogates mentioned in the CHCC 1994, plus others used in the Birmingham Vasculitis Activity Score and the Vasculitis Damage Index systems—Sørensen et al. concluded that the usefulness of the CHCC 1994 definitions during a five-year period of prospective patient collection was poor. Because the number of patients with each disease was low, their main evaluation focused on GPA and MPA patients. In their population, only 37 % of patients had findings supporting GPA, and this figure was much less for GPA localised to upper airways, which was observed histologically for only 4 %. When presence or lack of surrogates (defined in the article) was added to the evidence from histological samples, all GPA cases could be diagnosed, and the three of 12 MPA patients diagnosed without the proposed surrogates increased to nine of 12 with surrogates. This aspect is important, because biopsies cannot always be obtained, or their yield may be negatively affected by sampling errors resulting from the nature of tissue involvement. The authors proposed new criteria for GPA and MPA, based on the evaluation of the CHCC 1994 nomenclature system used for diagnosis [21].

A couple of years later, Lane et al. compared Sørensen et al.'s criteria with those of the ACR for GPA, CSS, and PAN, using the CHCC 1994 criteria for MPA and the Hammersmith criteria for CSS. The results were conflicting. The criteria were capable of diagnosing GPA in 50 of 56 patients diagnosed with this disease under the ACR criteria, but only three were diagnosed with MPA, despite 39 fitting the CHCC 1994 definitions. Of 60 patients diagnosed with PAN under the ACR criteria, 32 were reclassified as having GPA and two as having MPA under the proposed criteria. The authors concluded that the Sørensen criteria are limited, with a 68 % overlap between GPA and MPA as classified under the new criteria observed in the group of patients diagnosed with MPA using the CHCC 1994. Such an overlap may be unacceptable in a clinical context [22].

Attempting a rational and stepwise use of the different criteria, Watts et al. focused on the development and validation of a method to classify the ANCA-associated vasculitides and PAN. They applied the different criteria to both previously diagnosed patients and paper cases, in a stepwise fashion. First the Hammersmith and the ACR criteria for CSS were used; if negative, the case was then evaluated by use of the—then still-called—WG, ACR criteria (step 2a); if this too was negative, the WG CHCC 2014 definition was used (step 2b). If the case was still not allocated, the following step (2c) made use of histological findings. In cases with MPA histological compatibility but with WG surrogates present, the patient was diagnosed with the latter. This diagnosis was also made if there were no histology findings supporting diagnosis, but positive anti-proteinase 3 or anti-myeloperoxidase autoantibodies were present in conjunction with surrogates of WG (2d). If still negative, then a diagnosis of MPA would be made if clinical features and small vessel vasculitis in biopsy were present without WG surrogates (3a), or if no histology nor surrogate markers for WG were observed but positive surrogates of renal vasculitis were present with either anti-PR3 or anti-MPO autoantibodies (3b). Finally, the fourth step diagnosed PAN if either the biopsy revealed changes defined under "classical" PAN in the CHCC 1994 definitions, or angiographic findings supported diagnosis of this disease (step 4). If all steps were followed without confirming a patient as having any of the four diagnoses considered, then their disease was categorised as unclassified [23].

This stepwise classification made use of the tools previously described: it did not propose any new item creation or selection, but instead sequentially applied existing criteria. It went through a validation process using true cases from the group's original catchment area, then face validity was established using another 20 patients (after which the Hammersmith criteria were added into the first step, as described above), and finally the algorithm was applied to 99 paper cases by a multicentre and multinational experts group. Ninety-five percent of cases were correctly classified under this system, and there was very good interobserver agreement (91.5 %, with a κ value of 0.886). This algorithm was supported by the European Medicines Agency (EMA), which endorsed the system.

Further evaluation has come from different countries; this is an important step, both to confirm the applicability of the method and to ensure the geographical variation of the diseases is included in analysis. In China, of 550 patients previously classified using the CHCC 1994 and the surrogates proposed by Sørensen, 10 % of those with a diagnosis of MPA were reclassified to GPA and SCS when using the EMA algorithm, and all those previously classified as having PAN were reclassified to MPA. Sixty-four percent of those previously unclassified could then be diagnosed with GPA (97 %); this is one advantage of this method [24]. A Turkish study revealed reclassification of 6 % of GPA patients to MPA, with the opposite occurring in 22 % of cases. Once again, 75 % of non-classified patients were finally diagnosed

with either PAN (75 %) or MPA (25 %) [25]. Finally, in India, all patients previously unclassified could be diagnosed with either GPA or MPA [26]. This study also evaluated the newest CHCC 2012 nomenclature system, and found no difference from when the CHCC 1994 system was used.

A recent evaluation of the EMA algorithm using the most recent CHCC 2012 observed no negative effect associated with the reviewed nomenclature proposed, and the performance of the EMA held with the most recent definitions [27].

Newer Developments

All these systems use traditional methods. Newer approaches have recently become available. By use of a computational model, an artificial neuronal network (ANN) was used for diagnosing GPA and MPA and was compared with the ACR, the CHCC 1994, and the Sørensen criteria. In a process involving prior determination of the properties of the latter three criteria—which led to development of the ANN—coupled with traditional use of classification trees, the accuracy of the ANN based on four symptoms (nasal involvement, sinus disease, ear involvement, and presence of lung nodules) was 94 %. When coupled with use of logistic regression analysis, the accuracy was 93 %. Inclusion of ANCA in the analysis did not increase the accuracy. The authors state that it is useful to distinguish between MPA and GPA, which is not always easy, and they emphasise the weight placed on clinical data, which are the basis of the ANN method [28••]. Despite these results, a limitation of the ANN is that other diagnoses—either different vasculitides, or other diseases considered in the differential diagnosis of these conditions and having the same clinical manifestations—were not included. Also, some of the clinical data, including the first three, could be underestimated, either by physicians unfamiliar with these vasculitides, or by patients, something that happens in daily clinical practice.

In 2012 an important genome-wide association study from Europe revealed that the most common forms of ANCA-associated vasculitis (AASV) have different genetics [29••]. This, with the well-known clinical associations between GPA and MPA regarding prognosis, relapse, and treatment resistance [30–32], reinforces the theory that these two diseases will, in the future, be better defined by their associated autoantibody profile than by their clinical features.

Lionaki et al. recently revealed that categorisation of patients on the basis of their autoantibody profile (either MPO-ANCA or PR3-ANCA) performed better than the CHCC 1994 and the EMA algorithm in relation to specific outcome measures, including death, end-stage renal disease, relapse, and treatment-resistance. Both algorithms were unable to predict relapse, whereas classification on the basis of ANCA specificity did, and the other outcomes did not link to reliable predictors. This observation is of paramount importance: it has prognostic implications regarding both the diminished functional reserve of some organs with each bout of active disease, and the burden that re-treatment places on patients and the health system [33••].

Such relationships were analysed, using a different approach, by Mahr et al. Using cluster analysis with nine clinical variables as input, further conditioned by inclusion of the ANCA specificities, created models which provided the best hierarchically ascendant separation of patients enrolled in different European Vasculitis Society (EUVAS) trials. These models were related to outcomes including death and relapse. Of 673 patients with GPA or MPA, 651 (97 %) fit into any of five clusters (renal AASV with PR3-ANCA, renal AASV without PR3-ANCA, non-renal AASV, cardiovascular AASV, and gastrointestinal AASV; the latter three were less affected by the inclusion of ANCA specificities in the second model), all of which had different outcomes. This indicates that ANCA specificities probably have a function in defining disease behaviour; that proof of this concept could be more useful than merely separating the AASV into GPA and MPA; and that subcategorisation of these AASV by the presence of specific and better-defined clinical characteristics, with the input of ANCA specificities, may be better. However, as the authors stated, the last two clusters arose unexpectedly, and clinical manifestations attributable to AASV are much less frequent in such systems than other manifestations. This approach needs validation in other populations. Although the data used came from trials which collected information prospectively, bias might not be completely excluded and might affect the input used to create the models. One possible bias is that these trials mainly enrolled patients with renal disease, including fewer with localised forms of GPA: such patients, although probably included in the non-renal AASV cluster as expected, might still have been underrepresented [34••].

The results of both previously discussed studies, in which ANCA subtyping defines groups with different long-term evolutions, have led to the belief that incorporating ANCA into classification exercises is useful. Several recent articles support this notion, and we think it reasonable to suppose that this incorporation might take not long to occur [35–37]. It remains to be seen how the incorporation of specific histopathological features might further distinguish the groups; for example, a patient who is PR3-ANCA positive could have a different outcome, associated with the presence or predominance of usually distinct and clear-cut findings of granulomas, vasculitis, or both. Although it could be believed that such histopathological findings are linked with well-known clinical manifestations, incorporation of these characteristics into similar methods seems reasonable. A puzzling question would be raised if the same patient has both lesions, or when disease follows a course that would involve shifting from one type of

lesion to the other. Such possibilities have been proposed recently [38].

Ultimately, new methods make possible the development of better classification systems, based on the acquisition of biological knowledge. This would have more weight than systems based on the clinical manifestations which, although they do ultimately reflect the consequences of the interplay between genetic, environmental, and immunological pathophysiological mechanistic factors, are of limited use when distinction between similar diseases is the objective.

The lack of diagnostic criteria means that these, by nature imperfect, current classification systems suffer from disadvantages that make their use difficult. This holds true for many diseases whose origin is still obscure, and well-founded critics reasonably exist. This is even more evident for diseases (e.g. Behçet's disease) which are less common than those discussed here [39••]. However, while waiting for diagnostic criteria to be developed, classification systems have nonetheless been useful. They have enabled advancement in the design of many trials, and have both brought about multidisciplinary efforts leading to some questions being answered and, very importantly, raised doubts that will continue to increase interest in these complex diseases.

Conclusions

To date, all classification criteria are imperfect. Their usefulness must be evaluated in different settings, testing their strength and validity in diverse locations and circumstances, to determine which has better applicability. This applicability will depend on the conditions under which they are evaluated, and the purposes for which they are to be used. The different criteria have been interchangeably used as diagnostic surrogates; this will probably change in the future, with the results that will arise from the Diagnostic and Classification Criteria for Vasculitis (DCVAS) [40]. The development of diagnostic criteria is subject to perennial review, and future proposals will be continually replaced, until the knowledge of defined disease mechanisms advances and, more importantly, the aetiology of these diseases is finally revealed.

Compliance with Ethics Guidelines

Conflict of Interest Luis Felipe Flores-Suárez and Felipe de J. Contreras-Rodríguez declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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