Evaluation of a new algorithm in classification of systemic vasculitis

L.-J. Liu, M. Chen, F. Yu, M.-H. Zhao and H.-Y. Wang

Objective. Recently, a new consensus algorithm for classification of ANCA-associated vasculitis (AAV) and PAN had been proposed by Watt et al. for epidemiological studies. In order to evaluate this algorithm, the current study used the algorithm to reclassify the patients with AAV and PAN in our centre.

Methods. Five hundred and fifty Chinese patients with primary systemic vasculitis diagnosed in our referral diagnostic centre during the past 10 years were retrospectively studied. Four hundred and ninety-three out of 550 were ANCA positive. We compared the new consensus algorithm and the 1994 Chapel Hill Consensus Conference (CHCC) definitions supplemented with surrogate parameters, in the same cohort of patients with primary systemic vasculitis.

Results. Applying the CHCC definitions with surrogate parameters, the diagnoses were Churg–Strauss syndrome (CSS) (n=0), WG (n=127), microscopic polyangiitis (MPA) (n=363), PAN (n=4) and unclassified (n=56). Using the new consensus algorithm, the diagnoses were CSS (n=2), WG (n=199), MPA (n=329), PAN (n=0) and unclassified (n=20).

Conclusions. Watts’ algorithm was a useful method to classify patients into a single category, with less unclassified patients and without overlapping diagnosis, which allows their use in epidemiological studies.

Key words: Watts’ algorithm, ANCA, classification, AAV, PAN.

Introduction

The classification of systemic vasculitis has remained controversial during the past years. Two main classification systems had been proposed for a long time—the 1990 ACR criteria [1] and the 1994 Chapel Hill Consensus Conference (CHCC) definitions [2]. However, the above two classification systems were not perfect in several aspects. The 1990 ACR criteria were derived from the analysis of a large number of systemic vasculitis cases. It was designed to provide a standard method of describing groups of patients for research and had the highest discriminating value to distinguish one syndrome from another, but not to distinguish vasculitis from other diseases. It did not include microscopic polyangiitis (MPA) as a disease entity or ANCA as a potential marker of vasculitis was therefore introduced, but a list of classification or diagnostic criteria [4]. The concept of surrogate markers of vasculitis was therefore introduced, but a list of markers was not well defined. Sorensen et al. [5] provided a concise surrogate marker to CHCC for glomerulonephritis and granulomatous inflammation for clinical practice. However, the use of one of the two systems alone would lead to more unclassified patients and/or overlapping diagnosis.

The methodology used in the classification of ANCA-associated vasculitis (AAV) differed from one centre to another. Watts et al. had recently proposed a new consensus algorithm for the classification of systemic vasculitis including AAV and PAN [6]. They considered the ACR criteria together with the CHCC definitions and the Lanham criteria for Churg–Strauss syndrome (CSS). The aim of their algorithm was to classify patients with a clinical diagnosis of AAV and PAN, for the purpose of classification in epidemiological studies. PAN was included in the algorithm because patients classified as PAN by ACR might be diagnosed as MPA by the CHCC [6]. In this algorithm, ACR criteria for CSS and WG were given highest priority and were designed as classification criteria. In addition, the diagnosis of CHCC-MPA was established on the basis of exclusion of CSS and WG, and surrogate markers for WG were included to distinguish WG from MPA. MPA was classified using the CHCC definition and surrogate markers for renal vasculitis. In order to evaluate this algorithm, the current study used the algorithm to reclassify the patients with AAV and PAN in our centre.

Patients and methods

Patients

Five hundred and fifty consecutive patients, diagnosed as primary vasculitis from January 1997 to June 2007 in our referral diagnostic centre of Peking University First Hospital, were recruited in this study. All the patients fulfilled the three entry criteria (Table 1) [6] required by Watts’ algorithm with complete clinical data and 166 of them had histological data. Four hundred and ninety-three out of them were ANCA positive. All the patients were older than 16 yrs according to the requirement of Watts’ algorithm.

We applied the 1994 CHCC definitions to all patients, who were therefore defined as PAN, MPA, WG, CSS or undefined [2]. The surrogate parameters used are shown in Table 2 [5]. Patients were then classified according to Watts’ algorithm strictly (Fig. 1) [6]. Ethical approval was obtained for this study from the local ethics committee.

ANCA tests

ANCA tests were performed by both IIF assay and antigen-specific ELISAs (for PR3-ANCA and MPO-ANCA) for all patients at the time of presentation before immunosuppressive treatment was instituted.

Results

The distribution of ANCA

Four hundred and ninety-three out of 550 patients were ANCA positive by both IIF assay and antigen specific ELISAs. Four hundred and sixteen (75.64%) and 75 (13.64%) patients were pANCA and cANCA positive respectively, and other two...
A. Symptoms and signs characteristic or compatible with a diagnosis of AAV or PAN.

B. At least one of the following:
   (i) Histological proof of vasculitis (including necrotising glomerulonephritis) and/or granuloma formation
   (ii) Positive serology for ANCA (PR3-ANCA or MPO-ANCA). Indirect immunofluorescence result alone is only acceptable if ELISA is unavailable in a centre or the diagnosis made prior to 1995.
   (iii) Specific investigations strongly suggestive of vasculitis and/or granuloma from angiography (either magnetic resonance angiography or coeliac axis angiography in PAN), thoracic or neck MRI/CT imaging (showing retro-orbital or tracheal disease), neurophysiology
   (iv) Eosinophilia (>10% or >1.5 x 10^9/l)

C. No other diagnosis to account for symptoms/signs. The following are specifically excluded:
   (i) Malignancy
   (ii) Infection (including hepatitis B and C, HIV, tuberculosis, subacute bacterial endocarditis)
   (iii) Drugs (including hyalurazine, propylthiouracil, cocaine and allopurinol)
   (iv) Secondary vasculitis—PA, SLE, SS, CTD
   (v) Behcet’s disease, Takayasu’s arteritis, giant cell arteritis, Kawasaki’s disease, essential mixed cryoglobulinaemia, Henoch–Scho¨nlein purpura, anti-GBM disease
   (vi) Vasculitis mimics—e.g. cholesterol embolism, calciphylaxis, catastrophic antiphospholipid antibody syndrome, atrial myxoma
   (vii) Sarcoidosis and other non-vasculitic granulomatous disease

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**Table 2. Surrogate parameters for vasculitis**

<table>
<thead>
<tr>
<th>Organ involvement</th>
<th>Surrogate parameters</th>
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<tbody>
<tr>
<td>Glomerulonephritis</td>
<td>Proteinuria and haematuria with red blood cell casts</td>
</tr>
<tr>
<td>Arteritis</td>
<td>Angiographic or ultrasonar demonstration of aneurysms or stenoses in arteries provided the patient demonstrated other signs of vasculitis</td>
</tr>
<tr>
<td>Granulomatous inflammation in lower airways</td>
<td>Radiologically demonstrated pulmonary infiltrates or cavitations of more than 1 month’s duration provided that all other causes such as infections and malignancies were ruled out</td>
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<tr>
<td>Granulomatous inflammation in upper airways</td>
<td>Bloody nasal discharge and/or crusting of more than 1 month’s duration; chronic sinusitis, otitis and/or mastoiditis (proved by radiograph, CT or MRI); cranial bone and/or cartilage destruction; acute hearing loss, without signs of traumatic disease</td>
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patients (0.36%) were both pANCA and cANCA positive. Among the 416 patients who were pANCA positive, 408 were MPO-ANCA positive and eight were both MPO-ANCA and PR3-ANCA positive. Seventy-four out of 75 patients with cANCA were PR3-ANCA positive, and the remaining patient was both MPO-ANCA and PR3-ANCA positive. Among the two patients with both pANCA and cANCA, one was MPO-ANCA positive, the other was both MPO-ANCA and PR3-ANCA positive. In summary, 408 (74.18%) and 75 (13.64%) were ANCA positive, the other was both MPO-ANCA and PR3-ANCA positive. Among the two patients with both pANCA and cANCA, one was MPO-ANCA positive, the other was both MPO-ANCA and PR3-ANCA positive. The other 57 patients (10.36%) were ANCA negative (Table 3).

**Histology**

Biopsy specimens were obtained in 166 patients. Sixteen patients had a biopsy of respiratory tract showing granulomatous inflammation, and 12 patients with extra-respiratory biopsy suggesting granulomatous inflammation. Six patients had skin biopsies which showed necrotizing inflammation of small arteries. Eosinophil-rich inflammation involving the nervous system could be found in one patient. One hundred and thirty-one patients had eosinophilic crescentic and/or necrotizing glomerulonephritis. Patients without biopsy or biopsy without granulomatous inflammation were classified as WG according to the surrogate markers mentioned earlier [3] (Table 2).

**Comparison of Watts’ algorithm and the CHCC classification**

Comparisons were made using the CHCC classification and Watts’ algorithm. Applying the CHCC classification, 127, 363, 0 and 4 patients were classified as WG (CHCC-WG), microscopic polyangiitis (CHCC-MPA), CSS (CHCC-CSS) and PAN (CHCC-PAN), respectively. The remaining 56 patients were unclassified. The application of Watts’ algorithm was summarized as follows: of the 127 CHCC-WG, all could be classified into WG in Watts’ algorithm system. Among the 363 patients with CHCC-MPA, two (0.6%) patients were classified as CSS and 37 (10.2%) patients were classified as WG. Four (100%) patients with CHCC-PAN were all classified as MPA. In the 56 unclassified patients, 25 (44.6%) fulfilled the ACR criteria for WG and were defined as WG; another 10 (17.9%) patients without necrotizing vasculitis were re-classified as WG because of histology compatibility with CHCC WG; one patient with haematuria associated with dysmorphic red blood cells and without proteinuria was re-classified as MPA. The classification changes are shown in Fig. 2.

**Discussion**

The classification of primary vasculitis is a long-debated question. Many patients might fulfil more than one set of criteria. In particular, the specificity of the criteria for ACR-PAN was low. Many cases that could be classified as ACR-PAN also fulfilled the definitions for WG, CSS or MPA [5]. The CHCC definitions aimed to develop a consensus on the nomenclature of the major non-infectious vasculitis and provided working definitions of 10 different types of vasculitis. Though widely used, neither ACR criteria nor CHCC definitions provided an effective method of classifying primary systemic vasculitis [7]. Bruce and Bell [4] had found significant discordance between these two proposed systems for the nomenclature of primary systemic vasculitis.

CHCC definition with surrogate markers had been applied in two clinical attempts. In the European Union Vasculitis Study Group (EUVAS) trial, the CHCC definition was applied [8]. Hagen also used the definition in assessing the standardization of ANCA assays [9].

In the past, Lane et al. [10] used both CHCC and ACR definition in epidemiological studies. But some criteria in their attempt were not easy to take into practice sometimes. Recently, Watts et al. [6] proposed their new consensus algorithm in patients...
with a clinical diagnosis of AAV and PAN for the purpose of classification in epidemiological studies. Though the methodology had been validated twice by themselves, there were not any validation attempts by other authors. In the current study, Watts’ new algorithm was evaluated in patients with vasculitis in our centre.

Watts’ algorithm was employed to make a clinical diagnosis of AAV and PAN. Because ANCA were not necessary in the entry criteria and definitions [4], 493 out of the 550 patients enrolled in this study were ANCA positive, the others were ANCA negative but fulfilled the entry criteria.

The CHCC definition was well accepted by most studies. Therefore, this study just applied the new algorithm to classify the patients with primary systemic vasculitis and compared it with the CHCC definition supplemented with surrogate markers.

In the new algorithm, diagnoses of CSS and WG were given high priority. Therefore, all the 127 CHCC-WG patients could be classified as WG by the new algorithm.

CHCC-MPA was a group of patients with different diagnoses in the new algorithm. Two were re-classified as CSS. These two patients had asthma and peripheral eosinophilia (>10% of white cell count), one patient also had eosinophil-rich inflammation.
with necrotizing vasculitis in a biopsy of peripheral nerve. Because none of them had respiratory tract involvement other than asthma, therefore, no patient could be defined as CHCC-CSS. However, they both fulfilled the ACR criteria, and could be classified as CSS in the new algorithm. The number of patients with CSS would be increased because of the highest priority given to CSS by the new algorithm.

In the CHCC-MPA, 37 out of the 363 were re-classified as WG. All of them had nasal or oral inflammation or extra-respiratory tract granulomatous inflammation and fulfilled the ACR criteria for WG which was included in the definition of the new algorithm. The nasal or oral inflammation or extra-respiratory tract granulomatous inflammations of patients were unacceptable criteria for WG by CHCC definition.

Four patients with CHCC-PAN were all reclassified as MPA because of the application of MPA criteria prior to PAN criteria in the new algorithm. None of the four patients had glomerulonephritis, but skin biopsies showed necrotizing vasculitis of medium-sized or small arteries.

In the 56 unclassified patients, 25 patients who had nasal or oral inflammation and renal involvement with only haematuria could fulfill the ACR criteria for WG. Another 10 patients, without necrotizing vasculitis proved by biopsies and surrogate markers, were classified as WG, because histology was compatible with CHCC-WG. One patient with dysmorphic haematuria and without proteinuria was re-classified as MPA. Therefore, the new algorithm did not have stricter surrogate markers of renal involvement than those shown in Table 2. The number of unclassified patients reduced from 56 to 20 by the use of surrogate markers defined for WG and renal disease. Therefore, using Watts’ algorithm, the number of unclassifiable patients was minimized.

In this study, none was classified as PAN using the new algorithm. It might be due to the low priority to PAN. In our experience, patients with typical manifestations of systemic vasculitis and positive ANCA but without renal involvement or biopsy-proven vasculitis were always diagnosed as systemic vasculitis. However, in the new algorithm, these patients could not be classified into any one category. Some revision might be made in order to improve the new algorithm in the future.

We realized that the new algorithm could not reflect the underlying pathological processes or different aetiology. The reason of the limitation was that it gives priority to CSS and WG definition without considering pathological, aetiology and prognostic factors strictly. The shortcoming of Watts’ algorithm limited its use in some clinical researches, but it provided a better method in epidemiology application.

In our study, there was a high percentage of pANCA and MPO-ANCA positive patients in the WG group, which differed from other studies of WG. The reason was that more Chinese patients with WG were pANCA and MPO-ANCA positive, as our previous study suggested [11, 12]. It might be the epidemiological feature of Chinese patients with WG.

In conclusion, when entry criteria were fulfilled, using Watts’ algorithm could classify vasculitis patients into a single category with less unclassified patients and without overlapping diagnosis. The advantage of Watts’ algorithm made it easy to apply in clinical classification for AAV and PAN in epidemiological studies.

**Table 3. Distributions of ANCA**

<table>
<thead>
<tr>
<th></th>
<th>CHCC</th>
<th>Watts’ methodology</th>
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<tbody>
<tr>
<td></td>
<td>CSS</td>
<td>WG</td>
</tr>
<tr>
<td>MPO-ANCA (+)</td>
<td>0</td>
<td>87</td>
</tr>
<tr>
<td>PR3-ANCA (+)</td>
<td>0</td>
<td>22</td>
</tr>
<tr>
<td>ANCA (-)</td>
<td>0</td>
<td>14</td>
</tr>
<tr>
<td>Both (+)</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>0</td>
<td>127</td>
</tr>
</tbody>
</table>

**FIG. 2. The classification changes.**

Un: unclassified patients

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**Rheumatology key message**

- A large sample of 550 patients were used to evaluate the algorithm for the classification of vasculitis. It was found that the algorithm allows their use in epidemiological studies.

**Acknowledgements**

**Funding:** The work was supported by the National Natural Science Fund (30600557) and the Chinese 985 project (985-2-104-113).

**Disclosure statement:** The authors have declared no conflicts of interest.

**References**


