Clinical and pathological characteristics of Chinese patients with antineutrophil cytoplasmic autoantibody associated systemic vasculitides: a study of 426 patients from a single centre

M Chen, F Yu, Y Zhang, M H Zhao

Background: Antineutrophil cytoplasmic autoantibodies (ANCA) are serological markers of ANCA associated systemic vasculitides (AASV), which is one of the most common multisystem autoimmune diseases. Features of Chinese patients with AASV have not been fully investigated.

Objective: To analyse the clinical and pathological characteristics of Chinese patients with AASV.

Methods: 426 Chinese patients with AASV diagnosed in the past eight years were retrospectively studied and their clinical and pathological data were analysed.

Results: Of the 426 patients, 87 (20.4%) were Wegener’s granulomatosis, 337 (79.1%) were microscopic polyangiitis and two (0.5%) were Churg-Strauss syndrome. Only 201 of 426 (47.2%) patients were diagnosed within three months. Clinically, the patients had multisystem involvement. Altogether 371 of 426 (87.1%) had kidney involvement and 260 of 426 (61.0%) had lung involvement. The prevalences of renal involvement and fatigue were significantly higher in patients with MPO-ANCA than that in patients with PR3-ANCA; the prevalences of ophthalmic, nasal involvement, rash, and arthragia were significantly higher in patients with PR3-ANCA than those in patients with MPO-ANCA. The one and five year death rates were 13.1% and 22.4%, respectively. The percentage of patients progressing to end stage renal disease at one and five years was 15.9% and 27.1%, respectively.

Conclusions: AASV is not a rare autoimmune disease in Chinese people. Kidney and lung were the most vulnerable organs. For patients with multorgan damage, an ANCA test should be performed to make an early diagnosis and to start treatment in time.

AASV is one of the most common multisystem autoimmune diseases in the white population. A population based study from Norfolk, England, reported incidences of 8.5 cases per million for WG, 3.6 cases per million for MPA, and 2.4 cases per million for the CSS. In two large US cohorts studies of patients with WG, white people comprised more than 90% of all cases. Regional, geographical, ethnic, and seasonal differences in disease patterns and increasing incidence have been suggested, but lack confirmation. Studies from Norway suggested a doubling incidence of WG from 1992–1994 to 1995–1998. These figures probably reflect a real increase in incidence as well as improved awareness and diagnosis. AASV can occur at any age, especially elderly people.

The incidence of AASV in the Chinese population is unknown. In the early 1990s, after IIF-ANCA and ELISA using crude neutrophil acid extracts as solid phase ligands were established, a retrospective study of 50 hospitalised Chinese patients with crescentic glomerulonephritis or end stage renal disease showed that five of the 50 patients were ANCA positive. With the commercial IIF-ANCA kits being available and purified MPO and PR3 being used in routine ANCA screening assays, the prevalence of AASV increased substantially. In the past eight years, 426 patients with AASV were diagnosed in Peking University First Hospital. The

Abbreviations: ANCA, antineutrophil cytoplasmic autoantibodies; AASV, ANCA associated systemic vasculitides; WG, Wegener’s granulomatosis; MPA, microscopic polyangiitis; CSS, Churg-Strauss syndrome; ACR, American College of Rheumatology; ANA, antinuclear antibodies; ESR, erythrocyte sedimentation rate; MMF, mycophenolate mofetil; MPO, myeloperoxidase
prevalence of ANCA and the antigen specificities, as well as demographic features of some of the Chinese patients with AASV was investigated. It was suggested that AASV might not be rare in the Chinese population. In this study, the clinical and pathological manifestations of the Chinese patients with AASV were investigated.

METHODS

Patients

A total of 426 patients with AASV, diagnosed from 1997 to 2004 in the Institute of Nephrology, Peking University First Hospital, were enrolled into this retrospective study. All the patients met the criteria of the Chapel Hill consensus conference definition (for WG, MPA, or CSS) and ACR classification criteria (for WG or CSS). Systemic lupus erythematosus, Henoch-Schönlein purpura, rheumatoid arthritis were excluded. Acute renal failure was defined by the presence of progressively raised serum creatinine or 15% declined clearance rate of serum creatinine on the baseline within days or weeks. Clinical data were collected and analysed according to the organ involved.

IIF assay to detect ANCA

Standard IIF assay was performed according to the manufacturer (EUROIMMUN, Lübeck, Germany). Ethanol fixed human polymorphonuclear leucocytes (PMN) were used to detect ANCA and monkey liver sections were used to exclude antinuclear antibodies (ANA). cANCA and pANCA were distinguished according to staining patterns by two experienced technicians.

Antigen specific ELISAs

Two highly purified known ANCA antigens, PR3 and MPO, were used as solid phase ligands in ELISA, as previously reported.

Pathological examination

Renal pathological data of 122 cases were evaluated using direct immunofluorescence, light and electron microscopy. Specimens of kidney were required to have a minimum of 10 direct immunofluorescence, light and electron microscopy.

Figure 1

Patients with AASV diagnosed chronologically.
50% glomeruli had large crescents formation), and 11 (9.02%) had granulomatous lesion in renal interstitium.

**Pulmonary manifestations**

Two hundred and sixty cases (260 of 426, 61.0%) had lung symptoms such as cough, often with sputum production, of which 104 (40.0%) had haemoptysis. One hundred and fifty cases had alveolar infiltrates or interstitial changes on chest films or computed tomography, of which 130 cases (86.7%) had shadows in one or both lungs and 79 (52.7%) had pulmonary interstitial fibrosis, multiple nodules, or cavitations.

**Manifestations of other organs**

Of the 426 patients, 83 cases (19.5%) had ophthalmic disease manifested as conjunctivitis, keratohelesis, episcleritis and uveitis, optical nerve vasculitis, and declining vision. Ninety-nine cases (23.2%) had ear involvements, manifested as sinusitis, stuffiness, epistaxis, and brown or bloody crusts, rhinitis, septal erosions, or even perforation of the tympanic membrane, and declining tinnitus, perforation of the tympanic membrane, and declining vision. Ninety cases (21.7%) had neurological disorders such as peripheral mononeuritis multiplex, dizziness, headache, and coma. Three patients had cerebral haemorrhage. One patient had Guillain-Barre syndrome (fig 2).

Further analysis showed that the prevalences of renal involvement and fatigue were significantly higher in patients with MPO-ANCA than those in patients with PR3-ANCA involvement and fatigue were significantly higher in patients with MPO-ANCA than that in patients with PR3-ANCA (90.2% vs 79.7%, $\chi^2 = 6.21$, $p<0.05$; 63.7% vs 46.4%, $\chi^2 = 7.24$, $p<0.01$, respectively); the prevalences of ophthalmic, nasal involvement, rash, and arthralgia were significantly higher in patients with PR3-ANCA than those in patients with MPO-ANCA (31.9% vs 16.7%, $\chi^2 = 8.53$, $p<0.01$; 21.7% vs 5.76%, $\chi^2 = 19.1$, $p<0.01$; 27.5% vs 16.4%, $\chi^2 = 4.76$, $p<0.05$; 43.5% vs 28.0%, $\chi^2 = 6.54$, $p<0.05$, respectively) (table 2).

**Laboratory findings**

A total of 300 of 337 cases (89.0%) had anaemia, of which only 83 cases (27.7%) had mild anaemia with haemoglobin (Hb) over 90 g/l. 172 cases (53.3%) had moderate anaemia with Hb between 60 and 90 g/l, and 45 (15.0%) had severe anaemia with Hb less than 60 g/l. Altogether 125 of 287 (43.6%) cases had leucocytosis and 56 of 195 (28.7%) had thrombocytosis. A total of 265 of 285 cases (93.0%) had raised erythrocyte sedimentation rate (ESR), of which 92 (34.7%) were over 100 mm 1st h and 178 (67.2%) were over 60 mm 1st h. Altogether 132 of 185 cases (71.4%) had raised C reactive protein. No significant difference was found in these laboratory findings between PR3-ANCA and MPO-ANCA positive patients.

**Outcomes**

A total of 44 of 130 (33.8%) and 86 of 130 (66.2%) cases received prednisone together with daily oral or monthly intravenous CTX, respectively. After the induction phase treatment, 105 of 130 (88.5%) cases had complete or partial remission. One hundred and seven cases were followed up. The average duration of follow up was 29.7 (1–108) months. A total of 24 of 107 (22.4%) patients died and 29 of 107 (27.1%) patients progressed to end stage renal disease and received renal replacement treatment. The one and five year death rates were 13.1% and 22.4%, respectively. The percentage of patients progressing to end stage renal disease at one and five years was 15.9% and 27.1% respectively.

**DISCUSSION**

AASV is one of the most common multisystem autoimmune diseases in the white population. It is an important cause of mortality (if untreated) and morbidity (despite current aggressive treatment). The annual incidence and point prevalence of renal vasculitis in Europe is 10–20/million/year and 150–200/million, respectively. In China, after improved awareness and diagnostic techniques, more patients with AASV were diagnosed in recent years, but there is lack of systemic investigation on incidence. Over 400 patients with AASV were diagnosed in our centre in the past eight years and the number of patients increased chronologically. It was suggested that AASV was not rare in China.

In this study, it was found that the average age of Chinese patients with AASV was 56.1 (ranging from 5 to 83) years old. Over 40% of the cases were more than 65 years old, and nearly 1 of 10 of the cases were younger than 20 years old, showing that AASV could affect people of all age—elderly people were more susceptible, but children and teenagers were not rare. This is consistent with our previous studies and similar to the white population. In China, after improved awareness and diagnostic techniques, more patients with AASV were diagnosed in recent years, but there is lack of systemic investigation on incidence. Over 400 patients with AASV were diagnosed in our centre in the past eight years and the number of patients increased chronologically. It was suggested that AASV was not rare in China.

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FIGURE 2 Prevalences of organ involvement.

**Table 1** ANCA results of serum samples in IIF and ELISA

<table>
<thead>
<tr>
<th>ANCA</th>
<th>anti-PR3</th>
<th>anti-MPO</th>
<th>anti-PR3 and MPO</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>cANCA</td>
<td>69</td>
<td>0</td>
<td>1</td>
<td>70</td>
</tr>
<tr>
<td>pANCA</td>
<td>0</td>
<td>346</td>
<td>8</td>
<td>354</td>
</tr>
<tr>
<td>cANCA and pANCA</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>Total</td>
<td>69</td>
<td>347</td>
<td>10</td>
<td>426</td>
</tr>
</tbody>
</table>
AASV is characterised by multisystem involvement. All the above-mentioned findings showed that 23% also suffered from auditory, ophthalmic, and nasal involvement respectively. They were often neglected by clinicians and these might be underestimated in this retrospective study. Besides visceral vasculitis, about 8% to 43% and 15.7% of the cases had gastrointestinal and nervous system involvements, respectively. More than 60% had pulmonary involvement, with 40% having pulmonary haemorrhage, which was the major cause of acute respiratory failure or death. Although 43% and 15.7% of the cases had gastrointestinal and nervous system involvements respectively, they were often neglected by clinicians and these might be under-evaluated in this retrospective study. Besides visceral vasculitis, about 8% to 23% also suffered from auditory, ophthalmic, and nasal involvements. All the above-mentioned findings showed that AASV is characterised by multisystem injury.

Although cANCA/PR3-ANCA was mainly found in patients with WG and pANCA/MPO-ANCA was mainly found in patients with MPA and iRPGN, it was not exclusive. Our study also found that there were some differences in the clinical manifestations between patients with PR3-ANCA and MPO-ANCA. The prevalences of fatigue and renal involvement were significantly higher in patients with MPO-ANCA than those in patients with PR3-ANCA. The prevalences of ophthalmic, nasal involvement, rash, and arthralgia were significantly higher in patients with PR3-ANCA than those in patients with MPO-ANCA. Some authors argued that one of the possible reasons for higher proportion of renal disease in patients with MPO-ANCA than those with PR3-ANCA might be attributable to the delay of diagnosis. More patients with PR3-ANCA positive had upper respiratory and ophthalmic involvements, which probably reduce the patients' and doctors' delay. Earlier diagnosis and start of treatment might reduce the frequency of renal involvements. In this study, however, there is no significant difference of the intervals between onset of disease and diagnosis between PR3-ANCA and MPO-ANCA groups. Whether there are different mechanisms in the pathogenesis of renal disease in these ANCA subsets remains unclear.

<table>
<thead>
<tr>
<th>Table 2 Clinical manifestations of 426 patients with AASV</th>
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</thead>
<tbody>
<tr>
<td><strong>Frequency (%)</strong></td>
</tr>
<tr>
<td>Fever</td>
</tr>
<tr>
<td>Fatigue*</td>
</tr>
<tr>
<td>Weight loss</td>
</tr>
<tr>
<td>Muscle pain</td>
</tr>
<tr>
<td>Arthralgia*</td>
</tr>
<tr>
<td>Rash*</td>
</tr>
<tr>
<td>Renal*</td>
</tr>
<tr>
<td>Pulmonary</td>
</tr>
<tr>
<td>Ophthalmic**</td>
</tr>
<tr>
<td>Ear</td>
</tr>
<tr>
<td>Nasal**</td>
</tr>
<tr>
<td>Gastrointestinal</td>
</tr>
<tr>
<td>Nerve system</td>
</tr>
</tbody>
</table>

*p<0.05; **p<0.01.

The prognosis of untreated AASV is poor, with up to 90% of patients dying within two years. Early diagnosis is crucial, otherwise life-threatening disease such as acute renal failure or respiratory failure may develop quickly. In this study, unfortunately, more than 40% of the patients were diagnosed six months after onset of the disease, and more than 10% of the cases were more than one year, which would undoubtedly worsen the prognosis. This showed that the awareness of this disease still needs to be improved in clinicians. Vassilopoulos reported that in patients with severe multi-organ dysfunction or pulmonary disorders, there was a high prevalence of ANCA. Therefore, for the suspected patients, prompt ANCA detection is crucial for the early diagnosis of AASV.

CONCLUSION
AASV is not rare in the Chinese population. Renal and pulmonary involvement was common and life-threatening. For patients with multisystem involvement, ANCA testing using both IIF and antigen-specific ELISA is recommended and it provides a helpful tool facilitating earlier diagnosis.

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Ethics approval and patient consent: this research was approved by the ethics committee of Peking University First Hospital (Peking University First Hospital, Beijing 100034, PR China) and with informed consent of patients.
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