
Clinical analysis of nervous system involvement in ANCA-associated systemic vasculitides

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ABSTRACT

Objective. To assess the clinical features of nervous system (NS) involvement in patients with ANCA-associated vasculitides (AAV), including microscopic polyangiitis (MPA), Wegener's granulomatosis (WG), and Churg-Strauss syndrome (CSS).

Methods. One hundred and seventy-nine patients admitted to Peking Union Medical College Hospital from 1995 to 2008, including 93 cases of MPA, 61 cases of WG, and 25 cases of CSS, were enrolled in this study. Medical charts including demographic data, clinical features, laboratory findings, treatments and outcomes were systematically reviewed.

Results. NS involvements were observed in 36.6% of MPA, 50.8% of WG, and 76.0% of CSS patients. Peripheral neuropathy predominated in each type of AAV. In CSS and MPA, the majority was mononeuritis multiplex and distal symmetrical polyneuropathy, whereas, differently, 64.5% of WG patients with NS involvement had cranial neuropathy. Central nervous system (CNS) involvement accounted for 21.1%, 29.4%, and 32.3% of neuropathy respectively in CSS, MPA and WG patients, including arachnoid hemorrhage, cerebrovascular neuropathy, meningitis, and diffuse brain damage. 157 (87.7%) AAV patients responded to treatment with high dose of prednisone plus immunosuppressants. Thirteen (14.0%) MPA and four (6.6%) WG patients died. The leading causes of death were diffuse alveolar hemorrhage (DAH) (6, 35.3%) and infection (6, 35.3%). No patient died directly of neuropathy.

Conclusion. NS involvement was common in AAVs and the characteristic of NS involvement was different among MPA, WG and CSS patients. DAH and infection instead of NS damage remained the leading causes of death in AAVs.

Introduction

Nervous system (NS) involvement is one of the common clinical manifestations of anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV), including microscopic polyangiitis (MPA) (1), Wegener's granulomatosis (WG) (2, 3), and Churg-Strauss syndrome (CSS) (4, 5). In some patients, NS manifestation could be presenting feature of these diseases. In this study, we assessed clinical characteristics and outcomes of 179 Chinese AAV patients, emphasizing on their NS involvement.

Patients and methods

Patients

One hundred and seventy-nine patients admitted to Peking Union Medical College Hospital from 1995 to 2008, including 93 cases of MPA, 61 cases of WG and 25 cases of CSS, were retrospectively studied. Medical charts of these patients were systematically reviewed for demographic data, clinical features, laboratory findings, treatments as well as outcomes. Disease activities were assessed by the Birmingham Vasculitis Activity Score (BVAS) (6).

Diagnostic criteria

The Chapel Hill Consensus Conference definitions for MPA and CSS (7) and the American College of Rheumatology criteria for WG (8) were applied in this study.

Statistical analysis

Results were expressed as mean (\pm SD) and data were analyzed using SPSS10.0. Comparisons between groups were carried out using the Student's two-tailed *t*-test and Chi-square test.

Results

Clinical manifestations of AAV

Table I shows clinical manifestations of AAV. The age of onset in MPA was elder than in other two diseases

Table I. Clinical features of CSS, WG and MPA patients.

	CSS (n=25)	WG (n=61)	MPA (n=93)
M : F	16 : 9	29 : 32	44 : 49
Age of onset (ys) [§]	45. ± 16.5	43.2 ± 17.8	56.5 ± 7.6
Duration (months)	15.0 ± 10.8	11.9 ± 9.2	7.1 ± 6.4
Fever	12 (48.0%)	46 (75.4%)	65 (69.9%)
Skin and mucosa [#]	20 (80.0%)	20 (32.8%)	25 (26.9%)
Renal involvement [#]	6 (24.0%)	39 (63.9%)	82 (88.2%)
Lung involvement	16 (64.0%)	46 (75.4%)	73 (78.5%)
GI involvement	10 (40%)	20 (32.8%)	30 (32.3%)
Cardiac involvement ^{**}	6 (24%)	2 (3.3%)	22 (23.7%)
Nervous system [*]	19 (76.0%)	31 (50.8%)	34 (36.6%)
Elevated ESR	21 (84%)	57 (93.4%)	88 (94.6%)
Leucocytosis [#]	23 (92.0%)	36 (59.0%)	48 (51.6%)
ANCA [#]	6 (24.0%)	51 (83.6%)	73 (78.5%)
MPO-ANCA	4 (16.0%)	11 (18.0%)	67 (72.0%)
PR3-ANCA	1 (4.0%)	39 (63.9%)	3 (3.2%)

Data shown as mean±SD or number of cases (percentage).

GI: gastrointestinal tract; ANCA: anti-neutrophil cytoplasmic antibody; ESR: Erythrocyte sedimentation rate; WG: Wegener's granulomatosis; MPA: microscopic polyangiitis; CSS: Churg Strauss syndrome.

[§]CSS vs. MPA and WG vs. MPA, $p<0.05$; ^{*}CSS vs. MPA, $p<0.05$; ^{**}WG vs. CSS and WG vs. MPA;

[#]CSS vs. WG and CSS vs. MPA, $p<0.05$.

($p<0.05$). Skin and mucosa involvements were more frequently seen in CSS than in MPA and WG ($p<0.05$). Cardiac involvement was rarer in WG patients than in MPA and CSS patients ($p<0.05$), whereas renal involvement was less in CSS than in MPA and WG patients ($p<0.05$).

The positive rate of ANCA by immunofluorescence assay was the lowest in CSS patients (24%), the highest in WG patients (83.6%). Most ANCA in CSS and MPA targeted against myeloperoxidase (MPO), which was different from ANCA in WG patients.

It is noteworthy that most CSS patients (92%) had elevated white blood cell count, ranging between 12,500/mm³ and 38,000/mm³, in which eosinophils accounted for 20.1% to 60%. Fifteen CSS patients underwent bone marrow examination, and thirteen of them revealed increased eosinophils (12.5% – 52.5%).

Initial manifestation in AAV patients

Figure 1 illustrates the first symptom of AAV. In WG, it was ear, nose and throat (ENT) involvement, followed by systemic and respiratory manifestations. In

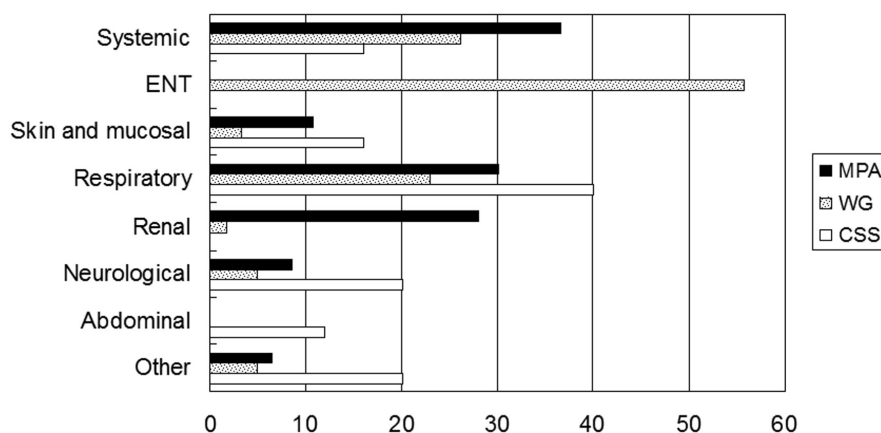
CSS, the presenting symptom was respiratory, followed by neurological manifestation. Whereas in MPA, systematic manifestations predominated, followed by respiratory and renal symptoms. Neurological symptom accounted for 20%, 4.9% and 8.6% of initial manifestation in patients with CSS, WG and MPA respectively.

Characteristics of NS involvement in AAV

As shown in Figure 2, CSS patients were more likely to have NS involvement (19 cases, 76.0%) (Table I), most of them (17/19, 89.5%) affecting peripheral nervous system (PNS), including distal symmetrical polyneuropathy and mononeuritis multiplex, but no cranial neuropathy. Four patients (21.1%) had central nervous system (CNS) involvement, including arachnoid hemorrhage, coma and neurocognitive deficits.

Thirty-one (50.8%) WG patients had NS involvement, the majority of them were peripheral neuropathy (27/31, 87.1%). Different from that in CSS and MPA patients, cranial neuropathy predominated, affecting III, VI, VII, VIII, IX or multiple cranial nerves (20/31, 64.5%, $p<0.05$), whereas mononeuritis multiplex was less in WG patients (10/31, 32.3%, $p<0.05$). Two patients developed vision loss due to optic neuritis. Ten (32.3%) patients had CNS involvement, manifesting as seizure and encephalopathy in seven cases, meningitis, subarachnoid hemorrhage and pituitary involvement in one case each.

MPA patients had the least NS involvement (34 cases, 36.6%), of which peripheral neuropathy predominated (29/34, 85.3%), and the majority were mononeuritis multiplex and polyneuropathy (25/34, 73.5%) instead of cranial neuropathy (9/34, 26.5%). Ten patients (29.4%) had CNS involvement, all manifesting as cerebrovascular neuropathy. For AAV patients with CNS involvement, lumbar puncture was conducted and cerebral spinal fluid (CSF) was analyzed. Half of them had elevated CSF pressure, ranging 210 mmH₂O to 280mmH₂O, and one third of them had slightly increased white blood cell number and elevated protein level in CSF.

**Fig. 1.** Initial symptom of ANCA-associated systemic vasculitides. (shown as percentage).

ENT: ear, nose and throat; WG: Wegener's granulomatosis; MPA: microscopic polyangiitis; CSS: Churg-Strauss syndrome.

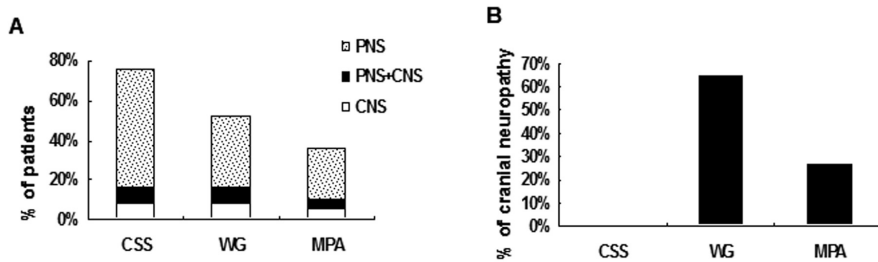


Fig. 2. Characteristics of NS involvement (A), and percentages of cranial neuropathy in NS involvement of AAV patients (B).

PNS: peripheral nervous system involvement only; CNS: central nervous system involvement only; PNS+CNS: both peripheral and central nervous system involvements.

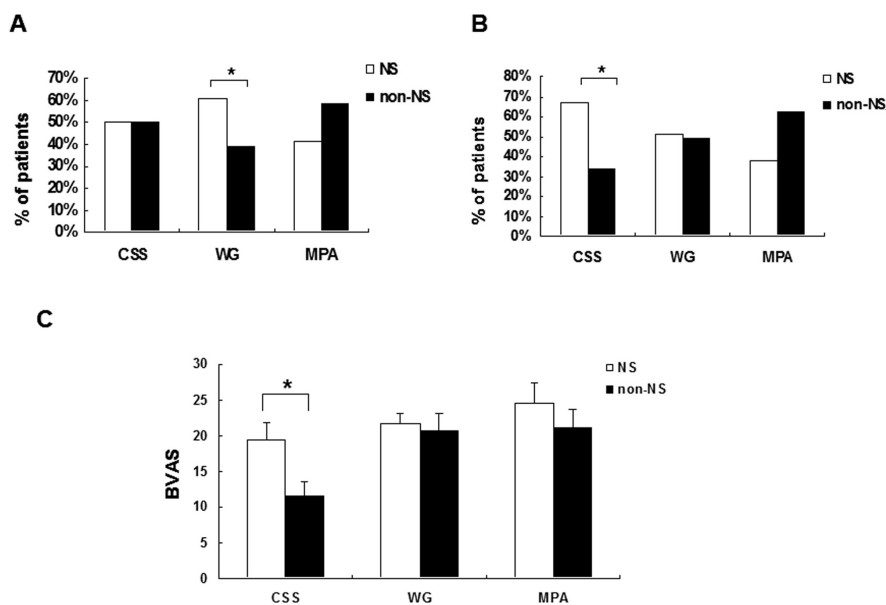


Fig. 3. Correlation of neuropathy with lung (A), kidney involvement (B), and disease activity (C) in CSS, WG and MPA patients. * $p < 0.05$.

Pathological findings of sural nerve biopsy in AAV

Eleven patients (including 7 cases of CSS, 2 cases each of WG and MPA) with symmetrical polyneuropathy or mononeuritis multiplex underwent sural nerve biopsy, and pathological findings revealed axonal degeneration in 10, necrotizing vasculitis in 6 patients, and perivascular infiltration of inflammatory cells in 5 patients.

Correlation of NS involvement with other organ damage and disease activity (BVAS) in AAV

Compared with AAV without neuropathy, lung involvement occurred more frequently in WG patients with neuropathy (Fig. 3A) ($p < 0.05$), while renal disease occurred more frequently (Fig. 3B) and BVAS were higher in CSS

patients with NS involvement (Fig. 3C) ($p < 0.05$). No correlation between cardiac or gastrointestinal involvement and neuropathy was found in either type of AAV ($p > 0.05$).

Treatment and prognosis

All patients were treated with high dose of prednisone (1mg/kg/daily), or bolus methylprednisolone (1000mg/daily iv for consecutive three days) in combination with immunosuppressants, including cyclophosphamide (CYC) (2mg/kg/daily) or azathioprine (2mg/kg/daily). The average duration of treatment in hospital was 46.3 ± 18.2 d. One WG patient refractory to above therapy was treated with anti-CD20 antibody (rituximab, 500mg iv once a week for consecutive four weeks), in combination with prednisone and CYC, and

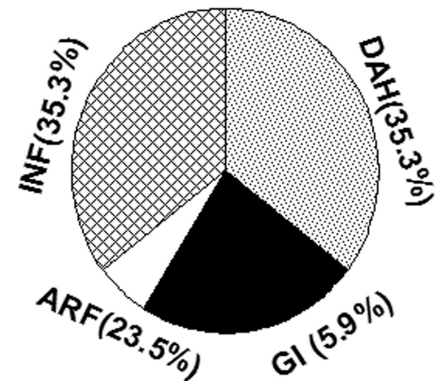


Fig. 4. Causes of death in MPA and WG patients. INF: infection; DAH: diffuse alveolar hemorrhage; ARF: acute renal failure; GI: gastrointestinal damage.

achieved complete remission. In total, 157 (87.7%) AAV patients responded to treatment (defined as $>30\%$ decrease of BVAS). The response rates did not show significant differences between patients with or without NS involvement in either AAV ($p > 0.05$). During hospitalization, thirteen (14.0%) MPA and four (6.6%) WG patients died. The leading causes of death were diffuse alveolar hemorrhage (DAH) (6, 35.3%) and infection (6, 35.3%), followed by acute renal failure (4, 23.5%) and gastrointestinal vasculitis leading to intestinal perforation (1, 5.9%) (Fig. 4). No patient died directly of NS involvement, though five succumbed MPA patients also complicated with NS involvement. Importantly, 9 (69.2%) of the thirteen MPA patients had elevated serum creatinine ($300 \pm 148 \mu\text{mol/L}$, $166-1273 \mu\text{mol/L}$) at the time of diagnosis, in comparison with 26 (32.5%) in the remaining 80 MPA cases ($p < 0.05$).

Discussion

The current study showed that the incidences of NS involvement in Chinese patients with CSS, WG were 76% and 50.8% respectively, which were in consistent with previous reports based on Caucasian patients (9-12). However, NS involvement in Chinese MPA patients (34%) was rarer than in previous reports (57.6%-80%) (1, 13-15). Neuropathy in these Chinese group mainly affected peripheral NS, in MPA and CSS patients manifesting as symmetrical polyneuropathy or mononeuritis multiplex, which was similar to that

in Caucasian (16-18) and Japanese patients (19). However, it was noteworthy that in Chinese WG patients, cranial neuropathy was the predominant type, with its frequency much higher than in previous reports (20, 21). Interestingly, some rare CNS manifestations, including meningeal involvement (22), subarachnoid hemorrhage (23, 24) and pituitary involvement (25) were all found in these Chinese WG patients.

In our study, neurological symptom was observed to be the presenting symptom in 20% of CSS patients, which was similar to previous study on a Caucasian population (14). We also found that NS could be the first symptom in a few WG and MPA patients, which was different from the literature (14, 26). In addition, respiratory involvement in our MPA patients was much higher than in other studies (24.7% – 30%) (1, 12, 14, 27-29). Though the true reason remains unclear, some environmental or genetic factors which was proposed to be risk factors for AAV (1, 30), might be associated with high incidence of lung involvement in Chinese MPA patients. Sural nerve biopsy were conducted in eleven AAV patients who had indicative symptoms, and only half of them had pathological confirmation of necrotizing vasculitis, while in most cases, axonal degeneration was the most common findings. Previous studies revealed that axonal degeneration of sural nerves was a major pathological process, and unlike myelinated fibers, unmyelinated fibers were likely to be well preserved in morphology and population, suggesting that unmyelinated fibers are relatively resistant to ischemia (31-33).

Corticosteroids and immunosuppressants, especially CYC, have been confirmed to considerably improve the outcome of systemic necrotizing vasculitides, and remain the mainstay of treatment for most vasculitic neuropathy (34-37). In our study, most patients responded to treatment with high dose of corticosteroids plus immunosuppressants. In consistent with other reports (4, 14, 38), our study found that the mortality rates were 14.0% and 6.6% in MPA and WG patients respectively, suggesting the prognosis of MPA be

the worst. In literature, older age, renal, hepatic or cerebral involvement indicated poor prognosis (39), while disease activity, sepsis and cardiovascular involvement were main causes of death in MPA (1, 40). In addition, Hattori *et al.* (19) found a five-year survival rate of 58% in Japanese MPA patients with peripheral neuropathy, which was similar to overall survival rate, suggesting peripheral neuropathy was not a prognostic predictor in MPA. Our study revealed that the leading causes of death in these Chinese AAV patients were DAH and infection, followed by renal failure and GI vasculitis. No correlation between NS involvement and risk of mortality was found, whereas impaired renal function was found to be associated with poor prognosis in our MPA patients.

In summary, in our study, NS involvement was common in AAV and the characteristic of NS involvement was different among MPA, WG and CSS patients. DAH and infection instead of NS damage remained the leading causes of death in AAV patients.

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