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Original Article

**Clinical characterization and successful treatment of 6 patients
with Churg-Strauss syndrome-associated neuropathy**

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Abstract

Objective: To confirm the reported findings and clarify unknown clinical features of Churg-Strauss syndrome (CSS) -associated neuropathy and design appropriate treatment.

Patients and Methods: We assessed the clinical features of 6 patients with **CSS-associated neuropathy**.

Results: Mononeuritis multiplex was present in 4 cases and polyneuropathy in the remaining cases. Both groups progressed to sensori-motor polyneuropathy in an acute or subacute course. All cases showed bronchial asthma and eosinophilia. Two cases with serum antineutrophil cytoplasmic antibodies to myeloperoxidase (MPO-ANCA) had an acute clinical course and severe symptoms. Nerve conduction studies (NCS) of these 2 cases revealed conduction blocks at the initial stage, although NCS finally indicated sensori-motor axonopathy at the involved extremities. For treatment, high-dose corticosteroid therapy for 4 cases, and cyclophosphamide combined with corticosteroids for one case, were effective. For the remaining case, intravenous immunoglobulin (IVIg) at the chronic phase resulted in a slow improvement of neuropathy in the symptomatic aspect. There was no relapse of neuropathy with low dose corticosteroid treatment for 14-24 months after the initial treatment, except one case. There was also no relapse in the other case that was treated with moderate-dose steroids.

Conclusion: Our study showed that CSS-associated neuropathy is a treatable disorder and that the first choice therapy is high-dose corticosteroid. In cases where corticosteroids are ineffective or for severe cases, immunosuppressive therapy (cyclophosphamide) with steroids should be considered, and IVIg might be a treatment option.

Keywords; Churg-Strauss syndrome, neuropathy, conduction block, ANCA, vasculitis, intravenous immunoglobulin, corticosteroid

Introduction

Churg-Strauss syndrome (CSS) is a systemic small-vessel vasculitis occurring in patients with eosinophilia and bronchial asthma; involvement of the peripheral nervous system is common (50-78 %) [1,2,3]. There are not many articles describing CSS-associated neuropathy. These reports describe CSS-associated neuropathy in the relation to systemic small-vessel vasculitis, Wegener's granulomatosis and microscopic polyangiitis [4,5], or with central nervous system involvement [6], or present a single case [7,8]; there is only one previous report solely describing CSS-associated neuropathy patients [9]. The mean onset age of neuropathy was about 50 years old, but the individual age of onset was wide-ranged, 15-78 years old [4,6,9]. There is controversy over the presence of a gender bias as the female ratio of CSS-associated neuropathy patients was reported to be 26.7 % [4], 55.3 % [6], and 78.6 % [9]. In these reports, the neuropathy initially presents as sensory disturbances of the extremities. These disturbances predominantly present as mononeuritis multiplex, and rapidly progress to polyneuropathy [9]. Electrophysiological examinations show axonopathy at the involved extremities and this is based on pathological findings of necrotizing vasculitis. This involves small to medium sized arteries, and is characterized by destruction and hyaline degeneration of the wall, inner elastic lamina destruction, thrombotic occlusion and eosinophilic perivascular invasion [1,2,7,9]. The first-line of therapy for CSS, with or without neuropathy, is high-dose corticosteroid therapy often combined with cyclophosphamide. There are other treatment options such as other immunosuppressants (e.g. azathioprine, methotrexate) or immunomodulators (e.g. intravenous immunoglobulin, interferon- α) [2,10]. Although corticosteroids were reported to be effective for neuropathy [9], the clinical improvements and long-term prognosis of these patients have not been fully characterized.

Serum antineutrophil cytoplasmic antibodies (ANCA) are reported to be detected in 38-50 % patients with CSS, most of which are specific to myeloperoxidase (MPO) [2]. Although two reports presented that ANCA-positivity in CSS patients reflects a more active vasculitic process and is correlated with the frequency of neuropathy [11,12], there are no previous reports clearly indicating the association between serum ANCA and the clinical features of neuropathy. We encountered 6 patients with CSS-associated neuropathy within 24 months. In order to confirm the reported findings and clarify unknown clinical features of the disease and design appropriate treatment, we analyzed their clinical features and prognosis.

Patients and Methods

The subjects of this study were 6 patients with CSS-associated neuropathy who were referred and admitted to the Department of Neurology, Hokkaido University Hospital, Tomakomai City Hospital, Sapporo Minami Hospital and Obihiro Kosei Hospital between April, 2006 and March, 2008. Four patients (cases 1, 3, 5, and 6) were diagnosed as probable CSS by the criteria of the American College of Rheumatology, 1990 [13]. The other two patients (cases 2 and 4) did not fulfill these criteria, but were diagnosed as definite CSS by the criteria of the Research Committee for Necrotizing Angiitis of the Ministry of Health and Welfare of Japan, 1998 [14]. We assessed their general condition, neurological findings, blood and cerebrospinal fluid (CSF) analysis, electrophysiological examinations, pathological findings, therapeutic responses, and clinical courses retrospectively. The observation period was variable, from 14 to 24 months. CSF study was not

conducted in one patient (case 6) and pathological assessments were restricted to 3 patients. Sural nerve biopsies (cases 1 and 5) and a muscle biopsy (case 3) at the rectus femoris were performed for diagnosis. To evaluate neurological disability, the modified Rankin scale (mRS) was used. The clinical course was classified as follows: when the interval from onset of neuropathy to completion of the symptoms was within one month, the clinical course was “acute”; when the interval was 1 to 3 months, it was “subacute”; when the interval was more than 3 months, it was “chronic”. Control of bronchial asthma was considered good when a patient did not need any additional relievers, and poor when additional relievers were constantly used for the month before admission; this information was obtained by interviews from patients or from clinical records, when available.

Results

Clinical features

Neuropathy appeared at higher middle age and there was no gender bias. All cases suffered from bronchial asthma occurring at middle age, and control of it was poor in half of the cases (Table 1). Their symptoms occurred with dysesthesia or pain at the distal portion of the lower extremities (LEs), followed by muscular weakness at the involved extremities. In 4 cases, the distribution of symptoms formed a mononeuritis multiplex and soon expanded to polyneuropathy, except in one case. The other 2 cases primarily showed polyneuropathy. All the cases showed an acute or subacute course, and a chronic course was not observed. The clinical features of cases 3 and 5 were similar to acute inflammatory demyelinating polyneuropathy

(AIDP) in that they primarily showed polyneuropathy, the features followed an acute course and conduction blocks (CBs) were detected in nerve conduction studies. There was a relatively long delay (mean 6.2 ± 4.6 weeks) till admission of all cases (Table 2). There was no cranial nerve involvement in any of the cases.

Laboratory data

Leukocytosis was found in 5 cases, and eosinophilia in all the cases. In 2 cases (case 3, and 5), serum immunoglobulin E (IgE) level was higher than in the other patients. A definite rise in the level of serum C-reactive protein (CRP) was detected in one case (case 5). Serum MPO-ANCA was positive in 2 cases, both these cases showed severe symptoms (mRS; V in case 3, IV in case 5). Cerebrospinal fluid showed a slight rise of protein in one case (case 4, Table 3).

Nerve conduction study

In nerve conduction studies (NCS) at admission, 4 cases (cases 1, 2, 4, and 6) showed reduced amplitude of distal compound muscle action potentials (CMAPs) and sensory nerve action potentials (SNAPs) at the LEs without altered conduction velocities. Conduction blocks (CBs) were detected in 2 cases (cases 3 and 5), both these cases were positive for MPO-ANCA. In case 3, CBs were detected at the median and peroneal nerves 9 days after onset, and a reduction in the amplitude of SNAP was found at the sural nerve. Twelve days after the first examination, distal CMAPs and SNAPs at the right upper and lower extremities were not evoked. Case 5 was reported to show CBs at 4 days after onset by the first-admitting hospital (data not available). Six days after onset, CBs were still detected at the right median, left ulnar and bilateral peroneal

nerves. Six days after our first examination, the amplitude of distal CMAPs and SNAPs at the four extremities (FEs) were extremely reduced and these CBs resolved, accompanied by a clinical deterioration (Figure 1A and 1B).

Pathological studies

Sural nerve biopsies from cases 1 and 5 demonstrated: eosinophil-rich lymphocyte infiltration into the walls of small arteries and extravascular connective tissue; severe hyaline degeneration of inner walls; fibrinoid occlusions and destruction of inner elastic lamina of small arteries. In muscle specimens from the left rectus femoris of case 3, there were moderate variations of muscle fiber size, perimysial fibrosis, and marked perivascular lymphocyte cuffing with eosinophils (co-existing with myositis).

Treatment and prognosis

In 3 cases (cases 1, 2, and 4), intravenous high-dose methylprednisolone (MP) administration (1 g/day for 3 days) followed by oral prednisolone (PSL; from 1 mg/kg/day, tapered gradually) was conducted twice. **The 1 or 2 grade decrement of mRS was achieved** by 6 weeks after the start of treatment. At that time, the dose of PSL was tapered to 25-27.5 mg/day, and all three cases had no recurrence of neuropathy with oral PSL at 5-10 mg/day until the end of the observation period (Table 4). Case 6 had previously been prescribed a moderate dose of PSL (30 mg/day) for 2 months, and we continued prescribing it for another month, with no improvement. We then prescribed an intravenous high-dose MP (**1 g/day for 3 days**), and after that added oral MP (**48 mg/day**). The mRS grade decreased by 1 and oral MP was tapered to 36 mg/day 2 months after

admission. He showed no relapse with 30 mg/day oral MP 15 months after the end of treatment (Table 4).

Case 3 and 5, with CBs and MPO-ANCA, showed especially severe symptoms, and needed longer-term treatment to fully recover. In case 3, IVIg (400 mg/kg/day for 5 days) was selected as the initial treatment because this case was primarily diagnosed with AIDP. But muscular weakness of the FEs deteriorated and the patient became bed-ridden for 2 weeks. She was finally diagnosed with CSS by muscle biopsy at the left rectus femoris, and given oral PSL 1 mg/kg/day (60 mg/day) for 1 month and the dose was then tapered slowly. A small improvement of symptoms was observed for 2.5 months, and after re-administration of IVIg (400 mg/kg/day for 5 days), improvement of the muscle force in the wrists and the proximal portion of the LEs were observed. Following two further treatments with IVIg (400 mg/kg/day for 5 days), the patient was able to walk with feet devices 9 months after the start of IVIg. At that time, PSL (5 mg/day) was maintained without recurrence (Table 4). Case 5 was referred to our hospital because of progressing weakness in the FEs following IVIg treatment (400 mg/kg/day for 3 days) started 4 days after onset. This case was also initially diagnosed with AIDP. However, he was diagnosed with CSS by right sural nerve biopsy, and intravenous high-dose MP (1 g/day for 3 days) followed by oral PSL (from 1 mg/kg/day, tapered gradually) was administered. Furthermore, intravenous cyclophosphamide administration (500 mg/m²/2weeks for the initial 8 weeks and the same dose/month for the following 10 months) was combined for the next 12 months. Three months after the start of treatment in our hospital, he had no need for support with walking and despite the tapering of PSL to 8.75 mg/day, his walking status was maintained for 14 months (Table 4).

Discussion

According to our study and previous reports [4,6,9], many CSS patients develop neuropathy at higher middle age, we also observed no gender bias in our patients. The initial symptom and expanding pattern was consistent with previous reports [9]. Due to the long time prior to admission in our hospital, all our cases showed polyneuropathy, except for one. CSF studies were of little value in diagnosis, consistent with a previous report [9].

In contrast to a previous report, 50% of our cases showed a deterioration of bronchial asthma following the onset of neuropathy. This discrepancy might be due to the definition of ‘control’. Conversely, the levels of eosinophilia and serum IgE density might also correlate with disease severity, as the severity of neuropathy seemed to be more intense in cases with higher eosinophilia and IgE levels, possibly due to increased vasculitis.

Initial electrophysiological findings of sensori-motor axonopathy in 4 cases were compatible with vasculitic neuropathy. The other 2 cases primarily showed demyelinating changes at a few nerves. After several days, an extreme reduction of distal CMAPs extinguished these CBs. Biopsy of the right sural nerve confirmed necrotizing vasculitis, and we consider these CBs to be a “pseudo-conduction block”, conduction block in vasculitic neuropathy [15,16,17]. In a previous report, acute ischemia of rat sciatic nerve showed secondary demyelination [18]. This same mechanism, mild ischemia in the early phase of vasculitis could cause transient demyelination in these 2 cases. Therefore some cases with CSS were misdiagnosed with AIDP. In our 3 cases, pathological findings were essential for the diagnosis, and crucial in selecting the proper treatment in the 2 cases primarily expressing AIDP. The pathological findings of the sural nerve biopsies in

cases 1 and 5, and muscle biopsy of rectus femoris in case 3, were compatible with eosinophilic necrotizing vasculitis of CSS [1,2,7,9].

For treatment, an intravenous high-dose MP therapy followed by oral PSL or MP with dosage tapering was effective, and repeating this course of treatment could induce a quicker remission and provide more pronounced efficacy. Cyclophosphamide combined with steroids was also effective. IVIg in the early phase of CSS-associated neuropathy is supposed to be of no therapeutic benefit, although it might provide significant improvement in the chronic phase. There are several reports which suggest efficacy of IVIg for CSS-associated neuropathy [8,19], where IVIg was conducted as a salvage therapy for the cases with no efficacy of corticosteroids or cyclophosphamide at the acute phase. This efficacy of IVIg may be associated with the difference of immune mediators working at the acute and chronic phases in CSS-associated neuropathy. But in this report, only one patient was given IVIg, and a delayed efficacy of steroids, or spontaneous remission could not be ruled out as contributing factors in the improvement of the patient's condition. All of the previous reports are also case reports, and more investigation is needed to determine the efficacy of IVIg in the chronic phase of CSS-associated neuropathy.

Our 2 cases with MPO-ANCA showed "pseudo-conduction blocks" electrophysiologically at the early phase, especially severe symptoms, and needed longer-term treatment to fully recover. We suppose that the pathogenic mechanisms in ANCA-positive CSS patients might differ from those in ANCA-negative ones [11,12]. These auto-antibodies might enhance focal inflammation and detection of them could be a poor prognostic factor in CSS-associated neuropathy. The start of treatment (3 weeks after onset) for case 3, with severe disability, was later than that of case 5 (1 week after onset), that recovered with slight disability. In

addition, there is a possibility that cyclophosphamide was useful in case 5. These observations may show that accurate diagnosis in the early stage and appropriate treatment are particularly necessary for patients with MPO-ANCA.

In our study, neuropathy did not re-occur in all cases except one with low-dose PSL treatment (5-10 mg/day) for 14-24 months. No relapse was found in the other one case treated with moderate-dose MP (30 mg/day) for 15 months. Low relapse rates of neuropathy (7 %) in CSS patients over 6.3 years have been reported [5], we intend to keep observing our patients to confirm this observation.

Finally, we demonstrated that CSS-associated neuropathy is a treatable disorder. First choice therapy for most cases with this condition is high dose corticosteroid and not IVIg. In cases where corticosteroids were ineffective or cases with severe symptoms or MPO-ANCA antibody, immunosuppressive therapy (cyclophosphamide) combined with steroids should be considered. IVIg might be a treatment option for patients with severe disability in the chronic phase.

There remain many unsolved problems about the clinical features and pathogenesis of CSS-associated neuropathy. As prognosis is heavily dependent on accurate diagnosis and proper treatment selection, further characterization of both the clinical and experimental aspects of this disease needs to be conducted.

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Legends

Table 1

Background of our cases

Table 2

Clinical characteristics of neuropathy

lt. ; left, rt ; right, LE ; lower extremity, FEs ; four extremities, d ; distal portion, p ; proximal portion, PN ;

polyneuropathy, MM ; mononeuritis multiplex

Course in which the interval till completion of symptoms is within one month or from one to three months is expressed by “acute” or “sub-acute”, respectively.

* Neuropathy type at our first examination, not at onset

Table 3

Blood and CSF examinations

WBC ; White blood cell, IgE ; Immunoglobulin E, CRP ; C-reactive protein, MPO-ANCA ; Antineutrophil cytoplasmic antibodies to myeloperoxidase, CSF ; Cerebrospinal fluid, N.E.; Not examined

The value in () * shows normal value.

Table 4

Treatment and efficacy

Intravenous MP ; Intravenous methylprednisolone 1 g /day for 3 days

Oral PSL ; Oral prednisolone tapered from 1 mg/kg /day (maintenance dose was variable)

Oral MP ; Oral methylprednisolone 48 mg/day tapered gradually to 30 mg/day

IVIg ; Intravenous immunoglobulin 400 mg/kg/day for 5 days

IVCY ; Intravenous cyclophosphamide planed for induction of 500 mg /m² /2weeks for 8 weeks followed monthly

by the same dose administration for 10 months .

mRS ; modified Rankin scale

*1 started to be administered at another hospital *2 The interval of treatment at the other hospitals is excluded.

Figure 1

Characteristic change of NCS (at the left ulnar nerve of case 5)

A; First study (6 days after onset)

At 6 days after onset, we detected a CB at the left ulnar nerve in case 5.

B; Second study (6 days after the first study)

Six days after the first examination, the amplitude of the distal CMAP was reduced and this CB resolved.

The same changes were detected at the right median nerve and bilateral peroneal nerves in case 5.

Table 1

Background of our cases

Patients	Age (years)	Gender (F/M)	Bronchial asthma		
			interval fom onæt to neuropathy (years)	Treatment	Control
1	55	F	15	+	poor
2	66	M	10	+	good
3	63	F	13	+	good
4	55	F	16	+	poor
5	51	M	2	+	good
6	49	M	1	+	poor

Table 2

Clinical characteristics of neuropathy

Patients	initial	course	interval fom onæt	symptom dñtribution		neuropathy type [*]
	symptoms		to admission (weeks)	motor	sensory	
1	dysesthesia of lt.leg and foot	subacute	10	LEs,d	LEs,d	PN
2	dysesthesia of rt.leg and foot	acute	3	LEs,d	LEs,d	PN
3	dysesthesia of both thighs and legs	acute	1	FEs,d	FEs,d	PN
4	pain of lateral side of rt.leg and ankle	subacute	10	LEs,d	LEs,d	PN
5	dysesthesia of both feet	acute	1	FEs,d	FEs,d	PN
6	pain of l.heel	acute	12	rt.LE,d	rt.LE,p/d lt.LE,d	MM

Table 3

Blood and CSF examinations

Patients	Blood					CSF	
	WBC (/μl) (< 9,800)*	Eosinophil (% / cell count /μl) (< 11.0 / < 700)*	IgE (IU/ml) (< 250)*	CRP (mg/dl) (< 0.39)*	MPO-ANCA (EU) (< 10)*	Cell count (/μl) (< 5)*	Protein (mg/dl) (< 40)*
1	11,800	40.0 / 4,720	546	0.91	—	1	21
2	32,300	60.0 / 19,703	N.E.	1.96	—	2	29
3	25,200	67.5 / 17,010	2021	3.01	640 <	1	15
4	28,000	69.0 / 19,320	701	2.83	—	1	44
5	37,200	65.5 / 24,403	2887	15.3	640 <	1	23
6	7,400	20.0 / 1,480	322	1.91	—		N.E.

Table 4

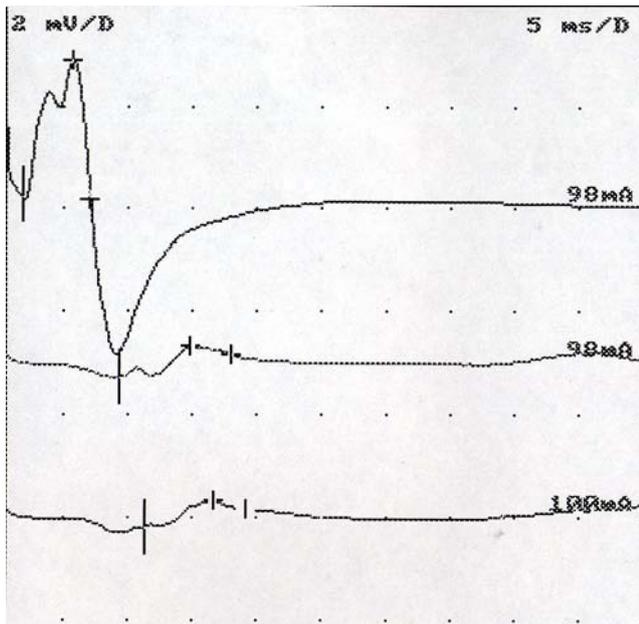
Treatment and efficacy

Patients	Initial and salvage treatments	Observation period	mRS
		(month)	pre → post treatment
1	Intravenous MP + Oral PSL	19	III → I
2	Intravenous MP + Oral PSL	14	IV → I
3	IVIg (not effective) → Oral PSL + MIg	24	V → IV
4	Intravenous MP + Oral PSL	14	IV → I
5	IVIg (not effective) ^{*1} → Intravenous MP + Oral PSL + IVCY	17 ^{*2}	IV → I
6	Oral PSL 30 mg/day ^{*1} → Intravenous MP + Oral MP	15 ^{*2}	III → I

Figure 1

Characteristic change of NCS (at the left ulnar nerve of case 5)

A; First study (6 days after onset)



B; Second study (6 days after the first study)

