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Clinicopathological features of Churg–Strauss syndrome-associated neuropathy

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Summary

We assessed the clinicopathological features of 28 patients with peripheral neuropathy associated with Churg–Strauss syndrome. Initial symptoms attributable to neuropathy were acute painful dysaesthesiae and oedema in the dysaesthetic portion of the distal limbs. Sensory and motor involvement mostly showed a pattern of mononeuritis multiplex in the initial phase, progressing into asymmetrical polyneuropathy, restricted to the limbs. Parallel loss of myelinated and unmyelinated fibres due to axonal degeneration was evident as decreased or absent amplitudes of sensory nerve action potentials and compound muscle action potentials, indicating acute massive axonal loss. Epineurial necrotizing vasculitis was seen in 54% of cases; infiltrates consisted mainly of CD8-positive suppressor/cytotoxic and CD4-positive helper T lymphocytes. Eosinophils were present in infiltrates, but in smaller numbers than lymphocytes. CD20-positive B lymphocytes were seen only occasionally. Deposits of IgG, C3d, IgE and major basic protein were scarce. The mean follow-up period was 4.2 years, with a range of 8 months to 10 years. Fatal outcome was seen only in a single patient, indicating a good survival rate. The patients who responded well to the initial corticosteroid therapy within 4 weeks regained self-controlled functional status in long-term follow-up (modified Rankin score was ⩽2), while those not responding well to the initial corticosteroid therapy led a dependent existence ($P < 0.01$). In addition the patients with poor functional outcomes had significantly more systemic organ damage caused by vasculitis ($P < 0.05$). Necrotizing vasculitis mediated by cytotoxic T cells, leading to ischaemic changes, appears to be a major cause of Churg–Strauss syndrome-associated neuropathy. The initial clinical course and the extent of systemic vasculitic lesions may influence the long-term functional prognosis.

Keywords: Churg–Strauss syndrome; vasculitic neuropathy; corticosteroids; T-cell infiltration; prognosis

Abbreviations: CMAP = compound muscle action potential; ESR = erythrocyte sedimentation rate; LDH = lactate dehydrogenase; PAN = polyarteritis nodosa; RA = rheumatoid arthritis; SNAP = sensory nerve action potential; SNVDI = systemic necrotizing vasculitis damage index; p-ANCA = perinuclear antineutrophil cytoplasmic antibody

Introduction

Churg and Strauss (1951) initially reported 13 patients with a systemic vasculitic disease involving the lungs, kidneys, skin, liver and peripheral nervous system. Churg–Strauss syndrome is characterized by bronchial asthma, eosinophilia and systemic necrotizing vasculitis involving medium- and small-sized vessels with or without granulomas. Diagnostic criteria for Churg–Strauss syndrome have been established by an American College of Rheumatology subcommittee (Masi *et al*., 1990). The main neurological complication of Churg–Strauss syndrome is peripheral neuropathy, with a reportedly high incidence (Chumbley *et al*., 1977; Backman *et al*., 1995; Sehgal *et al*., 1995). However, the clinical and pathological characteristics of peripheral neuropathy in Churg–Strauss syndrome have not been firmly established by studies of large numbers of patients.

Descriptions of the features of neuropathy associated with systemic vasculitis have focused on polyarteritis nodosa (PAN) or rheumatoid arthritis (RA) (Dyck *et al*., 1972; Moore and Fauci, 1981; Scott *et al*., 1981; Moore and Cupps, 1983; Kissel *et al*., 1985; Said *et al*., 1988; Sobue *et al*., 1989*a*; Hawke *et al*., 1991; Puéchal *et al*., 1995). The clinical and pathological characteristics of peripheral nerve lesions in PAN and RA reported by Dyck *et al*. (1972) and Sobue *et al*. (1989*b*) are similar to those obtained in systemic vascular occlusion experiments (Hess *et al*., 1979; Parry and Brown, 1981; Nukada and Dyck, 1984, 1987), indicating that the

underlying mechanism of peripheral nerve pathology is acute ischaemia due to vascular occlusion. In vasculitic lesions of PAN and RA, infiltrating suppressor/cytotoxic T cells are most prominent in early active lesions (Kissel *et al*., 1989; Hawke *et al*., 1991), or helper T cells are seen to some degree (Engelhardt *et al*., 1993), suggesting a pathological role of T cells.

Churg–Strauss syndrome-associated neuropathy is considered one of the systemic necrotizing vasculitis-associated neuropathies, grouped with PAN- and RA-associated neuropathies (Moore and Fauci, 1981; Conn, 1989; Hawke *et al*., 1991). However, Churg–Strauss syndrome is also considered a form of hypereosinophilic syndrome (Dorfman *et al*., 1983; Wichman *et al*., 1985; Monaco *et al*., 1988), and the cationic basic protein released from eosinophils is said to contribute to the pathogenetic mechanism of neuropathy. Since studies of Churg–Strauss syndrome-associated neuropathy have involved small numbers of patients or analysis in combination with other systemic vasculitic neuropathies (Kissel *et al*., 1985; Bouche *et al*., 1986; Said *et al*., 1988; Hawke *et al*., 1991; Inoue *et al*., 1992; Sehgal *et al*., 1995), understanding of the clinicopathological features of Churg–Strauss syndrome-associated neuropathy is still incomplete. Many issues remain to be addressed, including the spectrum of neuropathic symptoms; the causal relationships with peripheral neuropathy of eosinophil infiltration and cationic basic protein and IgE deposition; the nature of the infiltrating cells; the long-term prognosis and response to therapeutic agents; and differences from other systemic vasculitic neuropathies such as in PAN or RA.

This study was designed to review the clinicopathological features of 28 patients with Churg–Strauss syndrome-associated neuropathy, concentrating on clinical characteristics, response to treatment, prognosis and pathological findings of neuropathy.

Patients

The patients studied consisted of 22 females and six males from 22 to 78 years of age (mean ± SD, 52.4 ± 12.8 years; Table 1). Subjects were those referred to Nagoya University Hospital, Aichi Medical University Hospital or affiliated hospitals between 1986 and 1997. All patients were referred during the initial acute stage of neuropathy (at most 1 week after onset). Patients underwent neurological assessment, cerebrospinal fluid (CSF) analysis, cranial MRI, CT, routine blood and urine studies, nerve conduction studies, sural nerve biopsies and therapeutic trials. The diagnosis of Churg–Strauss syndrome was based on the criteria reported by the American College of Rheumatology (Masi *et al*., 1990) and by the Research Committee for Necrotizing Angiitis of the Ministry of Health and Welfare of Japan (Nagasawa and Yoshida, 1989). No patients were diagnosed with Churg–Strauss syndrome before the neurological symptoms appeared.

The functional state of patients was estimated according to the modified Rankin score (van Swieten *et al*., 1988): 0 = asymptomatic; 1 = non-disabling symptoms not interfering with lifestyle; 2 = mildly disabling symptoms leading to some restrictions of lifestyle but not interfering with capacity to look after oneself; 3 = moderately disabling symptoms significantly interfering with lifestyle or precluding totally independent existence; 4 = moderately severe disability precluding independent existence while not requiring constant attention around the clock; 5 = severe disability with total dependency requiring constant attention day and night. Functional scores for some patients studied were estimated retrospectively.

Method

For the assessment of the clinical course and response to therapeutic trials, clinical disability (modified Rankin) scores were used. To evaluate systemic involvement of visceral organs, we used a systemic necrotizing vasculitis damage index (SNVDI) developed by Abu-Shakra *et al.* (1994). The SNVDI includes 12 organ systems (ocular, pulmonary, cardiovascular, peripheral vascular, gastrointestinal, gonadal, renal, skin, neurological, malignancy, diabetes and musculoskeletal) and the full score was 43. These systemic manifestations were assessed from clinical symptoms, roentgenographic or CT appearances, ECG, urinalysis and endoscopic observation. Motor and sensory conduction studies were performed for the median, ulnar, tibial and sural nerves using a standard method in the acute phase and at follow-up during the chronic phase. Values for nerve conduction velocity and nerve action potentials were compared with the normal values reported by Behse and Buchthal (1971) and Kimura (1989*a*, *b*).

Sural nerve biopsies were performed as described previously (Sobue *et al*., 1988) between 3 days and 2 weeks (typically within 1 week) after onset of neuropathy. Specimens were divided into three portions. One portion was fixed in 2.5% glutaraldehyde in 0.125 M cacodylate buffer (pH 7.4) and embedded in epoxy resin. The density of myelinated fibres in toluidine blue-stained semithin sections was assessed using a computer-assisted image analyser (Luzex FS, Nikon) and densities of small and large fibres were calculated as described previously (Sobue *et al*., 1989*c*). For electron microscopic examination, Epon-embedded specimens were processed for ultrathin sectioning. To assess the density of unmyelinated fibres, electron microscope photomicrographs at a magnification of ×6000 were taken in random fashion to cover the ultrathin transverse section. The density of the unmyelinated fibres was estimated from the photomicrographs using a computer-assisted image analysis system. Some glutaraldehyde-fixed specimens were processed for a teased-fibre study in which at least 50 single fibres were isolated and assessed for pathological conditions according to criteria described previously (Sobue *et al*., 1989*c*; Dyck *et al*., 1993). The

Table 1 *Clinical features and follow-up*

Case	Age (years)	Sex	Asthma onset (years)	Initial symptom	Sensory symptom distribution	Motor symptom distribution	Systemic involvement					SNVDI	Peak impairment*	Follow-up outcome*	Response to initial treatment
							Lung	Skin	GI	Kidney	Heart				
1	67	F	NA	Pain, oedema	MM	U and L distal			+	+		6	5	4	0
2	51	F	NA	Dysaesthesia	MM	U and L distal	+			+		6	5	4	0
3	52	F	31	Pain, swelling	MM	L distal	+			+		8	4	4	0
4	55	F	41	Pain, oedema	MM	L distal	+			+		6	4	5†	1
5	43	F	38	Pain, vesicle	MM	L distal		+				4	4	1	1
6	52	F	50	Dysaesthesia, oedema	AS	U and L distal						3	3	1	1
7	46	M	43	Dysaesthesia, oedema	MM	U and L distal		+				4	5	2	1
8	27	F	NA	Dysaesthesia, swelling	AS	U and L distal			+	+		6	5	4	1
9	48	F	47	Weakness	MM	L distal					+	5	4	3	0
10	50	F	47	Painful dysaesthesia	MM	L distal	+	+				6	5	3	0
11	50	F	45	Arthralgia	MM	L distal						3	4	3	0
12	58	M	51	Dysaesthesia, weakness	AS	U distal/L proximal			+			4	4	1	0
13	22	F	20	Swelling	MM	L distal		+	+			5	5	1	1
14	78	M	58	Dysaesthesia	MM	L distal	+					4	5	4	0
15	55	F	50	Weakness	AS	U and L distal	+					4	4	3	0
16	33	F	32	Pain	MM	U and L distal		+				4	5	1	1
17	62	F	52	Swelling	AS	L distal			+			4	5	2	1
18	61	M	57	Dysaesthesia, weakness	MM	L distal	+		+			5	5	2	1
19	63	F	40	Pain, oedema	MM	U proximal/L distal			+			4	4	1	1
20	56	F	25	Painful dysaesthesia	AS	L distal	+		+			5	4	2	0
21	34	F	21	Dysaesthesia	MM	L distal		+				4	4	2	0
22	55	F	48	Dysaesthesia	MM	L distal						3	4	1	0
23	76	F	56	Dysaesthesia, swelling	AS	U and L distal						3	4	3	0
24	50	M	47	Arthralgia, dysaesthesia	MM	U and L distal						3	5	2	0
25	59	F	54	Pain, dysaesthesia	MM	L distal	+	+		+		7	4	3	0
26	49	F	47	Arthralgia, skin rash	MM	U and L distal						3	4	2	1
27	49	F	29	Dysaesthesia, swelling	MM	U and L distal	+	+				5	4	2	1
28	65	M	64	Oedema, weakness	AS	L distal			+			4	4	4	0

Distribution of the sensory and motor symptoms was determined in the acute phase. NA = not available; MM = mononeuritis multiplex; AS = asymmetrical polyneuropathy; U = upper limbs; L = lower limbs; GI = gastrointestinal; SNVDI = systemic necrotizing vasculitis damage index (Abu-Shakra *et al.*, 1994); '+' = systemic involvement present. Response to initial treatment: '0' = no therapeutic response within 4 weeks. '1' = positive therapeutic response with reduction of one or more points or the modified Rankin score within 4 weeks; *the modified Rankin score; †death.

second portion of the specimen was fixed in 10% formalin solution, embedded in paraffin, cut into transverse and longitudinal sections and stained using the haematoxylin–eosin, Klüver–Barrera or Masson trichrome method for conventional observation. The third portion of the specimen was snap-frozen in methylbutane chilled in dry ice and cut at 4 μm thickness in a cryostat; the sections were fixed with cold acetone and air-dried for immunohistochemistry. The primary antibodies were for CD3 (1 : 50, polyclonal anti-human T cell; DAKO, Denmark), CD4 (1 : 20, clone 1F6; Novocastra, UK), CD8 (1 : 20, clone C8/144B; DAKO), CD20 (1 : 50, clone L26; DAKO), CD45RO (1 : 125, clone UCHL1; DAKO), CD68 (1 : 10, clone KP1; DAKO), HLA-DR (1 : 50, clone CR3/43; DAKO), β2-microglobulin (1 : 500, polyclonal; DAKO), IgG (1 : 80, clone A57H; DAKO), IgE (1 : 25, clone C1A-E-7.12; DAKO), C3 (1 : 4, clone HAV3–4; DAKO) and major basic protein (1 : 20, clone BMK13; YLEM, Italy). Sections were treated with trypsin, EDTA (ethylenediamine-tetraacetate) and citrate before incubation with primary antibodies for CD3 or CD68, CD4 and CD8, respectively, or heated in a microwave oven before incubation for CD20, IgG and C3d. After antibody incubations, the specimens were washed in PBS (phosphate-buffered saline) and processed for avidin– ABC (biotin complex) staining (Vectastain Elite ABC kit; Vector Laboratories, USA). Antibody binding was visualized with DAB (diaminobenzidine tetrahydrochloride). In addition, some paraffin sections of formalin-fixed material were processed for immunohistochemistry.

Corticosteroids were prescribed for all patients as the initial treatment. Prednisone was initiated orally between 5 days and 5 weeks after onset, typically within 10 days after onset at an initial dose of 1 mg/kg/day, and continued for at least 1 month. In eight patients, methylprednisolone was administered intravenously at 1000 mg/day for 3 consecutive days before oral prednisone was started. The oral prednisone dose was tapered and discontinued according to the clinical response and the evolution of laboratory findings. Two patients additionally received cyclophosphamide (2 mg/kg/day). The patients who responded to the corticosteroid therapy and showed reductions in one or more points of the modified Rankin score within 4 weeks were designated as having ‘a therapeutic response’, whereas those not showing any recovery of the functional score within 4 weeks were taken to have ‘no therapeutic response’.

The patients were followed for a period of between 8 months and 10 years (mean 4.2 years), and the response to treatment and the long-term outcome were assessed using the modified Rankin score. At the end of follow-up, a score of $\geqslant 3$ was designated as a poor functional outcome and a score of $\leqslant 2$ as good.

All statistical analyses were performed using the Mann–Whitney *U* test, Pearson’s correlation coefficient analysis or Fisher’s exact probability test, as indicated. *P* values of <0.05 were considered significant.

Results

Clinical features (Table 1)

All patients had a history of bronchial asthma which was under good control when neuropathy developed. Although no patients showed symptoms of asthma at the onset of neuropathy, xanthine derivatives were taken orally by 15 patients and low-dose oral prednisone was taken by four patients for the management of asthma. Age at onset of asthma ranged from 20 to 64 years (mean ± SD, 43.7 ± 11.7 years), preceding onset of neuropathy by intervals ranging from 1 to 31 years (mean ± SD, 9.1 ± 8.6 years).

The initial symptom of neuropathy was the acute onset of tingling or painful paraesthesia distally in the legs in 23 patients and in the hands in five patients. Local oedema was seen in the distal limbs where painful paraesthesia was present. Arthralgia, general fatigue and high fever were common to all patients. In the initial phase, sensory involvement including all modalities was distributed in a mononeuritis multiplex pattern in 20 cases (71%) and in an asymmetrical polyneuropathy pattern in eight cases (29%). The mononeuritis multiplex pattern eventually evolved into an asymmetrical or symmetrical polyneuropathy as the disease progressed. Sensory impairments were restricted to the limbs and were not present over the trunk. Muscle weakness was evident in the involved limbs in a distal-dominant fashion corresponding to the area of sensory involvement, but variable in its extent and degree of asymmetry. Muscular atrophy was not prominent initially, but subsequently became apparent to a severe degree in most patients. The distribution of decreased or absent deep tendon reflexes also corresponded to the distribution of nerve involvement. The frequency of individual nerve involvement, as judged by sensory impairment, was highest in the common peroneal nerve (27 cases, 96%), followed by the tibial, sural and ulnar nerves (16 cases each, 57%) and the median nerve (13 cases, 46%). Cranial nerves were intact except in two patients with abnormal taste sensation and unilateral facial nerve palsy. The interval from onset of neuropathy to maximal impairment was 2–4 weeks. At the time of maximal impairment, the modified Rankin score ranged from 3 to 5 (mean 4.3).

In all cases, peripheral neuropathy preceded involvement of the visceral organs and skin. Systemic complications were seen in 21 cases, involving the lung in 12 cases, the skin and gastrointestinal tract in seven cases each and the kidney and heart in one case each. The SNVDI ranged from 3 to 7 (mean ± SD, 4.6 ± 1.3).

Laboratory data

All cases showed leucocytosis and eosinophilia (mean ± SD for neutrophils, 23 700 ± 14 700/mm^3; for eosinophils,

Table 2 *Pathological findings in the sural nerve*

Case	MF density (no./mm^2)			Small/large	UMF density (no./mm^2)	UMF/MF	Axonal degeneration (%)	Necrotizing vasculitis	Cell infiltration	Eosinophils	Granuloma	Subperineurial oedema
	Total	Large	Small									
1	1450	617	833	1.35			87	+	+++	++	0	+
2	820	265	555	2.09			98	+	+++	+	0	+
3	1185	55	1130	20.55	1166	0.98	96	+	+++	+++	+	0
4	205	40	165	4.13			91	0	+	0	0	++
5	1426	474	952	2.01			59	0	+	0	0	++
6	3713	1343	2370	1.76			75	+	+	0	0	+
7	944	124	820	6.61	1399	1.48	76	+	++	0	0	++
8	0	0	0	–	0	–	100	+	+	0	0	++
9	2054	470	1584	3.37			30	+	+	0	0	+++
10	4185	1580	2605	1.65	13456	3.22	48	0	0	0	0	+++
11	2135	111	2024	18.23	19598	9.18	42	0	0	0	0	+++
12	2291	1027	1264	1.23	8182	3.57	56	0	0	0	0	++
13	3274	1738	1536	0.88				0	+	0	0	0
14	453	12	441	36.75	1794	3.96	100	+	++	0	0	+
15	2200	948	1252	1.32	1598	0.73	57	0	+	0	0	++
16	1659	869	790	0.91	8290	5.00	100	0	0	0	0	+
17	0	0	0	–	900	–	100	+	++	0	+	+++
18	1085	79	1006	12.73	2394	2.21	66	0	0	0	0	+
19	553	230	323	1.40			95	0	0	0	0	+++
20	503	158	345	2.18	1025	2.04	100	+	+	+	0	++
21	1900	142	1758	12.38	12607	6.64	92	0	0	0	0	+
22	2121	790	1331	1.68	10195	4.81	80	0	0	0	0	+++
23	316	0	316	–	4916	15.56	99	+	+++	++	+	+
24	2607	182	2425	13.32	11781	4.52	75	+	+	0	0	++
25	0	0	0	–	3627	–	100	0	+	0	0	+
26	885	39	846	21.69	9289	10.51	89	+	+++	+++	0	0
27	237	28	209	7.46	3398	14.34	96	+	++	+	+	+++
28	1817	1185	632	0.53	8216	4.52	93	+	+	0	0	++
CV	8190 ± 511	3069 ± 294	5122 ± 438	1.7 ± 0.2	29913 ± 3457	3.65 ± 0.33	2.3 ± 1.9					

MF = myelinated fibre; UMF = unmyelinated fibre. Axonal degeneration was assessed by teased-fibre study. Necrotizing vasculitis, granuloma: '+' = present; '0' = absent. Cell infiltration, eosinophils: '+++' = massive; '++' = moderate; '+' = mild; '0' = no infiltration. Subperineurial oedema: '+++' = severe; '++' = moderate; '+' = mild; '0' = absent. CV = control value, based on seven cases (Sobue *et al*., 1989*c*).

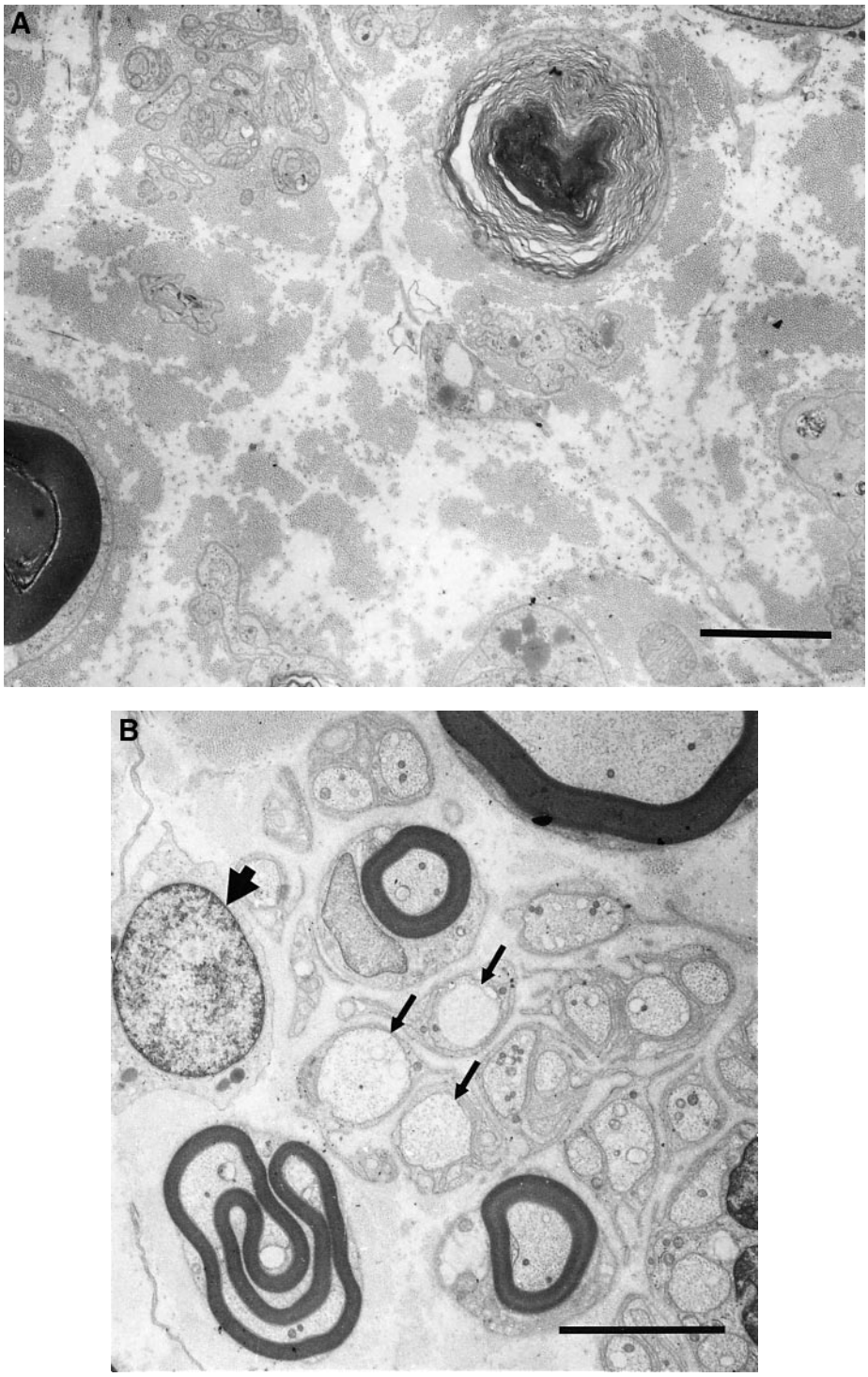

Fig. 1 Electron micrographs of transverse sections of the sural nerves. (**A**) Few myelinated fibres in axonal degeneration are visible in the oedematous endoneurial space. Unmyelinated fibres are not detected. Scale bar = 2 μm. (**B**) Swollen unmyelinated fibres (arrows) in a mildly involved lesion. A mononuclear cell is indicated by the thick arrow. Scale bar = 2 μm.

14 400 ± 13 800/mm^3) except two patients treated with oral corticosteroids for asthma. Platelet counts of >350 000/mm^3 were seen in nine cases. Plasma lactate dehydrogenase (LDH) exceeded the normal range in 70% and hypoalbuminaemia (<3.5 g/dl) was found in 64% of cases examined. C-reactive protein and erythrocyte sedimentation rate (ESR) were elevated in 93 and 83% of cases examined, respectively. The elevation in C-reactive protein was moderate (<10 mg/dl)

in most instances, and ESR elevations of >60 mm/h were seen in 42% of cases examined. Plasma IgE and IgG levels exceeded the normal range in 74 and 43% of cases, respectively. Levels of IgA and IgM remained within the normal range in all but one patient. Rheumatoid factor was positive in 86% and perinuclear antineutrophil cytoplasmic antibody (p-ANCA) was positive at low titres in 42% of the cases examined. Antinuclear antibody, anti-DNA antibody and hepatitus B virus surface antigen were not detected in any cases. A study of CSF disclosed no abnormalities in protein or cell content except in one case.

In nerve conduction studies, sensory nerve action potentials (SNAPs) were not evoked in 73% of subjects in the sural nerve and in 17% in the median nerve. SNAPs were reduced in amplitude in 15% of the subjects in the sural nerve and in 35% in the median nerve. Compound muscle action potentials (CMAPs) were absent in 45% of subjects in the tibial nerve and in 10% in the median nerve, and CMAP amplitudes were reduced in 35% in the tibial nerve and in 50% in the median nerve. On the other hand, slowing of conduction velocity was not seen in any sural nerves and conduction velocity was relatively well preserved in the median and tibial nerves, indicating predominantly axonal degeneration. Overall, abnormal findings were seen in 89% of subjects in the sural nerve, 71% in the tibial nerve and 62% in the median nerve.

Pathological findings in sural nerves (Table 2 and Figs 1, 2 and 3)

Myelinated fibre density was severely but variably diminished in 0–4185 fibres/mm^2 (mean ± SD, 1428 ± 1133). Numbers of large and small myelinated fibres showed fairly similar degrees of loss ($r = 0.54$, $P < 0.002$; Pearson's correlation coefficient). Vacuolated or dense, dark, myelinated fibres were seen occasionally. Unmyelinated fibre density also was variably diminished in 0–19 598 fibres/mm^2 (mean ± SD, 5670 ± 5660; Fig. 1). The degree of unmyelinated fibre loss correlated significantly with myelinated fibre loss ($r = 0.70$, $P < 0.0004$, Pearson's correlation coefficient; Fig. 1). In teased-fibre preparations, the frequency of fibres with active axonal degeneration ranged from 30 to 100% (mean ± SD, 81 ± 21%; normal range, 2.3 ± 1.9%); 20 cases showed degeneration of >70% of axons. Segmental demyelination was rare (0–6.5% of fibres). Apparent focal myelinated fibre loss in individual fascicles was seen in only three cases. Intra- and interfascicular variation of myelinated fibre loss was rather mild (Fig. 2). Subperineurial oedema was conspicuous in most cases (Fig. 2).

Necrotizing vasculitis involving arteries of medium (100–150 μm) to small (30–50 μm) size was seen in the epineurial space in 15 cases (54%). Vessel walls showed necrotizing and hyaline degeneration and the inner elastic lamina was destroyed in most of the arteries involved. Complete occlusion and recanalization were frequently seen. Granuloma formation associated with necrosis of vessels was seen in only four cases. Eosinophilic infiltrates were moderate to severe in four of 15 cases (Fig. 2) and mild in three cases. The eosinophils mostly occupied the outer zone of the adventitia at the margin of the active lesion (Fig. 2). Vasculitic infiltrates consisted predominantly of T lymphocytes positive for CD45 RO and CD3, revealing T-cell subtypes of the CD8- and CD4-positive cells in equal numbers in most cases (Fig. 3). CD68-positive macrophages were present in a moderate to high numbers in active vasculitis. Cells positive for β2-microglobulin (MHC class I) and HLA-DR (MHC class II) were seen in varying numbers in seven and nine cases, respectively. CD20-positive B cells were detectable in only four cases in small numbers only. In the endoneurium, on the other hand, CD68- and HLA-DR-positive macrophages predominated and T lymphocytes were rare.

With respect to humoral factors, IgG and C3d deposits were seen only occasionally in epineurial vessel walls, even in the vessels showing lesions. IgE and major basic protein were scarce in vessel walls with inflammatory lesions and in the endoneurial space.

Treatment and functional prognosis (Table 1 and Fig. 4)

One to two days after initiation of corticosteroid therapy, leukocytosis, eosinophilia and elevated LDH and ESR had normalized.

In 12 patients (a therapeutic response group), the modified Rankin score was reduced by ⩾1 point by 4 weeks. In 16 patients (no therapeutic response), the functional scores remained the same in the initial 4 weeks. In long-term outcome they were reduced to ⩽2 in 15 patients and remained at ⩾3 in 13 patients. The patients who showed a therapeutic response to initial corticosteroid therapy within 4 weeks (therapeutic response group) had a significantly favourable long-term outcome (modified Rankin score of ⩽2), while others, who showed no response to the initial therapy (no therapeutic response group), tended to show a poor functional long-term outcome (modified Rankin score of ⩾3, $P < 0.01$, Fisher's exact probability test; Fig. 4). The SNVDI score in patients with a poor long-term functional outcome was significantly higher than the score in patients with a good long-term functional outcome ($P < 0.05$, Mann–Whitney U test). No significant difference was evident between the groups with good and poor or no initial corticosteroid response with respect to the onset of age, onset age of asthma, Rankin score at the peak impairment, laboratory data, myelinated and unmyelinated fibre density of biopsied nerves, or time of initiation of corticosteroid therapy (for all, P = n.s., Mann–Whitney U test). The initial corticosteroid response was not affected by prior asthma management with low-dose corticosteroids or by whether intravenous corticosteroids were employed. Two patients (Cases 24 and 27) with poor initial responses to corticosteroids subsequently

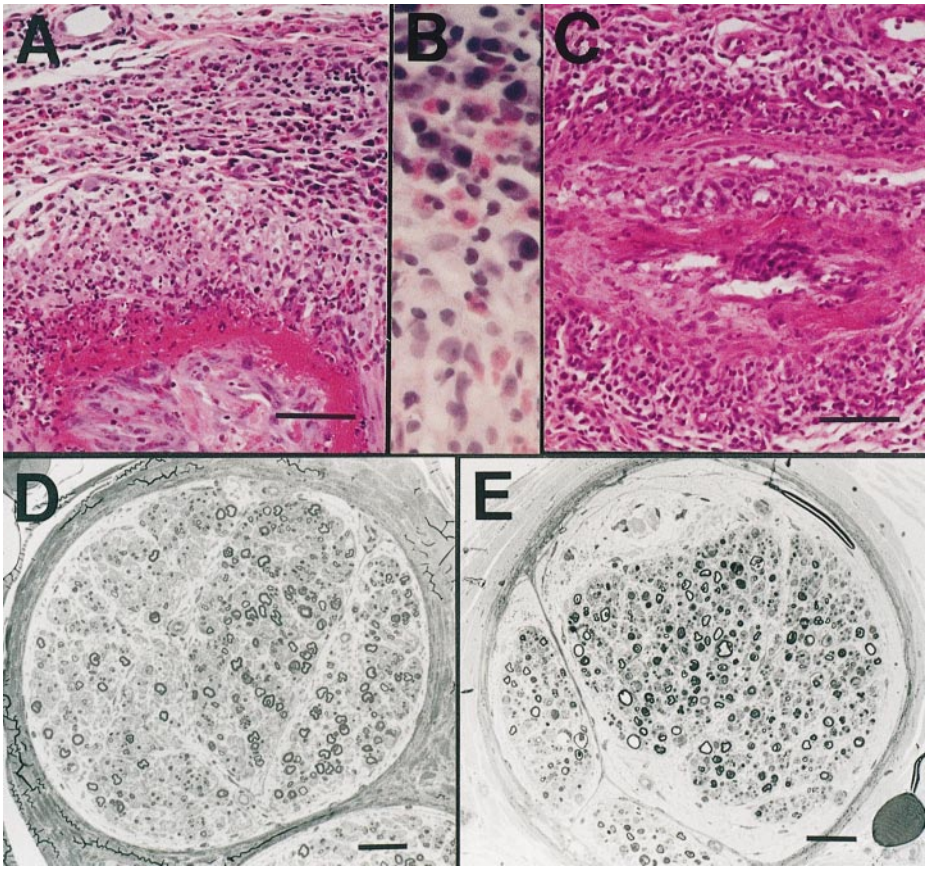

Fig. 2 Active vasculitic and nerve fascicular lesions of the sural nerves. (**A**) Eosinophils. Haematoxylin–eosin stain. Scale bar = 200 μm. (**B**) Eosinophilic infiltrations at higher magnification. Haematoxylin–eosin stain. Magnification ×160. (**C**) Infiltrating cells consist predominantly of lymphocytes, and eosinophils are rare. Haematoxylin–eosin stain. Scale bar = 200 μm. (**D**) Focal myelinated fibre loss. Toluidine blue stain. Scale bar = 200 μm. (**E**) Subperineurial oedema is prominent. Toluidine blue stain. Scale bar = 200 μm.

received the immunosuppressive agent cyclophosphamide (2 mg/kg) with apparent improvement in neurological symptoms. One patient died during the study period from pulmonary infection with respiratory failure. During the follow-up periods, only two patients (Cases 4 and 19) had a relapse of neuropathy, both within 8 months of onset.

Discussion

Clinical features and laboratory data

The onset of bronchial asthma occurred at ages ranging from 20 to 64 years (mean 43.7 years), similarly to previously described cases (Lanham *et al*., 1984; Sehgal *et al*., 1995) and notably older than the typical age of onset for asthma, particularly when childhood asthma is considered (Ford, 1969). The duration of asthma in our study ranged from 1 to 31 years (mean 9.1 years), again in agreement with previous reports (Sehgal *et al*., 1995). The specific pathophysiology of bronchial asthma associated with Churg–Strauss syndrome is unclear, but is likely to differ from that in childhood asthma since Churg–Strauss syndrome develops in childhood asthma only very rarely. The relationship between management condition of asthma and peripheral neuropathy observed in this study was impressive; all patients had good control of respiratory symptoms or were free of asthma when neuropathy became manifest. Bronchial asthma had preceded neuropathy by an average of 9 years, suggesting differences in the mechanisms underlying the asthma and the neuropathy.

Peripheral nerve involvement in Churg–Strauss syndrome has been reported frequently (Churg and Strauss, 1951; Chumbley *et al*., 1977; Inoue *et al*., 1992; Sehgal *et al*., 1995). In general, neuropathy is a common complication in systemic vasculitides such as PAN (Cohen *et al*., 1980; Wees *et al*., 1981; Moore and Cupps, 1983; Hawke *et al*., 1991; Chalk *et al*., 1993) and RA (Scott *et al*., 1981; Guillevin *et al*., 1988; Puéchal *et al*., 1995), although peripheral neuropathy may be the sole manifestation of systemic vasculitis (Chang *et al*., 1984; Kissel *et al*., 1985; Sobue *et al*., 1989*a*; Davies *et al*., 1996). While the prevalence of neuropathy in Churg–Strauss syndrome patients is not known precisely, the neuropathy and systemic vasculitis syndrome

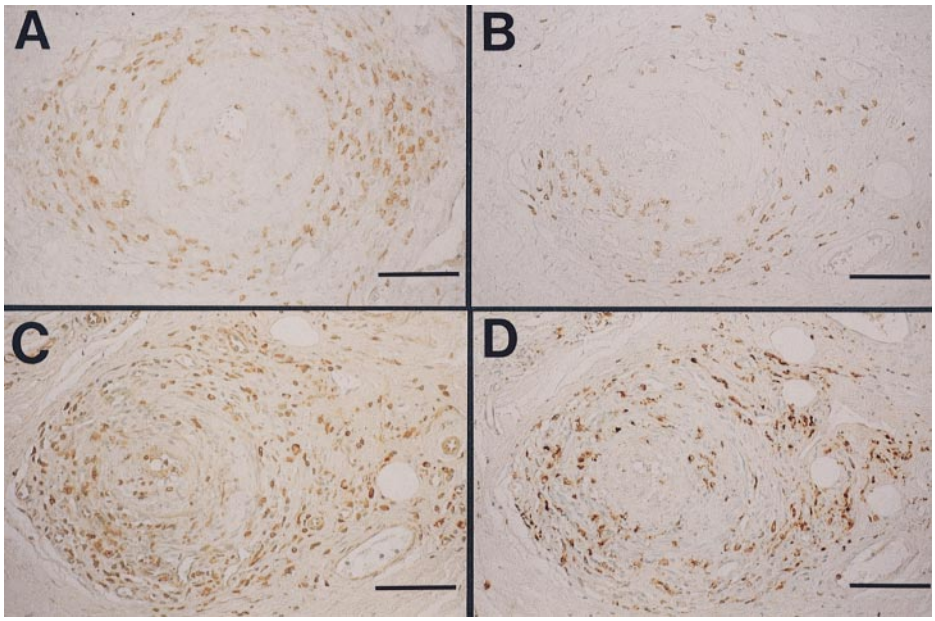

Fig. 3 Immunohistochemistry for T cell subsets and macrophages in the vasculitic lesion of the sural nerve. (**A**) Immunohistochemistry for CD4-positive T cells. (**B**) CD8-positive T cells. (**C**) Pan-T lymphocytes (CD3-positive). (**D**) CD-68 positive macrophages. Scale bar = 400 μm.

tended to occur among the patients with long-standing bronchial asthma, typically of adult onset.

Initial patterns of motor and sensory involvements indicated mononeuritis multiplex in 71% in our series, most frequently and severely affecting the peroneal nerves. The mononeuritis multiplex tended to evolve into a pattern of polyneuropathy. Mononeuritis multiplex is the typical neuropathic manifestation of acute systemic vasculitis (Moore and Fauci, 1981; Chang *et al*., 1984; Bouche *et al*., 1986; Sobue *et al*., 1989*a*; Hawke *et al*., 1991; Davies, 1994), although symmetrical polyneuropathy is also reported frequently (Wees *et al*., 1981; Kissel *et al*., 1985; Harati *et al*., 1986). As in our series, the latter pattern is associated with more advanced stages of disease. The patterns of distribution and subsequent spread resembled those of neuropathy in PAN and RA (Bleehen *et al*., 1963; Chang *et al*., 1984). Neuropathy at the worst point of the course was very severe, evidenced by a high modified Rankin score, and was indistinguishable from PAN- or RA-related neuropathy.

Among laboratory findings, elevated levels of plasma LDH and C-reactive protein, a high ESR and RA positivity were observed in 70–93% of patients and perinuclear antineutrophil cytoplasmic antibody in 42% of patients, indicating the widespread generalized inflammatory process. These inflammatory processes may reflect the systemic complications of peripheral nerves and visceral organs, but these inflammatory measures, as well as the SNVDI scores, were milder than those previously reported in PAN or RA (Scott *et al*., 1981; Moore and Cupps, 1983; Abu-Shakra *et al*., 1994), suggesting that the extent of systemic damage is less severe in Churg–Strauss syndrome.

To summarize the clinical features of Churg–Strauss syndrome-related neuropathy, the initial symptoms, initial distribution, severity and pattern of neuropathic spread were similar to those of systemic vasculitic neuropathy in RA and PAN (Bleehen *et al*., 1963; Weller *et al*., 1970; Dyck *et al*., 1972; Vital and Vital, 1985; Kissel *et al*., 1985; Said *et al*., 1988; Sobue *et al*., 1989*a*; Puéchel *et al*., 1995). However, the extent of the inflammatory process may be less severe in Churg–Strauss syndrome-related neuropathy.

Pathology

In sural nerve biopsies we detected necrotizing vasculitis in 15 of 28 cases (54%), a rate almost identical to those reported in PAN- or RA-associated neuropathy (Dyck *et al*., 1987; Said *et al*., 1988; Hawke *et al*., 1991; Puéchal *et al*., 1995). The pathological features of the affected arteries in the nerves involved, such as occlusive transmural inflammation with a mixed infiltrate of lymphocytes and other cells, resembled those of PAN and RA (Lovshin and Kernhan, 1948; Heathfield and Williams, 1954; Bleehen *et al*., 1963; Weller *et al*., 1970). Although eosinophilic infiltration and granuloma formation have been considered characteristic of vasculitic lesions in Churg–Strauss syndrome, these changes were not frequently seen in lesions of Churg–Strauss syndrome neuropathy. Prominent eosinophil infiltration was observed in three cases, but even in these cases the commonest cells were still T lymphocytes. In the most active vasculitic lesions, the prominent infiltrating cells were T lymphocytes and constituted a central focus of infiltration, with eosinophils present only in an outer zone to a lesser degree. This

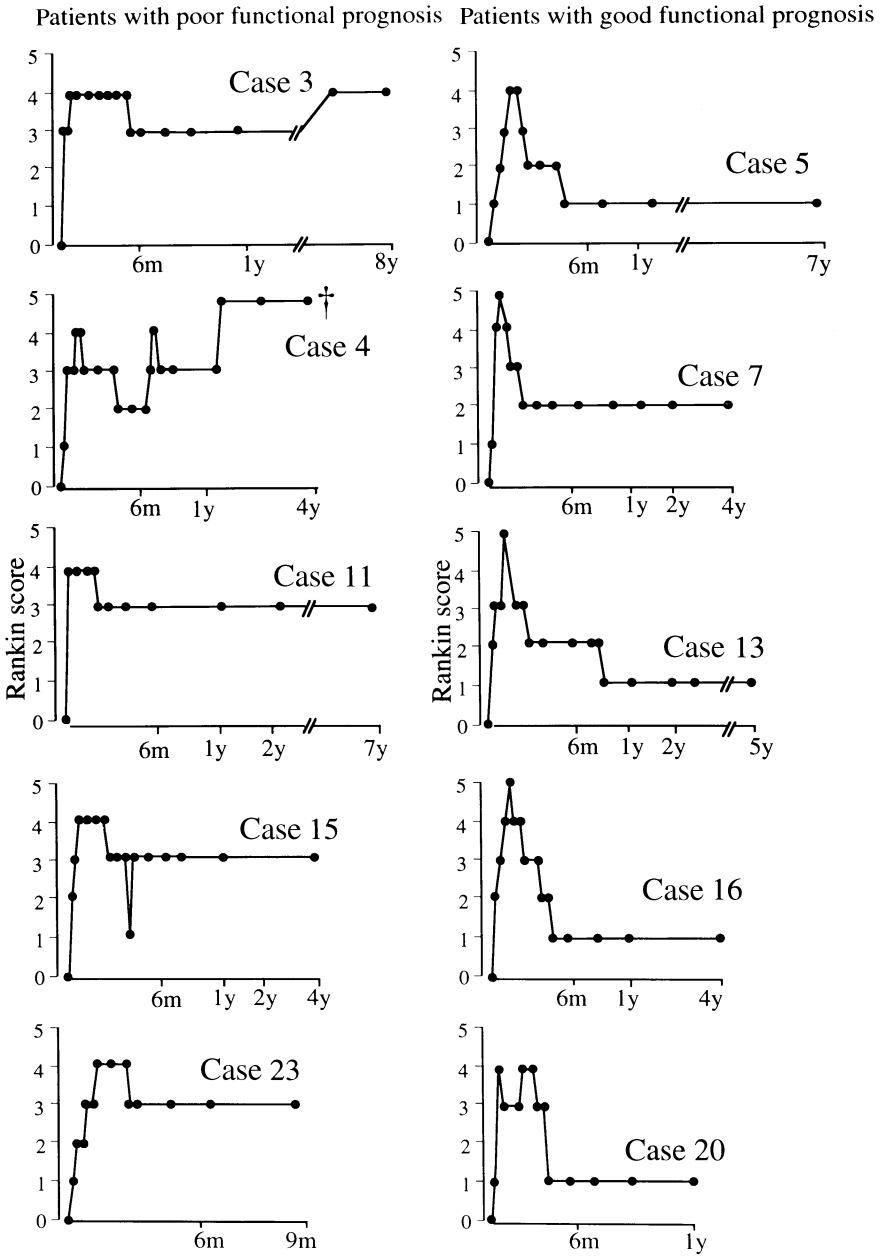

Fig. 4 Time-dependent profile of functional status (modified Rankin score). Patients who did not respond to the initial corticosteroid therapy exhibited a significantly poor long-term functional outcome.

distribution was observed even when the level of circulating eosinophils was high. These patterns in the vasculitic lesions suggest that eosinophils may play a role in the vasculitic process, but they may be less important than lymphocytes in the pathogenesis of vasculitis in Churg–Strauss syndrome. While eosinophilic invasion may be a hallmark of Churg–Strauss syndrome, it may not have high diagnostic and pathogenic significance in the peripheral nerve lesion of this disorder.

In PAN, RA (Kissel *et al*., 1989; Panegyres *et al*., 1996) and isolated peripheral nerve vasculitis (Davies *et al*., 1996), the major infiltrating cell component in the vasculitic lesion has been reported to be CD8-positive suppressor/cytotoxic T lymphocytes. These suppressor/cytotoxic T cells are thought to attack directly a vascular antigen or antigen-presenting endothelial cells as an initial early phase. In the vasculitic lesion of Churg–Strauss syndrome, however, CD8-positive T cells were present, but CD4-positive T cells were also present in similar or higher numbers in most cases. Both CD4-positive T cells and CD8-positive cells may play a role in the pathogenic background of vasculitis in Churg–Strauss syndrome. Since B cells were extremely rare in vascular lesions in Churg–Strauss syndrome neuropathy, their pathogenic significance is unclear.

Hawke *et al.* (1991) and Davies *et al.* (1996) have reported the deposition of immunoglobulin and complement in

perineurial and epineurial blood vessels in PAN, RA and non-systemic vasculitic neuropathy, suggesting that the immune complex-mediated humoral pathway may also contribute to the pathogenesis of vasculitic lesion in PAN and RA. However, these deposits are considered non-specific to vasculitic neuropathy by Kissel *et al.* (1989) and Engelhardt *et al.* (1993). In our Churg–Strauss syndrome cases, deposition of IgG and complement in epineurial vessels was rare or present only to a minor extent even in active lesions, supporting the view that the immune complex-mediated pathway is not significant in the pathogenic role of vasculitis in Churg–Strauss syndrome. Since epineurial vessels lack a functional blood–nerve barrier in contrast to endoneurial vessels (Lundborg, 1975), epineurial vascular deposition of IgG and complement could be non-specific if it is present, as has been suggested by some authors (Kissel *et al*., 1989; Engelhardt *et al*., 1993). Alternatively, rare IgG and complement deposition in the vasculitic lesion in Churg–Strauss syndrome may be different features from those of PAN, RA and non-systemic vasculitic neuropathy. Further, we could not detect significant IgE deposition in epineurial vessel walls despite having taken care to avoid IgE removal in the washing steps of our immunohistochemistry procedure. Although deposits of IgE in epineurial vessel walls have been reported occasionally (Inoue *et al*., 1992; Engelhardt *et al*., 1993), an IgE-dependent process may not be significantly involved in the pathogenesis of the vascular lesion leading to nerve damage.

Churg–Strauss syndrome, however, remains classified among the hypereosinophilic syndromes (HES), and neuropathy in Churg–Strauss syndrome could be caused by the major basic protein released from eosinophils. Deposits of major basic protein have been demonstrated in cardiac and splenic lesions in Churg–Strauss syndrome (Tai *et al*., 1984, 1987), suggesting that this protein is directly histotoxic, whereas the major basic protein was not found in the endoneurial space, and particularly not in relation to the degenerating nerve fibres in the present study. Soluble toxic protein may be difficult to demonstrate by immuno-histochemical techniques, and one cannot completely rule out a role for this protein in the nerve damage, but there is a considerable body of evidence supporting a direct role of ischaemia due to vascular occlusion and against a direct role of a neurotoxic protein derived from eosinophils.

Major nerve fibre pathology in sural nerves was characterized by massive axonal destruction. Massive reduction of SNAP and CMAP amplitudes was typical of such fibre pathology. Furthermore, the low frequency of segmental demyelination and remyelination and the parallel loss of myelinated fibres and unmyelinated fibres are highly consistent with acute ischaemic neuropathy (Parry and Brown, 1981; Vital and Vital, 1985; Nukada and Dyck, 1987; Korthals and Korthals, 1990; Fujimura *et al*., 1991). Restriction of clinical symptoms to specific nerve territories, especially the distal portions of limbs, was similar to the pathological features observed in experimental acute ischaemic neuropathy models (Hess *et al*., 1979; Parry and Brown, 1981; Nukada and Dyck, 1984, 1987). These resemblances also support the view that acute ischaemia is the major cause of Churg–Strauss syndrome neuropathy.

Taking into account these pathological findings, neither immunoglobulin- nor toxic protein-mediated processes represent the major cause of peripheral neuropathy in Churg–Strauss syndrome. Instead, acute ischaemic changes resulting from T-cell-mediated vasculitis are the major pathogenic mechanisms underlying this neuropathy.

Treatment and functional prognosis

In our series, only one death occurred during long-term follow-up, giving a strikingly low mortality rate compared with the systemic vasculitis of PAN and RA, which has a 5-year mortality rate of 40–50% (Cohen *et al*., 1980; Chang *et al*., 1984; Guillevin *et al*., 1988; Vollertsen *et al*., 1986; Abu-Shakra *et al*., 1994; Puéchal *et al*., 1995). Further, marked functional recovery from Churg–Strauss syndrome-related peripheral nerve involvement occurred in more than half of the patients. At the time of peak involvement, the peripheral nerves were severely damaged by vasculitis, as documented by complete sensory loss, paralysis, and failure of electrical stimuli to evoke SNAPs and CMAPs in affected nerves. In contrast, the typical long-term recovery was surprisingly good in individual nerves.

Poor prognostic factors for survival in systemic vasculitis due to PAN include age >50 years, renal insufficiency, proteinuria, cardiomyopathy and gastrointestinal involvement (Guillevin *et al*., 1988, 1996; Fortin *et al*., 1995). Significant prognostic factors for mortality with neuropathy associated with RA include older age, cutaneous vasculitis, extensive neuropathy and decreased complement level (Hawke *et al*., 1991; Puéchal *et al*., 1995). These reports suggest that the degree of systemic complication is one of the significant factors in determining long-term functional status in PAN and RA, but the incidence and extent of systemic visceral involvement indicated by SNVDI were likely to be lower in Churg–Strauss syndrome neuropathy than PAN and RA, in agreement with other reports (Abu-Shakra *et al*., 1994; Sehgal *et al*., 1995). Relapses of systemic visceral involvement were also very rare during the follow-up period, in striking contrast to PAN and RA vasculitic neuropathies (Abu-Shakra *et al*., 1994; Puéchal *et al*., 1995). The severity of the inflammatory process and the total extent of vasculitis may be less in Churg–Strauss syndrome neuropathy, in turn affecting the frequency of relapses and contributing to good survival and favourable functional prognosis in Churg–Strauss syndrome neuropathy.

Although oral corticosteroids or intravenous methyl-prednisolone were extremely effective in normalizing the leukocytosis, eosinophilia and elevated LDH and ESR, functional neurological recovery was less uniform. One group of patients showed an early response within 4 weeks of initiating treatment, but another group showed resistance to

initial corticosteroid treatment, associated with a sustained neurological deficit and a poor functional score. Over long-term follow-up, the outcome of the early responding group was fairly good while that of other patients was poor. Since no difference was obvious between these two groups with respect to other factors examined, the clinical course in the first 4 weeks may influence the long-term functional prognosis. Further, the total extent of vasculitic lesions may be less widespread and less severe in patients with a good outcome, as indicated by the SNVDI score. Hence it is supposed that the initial favourable clinical course and lesser systemic and nerve inflammatory involvement may eventually influence the long-term functional prognosis.

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