Tokyo, Japan) was given intravenously in Lugol's solution (200 mg iodine) to block the thyroid uptake. Cardiac MIBG uptake was expressed as a heart/ mediastinum ratio (H/M ratio) at 30 min (early scan) and 4 h (delayed scan) as described before (Watanabe *et al.*, 2001). Thermography and quantitative sweating measurements were performed on some selected patients as previously described (Kumazawa *et al.*, 1993).

Nerve conduction studies and somatosensory evoked potentials

Motor and sensory NCS were performed in the median, tibial and sural nerves using a standard method as described before (Sobue *et al.*, 1989). Motor nerve conduction velocity (MCV), distal motor latency (DL) and compound muscle action potential (CMAP) were recorded for the median and tibial nerves. Sensory nerve conduction velocity (SCV) and sensory nerve action potential (SNAP) were assessed for the median and sural nerves. Control values were obtained in 191 normal volunteers (mean age ± SD, 48.7 ± 16.5 years; men : women, 97 : 94) for the median nerve, 121 (mean age ± SD, 49.9 ± 15.0; men : women, 64 : 57) for the tibial nerve and 133 (mean age ± SD, 50.6 ± 15.6; men : women, 74 : 59) for the sural nerve (Koike *et al.*, 2001). Blink reflexes were recorded using a standard technique (Kimura, 2001).

SEPs were recorded using median nerve stimulation at the wrist (Kachi *et al.*, 1994). Cortical (N20), cervical (N13), and Erb's point (N9) peaks were assessed by separate stimulation. Controls of the latency of SEPs were obtained in 37 normal volunteers (mean age ± SD, 38 ± 7 years).

Sural nerve biopsy and autopsy study

Sural nerve biopsies were performed in 55 patients as described previously (Sobue *et al.*, 1989). Informed consent was established beforehand. Sural nerve biopsy specimens were examined by standard light microscopic methods and by teased fibre techniques. Specimens were divided into two portions. The first portion was fixed in 2.5% glutaraldehyde solution in 0.125 M cacodylate buffer (pH 7.4) and then embedded in an epoxy resin for morphometric and ultrastructural study. Density of myelinated fibres and morphological features were assessed in sections embedded in the epoxy resin and stained with toluidine blue using a computer-assisted image analyser (Luzex FS; Nikon, Tokyo, Japan), and densities of small and large myelinated fibres were calculated as described previously (Sobue *et al.*, 1989; Koike *et al.*, 2001). Some parts of specimens were processed for teased fibre study and were assessed for pathological conditions according to criteria described previously (Sobue *et al.*, 1989; Dyck *et al.*, 1993). For electron microscopic examination, epoxy resin-embedded specimens were processed for ultrathin sectioning. To assess the density of unmyelinated fibres, electron microscopic photomicrographs at a magnification of ×4000 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.

For the autopsy study, the brain, spinal cord, sympathetic and sensory ganglia, peripheral nerve trunks, submandibular and subauricular salivary glands as well as various visceral organs were sampled systemically at the time of autopsy and examined in paraffin and epoxy-resin embedded sections.

MRI assessment of cervical spinal cord

A total of 27 patients underwent MRI of the cervical spinal cord, including the C4 level on a 1.5 T unit. We used axial T2*-weighted gradient echo images (repetition time/echo time/excitations, 700/21/3; flip angle, 20°; matrix, 256 × 256) as described previously (Yasuda *et al.*, 1994; Sobue *et al.*, 1995; Mori *et al.*, 2001). MRI findings were assessed on their distributions of abnormal high intensity area in the posterior columns of the spinal cord.

Laboratory data

Routine blood tests were performed, including anti-SS-A and anti-SS-B antibodies. These autoantibodies were detected using enzyme-linked immunosorbent assay and immunoblotting [Mesacup-2 test, according to the manufacturer's instructions (MBL, Ltd. Japan)]. Alpha-fodrin, a candidate autoantigen for Sjögren's syndrome (Haneji *et al.*, 1997) also was examined as follows. The purified recombinant N-terminal portion of alpha-fodrin and GST (glutathione-*S*-transferase) fusion protein (JS-1) were loaded onto 10% polyacrylamide gels and transferred to nitrocellulose membranes by electroblotting. The membranes were blocked overnight at room temperature with Tris-buffered saline containing 3% non-fat dry milk. The membranes were incubated with sera from patients with Sjögren's syndrome (1 : 200 dilution) for 4 h at room temperature. Then, bound antibodies were detected with biotinylated anti-human IgG antibodies and alkaline phosphatase-conjugated streptavidin (both from Jackson Immunoresearch, West Grove, PA) using 5-bromo-4-chloro-3-indolyl phosphate and nitro blue tetrazorium as substrates.

Statistical analysis

All statistical analyses were performed using the Mann–Whitney *U*-test. *P*-values of <0.05 were considered significant.

Results

General clinical features and classification of neuropathy

All 92 patients fulfilled the diagnostic criteria for Sjögren's syndrome (Fujibayashi *et al.*, 1999; Vitali *et al.*, 2002). The majority of patients (86 patients) were diagnosed as having Sjögren's syndrome after neurological symptoms developed, while only six patients were diagnosed with Sjögren's syndrome before the neurological symptoms appeared. Thus most of the patients had been followed for a neuropathy of unknown cause for a while before being diagnosed with Sjögren's syndrome. We classified these patients into seven forms of neuropathy: sensory ataxic neuropathy, painful sensory neuropathy without sensory ataxia, multiple mononeuropathy, multiple cranial neuropathy, trigeminal neuropathy, autonomic neuropathy and radiculoneuropathy, based on the predominant neuropathic symptoms. Sensory ataxic neuropathy was defined as one with sensory neuropathy predominantly manifesting as impairment of joint-position sense leading to sensory ataxia but preserved muscle power, muscle volume and motor nerve function (Sobue *et al.*, 1993). A total of 36 patients were included in the sensory ataxic neuropathy group. Painful neuropathy without sensory ataxia (Mori *et al.*, 2003) was another form of sensory neuropathy but with predominant involvement of superficial sensation of pain and light touch sense without or with minor impairment of deep sensation resulting in a painful sensory neuropathy without sensory ataxia. Motor function was well preserved with this neuropathy. Eighteen patients were included in this group. Eleven patients were considered to have multiple mononeuropathy. This form of neuropathy was characterized by multiple mononeuropathy mainly distributed in the distal portion of the limbs with both motor and sensory involvement. Sensory involvement generally included both superficial and deep sensation. Twenty patients were classified as having cranial neuropathy. Of the 20, 5 patients had multiple cranial neuropathy and 15 patients had isolated trigeminal neuropathy. Multiple cranial neuropathy affects multiple cranial motor and sensory nerves including the trigeminal nerve. Trigeminal neuropathy was defined as a pure sensory neuropathy restricted to the territory of the sensory trigeminal nerves. Autonomic neuropathy was characterized by predominant autonomic dysfunction. Three patients were considered to have this neuropathy. Radiculoneuropathy was defined by lesions restricted predominantly to the spinal roots or the very proximal portion of the spinal nerves. Radiculoneuropathy often mimics chronic inflammatory demyelinating polyneuropathy. Four patients were included in this category of neuropathy.

The age at first examination and the age of onset of neuropathic symptoms varied to some extent, but did not differ among the forms of neuropathy (Table 1). A female predominance was commonly observed in all of the neuropathies. Sjögren's syndrome-related symptoms also were seen at similar rates among the neuropathies. More than half of the patients had sicca syndrome, manifested by either xerophthalmia or xerostomia. Schirmer's test and the Rose Bengal test were positive in >50% of the examined patients. Almost all of the examined patients had either lymphocytic infiltration of the salivary glands, salivary gland cell destruction or both on minor salivary gland biopsy. Sialography and salivary scintigraphy also were positive in a majority of patients in each neuropathic group. Antibodies to SS-A and SS-B were present in 20–100% and 0–50% of patients in each neuropathic group, respectively. Only 13 patients were both SS-A and SS-B positive. Anti-alpha-fodrin antibodies were detected in 60–100% of patients in each neuropathic group. This positive rate was extremely high as compared with those in the control group without neuropathy (<14% positive), while it was not significantly different between neuropathic groups. Mild increases in the CSF protein concentration were seen in some of the patients examined.

As complicating systemic inflammatory symptoms, hypothyroidism was seen in nine patients, dyshaematopoietic anaemia in two patients, interstitial pneumonia in three patients, myositis in one patient, liver dysfunction in four patients, pancreatitis in two patients, renal involvement in one patient and lymphoma in one patient (Table 1).

Neuropathic features of each form of neuropathy

Sensory ataxic neuropathy

A total of 36 patients had this form of neuropathy (Table 2). This neuropathy was characterized by sensory ataxia due to kinaesthetic deep sensory impairment without substantial motor symptoms. The initial symptom was usually paraesthesias in the digits of the foot or hand. These paraesthesias were often unilateral, and gradually spread to the limbs, trunk and face. In three patients, the initial paraesthesia was localized to the trigeminal nerve area. The time from the onset to the development of full-blown symptoms of sensory involvement was variable among the patients, weeks to months in four patients, but usually months to years. The sensory symptoms were mostly asymmetrical, segmental or multi-focal rather than presenting as a symmetrical polyneuropathy, particularly in the progression stage. Ten patients had trigeminal nerve involvement. Muscle weakness and mild atrophy were observed in four patients. Sensory impairment was mostly deep sensory predominant with Romberg's sign and pseudoathetosis being present in all of the patients. Pain or painful dysaesthesia was present in 18 patients. A total of 10 and 20 patients showed facial and truncal sensory involvement, respectively. There was generalized areflexia in all patients. The walking pattern was characteristic of sensory ataxia. In the patients with advanced disease, they were unable to walk and were wheel-chair bound.

With respect to autonomic symptoms, 17 of the 30 assessed patients exhibited abnormal pupils including Adie's pupils associated with anisocoric and elliptic pupils (Table 3). Orthostatic hypotension was present in 12 patients, mostly without syncope. Hypohidrosis or anhidrosis was observed in 21 patients, often with segmental anhidrosis in the trunk (Fig. 1). Marked decreases in ^{123}I-MIBG cardiac uptake were present in 8 of the 11 patients who were examined.

With respect to nerve conduction, SNAPs in the median and sural nerves were not evoked in 61 and 50% of patients, respectively (Table 4). In contrast, CMAPs were fairly well preserved in most patients. MCV and SCV were not slowed. Temporal dispersion of the CMAPs or conduction block was not seen. SEPs were not evoked in 67, 73 and 40% of the examined patients in N20, N13 and N9, respectively (Table 4). These conduction studies indicate that axonal features were almost exclusively present in this neuropathy, and the central rami of sensory ganglion neurons were also involved in parallel.

T2*-weighted MRI demonstrated posterior column high intensity signal in 9 of the 12 examined patients (Table 4; Fig. 1). The extent of dorsal column high intensity T2* signal was well correlated with the distribution and intensity of sensory involvement and sensory ataxia, indicating the presence of central rami involvement due to sensory ganglion neuron damage (Mori *et al.*, 2001).

Sural nerve biopsy was performed in 31 patients (Table 5). Total myelinated fibre density was variably reduced, ranging

Table 1 Clinical features of patients with peripheral neuropathy associated with Sjögren's syndrome

Clinical features	Sensory neuropathy		Multiple mononeuropathy (n = 11)	Cranial neuropathy		Autonomic neuropathy (n = 3)	Radiculo-neuropathy (n = 4)
	Ataxic (n = 36)	Painful (n = 18)		Multiple (n = 5)	Trigeminal (n = 15)		
Age (years)	65.2 ± 7.8	58.1 ± 15.9	59.1 ± 18.2	55.6 ± 12.7	55.6 ± 9.4	46.3 ± 18.0	57.0 ± 11.0
Age of onset of neuropathy (years)	64.9 ± 12.9	56.0 ± 13.8	58.1 ± 13.5	55.1 ± 14.8	51.7 ± 11.6	42.5 ± 17.4	49.0 ± 12.2
Sex, women:men (n)	26:10	16:2	10:1	4:1	15:0	2:1	3:1
Follow-up (years)	5.7 ± 4.6	3.6 ± 2.8	2.3 ± 1.3	5.2 ± 6.6	7.0 ± 4.1	1.7 ± 1.6	7.3 ± 3.8
(range) (years)	(1–18)	(1–12)	(1–4)	(1–7)	(2–10)	(1–3)	(3–10)
Sjögren's syndrome							
Dry eye: n (%)/dry mouth: n (%)	20 (56)/23 (64)	13 (72)/12 (67)	7 (64)/7 (64)	3 (60)/2 (40)	10 (67)/10 (67)	2 (67)/2 (67)	2 (50)/2 (50)
Positive findings							
Schirmer's test: n (%)	27/29 (93)	14/15 (93)	7/8 (88)	5/5 (100)	8/10 (80)	3/3 (100)	2/4 (50)
Rose Bengal test: n (%)	20/29 (69)	11/12 (92)	6/6 (100)	3/5 (60)	8/9 (89)	2/2 (100)	ND
Salivary gland biopsy: n (%)	26/28 (93)	13/16 (81)	8/9 (89)	5/5 (100)	11/11 (100)	2/2 (100)	4/4 (100)
Sialography, cintigraphy: n (%)	9/10 (90)	6/6 (100)	3/3 (100)	2/3 (67)	8/8 (100)	1/1 (100)	ND
SS-A: n (%)	19/36 (53)	7/18 (39)	7/11 (64)	1/5 (20)	6/15 (40)	2/3 (67)	4/4 (100)
SS-B: n (%)	4/36 (11)	3/18 (17)	2/11 (18)	1/5 (20)	0/15 (0)	1/3 (33)	2/4 (50)
Alpha-fodrin: n (%)	14/16 (88)	6/7 (86)	3/5 (60)	5/5 (100)	2/2 (100)	1/1 (100)	3/3 (100)
CSF protein elevation: n (%)	8/23 (35)	3/10 (30)	5/8 (63)	1/3 (33)	0/1 (0)	0/1 (0)	4/4 (100)
Associated symptoms (n)	T (4), P (2), Pa (2), L (3), Ly (1)	T (2), A (2), R (1), P (1), M (1)	T (2)	–	–	–	T (1), L (1)

n/n, positive patient number to all examined patient number. As for associated symptoms, T, hypothyroidism; P, interstitial pneumonia; Pa, pancreatitis; A, anaemia; M, myositis; L, liver dysfunction; Ly, lymphoma; R, renal involvement.

Table 2 Neuropathic symptoms

Clinical features	Sensory neuropathy		Multiple mononeuropathy (*n* = 11)	Cranial neuropathy		Autonomic neuropathy (*n* = 3)	Radiculo-neuropathy (*n* = 4)
	Ataxic (*n* = 36)	Painful (*n* = 18)		Multiple (*n* = 5)	Trigeminal (*n* = 15)		
Initial symptom							
Sensory disturbance: *n* (%)	36 (100)	3 (17)	11 (100)	0 (0)	15 (100)	0 (0)	4 (100)
Pain/painful dysaesthesia: *n* (%)	0 (0)	18 (100)	1 (9)	1 (20)	2 (13)	0 (0)	0 (0)
Weakness: *n* (%)	0 (0)	0 (0)	8 (73)	0 (0)	0 (0)	0 (0)	2 (50)
Autonomic symptoms: *n* (%)	0 (0)	1 (6)	0 (0)	0 (0)	0 (0)	3 (100)	0 (0)
Cranial nerve symptoms: *n* (%)	3* (8)	0 (0)	1 (9)*	5 (100)	15 (100)	0 (0)	1 (25)**
Initial progression							
Acute: *n* (%)	0 (0)	3 (17)	2 (18)	3 (60)	0 (0)	1 (33)	0 (0)
Subacute: *n* (%)	4 (11)	1 (6)	4 (36)	0 (0)	3 (20)	0 (0)	1 (25)
Chronic: *n* (%)	32 (89)	14 (78)	5 (45)	2 (40)	12 (80)	2 (67)	3 (75)
Cranial nerve involvement: *n* (nerve)	10 (V)	8 (V)	2 (V)	2 (III), 3 (V), 2 (VI), 3 (VII), 3 (IX), 3 (X), 1(XII)	15 (V)	1 (V)	1 (III)
Muscle weakness/atrophy: *n* (%)	4 (11)	1 (6)	10 (91)	0 (0)	0 (0)	0 (0)	2 (50)
Sensory impairment: *n* (%)	36 (100)	18 (100)	11 (100)	3 (60)	15 (100)	2 (67)	4 (100)
Modality							
Deep > superficial sensation: *n* (%)	33 (92)	0 (0)	1 (9)	0 (0)	0 (0)	1 (33)	3 (75)
Deep = superficial sensation: *n* (%)	3 (8)	0 (0)	7 (64)	0 (0)	0 (0)	1 (33)	1 (25)
Superficial > deep sensation: *n* (%)	0 (0)	18 (100)	3 (27)	3 (60)	15 (100)	0 (0)	0 (0)
Pain/painful dysaesthesia: *n* (%)	18 (50)	18 (100)	7 (64)	1 (20)	2 (13)	0 (0)	0 (0)
Sensory ataxia: *n* (%)	36 (100)	2 (11)	1 (9)	0 (0)	0 (0)	2 (67)	2 (50)
Distribution							
Face: *n* (%)	10 (28)	8 (44)	2 (18)	3 (60)	15 (100)	1 (33)	0 (0)
Trunk: *n* (%)	20 (56)	10 (56)	2 (18)	2 (40)	0 (0)	2 (67)	1 (25)
Limbs: *n* (%)	36 (100)	18 (100)	11 (100)	2 (40)	2 (13)	2 (67)	4 (100)
Areflexia: *n* (%)	36 (100)	9 (50)	7 (64)	0 (0)	0 (0)	2 (67)	4 (100)
Modified Rankin scale (mean ± SD)	3.3 ± 0.8	2.3 ± 0.8	2.3 ± 0.8	–	–	3.3 ± 1.2	2.3 ± 1.3
(range)	(2–5)	(1–4)	(1–3)			(2–4)	(1–4)

Cranial nerve symptoms in initial symptom: *, trigeminal nerve lesion; **, diplopia and ptosis. Modified Rankin scale: 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.

Table 3 Autonomic symptoms

Clinical features	Sensory neuropathy		Multiple mononeuropathy (*n* = 6)	Cranial neuropathy		Autonomic neuropathy (*n* = 3)	Radiculo-neuropathy (*n* = 4)
	Ataxic (*n* = 30)	Painful (*n* = 16)		Multiple (*n* = 5)	Trigeminal (*n* = 9)		
Abnormal pupils: *n*	17	3	0	1	3	3	0
Orthostatic hypotension: *n*	12	5	0	0	3	3	0
Faint: *n*	0	0	0	0	0	3	0
Hypohidrosis/anhidrosis: *n*	21	10	3	2	4	3	2
Diarrhoea: *n*	6	0	1	0	1	3	0
Constipation: *n*	6	5	2	1	1	3	2
Vomiting: *n*	2	0	0	0	0	1	0
Urinary disturbance: *n*	1	3	0	0	0	2	1
Decreased uptake of ^{123}I-MIBG: *n*	8/11	5/7	ND	ND	ND	2/2	0/2
Total: *n*	21/30	11/16	3/6	2/5	4/9	3/3	2/4

Decreased uptake of ^{123}I-MIBG = the ^{123}I-MIBG heart/mediastinum ratio (H/M ratio) of delayed scan was <1.8 (control–2 SD) (Hamada *et al.*, 2003). *n/n*, positive patient number to all examined patient number; ND, not determined.

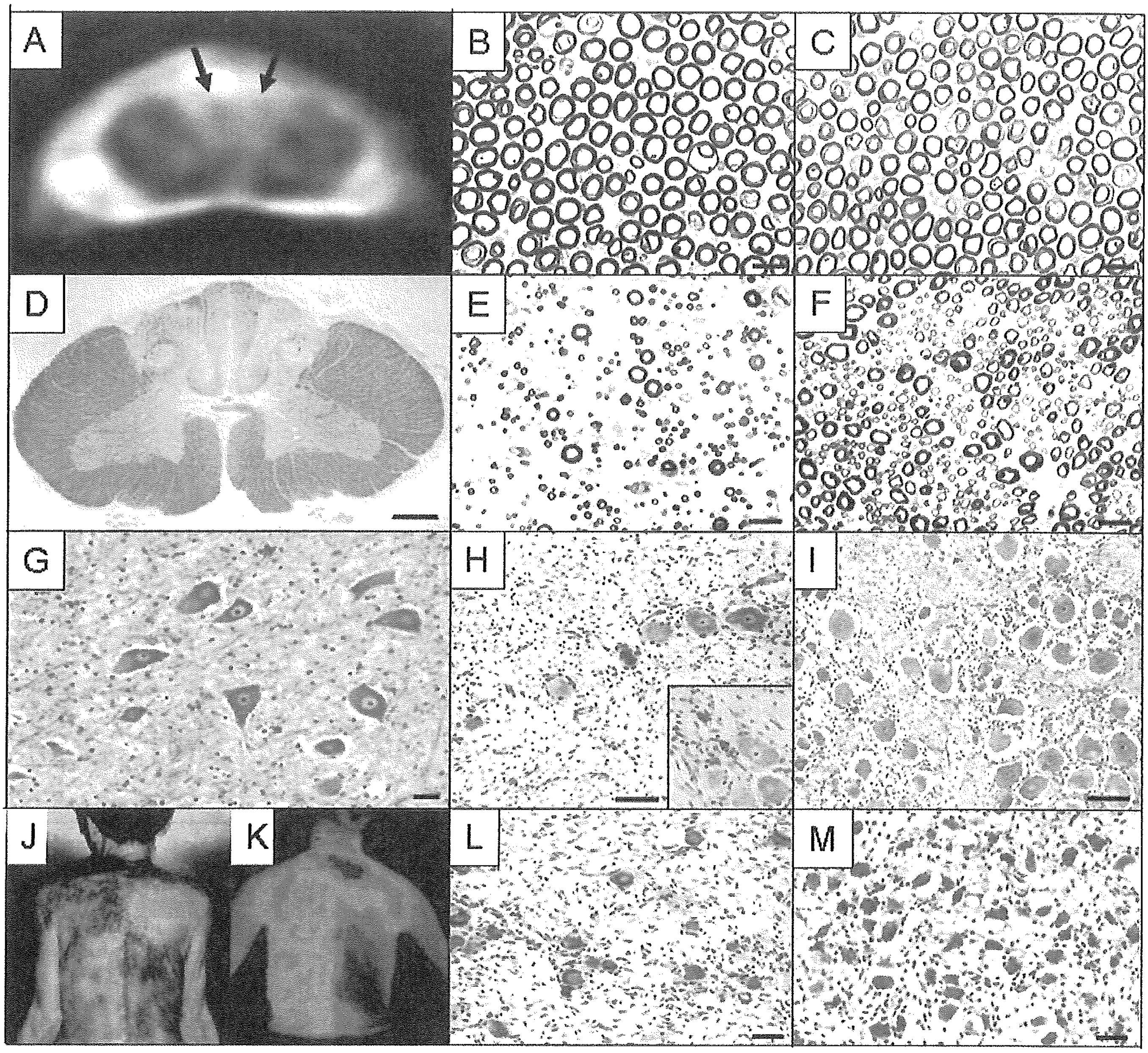

Fig. 1 Pathological findings, MRI and sweating assessment of an autopsied patient with the sensory ataxic neuropathy.
(**A**) Axial T2*-weighted gradient echo image of the cervical spinal cord (C4) of the patient. A high intensity area is present in the posterior column including both fasciculus cuneatus and gracilis as indicated by arrows. (**B** and **C**) Cross-section of the L4 ventral spinal root. Myelinated fibres are well preserved in the patient (**B**) and control (**C**). Scale bar = 20 μm. (**D**) Cross-section of the dorsal column of the cervical spinal cord. Axons are almost completely lost. Klüver–Barrera's stain. Scale bar = 1 mm. (**E** and **F**) Cross-section of the L4 dorsal spinal root. Large myelinated fibres are severely lost in the patient (**E**) compared with the control (**F**). Scale bar = 20 μm. (**G**) Cross-section of the L4 ventral horn. The population of the anterior horn cell is well preserved. Klüver–Barrera's stain. Scale bar = 40 μm.
(**H**) Cross-section of the L4 dorsal root ganglion. The population of the nerve cell is decreased (**H**). Nageotte's nodules are occasionally seen (**H**). (**I**) Control. Klüver–Barrera's stain. Scale bar = 100 μm. (**J**) Thermal sweating measured by Minor's iodine–starch test in an artificial climate chamber at an ambient temperature of 40°C and 40% relative humidity. The area of anhidrosis was very distinct and distributed in a segmental manner. (**K**) Plain thermograms monitored by infrared thermography. Surface skin temperature was also segmental in distribution (quoted from Kumazawa *et al.*, 1993 with permission for publication). (**L**) Section of the thoracic sympathetic ganglion. The population of the nerve cell bodies is decreased (**L**) compared with control case (**M**). Klüver–Barrera's stain. Scale bar = 40 μm.

from 131 to 6918/mm^2 (mean ± SD, 3287 ± 2843/mm^2), and that of unmyelinated fibres was also reduced. Mean densities of large, small myelinated and unmyelinated fibres were reduced to 18, 56 and 75% of normal controls, respectively, indicating large fibre predominant loss. Axonal sprouts were not conspicuous in any case. In teased-fibre preparations, axonal degeneration was observed in 30.9 ± 36.1% of samples, while segmental demyelination was seen in only

Table 4 Nerve conduction, sensory evoked potentials, and spinal cord MRI study

Nerve conduction, SEP and MRI	Sensory neuropathy		Multiple mononeuropathy	Cranial neuropathy		Autonomic neuropathy	Radiculo-neuropathy	Controls
	Ataxic	Painful		Multiple	Trigeminal			
Nerve conduction study	$n = 36$	$n = 18$	$n = 11$	$n = 5$	$n = 15$	$n = 3$	$n = 4$	$n = 121–191$
Median nerve								
MCV (m/s)	53.1 ± 4.0	53.3 ± 33.2	51.3 ± 3.7	51.2 ± 8.1	54.7 ± 3.5	53.2 ± 0.7	50.5 ± 10.3	57.8 ± 3.7
DL (ms)	3.7 ± 0.5	3.4 ± 0.2	3.5 ± 0.4	4.0 ± 0.5	3.9 ± 1.3	3.7 ± 0.6	4.4 ± 2.0	3.4 ± 0.4
CMAP (mV)	11.1 ± 2.8	11.2 ± 4.0	10.4 ± 2.4	11.4 ± 3.0	12.7 ± 3.4	10.5 ± 2.7	5.6 ± 3.1**	10.7 ± 3.5
SCV (m/s)	50.0 ± 4.7	51.5 ± 3.5	49.6 ± 7.8	61.4 ± 1.3	55.1 ± 2.6	58.5 ± 0.3	50.8 ± 9.5	57.8 ± 4.7
SNAP (μV)	4.1 ± 9.0***	4.4 ± 6.6***	4.9 ± 4.7***	23.9 ± 1.9	11.3 ± 4.1	25.6 ± 4.0	22.2 ± 1.0	23.5 ± 8.4
N.E. (%)	61	11	18	0	0	33	0	0
Tibial nerve								
MCV (m/s)	43.5 ± 2.8	44.5 ± 3.3	38.6 ± 3.9	48.3 ± 4.2	43.7 ± 2.3	44.7 ± 1.2	43.5 ± 1.1	46.9 ± 3.5
DL (ms)	4.8 ± 0.8	4.5 ± 0.4	5.1 ± 1.1	4.7 ± 1.0	5.1 ± 0.2	4.2 ± 0.9	6.0 ± 3.4	4.5 ± 0.8
CMAP (mV)	10.5 ± 7.0	14.5 ± 6.8	6.5 ± 9.1*	12.2 ± 9.1	16.4 ± 5.2	12.6 ± 1.0	9.2 ± 3.3*	10.9 ± 3.8
Sural nerve								
SCV (m/s)	45.3 ± 2.8	46.7 ± 6.5	46.4 ± 3.1	50.3 ± 3.5	53.4 ± 1.2	46.8 ± 0.0	45.0 ± 5.1	51.0 ± 5.1
SNAP (μV)	2.2 ± 3.6***	8.1 ± 8.1***	1.3 ± 1.5***	20.5 ± 3.5	22.5 ± 2.3	10.3 ± 1.4	18.3 ± 1.5	11.5 ± 4.7
N.E. (%)	50	17	55	0	0	33	0	0
SEP	$n = 15$	$n = 8$				$n = 3$	$n = 4$	$n = 37$
Median nerve stimulation								
N20 latency (ms)	20.2 ± 2.1	20.9 ± 2.3	ND	ND	ND	19.5 ± 0.7	21.4 ± 3.2	18.9 ± 1.1
N.E. (%)	67	0				33	0	
N13 latency (ms)	13.1 ± 0.8	14.4 ± 1.9	ND	ND	ND	13.1 ± 0.6	14.8 ± 2.6	12.8 ± 1.0
N.E. (%)	73	0				33	0	
N9 latency (ms)	9.1 ± 0.9	9.8 ± 0.9	ND	ND	ND	8.9 ± 0.4	10.1 ± 1.2	8.6 ± 0.6
N.E. (%)	40	13				33	0	
MRI	$n = 12$	$n = 8$				$n = 3$	$n = 4$	
Spinal cord abnormality	9[†]	3[†]	ND	ND	ND	1[†]	4[‡]	

Values are expressed as mean ± SD. Control values are those described previously (Koike *et al.*, 2001). MCV, motor nerve conduction velocity; DL, distal latency; CMAP, compound muscle action potentials; SCV, sensory nerve conduction velocity; SNAP, sensory nerve action potentials; N.E., not evoked; SEP, somatosensory evoked potentials; control values are from 37 conduction times. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$ as compared with control value. [†]In T2* weighted gradient echo images, a high intensity area is present in the posterior column. [‡]In T1 weighted echo images. Posterior spinal roots and cauda equina are enhanced by gadolinium.

Table 5 Pathological findings in the sural nerve

Clinical features	Sensory neuropathy		Multiple mononeuropathy ($n = 8$)	Cranial neuropathy		Autonomic neuropathy ($n = 2$)	Radiculo-neuropathy ($n = 4$)	Controls ($n = 7$)
	Ataxic ($n = 31$)	Painful ($n = 9$)		Multiple ($n = 0$)	Trigeminal ($n = 1$)			
Myelinated fibre density (no./mm^2)								
Total	3287 ± 2843**	4105 ± 2260**	1153 ± 920**	ND	8010	2924	5985 ± 1890*	8220 ± 614
Large	579 ± 697***	2039 ± 1136*	226 ± 262**	ND	2994	1113	1593 ± 913*	3150 ± 383
Small	2878 ± 2482*	2056 ± 1267**	927 ± 672***	ND	5111	1811	4391 ± 977	5071 ± 397
Small/large	13.7 ± 18.1**	0.9 ± 0.5*	10.3 ± 12.0*	ND	1.7	2.9	3.1 ± 1.2	1.6 ± 0.2
Unmyelinated fibre density (no./mm^2)	22 643 ± 9477*	9879 ± 9203**	ND	ND	ND	14 822	ND	29 901 ± 2623
Segmental de-/remyelination (%)	9.7 ± 9.4	10.0 ± 2.5	13.3 ± 13.1	ND	2.5	7.0	14.5 ± 9.2	7.2 ± 6.5
Axonal degeneration (%)	30.9 ± 36.1**	19.0 ± 16.1	61.0 ± 5.3**	ND	0	12.5	3.5 ± 4.9	1.4 ± 1.6
Vasculitis: n (%)	6 (19)	0 (0)	5 (63)	ND	0 (0)	0 (0)	0 (0)	–
Perivascular cell invasion: n (%)	9 (29)	1 (11)	6 (75)	ND	0 (0)	0 (0)	1 (25)	–

Values are expressed as mean ± SD. Control values (mean ± SD) were obtained from autopsy material and expressed as mean ± SD for 7 case. (Koike *et al.*, 2004). ND, not determined; Small < 6.73 μm; large ≥ 6.73 μm in fibre diameter (Sobue *et al.*, 1989); *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$ as compared with control values.

9.7 ± 9.4% of samples, indicating that axonal changes are the predominant pathological feature. Chronic vasculitis of the arterioles in the epineurial space was seen in six patients and mild perivascular lymphocyte infiltrates in the small vessels were also seen in nine patients.

Painful sensory neuropathy without sensory ataxia

A total of 18 patients had this form of neuropathy (Table 2). The initial symptoms were painful dysaesthesia in the most distal portions of the limbs, usually in unilateral limbs. In three patients, the initial progression was acute, occurring in days, and painful dysaesthesias were present over the entire body, including the trunk and face. In a majority of patients, spread of the dysaesthesias was chronic, occurring over months to years. The trigeminal nerve was involved in eight patients. Sensory impairment was relatively predominant with respect to superficial sensation of pain, temperature and light touch, and was associated with pain or painful dysaesthesia. Deep sensation was relatively well preserved, and motor function also was preserved. However, mild sensory ataxia in the limbs was seen in two patients. The face and trunk were involved in 8 and 10 patients, respectively, and segmental in distribution in some patients. In contrast to the sensory ataxic form, deep tendon reflexes were fairly well preserved in half of the patients. Seven patients could not walk because of severe pain.

Eleven patients showed symptoms consistent with autonomic neuropathy (Table 3). Abnormal pupils, including Adie's pupils and elliptic pupils, were seen in three patients. Orthostatic hypotension and hypohidrosis or anhidrosis were present in 5 and 10 patients. Segmental distribution of anhidrosis was often seen in the trunk. A severe decrease in ^{123}I-MIBG cardiac uptake was seen in five of the seven examined patients. These results suggest that autonomic nerves are also widely involved in this form of neuropathy.

In contrast to sensory ataxic neuropathy, unelicited SNAPs were present in only 11 and 17% of median and sural nerves, respectively (Table 4). SCV was well preserved. MCV showed no slowing and CMAPs were well preserved. Cortical (N20) and cervical (N13) SEPs were elicited in all of the examined patients and Erb's point (N9) SEP was not elicited in only one patient examined.

T2*-MRI of the spinal cord showed minimal high intensity signal in the posterior column in three out of the eight patients studied (Table 4). The extent of high intensity signal in these patients was relatively small compared with those seen with sensory ataxic neuropathy. The sural nerve biopsy specimen in nine patients mostly showed small fibre loss (Table 5). Mean densities of large, small myelinated and unmyelinated fibres were reduced to 65, 41 and 33% of normal control, respectively, indicating small fibre predominant loss. Axonal sprouts were essentially absent. In teased-fibre preparations, axonal degeneration was seen in 19.0 ± 16.1% of fibres, predominantly in the small-diameter fibres. Perivascular cell invasion was also present in one patient.

These relatively well preserved SNAPs and SEPs, and mild T2* posterior column abnormalities on MRI as well as the predominant decrease in small myelinated and unmyelinated fibres in the sural nerve suggest that small sensory neurons are predominantly impaired and large diameter sensory neurons are fairly well preserved in this form of neuropathy.

Patients were followed-up for 1–12 years. Deep sensory impairment developed in three patients over nine years. They showed sensory ataxia in the legs and fingers. Other patients showed persistent painful sensory neuropathy with a gradual extension of the distribution of the neuropathy, without sensory ataxia.

Multiple mononeuropathy

A total of 11 patients showed a form of multiple mononeuropathy (Table 2). The initial symptom of neuropathy was the acute onset of a tingling sensation or painful dysaesthesia in the distal portion of the limbs. Subsequently, motor and sensory symptoms episodically occurred and extended to the distribution of a multiple mononeuropathy pattern mostly restricted to the limbs. Initial progression was acute or subacute in half of the patients. Trigeminal nerves and truncal intercostal nerves were involved in only two patients, respectively. Impairment during one episode subsequently disappeared, and another area of sensory impairment developed in some patients. Sensory impairment involved all modalities of both superficial and deep sensation. Muscle weakness was evident in the involved limbs, but sensory symptoms were generally more pronounced. Perinuclear antineutrophil cytoplasmic antibody (p-ANCA) and cryoglobulins were negative in all the patients examined. Systemic autonomic symptoms were relatively rare (Table 3). CMAPs and SNAPs in the involved nerves were markedly reduced (Table 4). Both large and small myelinated fibres were markedly depleted with prominent active axonal degeneration in the sural nerves. The most prominent histological feature was the frequent occurrence of vasculitic lesions associated with perivascular cellular invasions (Table 5).

Multiple cranial neuropathy

Five patients had multiple cranial neuropathy (Table 2). Involvement of the cranial nerves was bilateral VII nerve involvement in one patient, recurrent III and VI nerve involvement in one patient, III, V, VI, VII, IX and X nerve involvement in one patient, V, IX and X nerve involvement in one patient, and V, VII, IX, X and XII nerve involvement in one patient. Abnormal pupils were seen in one patient (Table 3). Three patients had acute onset of the neuropathy. With respect to extra-cranial symptoms, painful dysaesthesia in the limbs was detected in the initial phase in one patient, and truncal and limb sensory impairment developed in two patients during the follow-up. All patients had cranial motor nerve involvement in spite of the fact that the extent and degree of cranial nerve involvement was variable among the patients.

Trigeminal neuropathy

A total of 15 patients had a pure sensory trigeminal neuropathy (Table 2). Nine patients had unilateral involvement and six had bilateral involvement. Numbness or paraesthesia restricted to the trigeminal nerve region was the characteristic feature. Appreciation of pin prick and soft touch was diminished in the trigeminal nerve region, and dysaesthesia was present. Dysaesthesia of the tongue was present in one patient. Motor symptoms referable to trigeminal nerve involvement were not seen. The progression of these symptoms was indolent in most patients. Sensory disturbances in the limbs were seen in two patients. Pupillary abnormalities were seen in three patients, and orthostatic hypotension and hypohidrosis were observed in three and four patients, respectively (Table 3). There were no marked abnormalities in the routine nerve conduction of the limbs (Table 4). Blink reflex tests were performed in three patients with unilateral involvement, which confirmed trigeminal nerve involvement on the affected side (data not shown). Nerve biopsy was obtained from one patient, the findings of which were normal (Table 5).

Autonomic neuropathy

Three patients had predominant and severe autonomic symptoms and were designated as autonomic neuropathy (Tables 2 and 3). All three patients showed Adie's pupils and all patients also showed severe orthostatic hypotension with syncope. Hypohidrosis or anhidrosis also was present in the trunk and all four limbs. All patients developed abdominal pain, constipation and diarrhoea. Cardiac ^{123}I-MIBG uptake was reduced in two patients examined. Lack of plasma norepinephrine increase in response to standing and hypersensitive blood pressure increase beyond 25 mmHg in response to low concentration of norepinephrine infusion at 3 μg/min were seen in two patients examined. These observations suggest that peripheral sympathetic nervous system was severely involved in this form of neuropathy. Limb and truncal sensory impairment was present with sensory ataxia, but without motor involvement. These symptoms appeared chronically. The SNAPs and SEPs were unelicited and high intensity MRI signal in the posterior column of the spinal cord was seen in one patient (Table 4). A moderate reduction in the myelinated and unmyelinated fibre populations was seen in the sural nerve (Table 5).

Radiculoneuropathy

Four patients had this form of neuropathy (Table 2). All patients had chronic sensorimotor polyradiculoneuropathy with progressive sensory impairment and muscle weakness. The sensory disturbance was in a glove and stocking pattern in all of the patients, with an associated sensory ataxia in three patients. Apparent muscle weakness was seen in two patients. Autonomic symptoms were generally absent, except for constipation, hypohidrosis and urinary disturbances (Table 3). The CSF protein concentration was elevated, ranging from

98 to 146 mg/dl, without pleocytosis. F-wave abnormalities, poor occurrence and prolonged latencies, were present in all patients, while motor and sensory nerve conductions were almost normal, except in one patient with mild elongated distal latency and decreased conduction velocities in the median and tibial nerves (Table 4). This nerve conduction feature was unusual in chronic inflammatory demyelinating polyradiculoneuropathy. SEPs were also substantially prolonged. MRI of the lumbar spine showed abnormal gadolinium enhancement predominantly of the dorsal spinal roots and cauda equine, in all four patients. Sural nerve biopsy showed variable degrees of myelinated fibre loss with minor to moderate demyelinating changes in all patients (Table 5). These clincopathological features suggest that the primary lesion in these patients is in the spinal nerve roots or most proximal nerve trunks, consistent with an inflammatory radiculoneuropathy.

Overlapping clinical features among the neuropathic forms

Each neuropathic form had principal and predominant clinical features characterizing each individual neuropathic form, while the clinical symptoms overlapped to some extent with each other. Sensory ataxic neuropathy frequently had painful features, autonomic symptoms and trigeminal nerve involvement. Painful sensory neuropathy also had autonomic and trigeminal nerve involvement, as well as sensory ataxic features. Multiple mononeuropathy had painful and sensory ataxic features. Trigeminal neuropathy had autonomic and painful features. Multiple cranial neuropathy had some degree of trigeminal, painful and autonomic features. Autonomic neuropathy also had sensory ataxic and trigeminal nerve involvement. These overlapping symptoms were the common features in the present analysis, while overlapping symptoms occurred during the long-standing clinical course. For instance, some patients with painful sensory neuropathy without sensory ataxia later developed sensory ataxia, or alternatively, patients with sensory ataxic neuropathy often developed painful dysaesthetic features during the clinical course. These overlapping clinical features strongly suggest that each individual neuropathic form is not the absolute clinical entity, but these individual forms share a common underlying pathological process.

Findings in an autopsied patient with the sensory ataxic form of neuropathy

An 88-year-old woman with the sensory ataxic form of neuropathy was examined at the time of autopsy. She had numbness on the right side of her face since the age of 64 years, and developed unsteadiness of gait and pseudoathetosis in the fingers at 71 years of age. She was diagnosed as having Sjögren's syndrome at the age of 71. Severe sensory ataxia in the limbs was present. A marked segmental distribution of sensory impairment, particularly with respect to a deep sensation and anhidrosis, was noted (Kumazawa *et al.*, 1993) in the limbs and trunk (Fig. 1). Severe orthostatic hypotension, with a decrease of up to 70 mmHg in systolic pressure, and marked decrease in cardiac MIBG uptake was present. T2*-high intensity signal lesions in the spinal dorsal column were observed (Fig. 1). Respiratory failure due to pneumonia was the cause of death. The autopsy was performed 5 h postmortem.

The population of sensory ganglion neurons was severely, but variably, diminished among the spinal segments; 45% of the control value in the C5, 37% in the Th11 and 26% in the L4 segments (Fig. 1). Nageotte's nodules (Fig. 1) and mild cell infiltrations that contained mainly T-cells were seen (Fig. 2). The large sensory ganglion neurons were diminished predominantly. Myelinated fibre density in the dorsal spinal roots was also variably diminished among the spinal segments; 48% of the control value in the C5, 42% in the Th11 and 22% in the L4 segments (Fig. 1). The large myelinated fibres also were depleted predominantly. The extent of fibre loss in the dorsal spinal roots correlated well with the corresponding dorsal root ganglion cell population. The spinal dorsal column fibre population was also markedly depleted (Fig. 1). These observations strongly suggest that ganglioneuronitis affecting the sensory neurons is the major pathological process. The sympathetic ganglion cells also were severely, but variably, diminished among the segments (23–51%), with mild T-cell invasion (Fig. 1). These segmental variations in the extent of sensory ganglion neuron involvement and sympathetic ganglion neuron involvement seem to correspond to segmental variation of sensory and sweat impairments seen in this patient (Fig. 1). These clinicopathological correlates also may support the view that the major responsible lesion is of sensory and sympathetic neurons. The myelinated fibres in the sciatic, median and tibial nerves in the proximal portion of these nerve trunks showed a remarkable multifocal patchy distribution of myelinated fibre loss, present mainly in the large diameter fibres. The sural nerve revealed loss of large myelinated fibres with active axonal degeneration. Multifocal and disseminated perivascular T-cell infiltrations were seen in the endoneurial and perineurial space of the peripheral nerve trunks (Fig. 2), although the extent of cell invasion was mild. Features of arterial vasculitis, mostly in the post-active state, were seen throughout the peripheral nerve trunks (Fig. 2). Examination of the skeletal muscles showed an almost normal appearance and spinal motor neurons and ventral roots also were normal in appearance and in population (Fig. 1). Submandibular and subauricular salivary glands had T-cell invasion and acinar cell destruction (Fig. 2). Relatively mild inflammatory cell invasion in this patient may be due to the extensive therapies including prednisone.

Therapeutic profiles for individual neuropathic forms

Corticosteroids (prednisone, 1 mg/kg/day) and intravenous immunoglobulin (IVIG) (400 mg/kg for 5 days) were prescribed for some of the patients (Table 6). Definite improvement in the modified Rankin scale measurement or in sensory impairments, including pain and painful dysaesthesias, after treatment was considered a favourable response (Table 6). Presence or absence of favourable response was evaluated 1 month after treatment.

Multiple mononeuropathy and multiple cranial neuropathy showed the most favourable response to corticosteroid therapy. Sensory ataxic neuropathy showed a favourable response to corticosteroid treatment in only 18% of the patients (Table 6). The rate of favourable response to IVIG therapy for radiculoneuropathy, painful sensory neuropathy and sensory ataxic neuropathy was 100, 67 and 23%, respectively, although the number of patients treated was limited (Table 6). This suggests that the rate of favourable response to corticosteroid or IVIG therapy was different among the

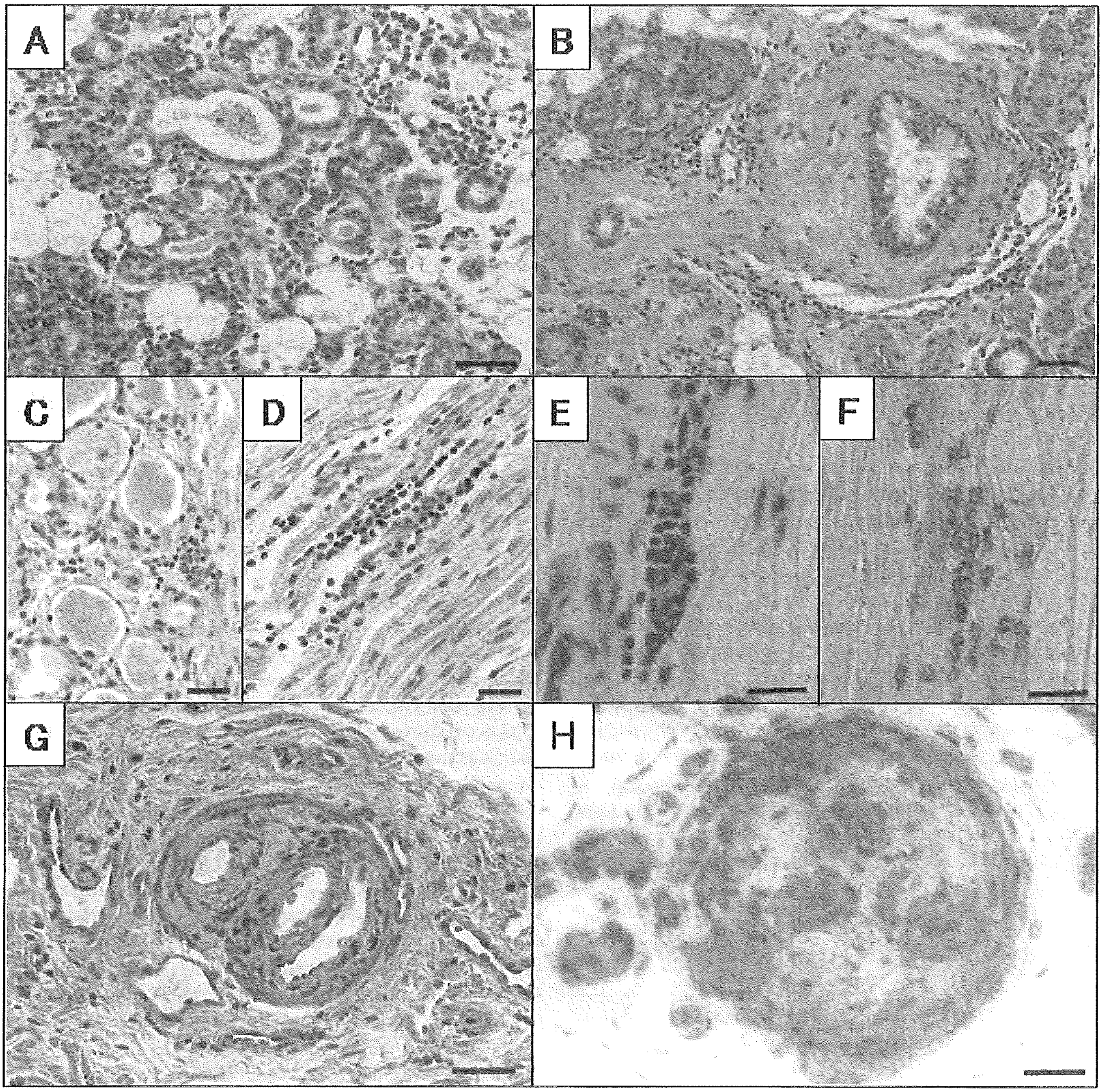

Fig. 2 Inflammatory aspects of the autopsied patient. (**A** and **B**) Lymphocytic infiltration at parotid gland (**A**) and submandibular gland (**B**). Haematoxylin-eosin stain. Scale bar = 40 μm. (**C** and **D**) Lymphocytic infiltration at the L4 dorsal root ganglions on axial section (**C**), and on longitudinal section (**D**). Haematoxylin-eosin stain. Scale bar = 20 μm. (**E** and **F**) Longitudinal section of the median nerve. Perivenular lymphocytic infiltrates in the endoneurium. Klüver–Barrera's stain (**E**) and UCHL-1 positive cells (**F**). Scale bar = 20 μm. (**G** and **H**) Chronic vasculitis in the perineurial space. (**G**) Median nerve. Haematoxylin-eosin stain. (**H**) Sural nerve. Toluidine blue stain. Scale bar = 20 μm.

Table 6 Therapeutic profiles in prednisone- and IVIG-treated patients

Neuropathic form	Prednisone				IVIG			
	Treated patients (*n*)	Favourable response (*n*)	No response (*n*)	% Response	Treated patients (*n*)	Favourable response (*n*)	No response (*n*)	% Response
Sensory neuropathy								
Ataxic*	22	4	18	18	13	3	10	23
Painful**	6	1	5	17	3	2	1	67
Multiple mononeuropathy*	11	8	3	73	1	0	1	0
Cranial neuropathy								
Multiple***	4	3	1	75	0	ND	ND	ND
Trigeminal***	3	1	2	33	0	ND	ND	ND
Autonomic neuropathy†	2	0	2	0	1	0	1	0
Radiculoneuropathy*	3	0	3	0	4	4	0	100
Total	51	17	34	33	22	9	13	41

IVIG, intravenous immunoglobulin therapy; ND, not determined. Favourable response: *For sensory ataxic neuropathy, multiple mononeuropathy and radiculoneuropathy, positive therapeutic response with reduction of one or more points of the modified Rankin scale. **For painful neuropathy, positive therapeutic response with three or more reduction of Visual Analogue Scale (VAS) rating for pain, ranging from 0 = no pain to 10 = maximal pain intensity. ***For cranial neuropathy, therapeutic response was assessed for the improvement of the symptoms of each cranial nerve. Favourable response was designated as definite subjective and objective improvement. †As for autonomic neuropathy, autonomic symptoms did not show a definite favourable response to the therapy.

neuropathic form, probably reflecting the underlying pathology. However, these favourable therapeutic responses were rather short-lived. In the long-term follow-up, these patients ultimately showed progression of symptoms.

Discussion

Underlying pathological features in each form of neuropathy

In this study, we assessed that Sjögren's syndrome-associated neuropathy has a broad clinical spectrum, including sensory ataxic neuropathy, painful sensory neuropathy without sensory ataxia, multiple mononeuropathy, multiple cranial neuropathy, trigeminal neuropathy, autonomic neuropathy and radiculoneuropathy. Here, we discuss the pathological background underlying several forms of neuropathy. Sensory ganglion cell destruction associated with lymphocytic infiltration detected by dorsal root ganglion biopsy provided direct proof that ganglioneuronitis is responsible for lesions in the sensory ataxic form of neuropathy (Malinow *et al.*, 1986; Griffin *et al.*, 1990). Most of our patients with sensory ataxic neuropathy had lesions of the central rami as well as the peripheral rami of the sensory neurons, as assessed by low amplitude or unelicitable SEPs and SNAPs, dorsal spinal column T2*-high intensity signal lesions and segmental sensory impairment. Furthermore, the autopsy findings of a patient with the sensory ataxic form had severe depletion of large-sized sensory ganglion neurons accompanied by T-cell invasion, which strongly support this view. In addition, substantial preservation of motor nerve function and a lack of axonal sprouting with large axon loss in the sural nerve biopsy specimens also support the view that the sensory neurons are primarily affected.

In contrast, in the painful sensory neuropathy form without sensory ataxia there is predominantly superficial sensory impairment, well preserved motor nerve function and small axon loss with relative preservation of large axons. SEPs are relatively well preserved compared with the sensory ataxic form, but T2*-high intensity signal lesions in the dorsal column of the spinal cord were observed, although the extent of high intensity was smaller than those in sensory ataxic neuropathy. Lack of axonal sprouts in the sural nerve biopsy also argues against the presence of a primary axonal lesion. We did not perform histological examination of the dorsal root ganglion. However, based on our clinical, laboratory, and electrophysiological data, we can speculate that this form of neuropathy is another form of sensory ganglioneuronopathy that affects small ganglion neurons. Some patients with painful sensory neuropathy eventually developed sensory ataxia due to the impairment of deep kinaesthetic sensation during long-term follow-up, although its distribution was restricted. Alternatively, some of the patients with sensory ataxic neuropathy had impairment of superficial sensation with painful dysaesthesias. These overlapping symptoms, observed in these two forms of neuropathy, may also support the hypothesis that these two neuropathies are part of a spectrum of disorders with a similar pathology.

The pathological basis of trigeminal neuropathy is not known. However, isolated sensory deficits along the territory of the trigeminal nerve are characteristic, and motor nerve dysfunction, even trigeminal motor dysfunction, is not present. Furthermore, pure sensory trigeminal neuropathy is occasionally the initial symptom of the sensory ataxic form of neuropathy or can present as one of the subsequent symptoms of sensory ataxic and painful sensory neuropathies. In addition, nature of autonomic symptoms such as pupillary abnormality and orthostatic hypotension, and highly chronic initial progression pattern in trigeminal neuropathy are similarly shared with those in sensory ataxic and painful neuropathy forms. These clinical features would suggest that trigeminal neuropathy is a cranial nerve version of sensory ganglionopathy, although further evidence is necessary to confirm this hypothesis.

In contrast to sensory ataxic neuropathy, painful sensory neuropathy and trigeminal neuropathy, multiple mononeuropathy and multiple cranial neuropathy often include motor nerve involvement with predominantly acute and subacute onset. Motor nerve involvement can be assessed accurately using the electrophysiological findings in these forms of neuropathy. In some patients with multiple mononeuropathy, evidence of motor nerve denervation on EMG or NCS can be detected. These observations suggest that this form of neuropathy represents a combined sensory and motor neuropathy, rather than an isolated sensory neuropathy. Furthermore, multiple cranial neuropathy and multiple mononeuropathy are not seen in the sensory ataxic and painful sensory forms of neuropathy, suggesting that these neuropathies are distinct from the sensory neuropathies. Vasculitis in the small arteries or arterioles in a sural nerve biopsy were detected in five out of eight patients with multiple mononeuropathy, the frequency of which was significantly higher than those in other forms of sensory neuropathies. Based on these observations, vasculitis and subsequent axonopathy might be the aetiology of multiple mononeuropathy, and possibly of multiple cranial neuropathy.

With respect to the pathological basis of Sjögren's syndrome-associated neuropathy, the autopsy findings of the patient with the sensory ataxic form suggest that there may be a continuous spectrum of pathological processes among the different forms of neuropathy. Sensory and autonomic ganglionitis accompanied by T-cell invasion was present in this patient, while disseminated vasculitis and perivascular T-cell infiltration were also present throughout the peripheral nerve trunks. The patients in whom the ganglionitis process was predominant, as in this autopsied patient, will present with the sensory ataxic form. In contrast, if the vasculitic process in the nerve trunk predominates, the patient would show the features of multiple mononeuropathy, including motor symptoms rather than symptoms of sensory or autonomic ganglionitis. We need further histological studies to confirm these findings, while we may speculate that sensory ganglionopathic lesions would contribute more profoundly to the sensory ataxic, painful sensory and trigeminal neuropathy forms, and vasculitic lesions would result in the multiple mononeuropathy and possibly multiple cranial neuropathy forms.

Neuropathy and other non-sicca symptomatic manifestations of Sjögren's syndrome

The striking feature was that the clinical manifestations of neuropathy preceded the development of sicca syndrome or laboratory findings consistent with Sjögren's syndrome in most patients. Thus, in most patients, neuropathy developed first and then the diagnosis of Sjögren's syndrome was made up to 12 years later, well in agreement with previous studies from our group and other groups (Sobue *et al.*, 1993; Grant *et al.*, 1997; Mori *et al.*, 2001, 2003). This chronological sequence is true for all forms of neuropathy, but is more characteristic in the ganglionitis-related neuropathy forms, such as sensory ataxic and painful sensory neuropathy. Extraneural symptoms, such as pancreatitis and interstitial pneumonia, also can precede the clinical manifestations of Sjögren's syndrome (Garcia-Carrasco *et al.*, 2002). These observations strongly suggest that neural tissues, particularly dorsal root sensory ganglion cells and probably autonomic ganglion cells, are the primary targets in Sjögren's syndrome in addition to the salivary and lacrimal glands (Greenspan *et al.*, 1974), and visceral organs including the pancreas, lung, and thyroid (Swigris *et al.*, 2002).

Antigens primarily responsible for the Sjögren's syndrome, which could be universally present among the target tissues, have been investigated. Whether alpha-fodrin antibody is specific to Sjögren's syndrome or not has been debated (de Seze *et al.*, 2004; Ruffatti *et al.*, 2004), but alpha-fodrin has still been proposed as a candidate antigen (Haneji *et al.*, 1997). We examined anti-alpha-fodrin antibodies in the serum of patients from the present study and found that this antibody is elevated in patients with Sjögren's syndrome-associated neuropathy. However, increases in this antibody were also observed in other types of neuropathy (data not shown) suggesting that this antibody is a candidate marker for Sjögren's syndrome, but its specificity needs to be assessed further. Additional antigens responsible for Sjögren's syndrome that are expressed in all of the target organs need to be identified.

We still do not know why the neuropathic symptoms precede the manifestations of sicca symptoms and other characteristic features in the Sjögren's syndrome-associated neuropathy patients. One possible situation would be that the patients with neuropathic symptoms as the initial symptom would first be referred to a neurology clinic rather than to a rheumatology clinic, while in the case of patients with sicca syndrome they would be referred to a rheumatology clinic. In the case of patients presenting with pancreatitis as the initial symptom, these patients tended to be referred to the gastroenterology clinic rather than to rheumatology clinic. The low prevalence of anti SS-A and SS-B antibodies in our neuropathic patients may also contribute to the earlier occurrence of neuropathies before the diagnosis of Sjögren's syndrome. Taken together, the current diagnostic criteria for Sjögren's syndrome based on the sicca syndrome may need to be re-evaluated.

Autonomic symptoms and the autonomic neuropathy form

Autonomic symptoms are widely present in Sjögren's syndrome-associated neuropathy, particularly in the sensory ataxic, painful sensory and autonomic neuropathy form. Autonomic symptoms may be attributed to a different pathologic cause, such as autonomic ganglioneuronitis and peripheral autonomic nerve involvement due to direct T-cell attack of the nerves or ischaemia due to vasculitis. The findings from the autopsied patient, including the loss of sympathetic ganglion neurons associated with T-cell invasion, strongly support the view that autonomic ganglion cells are primarily involved, in a fashion similar to the involvement of sensory ganglion cells. In this patient, the segmental distribution of anhidrosis and skin temperature changes corresponded to the segmental variation in the extent of autonomic ganglion cell involvement, also supporting the hypothesis that the primary lesions in autonomic ganglion cells are responsible for autonomic symptoms (Fig. 1). Two of three autonomic neuropathy patients also had sensory ataxia, suggesting that the autonomic ganglionopathy has a similar aetiology as sensory ataxic neuropathy. The presence of Adie's pupils, which is often associated with Sjögren's syndrome-associated neuropathy, is also probably attributable to ciliary ganglion cell involvement (Waterschoot *et al.*, 1991), although further histological assessment is needed. The degree of orthostatic hypotension, anhidrosis, constipation and loss of ^{123}I-MIBG uptake were unexpectedly severe when the autonomic system was involved. Autonomic symptoms in Sjögren's syndrome-associated neuropathy are generally considered mild in their manifestations compared with the sensory symptoms (Wright *et al.*, 1999). Our three patients with autonomic neuropathy were exceptions, since the autonomic symptoms, including bowel dysfunction, were extremely prominent symptoms, suggesting that severe autonomic neuropathy can be present in the spectrum of neuropathies associated with Sjögren's syndrome (Goto *et al.*, 2000; Sakakibara *et al.*, 2004). The present observations suggest that autonomic symptoms are one of the major symptoms in this neuropathy.

Therapeutic approach to Sjögren's syndrome-associated neuropathy

Corticosteroids and immunosuppressants have been employed for the treatment of Sjögren's syndrome, resulting in improvement of non-neuropathic Sjögren's syndrome-associated symptoms, such as sicca syndrome and pneumonitis (Zandbelt *et al.*, 2001; Swigris *et al.*, 2002).

For the therapy of neuropathy associated with Sjögren's syndrome, corticosteroids (Griffin *et al.*, 1990; Noguchi *et al.*, 2003), immunosuppressants (Griffin *et al.*, 1990), plasmapheresis (Chen *et al.*, 2001), D-penicillamine (Asahina *et al.*, 1998), infliximab (Caroyer *et al.*, 2002) and immunoglobulin (Molina *et al.*, 1996; Pascual *et al.*, 1998; Takahashi *et al.*, 2003) administration have been reported anecdotally and suggest a favourable therapeutic response. In the present study, a favourable response to treatment was assessed in an open manner, and both standard corticosteroid and IVIG treatment had similar frequencies of favourable response. Based on the limited number of patients treated, there may be marked differences in the rates of favourable therapeutic response among the neuropathic forms, reflecting major differences in the causes of neuropathy. Corticosteroid therapy is likely a good candidate for multiple mononeuropathy and multiple cranial neuropathy, and favourable improvement may be seen in the painful dysaesthesias of the painful sensory neuropathy and radiculoneuropathy forms with IVIG therapy. Although these symptomatic therapeutic responses were seen in certain patients, overall progression of the neuropathic symptoms as well as of Sjögren's syndrome itself occurred. The findings of this study suggest that IVIG and corticosteroids may be efficacious in treating the neuropathic symptoms of Sjögren's syndrome, although these favourable responses were only seen in certain subpopulations of patients. Randomized controlled studies are needed to assess the efficacy of these treatments for neuropathic symptoms of Sjögren's syndrome.

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Clinical and electrophysiologic correlates of IVIg responsiveness in CIDP

Abstract—To identify clinical and electrophysiologic features related to IV immunoglobulin (IVIg) responsiveness in chronic inflammatory demyelinating polyneuropathy (CIDP), the authors conducted a multicenter study on 312 patients with CIDP (199 responders and 113 nonresponders). Muscle atrophy and decreased compound muscle action potential were pronounced in nonresponders of IVIg. Male gender, longer disease duration, and slow progression of symptoms were also associated with IVIg unresponsiveness. Features suggesting axonal dysfunction in peripheral nerves indicated IVIg unresponsiveness in CIDP.

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Chronic inflammatory demyelinating polyneuropathy (CIDP) is characterized by insidious onset, chronicity with progressive or remittent clinical course, and segmental demyelination in peripheral nerves.[1] Among treatments for CIDP such as corticosteroids, plasmapheresis, and IV immunoglobulin (IVIg), IVIg is commonly used as an initial therapy because of relatively few side effects, immediate therapeutic response, and convenient administration without special equipment. However, some patients fail to show therapeutic response to IVIg,[2,3] and the features related to IVIg responsiveness are not well understood.[2-4] Thus, we investigated the clinical and electrophysiologic correlates of CIDP patients showing a good response or little or no response to IVIg.

Methods. We studied CIDP patients from June 2002 to April 2004 as members of the multicenter study group for hereditary neuropathy in Japan, working under the Auspices of the Ministry of Health, Labor, and Welfare of Japan. The Ethics Committee of the Nagoya University Graduate School of Medicine approved the study design in full. All patients fulfilled the diagnostic criteria established by the Ad Hoc Subcommittee of American Academy of Neurology AIDS Task Force.[1] Patients with monoclonal gammopathy of undetermined significance, anti-myelin-associated glycoprotein, and anti-sulfate-3-glucuronyl paragloboside antibodies were excluded, together with patients with severe diabetes mellitus, alcoholism, drug poisoning, hereditary neuropathy, and other diseases causing neuropathy. The subjects of the current investigation were the 312 of 372 patients initially entered, who met diagnostic and inclusion criteria and treated with IVIg (400 mg/kg/day for 5 days). The majority of the patients (90.7%) were treated initially by IVIg without any other prior therapy, whereas some patients (9.3%) who had received other treatments such as plasmapheresis or corticosteroids before IVIg were followed for >4 weeks before IVIg treatment to be sure they were not on some other form of treatment.

Clinical features including motor and sensory impairment and muscle atrophy were assessed. Weakness was estimated according to Medical Research Council criteria in proximal muscles (deltoid, biceps, and triceps muscles in upper limbs, iliopsoas and quadriceps muscles in lower limbs) as well as distal muscles (thenar, interosseous, and finger flexion muscles in upper limbs, ankle dorsiflexor and toe dorsiflexor muscles in lower limbs).[6] Activities of daily living (ADLs) involving upper limbs were evaluated according to the arm disability score of the overall disability sum score (ODSS).[7] ADLs involving lower limbs were evaluated according to the modified Rankin Scale.[8] We assessed ADLs 1 to 14 days before IVIg and reassessed then 4 to 6 weeks after IVIg for evaluation of clinical efficacy. Those patients who improved by ≥1 point in the ODSS or the modified Rankin Scale were termed responders, and those with no change, a minimal improvement of <1 point, or showing a worse score were termed nonresponders.

For electrophysiologic study, the previously described standardized method was adopted.[5,6] Motor nerve conduction was evaluated for the median, ulnar, and tibial nerves, whereas sensory nerve conduction was evaluated for median, ulnar, and sural nerves. Motor nerve conduction velocity (MCV), distal latency, compound muscle action potential (CMAP), and presence of conduction block was also assessed. Sensory nerve conduction velocity and sensory nerve action potential also were assessed. Control values were obtained from normal subjects for median (n = 191; 48.7 ± 16.5 years old), ulnar (n = 166; 48.9 ± 15.8 years old), tibial (n = 121; 49.9 ± 15.0 years old), and sural (n = 133; 50.6 ± 15.6 years old) nerves as previously described.[6] All electrophysiologic data were obtained 1 to 14 days before IVIg was started. For some patients who were assessed 4 to 6 weeks after IVIg, nerve conduction velocity findings were compared before and after IVIg.

The two-tailed Fisher exact test and Mann–Whitney U test were used to evaluate relative differences between responders and nonresponders and between data before and after IVIg, using

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Table 1 Clinical findings

Clinical features and CSF	Responders	Nonresponders	*p* value*
All patients (responders: n = 199; nonresponders: n = 113)			
Age, y	52.5 ± 18.3	55.5 ± 16.7	NS
Sex, M/F	1.8/1.0	2.9/1.0	<0.05
Duration from onset to IVIg, mo	7.8 ± 4.0	9.8 ± 3.5	<0.0005
Progression after onset,† %	45.9	22.9	<0.0005
MRC score,‡ 0–5			
Upper limb, proximal	4.1 ± 1.0	4.4 ± 0.9	<0.0005
Upper limb, distal	3.5 ± 1.0	3.8 ± 1.2	<0.005
Lower limb, proximal	4.0 ± 1.0	4.3 ± 1.1	<0.01
Lower limb, distal	3.4 ± 1.1	3.3 ± 1.4	NS
Muscle atrophy, % of patients			
Upper limb	28.9	42.4	<0.01
Lower limb	25.9	47.8	<0.0005
ADL score			
Arm disability score (ODSS)	2.3 ± 1.5	1.5 ± 1.5	<0.0001
Modified Rankin Scale	2.6 ± 1.2	2.2 ± 1.3	<0.005
CSF protein, mg/dL	94 ± 71	132 ± 158	NS
Patients with similar duration (<12 mo) (responders: n = 115; nonresponders: n = 29)			
Age, y	52.2 ± 9.0	50.3 ± 18.0	NS
Sex, M/F	1.5/1.0	2.5/1.0	<0.05
Duration from onset to IVIg, mo	4.5 ± 2.1	4.8 ± 2.2	NS
Progression after onset,† %	22.2	12.1	<0.01
MRC score, 0–5			
Upper limb, proximal	4.0 ± 1.0	4.4 ± 0.9	<0.05
Upper limb, distal	3.5 ± 1.0	3.8 ± 1.2	NS
Lower limb, proximal	3.9 ± 1.1	4.2 ± 1.1	<0.05
Lower limb, distal	3.4 ± 1.2	3.3 ± 1.5	NS
Muscle atrophy, % of patients			
Upper limb	20.2	48.9	<0.05
Lower limb	20.4	48.3	<0.01
ADL score			
Arm disability score (ODSS)	2.4 ± 1.5	2.0 ± 1.7	<0.01
Modified Rankin Scale	2.8 ± 1.2	2.6 ± 1.3	NS
CSF protein, mg/dL	129 ± 202	191 ± 206	NS

* *p* value indicates a significant difference between responders and nonresponders.

† Rate of patients with disability <3 mo after the onset.

‡ Mean score of the examined muscles.

ODSS (overall disability sum score) = 0, normal; 1, minor symptoms or signs in one or both arms but not affecting any function (dressing upper part of body, washing and brushing hair, turning a key in a lock, using knife and fork, doing/undoing buttons and zips); 2, moderate symptoms or signs in one or both arms affecting but not preventing any function listed; 3, severe symptoms or signs in one or both arms preventing at least one but not all functions listed; 4, severe symptoms or signs in both arms preventing all functions listed but some purposeful movements still possible; 5, severe symptoms and signs in both arms preventing all purposeful movements. Modified Rankin Scale = 0, normal; 1, nondisabling symptoms not interfering with lifestyle; 2, minor disability from symptoms leading to some restrictions of lifestyle but not interfering with patients' capacity to look after themselves; 3, moderate disability from symptoms that significantly interfered with lifestyle or prevented fully independent existence; 4, moderately severe disability from symptoms that clearly precluded independent existence, although patients did not need constant attention day and night; 5, severe disability involving total dependence, including constant care day and night. IVIg = IV immunoglobulin; MRC = Medical Research Council; ADL = activities of daily living.

***Table 2** Electrophysiologic findings*

Nerve	Responders	Nonresponders	*p* value*	Control, n = 121–191
All patients				
Median (R, n = 191; NR, n = 105)				
MCV, m/s	35.2 ± 13.2	39.8 ± 13.8	<0.01	57.8 ± 3.7
DL, ms	7.4 ± 5.3	6.4 ± 4.5	NS	3.4 ± 0.4
CMAP, mV	6.4 ± 4.6	5.3 ± 4.5	<0.05	10.7 ± 3.5
CB, %	45.5	27.5	<0.01	
Ulnar (R, n = 171; NR, n = 93)				
MCV, m/s	35.9 ± 12.7	39.0 ± 12.9	NS	58.6 ± 4.3
DL, ms	5.5 ± 5.0	5.0 ± 3.4	NS	2.7 ± 0.3
CMAP, mV	6.2 ± 4.2	4.8 ± 3.6	<0.005	8.4 ± 2.5
CB, %	50.9	41.3	NS	
Tibial (R, n = 168; NR, n = 81)				
MCV, m/s	33.7 ± 9.2	34.0 ± 9.4	NS	46.9 ± 3.5
DL, ms	7.5 ± 4.0	7.0 ± 3.0	NS	4.5 ± 0.8
CMAP, mV	5.7 ± 6.5	3.5 ± 5.9	<0.0001	10.9 ± 3.8
CB, %	40.5	35.6	NS	
Patients with similar duration (<12 mo)				
Median (R, n = 112; NR, n = 36)				
MCV, m/s	34.4 ± 12.5	40.5 ± 14.5	<0.05	57.8 ± 3.7
DL, ms	7.6 ± 4.8	8.3 ± 7.0	NS	3.4 ± 0.4
CMAP, mV	6.8 ± 4.6	4.2 ± 2.9	<0.01	10.7 ± 3.5
CB, %	33.0	20.0	<0.05	
Ulnar (R, n = 101; NR, n = 33)				
MCV, m/s	35.6 ± 11.4	37.6 ± 15.3	NS	58.6 ± 4.3
DL, ms	5.5 ± 3.6	5.5 ± 2.5	NS	2.7 ± 0.3
CMAP, mV	5.9 ± 4.2	4.0 ± 3.6	<0.05	8.4 ± 2.5
CB, %	50.8	44.4	NS	
Tibial (R, n = 102; NR, n = 25)				
MCV, m/s	33.5 ± 9.0	33.4 ± 8.5	NS	46.9 ± 3.5
DL, ms	7.9 ± 4.0	8.0 ± 3.1	NS	4.5 ± 0.8
CMAP, mV	5.2 ± 5.5	1.9 ± 2.8	<0.0005	10.9 ± 3.8
CB, %	48.8	44.4	NS	

* *p* value indicates a significant difference between responders and nonresponders.

R = responder; NR = nonresponder; MCV = motor nerve conduction velocity; DL = distal latency; CMAP = compound muscle action potential; CB = conduction block.

StatView software for Macintosh (version 4.5; Abacus Concepts, Berkeley, CA).

Results. *Clinical findings.* Efficacy of IVIg therapy was 63.8% (table 1 and table E-1 on the *Neurology* Web site at www.neurology.org). The rate of patients whose symptomatic exacerbation stopped 3 months after onset was higher in responders than in nonresponders. Responders showed significantly more severe weakness of the upper and proximal lower limbs, whereas nonresponders showed more marked muscle atrophy in the upper and lower limbs. As the disease duration from onset to IVIg differed significantly between responders and nonresponders in the patients as a whole, we additionally compared the subgroups of responders and nonresponders with disease duration of <12 months, eliminating significant differences about the disease duration.

Efficacy of IVIg in the patients with similar duration was 79.9%. The rate of patients whose symptomatic exacerbation stopped 3 months after onset was still higher in responders. Muscle atrophy of each limb was significantly more prominent in nonresponders, as was true for the patients as a whole.

Electrophysiologic findings. Mean CMAP was significantly more reduced in the median, ulnar, and tibial nerves in nonresponders (table 2 and table E-2). Frequency of conduction block showed a tendency to be more pro-

Table 3 *Electrophysiologic findings before and after IVIg therapy*

Nerve	Pre IVIg	Post IVIg	*p* value*
Responders, n = 71			
Median			
MCV, m/s	32.4 ± 13.2	35.3 ± 12.4	<0.05
DL, ms	6.6 ± 4.0	6.7 ± 4.7	NS
CMAP, mV	5.6 ± 4.1	6.7 ± 4.6	NS
CB, %	45.7	38.9	<0.05
Ulnar			
MCV, m/s	33.5 ± 11.3	36.7 ± 11.1	<0.01
DL, ms	5.3 ± 2.8	4.8 ± 2.7	NS
CMAP, mV	5.3 ± 3.1	5.8 ± 3.3	NS
CB, %	42.2	35.7	<0.05
Tibial			
MCV, m/s	31.5 ± 8.3	33.3 ± 10.4	<0.05
DL, ms	7.1 ± 3.1	7.1 ± 4.3	NS
CMAP, mV	3.5 ± 3.2	4.4 ± 4.3	NS
CB, %	44.8	27.6	<0.01
Nonresponders, n = 51			
Median			
MCV, m/s	38.5 ± 13.6	39.1 ± 13.7	NS
DL, ms	7.3 ± 4.1	7.7 ± 4.8	NS
CMAP, mV	5.9 ± 5.0	5.6 ± 4.7	NS
CB, %	32.7	23.5	NS
Ulnar			
MCV, m/s	36.0 ± 14.4	34.0 ± 12.5	NS
DL, ms	5.6 ± 2.4	5.5 ± 2.1	NS
CMAP, mV	4.4 ± 3.3	4.2 ± 3.9	NS
CB, %	40.9	35.0	NS
Tibial			
MCV, m/s	30.5 ± 9.7	32.7 ± 10.3	NS
DL, ms	7.8 ± 3.6	7.5 ± 3.7	NS
CMAP, mV	3.2 ± 4.1	4.1 ± 4.9	NS
CB, %	46.5	46.2	NS

* *p* value indicates a significant difference between responders and nonresponders.

IVIg = IV immunoglobulin; MCV = motor nerve conduction velocity; DL = distal latency; CMAP = compound muscle action potential; CB = conduction block.

nounced in responders. In the patients with similar durations, electrophysiologic findings also resembled those for patients as a whole. Mean CMAP was significantly more reduced in nonresponders, and conduction block tended to be more frequent in responders.

Electrophysiologic findings before and after IVIg therapy. We assessed electrophysiologic changes before and after IVIg (table 3). Mean MCV in the median, ulnar, and tibial nerves in responders improved significantly after IVIg, whereas mean CMAP in the same nerves did not. In contrast, both mean MCV and mean CMAP in nonresponders did not improve significantly. Conduction block became less frequent after IVIg in responders.

Discussion. One cardinal finding was that features related to axonal dysfunction were a major contribution to unresponsiveness to IVIg therapy in CIDP. More severe CMAP amplitude reduction and more severe muscle atrophy were seen in nonresponders than in responders. MCV and distal latency were essentially similar between responder and nonresponder groups, but conduction block was more frequent in responders, suggesting that IVIg responsiveness was linked to demyelinating as opposed to axonal features.

In the previous reports, nonresponsiveness has been suggested to be caused by the longer interval from symptom onset to initiation of IVIg therapy.[9] One possible explanation for the longer duration effect might be that secondary axonal degeneration could follow segmental demyelination in patients with long symptomatic intervals prior to effective therapy, as suggested in primary demyelination. Accordingly, we compared features between subgroups of responders and nonresponders who had similar disease duration from onset, obtaining similar results that axonal dysfunction remained the major determinant of IVIg unresponsiveness. These observations suggest that whereas symptom duration before treatment was one determinant of IVIg ineffectiveness in CIDP, duration-independent axonal dysfunction was another. According to recent reports, demyelination-independent primary axonal damage has been suggested to occur in a subgroup of CIDP cases, termed the axonal variant of CIDP. These findings support our view that duration-independent axonal features can exist in CIDP and thus contribute to treatment failure.[5,9,10]

In addition, electrophysiologic impairment is more reversible in responders than in nonresponders, and demyelinating features are effectively improved by IVIg. Axonal features, less reversible with IVIg, were more prominent in nonresponders. Nonresponders also did not show any improvement in MCV, CMAP, or frequency of conduction block. The current results suggest that the pathologic dysfunction of peripheral nerves differs between responders and nonresponders.

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