Table 1 Clinical features of POEMS syndrome

Case	Age/Sex	Organomegaly	Endocrinopathy	M-protein	Skin change	Bone lesion	VEGF level* (pg/ml)	Cerebrospinal fluid protein (mg/dl)
1	43/W	CM, HM, SM, LA	–	IgAλ	HP, HT	Sclerotic	1310	93
2	68/W	CM, HM, SM	–	IgAλ	HP, HT	Sclerotic	2290	63
3	47/W	HM, SM	–	IgGλ	HP	–	1670	38
4	47/W	CM, HM, SM, LA	Hy	IgAλ	HP, HT	–	>2000	95
5	31/M	HM, SM	Gy, Im	IgGλ	HP, HT	Sclerotic, lytic	5500	130
6	54/W	HM, LA	–	IgGκ	HP, HT	Sclerotic	756†	107
7	48/M	LA	Gy	IgGλ	HP	Sclerotic	1830	63
8	46/M	HM, LA	Gy	IgGλ	HP	Sclerotic	>2000	108
9	62/M	SM	Gy	IgAλ	HP, HT	Sclerotic	>2000	165
10	58/M	–	Im	IgAλ	HP, HT	Sclerotic	>2000	53
11	57/W	CM, HM, SM	Hy	IgAλ	HP, HT	Sclerotic	>2000	179
12	28/W	HM, SM	–	IgGλ	HP, HT	Sclerotic, lytic	1120	238
13	72/M	HM, SM	Gu	IgGλ	HP	–	ND	124
14	67/W	CM, SM, LA	Hy	IgGλ	HP	–	>2000	97
15	63/M	HM, SM, LA	Hy, Gy, Im	IgGλ	HP, HT	–	ND	82
16	45/M	LA	Gu, Hy, Im	IgAλ	HP, HT	–	ND	196
17	69/W	ND	–	IgAλ	HP	–	ND	108
18	60/M	LA	Hy	IgAλ	HP, HT	–	ND	62
19	63/M	SM	Im	–	HP	Sclerotic	814†	78
20	45/M	HM	Gu, Gy	–	HP, HT	–	1280	360
21	85/M	CM, HM, SM, LA	Gy	IgAλ	HP	–	500†	57
22	47/M	HM, SM	Im	IgGλ	HP, HT	Lytic	1280	81

VEGF, vascular endothelial growth factor (normal<707 pg/ml for serum, <115 pg/ml for plasma); –, abscent; CM, cardiomegaly; Gu, glucose intorelance; Gy, gynecomastia; HM, hepatomegaly; HP, hyperpigmentation; HT, hypertrichosis; Hy, hypothyroidism; Im, impotence; LA, lymphadenopathy; ND, not determined; POEMS, polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin changes; SM, splenomegaly.
*Serum VEGF levels were measured except in patients 6, 19 and 21.
†Plasma VEGF levels were measured.

Pathological assessment of sural nerve biopsy specimens

Sural nerve biopsy was performed in 21 patients before the initiation of treatment as described previously.[15–17] Specimens were divided into two portions. The first was fixed in 2.5% glutaraldehyde in 0.125 M cacodylate buffer (pH 7.4) and embedded in epoxy resin for morphometric and ultrastructural study. Densities of small and large myelinated fibres were assessed in toluidine-blue-stained semithin sections using a computer-assisted image analyser (Luzex FS; Nikon, Tokyo, Japan), as described previously.[15 16 18] To determine the extent of nerve fibre loss, the total number of nerve fibres in complete transverse sections of sural nerves was estimated because the density might be reduced without actual nerve fibre loss when the endoneurium was enlarged by a pathological condition such as endoneurial oedema. Therefore, the total endoneurial area and subperineurial space devoid of nerve fibres were assessed using the image analyser (Luzex FS) in cases in which complete transverse sections of the sural nerve could be obtained; we estimated the total number of nerve fibres in these cases. Two cases (patients 9 and 14) were excluded because their sural nerve was only partially obtained. To determine the total numbers per complete cross-section of the sural nerve, the density of each morphometric index was multiplied by the endoneurial area from which the subperineurial space devoid of nerve fibres was subtracted.[17] The remainder of the glutaraldehyde-fixed sample was processed for the teased-fibre study, in which at least 200 single fibres were isolated and their pathological condition was assessed microscopically according to criteria described previously.[15 19] Each teased fibre was divided into two categories based on the diameter of the middle portion of the largest segment. Fibres of 6.73 μm or more in diameter were designated as large fibres and those of less than 6.73 μm as small fibres.[15] Fibres showing axonal degeneration were not included when the diameter of the fibres was evaluated. The second portion of each specimen was fixed in 10% formalin solution and embedded in paraffin. Sections were cut by routine methods and stained with hematoxylin and eosin, Congo red, the Klüver–Barrera method and the Masson trichrome method.

For the electron microscopic study, epoxy resin-embedded specimens were cut into ultrathin transverse sections and stained with uranyl acetate and lead citrate. To assess the density of unmyelinated fibres, electron microscopic photographs were taken at a magnification of 4000× in a random fashion to cover the area of ultrathin sections, as described previously.[15 16 20] These electron micrographs were enlarged to about 6500×. The total area analysed in electron micrographs was at least 0.03 mm^2, obtained from at least three fascicles. Unmyelinated fibres were distinguished from Schwann cell cytoplasmic profiles by their round or oval shape, a lighter appearance than Schwann cell cytoplasm, and often a higher incidence of microtubules.[21] The presence of mesaxon-like structures and a greater density of axolemma than Schwann cell membranes were also criteria for identifying unmyelinated fibres.[21] Disproportionately large unmyelinated fibres over 3 μm in diameter were not counted because these fibres were considered to be originally myelinated fibres and formed as a consequence of demyelination.[17 22] A conglomerate of Schwann cell processes with or without unmyelinated axons, and enclosed by a continuous loop of basal lamina, was designated as a "Schwann cell subunit", as described previously.[17 22] Only Schwann cell subunits related to unmyelinated fibres were counted. Unmyelinated fibres found in Schwann cell subunits that previously contained myelinated axons (ie, bands of Büngner) were not counted because they could be sprouts from regenerating myelinated fibres.[21 23] In addition, unmyelinated fibres and Schwann cell subunits that took part in the formation of regenerating clusters of myelinated axons were not counted for the same reason.[22] The bands of Büngner were

Table 2 Neuropathic features of POEMS syndrome

Case	Initial symptom	Duration until biopsy (m)	Motor signs: Weakness UE (P/D)	Motor signs: Weakness LE (P/D)	Motor signs: Muscle atrophy	Sensory signs*: Spontaneous pain	Sensory signs*: Pain†	Sensory signs*: Vibration	Sensory signs*: Joint sense	Modified Rankin Scale‡
1	N	12	+1/+2	+2/+1	+1	0	+1	−3	−2	2
2	N	5	+1/+2	+2/+3	0	0	−2	−3	−2	4
3	N	3	+1/0	+2/+1	+1	+2	+2	−1	0	3
4	N	24	+2/+1	+2/+1	+1	+3	+3	−3	−2	2
5	W	12	0/0	+2/+3	0	+2	+2	−2	−2	3
6	N	7	0/+1	+1/+3	0	0	−2	−3	−1	3
7	N	10	0/0	+2/+1	0	+3	−3§	−3	−3	2
8	W	1	0/+1	+2/+3	0	0	0	−2	−1	3
9	N	6	+1/+1	+2/+3	+1	+3	+3	−2	−2	3
10	N	4	0/+2	+1/+3	+1	+2	+2	−3	−2	3
11	N	4	0/+2	+3/+3	+2	0	−2	−3	−3	3
12	W	9	+2/+3	+3/+3	+2	0	0	−2	0	4
13	W	5	+1/+1	+2/+3	0	0	+1	−1	−1	3
14	W	7	0/0	+2/+3	0	0	0	−2	0	2
15	N	6	+1+2	+1/+1	0	+3	+3	−3	−3	2
16	N	1	+1/+1	+1/+2	0	0	0	−3	−1	2
17	N	12	+1/+1	+2/+3	+1	+1	+2	−3	−1	3
18	N	3	+1/+1	+1/+1	+1	0	+2	−3	−2	2
19	N	7	0/0	+2/+3	0	+3	+2	−3	−2	3
20	W	2	0/0	+2/+3	0	+1	+3	−2	−2	3
21	N	12	0/0	0/0	0	+1	+1	−2	−1	2
22	N	3¶	0/0	+1/+3	+1	+2	+2	−1	0	2

+, positive findings; −, negative findings; 0, none.
+1, +2, and +3 represent mild, moderate and severe degree of muscle weakness, atrophy and sensory signs.
−1, −2, and −3 represent mild, moderate and severe reduction for sensory signs.
D, distal portion; LE, lower extremities; N, numbness of the lower extremities; P, proximal portion; POEMS, polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin changes; UE, upper extremities; W, weakness of the lower extremities.
*Sensory signs were assessed in the distal portion of the lower limbs.
†Pain is devided into two categories; hyperalgesia (+1, +2 or +3) and hypoalgesia (−1, −2 or −3).
‡Modified Rankin Scale:[14] 0, asymptomatic; 1, non-disabling symptoms not interfering with lifestyle; 2, minor disability from symptoms leading to some restriction of lifestyle but not interfering with patients' capacity to look after themselves; 3, moderate disability from symptoms significantly interfering with lifestyle or preventing totally independent existence; 4, moderately severe disability from symptoms clearly precluding independent existence, although not requiring 24-hour attention from a caregiver; and 5, severe disability and total dependence, requiring constant attention day and night.
§Painful sensation in patient 7 was so severe that the response to mechanical stimuli was not obvious.
¶Duration until first referral to the hospital.

distinguished from subunits of non-myelinating Schwann cells, as described previously.[17 21 22]

The widening of major dense lines of myelin lamellae was designated as uncompacted of myelin. Myelinated fibres were considered as presenting uncompacted myelin lamellae (UML) when at least three lamellae were not compacted along a semi-circumference of the myelin sheath or in an additional loop.[24] The percentage of fibres with UML in the large myelinated fibres and small myelinated fibres were separately assessed. The area of ultrathin section was overviewed by photographs at a magnification of 2000×. Fibres with UML confirmed by greater magnification were marked on the photographs and the diameter of each myelinated fibre was assessed using a computer-assisted image analyser (WinROOF; Mitani, Fukui, Japan). At least 300 fibres were assessed to determine the frequency of UML.

Control values were obtained from five autopsy cases in which the patients died of non-neurological diseases (male:female, 1: 4; age range: 35–71 years, mean ± SD: 55.8±14.5 years). Specimens were processed in the same manner as for POEMS syndrome patients.

Assessment of serum cytokines and cytokine receptors levels

All patients were examined before initiation of treatment. Measurements of IL-1β, IL-6 and TNF-α were performed in 15 patients and values were compared to 20 control patients with other neurological diseases, including spinocerebellar ataxia, multiple system atrophy and spinobulbar muscular atrophy. Measurements of IL-1 receptor antagonist (IL-1ra), soluble IL-6 receptor (sIL-6r), soluble TNF receptor I (sTFNrI) and soluble TNF receptor II (sTNFrII) were performed in 12 patients and values were compared to those of 7 patients with other neurological diseases. Peripheral blood was taken in dry tubes and centrifuged within 3 hours. The sera were kept frozen at −80°C until analysed. Blood samples were obtained in the absence of overt fever, infection and shock. An enzyme-linked immunosorbent assay kit was used for the quantification of IL-1β (BioSourse, Nivelles, Belgium), TNF-α (JIMRO, Takasaki, Japan), IL-1ra (R&D Systems, Minneapolis, USA), sIL-6r (R&D Systems), sTFNrI (R&D Systems) and sTFNrII (R&D Systems), and a chemiluminescent enzyme immunoassay kit was used for the quantification of IL-6 (Fujirebio, Tokyo, Japan).

Statistical analyses

Quantitative data, presented as the mean ± SD, were compared with control values. Statistical analyses were performed using χ^2 test or the Mann–Whitney *U* test as appropriate. Values of p less than 0.05 were considered to indicate significance.

RESULTS

Neuropathical features

Neuropathic features are summarised in table 2. All patients showed a symmetrical polyneuropathy pattern with greater

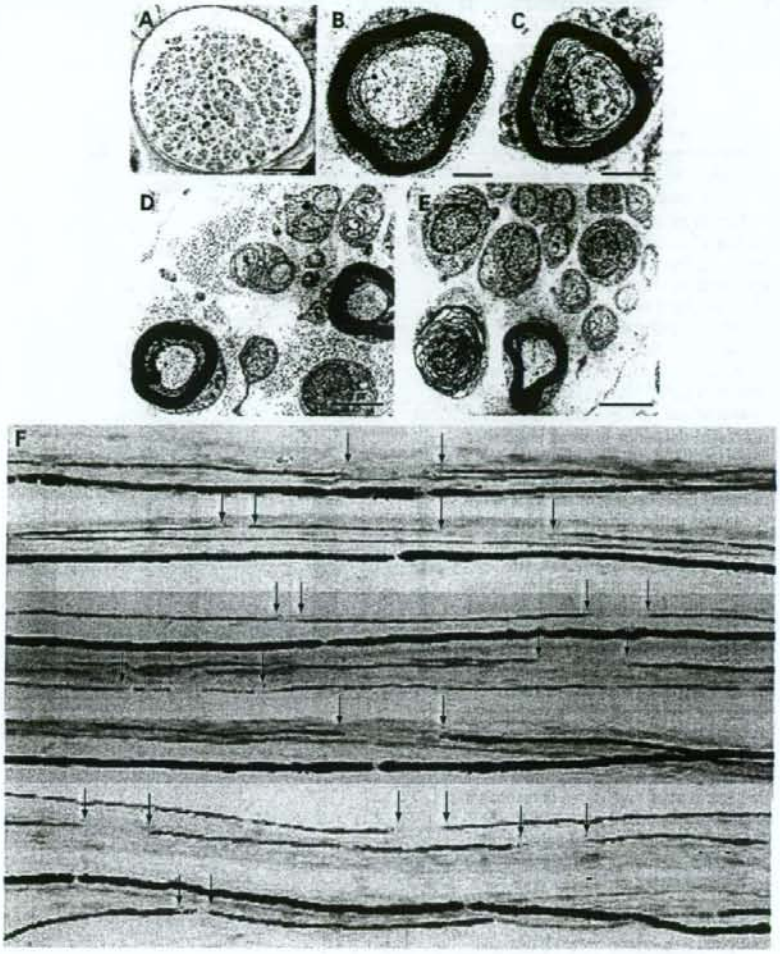

Figure 1 Sural nerve biopsy specimen from a patient with polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin changes (POEMS) syndrome. (A) In light microscopy, subperineurial oedema is conspicuous. (B, C and D) In electron microscopy, uncompacted myelin lamellae are more frequent in small myelinated fibres. (E) Unmyelinated fibres are preserved, whereas a remnant of myelin sheath, suggestive of axonal degeneration of myelinated fibres, is seen. (F) Teased fibres from a patient with POEMS syndrome. Segmental demyelination resulted from widening of nodes of Ranvier (arrows) is conspicuous in small myelinated fibres. Scale bars = 50 μm (A), 1 μm (B and C) and 3 μm (D and E).

involvement of the lower rather than the upper limbs. Sensory symptoms were moderate to severe in most patients in the distal portion of the lower extremities as a whole. Nineteen patients (86%) complained of numbness in the lower extremities, most of which were uncomfortable sensations, such as aching, tingling or prickling. Twelve patients (55%) reported spontaneous pain. Painful symptoms generally were brought on, or made worse, by gentle manual pressure or pinching. Many of the patients complained of pain as they walked because pressure was applied on the soles of their feet. Patients also reported pain when a blanket was put on their feet. Distally accentuated hyperalgesia to pin-prick or pinwheel was also observed. As a whole, 14 patients (64%) reported hyperalgesia, as described above. In some patients, pain was the most characteristic feature, significantly compromising activities of daily living. Seven patients (32%) reported having difficulty walking due to pain (patients 1, 4, 9, 10, 15, 18 and 21). On the other hand, three patients (14%) did not complain of any positive sensory symptoms despite the presence of subjective sensory deficit (patients 8, 12 and 14). Autonomic symptoms were reported in 4 patients (18%): these consisted of impairment of sweating in the extremities in patients 8, 13 and 15; urinary retention in patient 13; and constipation and orthostatic hypotension defined as a fall of 20 mm Hg in systolic blood pressure following arising from the supine position in patient 18. In addition, 6 of 13 male patients (patients 5, 10, 15, 16, 19 and 22) complained of impotence, although this may have been related to endocrine disorder.

Nerve conduction studies revealed slowing of motor and sensory conduction velocities and prolongation of distal latencies in all patients, as shown in Supplementary Material 1.

No significant difference in the type of M-protein, duration of neuropathy, or relative predominance of weakness and sensory deficit was present between the group with mechanical hyperalgesia and that without it. Functional status assessed by the modified Rankin Scale was not significantly different between the two groups. Electrophysiological features were different only in the amplitude of sensory nerve action potentials of the sural nerve, which was more profoundly reduced in the group with hyperalgesia ($p<0.05$).

Pathological findings of sural nerve biopsy specimens and their correlation to neuropathic pain

Quantitative data, including those of nerve fibre density of individual cases, are listed online in Supplementary Material 2.

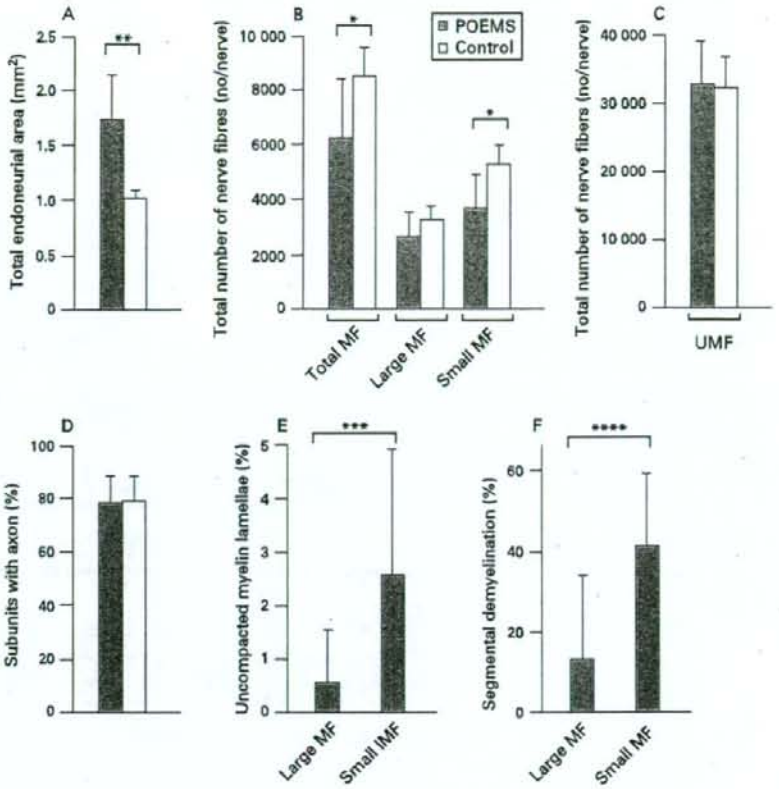

Figure 2 Morphometric assessments of sural nerve biopsy specimens. Black columns indicate polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin changes (POEMS) syndrome and white columns indicate controls. Each error bar represents the standard deviation. (A) Total endoneurial area. Total endoneurial area was markedly enlarged compared with controls ($p<0.01$). (B) Estimated number of myelinated fibres per complete cross-section of the sural nerve. The estimated number of total myelinated fibres per sural nerve cross-section was significantly reduced compared with controls ($p<0.05$). There was no significant difference in the number of large myelinated fibres between POEMS syndrome and controls, but there was a significant difference in small myelinated fibres ($p<0.05$). (C) The estimated number of unmyelinated fibres per complete cross-section of the sural nerve. In contrast to the reduction of myelinated fibres, there was no difference in the number of unmyelinated fibres. (D) Percentage of subunits with unmyelinated fibres in the total population of Schwann cell subunits associated with unmyelinated fibres. The percentage was not different from that of the control group, suggesting that unmyelinated fibres were preserved. (E) The percentage of fibres with uncompacted myelin lamellae in myelinated fibres. The percentage was significantly more frequent in small myelinated fibres than in large myelinated fibres ($p<0.001$). (F) Teased-fibre studies. The frequency of fibres with segmental demyelination due to widened nodes of Ranvier was significantly more frequent in small fibres than in large fibres ($p<0.0001$). *$p<0.05$, **$p<0.01$, ***$p<0.001$ and ****$p<0.0001$ with Mann–Whitney *U* test. MF, myelinated fibres; UMF, unmyelinated fibres.

As for myelinated fibres, the density varied from 1396 to 6558 fibres/mm². Density of large myelinated fibres was 1897 ± 652 fibres/mm² (61% of control), whereas that of small myelinated fibres was 2564 ± 832 fibres/mm² (50% of control), indicating a relatively predominant reduction of small myelinated fibres in most cases. Remarkable oedema in the endoneurium was present in most cases (fig 1A). The total endoneurial area was significantly increased compared with controls (1.725 ± 0.434 mm² vs 1.089 ± 0.061 mm², $p<0.01$; fig 2A). The estimated total number of myelinated fibres in the complete cross-section of the sural nerve was significantly reduced compared with controls (6367 ± 2123 fibres vs 8684 ± 959 fibres, $p<0.05$; fig 2B). The number of large myelinated fibres was reduced, but not to a significant extent (2663 ± 920 fibres vs 3289 ± 494 fibres; fig 2B), whereas the number of small myelinated fibres was significantly reduced (3704 ± 1340 fibres vs 5396 ± 628 fibres, $p<0.05$; fig 2B). Axonal sprouting of myelinated fibres and onion-bulb formation were not conspicuous in any case compared with controls.

In contrast to myelinated fibres, a reduction of unmyelinated fibres was not apparent. Although the densities of unmyelinated fibres ranged from 15736 to 32323 fibres/mm² and significantly decreased compared with controls (22947 ± 5032 fibres/mm² vs 30655 ± 2731 fibres/mm², $p<0.01$), the estimated total number of unmyelinated fibres in the complete cross-section of the sural nerve in POEMS syndrome was almost the same as that seen in controls (32932 ± 6570 fibres vs 32348 ± 4174 fibres; fig 2C). The population of unmyelinated fibres was preserved, even in cases with a marked loss of myelinated fibres. In two patients who had impaired glucose tolerance (patients 13 and 16), ballooning of unmyelinated fibres, suggestive of degenerating fibres, and clusters of small unmyelinated fibres, suggestive of regenerating fibres, were observed. One of the patients (patient 13) had increased numbers of unmyelinated fibres due to the regenerating fibres. Findings suggestive of unmyelinated fibre degeneration or regeneration were not obvious in other cases. The percentage of Schwann cell subunits with unmyelinated fibres

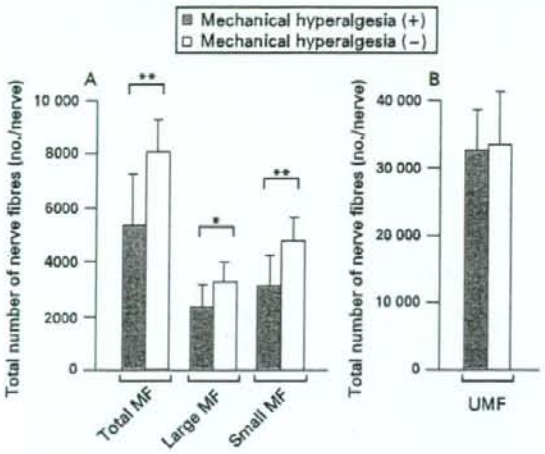

Figure 3 The relationship between hyperalgesia and total number of nerve fibres per complete cross-section of the sural nerve. Black columns indicate the group with hyperalgesia and white columns indicate the group without hyperalgesia. Each error bar represents the standard deviation. (A) The reduction of total myelinated fibres was significant in the group with hyperalgesia compared to those without it ($p<0.01$). Both large and small myelinated fibres were significantly reduced ($p<0.05$ for large myelinated fibres, $p<0.01$ for small myelinated fibres). (B) No difference in the number of unmyelinated fibres was observed between the groups with and without hyperalgesia. *$p<0.05$ and **$p<0.01$ with Mann–Whitney *U* test. MF, myelinated fibres; UMF, unmyelinated fibres.

was not different from that in controls (78.3±9.5% vs 79.6±8.3%; fig 2D). This finding suggests that there was no increase of empty subunits and further supports the view that unmyelinated fibres were preserved.[21]

The percentage of fibres with UML was 1.7±1.7%. They were more frequent in small myelinated fibres than in large myelinated fibres (2.5±2.4% vs 0.5±1.0%, $p<0.001$; fig 1B, C, D, and 2E).

In teased-fibre studies, irregularity of myelin was conspicuous and both segmental demyelination and axonal degeneration were frequently found. Segmental demyelination resulted from widening of the nodes of Ranvier, and was more frequently found in small fibres (41.8±17.6% of small fibres vs 14.2±19.3% of large fibres, $p<0.0001$; fig 1C, 2F).

The total myelinated fibres per complete cross-section of the sural nerve was significantly less in the group with hyperalgesia than those without it (5385±1895 fibres vs 8051±1304 fibres, $p<0.01$; fig 3A). Both large and small myelinated fibres were significantly reduced in the group with hyperalgesia compared with that without hyperalgesia (2290±820 fibres vs 3304±741 fibres, $p<0.05$ for large myelinated fibres; 3095±1144 fibres vs 4747±988 fibres, $p<0.01$ for small myelinated fibres; fig 3A). Compared with controls, the number of both large and small myelinated fibres was significantly reduced in the group with hyperalgesia ($p<0.05$ for large myelinated fibres, $p<0.01$ for small myelinated fibres). On the other hand, in the group without hyperalgesia, the number of large myelinated fibres was not reduced compared with controls, and the number of small myelinated fibres was only slightly reduced. There was no difference in the number of unmyelinated fibres in the complete cross-section of the sural nerve between the groups with and without hyperalgesia (32308±6010 fibres vs 33912±7764 fibres; fig 3B). As for the frequency of fibres with UML and the frequency of segmental demyelination in teased-fibre studies, these were not significantly different between the groups with and without hyperalgesia except for a higher frequency of segmental demyelination in small fibres in the group with hyperalgesia than that without it ($p<0.01$).

Cytokine profiles and their correlation to neuropathic pain

Individual cases showed extensive variation of the concentration for proinflammatory cytokines (IL-1β, IL-6 and TNF-α) in the group with POEMS syndrome (fig 4A, B and C). As a whole, a significant increase was found only for IL-6 ($p<0.01$). Levels of these proinflammatory cytokines for the POEMS syndrome and control groups were 17.3±25.9 and 5.6±5.4 pg/ml for IL-1β, 45.4±96.2 and 2.3±2.5 pg/ml for IL-6, and 138.7±349.5 and 2.8±6.7 pg/m for TNF-α. Levels of the anti-inflammatory cytokine (IL-1ra) were significantly lower in the POEMS syndrome group than in the control group (175.3±71.7 and 469.9±146.2 pg/ml, $p<0.001$; fig 4D). Levels of cytokine receptors (sIL-6r, sTNFrI and sTNFrII) were significantly higher in the group with POEMS syndrome than the control group (fig 4E, F and G). These levels for the POEMS syndrome and control groups were 28.9±6.6 and 22.6±4.1 ng/ml ($p<0.05$) for sIL-6r, 2241.7±671.2 and 1241.7±175.3 pg/ml ($p<0.001$) for sTNFrI, and 3178.3±738.1 and 2223.3±401.7 pg/ml ($p<0.01$) for sTNFrII.

All patients who showed extensive elevation of proinflammatory cytokines (IL-1β, IL-6 and TNF-α) had hyperalgesia. All of these proinflammatory cytokines were significantly elevated in the group with hyperalgesia compared to the group without it ($p<0.05$ for IL-1β and IL-6, $p<0.01$ for TNF-α; fig 4A, B and C). No significant difference between the two groups was found for IL-1ra, sIL-6r, sTNFrI and sTNFrII (fig 4D, E, F and G). Compared with controls, the group with hyperalgesia showed significant elevation of IL-1β ($p<0.05$; fig 4A), IL-6 ($p<0.01$; fig 4B), TNF-α ($p<0.05$; fig 4C), sTNFrI ($p<0.01$; fig 4F) and sTNFrII ($p<0.05$; fig 4G), and reduction of IL-1ra ($p<0.01$; fig 4D). The group without hyperalgesia showed significant elevation for sTNFrI ($p<0.01$; fig 4F) and sTNFrII ($p<0.05$; fig 4G) and reduction for IL-1ra ($p<0.01$; fig 4D) compared with controls. In patient 7, who complained of severe spontaneous pain without hyperalgesia, none of the proinflammatory cytokines was elevated compared with controls. On the other hand, proinflammatory cytokines were examined in two patients (patients 1 and 13) who had hyperalgesia without spontaneous pain and all cytokines were elevated in both patients.

DISCUSSION

Because POEMS syndrome affects a wide range of organs, its detailed neuropathic features have not yet been fully described. Evaluating the extent of nerve fibre loss in sural nerve biopsy specimens from POEMS syndrome patients is difficult due to marked enlargement of the endoneurial area due to extensive oedema. When nerve fibre loss is estimated by density, the extent may be overestimated when the cross-sectional area is enlarged. To exclude this possibility, we estimated the total number of nerve fibres in the compelete cross-section of the sural nerve and determined the precise extent of nerve fibre loss. Thus, we were able to clearly demonstrate the clinical and pathological correlates of POEMS syndrome. Although sensory symptoms were variable, ranging from the positive to the negative, the most characteristic feature in our series was the

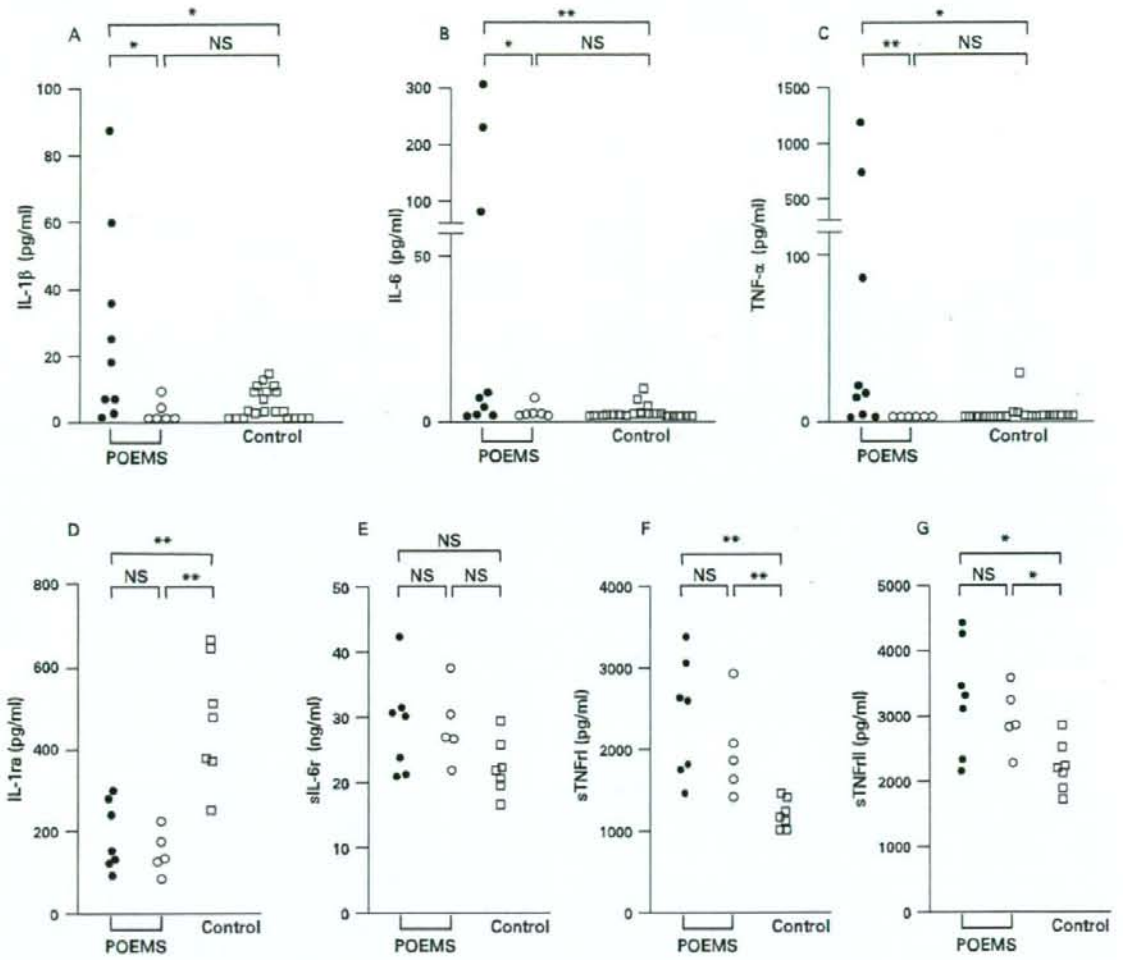

Figure 4 Serum cytokine and cytokine receptor levels in polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin changes (POEMS) syndrome and control groups. Filled circles represent POEMS syndrome patients with hyperalgesia, open circles represent POEMS syndrome patients without hyperalgesia, and open squares represent controls. (A) Interleukin-1β (IL-1β). (B) Interleukin-6 (IL-6). (C) Tumour necrosis factor-α (TNF-α). (D) IL-1 receptor antagonist (IL-1ra). (E) Soluble IL-6 receptor (sIL-6r). (F) Soluble TNF receptor I (sTNFrI). (G) Soluble TNF receptor II (sTNFrII). All patients who showed extensive elevation of proinflammatory cytokines (IL-1β, IL-6 and TNF-α) had hyperalgesia. All of these proinflammatory cytokines were significantly elevated in the group with hyperalgesia than that without it ($p<0.05$ for IL-1β and IL-6, $p<0.01$ for TNF-α). On the other hand, no significant difference between the two groups was found for IL-1ra, sIL-6r, sTNFrI and sTNFrII. Compared with controls, the group with hyperalgesia showed significant elevation for IL-1β ($p<0.05$), IL-6 ($p<0.01$), TNF-α ($p<0.05$), sTNFrI ($p<0.01$) and sTNFrII ($p<0.05$), and reduction for IL-1ra ($p<0.01$). The group without hyperalgesia showed significant elevation for sTNFrI ($p<0.01$) and sTNFrII ($p<0.05$) and reduction for IL-1ra ($p<0.01$) compared with controls. *$p<0.05$ and **$p<0.01$ with Mann–Whitney *U* test. NS, not significant.

presence of pain. More than half of our patients reported uncomfortably painful symptoms, including spontaneous pain and hyperalgesia. Indeed, many of the patients were referred to the hospital due to painful symptoms. On the other hand, patients with CIDP are predominantly characterised by motor weakness rather than sensory complaints, although painful symptoms are reported.[25] Both POEMS syndrome and CIDP are associated with demyelination in the peripheral nervous system, and electrophysiological findings are, therefore, to some extent similar. Indeed, some of our patients were initially diagnosed with CIDP before consultation to our hospital for sural nerve biopsy, particularly when the associated symptoms other than neuropathy were not conspicuous. The rarity of this syndrome also makes it difficult to diagnose correctly. Recognition of the characteristic clinical features, including spontaneous pain and hyperalgesia, may be useful in discriminating patients with POEMS syndrome from those with CIDP.

The mechanism as to why painful symptoms occur in a subgroup of patients with POEMS syndrome needs to be clarified. It is interesting that neuropathy of equal aetiology can be painful or painless. The prototype of known painful neuropathies, such as familial amyloid polyneuropathy, alcoholic neuropathy, Fabry disease, and the subgroups of polyneuropathies associated with diabetes mellitus, paraneoplastic

syndrome and Sjögren's syndrome, is characterised by small-fibre predominant axonal degeneration with relative preservation of large myelinated fibres.[16 18 20 26 29] In these neuropathies, unmyelinated fibres are the most profoundly affected and demyelinating change is not a primary feature. On the other hand, our POEMS syndrome patients revealed extensive demyelination and well-preserved unmyelinated fibres. Although we need to further assess whether the most distal portion of unmyelinated fibres are affected at the epidermal site, the mode of nerve fibre injury in the sural nerve biopsy specimens in POEMS syndrome was distinctive from that of known painful neuropathies with predominant small-fibre loss. According to a previous study,[30] hyperalgesia comprises a dynamic component (brush-evoked pain, allodynia) that is signalled by large myelinated afferents and a static component (hyperalgesia to pressure stimuli) that is signalled by unmyelinated afferents. Hyperalgesia in our series was similar to the latter.

Although the mechanism of neuropathic pain has been intensively investigated, existing knowledge has been based mainly on animal research or experimental studies of healthy human subjects. As for the pathological condition of human neuropathic pain, post-herpetic neuralgia, complex regional pain syndromes and diabetic neuropathy have been relatively well-investigated,[31–33] but little is known about neuropathic pain with other aetiologies. Neuropathic pain has been classified and studied according to its nature rather than to the nosology of the disease. Hyperalgesia has been thought to conduct through afferent A-fibres,[34] but recent observations suggest that hyperalgesia is also related to afferent C-fibres.[35–38] In our case, myelinated fibres were more profoundly affected in patients with hyperalgesia than those without it. In contrast, unmyelinated fibres were not reduced in both groups. These observations suggest that myelinated fibre injury, rather than unmyelinated fibre injury, is related to the appearance of painful symptoms in POEMS syndrome. This is similar to models of cold hyperalgesia in healthy human subjects, which suggest that hyperalgesia is induced by decreased inhibition of activated C-fibres due to the blockade of A-delta fibres.[36] In post-herpetic neuralgia, the reduction in skin unmyelinated fibre innervation was inversely correlated with severity of allodynia, suggesting that the presence of surviving unmyelinated fibres is important for the induction of allodynia.[31] Thus, neuropathic pain can be induced most effectively when unmyelinated C-fibres are well-preserved in the population under the condition that inhibition of C-fibre activity by myelinated A-delta fibres is lacking. The existence of well-preserved C-fibres and decreased A-fibres, including A-delta fibres, in POEMS syndrome is similar to the conditions in which neuropathic pain is effectively provoked. Taken together, the painful symptoms in POEMS syndrome could be generated by well-preserved afferent C-fibres when the inhibitory effect of afferent A-fibres is reduced.

In addition, serum levels of proinflammatory cytokines, including IL-1β, IL-6 and TNF-α, are known to be increased in patients with POEMS syndrome, although some variation exists.[8 37 38] Our data also show extensive variation in the levels of these proinflammatory cytokines among individual patients; they are not necessarily elevated. However, the elevation of these cytokines seemed to be related to the presence of hyperalgesia in our cases. The source of these cytokines in patients with POEMS syndrome remains uncertain as they are produced by a variety of host cells and tumour cells. For example, proinflammatory cytokines are known to be produced from Schwann cells undergoing axonal degeneration.[39] On the other hand, the cytokine itself may induce axonal degeneration.[40] In our cases, levels of one of the proinflammatory cytokines, IL-6, is positively correlated to the degree of myelinated fibre loss. It is interesting that these proinflammatory cytokines are known to be closely related to provocation of neuropathic pain.[41]

In summary, the painful symptoms in POEMS syndrome may be generated through well-preserved afferent C-fibres when the inhibition of C-fibres by A-fibres is decreased, especially in the presence of cytokine sensitisation, thus providing new insight into the pathophysiology of neuropathic pain.

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Research paper

Prevalence and incidence rates of chronic inflammatory demyelinating polyneuropathy in the Japanese population

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ABSTRACT

Objective and methods: To characterise the epidemiological features of chronic inflammatory demyelinating polyneuropathy (CIDP) in the Japanese population, this study performed a nationwide assessment of the prevalence and incidence rates in Japan.

Results: The prevalence rate per 100 000 was 1.61 in the total population; 2.01 in males and 1.23 in females. The age dependent prevalence rates were 0.23 in juveniles (<15 years old), 1.50 in young adults (15–55 years) and 2.31 in elderly adults (>55 years). The sex and age dependent prevalence rates were 0.22 in males and 0.24 in females in juveniles, 1.81 in males and 1.19 in females in young adults, and 3.12 in males and 1.64 in females in elderly adults. The annual incidence rate per 100 000 was 0.48 in the total population, 0.58 in males and 0.38 in females. The age dependent incidence rate was 0.06 in juveniles, 0.40 in young adults and 0.73 in elderly adults. The sex and age dependent incidence rate was 0.05 in males and 0.08 in females in juveniles, 0.50 in males and 0.30 in females in young adults, and 0.93 in males and 0.58 in females in elderly adults. Both the prevalence and incidence rates were very similar throughout the eight geographical areas studied, from the northern to the southern parts of Japan.

Conclusions: The prevalence and incidence rates were similar to those reported in the Caucasian population. The pathogenic background is suggested to be common throughout the different races and geographic areas, while gender and age effects should be taken into account in the pathogenesis of CIDP.

Chronic inflammatory demyelinating polyneuropathy (CIDP) is a motor and sensory neuropathy with an immune mediated inflammatory element. The clinical course is divergent, taking chronic, progressive, recurrent and regressive courses; the clinical symptoms of the motor and sensory modality and its symptomatic distribution are also divergent.[1 2] The therapeutic efficacies of intravenous immunoglobulin therapy, plasma exchange and corticosteroid therapy have been established in large scale case controlled studies.[3 4] Well recognised diagnostic criteria, a thorough understanding of the pathophysiology of the disease and beneficial therapeutics have led to the acceptance of CIDP as a clinical entity.[1 5 6] However, the epidemiology of CIDP has been rarely investigated, and thus this information is lacking, particularly in Asian populations.

In this study, the prevalence and incidence rates of CIDP in the Japanese population were determined, particularly as they relate to geographical, gender and age related distributions; these data were also compared with those from Caucasian populations.

METHODS

Data for a nationwide survey were collected according to previously described methods.[7 8] As this study included paediatric and internal medicine clinics as well as neurology clinics, we collected patients with CIDP who were diagnosed by the American Academy of Neurology (AAN) criteria,[9] Saperstein's modified criteria[10] and the inflammatory neuropathy cause and treatment (INCAT) criteria.[4] We reviewed each patient's data and ascertained if the patient fulfilled these diagnostic criteria. Patients with diabetes mellitus (17.2% of collected patients), hereditary diseases and obvious paraproteinaemia were excluded from the study.

As CIDP is a chronic disease and persists in its symptoms for more than 1 year in most patients, we computed prevalence and incidence rates for 1 year of data collection.[11] We first compiled a list of all of the hospitals in Japan with 20 or more beds from data reported by the Health, Labor and Welfare Ministry in Japan. The majority of the patients with CIDP (almost 95% of the patients in the preliminary survey in the Aichi prefecture in Japan) are seen in neurology clinics of general city hospitals, or the department of neurology or department of paediatrics of university hospitals in Japan; all of these hospitals and facilities with more than 20 beds in the whole of Japan were included in this survey. A few patients with CIDP (less than 5% of the patients in the preliminary survey in the Aichi prefecture in Japan) are seen in internal medicine or paediatric clinics of the city hospitals, and thus we selected the hospitals of internal medicine and paediatrics for data sampling according to the previously described randomised selection procedure. In brief: 5% of those hospitals with 20–99 beds, 10% of those with 100–199 beds, 20% of those with 200–299 beds, 40% of those with 300–399 beds, 80% of those with 400–499 beds and 100% of the hospitals with 500 or more beds.[7 8] For departments of neurology, we selected all hospitals because we speculated that most patients with CIDP should be correctly diagnosed by neurologists. We classified all hospitals into 30 strata depending on the type of clinical department and the size of the hospital (see supplementary table 1 online). We sent questionnaires directly to

Table 1 Prevalence and incidence rates in the total Japanese population

	Male	Female	Total
Prevalence rate (/100 000)			
Juvenile 0–15 y	0.22	0.24	0.23
Adults 15+ y	2.31	1.42	1.83
Young adult 15–55 y	1.81	1.19	1.50
Elderly adult 55+ y	3.12	1.64	2.31
Total population	2.01	1.23	1.61
Incidence rate (/100 000)			
Juvenile 0–15 y	0.05	0.08	0.06
Adults 15+ y	0.67	0.43	0.54
Young adult 15–55 y	0.50	0.30	0.40
Elderly adult 55+ y	0.93	0.58	0.73
Total population	0.58	0.38	0.48

the physicians of the departments of neurology, paediatrics and internal medicine in these hospitals, and independently to each hospital, asking each for the number, gender and other clinical and experimental information of patients who were newly diagnosed as CIDP (incidence number) or had been already diagnosed as CIDP and were still receiving treatment (prevalence number) over 1 year, from the beginning of September 2004 to the end of August 2005. We also asked how they diagnosed the patients as having CIDP by referring to the diagnostic criteria of the AAN research criteria, Saperstein's modified criteria, the INCAT criteria and other diagnostic backgrounds.[10 12] In addition, we obtained information on the gender and age distribution of the Japanese population in each prefecture based on the national census (October 2005). We calculated the number of patients with CIDP in each stratum and extrapolated the prevalence and incidence figures based on the response rates to the questionnaire and the population statistics. To calculate the geographical distribution, we arranged 47 prefectures into eight areas from the north to the south of Japan and assessed the prevalence and incidence rates based on the population in each area.

This study was performed as a project study in the Refractory Peripheral Neuropathy Research Study Group, under the auspices of the Ministry of Health, Labor and Welfare of Japan. The study design was agreed upon and approved by the Ethics Committee of Nagoya University Graduate School of Medicine.

RESULTS

The study received 1561 responses to the questionnaire out of 2827 surveyed facilities, for a total net recovery rate of 55.2%; 51.8% of the neurology clinics, 41.8% of the clinics of internal medicine and 70.1% of the paediatric clinics (see supplementary table 1 online). From September 2004 to August 2005, 742 men and 480 women were diagnosed with CIDP in the 1561 medical facilities out of the total of 2827 randomly selected surveyed hospitals in Japan having more than 20 beds. Based on these data, and the response rates from each stratum of the facilities, we obtained a prevalence number of 2433 patients (1495 men and 938 women) (see supplementary table 2 online). The CIDP prevalence rate per 100 000 of the Japanese population was 1.61 in the total population, 2.01 in the male population and 1.23 in the female population (table 1). The age dependent prevalence rate was 0.23 in juveniles, 1.50 in young adults and 2.31 in elderly adults. The sex dependent prevalence rate in each age group was 0.22 in males and 0.24 in females in juveniles, 1.81 in males and 1.19 in females in young adults, and 3.12 in males and 1.64 in females in elderly adults. The number of newly diagnosed patients with CIDP during the year from September 2004 to August 2005 was 601 (354 men and 247 women) (see supplementary table 3 online). The annual incidence rate per 100 000 was 0.48 in the total population, 0.58 in males and 0.38 in females. The age dependent annual incidence rate was 0.06 in juveniles, 0.40 in young adults and 0.73 in elderly adults. The sex dependent incidence rate in each group was 0.05 in males and 0.08 in females in juveniles, 0.50 in males and 0.30 in females in young adults, and 0.93 in males and 0.58 in females in elderly adults (table 1).

Additionally, there was no difference in the prevalence or the incidence rates in the total population in eight geographical areas (Hokkaido, Tohoku, Kanto, Koshin-etsu, Tokai, Kinki, Chugoku-Shikoku and Kyushu-Okinawa) in Japan (fig 1).

DISCUSSION

The higher prevalence and incidence rates in males compared with females, and the increasing rates with aging were the

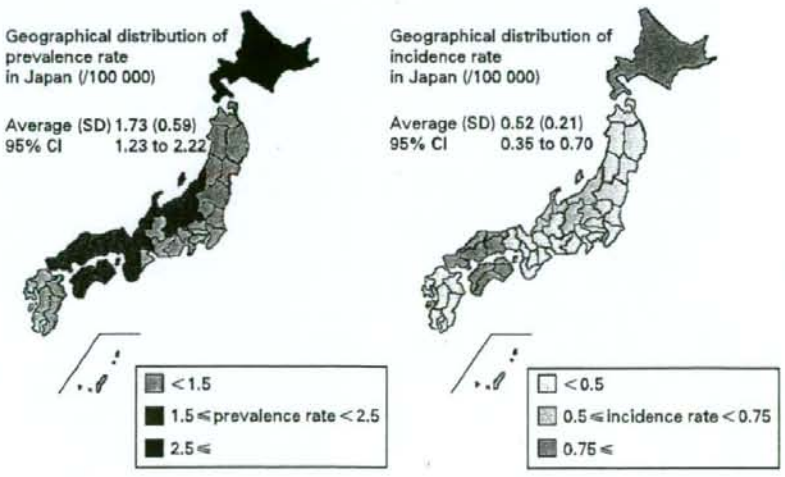

Figure 1 Geographic distribution of prevalence and incidence rates throughout Japan. There were no statistical preponderances in the geographical distributions of either the prevalence or incidence rates.

Table 2 Comparison of the prevalence and incidence rates among Caucasian and Japanese populations

Report	Location	Population	Prevalence rate (/100 000)			Incidence rate (/100 000)		
			Total	Adult	Juvenile	Total	Adult	Juvenile
Lunn[15] (1994–1995)	England (UK)	14 049 000	0.46–1.24	NA*	NA*	NA	NA	NA
McLeod[14] (1996)	New South Wales (Australia)	5 995 000	1.87	NA	0.48†	NA	NA	NA
	Newcastle (Australia)	448 000	NA	NA	NA	0.15	NA	NA
Chio[12] (2001)	Piemonte and Valle d'Aosta (Italy)	4 334 225	3.58	NA*	NA*	0.36	NA	NA
Iijima (2004–2005)	Whole areas of Japan (Japan)	127 655 000	1.61	1.83	0.23‡	0.48	0.54	0.06‡

*Although the exact data were not reported, the age dependent increase in the prevalence rate was discussed in each report.
†Juvenile population is designated as those under 20 years.
‡Juvenile population is designated as those under 15 years.
NA, not available.

major observations of the Japanese epidemiology of CIDP, as was the lack of a specific geographical distribution. As CIDP is a chronic disease generally lasting more than 1 year, our results on observations over 1 year are expected to represent the transverse epidemiology in the Japanese population.

A few well designed epidemiological studies have been reported from the UK, Australia and the north of Italy in Caucasian populations.[12–15] The most striking finding was that our data in the Japanese population were similar to those reported in these Caucasian populations (table 2). Compared with the UK–Australian data, we found epidemiological similarity in the total prevalence and incidence rates, male predominance over females, and the higher prevalence and incidence rates in the adult population compared with the juvenile population, although the ages categorising their juvenile populations were different to ours. The prevalence rate in northern Italy was slightly higher than ours (table 2), while the increasing prevalence and incidence rates in their elderly populations were similar to ours. The prevalence and incidence rates in our study may be somewhat underestimated as we excluded patients with diabetes mellitus or paraproteinaemia; these data were also collected in a hospital based manner, excluding those under home care or under private office follow-up not attending hospital during the survey period. Another source of bias is that we would have missed patients who were diagnosed before the survey, but who did not attend hospital during the survey period, which may have occurred because their disease was too mild, or patients were too ill or did not see any point in attending because their treatment was not helping.

In addition, our results clearly demonstrate that there is no significant preponderance in the geographical distribution from the north to the south of Japan for the epidemiology of CIDP. These results suggest that CIDP is similar in its epidemiological background in different races and different geographical environments, indicating that the pathogenesis of CIDP could be common worldwide, and independent of genetic and geographical environmental influences, although further studies are needed to confirm this.

Another interesting observation was the gender related difference in the prevalence and incidence rates. In the adult population, prevalence and incidence rates were significantly higher in males; the male to female ratio was 1.63 to 1 (1.52 to 1 in young adults and 1.90 to 1 in elderly adults) for the prevalence rate and 1.56 to 1 (1.67 to 1 in young adults and 1.60 to 1 in elderly adults) for the incidence rate. Whereas in the juvenile population a significant preponderance was observed in girls, the male to female ratio was 0.92 to 1 for the prevalence rate and 0.63 to 1 for the incidence rate. At present we do not understand the background mechanism underlying this gender related difference, particularly its reversed ratio among the adult and juvenile populations.[11 16] However, the gender and age related differences in the epidemiological indices were remarkable, especially given their reversal during puberty, suggesting that the effects of gender could be significant in the pathogenesis of CIDP.

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APPENDIX

Members of the Refractory Peripheral Neuropathy Research Study Group of Japan

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Intravenous immunoglobulin treatment for painful sensory neuropathy associated with Sjögren's syndrome

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ABSTRACT

Background: Patients with painful sensory neuropathy associated with Sjögren's syndrome-associated neuropathy often show severe neuropathic pain which is not relieved by conventional treatments.
Objective: To evaluate the effect of intravenous immunoglobulin (IVIg) therapy in the treatment of neuropathic pain associated with Sjögren's syndrome.
Patients and methods: We examined 5 patients affected by painful sensory neuropathy associated with Sjögren's syndrome. All patients were treated with IVIg (0.4 g/kg/day for 5 days) and pain rating was assessed by the Visual Analogue Scale (VAS).
Results: All five patients showed a remarkable improvement in neuropathic pain following IVIg therapy. Pain, assessed by the determination of mean VAS score, was reduced by 73.4% from days 2–14 following treatment. The observed clinical improvement persisted for 2 to 6 months. One patient, examined by quantitative sensory testing (QST), showed an improvement of superficial sensory deficit accompanied by pain relief.
Conclusion: IVIg might be an effective treatment for pain in Sjögren's syndrome-associated neuropathy. Further studies should be done in a controlled, blind study.

1. Introduction

Various forms of peripheral neuropathy have been reported to be associated with Sjögren's syndrome, including sensory ataxic neuropathy, painful sensory neuropathy without sensory ataxia, trigeminal neuropathy, multiple mononeuropathy, multiple cranial neuropathy, radiculoneuropathy, and autonomic neuropathy with anhidrosis [1–7]. The presence of such a diverse array of neuropathic states suggests that multiple mechanisms are involved in the pathogenesis of neuropathy associated with Sjögren's syndrome. Furthermore, the therapeutic efficacy of major treatments for Sjögren's syndrome, such as corticosteroid therapy, IVIg therapy and immunosuppressant therapy, appear to vary amongst the different forms of neuropathy [5], most probably reflecting differences in the underlying pathology. We previously reported, as an anecdotal case report, the effectiveness of IVIg therapy in the amelioration of painful symptoms of sensory neuropathy without the sensory ataxia associated with Sjögren's syndrome [8]. Pain in this type of neuropathy is often uncontrolled with conventional symptomatic treatment using NSAIDs, tricyclic antidepressant and anti-epileptic drugs, and can thus significantly compromise the activity of daily living [5]. Control of pain in the painful form of neuropathy without sensory ataxia is a major problem in Sjögren's syndrome-associated neuropathy, although this painful form is not widely recognized as a sub-form of Sjögren's syndrome-associated neuropathy [5].

In the present study, we evaluated the efficacy of IVIg therapy in five patients with painful sensory neuropathy associated with Sjögren's syndrome but without sensory ataxia and further characterize this type of neuropathy.

2. Patients and methods

We recruited five patients affected by the painful sensory neuropathy associated with Sjögren's syndrome. All five patients fulfilled the diagnostic criteria for Sjögren's syndrome. The diagnosis of primary Sjögren's syndrome was established by criteria proposed by the Diagnostic Committee of Health and Welfare of Japan [9] and by the American–European Community [10]. One of our patients (patient 1) has been described previously [8]. In the present study, we further present additional novel information regarding this patient, particularly in terms of long-term follow up and therapeutic outcome. Patients were excluded if they presented with other causes of neuropathy, including diabetes mellitus, impaired glucose tolerance, vitamin B12 deficiency, folic acid deficiency, autoimmune disease, and paraproteinemia. Hypothyroidism was evident in two patients (patients 4 and 5), although medication regulated thyroid function at

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Table 1
Laboratory findings and clinical features

Patient age/sex	Dry eye/ dry mouth	Positive findings of Sjögren's syndrome	Initial symptom	Progression	Motor involvement		Sensory involvement					Autonomic involvement
					Weakness	Atrophy	Distribution	Superficial[a]	deep[b]	Spontaneous pain	Characteristics of pain	
1 67/M	-/-	SS-A, B lip biopsy	Pain	Chronic	-	-	L[c] (distal)	+	-	+++[d]	Aching hyperalgesia	1.2.3.4.5.6.
							T[c] (middle portion)					
2 72/F	+/+	Lip biopsy	Pain	Chronic	-	-	L[c] (distal)	+	-	+++[d]	Tingling hyperalgesia	1.2.4
							H[c] (left side back)					
3 54/M	+/+	SS-B lip biopsy	Sensory disturbance	Subacute	-	-	Right hand (radial)	+	-	+++[d]	Tingling static allodynia hyperalgesia	-
							L[c] (dital)					
							T[c] (upper portion)					
4 57/F	+/+	SS-A lip biopsy	Pain	Subacute	-	-	L[c] (distal)	-	-	+/+	Aching hyperalgesia	2.4
5 59/F	+/-	SS-A lip biopsy	Pain	Chronic	+	-	F[c] (left side)	+	+	+++[d]	Tingling hyperalgesia	2.3.4
							L[c] (upper)					
							L[c] (right>left)					

1, Abnormal pupils; 2, Hypohidrosis; 3, Orthostatic hypotension; 4, Constipation; 5, Urinary disturbance; 6, Decreased uptake of ^{123}I-MIBG.
[a] Superficial; reduction of superficial sensation including light touch and pinprick perception and temperature sensation.
[b] Deep; reduction of deep sensation including vibration and joint position.
[c] F, Face; H, Head; L, Limb; T, Trunk.
[d] 'Â{Â{, moderate pain; 'Â{Â{Â{, severe pain.

normal levels in these patients. Prior to treatment, all patients underwent neurological examination, blood studies, CSF studies, nerve conduction studies (NCS), and sural nerve biopsy. Profiles of the patients are summarized in Tables 1, 2, and 3. The group of patients included two men and three women, ranging from 54 to 72 years old. In all patients, the initial symptom of neuropathy was paraesthesia or painful peripheral dysaesthesia in the distal portion of the extremities.

Patient 1, a 67 year old man, was diagnosed as Sjögren's syndrome 16 years ago, had suffered painful dysaesthesia and numbness in the feet for 10 years, which spread to the proximal portion of the legs and arms. Neurological examination revealed a reduction in superficial sensation, including light touch/pinprick perception and temperature sensation; painful dysaesthesias were elicited over the middle portion of the trunk and the four extremities. The pain experienced in this patient's hands was so intense that he could not extend his fingers or touch objects. The pain in his feet almost precluded ambulation. *Patient 2*, a 72 year old woman had experienced painful dysaesthesia and numbness in the legs and hands for 3 years. Neurological examination revealed reduced superficial sensation along with painful dysaesthesias in the distal portion of the four extremities. *Patient 3*, a 54 year old man, had experienced pain in all four extremities and the head for 4 years. Neurological examination revealed no reduction in superficial sensation. Hyperalgesia was evident over the left side of the back of the head, the upper portion of the trunk, and the radial side of the right hand and feet. The patient needed to wear gloves to protect himself from the hand pain during his normal daily life. Sometimes, the patient also experienced difficulty walking as a direct result of pain. *Patient 4*, a 57 year old woman had suffered pain in her left foot for 1 year. Neurological examination revealed a reduction in superficial sensation; painful dysaesthesias were elicited over distal parts of the four extremities. *Patient 5*, a 59 year old woman had suffered spontaneous pain for 20 years along with painful dysaesthesia and numbness in all four extremities, but predominantly on the right side. Neurological examination revealed reduced superficial sensation. Painful dysaesthesias were elicited over the left-side cheek, the radial side of the upper extremities, and the lower extremities, predominantly on the right side. The pain in this patient's legs almost precluded ambulation.

Fluctuation in the intensity of pain was seen, to some extent, in all patients. Asymmetric pain symptoms and sensory impairments were seen in three patients (patients 3, 4, and 5). Although deep sensation, such as joint position and vibration, was mildly impaired in the distal portion of the extremities in one patient (patient 5), this was not accompanied by sensory ataxia, pseudoathetosis in the hand, or a

Table 2
Nerve conduction study

Patient	Median nerve					Tibial nerve			Sural nerve	
	MCV (m/s)	DL (ms)	CMAP (mV)	SCV (m/s)	SNAP (μV)	MCV (m/s)	DL (ms)	CMAP (mV)	SCV (m/s)	SNAP (μV)
1	56	3.4	5.4	48	5.2	42	4.2	7.1	47	3.9
2	55	3.1	4.5	64	23	32	4.1	5.7	43	17
3	55	3.1	12.6	63	25.1	48	3.9	15.8	51	27.2
4	54	2.9	10.3	58	41.6	40	4.6	10.5	60	15.5
5	55	2.7	6.1	62	25.2	42	3.4	15.9	48	11.5
Controls	57.6±3.8	3.4±0.4	8.2±2.9	56.3±5.3	28.0±11.5	46.0±3.8	4.0±0.6	11.8±3.5	49.2±4.8	16.8±7.8

Control values were obtained in 171 normal volunteers for the median nerve, 161 for the ulnar nerve, and 163 for the sural nerve [11].
MCV = motor nerve conduction velocity; DL = distal latency; CMAP = compound muscle action potential.
SCV = sensory nerve conduction velocity; SNAP = sensory nerve action potential.

Table 3
Pathological findings in the sural nerve

Patient	Myelinated fiber density (no/mm^2)			Small/large ratio	Unmyelinated fiber density (no/mm^2)	Tested-fiber study (%)	
	Total fiber	Large fiber	Small fiber			De/re-myelination	Axonal degeneration
1	4557	1778	2779	1.6	19,245	3.0	24.0
2	5728	2594	3134	1.2	13,557	8.0	0.3
3	6085	2845	3240	1.1	17,118	0.5	0.5
4	6902	3530	3372	1.0	13,397	1.1	1.9
5	4807	2766	2041	0.7	21,531	6.2	2.8
Controls (n=10) mean±SD	7087±1413	2717±617	4363±1067	1.7±0.5	30,876±3713	9.0±5.9	1.8±2.0

Control values were obtained from subjects with nonneurologic disease at autopsy.

positive Romberg's sign. Muscle strength was preserved in all patients except for patient 5; this particular patient could not exert full muscle strength in the right lower extremity due to severe pain, and appeared to reveal slight weakness. Autonomic dysfunctions, including constipation, orthostatic hypotension and hypohidrosis were seen in four of the patients. Reduced uptake of ^{123}I-MIBG was evident in two patients (Table 1). Cerebrospinal fluid cell count was normal in all patients, while protein was elevated in two patients (patients 1 and 5). Nerve conduction studies revealed preserved motor and sensory conduction velocities and distal latencies (Table 2). Amplitudes of compound muscle action potential (CMAP) and sensory nerve action potential (SNAP) were greater than the mean±2SD of normal control subjects [11], except for SNAP of the median nerve in patient 1. Sural nerve specimens revealed mild reduction in small-myelinated fibers and unmyelinated fibers in all patients (Fig. 1, Table 3). The density of large myelinated fibers was 2720±627 fibers/mm^2 (100% of mean control values), while that of small myelinated fibers was 2913±535 fibers/mm^2 (66% of mean control values), indicating a predominant reduction in the number of small myelinated fibers. The density of unmyelinated fiber was 16,970±3550 fibers/mm^2 (55% of mean control values). Axonal degeneration was evident in patient 1. There was no evidence of axonal sprouting in any of the patients, suggesting ganglionopathy as a cause of neuropathy. Vasculitis was not observed in any patient.

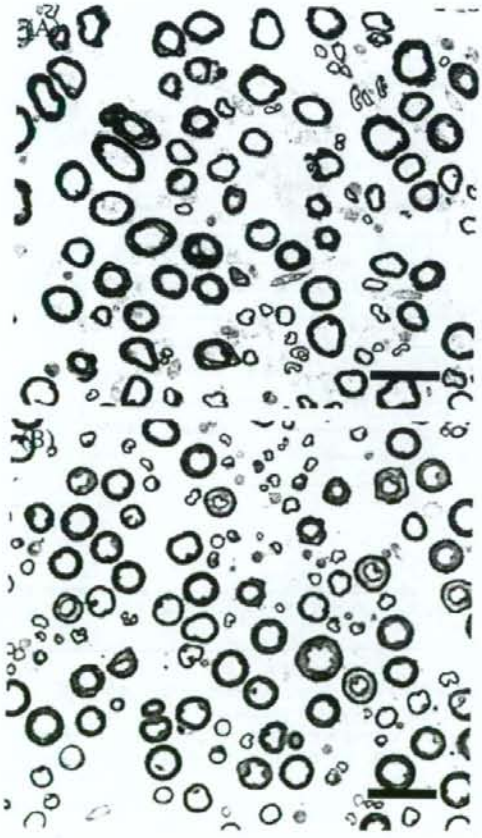

Fig. 1. Sural nerve pathology. (A) Specimen from patient 4. (B) Specimen from a control patient. Specimen from patient 4 revealed predominantly small-fiber loss. No axonal sprouting was seen. Vasculitis was not observed. Scale bar=20 μm.

All patients were treated with 0.4 g/kg intravenous immunoglobulin (IVIg) for 5 days. In all patients, the effect of IVIg treatment was scored by use of the Visual Analogue Scale (VAS) [12]. In addition, we performed quantitative sensory testing (QST) to determine the cold detection threshold (CDT), vibration detection threshold (VDT), and heat-pain (HP) threshold in both the upper and lower extremities using computer aided sensory evaluation version (CASE ; Medical Electronics, Michigan). This evaluation was carried out on one patient (patient 5), before and after treatment. For the CDT, a series of cold stimulation tests, using a range of different temperatures were delivered with a sensor placed on the dorsum of the foot. Patients were asked to respond when the stimulus was felt. The testing algorithms used were the 4, 2, and 1 stepping method for CDT [13], the aim being to determine the smallest temperature differential from the baseline temperature that can be reliably detected. For the VDT, a series of vibration stimulation tests were delivered with a sensor placed on the great toe using the 4, 2, and 1 stepping method. For the HP thresholds, a series of warm stimulation tests were delivered to the dorsum of the foot, using the non-repeating ascending with null stimuli algorithm [14]. HP: 0.5 is the heat-pain detection threshold, HP: 5.0 is a intermediate heat-pain response and the difference between the two (HP: 5.0−0.5). CASE IV normative data were used in accordance with previous studies [13]. Abnormal CDT and VDT were defined as above the 97th percentile (hypoesthesia), and an abnormal HP: 0.5 was defined as below the 3rd percentile (hyperalgesia). QST studies were performed by the same technician in two different patients (patients 4 and 5).

3. Results

All patients responded well to IVIg therapy. Severe pain had been reduced from 7.6±2.9 to 2.2±1.5, according to the Visual Analogue Scale (VAS) (Fig. 2). Several relapses were seen in two patients (patients 1 and 2) over long-term follow up. IVIg treatment was effective at each relapse, but the effect of IVIg became less pronounced in patient 2 after 6 years of treatment (Fig. 2 B). The effect on pain was reported to begin 2 to 14 days after the IVIg infusion started. The clinical improvement lasted for about 2 to 6 months (4.0±2.65 months). The second IVIg therapies were performed in four patients when relapse occurred, with the interval of second IVIg

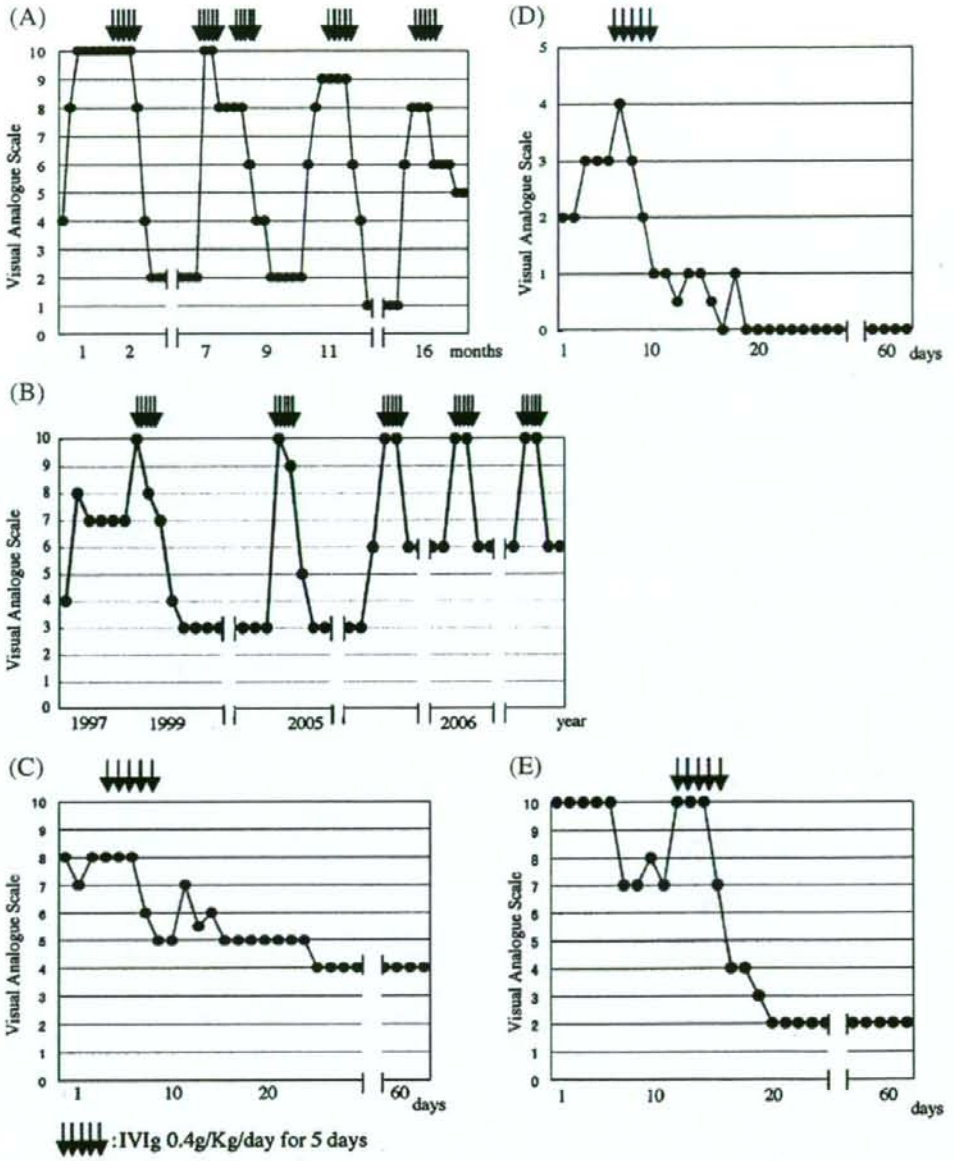

Fig. 2. Clinical course of the Visual Analogue Scale. A 10 cm VAS was anchored by two extremes of pain (left, no pain; right, the worst pain imaginable). Pain ratings were applied subjectively according to the manner described by Kelly [12]. (A) Clinical course of patient 1. (B) Clinical course of patient 2. (C) Clinical course of patient 3. (D) Clinical course of patient 4. (E) Clinical course of patient 5.

treatment ranging from 7 months to 1 year. IVIg therapy reduced pain by 50–100% on the VAS scale; the significant effect of IVIg upon pain relief was clearly evident ($p<0.01$). All patients experienced accompanied superficial sensation, such as numbness, tingling or painful dysaesthesia, but these showed simultaneous improvement. Muscle strength in patient 5 also improved. Following IVIg treatment, patients 1, 3 and 5 were able to walk smoothly and patient 3 no longer required gloves. Direct evidence of sensory improvement was clearly demonstrated by CASE IV analysis in patient 5. VDT 5 was less than +2SD and there was no significant difference before and after treatment. Before treatment, CDT was 28.1 °C (hand) and 10.0 °C (foot), representing abnormal levels greater than +2SD. Following IVIg therapy, CDT improved to 29.8 °C (hand) and 17.3 °C (foot), which was within the normal range of −1.04SD (hand) and +1.88SD (foot). These results clearly demonstrate significant improvement in superficial sensory impairment following IVIg therapy. HP threshold was not different before and after treatment.

4. Discussion

IVIg therapy was effective in alleviating pain symptoms in all 5 patients involved in the present study. Painful symptoms involved

proximal regions of the limbs, face, or trunk in a non-length dependent manner with predominantly superficial sensory involvement. Motor nerve function was well preserved. Pathologically, there was a predominantly small-fiber axon loss with relative preservation of large myelinated axons, without evidence of regenerating fibers. Pathological evaluation of the dorsal root ganglia in patients with major causes of ganglionopathy have been reported for patients with Sjögren's syndrome and paraneoplastic syndrome, via the analysis of tissue obtained by biopsy or autopsy [2,15]. The major symptom in these syndromes is sensory ataxia resulting from the impairment of deep kinaesthetic sensation corresponding to the involvement of large-sized neurons [2,15]. On the other hand, it is uncommon for ganglionopathy to preferentially affect small-diameter neurons [16,17]. However, recent studies have suggested that this type of ganglionopathy may occur in patients with Sjögren's syndrome accompanying painful symptoms [5,17]. Our patients were well concordant with these clinico-pathological features of ganglionopathy with preferential involvement of small-sensory neurons. The concept of ganglionopathy, preferentially involving small neurons, although not yet widely recognized, is rapidly becoming a clinically important field [17].

In our patients, painful symptoms were very severe and significantly interfered with the activity of daily living. Conventional treatments for painful neuropathies, including anticonvulsants, tricyclic antidepressants, SSRI (selective serotonin reuptake inhibitor) or opioids, were not sufficient to ameliorate pain in our patients. Consequently, it was highly evident that other new approaches were needed. Although the mechanisms of pain in painful sensory neuropathy associated with Sjögren's syndrome have yet to be fully clarified, it is considered that immunomodulatory therapy may be effective, based on the hypothesis that painful sensory neuropathy is a continuum of the sensory ataxic form as described above. In the sensory ataxic form, the lesion is located at the level of the sensory ganglion neurons associated with T-cell infiltration [2]. Indeed, IVIg therapy has proved to be effective, to some extent, in the sensory ataxic form [5,18–21]. The putative IVIg effect mechanism includes blockade of the Fc receptor, enhanced antibody catabolism and the suppression of pro-inflammatory cytokines. Therefore, macrophage and B-cell functions would be inactivated and circulating auto-antibodies reduced. IVIg can also exert effect upon superantigens and can modulate T-cell function and antigen recognition [22]. In the ataxic type of Sjögren's syndrome, some of the remaining dorsal root ganglion neurons, which tend to be impaired owing to inflammation, may have regained function because of the IVIg treatment [21]. We speculate that IVIg would elicit the same effect upon small dorsal root ganglion neurons in painful Sjögren's syndrome-neuropathy.

Pro-inflammatory cytokines such as TNF-alpha, IL-1 beta, and IL-6 contribute to the development of inflammatory and neuropathic pain, and hyperalgesia [23,24]. Indeed, in patients with painful neuropathy, or complex regional pain syndrome, TNF-alpha has been reported to correlate with the presence of mechanical hyperalgesia [25,26]. However, participation of such cytokines in painful sensory neuropathy associated with Sjögren's syndrome remains largely unknown. In one of our patients, some serum cytokines, e.g., TNF-α, IL-8 were shown to be reduced by IVIg (patient 3, data not shown). A question of IVIg treatment is cost. It is certain that IVIg is very expensive, but IVIg bring rapid and sufficient improvement. Therefore, IVIg treatment is considered to be useful for patients who have severe pain or have insufficient improvement by conventional treatment. Therefore, IVIg might be an effective treatment for pain in Sjögren's syndrome-associated neuropathy. Further studies should be done in a controlled, blind study.

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総　説

*PMP22*遺伝子異常によるCharcot-Marie-Tooth病の分子病態特異的な治療*

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1．はじめに

Charcot-Marie-Tooth病（CMT）は、遠位優位の筋力低下・感覚低下を主徴とする遺伝性の運動感覚ニューロパチーである。遺伝学的には不均質な疾患群であり、現時点で少なくとも31の疾患遺伝子と10の遺伝子座が明らかにされている[1]。優性遺伝形式のCMTは、神経伝導速度が低下する脱髄型（CMT1）と、神経伝導速度の低下しない軸索型（CMT2）の2型に大別され、劣性遺伝形式のものはCMT4に分類される。

髄鞘蛋白の約5%を構成する膜蛋白をコードする遺伝子*PMP22*の異常によるニューロパチーは、CMT全体の約50%、CMT1の約70%を占め、CMTの原因遺伝子として最も頻度が高いことが知られている[2]。その分子病態的な原因としては、*PMP22*を含む第17番染色体の1.4Mb領域（17p11.2）の重複（CMT1A）が98%を占めるが、*PMP22*の点変異によりニューロパチーをきたす一群も2%存在する[3]。近年、前者に関しては、CMT1Aのモデル動物にアスコルビン酸やプロゲステロン拮抗薬であるオナプリストンを投与することによって運動機能の改善がみられることが報告され[4),5]、2006年より欧州ではアスコルビン酸のヒトへの治験が開始されている[6]。最近われわれは、少数例のオープン試験ではあるがCMT1A患者にアスコルビン酸の治験を試み、指標の一部で有意な改善を認めることを報告した[7]。また*PMP22*の点変異によるCMTの新規治療法として、香辛料の成分である小分子クルクミンを投与することにより*Trembler-J*マウスの運動機能が改善することを報告した[8]。本稿では、分子病態特異的なCMTの治療的戦略を*PMP22*の遺伝子異常によるCMTを例として概説する。

2．*PMP22*重複によるCMT1Aに対する治療戦略

2-1．*PMP22*重複によるニューロパチーの分子病態

CMT1Aのニューロパチーが*PMP22*遺伝子の量的効果によって発症することは、以下の根拠により明らかにされている。(1) 非常に小さい領域の重複を持つ稀なCMT1A症例においても組み替え領域内に*PMP22*が含まれており、*PMP22*が3コピー存在することがニューロパチー発症に重要であること[9]、(2) CMT1Aの腓腹神経において*PMP22*のmRNAが増加しており[10]、またPMP22蛋白も増加し

* Molecular mechanism-specific therapies for CMT1A: from duplication to point mutation of *PMP22*

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ていること[11]、(3) マウスモデルとラットのトランスジェニックモデルにおいて、*pmp22*の過剰発現によりCMT1と表現型の類似したニューロパチーを呈すること[12),13)]。これらの事実より、CMT1Aでは*PMP22*の遺伝子の過剰発現がニューロパチーと直接関係していることが推定されており、その治療戦略としては遺伝子発現を抑制することが重要であると考えられる。現時点では、(1) プロゲステロン拮抗薬であるオナプリストン、(2) アスコルビン酸、(3) オリゴヌクレオチドなどによる*PMP22*発現の抑制による治療が考えられている（図1）。

2-2. *PMP22*重複によるニューロパチーに対する治療戦略

プロゲステロンの代謝産物が$GABA_A$のレセプターを介して*PMP22*の発現を亢進させていることは従来から知られていた[14]。Seradaらは、プロゲステロン拮抗薬であるオナプリストン[15]が$GABA_A$レセプターと*PMP22*プロモーター領域との結合を阻害することにより、*PMP22*遺伝子の発現を抑制することに着目した[4]。彼らは*pmp22*のトランスジェニックラットに、プロゲステロン、オナプリストンを投与し対照群と比較したところ、オナプリストン投与群で末梢神経障害が抑制されていることを病理学的・行動学的に示した[4]。残念ながら、オナプリストンは強い肝障害があるため[15]ヒトへの臨床応用は困難と考えられており、類似の薬理作用のある薬剤の開発がのぞまれている。

つぎに、アスコルビン酸は、細胞内cAMPとadenylate cyclase活性に作用して*PMP22*の発現を抑制することが報告されており[16]、アスコルビン酸投与により細胞内における*PMP22*遺伝子発現量を正常量に近づけることによって末梢神経障害が改善する可能性が考えられている。Passageらは、CMT1Aのモデルマウスを用いて、アスコルビン酸56mg/kg/週を投与したところ、対照群と比較してロッド把持時

PMP22

- 17p12に位置する全長35kbの遺伝子
- 4回膜貫通型の22kDa細胞膜構成蛋白
- Schwann cellのcompact myelinに分布
- CMT1の70%の原因遺伝子である

遺伝子変異	 重複	 欠失	 点変異
CMT表現型	CMT1A	*Hereditary neuropathy with liability to pressure palsies (HNPP)*	*HNPP/CMT1A* *Dejerine-Sottas Neuropathy* *Congenital Hypomyelinating Neuropathy*
分子病態機序	遺伝子の量的効果		優性ネガティブ効果
治療の標的	遺伝子発現の制御		翻訳後プロセスのコントロール 蛋白プロセシング 蛋白トラフィッキング 細胞内への蓄積
治療薬の候補	オナプリストン アスコルビン酸 オリゴヌクレオチド		クルクミン

図1．*PMP22*とCharcot-Marie-Tooth病

間の改善と有髄線維の増加と髄鞘の厚さの改善を認めたことを報告している[5]。そこでわれわれは、遺伝子診断で*PMP22*重複が確認されたCMT1A 13例（男性8例、女性5例）を対象として、アスコルビン酸投与により末梢神経障害の改善がみられるかどうか検討した[7]。試験コントローラーが無作為に、治験参加者を投与群と非投与群とに割り付けたところ、7例が投与群、6例が非投与群となった。投与群にはアスコルビン酸20mg/kg/日を3ヶ月間経口投与した。投与前、投与4週、投与8週、投与12週時に、自覚症状、運動機能障害度（CMT neuropathy score：CMTNS）、右尺骨神経の神経伝導検査を行い、非投与群との比較検討を行った（表1）。非投与群では（投与前を100とした場合）、右握力は12週後87（p=0.04）、左握力は12週後92と低下していたが、アスコルビン酸投与群では、右握力は12週後132、左握力は12週後139と改善を認めていた。CMTNSに関しては（投与前を100とした場合）、12週後非投与群で99、投与群で102と両群間で有意差を認めなかった。また、右尺骨神経の神経伝導検査では、12週間後の（投与前を100とした場合）CMAPは非投与群で101、投与群で107、同様に12週後のMCVは非投与群で89、投与群で95と有意差を認めなかった。自覚症状としては、投与群では1例で下肢感覚症状の改善、1例で前脛骨筋の筋力改善を認めた。本研究は少数例を対象とした比較的短期間のオープン試験であり、この結果のみからは

表1 CMT1Aに対するアスコルビン酸臨床試験の結果

			アスコルビン酸投与群（n=7）	アスコルビン酸非投与群（n=6）
握力	右	前	100	100
		4週間後	103±27	85±20
		8週間後	117±35	86±21
		12週間後	132±46*	87±13**
	左	前	100	100
		4週間後	100±38	86±12
		8週間後	128±79	90±19
		12週間後	139±88	92±26
CMTNS		前	100	100
		4週間後	101±3	98±3
		8週間後	101±3	98±3
		12週間後	102±3	99±2
尺骨神経	CMAP	前	100	100
		4週間後	201±157	140±101
		8週間後	151±175	116±57
		12週間後	107±64	101±52
	MCV	前	100	100
		4週間後	93±8	102±20
		8週間後	92±11	97±26
		12週間後	95±8	89±19

各測定値は投与前を100とした値で、mean±SD.

CMTNS：CMT neuropathy score、CMAP：Compound muscle action potential、MCV：motor conduction velocity.

*：投与4週間目との比較で有意に増加（p<0.05）

**：投与群と比較して有意に低下（p<0.05）（*末梢神経* 18: 210-212, 2007より改変）