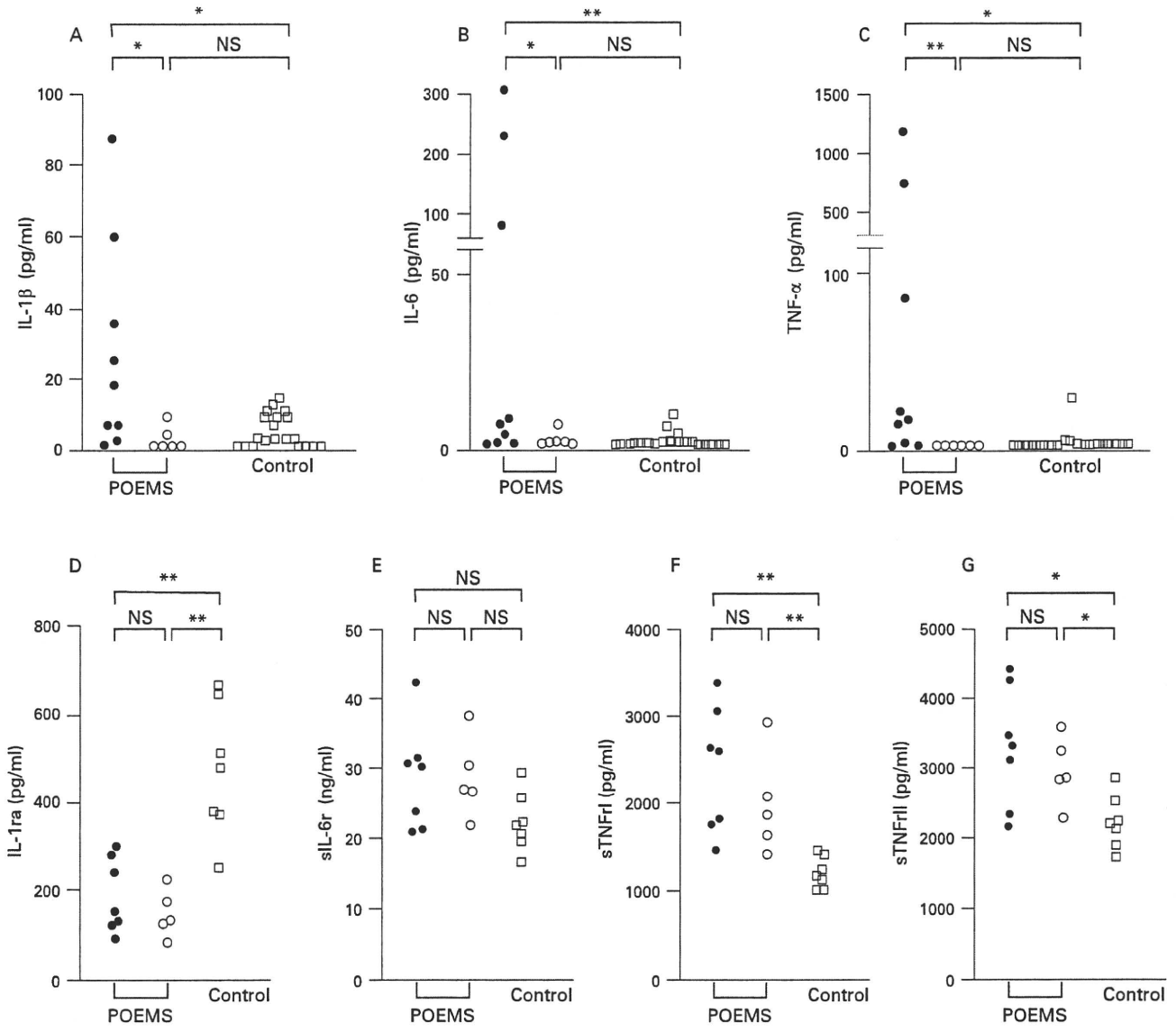

Figure 4 Serum cytokine and cytokine receptor levels in polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin changes (POEMS) syndrome and control groups. Filled circles represent POEMS syndrome patients with hyperalgesia, open circles represent POEMS syndrome patients without 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.[33–35] 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.[3 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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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

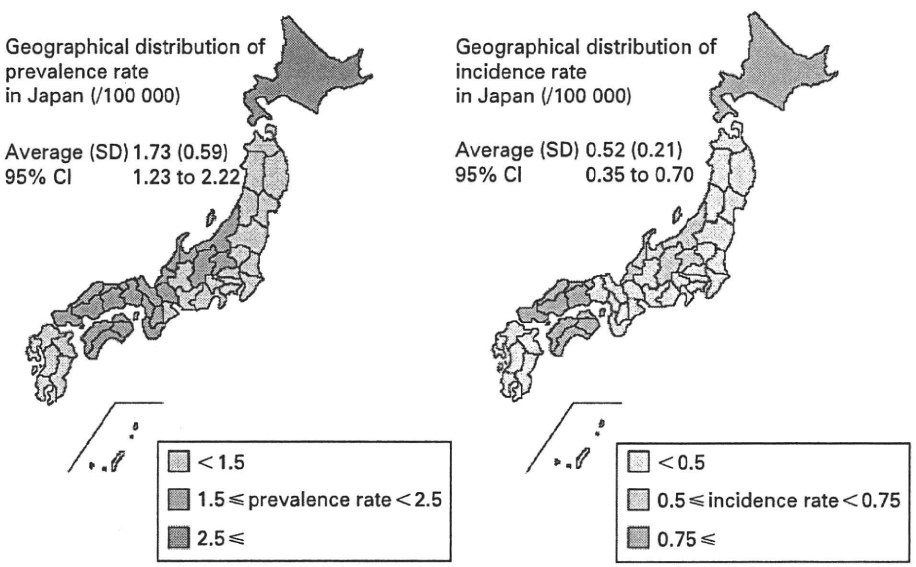

Figure 1 Geographic distribution of prevalence and incidence rates throughout Japan. There were no statistical preponderances in the geographical distributions of either the prevalence or incidence rates.

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[13] (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.[13–15] 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

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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) T[c] (middle portion)	+	–	+++[d]	Aching hyperalgesia	1.2.3.4.5.6.
2 72/F	+/+	Lip biopsy	Pain	Chronic	–	–	L[c] (distal) H[c] (left side back)	+	–	+++[d]	Tingling hyperalgesia	1.2.4
3 54/M	+/+	SS-B lip biopsy	Sensory disturbance	Subacute	–	–	Right hand (radial) L[c] (dital) T[c] (upper portion)	+	–	+++[d]	Tingling static allodynia hyperalgesia	–
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) L[c] (upper) L[c] (right> left)	+	+	+++[d]	Tingling hyperalgesia	2.3.4

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] 'Å{Å{, moderate pain; 'Å{Å{Å{, 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.

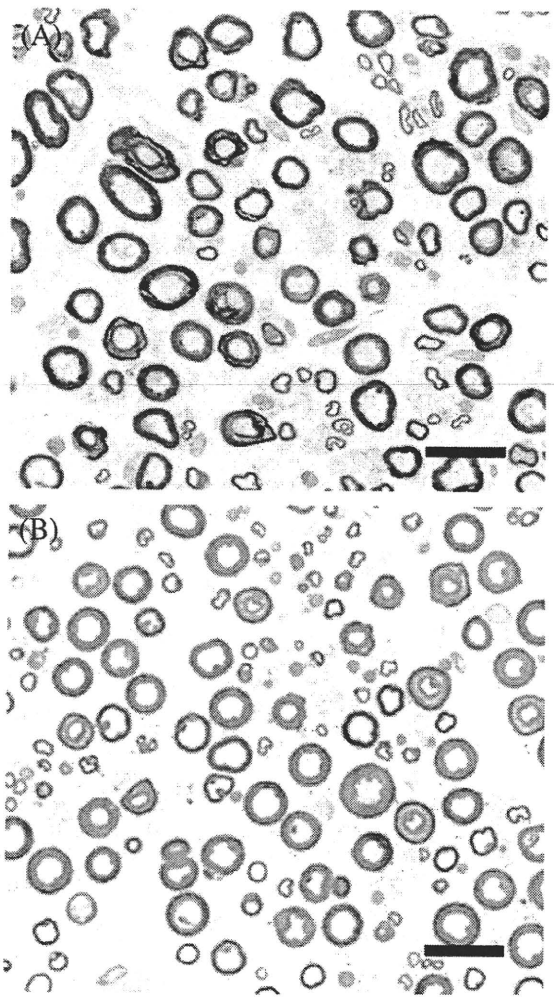

Fig. 1. Sural nerve pathology. (A) Specimen from patient 4. (B) Specimen from a control patient. Specimen from patient 4 revealed predominantly small-fiber loss. No axonal sprouting was seen. Vasculitis was not observed. Scale bar=20 μm.

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

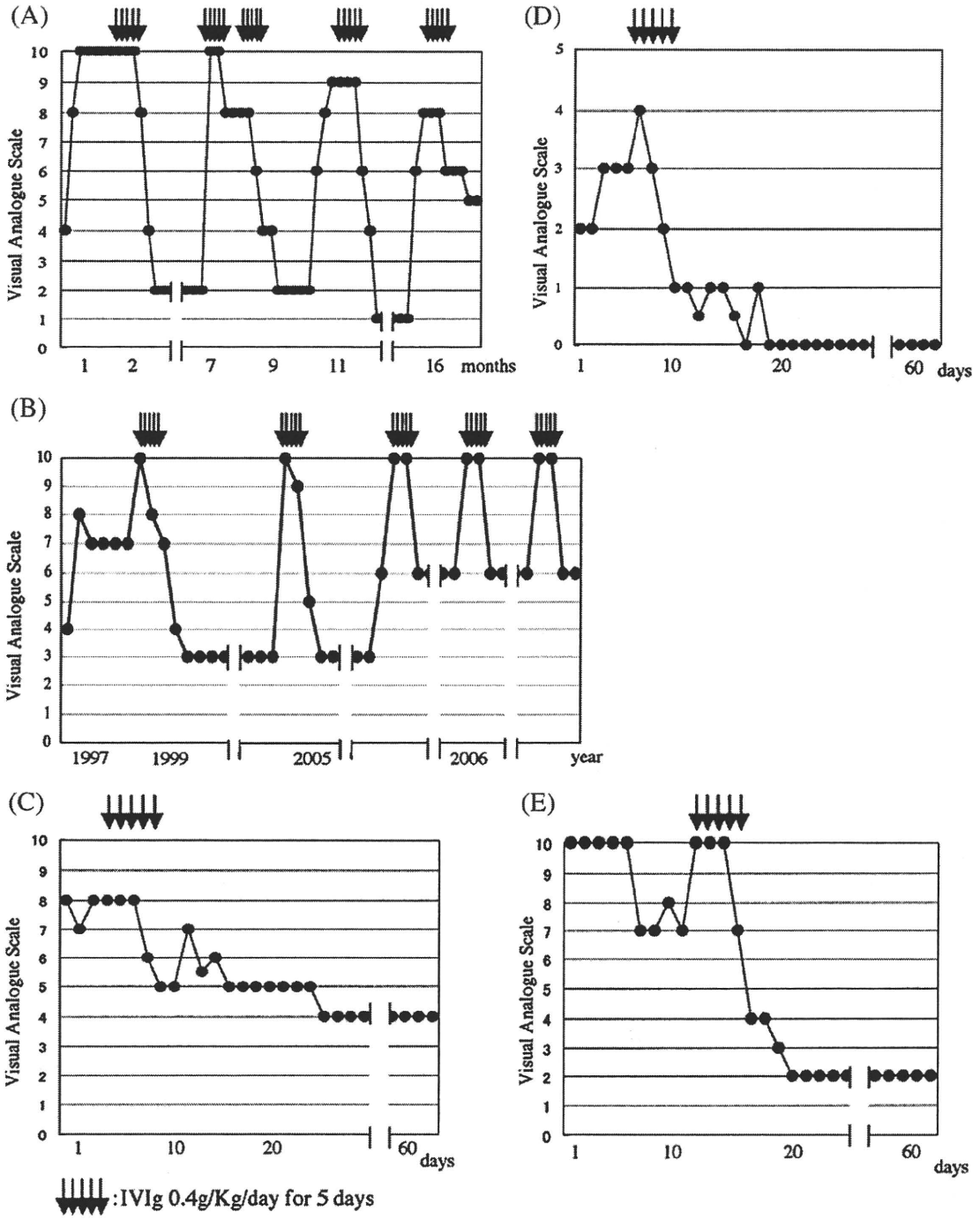

Fig. 2. Clinical course of the Visual Analogue Scale. A 10 cm VAS was anchored by two extremes of pain (left, no pain; right, the worst pain imaginable). Pain ratings were applied subjectively according to the manner described by Kelly [12]. (A) Clinical course of patient 1. (B) Clinical course of patient 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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Peripheral Nerve 2008; 19(1): 1–8

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

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

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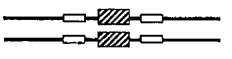
ていること[11]、(3) マウスモデルとラットのトランスジェニックモデルにおいて、*pmp22*の過剰発現によりCMT1と表現型の類似したニューロパチーを呈すること[12),13)]。これらの事実より、CMT1Aでは*PMP22*の遺伝子の過剰発現がニューロパチーと直接関係していることが推定されており、その治療戦略としては遺伝子発現を抑制することが重要であると考えられる。現時点では、(1) プロゲステロン拮抗薬であるオナプリストン、(2) アスコルビン酸、(3) オリゴヌクレオチドなどによる*PMP22*発現の抑制による治療が考えられている（図1）。

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

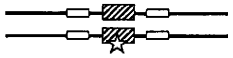
遺伝子変異	 重複	 欠失	 点変異
CMT表現型	CMT1A	*Hereditary neuropathy with liability to pressure palsies (HNPP)*	*HNPP/CMT1A* *Dejerine-Sottas Neuropathy* *Congenital Hypomyelinating Neuropathy*
分子病態機序	遺伝子の量的効果		優性ネガティブ効果
治療の標的	遺伝子発現の制御		翻訳後プロセスのコントロール 蛋白プロセシング 蛋白トラフィッキング 細胞内への蓄積
治療薬の候補	オナプリストン アスコルビン酸 オリゴヌクレオチド		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

ヒトCMT1Aに対するアスコルビン酸投与の有効性について論じるには不十分ではあるが、右手握力に関しては両群間で有意差を認めたことから、アスコルビン酸20mg/kg/日投与が有効である可能性が示唆された。2006年3月より、ヨーロッパにおいて、アスコルビン酸を用いたCMT1Aに対する二重盲検試験（CMT-TRIAAL）が開始されており[6]、その結果が待たれるところである。

最後に、オリゴヌクレオチドによる遺伝子発現の抑制に関しては、現時点ではTriplex-formationによるオリゴヌクレオチドによる*PMP22*のプロモーター領域を競合的に阻害する試みが*in vitro*の系で報告されているのみである[17]。siRNAやリボザイムなど、RNAを介した他の遺伝子発現抑制法はdrug delivery上の問題点が多く、CMT1Aに関しての*in vivo*の報告は、検索したかぎりではまだ存在しない。

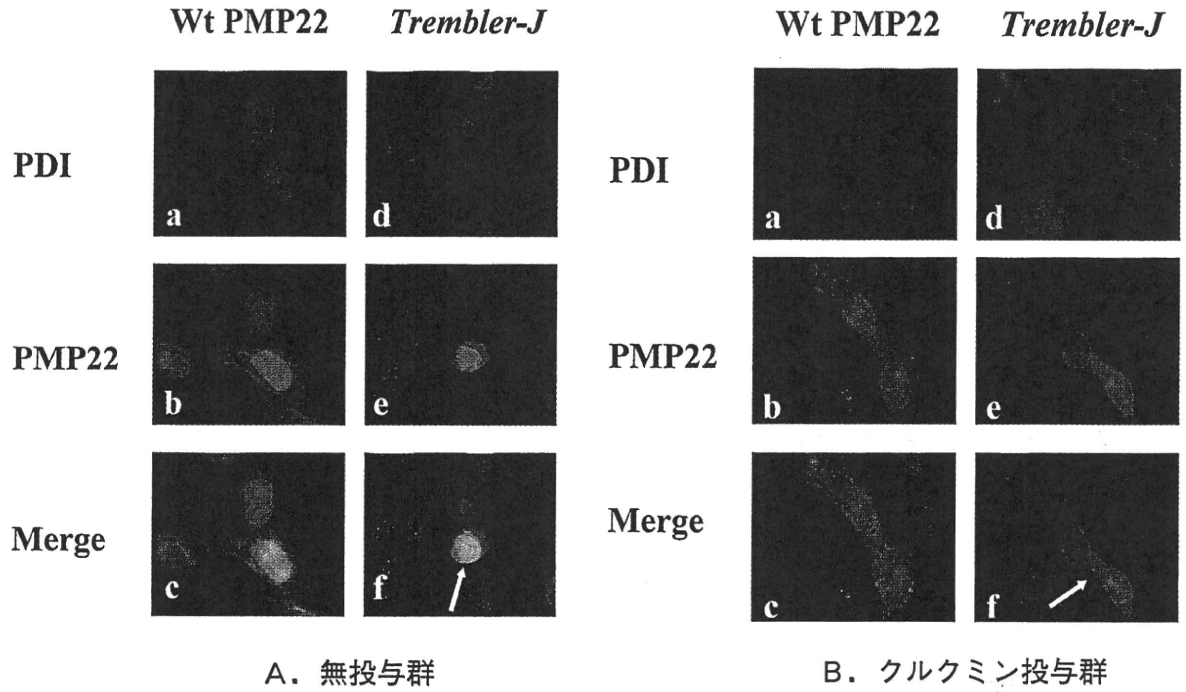
3．*PMP22*点変異によるCMTに対する治療戦略

3-1．*PMP22*点変異によるニューロパチーの分子病態

CMT1Aが*PMP22*遺伝子の量的効果により発症し、臨床的には比較的均一なニューロパチーを呈するのに対し、*PMP22*の点変異によるニューロパチーでは、比較的軽症のhereditary neuropathy with liability to pressure palsies（HNPP）やCMT1から、より重症のDejerine Sottas syndrome（DSS）、congenital hypomyelinating neuropathy（CHN）まで幅広い臨床病型をとることが知られている（Inherited peripheral neuropathy mutation database：http://www.molgen.ua.ac.be/CMTMutations/default.cfm）。*PMP22*のフレームシフト変異やナンセンス変異のほとんどはHNPPの表現型を取ることが知られており、*PMP22*のヘミ接合体（欠失）でHNPPを発症する機序と同様の分子病態（負の量的効果）が想定されている。その一方で、ミスセンス点変異では、CMT1、DSS、CHNなど、より重症のニューロパチーを発症する。その発症機序として翻訳蛋白のmisfoldingによる細胞毒性が想定されており、変異蛋白の細胞毒性の差によって重症度が異なる可能性が考えられる（図1）。ミスセンス点変異によるCMT発症には、大別して2つのメカニズムが関わっていると考えられる。第一のメカニズムとしては、正常なfoldingおよびtraffickingを受ける蛋白が減少し、蛋白が正常な生理的機能を維持できなくなる（loss-of-function）可能性が考えられ、第二のメカニズムとしては、変異蛋白が正常アリルから翻訳されるPMP22蛋白の機能に悪影響を及ぼしたり、あるいは細胞内小器官内に凝集物を形成したりするなど、細胞毒性を示す可能性（gain-of-function）が考えられている[18]。PMP22蛋白は粗面小胞体（endoplasmic reticulum；ER）において、ERシャペロンCalnexinと共存していることが示されている[19]。*PMP22*点変異によりニューロパチーをきたす*Trembler*変異（G150D）および*Trembler-J*変異（L16P）の一過性発現系において、変異型PMP22は野生型PMP22と比較してより長い時間ERと共存することが示されており[19]、その結果、変異蛋白がERストレス、ひいては細胞毒性を示す可能性が示唆されている。

3-2．*PMP22*点変異によるニューロパチーに対する治療戦略

興味深いことに、カレーに含まれる香辛料の成分であるクルクミンは、CMT1Bの原因である*MPZ*の点変異を一過性発現させた細胞モデルにおいてERストレスを緩和し、アポトーシスを抑制する[20]。またクルクミンは、アルツハイマー病モデルでもアミロイドの凝集を抑制させたり[21]、cystic fibrosisモデルでCFTR蛋白の凝集を阻害したりすることが知られている[22]。このようにクルクミンは、変異蛋白によるmisfoldingを機序とした病態に対して蛋白の細胞毒性を緩和する作用が期待される。前述の様に、*PMP22*の点変異によるCMTにおい



A．無投与群　　B．クルクミン投与群

図2．クルクミン投与による野生型および変異PMP22［L16P］の細胞内局在の変化
A．無投与群、B．クルクミン投与群．
矢印：変異型PMP22の細胞内局在．PDI：Protein disulfide isomerase．A．野生型蛋白（Wt PMP22, 緑）は細胞質全体に発現している（A-b, c）が、Tr-J変異型蛋白（*Trembler-J*, 緑）は細胞質に凝集しており（A-e）、この凝集はendoplasmic reticulum（ER）マーカーであるPDI（赤）と共存している（A-f）．B．クルクミンを投与すると、ERに凝集していた変異PMP22蛋白が細胞質に再分布しているのがわかる（B-e, f）．（*Am J Hum Genet* 81: 438-453, 2007より改変）

て変異蛋白のERへの凝集がERストレスを引き起こしていることが推測されていることから、*PMP22*点変異によるニューロパチーに対してもクルクミンの治療効果が期待できる可能性がある。

そこでわれわれは、*PMP22*点変異のCMTモデルマウスである*Trembler-J*（Tr-J）マウスにクルクミンを経口投与（50あるいは100mg/kg/日）し、運動機能評価と病理学的解析を行った[8]。ロタロッドへの把持時間で評価される運動機能は、投与したクルクミンの容量依存性に改善を示し[8]、また12週後に経口投与を中止すると運動機能は再び悪化した（図2）。さらに興味深いことに、投与継続した群ではひきつづき運動機能は改善を示した（図2）。クルクミンを投与されたTr-Jマウスの坐骨神経の病理解析では、シュワン細胞のアポトーシスが有意に減少しており、また髄鞘の厚さおよび軸索径が増加していた[8]。軸索径は野生型マウスまでには回復しなかったが、運動機能が改善するには十分であったのではないかと考えられた。その機序を明らかにするため、HeLa細胞を用いた変異*PMP22*［Tr-J変異：L16P］の一過性発現系にクルクミン（40μM）を投与したところ、ERに滞留していたPMP22蛋白が細胞質や細胞膜に再分布した（図3）[8]。また同様の変異*PMP22*の一過性発現系で細胞のアポーシスをannexin-FITC法で評価すると、アポトーシス細胞が23.9%と増加していた（野生型*PMP22*発現群では12.8%）が、クルクミン投与により12.3%まで減少した[8]。これらの結果より、クルクミンが、ERに蓄積した変異PMP22蛋白をERから細胞質へ解放することによりERストレスを減じ、ERストレス誘発

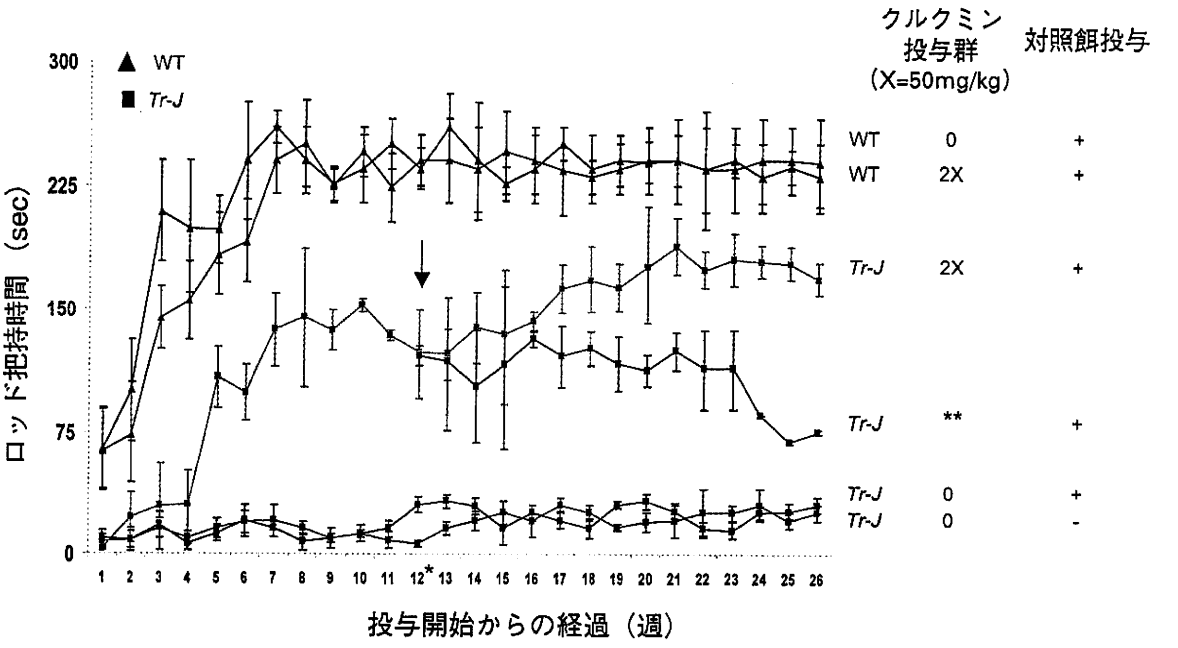


図3．Rotarod解析を用いた*Trembler-J*マウスの運動機能評価
クルクミン投与*Trembler-J*マウスでは、対照餌投与群・無投与群*Trembler-J*マウスと比較すると、運動機能（ロタロッドへの把持時間）が有意に改善していた。このクルクミン投与群に対し、第12週目にクルクミンの投与を中止すると、運動機能は経時的に低下した。投与を続けた群ではさらに運動機能は改善していた。
**：curcumin投与中止群．矢印：投与中止（第12週）．（*Am J Hum Genet* 81: 438-453, 2007より改変）

性のアポトーシスを抑制する機序が推側された。

4．今後の展望

CMTは、遺伝学的に不均一な症候群であり、現時点で少なくとも31の疾患遺伝子が明らかにされている。本稿では、CMTの半数を占めている*PMP22*遺伝子の異常によるCMTに限定して、新しい治療の試みを概説した。同一遺伝子が原因であるニューロパチーであっても、その遺伝子変異の質的な違いによって発病に至る分子病態も異なるため、各々の分子病態特異的な治療戦略を練る必要があると考えられる。今後、CMTに関わる種々の遺伝子の多様な変異の分子病態を一つずつ地道に明らかにしていくことが、将来のCMT治療につながっていくと考えられる。

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

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Genetic alterations of *peripheral myelin protein 22* (*PMP22*) result in a wide variety of demyelinating forms of Charcot-Marie-Tooth disease (CMT): the duplication results in a relatively homogeneous CMT1A, while different point mutations lead to distinct neuropathies; from milder phenotypes (hereditary neuropathy with liability to pressure palsies or CMT1) to severer phenotypes (Dejerine Sottas neuropathy or congenital hypomyelinating neuropathy). First, for the CMT due to *PMP22* duplication, wherein gene dosage effects play a role in its pathogenesis, therapeutic strategies focus on the inhibition of gene expression, such as administration of onapristone or ascorbic acid. As an open trial, we administered daily ascorbic acid (AA, 20 mg/kg) to 13 patients with CMT1A for 12 weeks. The patients who took AA had a significantly stronger hand grip compared to those who did not. Second, for the CMT due to missense mutations of *PMP22*, wherein distinct cellular toxicity of translated aberrant proteins seems to account for its molecular pathomechanisms, mitigating the cellular toxicity may be crucial for the treatment. We here demonstrated that administration of curcumin, a dietary supplement, in HeLa cells that were transfected with a *PMP22* point mutation partially mitigated the accumulation of aberrant PMP22 protein in the endoplamic reticulum. Administration of curcumin led to the release of PMP22 protein into cytoplasm and decreased the number of apoptotic cell populations. We also showed in *Trembler-J* mice, a rodent model of the corresponding point mutation, that oral administration of curcumin resulted in the increased number and size of myelinated axons in sciatic nerves leading to improved motor performance in a dose-dependent manner. We conclude that distinct therapeutic mechanisms are pivotal for different genetic alterations of *PMP22*. Likewise, regarding CMT due to genetic alterations of other genes, it is our views that clarifying distinct molecular mechanisms of different mutations is the key to the future therapeutic trial for CMT.

Key words : Charcot-Marie-Tooth disease, *PMP22*, ascorbic acid, curcumin