intake causes orthostatic hypotension because of impairment in the vasoconstrictor response to orthostatic stress and it can induce syncopal events. The dysregulation of cerebral perfusion due to the insufficiency of constriction of small cerebral arteries caused by the degeneration of smooth muscle cells, particularly after the consumption of alcohol, might have caused syncope in patient 1. Of course, careful considerations should be made prior to concluding whether the CADASIL vasculopathy by itself directly results in syncopal events. However, clinicians need to carefully monitor CADAIL patients who have drinking habits or have some other causes of orthostatic hypotension, because these patients might present an attack of syncope. Although it is widely accepted that some CADASIL patients could manifest epileptic seizures due to vascular symptomatic epilepsy (3, 17), there has so far been no report of CADASIL patients who showed only syncope as the sole phenotype.

On the other hand, patient 2 presented with recurrent ischemic attacks, which is the most frequent initial presentation of symptomatic CADASIL individuals (3). Although GOM was not detected in a skin biopsy specimen obtained from this patient, the results of a brain biopsy were positive. Recently Tikka et al demonstrated the high sensitivity of GOM detection in the skin biopsy of genetically verified CADASIL (18). They estimated the sensitivity of the skin biopsy to be more than 90%. But this report also indicated that in some cases a repeat skin biopsy was needed to detect GOM. Therefore, if GOM is not found in the first skin biopsy in the subjects showing typical clinical presentations with CADASIL, then additional biopsies should be considered.

The patient 2 received antiplatelet agents and unfortunately, he developed a large intracerebral hemorrhage (ICH) during the disease process. While CADASIL is considered to be a primarily ischemic form of cerebral vascular disorder, microbleeds have recently been reported in 31-69% of symptomatic *NOTCH 3* mutation carriers (19, 20). Viswanathan et al (21) reported that hypertension and HbA1c are associated with microbleeds in CADASIL. Because Patient 2 did not exhibit either hypertension or DM, ticlopidine might have been associated with his ICH. In fact, Oh et al (22) reported a patient with CADASIL who had developed ICH after taking aspirin. However, antiplatelet drugs are generally used for the prevention of recurrent ischemic attacks in CADASIL patients (23). Taking into account the incidence of microbleeds in CADASIL patients (31-69%) (19, 20), cilostazol, which has been reported to have lower rate for cerebral bleeding compared to low dose of aspirin (25), might be a better choice as the first line therapy for the prevention of recurrent ischemic attacks in these patients. Further studies are needed to establish the standard therapy for the prevention of ischemic attacks in patients with CADASIL.

In conclusion, this is the first report of the detailed clinical phenotypes of Japanese CADASIL families with the p.Arg332Cys mutation of *NOTCH3* gene, which is rare in Japan. Comprehensive genetic screening for *NOTCH3* mutations is definitely important in Japan, as well as in the other parts of the world;, when a patient shows recurrent syncope attacks as the presenting sole symptom and characteristic MRI findings, then CADASIL should be included in the differential diagnosis.

The authors state that they have no Conflict of Interest (COI).

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Nationwide survey on the epidemiology of syringomyelia in Japan

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ABSTRACT

Background: Syringomyelia is a rare disease characterized by abnormal fluid-filled cavities within the spinal cord, and is associated with Chiari malformations, arachnoiditis, or spinal cord tumors. The widespread availability of magnetic resonance imaging (MRI) in Japan has allowed for easy identification of syrinxes. The aim of this study was to survey the clinicoepidemiological characteristics of syringomyelia in Japan.
Methods: A 2-stage postal survey was conducted in late 2009. The first survey aimed to estimate the number of patients with syringomyelia, and the second survey aimed to elucidate clinicoepidemiological characteristics. Diagnosis of syringomyelia was based on the findings of MRI or computed tomographic myelography.
Results: In the first survey, we received 2133 responses from 2937 randomly selected departments and collected data of 1215 syringomyelia patients (543 men and 672 women). The total response rate for the first survey was 73%. The estimated prevalence of ambulatory syringomyelia patients in Japan was 1.94 per 100000. In the second survey, the proportion of asymptomatic syringomyelia patients was 22.7%. Chiari type I malformations and idiopathic syringomyelia were the first and second most common etiologies.
Conclusions: Our nationwide survey indicated that widespread MRI availability has contributed to the diagnosis of both asymptomatic and idiopathic cases.

1. Introduction

Syringomyelia is a heterogeneous disorder characterized by abnormal fluid-filled cavities or cysts within the spinal cord. The etiologies of syringomyelia can include Chiari malformations, arachnoiditis, trauma, and spinal cord tumors [1–3], but the pathophysiology of syrinx development remains enigmatic. Some cases with Chiari Type I malformations manifested asymptomatic syringomyelia [4]. The reported prevalence was 8.2 to 8.4 per 100 000 in Western countries [5,6]. An epidemiologic survey that collected data from 1243 patients between 1982 and 1991 in Japan showed the predominance of Chiari Type I malformations in syringomyelia, and identified a few cases of spontaneous remission [7]. Surgical treatment for syringomyelia is essential to stop the progression of the disease and further cavity enlargement. However, the previous epidemiologic survey did not determine the prevalence of the disease in the Japanese population [7].

The diagnosis of syringomyelia has been greatly aided by the development and widespread availability of magnetic resonance imaging (MRI) scanners, which have allowed for the relatively easy identification of syrinxes. Japan has the highest number of magnetic resonance imaging (MRI) scanners per capita, with national healthcare insurance coverage allowing universal access to outpatient hospital care. Hence, both symptomatic and asymptomatic syringomyelia patients can be more adequately examined than was possible prior to MRI facilities becoming widely accessible.

The characteristics of asymptomatic syringomyelia have not been sufficiently investigated. The aim of this study, therefore, was to estimate the prevalence of syringomyelia in Japan and identify its clinicoepidemiological characteristics by taking advantage of the current widespread availability of MRI facilities.

2. Methods

We conducted a 2-stage postal survey according to methods described previously [8,9] in late 2009. The first survey aimed to estimate the number of individuals with syringomyelia, and the second survey aimed to elucidate the clinicoepidemiological characteristics

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of syringomyelia. We collected data from patients diagnosed with syringomyelia by neuroimaging from the departments of neurosurgery, neurology, orthopedics, and pediatrics. We requested the numbers of male and female ambulatory syringomyelia patients from each department in the past year (August 2008 to July 2009).

In the first survey, we adopted a definition of syringomyelia based on neuroimaging: a central or lateralized syrinx detected on MRI (including syrinxes with septums), or a syrinx detected with computed tomographic myelography in patients who could not undergo MRI because of metal in the body. The number of patients with syringomyelia in each institution was counted based on this definition. The departments surveyed were randomly selected by stratified sampling from a list of all hospitals with 20 or more beds; the list was obtained from the Ministry of Health and Welfare. Sampling rates were approximately 5%, 10%, 20%, 40%, 80%, and 100% for the stratum of general hospitals with 20 to 99 beds, 100 to 199 beds, 200 to 299 beds, 300 to 399 beds, 400 to 499 beds, and 500+ beds, respectively. Additionally, all university hospitals in Japan were surveyed.

In the second stage of the survey, we requested details of individual patients from each department that had 1 or more syringomyelia patients. The detailed information for each patient was reported based on a retrospective chart review. Epidemiological items included sex, date of birth, time of onset and diagnosis, family history, symptoms and signs, imaging findings, treatment, and clinical course. Symptoms included motor function, sensory disturbance, autonomic failure, cranial nerve disturbance, and skeletal deformity. Motor functions included weakness, muscle atrophy, spasticity, hypotonus, and planter reflex. Autonomic failure included Horner syndrome, anisocoria, dyshidrosis, abnormal nail development, limb hypertrophy, bladder and rectal disturbance, orthostatic hypotension, impotence, and neurogenic arthropathy.

This study was approved by the Institutional Review Board of Hokkaido University.

2.1. Estimation and statistical analysis

We estimated the prevalence of syringomyelia based on the results from the first stage of the survey. The estimation was based on the assumption that the responses of the departments were independent of the frequency of patients [8,10]. Formulas used to estimate the total number of patients, and the 95% confidence intervals are described below.

The point estimation of prevalence was calculated using the following equation, where SRT_k, RRT_k, NS_k, n_k, N_k, and N_{ki} denote the sampling rate, response rate, the number of sampling departments, the total number of departments, the number of responding departments, and the number of departments with i patients in stratum k, respectively.

$$\hat{\alpha}_k = \frac{1}{SRT_k RRT_k}\sum_i iN_{ki} = \frac{1}{\frac{NS_k}{n_k}\frac{N_k}{NS_k}}\sum_i iN_{ki} = \frac{n_k}{N_k}\sum_i iN_{ki}.$$

3. Results

In the first survey, we received 2133 responses from 2937 randomly selected departments, and collected data regarding 1215 syringomyelia patients (543 men and 672 women). The total response rate of the first survey was 73%.

Results from the first survey (Table 1) showed that the number of syringomyelia patients who were referred to a hospital between August 2008 and July 2009 was 2475 (95% CI: 2051–2899). The

Table 1
Summary of data collected in the first stage of the survey.

Type s of departments	Type s of hospitals and beds	Total no. of departments	Sampling rate (%)	No. of surveyed departments	No. of departments that responded	Response rate (%)	No. of reported patients	No. of estimated patients
Neurosurgery	General hospitals with ≤99 beds	710	5%	35	22	63%	0	0
	General hospitals with 100–199 beds	528	10%	52	27	52%	7	137
	General hospitals with 200–299 beds	298	20%	59	37	63%	26	209
	General hospitals with 300–399 beds	296	40%	119	73	61%	23	93
	General hospitals with 400–499 beds	167	80%	133	94	71%	40	71
	General hospitals with ≥500 beds	216	100%	216	147	68%	133	195
	University hospitals	113	100%	113	94	83%	267	321
	Subtotal	2328		727	494	68%	496	1027
Neurology	General hospitals with ≤99 beds	506	5%	25	13	52%	0	0
	General hospitals with 100–199 beds	335	10%	34	18	53%	3	56
	General hospitals with 200–299 beds	170	20%	34	27	79%	6	38
	General hospitals with 300–399 beds	170	40%	68	38	56%	7	31
	General hospitals with 400–499 beds	91	100%	91	59	65%	21	32
	General hospitals with ≥500 beds	93	100%	93	60	65%	25	39
	University hospitals	118	100%	118	103	87%	53	61
	Subtotal	1483		463	318	69%	115	257
Orthopedics	General hospitals with ≤99 beds	2278	5%	114	66	58%	4	138
	General hospitals with 100–199 beds	1047	10%	105	70	67%	10	150
	General hospitals with 200–299 beds	436	20%	87	63	72%	10	69
	General hospitals with 300–399 beds	362	40%	145	110	76%	48	158
	General hospitals with 400–499 beds	190	80%	152	107	70%	20	36
	General hospitals with ≥500 beds	228	100%	228	178	78%	120	154
	University hospitals	118	100%	118	98	83%	300	361
	Subtotal	4659		949	692	73%	512	1065
Pediatrics	General hospitals with ≤99 beds	1069	5%	54	32	59%	0	0
	General hospitals with 100–199 beds	613	10%	62	41	66%	0	0
	General hospitals with 200–299 beds	356	20%	71	49	69%	0	0
	General hospitals with 300–399 beds	339	40%	136	105	77%	7	23
	General hospitals with 400–499 beds	184	80%	147	120	82%	11	17
	General hospitals with ≥500 beds	214	100%	214	183	86%	58	68
	University hospitals	114	100%	114	99	87%	16	18
	Subtotal	2889		798	629	79%	92	126
	Total	11359	26%	2937	2133	73%	1215	2475

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estimated prevalence of ambulatory syringomyelia patients in Japan was 1.94 per 100 000. In the second survey, we collected reports from 720 of the 1215 patients from the first survey. The response rate for the second survey was 59%. There were 12 duplicated reports, and thus, we integrated the data reported in them.

Results of the second survey (Table 2) described the characteristics of both symptomatic and asymptomatic syringomyelia. The proportion of patients with asymptomatic syringomyelia was 22.7% (161 cases). The mean ages at survey and diagnosis of asymptomatic syringomyelia (28.9 ± 23.3 and 24.4 ± 24.1 years, respectively) were lower than those of patients with symptomatic syringomyelia (40.8 ± 22.8 and 35.3 ± 22.5 years, respectively). Asymptomatic syringomyelia tended to be primarily associated with localized cavities. The proportion of syringomyelia cases with a Chiari type I malformation etiology was higher among symptomatic than asymptomatic syringomyelia patients. Conversely, the proportion of cases with idiopathic etiologies was higher in asymptomatic than in symptomatic syringomyelia.

A subset of patients with symptomatic syringomyelia (Table 3) included both those who had, and those who had not undergone surgical treatment. The mean age at onset and diagnosis of patients who had undergone surgical treatment (29.4 ± 21.0 and 31.6 ± 21.5 years, respectively) was lesser than that of patients who had not received surgical treatment (40.1 ± 22.6 and 44.8 ± 22.3 years, respectively). There were only 2 cases with a family history of the disease. Approximately 11% of patients in each group experienced an improvement in their symptoms. The most common symptom was sensory disturbance, which was reported in 75.3% of patients with surgical treatment and 68.8% of those without surgical treatment. Motor disturbance was the second most common symptom in each group (59.8% and 51.0%, respectively). Patient histories showed that approximately one-tenth of the patients in each group had previous injuries of the head or spine.

The characteristics of patients in each age group (Table 4) showed that the prevalence of idiopathic syringomyelia was higher in adults, particularly in the elderly, than in children.

Fig. 1 shows the distributions of patient's ages at the time of survey (Fig. 1A), age at diagnosis (Fig. 1B), age at surgical treatment (Fig. 1C), and year of diagnosis (Fig. 1D). The distribution of ages at survey consisted of 2 peaks, at 10 to 20 years of age, and at 60 to 70 years of age. The distribution of age at diagnosis showed a higher proportion of 0- to 20-year-olds. Finally, the distribution of diagnosis year showed an acute increment in the number of cases diagnosed in more recent years.

Table 2
Demographics of patients in the second stage of the survey.

	Symptomatic (N = 543)	Asymptomatic (N = 161)	Total (N = 708[a])	Missing
Age at survey (Mean ± SD)	40.8 ± 22.8	28.9 ± 23.3	38.0 ± 23.5	35
Age at diagnosis (mean ± SD)	35.3 ± 22.5	24.4 ± 24.1	32.7 ± 23.4	66
Sex (%)				
Male	41.6	44.1	42.1	1
Female	57.3	53.4	56.5	3
Missing	1.1	2.5	1.4	0
Morphology (%)				
Asymmetry	31.3	8.1	25.8	0
Symmetry	58.9	83.2	64.4	2
Missing	9.8	8.7	9.7	2
Distribution (%)				
Syringobulbia				
Bulbus only	1.5	0.6	1.3	0
Bulbus and spinal cord	5.7	1.2	4.8	1
Syringomyelia				
Cervical cord only	18.6	32.9	21.8	0
Thoracic cord only	7.9	8.7	8.2	1
Lumbosacral cord only	0.9	9.9	3.1	1
Cervical–thoracic	49.4	27.3	44.1	0
Thoracic–lumbosacral	2.6	4.3	3.0	0
Cervical–lumbosacral	4.6	4.3	4.5	0
Missing	8.8	10.6	9.3	1
Etiology (%)				
Chiari type I	53.6	30.4	48.0	0
Chiari type II	4.4	20.5	8.1	0
Bone anomaly	1.1	0.6	1.0	0
Arachnoiditis	5.7	2.5	4.9	0
Trauma	9.6	0.6	7.5	0
Spinal cord tumor	5.2	5.6	5.2	0
Idiopathic	12.9	24.8	15.7	1
Other	6.1	13.0	7.9	2
Suspected two or more	1.1	1.2	1.1	0
Missing	0.4	0.6	0.6	1

[a] Four patients who did not report on the existence of symptoms were excluded.

Table 3
Demographics, clinical history, and manifestations of symptomatic patients.

		Surgical treatment			
		Yes	No	Total	Missing
Number of cases		376	157	543	10
Age at onset (mean ± SD)		29.4 ± 21.0	40.1 ± 22.6	32.3 ± 22.0	
Age at diagnosis (mean ± SD)		31.6 ± 21.5	44.8 ± 22.3	35.3 ± 22.5	
Age at surgery (mean ± SD)		32.6 ± 21.0			
Family history (%)	Yes	0.3	0.6	0.4	0
	No	64.4	59.9	62.2	2
	Unknown/missing	31.1	35.0	32.4	
Course of symptoms after initial diagnosis (%)					
Worsen		51.1	22.3	42.2	2
Unchanged		26.3	56.7	35.5	5
Improved		11.2	10.8	10.9	0
Stop after progression		4.8	5.7	5.0	0
Missing		6.6	4.5	6.4	
Symptoms (%)					
Motor	Yes	59.8	51.0	57.5	7
	No	37.8	45.9	39.4	0
	Unknown/missing	2.4	3.2	3.1	
Sensory	Yes	75.3	68.8	72.7	4
	No	19.9	21.0	19.9	0
	Unknown/missing	4.8	10.2	7.4	
Autonomic	Yes	20.7	19.1	19.9	0
	No	65.2	65.6	64.6	3
	Unknown/Missing	14.1	15.3	15.5	
Cranial nerves	Yes	10.1	7.0	9.2	1
	No	83.2	80.9	81.4	2
	Unknown/missing	6.6	12.1	9.4	
Skeletal deformity	Yes	31.4	22.9	29.3	5
	No	64.9	75.2	67.4	4
	Missing	3.7	1.9	3.3	
Past history (%)					
CNS infections	Yes	3.5	3.8	3.7	1
	No	80.6	74.5	78.3	5
	Unknown/missing	16.0	21.7	18.0	4
Injuries of head or spine	Yes	11.4	10.2	10.9	0
	No	76.3	75.8	75.7	5
	Unknown/missing	12.2	14.0	13.4	
Surgery of head or spine	Yes	13.8	12.1	13.4	2
	No	77.4	77.7	77.0	5
	Unknown/missing	8.8	10.2	9.6	
Problems at delivery	Yes	2.1	1.3	2.0	1
	No	66.2	59.9	63.9	4
	Unknown/missing	31.6	38.9	34.1	

4. Discussion

This study revealed the prevalence (1.94 per 100 000) and characteristics of ambulatory syringomyelia patients in Japan. Among these patients, the prevalence of asymptomatic syringomyelia was 22.6%,

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Table 4
Summary of characteristics of patients according to age group.

Age	Female (%)	Asymptomatic (%)	Etiology 1st / 2nd / 3rd	%	Localized cavity (%)
<10	51.11	40.9	Chiari type I	40.6	36.9
			Chiari type II	34.8	
			Other	14.5	
10–19	66.07	23.9	Chiari type I	78.8	36.2
			Idiopathic	6.2	
			Other	5.3	
20–29	52.63	14.0	Chiari type I	47.4	47.1
			Idiopathic	22.8	
			Trauma	14.0	
30–39	46.34	20.5	Chiari type I	49.4	39.0
			Idiopathic	17.3	
			Trauma	14.8	
40–49	55.17	15.3	Chiari type I	55.9	27.8
			Idiopathic	18.6	
			Spinal cord tumor	10.2	
50–59	69.74	14.5	Chiari type I	42.1	40.6
			Idiopathic	23.7	
			Spinal cord tumor	10.5	
60–69	54.55	11.5	Chiari type I	28.2	42.9
			Idiopathic	24.4	
			Trauma	16.7	
>70	66.67	24.3	Idiopathic	37.8	40.0
			Chiari type I	27.0	
			Arachnoiditis	13.5	

and that of idiopathic syringomyelia was 15.8% according to the second survey.

The prevalence of syringomyelia in this survey is lower than that in previous studies that used different methods for estimation [5,6]. Estimation of prevalence in this survey was based on patients who were referred to a hospital for evaluation or treatment. Therefore, the data from patients whose syringomyelia was stable and who had discontinued their ambulatory care were not collected in this study. It is noteworthy that the early detection of syringomyelia by MRI can allow for early interventions, including surgery. Early diagnosis and intervention are more likely to lead to a positive outcome, and may therefore reduce the number of patients requiring ambulatory care. The lower number of patients diagnosed in the years preceding 2005 (Fig. 1-D) is consistent with our speculation. However, these results show the characteristics of ambulatory care among syringomyelia patients.

The etiology of syringomyelia can include Chiari malformation, trauma, arachnoiditis, and idiopathic origin, among other causes. In our study, Chiari malformations, including both types I and II, were the most common cause in both children and adults, and this finding is consistent with those of previous studies [7,11]. In particular, Chiari malformation is more frequent in children than in adults. These results may be associated with the widespread availability of MRI, which contributes to early diagnoses in cases of syringomyelia caused by Chiari malformation. Interestingly, idiopathic syringomyelia was the second most common cause according to our survey. Bogdanov et al. suggested that idiopathic syringomyelia is associated with a small posterior fossa with a narrow cerebrospinal fluid (CSF) space as well as with Chiari I malformation [12]. It is possible that some of the cases of idiopathic syringomyelia in our survey may be attributable to a small posterior

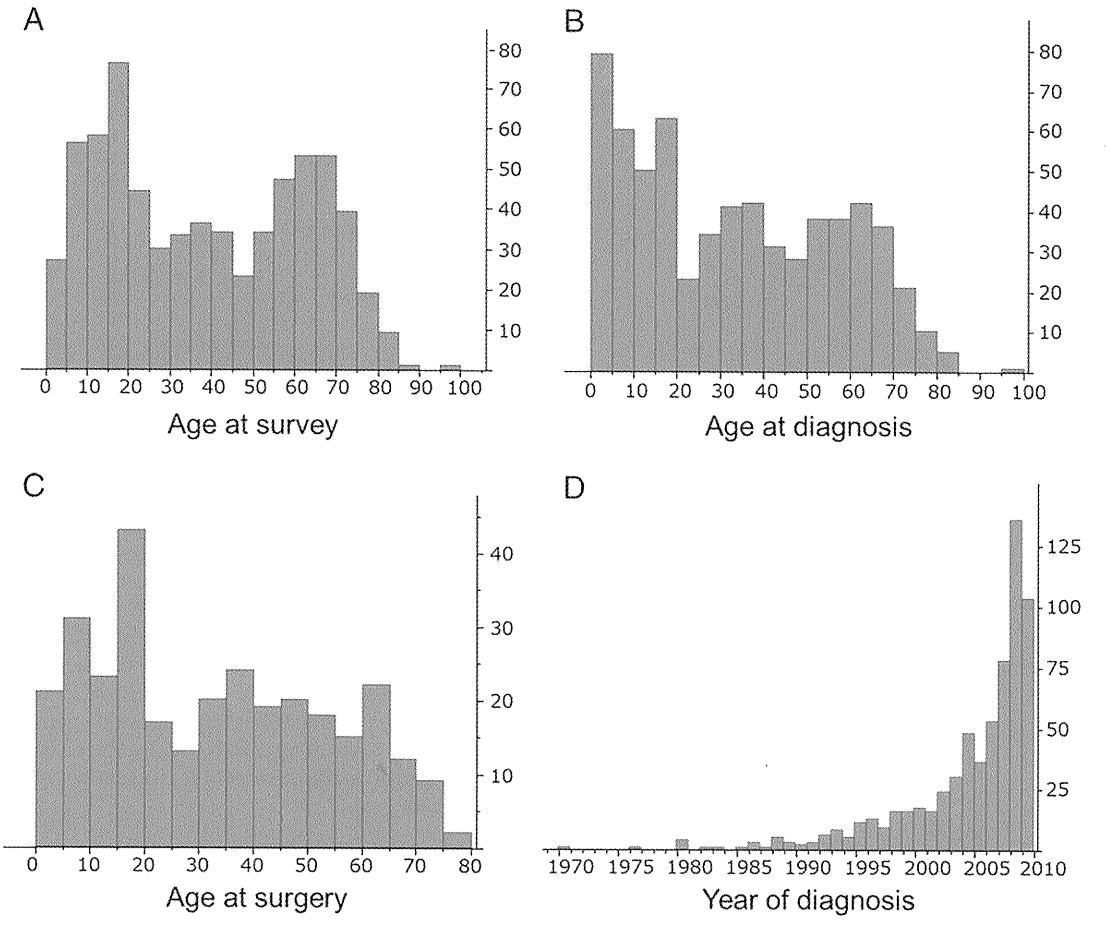

Fig. 1. (A) Histogram showing age distribution of patients at time of survey. (B) Histogram showing age distribution of patients at diagnosis. (C) Histogram showing age distribution at time of surgery. (D) Histogram showing the diagnosis by year.

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fossa. Holly et al. described slit-like syrinx cavities characterized by remnants of the central canal and an asymptomatic clinical course [13]. Therefore, idiopathic syringomyelia has several potential causes, including congenital remnants of the central canal and acquired dilations by a small posterior fossa. Hida et al. reported an association between syringomyelia with Chiari I malformation and birth injuries [14]. In this study, patients with problem at delivery accounted for 2.0% of symptomatic syringomyelia cases, but it had a higher unknown/missing proportion in the past history. Nakamura et al. discuss 2 types of idiopathic syringomyelia: localized and extended. Localized syringomyelia is associated with congenital enlargement of the central canal of the spinal cord and can be managed conservatively [15]. Actually, most of the patients with idiopathic cases in our study did not undergo surgical treatment. Idiopathic syringomyelia might be less progressive than syringomyelia with other causes.

Asymptomatic syringomyelia comprised 22.7% of all syringomyelia cases in our second survey. Prior to this survey, the proportion of asymptomatic syringomyelia cases was unknown. Cases of a few patients with asymptomatic syringomyelia caused by a brain tumor of the posterior fossa have been previously reported [16–18]. The infrequency of asymptomatic syringomyelia seems inconsistent with our survey results. There are 2 possible explanations for the relatively high proportion of asymptomatic syringomyelia in our survey. Firstly, the symptoms of patients who did not complain because of their age were underestimated. Secondly, the availability of MRI in Japan has resulted in an increase in the number of incidental diagnoses of asymptomatic syringomyelia including slit-like syrinx cavities.

Resolution of syringomyelia without surgical treatment was observed in 17 patients (3.2% of symptomatic patients) in our second survey. Spontaneous resolution of syringomyelia has recently been found to be more common than previously thought [19]. The mechanisms involved in the development and spontaneous resolution of syringomyelia are unclear despite multiple hypotheses [20]. The number of patients with spontaneous resolution may be underestimated because cases of asymptomatic syringomyelia patients who had not sought consultation were not evaluated in our survey.

Symptoms of syringomyelia include pain, sensory disturbance, and amyotrophy. Bogdanov et al. reported that 90% of patients had unilateral or bilateral sensory disturbances, while 79% of patients experienced weakness or wasting of the upper limbs [21].

Familial syringomyelia cases with autosomal dominant or recessive inheritance have been reported [22,23]. Chatel et al. suggested that the incidence of familial syringomyelia is approximately 2% [24]. However, a large-scale survey has not yet been conducted to determine the proportion of familial cases. In our study, familial syringomyelia comprised only 2 cases (0.6%) of patients with a reported family history. Although a potentially large number of patients who have been lost to follow-up affect the accuracy of the proportion of syringomyelia, familial syringomyelia cases are extremely rare.

This study has several limitations. Firstly, the prevalence of syringomyelia reported in this study was calculated using the estimated number of ambulatory patients. Cases of patients who did not receive ambulatory care in the past year were not evaluated. Therefore, the potential number of syringomyelia patients may be larger than that reported in this study. Secondly, this cross-sectional survey could not evaluate the entire clinical course of syringomyelia. The disease progression from asymptomatic to symptomatic is particularly unclear. The clinical course of idiopathic cases is also unclear. Further investigation is required to determine the most appropriate evaluations and treatments for these patients. Thirdly, the response rates in this study were 73% and 59% in the first and second stage surveys, respectively. Characteristics of patients whose cases were not reported in the second survey are unknown. The effect of this selection bias on our results is also unknown.

Finally, the definition of syringomyelia associated with spinal cord tumor has been changing, and peritumoral cysts have been differentiated from other distinct forms of syringomyelia. In this study, syringomyelia associated with spinal cord tumor was regarded as merely 1 type of syringomyelia.

Taken together, the findings of our survey can contribute to the development of healthcare services for syringomyelia patients. Knowledge of the characteristics of asymptomatic and symptomatic syringomyelia patients without surgical treatment can be useful for the optimization of those services. Further evaluations of the potential number of non-ambulatory syringomyelia patients should be performed to estimate the precise prevalence of syringomyelia.

In conclusion, we have investigated the epidemiology of syringomyelia in Japan. Asymptomatic and idiopathic syringomyelia cases are more common than was previously believed. The widespread availability of MRI scanners has potentially contributed to the early diagnosis of these cases.

Acknowledgments

We are grateful to Yoshikazu Nakamura for conducting this survey. We also appreciate the cooperation of Shoko Shimizu and all participants of this survey.

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症例報告

IgG4関連自己免疫性膵炎による膵腫大を呈したPOEMS症候群

西原　秀昭　　小笠原淳一　　古賀　道明
尾本　雅俊　　川井　元晴　　神田　　隆*

要旨：症例は57歳男性である．皮膚病変，M蛋白血症，高VEGF血症，脱髄・軸索障害混在のニューロパチーをみとめPOEMS症候群と診断した．膵腫大があり，病理，画像，血清学所見から自己免疫性膵炎の合併と判断した．自己末梢血幹細胞移植をともなう大量化学療法をおこない，POEMS症候群の症候・検査異常は改善したが，膵腫大に変化はなかった．POEMS症候群はモノクローナルな形質細胞増殖が特徴である一方，自己免疫性膵炎はポリクローナルな増殖をきたす疾患と考えられており，本例でも両者が存在することを血清の蛋白電気泳動，生検膵の免疫染色をもちいて証明した．POEMS症候群で膵腫大をきたした報告例はなく，本症例は両者の病因を考える上で貴重である．

（臨床神経 2011;51:417-421）
Key words：POEMS症候群，IgG4関連自己免疫性膵炎，膵腫大

はじめに

IgG4関連多臓器リンパ増殖症候群は，高IgG4血症とIgG4陽性形質細胞の組織浸潤を特徴とし，自己免疫膵炎を代表に多数の自己免疫病がふくまれる疾患群である[1]．POEMS症候群はorganomegalyを特徴とするが，膵腫大をきたしたとする報告はない．今回，われわれは膵腫大を呈するPOEMS症候群に対し，膵腫大は高IgG4血症と病理所見，画像所見からIgG4関連疾患の膵病変（自己免疫性膵炎）であると診断した．両者ともに免疫グロブリン高値が特徴で，形質細胞の病態への関与が考えられており，両者の合併は非常に興味深く，ここに報告する．

症　例

症例：57歳，男性
主訴：両手足のジンジン感，両足底の疼痛，歩行困難
既往歴：特記事項なし，家族歴：特記事項なし．

現病歴：2009年10月初旬より誘因なく両手足のジンジン感が出現した．10月中旬より両足の指先に電気が走るような疼痛を自覚するようになり，歩行が困難となった．近医を受診し，四肢の腱反射低下，下肢遠位部の筋力低下を指摘された．11月中旬より両趾先に発赤と熱感が出現した．精査のため11月下旬に入院した．

入院時現症：身長170cm，体重61kg．両趾先に発赤あり．神経学的には，意識清明で脳神経に異常なし．下肢遠位筋優位に筋力低下（徒手筋力検査で近位筋4＋，遠位筋4－）があり，四肢腱反射低下，四肢遠位部優位の痛覚過敏をみとめた．

検査所見：血算，凝固系，尿検査は正常．β_2-microglobulin 2.2mg/l（基準値＜2.0mg/l），IgG 1,860mg/dl（870～1,700mg/dl），IgG1 939mg/dl（320～748mg/dl），IgG2 230mg/dl（208～754mg/dl），IgG3 25.3mg/dl（6.6～88.3mg/dl），IgG4 392mg/dl（4.8～105mg/dl），血清でIgG-λ型M蛋白陽性，血清vascular endothelial growth factor（VEGF）777pg/ml（基準値＜220pg/ml），膵アミラーゼ123IU/l（基準値＜57IU/l），HbA1c 5.9%，CA19-9 5.0U/ml であった．脳脊髄液検査では細胞数2/mm^3，蛋白46mg/dl．骨髄穿刺で形質細胞は4.6%と軽度の増加を示したが異型性はなかった．末梢神経伝導検査では，感覚神経，運動神経にブロックをともなわない潜時延長と速度低下がみられ，脱髄の所見と考えられた．また，複合筋活動電位振幅は尺骨神経で軽度低下し，下肢では高度に低下し軸索障害もともなっていた（Table 1）．針筋電図では左前脛骨筋，左長母趾伸筋で線維自発電位をともない，高振幅電位の混在する神経原性変化をみとめた．左腓腹神経でおこなった神経生検標本のエポン包埋切片トルイジンブルー染色では，有髄神経線維密度は比較的保たれ，神経周膜直下と神経内膜に軽度の浮腫があり，ミエリン球がみられた．また，髄鞘の非薄な線維も散見され，現在進行性の軸索変性と脱髄の所見が混在していると判断された（Fig. 1）．腹部CTで，膵臓は頭部・体部ともびまん性に腫大していたが（Fig. 2），肝脾腫はなかった．ERCP（endoscopic retrograde cholangio-pancreatography）では，主膵管のびまん性狭小化が確認された（Fig. 3）．EUS-FNA（endoscopic ultrasoundscopy-fine needle aspiration）でえら

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（受付日：2011年1月31日）

Table 1　Peripheral nerve conduction study.

MNC	Distal latency (msec)	CMAP amplitude (mV) (baseline-peak)	Conduction velocity (m/sec)
Rt. median	4.8	8.2	53.4
Lt. median	4.8	6.4	56.0
Rt. ulnar	3.8	4.7	59.1
Lt. ulnar	3.5	4.9	53.5
Rt. tibial	4.0	3.5	38.2
Lt. tibial	5.3	1.4	36.6
SNC	Peak latency (msec)	SAP amplitude (μV) (baseline-peak)	Conduction velocity (m/sec)
Rt. median	3.7	15.7	47.0
Lt. median	3.9	5.8	43.2
Rt. ulnar	3.7	11.1	52.6
Lt. ulnar	3.7	5.2	49.0
Rt. sural	3.3	11.9	54.3
Lt. sural	3.6	10.4	47.0

CMAP: compound muscle action potential; MNC: motor nerve conduction; SAP: sensory action potential; SNC: sensory nerve conduction

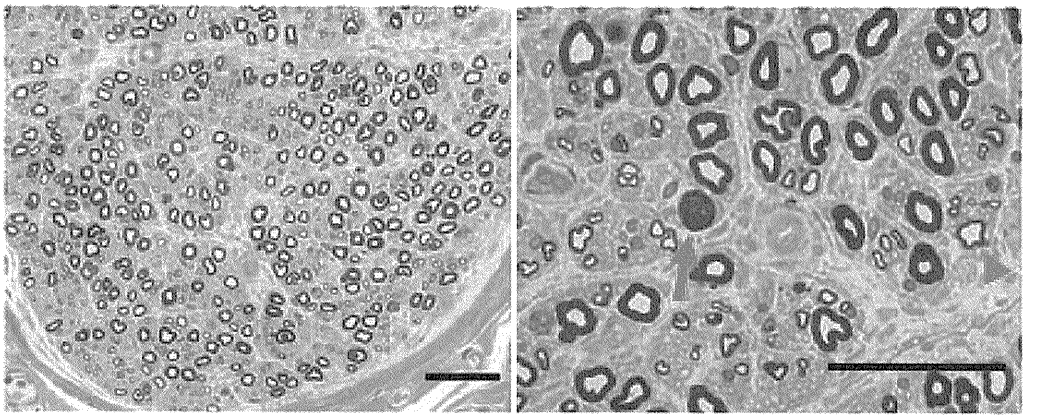

Fig. 1　Sural nerve biopsy specimen (Toluidine blue staining, bars＝50 μm).
Endoneurial and subperineurial spaces are edematous. Both myelin ovoids (arrow) and nerve fibers with thin myelin (arrowhead) are occasionally observed, indicating axonal degeneration with demyelination.

れた膵組織には悪性腫瘍の所見はなく，膵管周囲に線維化がみられ，その間にIgG4陽性の形質細胞が浸潤していた（Fig. 4）．腺房間にも軽度の線維化をともなっていた．浸潤した形質細胞はλ軽鎖，κ軽鎖ともに染色された．

経過：入院後，下肢DIP関節付近と足背に暗赤色の色素沈着が出現し，四肢の痛覚過敏は進行性に悪化し，下肢遠位筋の筋力低下は徒手筋力検査で3レベルに増悪した．POEMS症候群と診断し，移植前治療はおこなわず，2010年1月にメルファランをもちいた自己末梢血幹細胞移植をともなう大量化学療法目的で当院血液内科に転科した．自己末梢血幹細胞移植をともなう大量化学療法3カ月後には両手足のジンジン感，痛覚過敏は軽快し，筋力も正常となり，色素沈着は消失した．治療開始直前には1,700pg/m*l*まで上昇したVEGF値は，治療5カ月後には548pg/m*l*まで低下し，血中のM蛋白は消失した．膵アミラーゼは41IU/*l*と低下したが，IgG4は735 mg/d*l*と上昇し，膵臓のびまん性腫大に変化はなかった．

考　察

本症例は，皮膚病変やIgG-λ型M蛋白血症，高VEGF血症，骨髄穿刺での形質細胞の軽度増加，電気生理と病理所見での脱髄と軸索障害が混在した進行性の多発ニューロパチーをみとめ，POEMS症候群と診断した．POEMS症候群では臓器腫大は肝臓，脾臓，腎臓などでの頻度が高いが，本例のように膵腫大をきたした報告例は過去にない．膵臓のびまん性腫大とM蛋白血症をともなう多発ニューロパチーの両者を呈する疾患として，当初は悪性リンパ腫や髄外形質細胞腫の可能性を考え，膵生検を施行したが悪性腫瘍の所見はえられなかった．膵臓に線維化とIgG4陽性形質細胞浸潤をみとめる病理所見と，膵画像検査でびまん性の膵腫大と膵管の狭小化

があること，血清学的に著明な高 IgG4 血症をみとめることから，IgG4 関連多臓器リンパ増殖症候群の膵病変（自己免疫性膵炎）の合併と診断した．

IgG4 関連多臓器リンパ増殖症候群は，2008 年に Masaki ら[1]によって本邦より提唱された疾患概念で，①高 IgG4 血症があり，②組織に線維化や硬化をともなった IgG4 陽性形質細胞浸潤をみとめる，の 2 点をもって診断するとされる．自己免疫性膵炎は IgG4 関連多臓器リンパ増殖症候群の膵病変であると考えられている．同様の概念として IgG4 関連硬化性疾患や全身性 IgG4 関連形質細胞症候群も提唱されている[2][3]．POEMS 症候群と IgG4 関連多臓器リンパ増殖症候群の合併した症例は既報にはない．POEMS 症候群では，モノクローナルな形質細胞の増殖が報告されており[4]，蛋白電気泳動

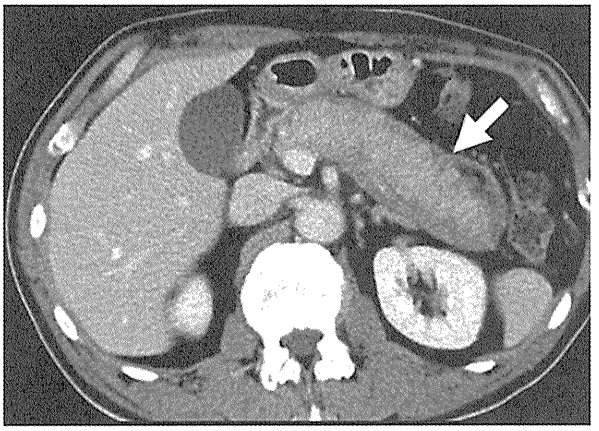

Fig. 2　Contrast-enhanced computed tomography showing diffuse enlargement of pancreas with capsule-like rim (arrow).

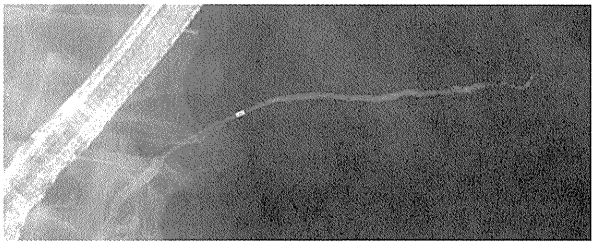

Fig. 3　Endoscopic retrograde cholangio-pancreatography demonstrating irregular narrowing of the main pancreatic duct.

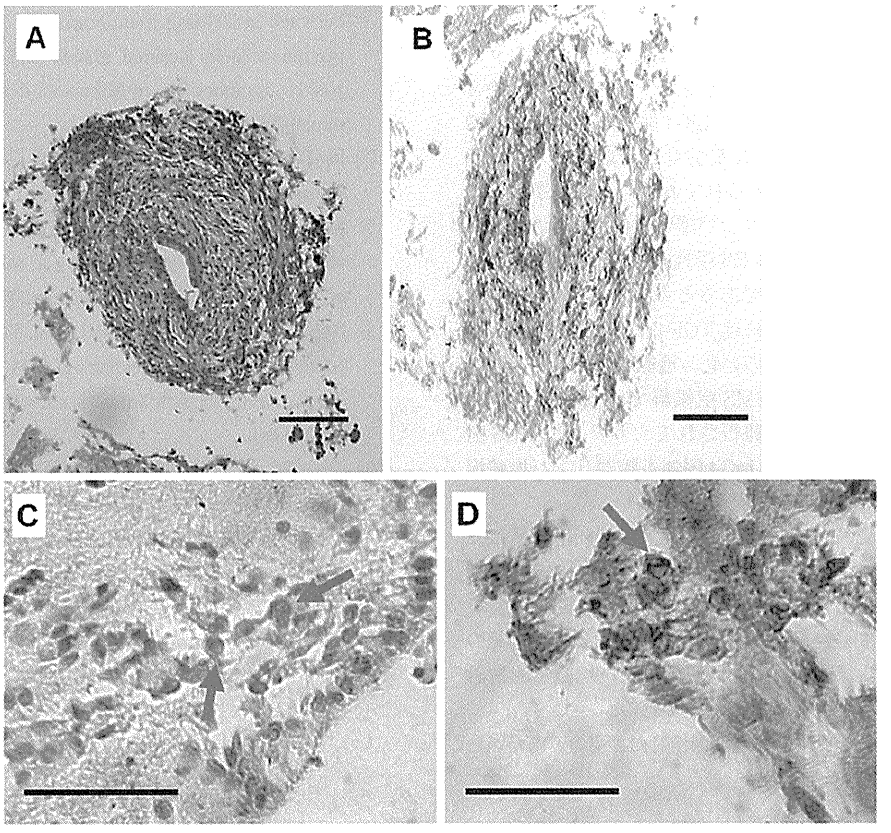

Fig. 4　Pancreas biopsy specimen.
A. Fibrosis is observed around the pancreatic duct. Hematoxylin and eosin. Bar = 100 μm
B. Immunohistochemical staining of IgG4 demonstrating the massive infiltration of IgG4-positive plasma cells, especially around the pancreatic duct. Bar = 100 μm
C.D. Immunohistochemical staining using anti-λ (C) and anti-κ (D) antibodies. Representative immunoreactive plasma cells are indicated by arrows. Bars = 50 μm

では急峻なMピークを形成する．一方，IgG4関連多臓器リンパ増殖症候群では，組織に浸潤したIgG4陽性細胞と末梢血のIgG4陽性細胞はポリクローナルであり[5)6)]，Mピークはみられない．本症例では，蛋白電気泳動で急峻なMピークがあり血清からλ型IgGがモノクローナルに検出された．一方，膵臓組織にみとめたIgG4陽性の形質細胞はλ軽鎖，κ軽鎖ともに陽性でありポリクローナルな形質細胞の増加が膵内に存在すると考えられた．また，自己末梢血幹細胞移植をともなう大量化学療法後にはPOEMS症候群の症候や高VEGF血症は改善し，血中のM蛋白は消失したが，膵臓に対する治療効果はなく，2つのことなる病態が共存していたと推定される．

POEMS症候群とIgG4関連多臓器リンパ増殖症候群ともにきわめてまれな疾患であるが，形質細胞が病態に関与する点で両疾患は類似することから，お互いの発症に関与している可能性が想定される．しかし，自己免疫的機序が病因として想定されているIgG4関連多臓器リンパ増殖症候群が，腫瘍随伴性疾患と考えられているPOEMS症候群の原因であるとは考えにくい．一方，POEMS症候群で上昇するIgGサブクラスは明らかにされていないが，本症例ではIgG4の上昇が他のIgGサブクラスに比較してきわめて高く，POEMS症候群をひきおこした形質細胞群が，モノクローナルなIgGだけでなくポリクローナルなIgG4も過剰産生していた可能性が想定される．つまり，過剰に産生されたIgG4が病因となり自己免疫性膵炎をひきおこしたと考えると，2つの症候群の合併を一元的に説明できる．しかし，IgG4関連多臓器リンパ増殖症候群でみられるIgG4増加は病的意義が乏しく，組織障害にともなう結果であると考えられており[7)]，この機序も考えにくい．現在IgG4関連多臓器リンパ増殖症候群では，自己に反応するTh1タイプのCD4，CD8陽性細胞を抑制する制御性T細胞の障害が要因の1つであると考えられている[8)]．制御性T細胞の分化や機能発現にはTGF-βが重要であり[9)10)]，その減少により制御性T細胞の分化，機能が障害される．本例では未測定であるが，POEMS症候群では血中のTGF-βレベルが低下していることが報告されており[11)]，POEMS症候群ではTGF-βの減少によりIgG4関連多臓器リンパ増殖症候群を誘発しやすい可能性が考えられる．

本症例では，免疫グロブリンのクローナリティに着目してPOEMS症候群とIgG4陽性多臓器リンパ増殖性症候群が共存していることを証明した．両者の合併は2つのきわめてまれな症候群の病因に示唆を与えた．今後，POEMS症候群での免疫グロブリンのサブクラス分画の解析や免疫組織学的検討の蓄積が両疾患の病態解明のために望まれる．

謝辞：稿を終えるに当たり，病理学的検討にご協力いただいた山口大学大学院医学系研究科分子病理学教室伊藤秀明先生に深謝申し上げます．

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Abstract

A case of POEMS syndrome with enlarged pancreas due to IgG4-related autoimmune pancreatitis

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A 57-year-old man developed bilateral hands and feet numbness, followed by weakness with the legs and skin pigmentation. These symptoms became gradually worsened, and we made a diagnosis of POEMS syndrome because of progressive polyneuropathy, skin changes, IgG lambda type monoclonal proteinemia, and elevated level of serum vascular endothelial growth factor (VEGF). Diffusely enlarged pancreas was noticed in computed tomography. Serological, radiological, and histological findings revealed enlarged pancreas was due to IgG4-related autoimmune pathogenesis. After high dose chemotherapy with autologous peripheral stem cell transplantation, his clinical manifestations, IgG lambda type monoclonal proteinemia, and elevated level of serum VEGF were improved, whereas diffuse enlargement of the pancreas did not change. This is the first case report of POEMS syndrome accompanied with IgG4-related autoimmune pancreatitis. Co-existence of monoclonal and polyclonal plasmaproliferative changes in the present patient may provide keys to clarify common mechanisms shared by these two rare disorders, POEMS syndrome and IgG4-related autoimmune disease.

(Clin Neurol 2011;51:417-421)

Key words: POEMS syndrome, IgG4-related autoimmune pathogenesis, pancreas swelling

症例報告

感覚障害を主徴とし，免疫グロブリン静注療法によりすみやかに改善した遠位型慢性炎症性脱髄性多発ニューロパチーの46歳男性例

竹下　幸男　　古賀　道明　　尾本　雅俊
小笠原淳一　　川井　元晴　　神田　　隆*

要旨：症例は46歳男性．3カ月前より，両手両足部のビリビリとした異常感覚が出現した．両側上肢遠位筋に軽度の筋力低下と四肢遠位部に感覚障害をみとめた．運動神経伝導検査で，明らかな脱髄所見をみとめ，感覚神経活動電位は導出不可であった．生検腓腹神経では，薄い髄鞘を有する大径有髄神経線維が散見された．感覚障害を主徴とする遠位型の慢性炎症性脱髄性多発ニューロパチー(CIDP)と診断し，免疫グロブリン静注療法をおこなった．2週間で症状は軽快，神経伝導検査の異常所見も改善し，以降は維持療法なく経過した．遠位型のCIDPは，免疫学的治療が著効し，維持療法なしに一相性の経過をとることが多く，早期の積極的な治療介入が望ましい．

(臨床神経 2011;51:478-482)

Key words：慢性炎症性脱髄性多発ニューロパチー，遠位型，免疫グロブリン静注療法，distal acquired demyelinating symmetric neuropathy

はじめに

慢性炎症性脱髄性多発ニューロパチー（CIDP）は，1975年にDyckら[1]により提唱された疾患概念で，臨床像，経過，治療反応性，予後など症例により多様であることから，ことなった病態をふくむ症候群である．CIDPには多くの臨床亜型があるが[2]，典型的には症状が両側対称性で近位筋が遠位筋と同様に障害を受け，運動神経の障害が優位である[3]．今回われわれは，四肢遠位部の左右対称性感覚運動障害を主徴とする非典型的なCIDP患者に，免疫グロブリン大量静注療法(IVIg)を施行し，短期間で著明な症状と電気生理学的の改善をみとめた．その後も維持療法をおこなうことなく一相性の良好な経過を示した．四肢遠位部の感覚障害を主徴とするCIDP亜型としては，distal acquired demyelinating symmetric neuropathy(DADS)という概念が提唱されているが[2]，本症例ではM蛋白陰性であり治療反応性が非常に良好であった点から，通常のDADSとはことなるCIDP亜型が想定される．近年，電気生理学的な脱髄病変の分布が四肢遠位部に限局し，治療反応性が良好なCIDP亜型として遠位型CIDPが報告されており[3]，本症例は脱髄病変の分布や治療反応性の点から，遠位型CIDPの範疇にふくまれるものと考えられる．これまで遠位型CIDPに関する詳細な症例報告例はなく，同症の発症機序に関する考察を加え報告する．

症　例

患者：46歳，男性

主訴：四肢の感覚障害

既往歴，家族歴：特記事項なし．

職業：害虫駆除の研究員（農薬を頻回に使用）．

現病歴：2007年11月下旬，起床時に両手のビリビリとした異常感覚を自覚し，両足部にも拡大した．12月中旬に近医を受診し，末梢神経障害がうたがわれるも原因が不明であった．その後も症状は増悪し，翌年2月中旬，精査目的で当科入院となった．

入院時現症：

一般身体所見：身長162cm，体重61kg，体温36.6℃，脈拍50回/分，血圧125/75mmHg，呼吸音，心音，腹部異常なし．

神経学的所見：意識清明．脳神経に異常はなかった．徒手筋力テストでは左右の母指対立筋，背側骨間筋に4程度の筋力低下があり，握力は右16kg，左12kgであった(右きき)．その他，下肢をふくめ明らかな筋力低下はみられなかった．温痛覚は左右手指末端，下腿以下で低下し，同部位に異常感覚をみとめた．関節位置覚は左右手指で低下し，振動覚は左右内踝で軽度低下していた．左右の上腕二頭筋反射は消失し，上腕三頭

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(受付日：2010年10月14日)

Table 1　Nerve conduction studies.

Motor conduction study

		Right (*)	Left
Median	MCV (m/sec)	40.7 (>50.0)	33.0
	CMAP amplitude (distal/proximal) (mV)	2.0/1.4 (>6.0/>5.0)	0.9/0.9
	Distal latency (msec)	29.0 (<3.8)	21.0
	F wave latency	not evoked	not evoked
Ulnar	MCV (m/sec)	42.5 (>51.0)	65.0
	CMAP amplitude (distal/proximal) (mV)	2.6/1.5 (>6.0/>5.0)	1.5/1.5
	Distal latency (msec)	11.0 (<3.0)	8.6
	F wave latency (msec)	not evoked	57.4
Tibial	MCV (m/sec)	28.2 (>42.0)	not examined
	CMAP amplitude (distal/proximal) (mV)	0.21/0.21 (>7.0/>6.0)	
	Distal latency (msec)	7.9 (<6.5)	
	F wave latency	not evoked	

Sensory conduction study

		Right	Left
Median	SCV (m/sec)	not evoked	not evoked
	SAP amplitude		
Ulnar	SCV (m/sec)	not evoked	not evoked
	SAP amplitude		
Sural	SCV (m/sec)	55.2 (>40)	55.2
	SAP amplitude (μV)	6.7 (>9.0)	6.7

CMAP amplitude was measured from onset to the peak of the initial monophasic negative muscle response.
Sensory nerve conduction studies were performed using an antidromic method. Skin temperatures was kept to range between 32℃ and 34℃.
SAP from the median nerve was recorded at the digit II. The stimulating electrode is place on the skin over the patient's median nerve at the wrist (stimulation-recording distance standardized at 140 mm).
SAP from the ulnar nerve was recorded at the digit V. The stimulating electrode is place on the skin over the patient's ulnar nerve at the wrist (stimulation-recording distance standardized at 140 mm).
SAP from the sural nerve was measured at the lateral malleolus with stimulation of the nerve at the posterolateral side of the calf (stimulation-recording distance standardized at 140 mm).
*: At our institute
MCV: motor conduction velocity　SCV: sensory conduction velocity　CMAP: compound muscle action potential　SAP: sensory action potential

筋反射と橈骨反射は低下，膝蓋腱反射は低下し，アキレス腱反射は消失していた．病的反射はなく，協調運動や歩行，自律神経系に異常はみられなかった．

検査結果：血算・生化学検査では，血糖や電解質，甲状腺機能，抗核抗体，抗好中球細胞質抗体，抗SS-A抗体，抗SS-B抗体，抗ガングリオシド抗体，TNF-αをふくめ特記すべき異常はなかった．リウマトイド因子が軽度上昇していたが，免疫グロブリンや補体価は正常，血中M蛋白（電気泳動）も陰性であった．仕事が農薬をもちいた研究であるため，DDVPなど過去に使用歴のある農薬の血中濃度を測定したが，異常はみられなかった．胸部および頸椎X線，胸腹部CT，頭部MRIにも特記すべき異常はみとめなかった．脳脊髄液検査では，蛋白が86mg/dlと上昇していたが，細胞数3/μl，糖62 mg/dl（血糖95mg/dl）もいずれも正常範囲内であり，IgG index 0.69と明らかな異常高値はみられなかった．末梢神経伝導検査では，正中・尺骨・脛骨神経の運動神経において遠位潜時が高度に延長しており，異常な時間的分散と複合筋活動電位の振幅低下をみとめた(Table 1)．伝導ブロックはいずれの神経においてもみられなかった．感覚神経では，腓腹神経の感覚神経活動電位振幅は低下しており，上肢では導出不能であった．針筋電図では右前脛骨筋で異常はなかった．

左腓腹神経では有髄神経線維密度が同年代の正常者と比較して軽度低下しており，比較的薄い髄鞘を有する大径有髄線維が散見され，神経周膜下に浮腫がみられた(Fig. 1A)．炎症細胞の浸潤や，ミエリン球，naked axon, onion bulbの形成などはみとめなかった．ときほぐし標本では，節性に菲薄化した髄鞘をもつ線維を4.2%みとめたが，paranodeに明らかな形態変化はみられなかった(Fig. 1B)．左短腓骨筋には異常所見

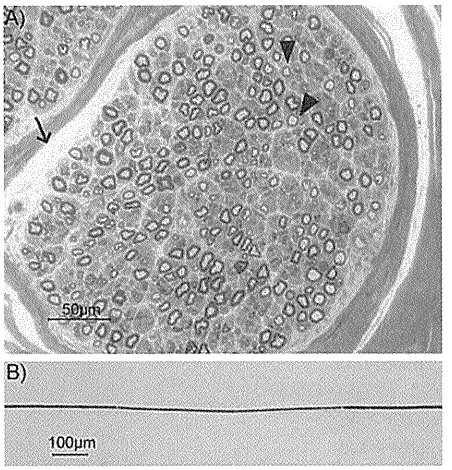

Fig. 1　Histopathlogical findings of the left sural nerve. (A) Cross section of toluidine blue-stained epon-embedded semithin shows mild subperineurial edema (allow), some fibers with thinning myelin sheath (allow heads), and mild reduction of myelinated nerve fibers. No naked axons, myelin ovoids or onion bulb formations are observed. (B) Teased fiber preparations show segmentally thin myelin sheaths.

はなかった.

入院後経過：筋力低下はごくわずかであるのに対し運動神経伝導検査上の異常が高度で,両者に解離があることから,自己免疫性および遺伝性ニューロパチーが想定された.針筋電図で慢性神経原性変化をみとめなかったことから遺伝性の可能性は低く,また末梢神経伝導検査で左右差が比較的めだったことから自己免疫性機序の可能性を第一に考え,IVIg(400 mg/kg/日×5日間)を行った.IVIg後,2週間の経過で四肢末梢の異常感覚や感覚鈍麻,筋力低下は軽快し,左右の上腕二頭筋反射,アキレス腱反射も出現した.IVIg施行2週間後に行った運動神経伝導検査では,正中・尺骨・脛骨神経のいずれにおいても,延長していた遠位潜時は短縮し,時間的分散の回復がみられた(Fig. 2).IVIgへの反応性を考慮し,非典型的ながら遠位部に病変の強いCIDPと診断した.IVIg終了2週後よりプレドニゾロン60mg/日を4週間投与し,以降は漸減中止した.運動神経伝導検査での異常はさらに改善し(Fig. 2),腓腹神経の感覚神経活動電位振幅は増加,上肢でも感覚神経活動電位が導出可能になった.維持療法は施行せず,IVIg終了後から約2カ月で症状が完全消失した.以降2年の経過で再発や増悪をみとめていない.

考　察

本例は,左右対称性で四肢遠位部の感覚障害を主体としたポリニューロパチーを示し,髄液蛋白細胞解離がみられた.さらに電気生理学的には四肢遠位部を主体に脱髄障害パターンを呈し,神経生検で脱髄性所見をみとめた.これらの結果から神経終末部を中心としたCIDPと想定される.また本例の特

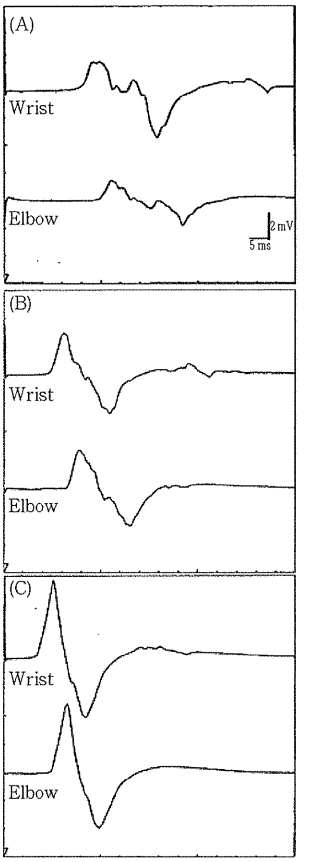

Fig. 2　Motor conduction studies on median nerve. Motor conduction studies on median nerve show markedly prolonged distal latency and abnormal temporal dispersion before intravenous immunoglobulin (IVIg) treatment (A). These abnormalities apparently were lessened 5 days after IVIg treatment (B), and abnormal temporal dispersion disappeared shortly after oral administration of prednisolone (C).

徴として,IVIg治療による反応が良好で経過が一相性であることが挙げられる.

従来CIDPは,神経障害の分布により経過,治療への反応性が均一でないことが知られており,多数の疾患が混在する症候群として考えられている.遠位型で感覚障害が主体のCIDPの亜型として,distal acquired demyelinating symmetric neuropathy (DADS)という概念が提唱されている[2)3)].DADSは遠位型感覚障害が主体で,しばしばM蛋白血症をともない,治療反応性が非常に不良な疾患群として考えられている.しかし,M蛋白血症をともなわず遠位型感覚障害の分布からDADSとされている疾患の中には,治療反応性が非常に良好である一群の存在が報告されている[2)4)].自験例も,神経障害の分布,M蛋白血症をともなわない点,治療反応性が良い点から,この一群の範疇に入ると考えられ,通常のDADSとはことなるCIDP亜型として理解することが可能であると考えられる.

Kuwabaraら[5]は，電気生理学的な脱髄病変の分布により遠位型，びまん型，中間型に分類し，これらの型により発症様式，臨床経過，治療反応性がことなる可能性を示している．電気生理学的な脱髄病変の分布からは，本例はこの報告でのびまん型に分類されるが，神経症状は四肢遠位部に限局しており，治療反応性からも，本例は遠位型ととらえることが可能と考えられる．びまん型では，血中TNF-αが上昇するとされているが，本例では血中TNF-αは正常であったこともこれを支持する所見である．また，左腓腹神経生検標本で脱髄所見が軽度であるにもかかわらず，上肢の感覚神経伝導検査では波形が検出できないことからも，手指末端に限局した脱髄が生じていることが推察される．

Kuwabaraらの分類はあくまで電気生理的な脱髄病変の分布によるものであり，本症例のようなM蛋白血症をともなわない通常のDADSとはことなる疾患群が遠位型CIDPにどの程度ふくまれているかについては不明である．しかしながら，M蛋白血症をともなう通常のDADSでは一般的に治療反応性が不良であることから，治療反応性良好な遠位型CIDPが本症例のようなDADSとはことなる疾患群の主体となっていることが推察される．

通常CIDPは，免疫学的治療がなされないばあいには，自然寛解にいたる例は少なく，一部は慢性進行性に増悪するため，できるだけ早期の積極的な治療介入が望ましい．Kuwabaraら[5]は，遠位型CIDPにおける免疫学的治療をもちいた治療反応性は非常に良好で[6]，臨床的予後も多くの症例で長期完全寛解がえられると主張している．本例においても，IVIg治療が著効し，維持療法をおこなわず長期完全寛解がえられていることから，このような遠位型CIDPの特徴を呈している．また，通常CIDPは再発予防としてステロイドによる維持療法をおこなうばあいが多い．しかしながらこのタイプの遠位型CIDPにおいては，免疫学的治療後に一相性の経過をたどるものが多いため[5]，再発予防としてプレドニンを漫然と継続する必要性はなく，本例のように注意深い観察のもと維持療法せずに完治する症例も存在する．

遠位型CIDPの病態については，治療反応性や予後についての報告はあるが，その病態についてはまだ明らかとなっていない．遠位型CIDPの病変の主体となる神経終末端部は，解剖学的に血液神経関門が脆弱とされている[7]．遠位型CIDPは，免疫学的治療に反応性が良好であることから，こうした神経終末端部において液性因子の関与した自己免疫疾患である可能性が高いと考えられる．さらに本例では，IVIg投与後の電気的回復までの時間的経過が短時間であったことから，脱髄ではなく自己抗体によるchannel blockなどの機能性障害が病態の主体であると予想され，遠位型CIDPの一つの病態を呈しているものと考えられる．

本例の要旨は，第84回日本神経学会中国・四国地方会（2008年7月5日，鳥取）で発表した．

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Abstract

Good response to intravenous immunoglobulin therapy in sensory dominant distal variant of chronic inflammatory demyelinating polyneuropathy

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A 46-year-old man experienced numbness and muscle weakness in the distal portions of both hands, which progressed over following three months. Neurological examination showed mild muscle weakness only in distal arms, hypoflexia or areflexia, and hypesthesia in glove and stocking distribution. Motor conduction study revealed markedly prolonged distal latency and abnormal temporal dispersion. Sensory nerve potentials were reduced or could not be recorded. Histopathlogical findings of the sural nerve showed several nerve fibers with thinning myelin sheath and mild reduction of myelinated fibers. These results suggested the diagnosis of chronic inflammatory demyelinating polyneuropathy (CIDP). Two weeks after intravenous immunoglobulin therapy, neurological deficits rapidly improved and electrophysiological abnormalities were also ameliorated. Thereafter, there was no clinical deterioration for two years without further treatment. Our patient suggested that immunomodulating treatment is needed for stopping the initial progression of neurological deficits, but maintenance therapy is not always necessary for keeping the remitting state in distal variant of CIDP.

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Key words: chronic inflammatory demyelinating polyneuropathy, distal variant, intravenous immunoglobulin, distal acquired demyelinating symmetric neuropathy

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Short communication

Four cases of anti-ganglioside antibody-positive neuralgic amyotrophy with good response to intravenous immunoglobulin infusion therapy

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ABSTRACT

Neuralgic amyotrophy (NA), which is an idiopathic disorder in the peripheral nerves, is characterized by an acute onset of unilateral pain in the proximal limbs followed by muscular weakness and wasting. Some cases of NA are thought to be related to immune pathogenic disorders such as Guillain–Barré syndrome (GBS). We report the case of four patients with NA who were positive for anti-*N*-acetylgalactosaminyl GD1a (anti-GalNAc-GD1a) antibodies, had a preceding infection, and showed a good response to intravenous immunoglobulin infusion therapy. Anti-ganglioside antibodies, especially the anti-GalNAc-GD1a antibody, may be a useful marker for predicting response to immune therapy.

1. Introduction

Neuralgic amyotrophy (NA), or Parsonage–Turner syndrome, is an idiopathic disorder in the peripheral nerves that is characterized by an acute onset of shoulder and arm pain, which is followed by muscular weakness and wasting (Parsonage and Turner, 1948). Similar symptoms in the lower extremities have been reported and are considered to be a variant of NA (Takata et al., 2007). Although some cases have developed subsequent to surgery or trauma, the frequent association of this disorder with preceding infections and immunizations indicates an autoimmune pathogenesis (Suarez et al., 1996).

Frequent findings of increased levels of anti-ganglioside antibodies in sera obtained from patients in the acute phase of Guillain–Barré syndrome (GBS) and other inflammatory neuropathies have been reported, and clinical features of these diseases were associated with the reactivity of anti-ganglioside antibodies (Hartung et al., 1995; Kaida et al., 2000). Herein, we report the case of four patients with NA who presented with increased levels of anti-ganglioside antibodies in their sera and who had a good response to intravenous immunoglobulin infusion therapy (IVIg).

2. Case Report

2.1. Case 1

A 34-year-old woman presented with fever and vomiting which was followed by right shoulder pain that radiated to the forearm after 2 weeks and weakness in the right arm after 4 weeks. Her medical history was normal. Physical examination showed slightly decreased strength in the proximal and distal muscles of the right arm (Medical Research Council [MRC] score, 4). There was a slight diminution of touch sensation in the right hand. Tendon reflexes were normal. Laboratory tests were normal for complete blood counts, liver and renal function tests, thyroid hormone tests, and immunological screening. An enzyme-linked immunosorbent assay (ELISA) was performed for antibodies to the ganglioside as described previously (Kusunoki et al., 1994). Ganglioside antigens used in the ELISA were 200 ng each of GM1, GM2, GD1a, GD1b, GD3, GT1a, GT1b, GQ1b, and *N*-acetylgalactosaminyl GD1a (GalNAc-GD1a). The ELISA was also performed for antibodies to ganglioside complex containing 100 ng each of GD1a and GD1b.

ELISA revealed an IgM antibody to GalNAc-GD1a and an IgG antibody to cytomegalovirus (CMV) in her serum. IgM antibody against GM2 was negative. An examination of cerebrospinal fluid (CSF) showed slightly increased proteins (0.42 g/L). An electrophysiological investigation showed low F-wave persistence in the right median nerve (25%). Needle electromyography was unremarkable. Brain and cervical magnetic resonance images (MRIs) were normal. The patient underwent a course of 5-day IVIg (400 mg/kg) because her symptoms

Abbreviations: NA, neuralgic amyotrophy; GalNAc-GD1a, *N*-acetylgalactosaminyl GD1a; GBS, Guillain–Barré syndrome; IVIg, immunoglobulin infusion therapy; CMV, cytomegalovirus; MRC, Medical Research Council.

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were suspected to be caused by an immune-mediated mechanism. Neuropathic symptoms improved during the regimen. On day 2 of the IVIg, muscle strength returned to the preillness state. The right arm pain subsided gradually, and 2 months later, she showed complete recovery (Fig. 1A).

2.2. Case 2

A previously healthy 26-year-old woman developed pain in both legs 2 weeks after an upper respiratory infection. Upon examination, muscle strength testing revealed mild weakness of both distal dominant legs (MRC, 4). Sensory examination showed hyperalgesia in her legs. Tendon reflexes were normal. The routine blood test results were normal. Serum antibody testing showed high titers of the anti-GalNAc-GD1a IgM antibody and the anti-CMV IgG antibody. IgM antibody against GM2 was negative. CSF examination was normal. An electrophysiological study showed decreased motor conduction velocity and F-wave persistence in the right ulnar nerve (50%). Brain and cervical MRIs were normal. Treatment with IVIg was effective for alleviating her pain, and muscle strength improved. On the 14th day after onset, she showed complete recovery (Fig. 1B).

2.3. Case 3

A previously healthy 54-year-old man presented with fever and developed left shoulder and forearm pain the next day. On day 2, he developed weakness in left arm elevation, and his pain continued to progress. Examination showed muscular weakness and atrophy in only the left deltoid muscle (MRC, 3). A sensory examination showed a moderate loss of vibration sensation and a mild loss of touch and pinprick sensation in the left upper extremity. Tendon reflexes were normal. Blood tests showed liver function disorder (AST, 137 IU/L; ALT, 234 IU/L) and high titers of the anti-GalNAc-GD1a IgM antibody, anti-GM2 antibody, and anti-CMV IgG antibody. A CSF examination showed slightly increased proteins (0.48 g/L). An electrophysiological study showed low F-wave persistence in the left median nerve (45%). Brain, cervical, and thoracic MRIs were normal. The patient recovered completely within 30 days without any treatment.

2.4. Case 4

A 37-year-old man had a history of three operations to his right arm when he was 16, 25, and 28 years old. He had a 2 years and 5 months history of right neck pain that extended to the elbow. From the seventh month after the onset of the right arm pain, he had developed weakness and muscular atrophy in his right chest and arm. Although prednisolone was administered by his local doctor, his symptoms were aggravated gradually. After his pain and weakness spread to his right leg, he visited our hospital. An examination showed muscular weakness in the right neck extensor and the right upper and lower extremities. A sensory examination showed a mild loss of vibration, touch, and pinprick sensations in the right upper and lower extremities. Deep tendon reflexes were decreased in both upper and lower extremities. Laboratory studies were normal except for the positivity of the IgG anti-GalNAc-GD1a antibody and the anti-CMV IgG antibody. IgM antibody against GM2 was negative. CSF examination on admission showed slightly increased proteins (0.5 g/L). An electrophysiological investigation, including needle electromyography, showed no remarkable findings. Brain and cervical MRIs were normal. Because his clinical course was different from that of other 3 cases, it may be difficult to have a diagnosis of NA. However, the existence of anti-GalNAc-GD1a antibodies and neurological symptoms inexplicable by his history of operations allowed us to consider as immune-pathogenesis. The patient was treated with IVIg, which

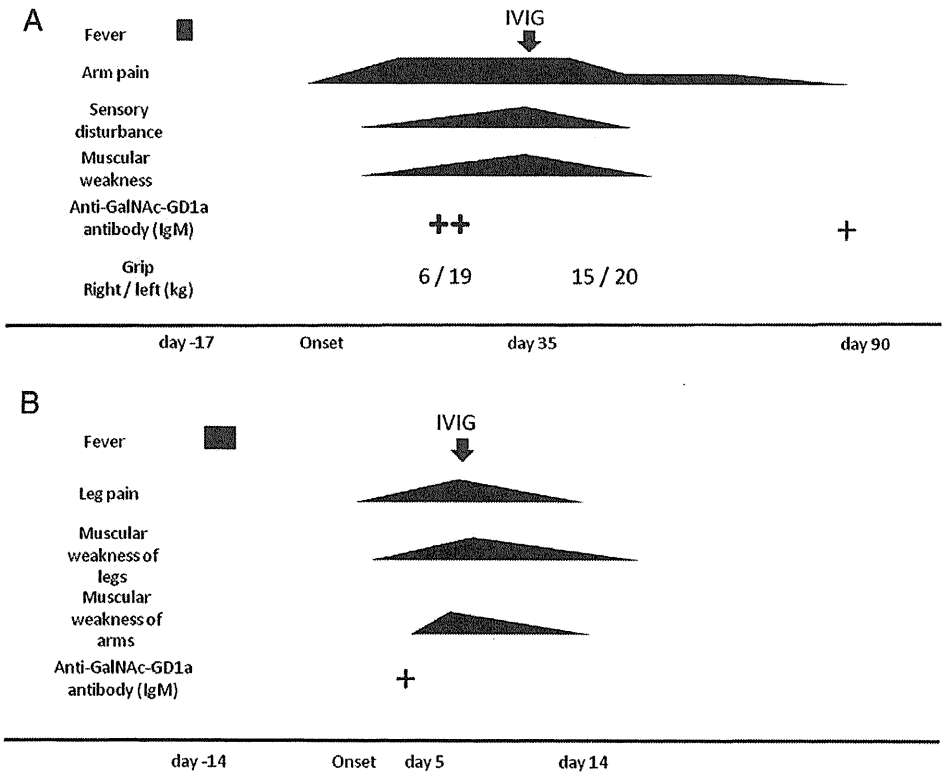

Fig. 1. The clinical course of Case 1 and Case 2. A) Case 1: The acute onset of arm pain and muscular weakness after a preceding infection is illustrated. The patient's neurological symptoms improved gradually after immunoglobulin infusion therapy (IVIG), and the titers of the serum anti-*N*-acetylgalactosaminyl GD1a (GalNAc-GD1a) antibody decreased. Her clinical course was considered to be monophasic. B) Case 2: The patient developed acute leg pain and muscular weakness of the extremities after an antecedent infection. Her symptoms improved immediately after IVIG.