Table. The Clinical Characteristics of the Patients with Fisher Syndrome (FS).

subject	age	sex	antecedent infection	prodrome	dysesthesia	hypesthesia		GQ1b-Ab	NCS date
						vibration	pinprick		
normal sensory group (group NS, n = 6)									
1	59	M	none	dysesthesia	present	none	none	positive	day 10
2	28	M	URI	ataxia	present	none	none	negative	day 7
3	23	M	diarrhea	diplopia	absent	none	none	not done	day 16
4	68	M	URI	diplopia	present	none	none	positive	day 17
5	36	F	URI	diplopia	absent	none	none	positive	day 4
6	34	M	diarrhea	diplopia	present	none	none	positive	day 4
hypesthesia group (group H, n = 4)									
7	38	M	URI	diplopia	present	hypesthesia	none	negative	day 11
8	21	F	none	diplopia	present	hypesthesia	none	positive	day 5
9	38	F	URI	diplopia	present	hypesthesia	hypesthesia	positive	day 14
10	68	M	URI	ataxia	present	hypesthesia	hypesthesia	positive	day 4

The patients were divided into the following Two groups: those without hypesthesia (cases 1-6) and those with hypesthesia (cases 7-10). The days listed in the nerve conduction studies (NCSs) column indicate the timing of the NCSs from the onset of FS.

Abbreviations: URI: upper respiratory infection

case series indicate that demyelinating processes cause the decreased amplitudes of SNAPs observed in patients with FS (11-14), whereas the results from two large case series suggest that axonal neuropathy or dorsal root ganglionopathy are responsible (8, 10). Therefore, the question of whether decreases in SNAP amplitudes result from a demyelinating process or an axonal mechanism remains controversial. In this study, the results of SNCSs in two different groups of FS patients (one group with hypesthesia and one without) were compared in order to elucidate the correlation between sensory symptoms and neurophysiological parameters. In addition, follow-up studies were conducted in two representative FS patients, one from each group.

Materials and Methods

Subjects

Ten consecutive FS patients were identified from patients admitted to our facility between 1991 and 2011. The patients were diagnosed with FS if they demonstrated an acute onset of the clinical triad (i.e., ataxia, diplopia and diminished tendon reflexes) and the resolution of symptoms within one or two months. The clinical records of these patients and the results of the NCS were retrospectively reviewed for further analysis. The clinical details of each patient, including antecedent infections, sensory symptoms, results of serum GQ1b antibody screening and the timing of the NCS from disease onset are shown in Table.

Nerve conduction studies

Standard testing procedures were performed in all patients in our facility as follows: motor nerve conduction studies (MNCSs) and F-wave conduction studies (FWCS) were conducted on the right median and tibial nerves, and SNCSs were conducted on the right median and sural nerves in an anti-dromic fashion. The parameters were evaluated as follows: in the SNCSs, we analyzed SNAP amplitudes (measured from the baseline to the negative peak), sensory conduction velocities (SCVs) and the duration of the SNAPs (defined here as the time between take-off and the positive peak); in the MNCSs, we measured the distal motor latencies (DLs), CMAPs (measured from the baseline to the negative peak) and MCVs; in the FWCSs, we measured F-wave frequencies and the shortest F-wave latencies. The temperature was monitored and maintained above 32℃ during all recordings. The NCS parameters were compared with those of control subjects (aged 24.0±3.0 years). In some cases, NCSs were performed on several occasions during the patient's illness. In such cases, NCS parameters recorded during the most severe period were selected for statistical analysis (the days on which the NCSs were conducted after admission are listed in Table as the NCS date). In particular, parameters obtained on day 14 were used in case number 9 (the case depicted in Fig. 2) and those obtained on day four were used in case number 5 (the case depicted in Fig. 3).

For the statistical analyses, each electrophysiological parameter obtained in the MNCSs, SNCSs and FWCSs (DLs, CMAPs and MCVs in the MNCSs; SNAP amplitudes, SCVs and the duration of SNAPs in the SNCSs; F-wave frequencies and minimal F latencies in the FWCSs) was compared between the patients without hypesthesia (group NS) and those with hypesthesia (group H). Comparisons between the two groups were performed using the nonparametric Mann-Whitney test (SPSS Base ver 11.J, SPSS Inc., Chicago, Illinois, USA).

Results

Patient characteristics

Out of the ten patients examined in this study, seven were male and three were female. The average age at onset of FS was 41.3 years (range: 21-68 years) (Table). The average age at onset was similar between group NS (41.3±18.0 years) and group H (41.3±19.6 years). Eight patients had antecedent infections (six had upper respiratory infections and two had diarrhea) that manifested four to 11 days be-

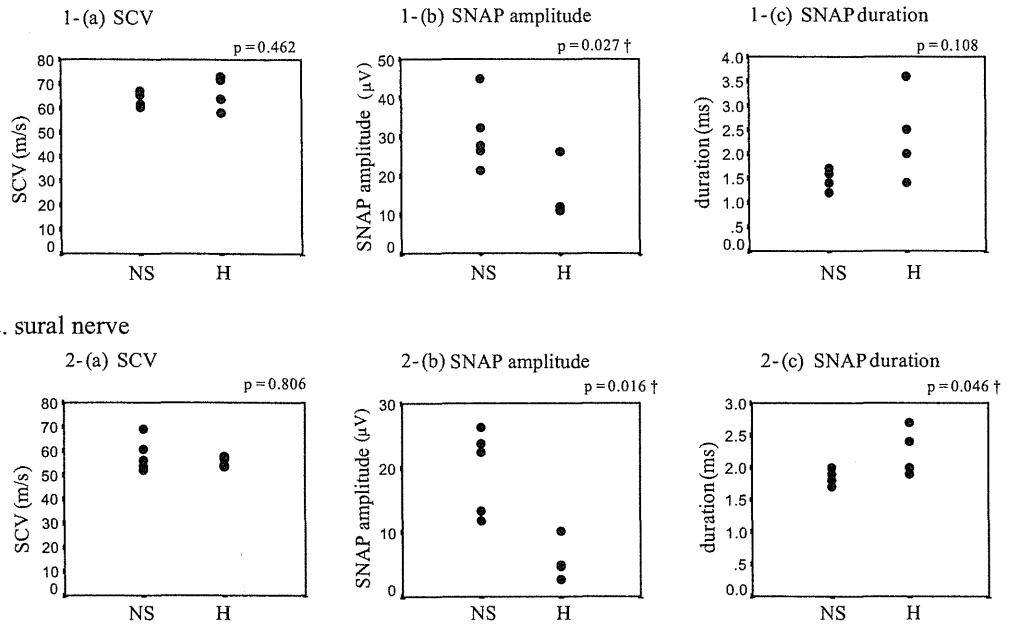

Figure 1. The three parameters of the sensory nerve conduction studies (SNCSs) performed on the median and sural nerves of the Fisher syndrome (FS) patients without hypesthesia (group NS, n=6) and those with hypesthesia (group H, n=4) were analyzed. 1-(a) and 2-(a): Sensory conduction velocities (SCVs) in the median and sural nerves, respectively. 1-(b) and 2-(b): Amplitudes in sensory nerve action nerve potentials (SNAPs) in the median and sural nerves, respectively. 1-(c) and 2-(c): SNAPs duration in the median and sural nerves, respectively. The statistical analysis was performed using the non-parametric Mann-Whitney test.

fore the presentation of the initial symptoms of FS (data not shown). Seven patients were positive for serum GQ1b antibodies. All patients exhibited the clinical triad of FS, which consists of ophthalmoplegia, ataxia and hyporeflexia/areflexia. Regarding the sensory symptoms, eight patients (80%) complained of distal dysesthesia. Among these, one patient (case 1) presented with dysesthesia as the initial symptom of FS before the appearance of the clinical triad. Six patients did not show hypesthesia (group NS), whereas four patients complained of sensory deficits (group H) (Table). All four patients with hypesthesia had impaired vibration sensation, and two patients also had decreased pinprick sensation. No patient in either group showed limb weakness; however, two patients (cases 1 and 9) showed dysarthria and dysphagia. Both patients were alert and neither exhibited extensor plantar signs or brisk tendon reflexes, thus negating the possibility of Bickerstaff brainstem encephalitis.

Results of NCS in the two groups

In the MNCSs and FWCSs, all electrophysiological parameters were normal in all patients and no differences were found between groups NS and H (data not shown). In the SNCSs, both the median and sural SCVs were within the normal ranges and showed no statistical differences between the two groups (median SCV: 63.0±3.1 m/s in group NS, 66.7±7.0 m/s in group H and 63.2±4.0 m/s in the normal controls; sural SCV: 58.2±6.8 m/s in group NS, 55.3±2.1 m/s in group H and 59.0±1.7 m/s in the normal controls) [Fig. 1.1-(a), 2-(a)]. In the SNCSs, however, both the median and sural nerve SNAP amplitudes were significantly decreased in group H (median SNAP: 30.5±9.0 μV in group NS, 15.0±7.4 μV in group H and 37.8±9.4 μV in the normal controls, p=0.027 between groups NS and H; sural SNAP: 19.5±6.5 μV in group NS, 5.6±3.2 μV in group H and 19.1±4.7 μV in the normal controls, p=0.016 between groups NS and H) [Fig. 1.1-(b), 2-(b)]. In addition, the duration of the sural SNAPs was prolonged in the patients with hypesthesia (1.8±0.1 ms in group NS, 2.3±0.4 ms in group H and 1.7±0.3 ms in the normal controls, p=0.046 between groups NS and H), whereas the difference in the duration of the median SNAPs between the two groups was not statistically significant (1.5±0.2 ms in group NS, 2.4±0.9 ms in group H and 1.14±0.1 ms in the normal controls, p=0.108 between groups NS and H) [Fig. 1.1-(c), 2-(c)].

Morphological changes in SNAPs during the clinical courses of the two representative patients

Follow-up SNCSs were conducted in two patients: one patient with hypesthesia (case 9, group H) and one patient without hypesthesia (case 5, group NS) (Fig. 2 and 3, respectively). In case 9, a second low-amplitude negative peak appeared in the median nerve on day 1 approximately 2 ms after the initial negative peak (arrow in Fig. 2A; day 1). The latency of this peak gradually decreased through days 1 to

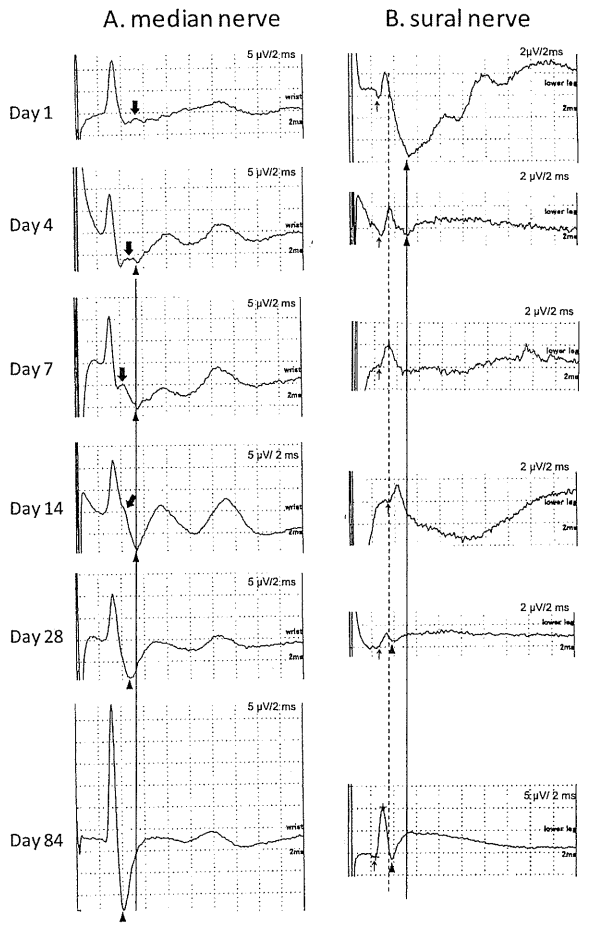

Figure 2. The time course of the sensory nerve conduction studies in the median nerve (A) and the sural nerve (B) of a patient with hypesthesia (case 9). A. The sensory nerve action potentials (SNAPs) in the right median nerve were recorded on days 1, 4, 7, 14, 28 and 84 (day 1 was defined as the day of admission). The arrows indicate the second negative peak that followed the first negative peak. The arrowheads indicate the positive peak that followed the first negative peak. The solid line indicates the most prolonged period of latency associated with the positive peak (days 4 and 7). B. The SNAPs in the right sural nerve recorded on days 1, 4, 7, 14, 28 and 84. The arrows indicate the SNAP take-off and the broken line indicates the most prolonged latency of SNAP onset (day 14). The arrowheads indicate the positive SNAP peak that followed the negative peak. The solid line indicates the most prolonged latency of the positive peak (days 1-4).

14 and was incorporated into the first negative peak on day 28 (arrows in Fig. 2A; days 4, 7, 14 and 28). SNAP duration, which was defined by the time difference between take-off and the positive peak, gradually decreased from days 4 to 84 (arrowheads in Fig. 2A; days 4, 7, 14, 28 and 84). After the complete fusion of both negative peaks on day 28, the duration decreased even further until it reached a normal SNAP amplitude on day 84. A comparable SNAP dispersion was also observed in the sural nerve of the same patient (Fig. 2B).

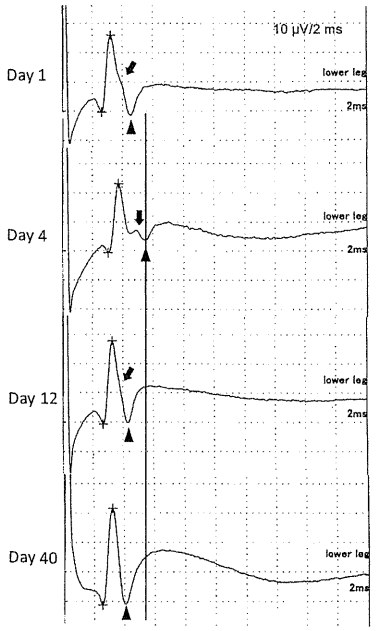

Figure 3. The time course of the sural nerve conduction studies performed in a patient without hypesthesia (case 5). The SNAPs of the right sural nerve were recorded on days 1, 4, 12 and 40 (day 1 was defined as the day of admission). The arrows indicate notches on the descending part of the sensory nerve action potentials (SNAPs) (days 1 and 12) and a negative peak that followed the first negative peak (day 4). The arrowheads indicate the positive peak that followed the negative peak. The solid line indicates the most prolonged latency on day 4. Note that the latencies of the positive peak were prolonged on days 1-4 and thereafter gradually decreased through day 40.

Interestingly, a similar desynchronization pattern was observed in case 5. The patient did not have either dysesthesia or hypesthesia throughout her clinical course (Fig. 3). A dull notch on the descending SNAP slope was identified on day 1 (arrow in Fig. 3; day 1). On day 4, a second negative peak appeared just after the first negative peak (arrow in Fig. 3; day 4). This peak was then completely incorporated into the first negative peak (Fig. 3; day 12). The latency of the second positive peak (arrowhead in Fig. 3) was prolonged on day 4 and then gradually shortened through day 40.

Discussion

The following three results were obtained in the SNCSs: (1) the patients with hypesthesia had lower SNAP amplitudes with longer durations than those without hypesthesia, (2) a distinct desynchronization SNAP pattern was observed in the acute phase in the two patients who underwent follow-up studies and (3) subsequent SNAP resynchronization resulted in the recuperation of the SNAP amplitudes in the convalescent phase in these two patients (Fig. 2).

First, the SNAP amplitudes in both the median and sural nerves in the patients in group H were smaller than those in the patients in group NS (Fig. 1). These results suggest that a correlation exists between the presence of severe sensory symptoms (hypesthesia) and decreased SNAPs in FS patients. Therefore, it is plausible that, in FS patients, decreases in SNAP amplitudes reflect pathological alterations in large myelinated sensory fibers.

Second, this study provides two pieces of evidence regarding the desynchronization of sensory nerves. SNAP durations were prolonged in the sural nerves of the patients with hypesthesia (p=0.046, Fig. 1), thus suggesting the possible desynchronization of the sensory nerves in these patients. In addition, temporal SNAP dispersions were observed in the two representative patients (cases 5 and 9, Fig. 2, 3), thus indicating uneven desynchronization of a fraction of the distal portion of the sensory nerves.

Third, the follow-up SNCSs conducted on the median nerve in case 9 showed that the second negative peak was gradually incorporated into the first negative peak. The second negative peak was presumed to be a delayed segment of partially demyelinated sensory nerve fibers. The remyelination of these fibers possibly led to a gradual improvement in the latency of the second negative peak, which eventually resulted in the recuperation of the SNAPs. In case 9, the SNAP dispersion paralleled clinical improvements in hypesthesia, reflecting possible pathological desynchronization in the acute stage and subsequent resynchronization in the convalescent stage.

Another intriguing finding was a similar desynchronization/resynchronization pattern in a patient who did not manifest any sensory symptoms throughout the entire clinical course (case 5, Fig. 3). This finding implies that even FS patients without sensory symptoms can harbor subclinical demyelination of sensory nerves, although to a lesser extent, thus widening the scope of sensory neuropathies in FS. In this regard, the severity of demyelination may partially explain the severity of sensory symptoms in FS patients.

This case series had some limitations. First, this study was retrospective and included a relatively small number of patients. Ideally, the timing of NCSs should be prospectively studied in a larger number of patients. Second, in the morphological analyses of the SNAP configurations (Fig. 2, 3), the presumed termination points of the SNAPs could be inaccurate to some extent because the baseline deviated during recording and because volume conduction of the muscle responses was recorded from the electrodes. Lastly, SCV, a parameter that indicates the degree of demyelinating pathology, was not decreased in FS patients, even in the hypesthesic group (group H), thus suggesting that a demyelinating process may not be the key underlying pathology. SCVs are essentially determined by the latency of the fastest fraction of the depolarized nerve trunk of the sensory nerves. In acute and curable neuropathies, and especially in mild neuropathies such as FS, it may be assumed that only a portion of nerve fibers will exhibit mild demyelination, thus leaving a certain amount of the fastest nerve fibers intact and maintaining normal SCVs with mild SNAP dispersions.

Two large case series hypothesized that either sensory nerve axonopathy or dorsal root ganglion (DRG) neuronopathy cause decreases in SNAP amplitudes because a smaller number of axons or DRG neurons could result in a decreased number of depolarized axons of sensory nerves (8, 10). However, demyelinating neuropathies, such as acute inflammatory demyelinating polyneuropathy, chronic inflammatory demyelinating polyneuropathy and the demyelinating type of Charcot-Marie-Tooth disease, can also result in decreased SNAP amplitudes, largely due to temporal dispersion or to uneven desynchronization of the sensory nerve fibers (15). Furthermore, two case reports on peripheral nerve pathology in FS patients reported the presence of segmental demyelination with little axonal pathology (16, 17). In our case series, most sensory symptoms, including hypesthesia, abated at an early stage of the disease, typically within a couple of weeks. This suggests that a demyelinating process rather than an axonal pathology is involved because axonal pathologies require several months for recovery. In summary, this study identified three features of reduced SNAPs that imply the presence of an underlying concomitant demyelinating pathology in FS patients: prolonged SNAP duration, temporal dispersion in the acute phase and resynchronisation and recuperation of SNAPs during the convalescent phase.

Conclusion

FS patients exhibit sensory polyneuropathies to varying degrees, ranging from asymptomatic subtle electrophysiological findings to symptomatic sensory deficits with decreased SNAP amplitudes. Decreases in the SNAP amplitudes, increases in the SNAP duration and the temporal dispersion pattern observed at the early clinical stage in FS provide evidence that a mild demyelinating process is involved, at least in part, in this postinfectious polyneuropathy.

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

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INTERNAL MEDICINE

□ CASE REPORT □

Chronic Inflammatory Demyelinating Polyneuropathy Due to the Administration of Pegylated Interferon α-2b: A Neuropathology Case Report

Kensuke Shiga[1], Eijiroh Tanaka[1], Reina Isayama[1], Toshiki Mizuno[1], Kyoko Itoh[2] and Masanori Nakagawa[1]

Abstract

We report a 35-year-old man who developed weakness in his extremities five months after pegylated interferon α (IFNα)-2b was administered. The serum tumor necrosis factor-α (TNFα) was elevated and nerve conduction studies revealed demyelination both in the distal and intermediate segments. The sural nerve pathology showed mild demyelinating process. The cessation of IFNα and administration of intravenous immunoglobulin improved both his clinical symptoms and the temporal dispersion in motor nerve conduction study. IFNα-induced CIDP is presumably a transient immunological condition that requires immunomodulatory therapy. The elevated serum TNFα may implicate the degree of downstream autoimmunitiy induced by IFNα.

Key words: chronic inflammatory demyelinating polyneuropathy, interferon α-2b, adverse effect, immunoglobulin

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Introduction

Interferons comprise an evolutionarily conserved family of secreted proteins that participate as extracellular messengers in a variety of responses, including antiviral, antiproliferative, and immunomodulatory properties that maintain host defense systems and homeostasis (1). The administration of interferon alpha (IFNα) is commonly used as the first-line therapy for patients with chronic viral hepatitis because of its antiviral effects (2). On the other hand, autoimmunity is a well-recognized complication of IFNα therapy, with reported frequencies ranging between 4.3% and 18.5% in large observational studies (3-5). Neuropathies due to administration of IFNα are a rare complication (3, 4); however, eight distinct case reports have shown that chronic inflammatory demyelinating polyneuropathy (CIDP) can result from administration of IFNα, presumably due to perturbations in the host immune system (6-13). We here report a biopsy-proven case with IFNα-induced CIDP in which the serum value of tumor necrosis factor-α (TNFα) was elevated. The correlation between the anatomical distribution of demyelination and the serum value of TNFα was discussed.

Case Report

A 35-year-old man was admitted to our facility because of progressive weakness and numbness in his extremities five months after the antiviral therapy was initiated to treat chronic type C hepatitis using pegIFN α-2b and ribavirin. At first, he felt subtle numbness in his toes and fingers. Two months later, the tingling sensations gradually spread to his soles and palms, and he began to have difficulty climbing upstairs. In the following month, he became unable to screw caps of bottles or button up his shirts. Five months after the beginning of his neurological symptoms he was referred to our department, at which point the referred neurologist discontinued pegIFN α-2b and ribavirin due to the possible ad-

[1]Department of Neurology, Kyoto Prefectural University of Medicine, Japan and [2]Department of Molecular Pathology, Kyoto Prefectural University of Medicine, Japan
Received for publication August 3, 2011; Accepted for publication October 7, 2011
Correspondence to Dr. Kensuke Shiga, kenshiga@koto.kpu-m.ac.jp

Table 1. Summary of Nerve Conduction Studies on Admission

	left median	left ulnar	left tibial
DL (ms)	5.2* (< 4.2)	4.4* (< 3.4)	4.8 (< 6.0)
CMAP (mV)	4.4 (> 3.5)	4.8 (> 2.7)	5.7 (> 2.9)
MCV (m/s)	24.7* (> 48)	33.6* (> 49)	43.6 (> 41)
min F-latency (ms)	54.8* (< 31)	49.2* (< 32)	70.8* (< 58)
F occurrence (%)	56.0	50.0	43.6* (> 93)

	left median	left ulnar	left sural	right sural
SNAP (μV)	n.e.* (> 19)	1.8* (> 19)	10.9 (> 8.3)	15.3 (> 8.3)
SCV (m/s)	(< 47)	19.2* (< 44)	53.1 (< 48)	55.1 (< 48)

DL: distal latency, CMAP: compound muscle action potential, MCV: motor conduction velocity, SNAP: sensory nerve action potential, SCV: sensory conduction velocity. MCVs were calculated between wrist and elbow in the median and ulnar nerves and between ankle and popliteal fossa in the tibial nerve. SCVs were measured between index finger and wrist in the median nerve and between ring finger and wrist in the ulnar nerve. The sural SCV was calculated between posterior calf and the lateral foot. Asterisks indicate abnormal values. n.e.: not elicited. The values in parentheses indicate normal value in each parameter in our facility.

verse side effects. However, the cessation of pegIFN α-2b did not alleviate the weakness or the numbness in his extremities, and he was admitted to our facility. On neurological examination, the patient was alert and cranial nerves were intact. His muscle bulk was preserved and no fasciculation was observed. His Medical Research Council (MRC) scores were as follows: deltoid, 5; biceps brachii, 4; triceps brachii, 5; wrist extensors and flexors, 4; iliopsoas, 5; quadriceps femoris, 5; tibialis anterior, 3; extensor hallucis longus, 3. The patient complained of paresthesia in a stocking-and-glove distribution. Pinprick and vibration sensation were decreased in his toes and fingers. The deep tendon reflexes were diminished. Bilateral plantar reflexes were flexor. Neither orthostatic hypotension nor dysuria was evident.

The urine analysis, the complete blood count and the biochemical analysis were normal. Serum M-protein was negative by means of immunoelectrophoresis. Also, serum antibodies against glycolipids, including GM1, GM2, GM3, GA1, GD1b, GD3, GT1b, GQ1b, and galactocerebroside-C were negative. The antibody against α-2b was negative. It is noteworthy serum tumor necrosis factor-α was elevated at 9.2 pg/mL (normal value; 0.6-2.8 pg/mL). The protein level in the cerebrospinal fluid (CSF) was slightly elevated at 50 mg/dL, while the number of CSF cells was 3/mm^3. The results of the nerve conduction studies are shown in Table 1. In the motor nerve conduction studies, the distal motor latencies were prolonged; 5.2 ms and 4.4 ms in the left median and left ulnar nerves, respectively. The motor nerve conduction velocities were markedly reduced; 24.7 m/s and 33.6 m/s, in the left median and in the left ulnar nerve, respectively. One notable finding was a temporal dispersion of the compound muscle action potentials (CMAPs) of the left median nerve at the elbow, while the distal CMAP was relatively unaffected following stimulation at the wrist (Fig. 1A). A similar dispersion pattern was also observed in the right median and the left tibial nerves (data not shown). The sensory nerve action potentials (SNAPs) were not elicited or were only barely elicited in the left median and left ulnar nerves, respectively, whereas the SNAP in the right sural nerve and that in the right counterpart was 15.3 μV and 10.9 μV, respectively. Over the following three weeks, the SNAP in the right sural nerve was reduced from 15.3 μV to 3.6 μV. A nerve biopsy was then performed on the right sural nerve and the teased fiber analysis revealed mild demyelinating pathology, including myelin wrinkling, segmental demyelination and remyelination (Fig. 2A). On toluidine blue-stained, semi-thin sections, the number of large myelinated fibers was slightly decreased and variably thinned myelin sheaths were scattered (Fig. 2B, thin arrows). In contrast, both the axons and unmyelinated nerve fibers were relatively preserved. Invasion of macrophages into the endoneurium was also demonstrated (Fig. 2B, thick arrow). A myelinated fiber (Fig. 2C, arrow) showed electron-dense materials which looked like lysosomes (Fig. 2C, small arrowhead, inset) situated in the Schwann cytoplasm at the node of Ranvier. Another myelinated fiber showed lamellated body in the Schwann cytoplasm (Fig. 2C, large arrowhead). Axons were well preserved in myelinated fibers (Fig. 2C, asterisks). The results of the nerve conduction and the pathological evidence of mild demyelination led us to diagnose him as having CIDP.

To determine any possible improvement after the cessation of pegIFN α-2b, the patient was observed for three weeks without any additional treatment; however, the weakness in the patient's legs further deteriorated. High-dose intravenous immunoglobulin (IVIG; 0.4 mg/kg/day for five consecutive days) was then administered. Within a week after the administration of IVIG, both the averaged hand grip and the neuropathy disability scores (NDS) (14) recovered to a remarkable extent; however, weakness in the extremities started to deteriorate in three weeks. Two additional courses of IVIG were administered during the following two months; the patient's neurological status showed marked improvement within a week following each administration (Fig. 3). The fourth administration of IVIG was canceled due to a moderate elevation in the levels of liver enzymes, probably an adverse effect of immunoglobulin administration. Fortunately, both the hand grip and NDS showed a

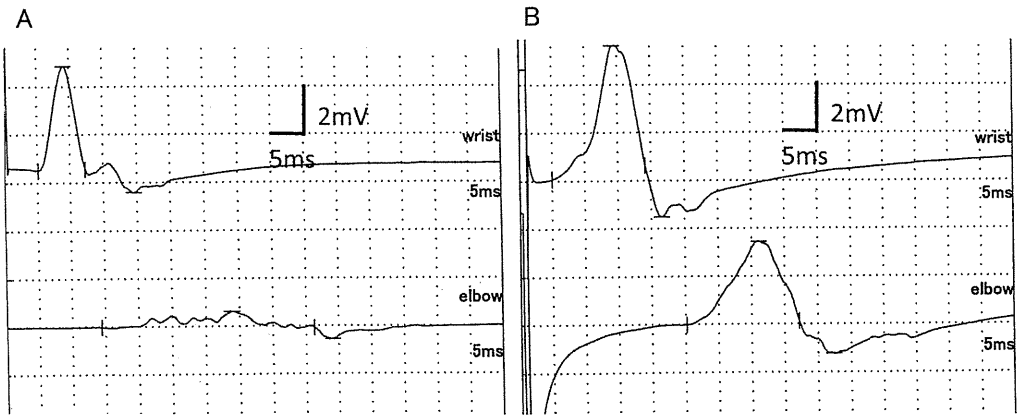

Figure 1. A. Results of the motor conduction study performed on the left median nerve upon admission (five months after onset). The compound muscle action potentials (CMAP) elicited at the elbow shows a marked temporal dispersion, suggesting uneven demyelination between the wrist and elbow. The dispersion pattern and duration of the CMAP was almost the same at the axilla. B. Results of the motor nerve conduction study performed on the left median nerve after three courses of high-dose IVIG therapy (eight months after onset). The CMAP elicited at the elbow shows marked improvement in terms of the dispersion pattern, although the latency period is prolonged compared to Fig. 1A, which is suggestive of a remyelination process.

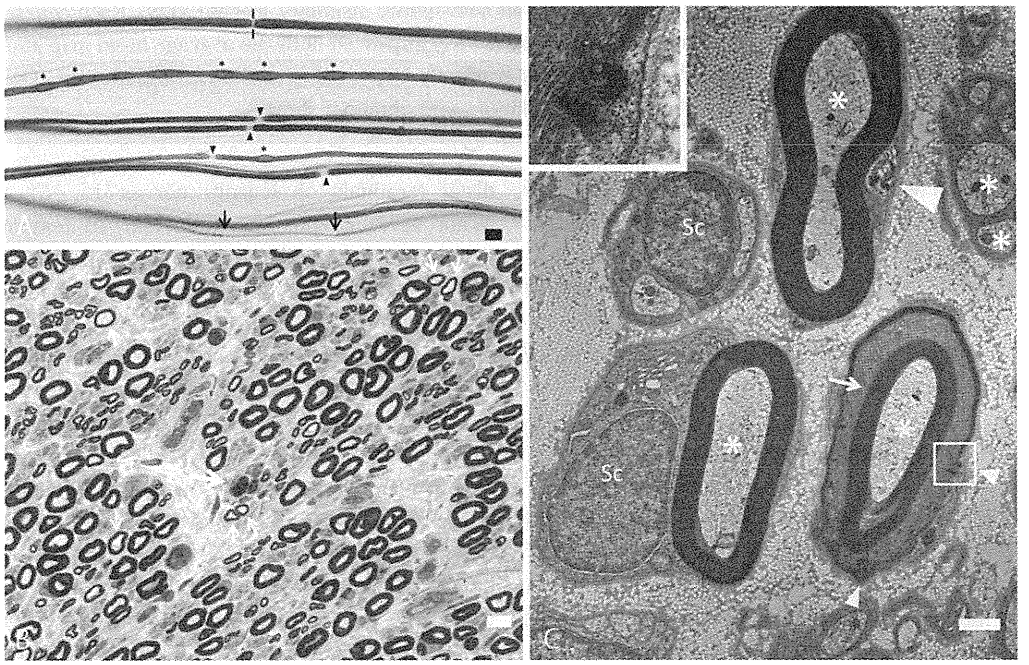

Figure 2. A. Teased fiber specimen. The pair of short longitudinal lines (top) indicates the normal hiatus of Ranvier node. The asterisks indicate wrinkling of myelin. The small arrowheads indicate segmental demyelinations or the widening of Ranvier node. The arrows on the nerve (bottom) indicate the shortening of the intermodal segment of the remyelinated nerve. Bar=10 μm. B. Sections of the sural nerve showing a large number of variably thinned myelin sheaths (thin arrows) and macrophages invading into the endoneurium (thick arrow). Toluidine blue-stained semi-thin section. Bar=10 μm. C. At the Schmidt-Lanterman incisure (arrow), irregularly shaped electron-dense materials (small arrowhead) were found in the cytoplasm of the Schwann cells (Sc). Other Sc show electron-dense granules and myelin-like materials in the cytoplasm (large arrowhead). The axons were well preserved in both the myelinated and unmyelinated fibers (*). Bar=2 μm.

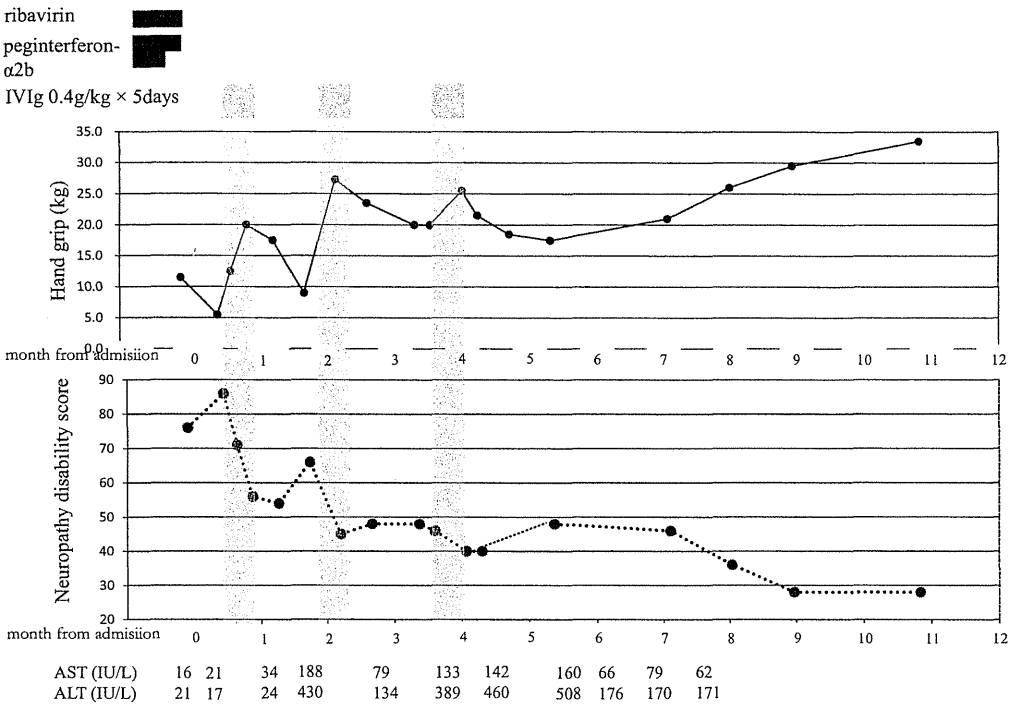

Figure 3. The clinical course of the patient based on two neurological indices that were measured over the course of one year; average hand grip and neuropathy disability scores (NDS). Each course of high-dose intravenous immunoglobulin therapy (IVIG) improved both the average hand grip and NDS. After the third course of IVIG, the indices gradually improved over the ensuing months. The patient's neurological status has been stable for three years (data not shown).

gradual improvement without further administration of IVIG (Fig. 3). Follow-up NCS revealed improved synchronization of the CMAP at the elbow (Fig. 1B), indicating a remyelination process at this segment. The patient did not require further maintenance therapy, such as oral prednisone or immunosuppressants, and he has been free of neurological symptoms for three years.

Discussion

We reported the clinical characteristics of a patient with CIDP whose symptoms started one month after the administration of pegIFN α-2b and gradually worsened over the subsequent five months. The patient's neurological status did not improve after the discontinuation of pegIFN α-2b, whereas the subsequent administration of IVIG resulted in rapid improvement of the patient's motor weaknesses. Two additional courses of IVIG were required during the following months; however, no maintenance therapy was needed for three years.

The results of nerve conduction studies indicated that the demyelinating process involved both the distal and the intermediate segments of the nerve trunks for the following reasons. First, the sensory nerve conduction study revealed decreased SNAPs in the median and the ulnar nerves and a relatively unaffected SNAP in the sural nerves: this pattern, called an abnormal median and normal sural sensory response (AMNSSR) pattern, indicates demyelination in the distal terminals of sensory nerves (15, 16). Secondly, the motor nerve conduction study showed temporal dispersion within the intermediate segments of the median (Fig. 1A) and tibial nerves, indicating that the demyelination process also involved the intermediate nerve segments. In other words, the demyelination occurred in both the distal and intermediate segments; thus, the condition was classified as the diffuse type, according to the regional classification of CIDP (15).

Kuwabara et al reported that the serum value of tumor necrosis factor (TNF)-α is elevated only in patients with the diffuse type, among the three regional variatns of CIDP (15). In the patient described here, the serum TNF-α value was three fold the upper limit of the normal value. TNF-α, a proinflammatory cytokine, is secreted from T-cells and macrophages and exerts toxic effects on peripheral myelin and endothelial cells (17). The sural nerve pathology of this patient indicated extravasation of macrophages into the endoneurium (Fig. 2B), which is possible evidence of breakdown of the BNB and activation of macrophages within the intermediate nerve segment. It can therefore be speculated that exogenous IFNα might have induced the release of adhesion molecules or cytokines, such as TNF-α, leading to the possible breakdown of the BNB and migration of macrophages into the endoneurium.

In studies on IFNα-related complications, therapy-related neuropathies were reported in only 3 of 11,241 patients with hepatitis C in one study (3) and in 0 of 987 patients in an-

other study (4); thus, therapy-related neuropathies are considered a rare complication of IFNα treatment. Nevertheless, seven distinct cases of CIDP have been reported after the administration of a variety of IFNα species, including IFNα (6-9), pegIFN α-2a (10), and pegIFN α-2b (11, 12). The interval between the administration of IFNα and the onset of CIDP ranged from 3 weeks to 11 months. Among these cases, three cases were observed following the absence of therapeutic intervention for up to 6 weeks (6, 7, 11); however, the neurologic symptoms deteriorated in all of these cases, similar to the present patient. It seems that once a causative immunologic trigger is initiated, the pathologic process leading to demyelination is not interrupted even if IFNα is discontinued. Autoimmunity, once induced by IFNα, may trigger multiple downstream mechanisms, including the increased expression of MHC class I antigens and stimulation of the transcription of cytokines (including TNF-α), leading to the activation of lymphocytes, macrophages, and natural killer cells (2). Among the six reported cases of IFN-α-induced CIDP, three cases were classified as the diffuse type and three cases the intermediate type, suggesting the breakdown of BNB within the intermediate segments in IFN-α-induced CIDP and possible involvement of TNF-α in the pathogenesis of demyelination.

On the other hand, however, a favorable outcome was reported in all of the reported cases of IFNα-induced CIDP when the patients were treated with any of the standard therapies for CIDP, including oral steroids (6, 8), plasma exchange (7, 11), or IVIG (8-10, 12). In the present case, three courses of IVIG were administered, but no maintenance immunomodulatory therapy was needed. In the reported cases of IFNα-induced CIDP, a few of relapses occurred; however, no single case required the administration of prednisone or immunosuppressants. These features imply that IFNα-induced CIDP is a transient condition that requires a certain period of immunomodulatory therapy, but does not require the administration of a long-term maintenance therapy.

Conclusion

Here, the clinical characteristics of a patient with CIDP due to administration of pegIFNα-2b are reported. IFNα-induced CIDP is, in general, a benign and transient condition; however, immunomodulatory therapy is required to reverse the demyelinating process once it develops. The measurement of the serum TNFα may be useful to assess the degree of autoimmunity in IFNα-induced CIDP.

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

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(会)

遺伝性ニューロパチーの臨床的、遺伝学的研究：自験例60例の検討*

中川 正法[1)], 滋賀 健介[1)], 能登 祐一[1)], 水田依久子[1)], 橋口 昭大[2)], 髙嶋 博[2)]

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目 的

遺伝性ニューロパチーには、Charcot-Marie-Tooth病（CMT）、hereditary motor neuropathy、familial amyloid neuropathy（FAP）など種々の疾患が知られているが、その確定診断には遺伝子診断が不可欠である[1)]。今回、自験例60例について、遺伝子診断を行い臨床病型との関連を検討した。

対象・方法

対象は臨床的に遺伝性ニューロパチーが疑われた60例（男34例、女26例）である。臨床症状、電気生理学的検査所見から脱髄型CMTが疑われた場合は*PMP22*重複または欠失の有無をFISH法で検討した。FISH法で異常を認めなかった例および軸索型CMTが疑われた例は、CMT遺伝子解析用DNAチップを用いて遺伝子解析を行った。遺伝子変異の確認のために、*MPZ*、*GJB1*、*MFN2*、*DNMT1*、*TTR*、*TFG*の直接塩基配列解析を行った。12歳未満の1例を除く59例から本人自身の同意を得て遺伝子解析を行った.

結 果

臨床症状、遺伝形式および電気生理学的検査所見に基づいて、脱髄型CMT（CMT 1、4、CMTX）と軸索型CMT（CMT2）に分類した。CMT1型31例中CMT1Aが24例で、男13例、女11例、平均年齢52 ± 16歳、平均発症年齢33 ± 24歳であった。車いすを使用している例はなかった。CMT1Aの59歳男性と70歳女性が経過中にCIDPを疑われていた。CMT2型は、男11例、女9例、平均年齢50 ± 19歳、平均発症年齢31 ± 23歳であった。車いす使用は3例でCMT1型例よりも重症例が多い傾向がみられた。CMT2型の70歳女性が経過中にCIDPを疑われて、IVIg治療を受けていたが改善はみられていない。CMT1型と2型の発症年齢は両型ともに20歳以下の発症が過半数であったが、50歳台にもピークがあり発症年齢に二峰性を認めた。

遺伝子解析では、*PMP22*重複が24例（40%）と最も多く、*NFL*変異3例、*MFN2*変異3例、*EGR2*変異2例、*MPZ*変異2例、*DNMT1*変異1例[2)]、*TTR*変異1例、*TFG*変異1例[3)]など計43例に遺伝子異常を認めた（表）。未確定例が17例（28%）であったが、CMT2型の20例中11例（55%）で検索した限りでは遺伝子異常がみつからなかった点が特徴的であった。

考 察

これまでCMT疑い例の半数以上で遺伝子異常が未同定であると報告されているが[4)]、今回の自験例の検討ではCMT1の約8割、CMT2の約3割の症例で遺伝子異常が明らかとなった。これは、新たな原因遺伝子の発見と解析技術の向上によるものと考える。原因遺伝子未確定例が約3割であり、今後、エキソーム解析を含めた詳細な検討を計画している。

遺伝性ニューロパチーが疑われた場合には、

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* Clinical and genetical study of hereditary neuropathy: 60 case analysis.

[1)] Masanori NAKAGAWA, M.D., Kensuke SHIGA, M.D., Yuichi NOTO, M.D. and Ikuko MIZUTA：京都府立医科大学神経内科［〒602-0841 京都市上京区河原町通広小路上ル梶井町465］; Department of Neurology, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto

[2)] Akihiro HASHIGUCHI and Hiroshi TAKASHIMA：鹿児島大学医学部神経内科・老年病学［〒890-8520 鹿児島市桜ヶ丘8-35-1］; Department of Neurology and Geriatrics, School of Medicine, Kagoshima University, Kagoshima

表. 自験例 60 例の臨床病型と遺伝子異常

臨床病型	症例数（%）	遺伝子異常	症例数（%）
CMT1	31 (52)	*PMP22* 重複	24 (40)
		EGR2	2 (3.3)
		MPZ	2 (3.3)
		NFL	1 (1.7)
CMT2	20 (33)	*MFN2*	3 (5.0)
		ARGEF10	3 (5.0)
		NFL	3 (5.0)
CMT4	3 (5.0)		
CMTX	1 (1.7)	*GJB1*	1 (1.7)
HNPP	1 (1.7)	*PMP22* 欠失	1 (1.7)
FAP	1 (1.7)	*TTR*	1 (1.7)
HMSN-P	1 (1.7)	*TFG*[3]	1 (1.7)
HSN	1 (1.7)		
認知症、運動失調、難聴を伴う Neuropathy	1 (1.7)	*DNMT1*[2]	1 (1.7)
		未確定	17 (28)
合計	60		60

臨床症状、家系調査および電気生理学的検査を行い、遺伝子解析の同意が得られた場合は、新規原因遺伝子同定の最新の情報を踏まえた積極的な原因遺伝子の解明が必要であると考える。

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CMT1A患者に対するアスコルビン酸治療の効果：軸索興奮性測定による治療前後評価を中心に*

能登　祐一，滋賀　健介，藤井ちひろ，
辻　有希子，中川　正法

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目　的

Charcot-Marie-Tooth 病（CMT）は、臨床的、遺伝的に多様な疾患であり、多くの原因遺伝子が明らかになってきているが、有効な治療法の確立が求められている。アスコルビン酸、クルクミン投与などが新たな治療として注目されているが、有効性は未だ証明されていない。また、Noderaらは、CMT1A患者に対し、軸索興奮性測定を行い、K^+チャネルの機能亢進、軸索興奮性の低下の所見を報告している[1]。

我々の施設を中心に本邦で行ったCMT1A患者に対するアスコルビン酸投与試験では、投与群では、投与前に比較して右握力が有意に改善したという結果を得ているが、CMT neuropathy score（CMTNS）や神経伝導検査におけるCMAPなどのパラメーターに関して有意差は得られなかった。当科にてアスコルビン酸治験に参加したCMT1A患者に対しては、握力など臨床症状の評価に加え、正中神経にて軸索興奮性測定による軸索機能評価を行っており、今回我々は、アスコルビン酸投与前後での軸索機能変化について検討する。

対象・方法

対象は当科にてアスコルビン酸投与（20/kg/日）後、１年間以上経過を追えたCMT1A患者７名（男性５名、女性２名）。アスコルビン酸投与前、投与後12週間、48週間（１年）の時点で、握力を含めた神経学的評価と、非利き手の正中神経の運動成分におけるQTRAC programを用いた軸索興奮性測定を行い、投与前後での短期（投与後12週）と長期（投与後48週）での各パラメーター変化を解析した。

結　果

アスコルビン酸投与前、投与後短期、長期での３回の軸索興奮性測定の全プログラムがエラーなく遂行できたのは７名中４名であった。投与前の評価では、正常コントロール群のデータと比較して、Stimulus-response curveからは目標のCMAP振幅を得るための刺激強度が著しく増大し、電気緊張閾値法（Threshold electrotonus）では大きな閾値変化（fanning-out）とfast K^+チャネル、内向きK^+チャネルの機能亢進、の所見を認めた。投与後短期の評価では、電気緊張閾値法にて、統計学的有意差は認めなかったが、投与前と比較してfanning-outの程度が小さくなった。長期の評価では、Stimulus-response curveにおいて、治療前と比較して必要刺激強度の増大の程度が小さくなる所見を得たが、電気緊張閾値法でのfanning-outの程度の変化は短期のほうがより目立つ結果であった。

若年群（２名）と高齢群（２名）に分けたサブ解析では、投与後48週の時点で、若年群はfanning-outの程度の改善を維持するものの、高齢群では、投与後12週の評価に比しfanning-outの程度が再度大きくなった。

考　察

今回我々の得た結果は、CMT1A患者の神経軸索特性であるparanode部の脱髄による軸

* Ascorbic acid in Charcot-Marie-Tooth disease type 1A: nerve excitability assessment.

Yu-ichi NOTO, Kensuke SHIGA, Chihiro FUJII, Yukiko TSUJI, Masanori NAKAGAWA：京都府立医科大学大学院医学研究科神経内科学［〒602-0841 京都市上京区河原町通広小路上る梶井町465］；Department of Neurology, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto

索膜のcapacitanceの増大を、アスコルビン酸治療により改善させうる可能性を示唆するかもしれない。サブ解析からは、アスコルビン酸治療は若年患者への神経軸索改善効果がより大きい可能性があり、今後、多数例での検討が必要である。

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(会)

シャルコー・マリー・トゥース病患者を対象とした自己記入式アンケート調査結果*

滋賀　健介，能登　祐一，中川　正法

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目　的

シャルコー・マリー・トゥース病（CMT）は、遠位優位の筋萎縮・筋力低下を主症状とする進行性の遺伝性ニューロパチーである。「進行は緩徐で軽症疾患である」との必ずしも正しくない認識から、医師や患者自身が継続診療を中断する場合も多く、長期的な実態把握は十分ではない。今回、医療機関を通じて自己記入式アンケートを施行し、CMTの実態把握を行ったので報告する。

対象・方法

2010年に施行した全国神経内科学会・小児科学会・足の外科学会教育関連施設に対して行ったアンケート調査[1]で、1人以上のCMT患者を診療していると回答した244施設を対象とした。該当施設に通院中のCMT患者に自己記入式アンケートの配布を依頼し、患者あるいは家族に回答してもらった。アンケートの内容は、年齢・就労状態・発症年齢・初発症状・家族歴・現在のADL（推定modified Rankin Scale、以下mRS）・しびれや痛みの有無・受けている医療処置・通院頻度などである。mRS=2については、2a（自立し、動作も遅くない）と2b（自立しているが動作には時間を要する）に二分した[2]。なお、本研究は京都府立医科大学倫理委員会の承認を得て行った。

結　果

（1）計131名から回答を得た。患者の年齢は3歳～81歳（中央値52歳）、男性71名・女性60名であった。

（2）発症年齢は平均27.1 ± 20.0歳、中央値は22歳。20歳未満に発症した患者が46.9%を占めたが、40歳台にもピークがある二相性分布を示した（図1a）。初発症状については、下肢症状（76.2%）、上肢症状（16.4%）、上下肢同時（5.7%）と約3/4が下肢症状で発症していた。処女歩行が遅れていた患者は全体の26.2%であった。

（3）患者のADL・就労状況について：推定mRSは、0（2.3%）、1（20.0%）、2a（17.7%）、2b（26.9 %）、3（9.2 %）、4（20.8%）、5（3.1%）であった。就労状況等については、就労中（35.7%）、休職中（11.9%）、就労をあきらめている（16.9%）、主婦（15.1%）、就学（8.7%）、就学前（1.6%）であった。就労状況別のmRS中央値は、就労中の患者は2a、休職中の患者は2b、就労をあきらめている患者は3であった。一方、就労中のCMT患者の22.2%はmRS3-4であった（図1b）。

（4）自分のCMT病型について知っている患者は全体の31.3%であった（CMT1は57.1%、CMT2は34.3%、CMT-Iは8.6%）。

（5）痛みがある患者は48.8%、しびれがある患者は56.8%であった。医療機関への受診間隔の中央値は3カ月で、受けた医療処置で多いものとしては、短下肢装具（44.3%）、杖（37.4%）、下肢リハビリ（40.5%）であった。

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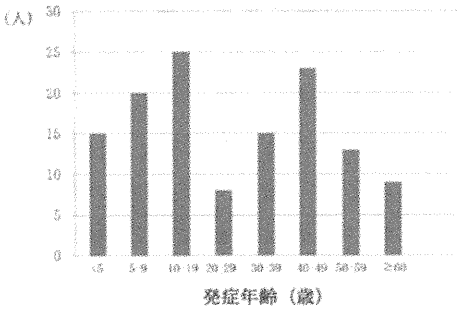
* Questionnaire on clinical profiles for patients with Charcot-Marie-Tooth disease.

Kensuke SHIGA, Yu-ichi NOTO and Masanori NAKAGAWA：京都府立医科大学医学部神経内科［〒602-8566 京都市上京区梶井町465］；Department of Neurology, Kyoto Prefectural University of Medicine, Kyoto

(a) 発症年齢分布



(b) 就職状況別の推定modified Rankin Scale

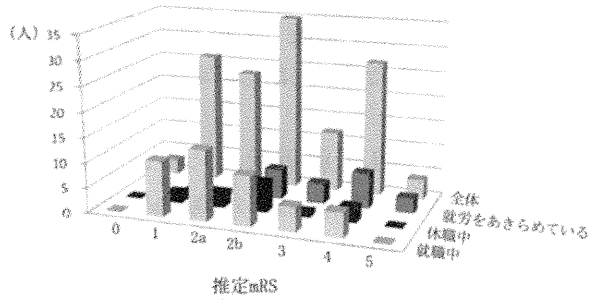


図1

考　察

欧米のCMT1Aに関する報告では、10歳までに発症する患者の占める割合は50–75%[3),4)]とされているが、本調査結果では27.3%と比較的高齢発症者が多かった。欧米の報告と比べて若年発症者が少ない原因としては、人種による発症年齢の違いが関与している可能性や、CMT1A以外のCMTの影響が考えられる。患者のADLは、mRS 4=20.8%、mRS 5=3.1%と車椅子を利用する患者が約20%を占めていた。これまでの医療機関アンケートやCMT患者会へのアンケート[1)]とも一致する結果であるが、欧米の報告にくらべると（mRS 4=0–2%、mRS 5=0%）[2),5)]、重症患者が多いのが特徴であった。また今回の調査で、患者のADLが就労状況に影響していることが明らかとなった。今後CMTの就労支援を考えていく上で重要であると考える。

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1) Charcot-Marie-Tooth 病に対する治療の進歩

京都府立医科大学大学院医学研究科神経内科学教授　中川正法

key words　diagnosis of CMT, medicinal therapy, surgical therapy, rehabilitation, social welfare, Mechanism-Based Therapeutic Strategies

要　旨

シャルコー・マリー・トゥース（Charcot-Marie-Tooth: CMT）病は，最も頻度の高い遺伝性ニューロパチーであり世界の患者数は約260万人と推定されている．CMTは運動神経伝導速度に基づいて，脱髄型，軸索型，中間型に大別される．一般的に生命的予後はよいが，厚労省研究班報告では車椅子使用患者は約20%，寝たきり患者は1%とされている．CMTの原因遺伝子は40種類以上が特定され，CMTの遺伝子診断は大きく進展している．今後は次世代シークエンサーを用いた解析が主流になる．CMT1Aに対するアスコルビン酸臨床試験が国内外で行われたが，その有効性は確認できなかった．*PMP22*の発現抑制化合物を機械的にスクリーニングする方法が開発されている．Network pharmacologyによる新しい治療薬開発法が注目されている．最近，モデル動物を用いたバイオマーカーや治療法の研究が進んでいる．CMT患者250人に1人がCIDP様の炎症性ニューロパチーを発症すると推定されている．わが国を中心にロボットスーツ「HAL」の医師主導臨床治験が計画されている．外科的治療，リハビリテーション，装具療法，日常生活上の工夫もCMT患者の機能維持・改善にとって重要である．

動　向

CMTの原因遺伝子は40種類以上が特定され，CMTの遺伝子診断は大きく進展している．今後は次世代シークエンサーを用いたエキソーム解析が主流になる．CMT1Aに対するアスコルビン酸臨床試験が国内外で行われたが，その有効性は確認できなかった．*PMP22*の発現抑制化合物を機械的にスクリーニングする方法が開発されている．Network pharmacology（ネットワーク薬理学）というバイオインフォマティクスに基づく新しい治療薬開発法が注目されている．このネットワーク薬理学からデザインされたCMT1Aの治療法開発が進められている．最近，動物モデルでのバイオマーカーや治療法に関する研究が進んでいる．TrkB･TrkC作動性抗体とTremblerJ マウス，間葉系幹細胞と脱髄性CMT，CMT1AとWlds，CMT2EとテトラサイクリンCMTX1とColony-stimulating factor-1，CMT2F/distal HMN2B と HDAC6 阻害薬，CMT2Bとバルプロ酸などの研究が注目される．抗癌化学治療薬の投与により末梢神経障害が顕在化し，CMTの遺伝子変異が明らかとなった例が

報告されている．抗腫瘍薬投与前の神経伝導検査の実施は，末梢神経障害の重症化を防ぐ点で可能な限り推奨される．CMT患者250人に1人がCIDP様の炎症性ニューロパチーを発症すると推定されている．CMT患者で臨床症状の急性悪化を認めた場合には，CIDPの治療法に準じた対応を考慮してよいかもしれない．わが国を中心にロボットスーツ「HAL」の医師主導臨床治験が計画されている．外科的治療，リハビリテーション，装具療法，日常生活上の工夫もCMT患者の機能維持・改善にとって重要である．厚労省難治性疾患克服研究事業として，シャルコー・マリー・トゥース病に関する研究班が組織されている．

A. CMTの臨床症状と遺伝子診断

シャルコー・マリー・トゥース（Charcot-Marie-Tooth: CMT）病は，1886年にJM. Charcot, P. Marie, HH. Toothによって報告された最も頻度の高い遺伝性ニューロパチーであり，すべての民族に認められる．CMTの有病率は，欧米ではこれまで2500人に1人といわれてきたが[1]，最近の疫学調査でも人口10万人対9.7～82.4人とその頻度は高い[2-6]．わが国では人口10万人対10.8人との報告があるが[7]，実際の有病率はより高いと推定される．

CMTは一般的に0～20歳頃までに発症する緩徐進行性の疾患である．厚労省難治性疾患克服研究事業報告によれば，車椅子使用患者は約20%，寝たきり患者は1%とされている[8]．原因遺伝子の解明にともない中枢神経障害を含む多様な臨床症状が明らかとなってきた．CMTは正中神経の運動神経伝導速度（MNCV）38m/秒を基準に，脱髄型（CMT1/CMT4），軸索型（CMT2），中間型（Intermediate-CMT）に大別される．CMTの原因遺伝子は40種類以上が特定され（http://www.molgen.ua.ac.be/CMTMutations）[9,10]，わが国においてもCMTの遺伝子診断に関しては大きな進展が見られている[11]．Choiらは，エキソーム解析法により通常のDNA解析法では異常を見いだせなかった25例中8例（32%）に遺伝子異常を検出したと報告した．エキソーム解析はCMT患者の遺伝子異常をより迅速，低コスト，かつより正確に見いだすことが可能であり，今後は次世代シークエンサーを用いたエキソーム解析が主流になると考えられる[12]．

B. CMTに対する薬物治療

遺伝子診断が不十分な時代のCMT治療研究として，Cronassial筋注（ガングリオシド製剤），linoleic/γ-linoleic essential fatty acids, vitamin E, coenzyme Q10, modafinilなどの使用報告がある[13]．いずれの研究も十分な規模の無作為化比較対照試験（randomized controlled trial: RCT）ではない．

1. CMT1Aの薬物療法

最も頻度が高いCMT1Aは*PMP22*の重複によって引き起こされる病態であり，*PMP22*はミエリン形成におけるSchwann細胞の分化制御に重要であり，その軸索-髄鞘相互作用に関与している．

2. アスコルビン酸臨床試験

アスコルビン酸は，後根神経節－Schwann細胞の培養系におけるmyelinationに必須であり，アスコルビン酸欠乏が大腿神経障害を引き起こすことが報告されている[14]．cAMPはCREBによる*PMP22*プロモーターへの結合を促進し，*PMP22*の発現を増加させるが，アスコルビン酸はこの結合を競合的に阻害することによって，*PMP22*mRNA発現量を低下させる可能性がある．アスコルビン酸がCMT1Aモデルマウスに有

効であるとの報告があり[15]，国内外で臨床試験が行われた．

厚生労働省精神神経疾患研究委託費「難治性ニューロパチーの病態に基づく新規治療法の開発」研究班のもとで，「Charcot-Marie-Tooth病1Aに対するアスコルビン酸の安全性・有効性に関する臨床試験」(UMIN試験ID: UMIN000001535）が投与群と非投与群によるオープン試験として行われた[16]．40例が本臨床試験に登録された．残念ながら，プライマリーエンドポイントであるCMT neuropathy score（CMTNS）に有意な改善はなくアスコルビン酸の有効性は確認できなかった．海外でのアスコルビン酸投与試験での結果もわが国の研究班の結果と同様にアスコルビン酸の有効性は証明されなかった[17-21]．しかし，Burnsらは，12カ月のアスコルビン酸RCT後に，12カ月の追加オープン試験（アスコルビン酸25～37mg/kg/day）を7～16歳の5例のCMT1A（男性4例，女性1例）患者に行い，CMAPは減少したが，四肢遠位部の筋力は有意に改善した．以上から，比較的軽症の若年CMT1Aにはアスコルビン酸の大量長期投与が有効である可能性が示された[22]．わが国の研究班で行った臨床試験でも，右握力は有意に改善しており，ある程度の効果はあるのではかと考えられる．現在，軸索興奮性を測定するQtracプログラム（ミユキ技研）を用いて非利き手正中神経運動神経の軸索興奮性を測定し，アスコルビン酸20mg/kg/日を12カ月間投与し，投与前後での変化を検討中である．

3. Neurotrophin-3 (NT-3)

Sahenkらは，CMT1A患者末梢神経をヌードマウスに直接異種移植し，神経栄養因子であるNT-3を皮下注射し，Schwann細胞増加と軸索再生が観察されることに基づいて，NT-3を4例のCMT患者に150 μg/kg/週3回，24週またはプラセボ投与を行った．その結果，NT-3投与群では末梢神経障害スコア（NIS）が改善し，再生軸索が増加したことを報告した[23]．この研究は，RCTで効果が示されている現時点で唯一の臨床研究であるが，少数例の検討であること，その後，この結果を再現する報告がなく，エビデンスレベルとしてはIbに留まっていること，運動機能の改善はなかったことなどの問題点がある．

4. プロゲステロン拮抗薬

プロゲステロンはSchwann細胞や神経細胞で産生され，*PMP22*，*MPZ*などの発現を促進し，CMT1A動物モデルの症状を悪化させること，プロゲステロン拮抗薬であるオナプリステロンがCMT1A動物モデルに有効であることが報告された[24]．しかし，オナプリステロンは肝毒性のためヒトに使用することはできない．一方，プロゲステロン刺激薬は*PMP22*，*MPZ*のmRNA発現を増加させる作用があり，ハプロ不全を示すhereditary neuropathy with liability to pressure palsies（HNPP）やnonsense-mediated mRNA decay関連*MPZ*変異CMTに有効であるかもしれない．この点に関する細胞レベルでの研究が必要である．

最近，培養細胞に*PMP22*を発現させ，その発現を抑制する化合物をオートマチックにスクリーニングするハイスループットな方法が開発されている[10]．

5. 点変異によるCMTの薬物療法

クルクミン

クルクミンは秋ウコンやカレー粉に多く含まれている自然の黄色色素である．Khajaviらは，クルクミンが変異PMP22蛋白を細胞膜へ解放し，変異*PMP22*発現によるアポトーシスを減少させることを報告した[25]．動物レベルにおいてもクルクミンは用量依存的に運動機能を改善し．坐骨

神経の軸索径を増加させ，Schwann細胞におけるアポトーシスを減少させている．以上の検討からクルクミンが*pmp22*点変異マウスに有効であることが示された[26]．Burnsらは，*PMP22*点変異（Ser72Leu）を有する15歳の白人女性にクルクミンを50 mg/kg/day（1500mg，250mg×6カプセル/分2）4カ月，その後，75 mg/kg/day（2500mg，250mg×10カプセル/分3）8カ月の計12カ月間，経口投与した．安全性に問題はなかったが，評価指標の改善はなかった．しかし，幸福感，満足感に関する自覚的な改善があったと報告している[27]．

6. バイオマーカーの開発

患者数が少ないCMTの場合，臨床試験デザインについても検討する必要がある[28]．最近の無作為化臨床試験では，皮膚生検による末梢神経の形態およびmRNA発現の評価が行われているが，今後，新しいサロゲートマーカーの開発も必要である．Fledrichらは，CMT1Aラットモデルの坐骨神経と皮膚組織のメッセンジャーRNA（mRNA）解析の結果から，*peroxisome proliferator-activated receptor gamma*などの脂質代謝に関わる遺伝子発現がCMTラットの重症度と関連することを見出した．さらに，46例のCMT1A患者の皮膚生検のRNA解析から，*glutathione S-transferase theta 2*と*cathepsin A*のmRNAレベルがCMT1Aの軸索障害のバイオマーカーになる可能性を示した[29]．

7. Network pharmacology

Network pharmacology（ネットワーク薬理学）というbioinformaticsに基づく新しい治療薬開発法が注目されている．このネットワーク薬理学からデザインされたCMT1Aの治療法開発が進められている[30]．パリにあるPharnext社がCMT1A 60例を対象にPXT3003（バクロフェン，ナルトレキソン，ソルビトールの合剤）の治験を2010年から行っている．この3剤の特徴は，すでに臨床現場で使用されている，通常用量の10～100分の1量を使用している，対象となったCMT1A 60例全例がこの3剤の本来の適応症となる疾患に罹患していないことである．2012年末には治験結果が発表される予定である．この治験の結果によっては，他のCMTに対してもネットワーク薬理学に基づく新たな創薬が期待される．

C. モデル動物を用いた治療法の開発の最近の進歩

CMTのモデル動物のよる研究も進展しており，脱髄型CMTでは約25種類の動物モデルが報告されている（http://www.molgen.ua.ac.be/CMTMutations）[31]．

Sahenkらは，TrkBとTrkCに対する作動性抗体がTremblerJ マウスの運動機能，電気生理所見，病理所見を改善すると報告している[32]．Lealらは，間葉系幹細胞は，ミエリン再生，神経保護的作用/抗アポトーシス作用，静注後障害部位に集積，炎症抑制作用などがあることから，CMT1Bを含む脱髄性CMTの治療として有望であると指摘している[33]．*Neurofilament light subunit gene*（*NF-L*）は，CMT2Eの原因遺伝子である．Dequenらは，hNF-L^{P22S}変異遺伝子とテトラサイクリン感受性遺伝子を発現させたトランスジェニックマウス（hNF-L^{P22S}; tTaマウス）に変異遺伝子の発現を抑制するドキシサイクリンを3カ月投与したところ，hNF-L^{P22S}; tTaマウスのCMT症状が改善したと報告している[34]．CMT1A，1B，および1Xではマクロファージが関与する軽度の炎症性変化がみられ，これらの疾患の脱髄や軸索障害に関与していることが示されている．Groh らは，CMTX1マウスとColony-