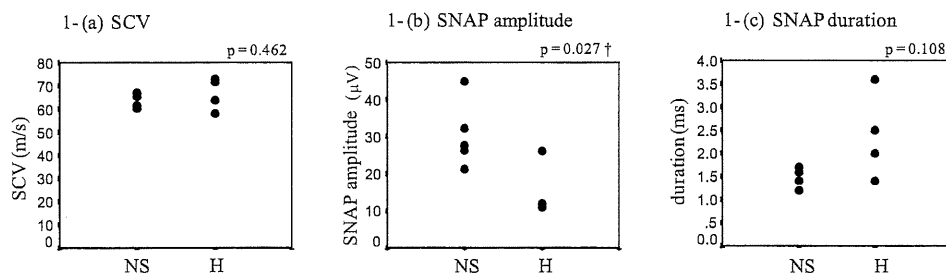


1. median nerve



2. sural nerve

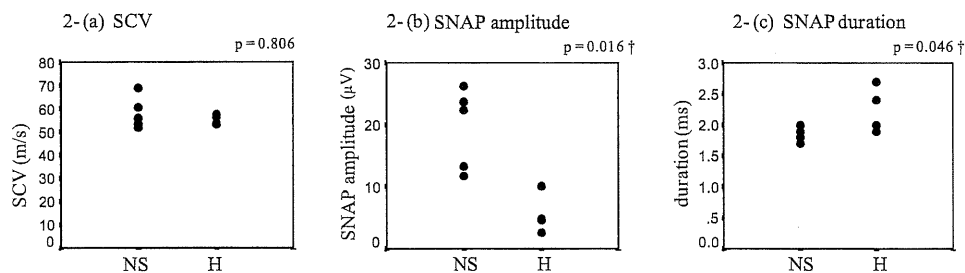


Figure 1. The three parameters of the sensory nerve conduction studies (SNCSs) performed on the median and sural nerves of the Fisher syndrome (FS) patients without hypesthesia (group NS, n=6) and those with hypesthesia (group H, n=4) were analyzed. 1-(a) and 2-(a): Sensory conduction velocities (SCVs) 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.

for 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

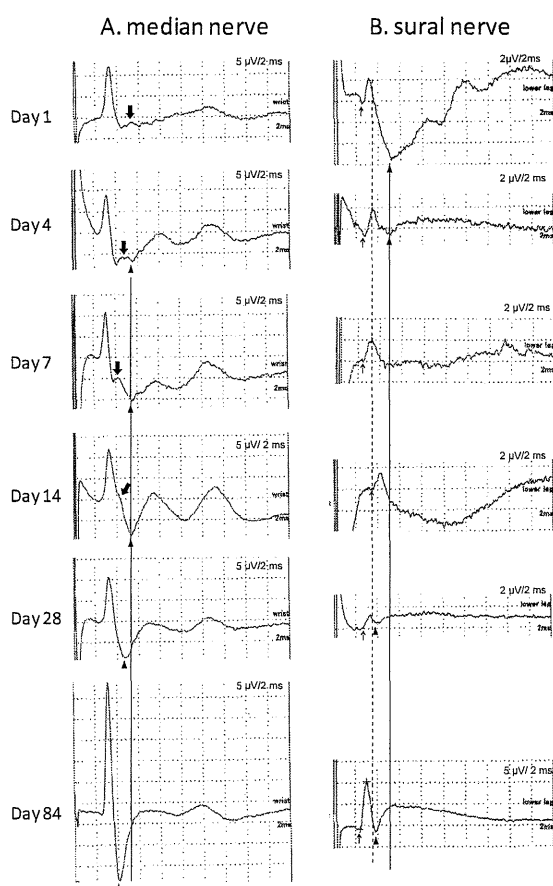


Figure 2. The time course of the sensory nerve conduction studies in the median nerve (A) and the sural nerve (B) of a patient with hypesthesia (case 9). A. The sensory nerve action potentials (SNAPs) in the right median nerve were recorded on days 1, 4, 7, 14, 28 and 84 (day 1 was defined as the day 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).

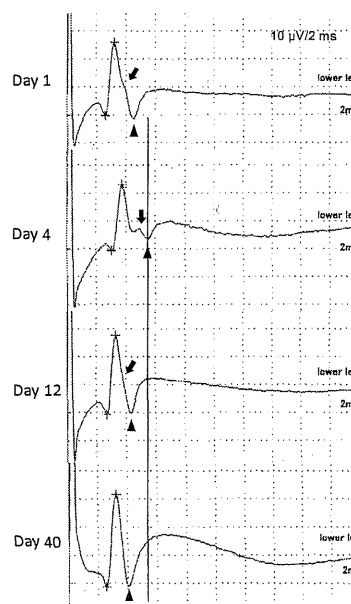


Figure 3. The time course of the sural nerve conduction studies performed in a patient without hypesthesia (case 5). The SNAPs of the right sural nerve were recorded on days 1, 4, 12 and 40 (day 1 was defined as the day of admission). The arrows indicate notches on the descending part of the sensory 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 SNCs 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 hypesthetic 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 resynchronization 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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Chronic Inflammatory Demyelinating Polyneuropathy Due to the Administration of Pegylated Interferon α -2b: A Neuropathology Case Report

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Abstract

We report a 35-year-old man who developed weakness in his extremities five months after pegylated interferon α (IFN α)-2b was administered. The serum tumor necrosis factor- α (TNF α) 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 IFN α and administration of intravenous immunoglobulin improved both his clinical symptoms and the temporal dispersion in motor nerve conduction study. IFN α -induced CIDP is presumably a transient immunological condition that requires immunomodulatory therapy. The elevated serum TNF α may implicate the degree of downstream autoimmunity induced by IFN α .

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 (IFN α) 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 IFN α therapy, with reported frequencies ranging between 4.3% and 18.5% in large observational studies (3-5). Neuropathies due to administration of IFN α are a rare complication (3, 4); however, eight distinct case reports have shown that chronic inflammatory demyelinating polyneuropathy (CIDP) can result from administration of IFN α , presumably due to perturbations in the host immune system (6-13). We here report a

biopsy-proven case with IFN α -induced CIDP in which the serum value of tumor necrosis factor- α (TNF α) was elevated. The correlation between the anatomical distribution of demyelination and the serum value of TNF α 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-

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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 (μ V)	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/mm³. 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 μ V and 10.9 μ V, respectively. Over the following three weeks, the SNAP in the right sural nerve was reduced from 15.3 μ V to 3.6 μ V. 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

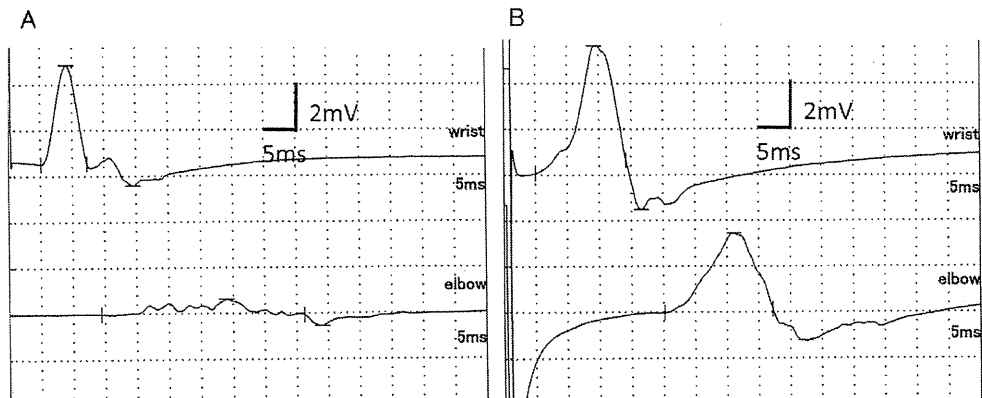


Figure 1. A. Results of the motor conduction study performed on the left median nerve upon admission (five months after onset). The compound muscle action potentials (CMAP) elicited at the elbow shows a marked temporal dispersion, suggesting uneven demyelination between the wrist and elbow. The dispersion 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.

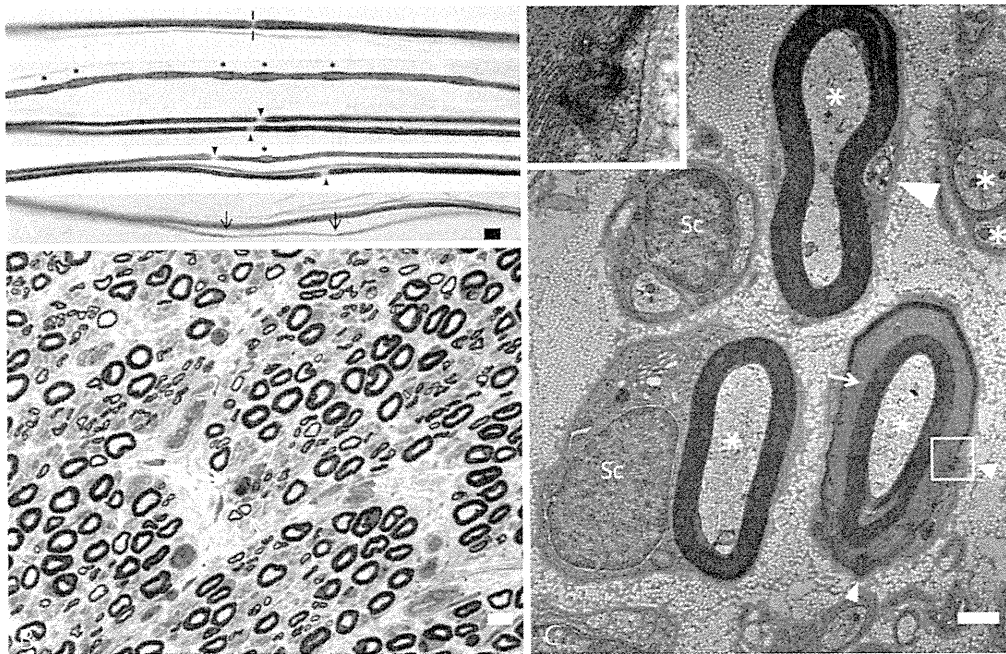


Figure 2. A. Teased fiber specimen. The pair of short longitudinal lines (top) indicates the normal hiatus of Ranvier node. The asterisks indicate wrinkling of myelin. The small arrowheads indicate segmental demyelinations or the widening of Ranvier node. The arrows on the nerve (bottom) indicate the shortening of the intermodal segment of the remyelinated nerve. Bar=10 μ m. 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 μ m. 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 μ m.

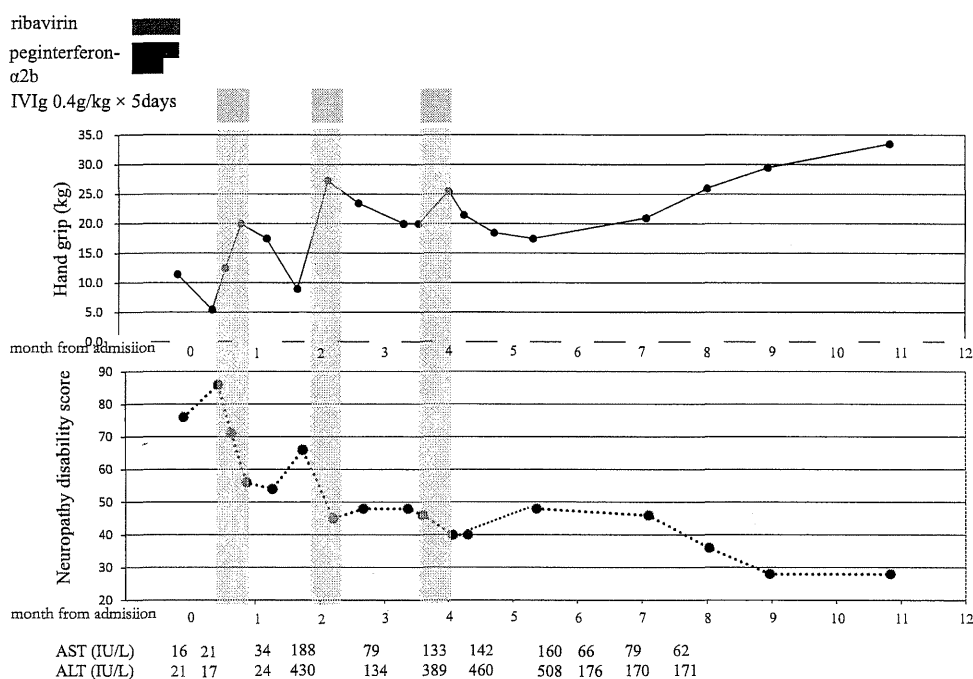


Figure 3. The clinical course of the patient based on two neurological indices that were measured over the course of one year; average hand grip and neuropathy disability scores (NDS). Each course of high-dose intravenous immunoglobulin therapy (IVIg) improved both the average hand grip and NDS. After 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 variants 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 IFN α 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 IFN α -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 IFN α treatment. Nevertheless, seven distinct cases of CIDP have been reported after the administration of a variety of IFN α species, including IFN α (6-9), pegIFN α -2a (10), and pegIFN α -2b (11, 12). The interval between the administration of IFN α 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 IFN α is discontinued. Autoimmunity, once induced by IFN α , 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 IFN α -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 IFN α -induced CIDP, a few of relapses occurred; however, no single case required the administration of prednisone or immunosuppressants. These features imply that IFN α -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 pegIFN α -2b are reported. IFN α -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 TNF α may be useful to assess the degree of autoimmunity in IFN α -induced CIDP.

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

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7 腎不全に伴う末梢神経障害例へのリハビリテーション

腎不全に伴う神経系の障害には、尿毒症性脳症 (uremic encephalopathy), 透析不均衡症候群 (dialysis disequilibrium syndrome), 透析脳症 (透析認知症) [dialysis encephalopathy (dialysis dementia)], 腎移植の神経系合併症, 尿毒症性ニューロパチー (UN: uremic neuropathy), 手根管症候群, 自律神経ニューロパチーなどがある。これらの合併症はリハビリの阻害要因となり, 重複障害として重大な問題を生じることがある。本項では UN の病態を解説し, リハビリ処方のポイントを述べる。

1 神経系障害の概要

尿毒症性脳症は急性あるいは慢性腎不全で腎機能低下が増悪する際に発症する。初期には意欲低下, 倦怠感, 注意障害, 被刺激性亢進などがみられ, 進行すると錯乱, 構音障害, 振戦, 姿勢保持困難などを生じる¹⁾。透析不均衡症候群は, 透析導入開始時にみられる一過性の脳症であり, 頭痛, 悪心, 有痛性筋痙攣, 被刺激性亢進などを生じる。透析脳症は透析導入後1年以上を経過して亜急性に進行する脳症で, 吃音や構音障害, 発語失行, 嚥下障害, てんかん, 知的低下, 精神症状を呈する。透析液中のアルミニウムが原因であり²⁾, 透析液の適切な管理により発症はなくなった。腎移植による神経系合併症として, 中枢神経原発の悪性リンパ腫, 感染症が報告されている。

UNは腎不全に伴う神経系障害のなかでも最も頻度が高く, 四肢遠位部に対称性の感覚運動麻痺を生じる。尿毒症性単ニューロパチーとしては手根管症候群が代表的であり, 前腕に造設した動静脈シャントによる影響もあるが, 透析で除去されない β_2 ミクログロブリンからなるアミロイド沈着が原因である。自律神経ニューロパチーでは, 起立性低血圧, 発汗障害, インポテンツ, 透析中の低血圧を生じる³⁾。糖尿病の患者では, 糖尿病性ニューロパチーや末梢循環障害を生じていることが多く, これらが相乗的に作用して複雑で重度な障害となる。

2 尿毒症性ニューロパチー

① 成因

UNは透析を導入する患者の2/3に認められ, すでに透析を受けている患者の70%にUNがあり, 30%は中等度か重度のUNがある⁴⁾。このUNは, 通常は痛みを生じることではなく, 進行する対称性の遠位優位の感覚運動障害がある。一方, 足の灼熱感, むずむず感, 痒痒感を訴える患者もいる。そのなかで, 感覚異常のため脚をじっとしていることが困難で夜間に増悪し, レストレスレッグ症候群 (restless legs syndrome) (むずむず足) とよばれる病態がある (p349 参照)。

UNは腎不全の進行に伴い増加し, 透析を導入すると軽減する。腹膜透析は血液透析よりもUN改善効果が大きく, 腎移植を行うと6~12カ月の経過でUNは消失する。これらの臨床経験より, 血液透析では除去されにくい300~12,000 Daの中分子量物質がニューロパチーの原因と考えられ

ていた⁵⁾。中分子量物質として副甲状腺ホルモン、 β_2 ミクログロブリン、メチルグアニジン、ミオイノシトールなどが想定され、透過性に優れる膜を利用すると UN の発症は劇的に減少する。しかし、ミオイノシトールは感覚神経伝導速度に関連はあるが神経毒性を示す証拠はない。副甲状腺ホルモンは動物実験では運動神経伝導速度の遅延と関連するが、腎不全患者では関連は明確ではない。結局、中分子量物質には神経障害を引き起こす直接的な証拠がなく、依然として原因は不明である。

Krishnan は総説の中で、尿毒素が軸索の Na^+/K^+ ポンプの活動を抑制してニューロパチーを生じるという Nielsen の仮説を提示している⁶⁾。軸索の興奮性を調べる新しい測定方法を用いると、透析前は末梢神経の慢性的な脱分極状態にあるが、透析後は膜電位が改善した。また、脱分極の程度は血中 K^+ と関連があり、慢性的な高カリウム性脱分極が神経障害の発症に重要な役割を果たしていた。したがって、腎機能が低下しても透析導入までの間、血中 K^+ を正常範囲内に維持して高カリウム血症を防止すると、UN の発症頻度を減少させ、障害を軽減できる可能性がある。

② 臨床所見

UN は慢性腎不全の一般的な合併症と考えられていたが、透析が導入され腎移植も行われるようになり、重度の UN は減少してきた。UN の基本形は、左右対称性で四肢遠位優位の感覚運動多発ニューロパチーであり、下肢は上肢よりも障害が高度である。初期症状は、アキレス腱反射の消失、振動覚の閾値上昇であるが、重症度、障害の進行と分布、dysesthesia（錯感覚）には個人差が大きい。一般に歩行障害は軽度であるが、下肢遠位部の筋力低下により遊脚期のつま先接地や立脚後期の蹴り出しが低下することがある。

筋痙攣やレストレスレッグ症候群は慢性腎不全の患者にしばしばみられる所見であるが、筋力低下や感覚障害はないこともある。筋痙攣は非特異的所見であり必ずしも UN の存在を示すものではないが、レストレスレッグ症候群は UN を伴うことが多い。多くの患者は手掌や足底に dysesthesia を認めるが、灼熱感よりもチクチクする感じ、不快な感じ、締め付けられる感じ、むくんだ感じと表現する。

UN の診断は、腎不全があり下腿・足部や手内筋の萎縮または筋力低下、四肢遠位部の感覚障害、特に母趾の振動覚低下、神経伝導速度の遅延があれば容易である。

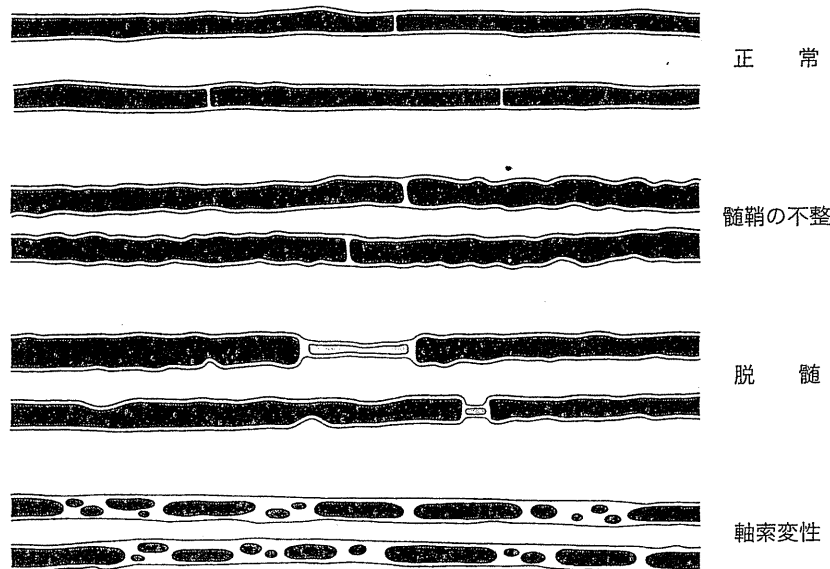
③ 電気生理学的検査

臨床所見に先立ち、運動神経や感覚神経の伝導速度遅延を認める。運動神経伝導速度が遅延しても複合筋活動電位の振幅は比較的保たれる。腓腹神経の感覚神経活動電位の振幅減少や下肢全体の伝導速度を反映する F 波の最短潜時も、UN のよい指標となる。単一線維筋電図 (single-fiber EMG)^{*1} によれば、運動単位における筋線維密度は正常であり再神経支配は起こりにくいと予想される。しかし、ジッター (2 個の筋線維電位が反復して放電する際の時間差) は増加するので、軸索変性に伴う節性脱髄を反映している可能性がある。単一線維筋電図のジッター異常は透析により改善する。

side memo

*1 | 単一線維筋電図

単一線維筋電図 (single-fiber electromyography) は、専用の特殊な針電極を用いて個々の筋線維からの活動電位を選択して判定する筋電図検査のことである。



[図 7-1] 尿毒症性ニューロパチーの有髄神経線維病変
 腓腹神経生検試料をグルタルアルデヒドとオスミウムで固定し、グリセリンに浸漬した後で有髄神経を1本1本にときほぐした標本である。

④ 病理学的検査

Asbury らの剖検例の報告によれば⁷⁾，末梢神経遠位部の軸索萎縮と変性が足底神経に際立っており，腓骨神経や脛骨神経にも同様の所見があった。下肢近位部では異常所見に乏しく，坐骨神経や神経根には異常はなかった。脊髄内では前角細胞の中樞性染色質溶解 (central chromatolysis) があり，頸髄後索内側にある薄束では髄鞘の染色性低下を認めた。これらは軸索変性を伴う多発ニューロパチーの典型的な所見である。Dyck らは，腓腹神経生検により大径有髄線維の消失，節性脱髄および菲薄化した再生髄鞘を認め (図 7-1)，定量的解析により軸索萎縮と変性に伴い髄鞘の変化や節性脱髄を生じると報告した⁸⁾。また，猫の下肢切断による軸索切断モデルを作成して，残存する末梢神経を詳細に観察し，髄鞘に不整や節性脱髄を生じると報告した⁹⁾。触覚，位置覚，振動覚に参与する大径有髄感覚神経では，神経節を経由して中枢側に伸びる薄束核近傍の軸索終末でも微細構造の変化を生じていた¹⁰⁾。これらの実験的軸索切断モデルにより，UN の軸索変性と随伴する節性脱髄および振動覚障害の病態をある程度説明することができる。

3 リハビリテーション

① 障害の評価

UN の障害評価は原則として他のリハビリ対象疾患と同様である。

機能障害として，筋萎縮の有無 (特に母指球，骨間筋，母趾外転筋)，四肢主筋の徒手筋力テスト (特に第 1 背側骨間筋，短母指外転筋，前脛骨筋，腓腹筋，母趾屈筋・伸筋)，感覚障害 (特に手指の触覚，母趾の振動覚，足部・足趾の位置覚)，主関節の可動域を診察する。四肢遠位部に軸索変性があるので^{7, 8)}，手指や足部・足趾の筋力を，また，頸髄薄束および薄束核近傍の大径有髄線維に異常があるので^{7, 10)}，手指触覚と母趾振動覚もていねいに診察する必要がある。UN は弛緩性麻痺なので関節拘縮は少ない。

[表 7-1] Karnofsky Performance Scale

スコア (%)	定義
100	正常、自覚症状がない。
90	通常の活動ができる。軽度の自覚症状がある。
80	通常の活動に努力を要する。中等度の自覚症状がある。
70	自分の身の回りのことはできる。通常の活動や活動的な作業はできない。
60	ときに介助が必要であるが、自分でやりたいことの大部分はできる。
50	かなりの介助と頻回の医療ケアが必要である。
40	活動にかなりの障害があり、特別なケアや介助が必要である。
30	高度に活動が障害され、入院が必要である。死が迫った状態ではない。
20	非常に重篤で入院が必要である。死が迫った状態ではない。
10	死が迫っており、死に至る経過が急速に進行している。
0	死亡。

(Karnofsky et al, 1948 より)¹¹⁾

[表 7-2] ニューロパチー重症度ステージ

ステージ 0	ニューロパチーなし 無症候性ニューロパチー
ステージ 1	神経学的所見、伝導速度、定量的検査所見の中で2項目以上該当する。 神経学的自覚症状はない。 症候性ニューロパチー
ステージ 2	神経学的所見、伝導速度、定量的検査所見の中で2項目以上該当する。 神経学的自覚症状があるが、障害は生じていない。
ステージ 3	障害のあるニューロパチー 神経学的所見、伝導速度、定量的検査所見の中で2項目以上該当する。 神経学的自覚症状があり、障害を生じている。

(Dyck, 1993 より)¹³⁾

活動制限・参加制約として、Barthel Index または Functional Independence Measure を用いて日常生活動作を評価し、椅子からの立ち上がり、移乗や歩行なども観察する。全身的総合評価として Karnofsky Performance Scale (表 7-1)¹¹⁾、生活の質の評価として Short Form-36 (SF-36 日本語版)¹²⁾ などを用いる。

疾患に特異的な機能障害評価に Neuropathy Symptom Score があるが、包括的な重症度分類であるニューロパチー重症度ステージ (表 7-2) の方が有用である¹³⁾。これを用いて UN の重症度を分類すると、Laaksonen らによれば¹⁴⁾、ステージ 1 (無症候性ニューロパチー) 19%、ステージ 2 (症候性ニューロパチー) 48%、ステージ 3 (障害のあるニューロパチー) 14%であった。

② リハビリテーションの内容

典型的な UN であれば身体障害の程度は軽度であり、必要に応じて起立訓練や抵抗運動による下肢筋力強化を行う。遊脚期につま先接地や下垂足の傾向があれば、足関節サポーターまたは後方板バネ型プラスチック短下肢装具 (オルソレン[®]) を処方する。また、散歩やエルゴメーターなどを用いた体力向上を勧める。日常生活動作の制限は少ない。

③ 問題となる病態

リハビリ医療上難渋するのは UN 患者の重複障害である。UN に脳卒中片麻痺が加わると、非麻

[表 7-3] 症例の神経伝導速度

	運動神経			感覚神経		
	伝導速度 (m/sec)	遠位潜時 (msec)	振幅 (mV)	伝導速度 (m/sec)	遠位潜時 (msec)	振幅 (mV)
(右) 正中神経	46.2	4.34	4.5	41.7	3.36	11.7
(左) 正中神経	48.2	4.02	5.3	44.9	3.12	4.0
(右) 尺骨神経	48.7	3.12	4.8	44.8	3.06	11.4
(左) 尺骨神経	45.1	3.32	3.2	42.2	3.32	5.4
(右) 脛骨神経	39.6	6.36	1.9			
(左) 脛骨神経		—				
(右) 腓骨神経	No evoked response					
(左) 腓骨神経		—				
(右) 腓腹神経				38.3	3.36	2.0
(左) 腓腹神経				—		

上肢正常値：神経伝導速度 \geq 45 m/sec, 下肢正常値：神経伝導速度 \geq 40 m/sec

側下肢にも UN による筋力低下や感覚障害があるので立位・歩行がより不安定になる。一方、糖尿病があり、閉塞性動脈硬化症や壊疽を生じ大腿切断や下腿切断に至った場合はさらに問題は大きい。非切断下肢に UN による筋力低下や感覚障害があるので立位や歩行は不安定になり、手指巧緻障害、糖尿病性白内障による視力障害、透析による断端周径変動が加わり、ソケット装着自体が難になる。そのため、患者が装着しやすいソケット形状を選択し、ソケット型取りは断端周径が大時に行い、周径減少時は断端袋で調節する。

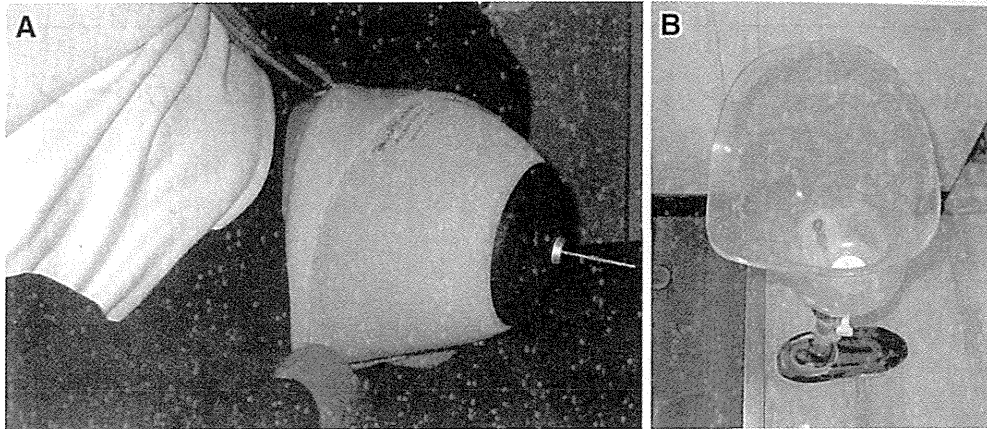
1 ソケットに工夫を要した大腿切断症例

症例：49 歳，男性，運送業。

障害名：左大腿切断，末梢神経障害。

診断名：慢性腎不全，閉塞性動脈硬化症，2 型糖尿病，UN および糖尿病性ニューロパチー。

現病歴と入院後経過：X-7 年に糖尿病，X-5 年に慢性腎不全と診断され，血液透析を開始した。-1 年に閉塞性動脈硬化症と診断され，X 年 2 月，左大腿切断術が施行された。6 月に義足作製目でリハビリ科に紹介入院した。断端は中断端であり，透析前/後で周径変動があり，手指と足部筋力低下と感覚障害を認め，神経伝導速度は遅延した（表 7-3）。最初に，断端周径変動を考慮吸着式四辺形大腿義足を処方した。仮義足を用い歩行は自立したが，義足装着が困難であった。位置覚障害のため，片脚で立ちながら断端に布を巻きつけソケットに差し込むのが不安定だった。さらに手指筋力低下と巧緻性障害のため，断端に巻いた布をソケット先端のバルブ穴からき出し，断端を差し込みながら布を引き抜く動作が困難であった。そこでシリコンライナーをソケットとする二重ソケットに変更し，座位で断端にシリコンライナーを転がすように装着できるようにした（図 7-2A）。その後で立位になり，断端を外ソケット（図 7-2B）に差し込み，ヤッチピンを外ソケット底部の接合装置に固定させるようにした。ソケット変更により義足装着ようやく自立した。



〔図 7-2〕 大腿義足

A：内ソケットを装着（有菌製作所 狩野綾子氏提供），B：外ソケット。ソケット底部に接合装置が見える。

UN は、慢性的な高カリウム性脱分極による軸索変性により発症する可能性があり、左右対称性で四肢遠位優位の感覚運動多発ニューロパチーを呈する。起立訓練や抵抗運動による下肢筋力強化や、要すれば下肢装具を処方し、体力向上のために散歩やエルゴメーターを勧める。重複障害では著しい障害となるので注意を要する。（蜂須賀研二，和田 太）

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ポリオ後症候群

A 疾患の概要

ポリオはポリオウイルス1型, 2型, 3型による感染症であり, 感染者の0.05~0.1%に上下肢麻痺あるいは嚥下障害や呼吸障害を生じる。急性灰白髄炎, 脊髄性小児麻痺あるいは小児麻痺と呼ばれることもある。わが国では1960年に大流行があったが, 経口生ポリオワクチン〔Sabin(セービン)ワクチン〕の導入により発症は急激に減少し, 1980年以降は野生株による発症はなくなった。しかし, ワクチン接種後あるいはワクチン服用者と接触した者に年間0~3件のポリオ発症を認める(ワクチン関連麻痺)。

ポリオ後症候群(post-polio syndrome)とは, ポリオ感染の後に安定した時期が続いた後で, 既存の障害が悪化するか, または新たな健康問題を生じる病態のことである。代表的な症状は, 筋力低下, 易疲労性, 全身倦怠, 筋痛, 下肢冷感などであるが, 自覚的には, 歩行時に膝折れを生じるようになった, しばしば転倒するようになった, 階段昇降が困難になった, 長く歩けなくなったと訴えることが多い。

ポリオ後症候群はポリオ罹患者の20~85%に生じる。ポリオ罹患者は, 運動神経の一部に変性が持続し骨格筋に脱神経を生じているが, 運動神経の側芽による筋再支配で機能的には代償されている。その結果として運動単位は拡大し筋力低下はある程度代償されるが, この再支配による代償が不十分になれば新たな筋萎縮や筋力低下を生じる。脱神経・再支配の過程に破綻を生じる機序は明らかではないが, 過用(使いすぎにより生じる障害)が大きな要因である。その他に, 加齢, 持続感染, 慢性炎症, 遺伝子などが関与している可能性がある。

B 診断・評価

ポリオ後症候群の診断基準は以下のとおりである。

- ①運動ニューロン消失を伴うポリオによる麻痺があり, 神経学的診察で病歴, 筋力低下と筋萎縮, 筋電図で脱神経所見が確認される。
- ②ポリオ急性期を過ぎて, 部分的にあるいは完全に機能を回復して神経学的に安定している時期が15年以上持続する。
- ③進行あるいは持続する新たな筋力低下または易疲労性が, 次第にあるいは突然生じる。全身疲労, 筋萎縮, 筋または関節の痛みを伴うこともあり, まれに呼吸や嚥下に関する障害を生じることがある。
- ④これらの症状は1年以上持続する。
- ⑤これらの症状を呈する神経疾患, 内科疾患, 整形外科疾患を除外できる。

C 医学的リハビリテーション

1 筋力低下の対策

ポリオ罹患者の膝伸展筋力は年間8~9%, 膝屈曲筋力は2~5%低下する。筋力低下の誘因として, 過用と廃用が考えられる(図11-7)。過用の要素が大きい場合は, しばしば「頑張り気質」を認めるので(図11-8), 病態を十分説明して過度の筋力強化訓練を控えるように指示し, 特に, 遠心性筋収縮は筋傷害を生じやすいので, 階段昇降や山登りは避けるようにする。また, 仕事などでも頑張りすぎないように自分に合ったペース配分の習得を助言し, 装具, 杖, 車いすを適宜活用して負荷を軽減するように指導する。廃用の要素が大きい場合は, 身のまわりの動作は自分でを行い, 適度な散歩を勧め, 仕事や社会参加を促し廃用を予防するように指導する。

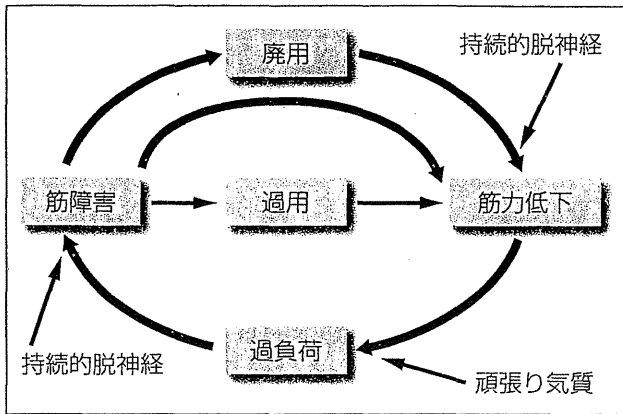


図 11-7 廃用と過用の関係

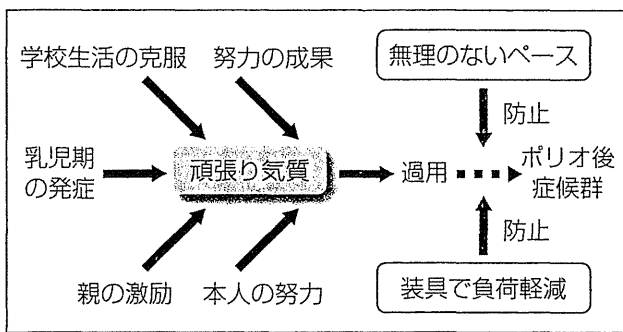


図 11-8 頑張り気質とポリオ後症候群

2 関節可動域の維持

ポリオは弛緩性麻痺なので、片麻痺ほどは関節拘縮を生じないが、拮抗筋筋力にアンバランスや脚長差があれば関節可動域 (range of motion; ROM) が制限されることがある。たとえば、大腿四頭筋の筋力低下があれば膝伸展制限を生じやすくなる。ROM が減少するときはストレッチを指導する。

3 ライフスタイルの再構築

ポリオは乳児期の感染であり、両親は健常な子どもに負けないで学校生活で遅れないように激励し、実際、患者の努力により筋力は一定の回復を示し、歩行障害もある程度改善する。これらの体験の積み重ねで「頑張り気質」をもつようになるのであろう。中高年になってもこのライフスタイルを続けると、二次障害を促進する要因となるので、身体的に無理のないペースを見つけ、頑張りすぎないことを指導する。

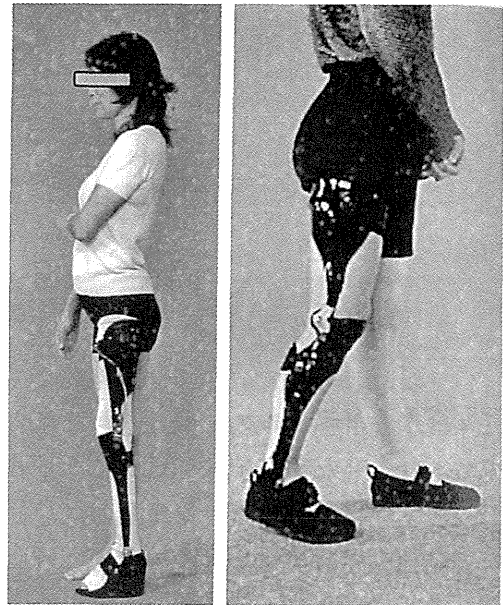


図 11-9 カーボン繊維強化プラスチック長下肢装具
左は膝継手にスイスロックを、右はオフセットを用いている。

4 補装具

歩行障害に対して装具や車いすを処方する。下垂足には短下肢装具、歩行時の膝の不安定感には足部をやや底屈位にしたプラスチック短下肢装具、歩行時の膝折れには膝継手を固定(リングロックまたはスイスロック)した両側支柱付き長下肢装具を処方する。カーボン繊維強化プラスチックを用いた長下肢装具は、通常の両側支柱付き長下肢装具よりも軽量でよく適合し耐久性にも優れており、ポリオ後症候群の患者にはもっとも適した装具である(図 11-9)。また、このカーボン製の装具は、両側支柱付き長下肢装具よりも歩行効率がよい。下肢に脚長差がある場合は、その 1/3~1/2 を靴底あるいは中敷きとして補高する。なお、歩行障害の程度に応じて、適宜、杖、車いすを併用し、過負荷を避けることが大切である。

[参考文献⇒ 398 頁]

平成24年度厚生労働科学研究費補助金（難治性疾患等克服研究事業）

「希少難治性神経疾患の疫学、病態解明、診断・治療法の開発に関する研究」班

（研究代表者 京都府立医科大学神経内科 中川正法）

平成24年度第1回班会議

平成25年1月20日（日）11:00～12:00 東京ステーションコンファレンス

議題

1. 研究費の経理処理について
今後の提出について（山崎）
研究報告書類・経理報告書類

2. 分担研究発表

演題1. 遺伝性ニューロパチー研究の課題

京都府立医科大学大学院神経内科学
中川正法

演題2. CMT病における神経超音波検査の有用性の検討

京都府立医科大学大学院神経内科学
滋賀健介

演題3. 脳梗塞に遺伝性圧脆弱性ニューロチーを合併した症例

産業医科大学リハビリテーション医学
松嶋康之 蜂須賀研二

3. 来年度の研究班の活動内容について

4. その他

本研究に関連する論文発表の際には本研究事業についての謝辞を必ず記載してください。

<英文例>

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<和文例>

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シャルコー・マリー・トゥース病(CMT)市民公開講座

皆さん、「CMT」ってご存じですか？

シャルコー・マリー・トゥース病という病気の略語です。「CMT」は、末梢神経が障害される疾患の総称です。CMT 患者さんの多くは、足や手の先の筋肉がゆっくりと進行性に痩せていく、痛みや冷たさに対する手足の感覚が鈍くなる病気です。私たちは厚生労働省の科学研究補助金 を受けて、「シャルコー・マリー・トゥース病の診断・治療・ケアに関する研究」を行っております。その一環として、市民の皆様にご理解を深めて頂きたいと考え、今回の市民公開講座を企画致しました。一人でも多くの市民の皆様のご参加をお待ちしております。

日時：平成 24 年 10 月 8 (月・祝) 10 : 30-13 : 00

会場：札幌国際ビル 8 階 A 会議室

入場無料

講演内容

主催者あいさつ

中川正法

CMT 病の病態と治療法および研究の現状について

中川正法

CMT の手術療法と術後療法&痛みとしびれの対処法

渡邊耕太

CMT 病のリハビリテーション

松嶋康之

CMT 病患者を対象とした自己記入式アンケート調査

滋賀健介

日常生活と工夫、社会資源の利用

大竹弘哲

CMT 友の会～その活動について～

山田隆司

質疑応答

中川正法

主催

平成24年度厚生労働科学研究費補助金 難治性疾患等克服研究事業(難治性疾患克服研究事業)

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(研究代表者 京都府立医科大学神経内科 中川正法)

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日時：平成24年11月4（日） 13：00-15：30

会場：岡山国際交流センター 会議室（1）

入場無料

講演内容

主催者あいさつ

中川正法

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