INTERNAL MEDICINE

□ ORIGINAL ARTICLE □

Intravenous Immunoglobulin (IVIg) with Methylprednisolone Pulse Therapy for Motor Impairment of Neuralgic Amyotrophy: Clinical Observations in 10 Cases

Ko-suke Naito[1], Kazuhiro Fukushima[1], Seiko Suzuki[2], Motoi Kuwahara[2], Hiroshi Morita[1], Susumu Kusunoki[2] and Shu-ichi Ikeda[1]

Abstract

Background Neuralgic amyotrophy (NA) is a distinct peripheral nervous system disorder characterized by attacks of acute neuropathic pain and rapid multifocal weakness and atrophy unilaterally in the upper limb. The current hypothesis is that the episodes are caused by an immune-mediated response to the brachial plexus, however, therapeutic strategies for NA have not been well established.

Methods and Results We retrospectively reviewed 15 case series of NA; 10 of the 15 patients received intravenous immunoglobulin (IVIg) with methylprednisolone pulse therapy (MPPT) and 9 of these10 patients showed clinical improvement of motor impairment.

Conclusion Our clinical observations do not contradict the possibility that IVIg with MPPT may be one of the potential therapeutics for NA, however the efficacy remains to be established. Further confirmatory trials are needed in patients with various clinical severities and phases of NA. Further basic research and confirmatory trials should be performed to survey the efficacy of such immunomodulation therapy for NA.

Key words: neuralgic amyotrophy, intravenous immunoglobulin, methylprednisolone pulse therapy, Parsonage-Turner syndrome, brachial plexus

(Intern Med 51: 1493-1500, 2012)
(DOI: 10.2169/internalmedicine.51.7049)

Introduction

Neuralgic amyotrophy (NA, also known as Parsonage-Turner syndrome) is a distinct peripheral nervous system (PNS) disorder, characterized by sudden attacks of severe neuropathic pain usually unilaterally in the shoulder and/or arm. The neuralgia commonly disappears after hours to weeks, and consequently patchy paresis with amyotrophy appears. The minimum incidence of NA is 2-3 cases per 100,000 individuals in the general population per year (1, 2), but under-recognition and misdiagnosis are frequent and the true annual incidence rate could be at least 20-30 cases per 100,000 individuals (3).

The available evidence suggests that NA is essentially idiopathic immune-mediated neuritis of the brachial plexus, and also has a complex pathogenesis that includes an underlying predisposition, a susceptibility to dysfunction of some PNS structures, and a trigger for the attacks, such as viral infection, vaccination, trauma, surgery, and strenuous exercise. Genetic factors also contribute to the pathogenesis of NA. NA occurs in both idiopathic and hereditary forms (INA: idiopathic neuralgic amyotrophy and HNA: hereditary neuralgic amyotrophy, respectively), and HNA is thought to be 10 times less common than INA. HNA is an autosomal dominant, monogenic disorder with high but incomplete penetrance and evidence of genetic heterogeneity. In over half of the families investigated, causal mutations of the septin-9 (SEPT9) gene on chromosome 17q25.3 have been demonstrated (4). NA has been considered to be a self-limiting, benign disorder showing good recovery without specific treatment (5-7). However, recent studies have indi-

[1]Department of Medicine (Neurology and Rheumatology), Shinshu University School of Medicine, Japan and [2]Department of Neurology, Kinki University School of Medicine, Japan
Received for publication December 4, 2011; Accepted for publication March 4, 2012
Correspondence to Dr. Kazuhiro Fukushima, kfuku@shinshu-u.ac.jp

Table 1. Clinical Profiles of the Patients

Case	Age	Affected side	Predominancy in distribution of affected muscles	Duration from onset (months)	Treatment	Number of courses	Pre-treatment ULSD	Post-treatment ULSD	Follow-up period (months)
1	64/F	R	Proximal	9	MPPT	1	2	1	12
2	55/M	L	Proximal	1	IVIg	1	3	0	4
3	74/M	L	Proximal	2	IVIg + MPPT	1	2	1	8
4	63/M	R	Proximal	2	IVIg + MPPT	1	2	0	60
5	49/M	R	Proximal	3	IVIg + MPPT	3	3	1	
		R	Proximal	3	IVIg + MPPT	2	3	2	21
6	51/M	L	Distal	6	IVIg + MPPT	1	3	1	24
7	62/M	R	Proximal	1	IVIg + MPPT	3	3	1	
		R	Proximal	2	IVIg + MPPT	1	3	1	51
8	57/M	L	Distal	3	MPPT	1	2	1	59
9	42/M	L	Distal	24	MPPT	1	2	2	2
10	61/M	L	Proximal	2	IVIg + MPPT	2	3	2	48
11	67/M	L	Proximal & Distal	4	MPPT	1	2	1	3
12	45/M	R	Proximal	4	IVIg + MPPT	2	2	1	11
13	50/M	L	Proximal	2	IVIg + MPPT	1	2	1	7
14	38/M	R	Distal	1	IVIg + MPPT	2	2	2	2
15	54/M	L	Proximal	6	IVIg + MPPT	1	2	1	3

Two cases (cases 5 and 7) showed recurrent attacks during the follow-up period. Information of the second attack in each case is shown on the lower line. MPPT: methylprednisolone pulse therapy, IVIg: intravenous immunoglobulin, ULDS: upper limb disability score

cated that the long-term prognosis of NA is less favourable than has been assumed (3, 8-10).

In 2009, a Cochrane review identified only one open-label, retrospective series, the results of which suggested that administration of corticosteroids in the acute phase of NA (during the first month of an attack) could shorten the duration of painful symptoms and also accelerate recovery in some patients (10, 11). However the efficacy of other immunomodulatory agents or therapeutic strategies for the late phase of NA have not been well established. In fact, most NA patients were diagnosed in the late phase (median: 10.7 weeks from onset) (3).

Here, we retrospectively reviewed 10 patients with NA received treatment including intravenous immunoglobulin (IVIg) with methylprednisolone pulse therapy, and most showed a favourable clinical outcome of motor disability.

Materials and Methods

Subjects

We retrospectively reviewed all medical records of our institution from April 2003 until March 2011. For the diagnosis of NA, we adopted the HNA diagnostic guidelines presented at a 1999 European Neuromuscular Centre workshop (12). We did not consider family history or molecular genetics criteria. A diagnosis of NA was made in patients fulfilling the following criteria: 1) Clinical manifestations: acute, unilateral brachial plexopathy, severe pain preceding the onset of weakness by days to a few weeks, predominantly motor neurological deficits. 2) Electrophysiological criteria: electromyography shows signs of denervation or reinnervation in affected muscles (3). We excluded patients with clinical signs of generalized neuropathy, concomitant disease (cerebrovascular diseases, diabetes mellitus, connective tissue disease, malignancy, or paraproteinaemia), or a history of treatment using corticosteroids or any immunomodulatory agents. 15 patients (14 men, 1 woman) were selected (Table 1, 2). This study was approved by the Ethics Committee of Shinshu University School of Medicine.

Electrophysiological study

Electrophysiological study in the affected limb was performed in all 15 NA patients within 7 days of admission. All electrophysiological tests were performed by the same experienced neurophysiologist. Median, ulnar, and radial nerve conduction studies were performed in 14, 13, and 8 of the 15 patients, respectively. Compound muscle action potential (CMAP), maximal motor nerve conduction velocity (MCV), distal latency (DL), F-wave conduction velocity (FWCV, maximum velocities taken from 10 responses), and F-wave frequency (frequency in 10 responses) were recorded at motor nerves. Stimulation was performed at the wrist and elbow for the median and ulnar nerves, and at the elbow and axilla for the radial nerve. Needle electromyography (needle EMG) was performed in the affected limb of all patients in at least 12 upper and lower limb muscles (supraspinatus, infranspinatus, deltoid, biceps brachii, triceps brachii, extensor carpi radialis, flexor carpi ulnaris, quadriceps, tibialis anterior and soleus) using standard concentric needle electrodes.

Laboratory tests

Serum titres of both IgM and IgG antibodies against 11 gangliosides (GM1, GM2, GM3, GD1a, GD1b, GD3, GT1b, GQ1b, CA1, Gal-C, and GalNAc-GD1a) were measured by enzyme-linked immunosorbent assay (ELISA) as described previously (13, 14). Serum monoclonal proteins were examined by immunofixation electrophoresis assay.

Table 2. Results of Electrophysiological Studies in the Affected Limb and Laboratory Tests

Case	Reinnervation findings in needle EMG	MCV	F-wave study		CSF analysis		Serum anti-ganglioside antibodies
			Reduced FWCV	Reduced frequency	Cell count (/μL)	Total protein (mg/dL)	
1	(+)	nl	(-)	M	1	32	ns
2	(+)	nl	(-)	(-)	2	39	(-)
3	(+)	*1	M	(-)	1	40	ns
4	(+)	nl	(-)	(-)	0	19	ns
5	(+)	nl	R	M. U, R	0	37	(-)
	(+)	nl	R	U, R	ns	ns	ns
6	(+)	nl *2	U, R	M, U, R	1	35	(+)
7	(+)	nl	U, R	M, U, R	0	41	(-)
	ns	nl	R	U, R	1	49	ns
8	(+)	nl	(-)	(-)	1	41	ns
9	(+)	nl	(-)	(-)	0	46	(-)
10	(+)	nl	M	U	0	59	(-)
11	(+)	*3	U	U	1	32	(+)
12	(+)	nl	R	R	1	40	(-)
13	(+)	nl	R	U, R	0	21	ns
14	(+)	nl	R	U	0	28	ns
15	(+)	nl	R	R	0	26	ns

Two cases (cases 5 and 7) showed recurrent attacks during the follow-up period. Information of the second attack in each case is shown on the lower line. EMG: electromyography, MCV: maximal motor nerve conduction velocity, FWCV: F-wave conduction velocity, CSF: cerebrospinal fluid, nl: normal, ns: not studied. The nerves that showed abnormal findings in F-wave studies are indicated in the capitals (M: median nerve, U: ulnar nerve, R: radial nerve). The normal values of electrophysiological studies in our laboratory were as follows: MCV: median and ulnar nerve (wrist-elbow) > 55 m/s, radial nerve (elbow-axilla) > 60 m/s; F wave: median, ulnar and radial nerves: FWCV > 60 m/s, frequency ≥ 80%. In two cases, mild abnormal values were recorded in MCV. *1: In case 3, MCV of the ulnar nerve was decreased (44.9 m/s). *2: In case 11, MCV of the ulnar nerve was decreased (48.5 m/s).

Cervical magnetic resonance (MR) imaging study

Conventional cervical MR imaging study was performed in all cases using a Siemens 1.5-T imager (Siemens, Erlangen, Germany).

Clinical evaluation

Severity of motor impairment was scored before and after treatment according to the upper limb disability score (ULDS, from 0 to 5), as described previously (15): 0, no symptoms; 1, upper limb symptoms without functional impairment; 2, some minor difficulties in manual activities; 3, inability to perform some manual activities; 4, inability to perform manual tasks; 5, total paralysis.

Statistics

For data analysis and evaluation of the difference in ULDS between before and after therapy, Mann-Whitney *U* test was employed. The results represented the mean ± standard error where applicable, and the level of significance was $p<0.05$ in all analyses. Commercially available statistics software was used for data analysis (Microsoft Excel for Mac 2011, Microsoft Corporation, NY, NY USA).

Results

Patients and clinical features

We identified 15 patients with a diagnosis of NA (Table 1). The patients included 14 men and 1 woman. None of the patients had any relevant family history. The median age at diagnosis was 57 years (range: 38-74 years). All patients had a sudden attack of severe neuropathic pain that preceded the onset of limb amyotrophy by days to a few weeks. Precipitating factors were described in 6 cases: unusual strenuous exercise in 4 cases, shoulder bruising in 1 case, and herpes zoster in 1 case. The median duration of disease before the first treatment was 3 months (range: 1-24 months). All cases showed unilateral upper limb involvement: right in 6 cases, and left in 9 cases. Distribution of affected muscles was predominantly in the proximal limb (80%, 12/15 cases), especially in the supraspinatus, infranspinatus and deltoid muscle. In 3 cases, minor sensory abnormalities (dysesthesia or pain) were present in the affected limb. In all cases, patch or spotty distribution of affected muscles was observed. Muscle weakness of the serratus anterior muscle was described in two cases (cases 5 and 11). None of the patients showed noticeable neurological impairment outside of the affected limb.

Electrophysiological study

The results of electrophysiological studies are summarised in Table 2. In both median and ulnar nerves of the affected limb, distinct abnormal findings in MCV, CMAP and DL were scarcely observed in all cases examined. In contrast, in the radial nerve study, CMAP was markedly decreased in six of the 10 cases examined.

In the F-wave study, reduced frequency and/or reduced FWCV were recorded in 6/15 and 7/11 cases, respectively, in the median, and ulnar nerve. In all cases examined, F-wave study in the radial nerve showed abnormal findings (reduced frequency and/or reduced FWCV).

Needle EMG revealed mild findings of reinnervation and late recruitment of motor units during contraction in affected

Table 3. Profiles of Patients Treated with MPPT or IVIg with MPPT

Treatment	MPPT (n = 4)	IVIg + MPPT (n = 10)	
Age (years)	57.5 ± 5.6	54.7 ± 3.3	ns
Gender, male (%)	3 (75%)	10 (100%)	ns
Duration from onset at initial therapy (months)	10.0 ± 4.6	3.0 ± 0.6	p= 0.04
Pre-treatment ULDS	2.0 ± 0	2.4 ± 0.2	ns
Post-treatment ULDS	1.3 ± 0.3	1.2 ± 0.2	ns
Decrease of ULDS	0.8 ± 0.3	1.2 ± 0.2	ns
Follow up period (months)	32.5 ± 6.9	19.0 ± 13.5	ns

MPPT: methylprednisolone pulse therapy, IVIg: intravenous immunoglobulin, ULDS: upper limb disability score, ns: not significant. The results are presented as the means ± standard error where applicable, and the level of significance was $p<0.05$ in all analyses.

muscles in all cases. In some cases we also found fibrillation potential and positive sharp waves at rest indicating denervation.

Laboratory tests

The results of laboratory tests are summarized in the Table 2. None of the patients were previously diagnosed as having diabetes mellitus. All patients showed fasting plasma glucose levels of ≤126 mg/dL, and HbA1c levels were normal (mean: 5.1%, range: 4.1-6.3%). Serum monoclonal proteins were not detected in any of the patients on immunofixation electrophoresis assay. Serum titres of both IgM and IgG antibodies against 11 gangliosides (GM1, GM2, GM3, GD1a, GD1b, GD3, GT1b, GQ1b, CA1, Gal-C, and GalNAc-GD1a) were measured by ELISA in 10 patients; the levels were not significantly increased in 8 of the patients examined. A low titer of IgG antibodies against gangliosides was shown in case 6 (anti-GM1) and case 11 (anti-Gal-C). Cerebrospinal fluid (CSF) analysis was performed in all cases: white blood cell counts (mean: 1/μL, range: 0-2/μL), and total protein concentrations [mean: 39.5 mg/dL, range: 19-59 mg/dL; normal value <60 mg/dL (16)] were not elevated.

Cervical MR imaging study

No abnormal findings were recorded in any patients on MR imaging study, including spinal cord tumor, syringomyelia, or arteriovenous malformation. In 8 of 14 patients, slight or moderate degrees of spondylotic changes in the cervical spine were detected, but these were inadequate to explain the neurological syndromes in these cases.

Treatments

Four patients treated with a single course of methylprednisolone (MP) pulse therapy (MPPT: intravenous MP 1 g daily in 100 mL of saline for 3 consecutive days), 1 patient with a single course of IVIg (intravenous immunoglobulin 400 mg/kg body weight daily for 5 consecutive days) and 10 patients with single or more courses (mean: 1.8 courses, range: 1-5 courses) of combination therapy using IVIg with MPPT (simultaneous administration of IVIg and MPPT according to the regimens mentioned above).

Clinical courses

The median duration of follow-up after the initial treatment was 12 months (range: 1-60 months). In 13 patients, clinical improvement of motor dysfunctions resulting in a decrease in ULDS were observed within 1 month after the first therapy to a greater or lesser degree in each case. However, in 2 cases (cases 9 and 14), ULDS was not decreased although minor improvements were observed in each case. During the follow-up period, neurological impairments were limited within the initially affected limb in all patients, and did not spread to the contralateral upper limb or lower limbs. Recurrent attacks were observed in two cases (cases 5 and 7, see case report below for further details regarding case 5). In case 7, 34 months after onset, recurrent attack developed in the upper limb on the initially affected side after herpes zoster infection (C4-5 dermatome). The patient was treated with a single course of IVIg with MPPT, and recovered fully within 2 months.

Nine of the 10 patients treated with IVIg + MPPT (age: 54.7±3.3 years) showed improvement of ULDS. The ULDS was decreased from 2.4±0.2 (pre-treatment) to 1.2±0.2 (post-treatment), representing a decrease of 1.2±0.2. On the other hand, in MPPT-treated patients (4 patients, age: 57.5± 5.6 years), pre- and post-treatment ULDS were 2.0±0 and 1.3±0.3, respectively, representing a decrease of 0.8±0.3. Both pre-treatment ULDS and the decrement of ULDS tend to be high in patients treated IVIg + MPPT, although these showed no significant differences between the two groups. The duration from onset at initial therapy of patients treated with IVIg + MPPT and MPPT was 3.0±0.6 and 10.0±4.6 months, respectively, and this difference was statistically significant (Table 3). One case treated with IVIg (without MPPT) also showed a favourable clinical response. Although side effects were observed in 2 patients treated with IVIg + MPPT (transient elevation of serum hepatic enzymes), it was not necessary to discontinue treatment.

Illustrative case reports

Case 5: A 49-year-old right-handed man (office worker) suddenly developed severe aching pain in his right shoulder, radiating to the trapezius and scapula. He had changed the wheels on his car by himself a few days before the attack of neuralgia. The pain persisted for few days and gradually im-

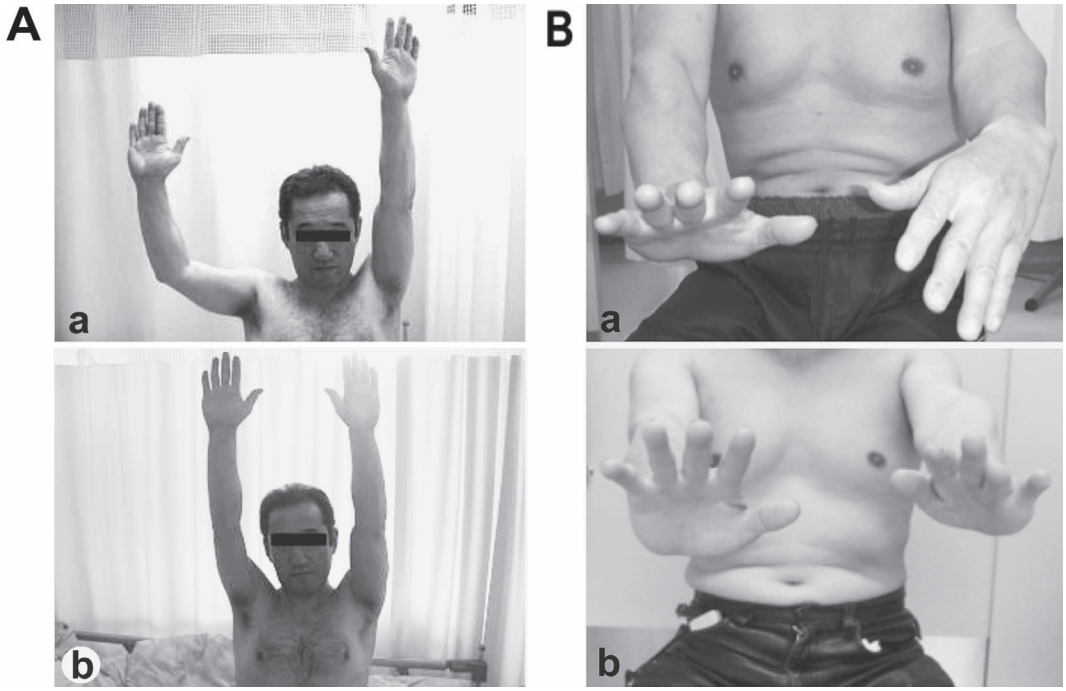

Figure 1. **(A) Case 5. On admission, the patient was unable to abduct his arm (a). Six months after commencement of therapy, functional recovery of the shoulder was observed (b). (B) Case 6. On admission, the patient showed left dropped-hand because of amyotrophy particularly in the wrist and finger extensor musculature (a). Functional recovery of wrist and finger extensor musculature was observed 5 months after commencement of therapy (b).**

proved over the following 2 weeks, then he noticed weakness in the right shoulder. He consulted an orthopaedist and was assumed to have cervical spondylosis. However, MR imaging and cervical myelography showed no abnormal findings. The patient was referred to our hospital 3 months after onset. On physical examination, he was unable to abduct his arm (Fig. A-a). On the right side, he had 3/5 muscle strength in deltoid, infraspinatus and supraspinatus muscles, and normal strength in the elbow and hand. Examination also revealed atrophy of the right shoulder musculature, with lowering and protrusion of the shoulder blade. No sensory involvement was found. In neurophysiological study, SCV and MCV were normal. CMAP was decreased in the right radial nerve (3.79 mV, normal: >7.0 mV). F-wave frequency was decreased in the right median (40%, normal: ≥80%), ulnar (30%, normal: ≥80%) and radial nerves (30%, normal: ≥80%), and FWCV was decreased in the right radial nerve (48.1 m/s, normal: >60 m/s). Needle EMG showed mild reinnervation in the right infranspinatus, deltoid and biceps brachii muscles. A diagnosis of NA was made, and IVIg with MPPT was commenced. Improvement of his motor dysfunctions was observed within 2 weeks after commencement of therapy. The patient was treated with 3 monthly courses of IVIg with MPPT. He also received treatment from a physical therapist to prevent pain and stiffness during daily use of the right shoulder. After 6 months of initial therapy, the patient showed functional recovery of the shoulder (Fig. A-b). Twelve months after the last therapy, he noticed muscle weakness in the right shoulder, and was readmitted to our hospital. Examination showed atrophy and weakness in the right shoulder muscles and biceps muscle. Although it was only partially affected compared to after the initial treatment; muscle weakness improved after 2 courses of IVIg with MPPT.

Case 6: A 51-year-old right-handed man (a cook) experienced severe, sharp pain in the region of his left shoulder. It was resolved over several days, and progressive muscle weakness of the left shoulder subsequently developed. He was admitted to our hospital 6 months after the onset of neuralgia. Physical examination showed diffuse muscle atrophy in the muscles of his left hand. His left finger extensors and median nerve-innervated hand muscles were disturbed. The left extensor carpi radialis (2/5 muscle strength), extensor carpi ulnaris (2/5 muscle strength) and extensor digitorum communes (3/5 muscle strength) showed particularly marked impairment (Fig. B-a). Sensory involvement was not found. On neurophysiological study, SCV and MCV were normal. CMAP was decreased in the left median nerve (3.20 mV, normal: >4.5 mV) and radial nerve (3.96 mV, normal: >7.0 mV). F-wave frequency was decreased in the right median (70%, normal: ≥80%), ulnar (30%, normal: ≥80%) and radial nerves (60%, normal: ≥80%), and FWCV was decreased in the right ulnar (55.9 m/s, normal: >60 m/s) and radial nerves (51.4 m/s, normal: >60 m/s). Needle EMG showed mild reinnervation in his left extensor carpi radialis, adductor pollicis and opponens pollicis muscles. Cervical MRI and CSF analyses showed no abnormalities. A diagnosis of NA was made and he was treated with 2 courses of

IVIg with MPPT and physical therapy. Improvement of his motor dysfunctions was observed within 4 weeks after commencement of therapy. Five months after the initial therapy, recovery of muscle weakness was observed (Fig. B-b).

Discussion

NA has been previously considered to be a self-limiting disorder showing good recovery without specific treatment in the majority of patients. In 1960, Magee and Dejong reported a series of 23 patients with paralytic brachial neuritis (21 males and 2 females, age: 8-64 years), and described that the prognosis is usually satisfactory for the return to good function, but recovery for customary physical activities is usually slow. In this report, during the follow-up period (0-6 months), 15 patients (65.2%) showed complete or good recovery, and 8 patients (34.8%) showed slight recovered or no recovery (5). In 1987, England and Sumner reported 9 patients with NA (6 males and 3 females, age: 21-56 years). During follow-up period (1-18 months), 2 patients showed complete or good recovery, 3 patients showed mild or partial recovery, and 3 patients showed no recovery (in one case, the detailed clinical course was not included) (6). In 2002, Cruz-Martínez et al. reported 40 patients with NA (28 males and 12 females, age: 15-70 years) and described that the overall prognosis of NA is good in general, despite the severity and extent of the lesions. In follow-up studies in 22 of 40 patients (43 affected nerves), the muscles innervated by 41 of 43 (95.3%) nerves reached good function within the 2-year follow-up period (7).

On the other hand, some recent reports described that the prognosis of NA is less favourable than has been assumed (3, 9, 10). In 2006, Van Alfen and van Engelen reported long-term prognosis of 39 patients with INA. Mild paresis was still present in 69.4% of cases, moderate paresis in 13.9% and severe paresis in 2.8% with a long-term follow-up of three years or more. Only two patients (4.1%) had made a full recovery. The median Rankin score for patients with a follow-up of 3 years or more was 2, meaning that patients experienced some impairments in daily life but did not need help from others; 22.3% were unable to work and 36.8% had had to find a different type of job because of NA. The disability is considerable particularly when the dominant side is involved (3). In addition, in 2009, van Eijk et al. reported the clinical courses of 203 untreated patients with NA (male 69.5%, age: 12-83 years; median: 45.7 years). Only 11 of 174 (6.3%) patients showed recovery of muscle strength within 1 month of onset. Good but not full recovery within 12 months was reported in 11 of 103 (10.7%) patients, and only 2 of 189 patients showed full recovery within the first year after onset (10).

In the present case series, 9 of 10 patients treated with IVIg + MPPT showed clinical improvement; 1 patient showed no symptoms and 6 patients showed no functional impairment. As for MPPT treatment alone, 3 of 4 showed clinical improvement. Although this comparison was with a few patients treated with MPPT, there were no statistically significant differences between the two groups. In patients treated with IVIg + MPPT, both post-treatment UEDS and the decrement of UEDS tended to be more favourable than those seen in patients treated with MPPT alone. However, this tendency may in part be due to the duration from onset at initial therapy, it was shorter in patients treated with IVIg + MPPT than patients treated with MPPT with statistically significance.

In patients treated with IVIg + MPPT in our case series, the outcome of motor function showed no prominent superiority compared to some previous reports (5, 7), on the other hand, it seems to be preferable than that of untreated patients with NA in the two recent reports (3, 10). However, the racial difference between countries also should be considered. NA is more frequently reported in western countries than in Japan. At least in this regard, a simple comparison between our case series and reports in western countries may be inadequate.

It is unclear why there are discrepancies in the results of functional prognosis of patients with NA between previous studies. The reason for the discrepancies may be partially explained by the heterogeneous nature of the disease. Actually, NA has a certain degree of clinical heterogeneity. Except for the classical presentation of NA, there are some phenotypic variations including involvement of nerves outside the brachial plexus (cranial nerves, phrenic nerve, or lumbosacral plexus), mononeuropathic form, bilateral symptoms, prominent sensory symptoms, or painless attack (17). For instance, Cruz-Martínez reported 7 bilateral impairment, 4 accessory nerve, 4 facial nerve, and 1 phrenic nerve involvement in the above-mentioned report (7). Moreover, the severity of an episode can vary hugely between patients, and even between different attacks in the same patient (17). Diagnostic criteria adapted in each study were, as well as in our study, essentially emphasized on the clinical manifestations and differential diagnosis, and had no notable differences. For the future, identifications of novel diagnostic biomarkers, neuroradiological, or neurophysiological hallmarks are needed to make this clinical entity more discriminatively.

A few cases of NA treated with IVIg have been reported in the literature. Tsao et al. reported two fraternal cases of Epstein-Barr virus-associated NA. One patient (20-year-old man) was initially treated with MPPT in the acute neuralgic phase. However, he showed continuous progression of limb muscle atrophy. He was then treated with IVIg and recovered. Another patient (22-year-old woman) was treated with IVIg during the acute phase, and showed significant recovery (18). Nakajima et al. reported a 39-year-old man with NA who was initially treated with intravenous MP, but he showed no response. He was then treated with IVIg and showed good recovery (19). Al Masri et al. described an 8-year-old girl with NA during immunosuppression therapy using tacrolimus. Her neurological impairments fully recovered after IVIG and MPPT (20). Moriguchi et al. reported

three cases of anti-ganglioside antibody-positive NA who were treated with IVIg, and two of three patients showed good clinical response (14). In these reports, IVIg was begun in a relatively early disease phase, and was effective in non-responders to corticosteroid therapy.

In contrast, in the present case series, IVIg was begun 1 month or more after disease onset in all patients. In our clinical observations it seems as if IVIG with MPPT positively affected the outcome of motor impairment in the late phase of NA. However, recovery of motor function in the late phase NA must represent the natural disease course to some extent. There are some difficulties to evaluate the efficacy of immunomodulation therapy in such conditions.

NA has been considered to show a monophasic clinical course. However, a recent study has shown that the recurrence rate of NA after the first attack is unexpectedly high, with 26.1% of patients developing recurrence 6 years after the initial attack (3). Furthermore, some patients show progressive course of symptoms from disease onset (3, 18). Such clinical courses in a proportion of NA patients cannot be adequately explained only by monophasic damage to the affected nerves. Given that some of the autoimmune conditions evoked at disease onset may be prolonged during the chronic phase in a proportion of NA patients, the long-lasting immunomodulatory action of IVIg seems to be efficacious in the treatment of NA in the late phase. To confirm the efficacy of immunomodulation therapy in late disease phase of NA, further basic studies are needed to investigate autoimmune conditions in such variant cases with NA.

Some studies have reported serum anti-ganglioside antibodies in NA patients, however it is still unclear whether these are actually involved in the pathogenesis of NA (3, 21). In particular, the anti-GalNAc-GD1a antibody was reported as a candidate biological marker for predicting response to immune therapy (14). In the present study, a low titer of the IgG antibodies against gangliosides was shown in two cases, however, this finding might be a consequence of neural damage rather than its cause.

In summary, the present clinical observations do not contradict the possibility that IVIg with MPPT may be one of potential therapeutics for NA, however the efficacy remains to be established. Further confirmatory trials are needed in patients with various clinical severities and phases of NA. At this time, physicians should be circumspect in aggressive immunomodulation therapy, especially in patients in the late phase of NA. In addition, further basic studies are also needed to understand the pathogenesis of NA and to find novel biological markers, neuroradiological, or neurophysiological hallmarks that contribute to early diagnosis and make this clinical entity more discriminative.

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

Acknowledgement

We are most grateful to Dr. Kana Tojo-Fukushima, Dr. Akiyo Hinone and Ms. Teruko Asawa for technical assistance during neurophysiological evaluation and helpful suggestions. This work was supported by a grant from Neuroimmunological Disease Division, the Ministry of Public Health, Labour and Welfare, Japan; the Health and Labour Sciences Research Grant on Intractable Diseases (Pathogenesis and Diagnostic Accuracy of Neuropathic Pain, 23170301 to SI), the Ministry of Public Health, Labour and Welfare, Japan.

References

1. MacDonald BK, Cockerell OC, Sander JW, Shorvon SD. The incidence and lifetime prevalence of neurological disorders in a prospective community-based study in the UK. Brain: a journal of neurology **123**: 665-676, 2000.
2. Beghi E, Kurland LT, Mulder DW, Nicolosi A. Brachial plexus neuropathy in the population of Rochester, Minnesota, 1970-1981. Ann Neurol **18**: 320-323, 1985.
3. van Alfen N, van Engelen BG. The clinical spectrum of neuralgic amyotrophy in 246 cases. Brain **129**: 438-450, 2006.
4. Collie AM, Landsverk ML, Ruzzo E, et al. Non-recurrent SEPT9 duplications cause hereditary neuralgic amyotrophy. J Med Genet **47**: 601-607, 2010.
5. Magee KR, Dejong RN. Paralytic brachial neuritis. Discussion of clinical features with review of 23 cases. JAMA **174**: 1258-1262, 1960.
6. England JD, Sumner AJ. Neuralgic amyotrophy: an increasingly diverse entity. Muscle Nerve **10**: 60-68, 1987.
7. Cruz-Martinez A, Barrio M, Arpa J. Neuralgic amyotrophy: variable expression in 40 patients. J Peripher Nerv Syst **7**: 198-204, 2002.
8. Brooks BR. El Escorial World Federation of Neurology criteria for the diagnosis of amyotrophic lateral sclerosis. Subcommittee on Motor Neuron Diseases/Amyotrophic Lateral Sclerosis of the World Federation of Neurology Research Group on Neuromuscular Diseases and the El Escorial "Clinical limits of amyotrophic lateral sclerosis" workshop contributors. J Neurol Sci **124** (Suppl): 96-107, 1994.
9. van Alfen N, van der Werf SP, van Engelen BG. Long-term pain, fatigue, and impairment in neuralgic amyotrophy. Arch Phys Med Rehabil **90**: 435-439, 2009.
10. van Eijk JJ, van Alfen N, Berrevoets M, van der Wilt GJ, Pillen S, van Engelen BG. Evaluation of prednisolone treatment in the acute phase of neuralgic amyotrophy: an observational study. J Neurol Neurosurg Psychiatry **80**: 1120-1124, 2009.
11. van Alfen N, van Engelen BG, Hughes RA. Treatment for idiopathic and hereditary neuralgic amyotrophy (brachial neuritis). Cochrane Database Syst Rev CD006976, 2009.
12. Kuhlenbaumer G, Stogbauer F, Timmerman V, De Jonghe P. Diagnostic guidelines for hereditary neuralgic amyotrophy or heredofamilial neuritis with brachial plexus predilection. On behalf of the European CMT Consortium. Neuromuscul Disord **10**: 515-517, 2000.
13. Kusunoki S, Chiba A, Kon K, et al. N-acetylgalactosaminyl GD1a is a target molecule for serum antibody in Guillain-Barre syndrome. Ann Neurol **35**: 570-576, 1994.
14. Moriguchi K, Miyamoto K, Takada K, Kusunoki S. Four cases of anti-ganglioside antibody-positive neuralgic amyotrophy with good response to intravenous immunoglobulin infusion therapy. J Neuroimmunol **238**: 107-109, 2011.
15. Nobile-Orazio E, Meucci N, Barbieri S, Carpo M, Scarlato G. High-dose intravenous immunoglobulin therapy in multifocal motor neuropathy. Neurology **43**: 537-544, 1993.
16. Lott JA, Warren P. Estimation of reference intervals for total protein in cerebrospinal fluid. Clin Chem **35**: 1766-1770, 1989.
17. van Alfen N. Clinical and pathophysiological concepts of neural-

gic amyotrophy. Nat Rev Neurol **7**: 315-322, 2011.

18. Tsao BE, Avery R, Shields RW. Neuralgic amyotrophy precipitated by Epstein-Barr virus. Neurology **62**: 1234-1235, 2004.

19. Nakajima M, Fujioka S, Ohno H, Iwamoto K. Partial but rapid recovery from paralysis after immunomodulation during early stage of neuralgic amyotrophy. Eur Neurol **55**: 227-229, 2006.

20. Al Masri O, Fathallah W, Quader S. Recovery of tacrolimus-associated brachial neuritis after conversion to everolimus in a pediatric renal transplant recipient: case report and review of the literature. Pediatr Transplant **12**: 914-917, 2008.

21. Vriesendorp FJ, Dmytrenko GS, Dietrich T, Koski CL. Anti-peripheral nerve myelin antibodies and terminal activation products of complement in serum of patients with acute brachial plexus neuropathy. Arch Neurol **50**: 1301-1303, 1993.