Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.1723-18
Intern Med 58: 855-859, 2019
http://internmed.jp

【 CASE REPORT 】

Severe Chronic Inflammatory Demyelinating Polyneuropathy Ameliorated following High-dose (3 g/kg) Intravenous Immunoglobulin Therapy

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Abstract:
We report the case of a 53-year-old woman with severe chronic inflammatory demyelinating polyneuropathy (CIDP) who developed progressive tetraplegia with respiratory failure despite receiving a standard dose of intravenous immunoglobulin therapy (IVIg), steroid pulse therapy, plasma exchange, and cyclosporine. We administered high-dose IVIg (3 g/kg; 0.6 g/kg/day for 5 consecutive days at monthly intervals). The patient's muscle weakness gradually improved after IVIg. She recovered completely 2 years after the onset of symptoms. The effects of IVIg treatment in individuals with CIDP may vary in each patient. In patients with refractory CIDP receiving standard-dose IVIg, repeated high-dose IVIg treatment can be considered.

Key words: chronic inflammatory demyelinating polyneuropathy (CIDP), pentaplegia, respiratory failure, high-dose intravenous immunoglobulin therapy (IVIg)

(Intern Med 58: 855-859, 2019)
(DOI: 10.2169/internalmedicine.1723-18)

Introduction

Chronic inflammatory demyelinating polyneuropathy (CIDP) is treated with intravenous immunoglobulin therapy (IVIg), corticosteroids, and/or plasma exchange (PE). Retrospective studies have indicated that, overall, 64-76% of CIDP patients respond to IVIg (1, 2). IVIg has been established as the first-choice treatment for CIDP (3), and CIDP rarely becomes severe or causes respiratory failure when standard treatments are used (4). The standard dose of IVIg is 2 g/kg (0.4 g/kg/day for 5 consecutive days). However, the degree of treatment response to immunoglobulin differs between patients with CIDP, and the time to and duration of the maximum effect can vary from weeks to months (5). The standard dose of IVIg is sometimes insufficient, and higher doses or repeated administrations are required. We herein report a severe case of CIDP that persisted-despite the administration of standard-dose IVIg-that was effectively treated with repeated high-dose IVIg (3 g/kg; 0.6 g/kg/day for 5 consecutive days at monthly intervals).

Case Report

The patient was a 53-year-old woman who had been diagnosed with diabetes mellitus at 50 years of age, who became aware of numbness in both lower legs 3 months prior to seeking medical intervention. She realized that she was experiencing difficulty walking 1 month prior to visiting a local hospital. She had no family history of neurological disease.

When she visited the local hospital, muscle weakness and sensory disturbance were observed in the distal parts of all limbs. Deep tendon reflexes were absent. Nerve conduction studies (NCSs) revealed that the motor nerve conduction velocity (MCV) in her median nerve was decreased to 15.1 m/s. We were unable to evoke F-wave or sensory nerve action potentials (Table). These findings met the definite category of electrodiagnostic criteria for CIDP according to the definition of the European Federation of Neurological Socie-

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Received: June 19, 2018; Accepted: September 6, 2018; Advance Publication by J-STAGE: November 19, 2018
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Table. The Nerve Conduction Study Results.

Nerve	Amplitude (mV)					Conduction Velocity (m/sec)					Latency (msec)				
	0 M	3 M	12 M	16 M	normal range	0 M	3 M	12 M	16 M	normal range	0 M	3 M	12 M	16 M	normal range
Rt.Median															
Wrist	2.3	0.8	0.5	1.8	11.8 (4.6-19.0)	15.1	10.3	NE	NE	58 (51-65)	9.5	11.3	14.2	11.9	3.5 (2.3-4.6)
Elbow	1.2	0.4	NE	NE							20.5	30.5	NE	NE	
F-wave	NE	NE	NE	NE											
Rt.Ulner															
Wrist	3.2	1.1	0.4	1.2	15.5 (9.1-21.9)	20.4	15.2	12.1	12.1	60 (50-65)	6.3	10.2	10.7	10.6	2.6 (2.1-3.2)
Elbow	2.3	0.6	0.2	0.2							16.8	24.8	27.5	27.4	
F-wave	NE	NE	NE	NE											
Rt.Tibial															
Medial malleolus	0.9	NE	NE	NE	13.2 (5.0-21.4)	19.5	NE	NE	NE	48 (41-55)	13.3	NE	NE	NE	5.4 (4.2-6.5)
Popliteal fossa	0.4	NE	NE	NE							31.7	NE	NE	NE	
F-wave	NE	NE	NE	NE											

0 M: The first time the patient visited the hospital, 3 M: following the initial administration of IVIg, plasma exchange, and steroid pulse therapy, 12 M: after repeated high-dose IVIg (3 g/kg/month), 16 M: the patient was able to walk after repeated standard-dose IVIg (2 g/kg/month), NE: not evoked

ties/Peripheral Nerve Society (6).

A sural nerve biopsy was performed. Thin myelin sheaths and a reduction in the myelinated fiber density were found. Subperineurial edema, inflammation, and onion bulb formation were absent. Based on these results, the patient was diagnosed with CIDP. Standard-dose IVIg with steroid pulse therapy (methylprednisolone 1 g/day for 3 days) was provided. Prednisolone (PSL; 60 mg/day) was continued after these therapies. There was a transient improvement in the patient's numbness, but her muscle weakness progressed. She was transferred to our hospital.

The patient had distally-dominant symmetrical muscle weakness. In a manual muscle strength test, the patient's distal muscle strength was grade 3 and her proximal muscle strength was grade 4. No muscle atrophy was observed. It was difficult for her to stand without assistance. Paresthesia and disturbance of the superficial and deep sensations were recognized in the distal parts of all limbs. Deep tendon reflexes had disappeared in all limbs. No abnormalities were found in the patient's cranial nerves or autonomic nervous system. The NCS revealed that the MCV of the patient's median nerve had further decreased to 10.3 m/s. Temporal dispersion, extension of the distal latency, and prolongation of the F-wave latency were observed at the median, ulnar, and posterior tibial nerves. Complex sensory nerve potentials were not evoked (Table). Magnetic resonance imaging (MRI) confirmed remarkable contrast enhancement of the lumbar nerve root (Fig. 1a).

A biochemical examination revealed no abnormal findings, with the exception of a glycated hemoglobin level of 8.4%. The results of screening tests for anti-ganglioside antibody, monoclonal immunoglobulin, Hu, Yo, Borrelia, human T-lymphotropic virus 1, human immunodeficiency virus, and syphilis reaction were negative. The patient's levels of serum angiotensin-converting enzyme and vitamins B1, B12, and E were normal. No malignant tumors or tumor markers were detected. The individual's cerebrospinal fluid (CSF) protein level was 91 mg/dL, the number of cells was 4/mm^3, and the IgG index was 0.76. No malignant cells were detected in CSF cytology.

The patient was treated using plasma exchange, standard-dose IVIg, weekly maintenance IVIg (0.4 g/kg/day weekly), and cyclosporine (5 mg/kg/day). Nevertheless, the muscle weakness and sensory disturbance progressed. The patient exhibited quadriplegia, respiratory muscle paralysis, and facial muscle weakness. As a result, mechanical ventilation was introduced (Fig. 2). Bilateral pupillary dilatation appeared. At this time, MRI revealed contrast in the facial and trigeminal nerves Fig. 1b and c. The CSF protein level was increased to 452 mg/dL. High-dose IVIg (3 g/kg; 0.6 g/kg/day for 5 consecutive days) was therefore administered alongside steroid pulse therapy and PSL (60 mg/day) was continued. After receiving this treatment, the individual experienced improvements in her numbness and muscle weakness, although the effects diminished the following month. High-dose IVIg was therefore administered again 1 month later, and was repeated at monthly intervals over the course of 6 months. The patient's muscle strength improved, and she was weaned off the ventilator after the second administration of high-dose IVIg. The patient was able to lift her upper limbs after 3 courses of high-dose IVIg and was able to lift her lower limbs after 6 courses of high-dose IVIg. The dose of IVIg was then changed to the standard dose and IVIg was administered at monthly intervals. The patient's muscle weakness gradually improved after repeated administrations of standard-dose IVIg. She was able to walk 1 year after the initial administration of high-dose IVIg. After 12 administrations of standard-dose IVIg, the patient's CIDP no longer interfered with her daily life. Although she complained of the recurrence of slight muscle weakness, the IVIg administration schedule was changed from once per month to once per year. The patient has not had any recur-

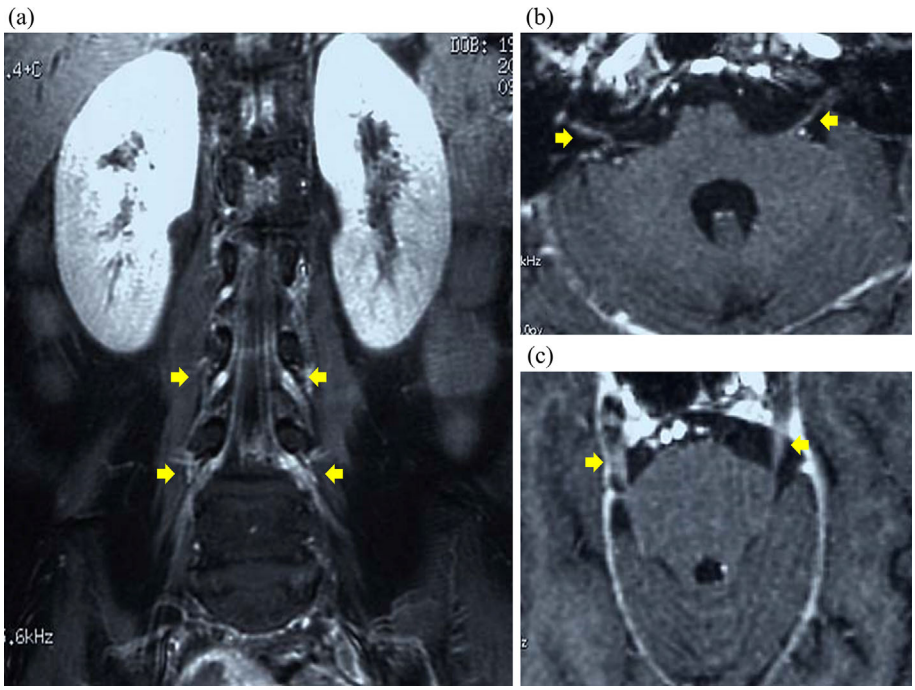

Figure 1. The MRI findings. T1-weighted MRI with contrast agent in the most advanced stage at 7 months from admission. Enhancement was clearly observed (a) in the lumbar nerve root and nerve (a), the facial nerve (b) and the trigeminal nerves (c) (arrows).

rences in the past 8 years. The total amount of IVIg administered was 2,875 g, and no marked adverse reactions were observed. This was a case of severe CIDP with pentaplegia and respiratory failure that required a large total dose of IVIg and was characterized by a long recovery period.

Discussion

IVIg has been established as the first choice of treatment for CIDP (3). However, the efficacy at the standard dose is often insufficient and additional or repeated administrations are often required for it to be effective (7). PE and steroid pulse therapy are performed when IVIg is not sufficiently effective. Nevertheless, improvement may not be observed, even with the addition of these treatments. Standard CIDP treatment should be attempted first. However, increased doses of IVIg can be considered if the effect is insufficient.

A dose-response study was performed in 40 patients with CIDP to assess the efficacy of IVIg (0.25, 1, and 2 g/kg) (8). In that study, higher doses were significantly more effective than lower doses, and additional higher doses of IVIg were sometimes effective in cases for which IVIg was ineffective. These results suggest that higher doses and the serial administration of IVIg are more effective in cases in which standard IVIg is ineffective.

The Japanese clinical guidelines recommend the intravenous injection of immunoglobulin (0.4 g/kg/day) over 5 consecutive days (2 g/kg) (9). The European Federation of Neurological Sciences/Peripheral Nerve Society 2010 guidelines recommend individualization of the appropriate IVIg maintenance dose and frequency based on the patient's treatment response, typically between 0.4 and 1.2 g/kg, every 2 to 6 weeks (6). A dose of 1 g/kg/day over 2 consecutive days (2 g/kg) is commonly administered in Europe and the United States. Lunn reported treatment with 2 g/kg IVIg every week to 3 weeks in severe cases of CIDP (10).

There have been no reports of treatment with IVIg at a dose greater than 2 g/kg every third week in Japan until now. However, in this case, sufficient effectiveness was observed without adverse events (*e.g.*, thrombosis), which can occur in a dose-dependent manner. The initial standard dose of IVIg is 2 g/kg. However, the IVIg dose and administration interval should be defined on an individual basis for each patient, especially in severe cases.

In this case, the standard IVIg dose was slightly effective, but the weekly administration (0.4 g/kg for one day) was ineffective. Although combined with steroid pulse therapy with PSL (60 mg/day), the addition of high-dose IVIg (0.6 g/kg/day for 5 consecutive days) clearly facilitated the faster improvement of parent's symptoms.

During standard IVIg administration and weekly maintenance IVIg (0.4 g/kg/day weekly), the serum IgG concentration was 1,400-2,230 mg/dL. During high-dose IVIg administration, the serum IgG concentration was 2,356-3,520 mg/dL. Debs reported that the serum IgG concentration is correlated with the clinical state, and that the monitoring of the serum IgG level is helpful for guiding the dosage and frequency of IVIg treatment (11). In this study, achieving a high serum IgG level was effective.

Based on these findings, if the standard dose of IVIg is ineffective, effectiveness might be achieved by increasing the dose. Thus, high-dose IVIg treatment can be considered

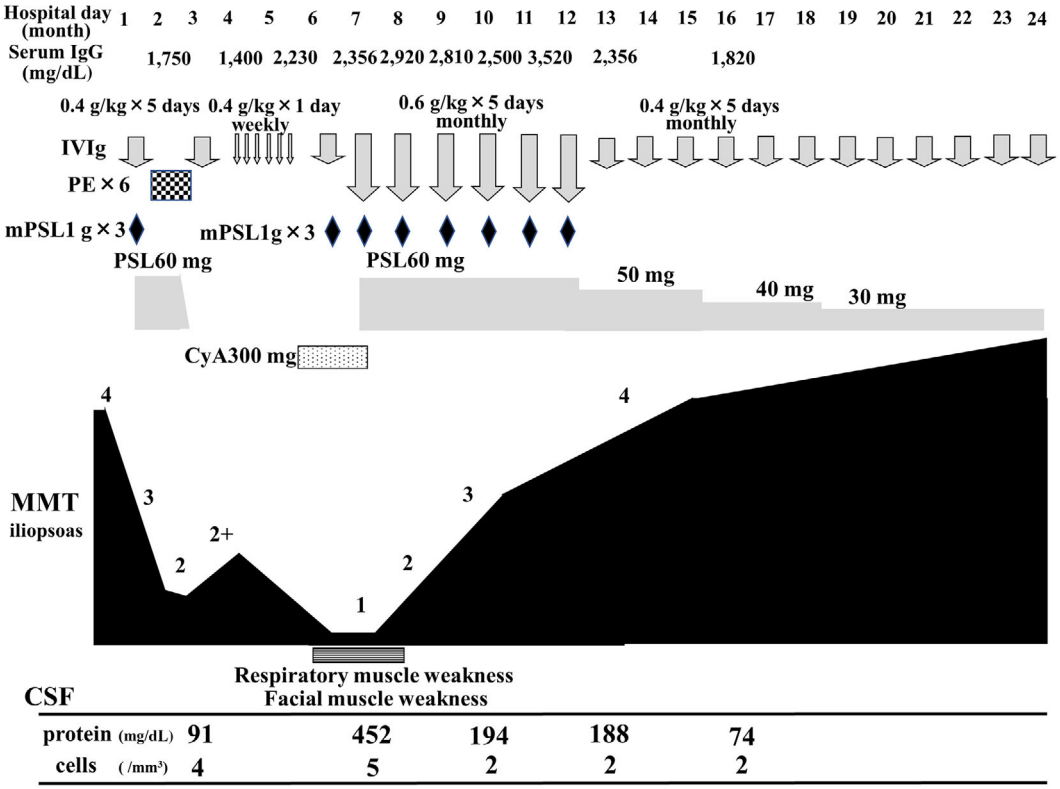

Figure 2. **The clinical course and therapy. The initial administration of standard-dose IVIg, plasma exchange (PE), steroid pulse therapy (mPSL) with oral prednisolone (PSL) did not improve the patient's symptoms. The additional administration of cyclosporine A (CyA) was not effective. The patient developed pentaplegia requiring respirator support during hospital months 6 to 8. After the introduction of high-dose IVIg (0.6 g/kg/day for 5 consecutive days) combined with mPSL and PSL, the patient showed a marked improvement from pentaplegia and was weaned off the artificial ventilator after the repeated administration of high-dose IVIg. After 12 months of hospitalization, the dose of IVIg was changed to the standard dose and the oral PSL dose was gradually decreased. She was able to walk at 1 year after the initiation of therapy. Although she complained of the recurrence of slight muscle weakness, the IVIg administration schedule was changed from once per month to once per year. The patient has not had any recurrences in the past 8 years. The total dose of IVIg was 2,875 g, and no marked adverse reactions were observed.**

for cases of severe and treatment-resistant CIDP, such as ours. In our case, a complete recovery from respiratory failure and pentaplegia was achieved.

Currently, there are no conclusions as to whether the peak or trough value is important in IVIg administration. In the future, it will be necessary to consider increasing the dose of IVIg (frequency or 1-course dose).

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

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