Journal of the Neurological Sciences 384 (2018) 107–112

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Clinical Short Communication

Parallel fluctuation of anti-neurofascin 155 antibody levels with clinico-electrophysiological findings in patients with chronic inflammatory demyelinating polyradiculoneuropathy

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ARTICLE INFO

Keywords:
Neurofascin 155
Chronic inflammatory demyelinating polyradiculoneuropathy
Node of Ranvier
Paranode
Autoantibody
Nerve conduction study

ABSTRACT

Background: The long-term clinical course and closely related biomarkers in chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) with anti-neurofascin 155 (NF155) antibodies remain to be elucidated.
Methods: We retrospectively studied the longitudinal clinical courses of three Japanese male anti-NF155 antibody-positive CIDP patients. Anti-NF155 antibody levels were measured by flow cytometry using HEK293 cell lines stably expressing human NF155.
Results: All three patients presented with chronic progressive sensorimotor disturbance, with ages at onset of 16, 26, and 34 years old, and they were followed for 58, 31, and 38 months, respectively, from the onset. All patients had postural tremor and generalized decreased deep tendon reflexes. Peak cerebrospinal fluid protein levels were > 400 mg/dl, and nerve conduction studies (NCS) showed severe demyelination patterns. Combined immunotherapies including intravenous immunoglobulin, plasma exchange, corticosteroids, and other immunosuppressants ameliorated clinical severity and NCS abnormalities, with improvements of > 10 kg in grip strength and at least 20% in F-wave latencies. However, their symptoms exacerbated after the immunotherapies were tapered. Anti-NF155 antibody levels varied in parallel with the clinical and electrophysiological changes, or preceded them.
Conclusion: The patients' clinical courses suggest that anti-NF155 antibody levels and NCS findings could be disease activity markers in anti-NF155 antibody-positive CIDP.

1. Introduction

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is an acquired immune-mediated disorder affecting the peripheral nerves. CIDP has heterogeneous mechanisms with both cell-mediated and humoral immunities playing pathogenic roles [1]. Recently we, and others, reported that subsets of CIDP patients harbor autoantibodies against paranodal proteins, such as neurofascin 155 (NF155) [2–6], contactin-1 (CNTN1) [7–9], and contactin-associated protein 1 [10].

CIDP patients with anti-NF155 antibodies have several distinctive features compared with those without [3–5]. Although poor responses to intravenous immunoglobulin (IVIg) and the efficacy of corticosteroids have been documented in the treatment of CIDP with anti-NF155 antibodies [3–5], its long-term clinical course remains elusive. In this study, we investigated the longitudinal clinical courses of three anti-NF155 antibody-positive CIDP patients whose clinical and electrophysiological findings were improved by immunotherapies and then deteriorated again after treatment was tapered. Interestingly, fluctuations in their anti-NF155 antibody levels were paralleled by clinical and electrophysiological changes.

2. Materials and methods

2.1. Patients and data collection

We retrospectively reviewed the medical records of three Japanese male anti-NF155 antibody-positive CIDP patients with ages at onset of

Abbreviations: CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; CNTN1, contactin-1; CSF, cerebrospinal fluid; DTRs, deep tendon reflexes; EFNS/PNS, European Federation of Neurological Societies/Peripheral Nerve Society; turbo GFP, turbo green fluorescent protein; IVIg, intravenous immunoglobulin; MCV, motor nerve conduction velocity; MFI, mean fluorescence intensity; MRI, magnetic resonance imaging; NCS, nerve conduction studies; NF155, neurofascin 155; PSL, prednisolone

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https://doi.org/10.1016/j.jns.2017.11.035
Received 25 July 2017; Received in revised form 7 November 2017; Accepted 26 November 2017
Available online 27 November 2017
0022-510X/

16, 26, and 34 years old. All were included in our previous Japanese prevalence study [4]. The disease onset dates of Patients 1, 2, and 3 were November 2011, February 2014, and July 2013, respectively, and follow-up was continued until September 2016. Thus, the time of observation was 58 months for Patient 1, 31 months for Patient 2, and 38 months for Patient 3. Their clinical severities were evaluated by a full neurological examination, deep tendon reflexes (DTRs), grip strength test, Hughes functional grading [11], and nerve conduction studies (NCS). Sera were collected at various time points for anti-NF155 antibody assays. This study was approved by the Ethical Review Boards of Kyushu University Hospital. All patients provided written informed consent.

2.2. Electrophysiological studies

NCS were performed by conventional procedures using a Neuropack MEB-2200 (Nihon Kohden, Japan) as described previously [12]. Skin temperature was routinely maintained at 32–35 °C for the hands and 30–35 °C for the feet during experiments. As the follow-up time was approximately 2–5 years, a series of skilled examiners were involved in the NCS studies. Motor NCS including F-wave analyses were evaluated in the median, ulnar, and tibial nerves. Sensory NCS were performed in the median, ulnar, and sural nerves. Base-to-peak amplitudes were measured for compound muscle action potentials and sensory nerve action potentials.

2.3. Flow cytometric assay for anti-NF155 antibodies

Anti-NF155 antibodies were measured as described previously [4]. In brief, NF155-turbo green fluorescent protein (turbo GFP)-transfected and naive HEK293 cells were mixed in equal proportions. Serum samples were added to cell-containing solution (1:20 dilution). After incubation at 4 °C for 60 min, the cells were washed and bound IgG was detected with Alexa 647-labeled anti-human IgG antibodies (Life Technologies, Carlsbad, CA), diluted 1:500. After further incubation at 4 °C for 60 min, cells were washed and analyzed by MACSQuant Analyzer (Miltenyi Biotec, Bergisch Gladbach, Germany). The mean fluorescence intensities (MFI) of cell-associated turbo GFP and Alexa 647 were measured for each sample. The MFI ratio was calculated by dividing the Alexa 647 MFI of NF155-transfected cells by the Alexa 647 MFI of NF155-untransfected cells. ΔMFI was calculated by subtracting the Alexa-647 MFI of NF155-untransfected cells from the Alexa 647 MFI of NF155-transfected cells. Both MFI ratio and ΔMFI were successively decreased with serial dilutions of each patient's pooled sera (Fig. S1). We had previously shown that both MFI ratio and ΔMFI values significantly positively-correlate with ELISA optical density values in anti-human NF155 antibody-positive sera [6]. All frozen serum samples were thawed just before antibody measurements were performed and analyzed concurrently under the same conditions.

3. Results

3.1. Clinical course

Patient 1, a 16-year-old man, developed progressive gait disturbance over 3 months (Fig. 1). His initial neurological examination revealed distal-dominant weakness of the lower extremities, severe sensory ataxia, generalized areflexia, and postural tremor of the upper limbs. He had no cerebellar ataxia. His cerebrospinal fluid (CSF) protein level was 412 mg/dl at the peak of his illness and his CSF white blood cell count was 7/μl. NCS showed prolonged distal and F-wave latencies and decreased motor nerve conduction velocity (MCV) in all nerves tested, meeting the European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS) electrophysiological criteria for definite CIDP (Table S1). Brain magnetic resonance imaging (MRI) showed no demyelinating lesions. Accordingly, he was diagnosed with CIDP. Although IVIg treatment (400 mg/kg/day for 5 days) was carried out, his symptoms, including grip strength, worsened. He then received methylprednisolone pulse therapy (1000 mg/day for 3 days) followed by oral prednisolone (PSL) at a dose of 60 mg/day. This was gradually tapered and ameliorated his muscle weakness, areflexia, and sensory impairment over the following 2 years. Although MRI neurography disclosed hypertrophy of the cervical and lumbosacral roots/plexuses (Fig. S2), NCS findings at the 33rd month from onset showed clear improvement compared with those at the 7th month (Table S1). After tapering oral corticosteroids to 5 mg/day, his grip strength gradually worsened and almost all of his NCS parameters were consistently exacerbated again by the 58th month from onset. However, he did not complain of any subjective symptoms. Therefore, we carefully observed his symptoms without any additional immunotherapy during the follow-up period.

Patient 2, a 26-year-old man, developed paresthesia of the lower extremities and gait disturbance over 2 months (Fig. 2). He could not run because of a severe disturbance of deep sensation in the lower extremities, although his muscle strength was maintained. His DTRs were decreased in all four limbs. His peak CSF protein level was 454 mg/dl and his CSF white blood cell count was 6/μl. Prolongation of distal and F-wave latencies was evident on NCS, which met EFNS/PNS electrophysiological criteria for definite CIDP (Table S1). Neither brain nor spinal cord lesions were found by MRI. Although IVIg (400 mg/kg/day for 5 days) was administered, his paresthesia worsened and his grip strength further decreased. Therefore, methylprednisolone pulse therapy (1000 mg/day for 3 days) followed by oral PSL (50 mg/day) with gradual taper was introduced. Oral azathioprine (25–50 mg/day) and a second course of IVIg (400 mg/kg/day for 5 days) were added. After starting intensive therapy, his sensory disturbance gradually improved enough to enable running. His DTRs and grip strength also returned to normal. Although hypertrophy of cervical and lumbosacral roots/plexuses was revealed by MRI neurography (Fig. S2), distal and F-wave latencies of all nerves recorded at the 13th month from onset were improved compared with those at the 8th month. However, at the 19th month from onset, when his dose of oral PSL was tapered to 8 mg/day, he complained of a deterioration of walking and paresthesia in the distal parts of all four limbs. Postural finger tremor without cerebellar ataxia was observed. His NCS findings also deteriorated, while the hypertrophy of roots/plexuses did not change (Fig. S2). Although the immunotherapy was again reinforced by increasing the dosage of oral PSL up to 25 mg/day and adding 200 mg/day of cyclosporine A, his grip strength did not improve and his NCS results continued to worsen (Fig. 2 and Table S1).

Patient 3, a 34-year-old man, noticed paresthesia and weakness in both lower extremities, which progressively worsened over the following 6 months (Fig. 3). Neurological examinations revealed bilateral facial weakness and paresthesia, weakness of both proximal and distal muscles, sensory impairment in a glove and stocking distribution, and generalized areflexia. His peak CSF protein level was 406 mg/dl, and his CSF white blood cell count was 6/μl. NCS disclosed prolonged distal latencies and decreased MCV in all recorded nerves (Table S1). Prolongation or absence of F-waves was also observed in these nerves. These findings fulfilled the EFNS/PNS electrophysiological criteria for definite CIDP. No brain or spinal cord lesions were identified by MRI. He was diagnosed with CIDP. As his symptoms worsened significantly, two courses of IVIg (400 mg/kg/day for 5 days) and methylprednisolone pulse therapy (1000 mg/day for 3 days) were given, followed by oral PSL (60 mg/day) with gradual taper. When he was referred to our clinic, 3 months on from these initial treatments, he still had severe hand weakness with intrinsic hand muscle atrophy, postural tremor of the upper limbs, and difficulty walking, even though he subjectively felt some improvement from the worst stage of his condition. Hypertrophic cervical and lumbosacral roots/plexuses were revealed by MRI neurography (Fig. S2). Two courses of plasma exchange (a total of eight sessions, median exchanged plasma volume per session 1873 ml, range