JCN Open Access ORIGINAL ARTICLE

pISSN 1738-6586 / eISSN 2005-5013 / J Clin Neurol 2024;20(2):186-193 / https://doi.org/10.3988/jcn.2023.0055

Clinical Features of Autoimmune Nodopathy With Anti-Neurofascin-155 Antibodies in South Koreans

Hyun Ji Lyou[a,b*]
Yeon Hak Chung[c*]
Min Ju Kim[a]
MinGi Kim[a]
Mi Young Jeon[c]
Seung Woo Kim[a]
Ha Young Shin[a]
Byoung Joon Kim[c]

[a]Department of Neurology, Yonsei University College of Medicine, Seoul, Korea
[b]Department of Neurology, Korea University Guro Hospital, Korea University College of Medicine, Seoul, Korea
[c]Department of Neurology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

Background and Purpose Anti-neurofascin-155 (NF155) antibody is one of the autoantibodies associated with autoimmune nodopathy. We aimed to determine the clinical features of South Korean patients with anti-NF155-antibody-positive autoimmune nodopathy.

Methods The sera of 68 patients who fulfilled the diagnostic criteria for chronic inflammatory demyelinating polyneuropathy (CIDP) were tested for anti-NF155 antibodies using a cell-based assay (CBA) and enzyme-linked immunosorbent assay (ELISA). The anti-NF155-positive sera were also assayed for NF155 immunoglobulin G (IgG) subclasses, and for anti-NF186 and NF140 antibodies. The clinical features of the patients were reviewed retrospectively.

Results Among the 68 patients, 6 (8.8%) were positive for anti-NF155 antibodies in both the CBA and ELISA. One of those six patients was also positive for anti-NF186 and anti-NF140 antibodies. IgG4 was the predominant subclass in four patients. The mean age at onset was 32.2 years. All six positive patients presented with progressive sensory ataxia. Five patients treated using corticosteroids presented a partial or no response. All six patients were treated using intravenous immunoglobulin (IVIg). Among them, five exhibited a partial or poor response and the other exhibited a good response. All three patients treated using rituximab showed a good response.

Conclusions The clinical characteristics of the patients were consistent with those in previous studies. Anti-NF155 antibody assay is necessary for diagnosing autoimmune nodopathy and its appropriate treatment, especially in young patients with CIDP who present with sensory ataxia and poor therapeutic responses to corticosteroids and IVIg.

Keywords peripheral neuropathy; autoimmune diseases; autoantibodies; neurofascin; nodes of Ranvier.

Received February 7, 2023
Revised May 2, 2023
Accepted June 14, 2023

Correspondence
Ha Young Shin, MD, PhD
Department of Neurology, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, Korea
Tel +82-2-2228-1600
Fax +82-2-393-0705
E-mail hayshin@yuhs.ac

Byoung Joon Kim, MD, PhD
Department of Neurology, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81 Irwon-ro, Gangnam-gu, Seoul, 06351, Korea
Tel +82-2-3410-2379
Fax +82-2-2341-0052
E-mail bjkim@skku.edu

*These authors contributed equally to this work.

INTRODUCTION

Autoantibodies against proteins at the nodes and paranodes of Ranvier, such as neurofascin (NF)-155 (NF155), NF186, contactin-1, and contactin-associated protein 1, were recently found in a small proportion of patients who fulfilled the clinical and electrodiagnostic criteria for chronic inflammatory demyelinating polyneuropathy (CIDP).[1,2] Patients with these autoantibodies have characteristic clinical features, pathological findings, and poor responses to intravenous immunoglobulin (IVIg) treatment that can distinguish them from patients with CIDP, and autoimmune nodopathy has been proposed as a new category of acquired immune neuropathy associated with autoantibodies against nodal and paranodal proteins.[3]

Anti-NF155 is the most common autoantibody in autoimmune nodopathy. NF155 is a cell adhesion molecule expressed in the myelin loop and involved in the formation of septate-like junctions that anchor the myelin loop to axons at paranodes.[4] These junctions play an important role in the compartmentalization of nodal-voltage-gated sodium channels

and juxtaparanodal-voltage-gated potassium channels, and in the generation of action potentials.[5,6] Previous studies have identified distinct features in patients with anti-NF155 antibody, including predominant distal involvement, sensory ataxia, tremor, highly elevated protein levels in the cerebrospinal fluid (CSF), poor responses to IVIg, good responses to rituximab, and predominance of the immunoglobulin G (IgG)-4 subclass of anti-NF155 antibodies.[7-10] However, autoimmune nodopathy with anti-NF155 antibodies has not yet been observed in South Korea.

In this study we aimed to identify anti-NF155 antibodies in patients who fulfilled the diagnostic criteria for CIDP using a cell-based assay (CBA) and enzyme-linked immunosorbent assay (ELISA), and to determine the clinical features of South Korean patients with anti-NF155-antibody-positive autoimmune nodopathy.

METHODS

Patients and samples

This study obtained 72 serum samples from 68 patients who fulfilled the 2010 European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS) diagnostic criteria for CIDP (52 with definite, 11 with probable, and 5 with possible CIDP) from Samsung Medical Center and Severance Hospital in South Korea. Five serum samples were collected from one patient at various points during the disease course. Sera were also collected from 12 healthy individuals, 16 patients with inflammatory CNS diseases (10 with multiple sclerosis, 2 with myelin oligodendrocyte glycoprotein antibody disease, 1 with neuromyelitis optica spectrum disorder, and 3 with unspecified inflammatory brain lesions), and 4 patients with other immune-mediated neuropathies (2 with IgM paraproteinemic neuropathy, 1 with multifocal motor neuropathy, and 1 with Miller Fisher syndrome). All serum samples were stored at -70°C until they were further analyzed.

Cell-based assay

Serum samples were analyzed to detect autoantibodies against NF155 using a CBA with NF155-transfected human recombinant embryonic kidney 293 (HEK293) cells. HEK293 cells were placed on a coverslip (SPL Life Sciences, Pocheon, South Korea) coated with poly-L-lysine (Sigma Aldrich, St. Louis, MO, USA) and then placed on 24-well cell culture plates. Cells were grown in Dulbecco Modified Eagle Medium (GE Healthcare, Chicago, IL, USA) that contained 10% Fetal Bovine Serum (GE Healthcare) and 5% penicillin (Invitrogen, Waltham, MA, USA) at 70%−80% confluence. The cells were transfected with a green fluorescent protein (GFP)-tagged RG22907 NF155 plasmid (OriGene, Rockville, MD, USA). Immunofluorescence staining was performed after 48 h of incubation.

HEK293 cells that expressed GFP-tagged NF155 were fixed in phosphate-buffered saline using 4% paraformaldehyde and blocked using 5% bovine serum albumin. The cells were incubated for 1 h at room temperature with rabbit anti-NF polyclonal antibody (Invitrogen) or serum samples from patients and healthy controls (dilution, 1:20). The cells were then incubated for 45 min in the dark at room temperature, with goat antirabbit IgG or goat antihuman IgG (H+L) conjugated using Alexa Fluor 594 (Invitrogen; dilution, 1:750). CBA results were evaluated using a fluorescence microscope (Zeiss, Oberkochen, Germany), which included measuring the fluorescence intensity of NF155-transfected HEK293 cells and the overlapping of GFP-tagged NF155 (green fluorescence) and Alexa-Fluor-594-conjugated antibody (red fluorescence). The colocalization of green and red fluorescence on the cells was considered a result of anti-NF155 antibody positivity.

Enzyme-linked immunosorbent assay

An ELISA was performed on all serum samples to confirm the presence of anti-NF155 antibodies. Serum samples that were positive for anti-NF155 antibodies in both the CBA and ELISA were further evaluated for anti-NF186 and anti-NF140 antibodies, and to identify the IgG subclass.

Human recombinant NF155 (OriGene), NF186 (OriGene), or NF140 (Sino Biological) was coated onto 96-well plates, where they remained at 4°C overnight. The serum samples (dilution, 1:100) were then added after blocking. Horseradish-peroxidase-conjugated antihuman IgG (Dako; dilution, 1:5,000) was added for 1 h at room temperature after 1 h of incubation and washing. The ELISA was performed using TMB substrate solution, and the reaction was stopped using 1%-HCl-based solution (SeraCare, Milford, MA, USA). The optical density (OD) was measured at 450 nm using a VersaMax Microplate Reader (Molecular Devices, San Jose, CA, USA). The OD of a blank sample was subtracted from the values for the serum samples. The test was considered positive when the OD was 5 standard deviations (SDs) higher than that in an average healthy control. Horseradish-peroxidase-conjugated mouse antihuman IgG1, IgG2, IgG3, and IgG4 secondary antibodies (Invitrogen; dilution, 1:5,000) were used to identify IgG subclasses. Additional tests were also performed on a patient with anti-NF155 seropositivity who had undergone serial serum sampling to evaluate changes in OD values during the course of the disease. All serum samples were tested in duplicate.

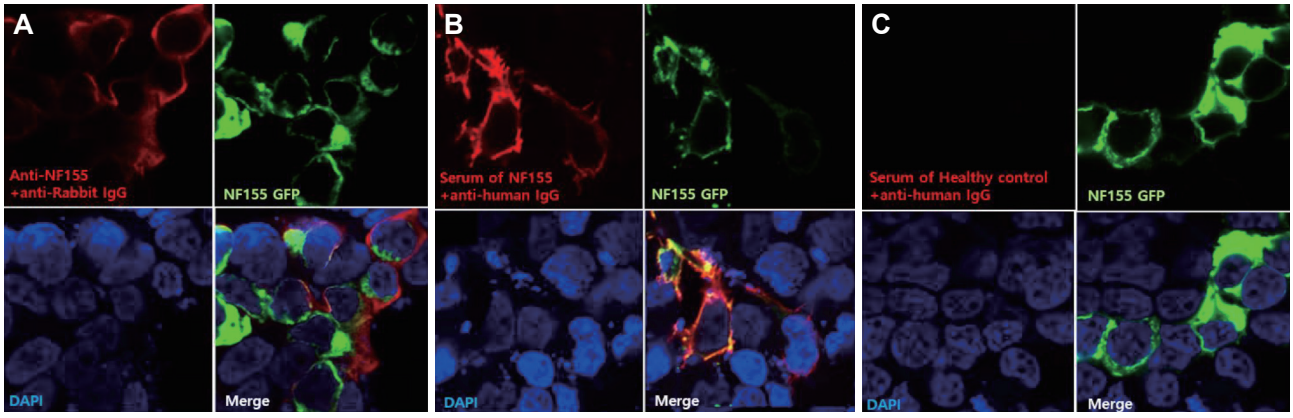

Fig. 1. Results from cell-based assays with human recombinant NF155-transfected HEK293 cells. HEK293 cells that expressed NF155 were incubated using (A) commercially available polyclonal anti-NF155 antibodies, (B) serum from patient 1, and (C) serum from a healthy control. A and B: Alexa-Fluor-594-conjugated anti-IgG antibody binding was observed along the cell surface (red fluorescence). This was colocalized with GFP-labeled NF155 expressed on the HEK293 cells (green fluorescence), indicating the presence of anti-NF155 antibodies. C: Antihuman IgG antibody binding (red fluorescence) was not observed when the serum from the healthy control was applied. DAPI, 4',6-diamidino-2-phenylindole; GFP, green fluorescent protein; HEK293, human embryonic kidney 293; IgG, immunoglobulin G; NF, neurofascin.

Clinical data collection

Demographic and clinical data were collected by reviewing medical records, including age, sex, age at onset, diagnosis, clinical features, distribution patterns of neurological deficits, modified Rankin Scale (mRS) score, comorbidities, laboratory findings, imaging findings, electrodiagnosis findings, and treatment response. Functional status was evaluated using the mRS, whose scores range from 0 to 6. The treatment response was defined as good, partial, or poor. The response was considered good if the mRS score improved by at least 1 point. It was considered partial if there was no change in the mRS score but the primary neurologist judged the treatment to have been effective based on a review of medical records including neurological examination results. All other responses were defined as poor.

Ethics statement

All patients provided written informed consent, and the study protocol was approved by the Institutional Review Boards of Severance Hospital (IRB No. 4-2021-1328) and Samsung Medical Center (IRB No. 2015-04-086).

RESULTS

Detection of antineurofascin antibodies

The CBA with human recombinant NF155-transfected HEK293 cells demonstrated that the serum samples from 6 of 68 (8.8%) patients who fulfilled the CIDP diagnostic criteria were positive for anti-NF155 antibodies (Fig. 1). All serum samples positive in the CBA were also positive for anti-NF155 antibodies in the ELISA (Fig. 2A). The IgG4 subclass was predominant in four of the six patients with anti-NF155 antibodies (Fig. 2B). One of these six patients were distinctly reactive to NF186 and NF140 (Fig. 2C and D). Among the serum samples of healthy and disease controls, none were positive for anti-NF155, anti-NF186, or anti-NF140 antibodies. The ELISA results are listed in Table 1.

Clinical features of autoimmune nodopathy with anti-NF155 antibody

The clinical features of six patients with anti-NF155 antibodies are listed in Table 2. These patients comprised three males and three females with a mean age at onset of 32.2 years. Patient 5 had pancreatic cancer and patient 6 had Sjogren's syndrome and focal segmental glomerulosclerosis (FSGS). All six patients presented with progressive sensory ataxia and paresthesia in the hands and feet. Motor and sensory deficits were prominent in the distal limbs. Two patients were initially diagnosed with Guillain-Barre syndrome (GBS) and had moderate-to-severe disability (mRS score ≥4) at the nadir. Three patients experienced tremors, two had peripheral-type facial palsy, and one had ophthalmoplegia. Protein levels in the CSF were markedly elevated in four of the five patients who underwent lumbar puncture. Enhancement of the cauda equina was observed in three of the four patients who underwent lumbar spinal magnetic resonance imaging. All six patients met the 2010 EFNS/PNS criteria for CIDP according to electrodiagnostic evaluations.

All six patients were treated using IVIg, among whom five exhibited a poor or partial response and one exhibited a good response. None of the patients responded well to corticosteroids, azathioprine, or therapeutic plasma exchange. Three patients were treated using rituximab (375 mg/m^2 each week for 4 consecutive weeks), all of whom exhibited a

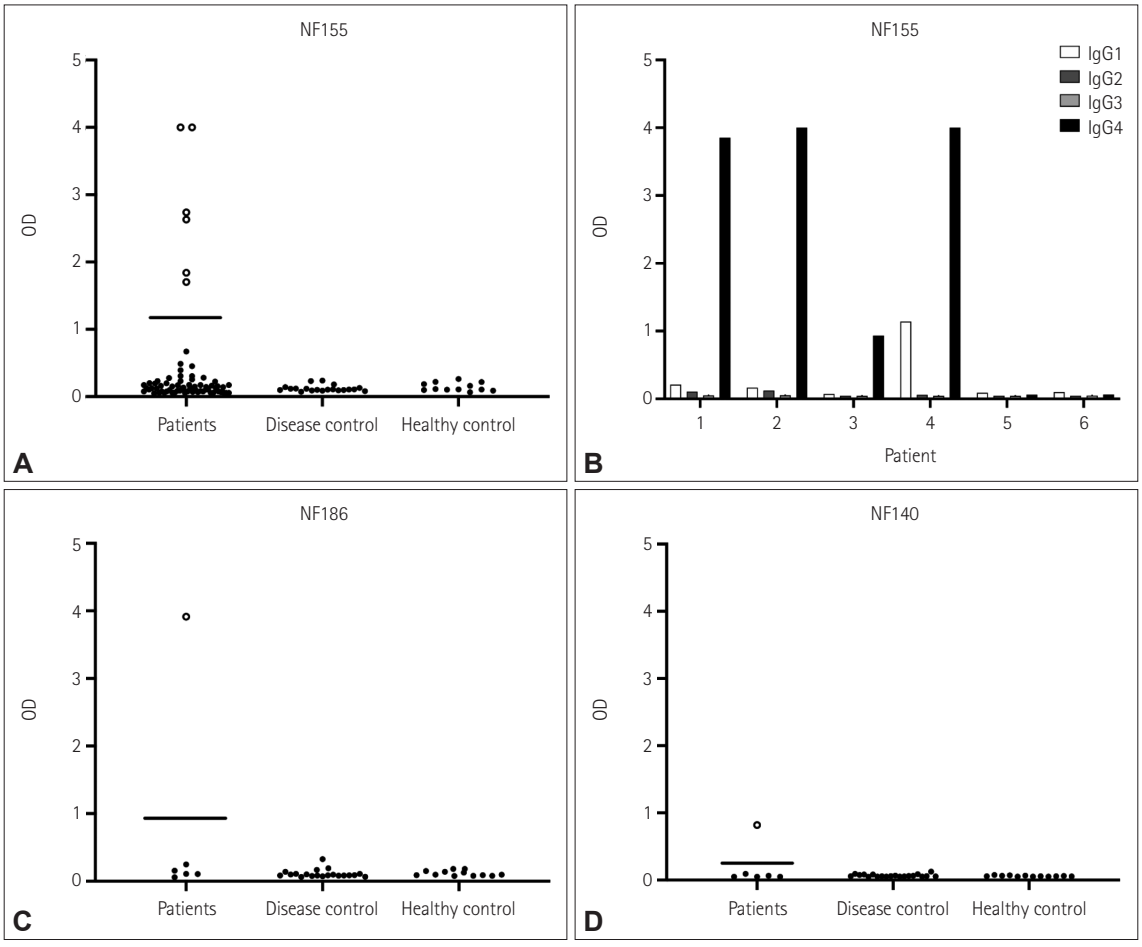

Fig. 2. Reactivity to anti-NF antibodies in the ELISA. A: Serum samples from patients who fulfilled the CIDP diagnostic criteria (*n*=68), controls with disease (*n*=20), and healthy controls (*n*=12) were tested for anti-NF155 IgG autoantibodies. The line represents the mean OD of healthy controls plus 5 standard deviations. B: IgG subclass was evaluated in patients with anti-NF155 seropositivity. C and D: Anti-NF186 and anti-NF140 autoantibodies were examined in the sera of controls and those with anti-NF155 positivity. The line represents the mean OD of healthy controls plus 5 standard deviations. CIDP, chronic inflammatory demyelinating polyneuropathy; IgG, immunoglobulin G; NF, neurofascin; OD, optical density.

Table 1. Autoantibodies against NF isoforms in patients with anti-NF155 antibodies

Patient	Antibodies against NF isoforms	Predominant IgG subclass
1	NF155 IgG	IgG4
2	NF155 IgG	IgG4
3	NF155 IgG	IgG4
4	NF155 IgG	IgG4
5	NF155 IgG	Undetermined
6	NF155/NF140/NF186 IgG	Undetermined

IgG, immunoglobulin G; NF, neurofascin.

good response.

Patient 6 was positive for anti-NF155, anti-NF186, and anti-NF140 antibodies. Her clinical presentation was rapidly progressive sensory ataxia and paresthesia, and her symptoms were moderate proximal and distal limb weakness as well as bulbar palsy. She was initially diagnosed with GBS. Urinalysis revealed newly developed nephrotic-range proteinuria, which led to FSGS being diagnosed after a renal biopsy. The neurological deficits rapidly worsened, and the patient lost the ability to walk. The condition improved briefly and then worsened following two cycles of IVIg treatment. CIDP was diagnosed and then treated using corticosteroids, azathioprine, and therapeutic plasma exchange, which were all ineffective. However, the condition improved dramatically and the patient was able to run after rituximab treatment. Neurological function was maintained without deterioration for 6 months after the rituximab treatment, and the proteinuria was also resolved.

Relationship between anti-NF155 antibody titers and clinical status

Serum samples were collected five times from patient 2 during the disease course (Fig. 3). His clinical presentation included progressive sensory ataxia and paresthesia in the

Table 2. Clinical features of patients with anti-NF155 antibodies

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Age at onset (years)	30	19	51	24	30	39
Sex	Female	Male	Female	Male	Male	Female
Initial diagnosis	CIDP	CIDP	CIDP	CIDP	GBS	GBS
Clinical course	Progressive	Progressive	Progressive	Progressive	Progressive	Progressive
Weakness	Yes	Yes	Yes	Yes	Yes	Yes
Weakness distribution	Symmetric, distal	Symmetric, distal	Symmetric, distal	Symmetric, distal	Symmetric, proximal/distal	Symmetric, proximal/distal
Paresthesia	Yes	Yes	Yes	Yes	Yes	Yes
Paresthesia distribution	Symmetric, distal	Symmetric, distal	Symmetric, distal	Symmetric, distal	Symmetric, distal	Symmetric, distal
Muscle stretch reflex	Decreased	Decreased	Absent	Decreased	Absent	Absent
Sensory ataxia	Yes	Yes	Yes	Yes	Yes	Yes
Tremor	No	Yes	Yes	Yes	No	No
Cranial nerve involvement	No	No	No	No	Facial palsy, bilateral ophthalmoplegia	Facial palsy, right-sided
Comorbidities	(–)	(–)	(–)	(–)	Pancreatic cancer	Sjogren's syndrome FSGS
Laboratory findings						
CSF WBC, /mL	4	2	5	ND	0	0
CSF protein, mg/dL	394.1	414.5	121.8	ND	313.0	32.6
Plexus/root enhancement in MRI	(+)	(+)	ND	ND	(+)	(–)
EFNS/PNS electrodiagnostic criteria for CIDP	Definite	Definite	Definite	Definite	Definite	Definite
NCS						
Prolonged DML	(+)	(+)	(+)	(+)	(+)	(–)
Reduced MCV	(+)	(+)	(+)	(+)	(+)	(–)
Conduction block	(–)	(–)	(+)	(+)	(–)	(+)
Temporal dispersion	(–)	(–)	(–)	(–)	(+)	(–)
mRS score at nadir	2	2	3	3	4	5
mRS score at last follow-up	1	0	3	3	6*	2
Treatment response						
Corticosteroids	Poor	Poor	Poor	Poor	ND	Poor
Azathioprine	Poor	Poor	ND	ND	ND	Partial
IVIg (dose per course, g/kg)	Poor (2)	Poor (2)	Poor (2)	Poor (2)	Partial (2)	Good (2)
Plasma exchange (number of sessions)	Partial (5)	NA† (5)	ND	ND	Poor (6)	Poor (6)
Rituximab‡	Good	Good	ND	ND	ND	Good

*In patient 5, anti-NF155 antibody was detected postmortem due to death caused by cancer complications; †It was difficult to determine the response to therapeutic plasma exchange in patient 2 because this was immediately followed by rituximab; ‡Rituximab treatment protocol: 375 mg/m^2 each week for 4 consecutive weeks.

CIDP, chronic inflammatory demyelinating polyneuropathy; CSF, cerebrospinal fluid; DML, distal motor latency; EFNS/PNS, European Federation of Neurological Societies/Peripheral Nerve Society; FSGS, focal segmental glomerulosclerosis; GBS, Guillain-Barre syndrome; IVIg, intravenous immunoglobulin G; MCV, motor conduction velocity; MRI, magnetic resonance imaging; mRS, modified Rankin Scale; NA, not applicable; NCS, nerve conduction study; ND, not done; NF, neurofascin; WBC, white blood cells.

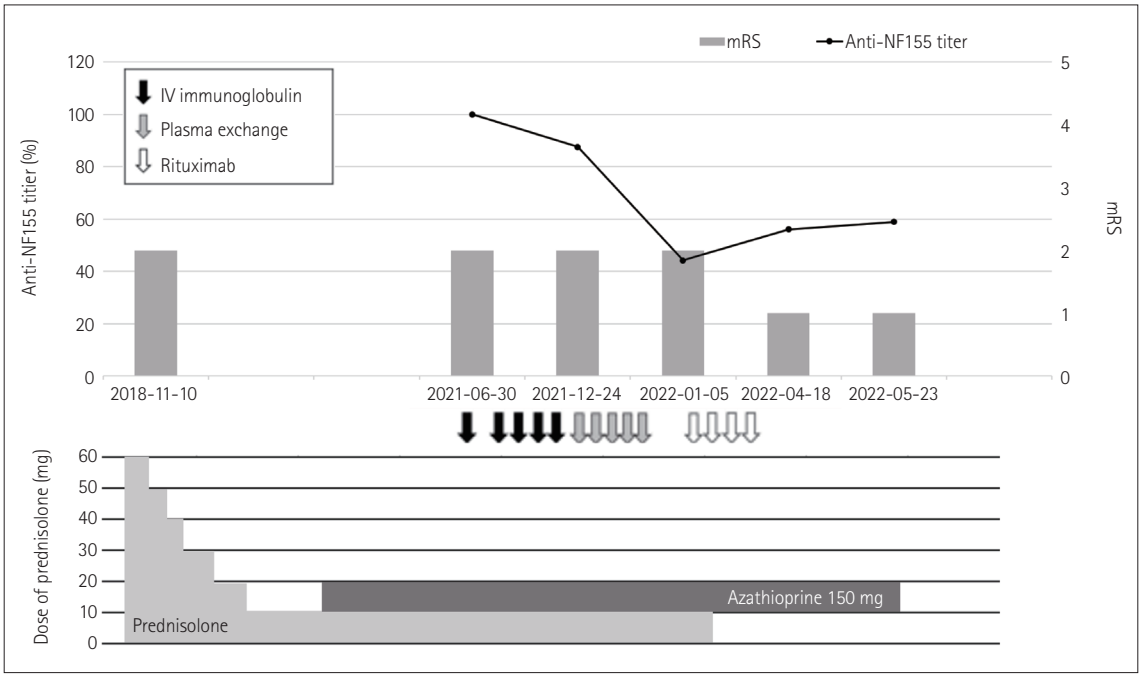

Fig. 3. Clinical status and anti-NF155 titers in patient 2. After treatment with plasma exchange and rituximab, the mRS score improved and anti-NF155 antibody titers decreased. Titer variation within patient 2 was expressed as the percentage titer change relative to baseline levels. IV, intravenous; mRS, modified Rankin Scale; NF, neurofascin.

hands and feet. Corticosteroid, azathioprine, and IVIg treatments were ineffective. After therapeutic plasma exchange and rituximab treatment, the condition of the patient improved and he was able to perform all his usual activities, including sports, with only mild symptoms. The mRS score improved from 2 to 1. The anti-NF155 antibody titer also decreased to approximately 50% of the baseline concentration after therapeutic plasma exchange and rituximab treatment.

DISCUSSION

In the present study, anti-NF155 antibodies were identified in 6 of 68 (8.8%) South Korean patients who fulfilled the 2010 EFNS/PNS diagnostic criteria for CIDP based on the detection methods of the CBA and ELISA. Six patients could be diagnosed with autoimmune nodopathy based on the results of these antibody tests. Previous studies have observed anti-NF155 antibodies at rates of 4%–25% in patients with CIDP.[11-17] This wide range of prevalence rates among studies may be due to differences in the inclusion criteria for subjects and in antibody detection methods. Most previous studies involved small numbers of patients with anti-NF155 antibodies, which may be another reason for this wide range. In a recent study on 40 patients, which is the largest previous anti-NF155-antibody-positive autoimmune nodopathy cohort, anti-NF155 antibodies were positive in approximately 5% of all patients with CIDP.[18] CBA and ELISA were used to detect anti-NF155 antibodies in the previous study, like in the present one. In another study with a large sample of 38 patients, anti-NF155 antibody was detected using the ELISA in 7% of patients diagnosed with CIDP.[19] The anti-NF155 positivity rate (8.8%) of the patients who fulfilled the CIDP diagnostic criteria in the present study was similar to those (5% and 7%) in the two largest anti-NF155 autoimmune nodopathy cohorts.

The clinical features of the patients with autoimmune nodopathy with anti-NF155 antibody in this study were consistent with those of previous studies. Anti-NF155 antibodies were positive in patients diagnosed with CIDP who were younger at onset, and who presented with a subacute or chronic disease course, distal acquired demyelinating symmetric polyneuropathy pattern, ataxia, tremor, predominant IgG4 subclass of anti-NF155 antibody, a poor response to IVIg treatment, or a good response to rituximab treatment.[9,16-19] The mean age at disease onset in the present study was 32.2 years, which was younger than that typically observed in patients with CIDP, which according to epidemiological data predominantly presents in adults aged 40–60 years.[20] All six patients in the present study presented with progressive sensory ataxia and paresthesia in the hands and feet. Three patients experienced tremors. All six patients were treated using IVIg, five of whom exhibited a poor or partial response. Rituximab was administered to three patients at 375 mg/m^2 each week for 4 consecutive weeks,

all of whom exhibited a good response. The IgG4 subclass was predominant in four of the six patients with anti-NF155 antibodies.

In the present study, patients with anti-NF155 antibodies whose predominant IgG subclass could not be determined (patients 5 and 6) presented different clinical features to those with anti-NF155 IgG4 (patients 1, 2, 3, and 4). The clinical courses of patients 5 and 6 were rapid and serious, and they were initially diagnosed with GBS. Their condition rapidly deteriorated and they became unable to walk. Cranial nerve dysfunction was also observed. In particular, patient 6 was positive for antibodies against the nodal isoforms of NF186 and NF140, as well as against the paranodal isoform of NF155. She also had concurrent proteinuria caused by FSGS. This patient responded well to IVIg treatment, and their concomitant renal disease was resolved after rituximab treatment. These features differed from those of the other four patients with anti-NF155 IgG4. These differences in clinical features might be related to the properties of the autoantibodies. In a recent study of eight autoimmune nodopathy patients with antibodies against NF155, NF186, and NF140, all of the patients developed acutely or subacutely progressive tetraplegia with cranial nerve palsy.[21] Five of these patients were initially diagnosed with GBS, and three had concurrent nephrotic syndrome. Several other cases of patients with autoantibodies against all NF isoforms and with severe autoimmune neuropathy have also been reported.[11,22,23] In a previous study that investigated the correlation between the clinical features of autoimmune nodopathy and the properties of autoantibodies, anti-NF155 IgG4 against the NF155-specific fibronectin domain was associated with subacute-onset sensory ataxia with tremor, whereas the IgG3 antibody against the Ig domain shared among the three NF isoforms was associated with severe tetraplegia with cranial nerve involvement.[23] These observations suggest that the properties of autoantibodies influence the clinical phenotype of autoimmune nodopathy and the therapeutic response, and emphasize the importance of testing for both the paranodal and nodal isoforms of NF and determining the IgG subclass of patients with suspected autoimmune nodopathy.

Serum samples were collected from patient 2 before and after therapeutic plasma exchange and subsequent rituximab treatment. This patient exhibited clinical improvement after the treatments, with their mRS score decreasing from 2 to 1. The titer of the anti-NF155 antibodies correspondingly decreased to approximately 50% of that before treatment. A recent study demonstrated that the serum anti-NF155 antibody titer decreased with the clinical improvement that occurred after rituximab treatment in seven patients.[18] These observations suggest that the serum anti-NF155 antibody titer can be used as a biomarker to monitor the disease activity of autoimmune nodopathy and its treatment response. We are planning a prospective study to investigate the association between anti-NF155 antibody titers and disease activity in patients with anti-NF155-antibody-positive autoimmune nodopathy.

The main limitations of the present study were its retrospective design of using a medical chart review and the small sample. Although CBA and ELISA were used to detect autoantibodies, the results of which were consistent, there was also the possibility of false-positive and false-negative results for autoantibodies against NF isoforms. The CBA and ELISA have been widely used to detect anti-NF155 antibodies in previous studies;[17-19,24,25] however, there has been no comparative analysis of the test methods used in each laboratory. Further studies are necessary to establish a gold-standard method for detecting anti-NF155 antibodies.

In conclusion, anti-NF155 antibodies were found in approximately 9% of South Korean patients who fulfilled the diagnostic criteria for CIDP. Their clinical characteristics and treatment responses were consistent with those observed in previous studies. Detecting anti-NF155 antibody in patients with acquired demyelinating neuropathies, especially in young patients with CIDP who present with sensory ataxia and poor therapeutic responses to corticosteroids and IVIg, is necessary for diagnosing autoimmune nodopathy and providing appropriate treatment, including B-cell depletion therapy.

Availability of Data and Material

The datasets generated or analyzed during the study are available from the corresponding author on reasonable request.

ORCID iDs

Hyun Ji Lyou	https://orcid.org/0000-0001-9020-8558
Yeon Hak Chung	https://orcid.org/0000-0002-7052-2432
Min Ju Kim	https://orcid.org/0000-0001-8337-8444
MinGi Kim	https://orcid.org/0000-0002-6921-3085
Mi Young Jeon	https://orcid.org/0000-0001-9920-8044
Seung Woo Kim	https://orcid.org/0000-0002-5621-0811
Ha Young Shin	https://orcid.org/0000-0002-4408-8265
Byoung Joon Kim	https://orcid.org/0000-0001-8424-881X

Author Contributions

Conceptualization: Ha Young Shin, Byoung Joon Kim. Data curation: Hyun Ji Lyou, Yeon Hak Chung. Formal analysis: Min Ju Kim, Mi Young Jeon. Funding acquisition: Ha Young Shin, Byoung Joon Kim. Investigation: Min Ju Kim, MinGi Kim, Mi Young Jeon. Methodology: Ha Young Shin, Byoung Joon Kim. Project administration: Ha Young Shin, Byoung Joon Kim. Resources: Ha Young Shin, Byoung Joon Kim. Software: Ha Young Shin. Supervision: Ha Young Shin, Byoung Joon Kim. Validation: Seung Woo Kim. Visualization: Hyun Ji Lyou. Writing—original draft: Hyun Ji Lyou, Yeon Hak Chung. Writing—review & editing: Seung Woo Kim, Ha Young Shin, Byoung Joon Kim.

Conflicts of Interest

Ha Young Shin, a contributing editor of the Journal of Clinical Neurology, was not involved in the editorial evaluation or decision to publish this article. All remaining authors have declared no conflicts of interest.

Funding Statement

This work was supported by the National Research Foundation of Korea grant funded by the South Korea government (MSIT) (No. RS-2023-00212125).

REFERENCES

1. Querol L, Devaux J, Rojas-Garcia R, Illa I. Autoantibodies in chronic inflammatory neuropathies: diagnostic and therapeutic implications. *Nat Rev Neurol* 2017;13:533-547.
2. Rasband MN, Peles E. Mechanisms of node of Ranvier assembly. *Nat Rev Neurosci* 2021;22:7-20.
3. Van den Bergh PYK, van Doorn PA, Hadden RDM, Avau B, Vankrunkelsven P, Allen JA, et al. European Academy of Neurology/Peripheral Nerve Society guideline on diagnosis and treatment of chronic inflammatory demyelinating polyradiculoneuropathy: report of a joint task force-second revision. *Eur J Neurol* 2021;28:3556-3583.
4. Koike H, Katsuno M. Pathophysiology of chronic inflammatory demyelinating polyneuropathy: insights into classification and therapeutic strategy. *Neurol Ther* 2020;9:213-227.
5. Gao Y, Kong L, Liu S, Liu K, Zhu J. Impact of neurofascin on chronic inflammatory demyelinating polyneuropathy via changing the node of Ranvier function: a review. *Front Mol Neurosci* 2021;14:779385.
6. Dziadkowiak E, Waliszewska-Prosół M, Nowakowska-Kotas M, Budrewicz S, Koszewicz Z, Koszewicz M. Pathophysiology of the different clinical phenotypes of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). *Int J Mol Sci* 2021;23:179.
7. Kira JI. Anti-neurofascin 155 antibody-positive chronic inflammatory demyelinating polyneuropathy/combined central and peripheral demyelination: strategies for diagnosis and treatment based on the disease mechanism. *Front Neurol* 2021;12:665136.
8. Ogata H, Yamasaki R. Anti-neurofascin 155 antibody-related neuropathy. *Clin Exp Neuroimmunol* 2018;9:54-64.
9. Vural A, Doppler K, Meinl E. Autoantibodies against the node of Ranvier in seropositive chronic inflammatory demyelinating polyneuropathy: diagnostic, pathogenic, and therapeutic relevance. *Front Immunol* 2018;9:1029.
10. Wang W, Liu C, Li W, Zhang D, Shan Y, Zheng J, et al. Clinical and diagnostic features of anti-neurofascin-155 antibody-positive neuropathy in Han Chinese. *Ann Clin Transl Neurol* 2022;9:695-706.
11. Burnor E, Yang L, Zhou H, Patterson KR, Quinn C, Reilly MM, et al. Neurofascin antibodies in autoimmune, genetic, and idiopathic neuropathies. *Neurology* 2018;90:e31-e38.
12. Devaux JJ. Antibodies to gliomedin cause peripheral demyelinating neuropathy and the dismantling of the nodes of Ranvier. *Am J Pathol* 2012;181:1402-1413.
13. Guo X, Tang L, Huang Q, Tang X. A systematic review and meta-analysis of autoantibodies for diagnosis and prognosis in patients with chronic inflammatory demyelinating polyradiculoneuropathy. *Front Neurosci* 2021;15:637336.
14. Kadoya M, Kaida K, Koike H, Takazaki H, Ogata H, Moriguchi K, et al. IgG4 anti-neurofascin155 antibodies in chronic inflammatory demyelinating polyradiculoneuropathy: clinical significance and diagnostic utility of a conventional assay. *J Neuroimmunol* 2016;301:16-22.
15. Mathey EK, Garg N, Park SB, Nguyen T, Baker S, Yuki N, et al. Autoantibody responses to nodal and paranodal antigens in chronic inflammatory neuropathies. *J Neuroimmunol* 2017;309:41-46.
16. Ogata H, Yamasaki R, Hiwatashi A, Oka N, Kawamura N, Matsuse D, et al. Characterization of IgG4 anti-neurofascin 155 antibody-positive polyneuropathy. *Ann Clin Transl Neurol* 2015;2:960-971.
17. Querol L, Nogales-Gadea G, Rojas-Garcia R, Diaz-Manera J, Pardo J, Ortega-Moreno A, et al. Neurofascin IgG4 antibodies in CIDP associate with disabling tremor and poor response to IVIg. *Neurology* 2014;82:879-886.
18. Martín-Aguilar L, Lleixà C, Pascual-Goñi E, Caballero-Ávila M, Martínez-Martínez L, Díaz-Manera J, et al. Clinical and laboratory features in anti-NF155 autoimmune nodopathy. *Neurol Neuroimmunol Neuroinflamm* 2022;9:e1098.
19. Devaux JJ, Miura Y, Fukami Y, Inoue T, Manso C, Belghazi M, et al. Neurofascin-155 IgG4 in chronic inflammatory demyelinating polyneuropathy. *Neurology* 2016;86:800-807.
20. Dimachkie MM, Barohn RJ. Chronic inflammatory demyelinating polyneuropathy. *Curr Treat Options Neurol* 2013;15:350-366.
21. Fehmi J, Davies AJ, Walters J, Lavin T, Keh R, Rossor AM, et al. IgG1 pan-neurofascin antibodies identify a severe yet treatable neuropathy with a high mortality. *J Neurol Neurosurg Psychiatry* 2021;92:1089-1095.
22. Vallat JM, Mathis S, Magy L, Bounolleau P, Skarzynski M, Heitzmann A, et al. Subacute nodopathy with conduction blocks and anti-neurofascin 140/186 antibodies: an ultrastructural study. *Brain* 2018;141:e56.
23. Stengel H, Vural A, Brunder AM, Heinius A, Appeltshauser L, Fiebig B, et al. Anti-pan-neurofascin IgG3 as a marker of fulminant autoimmune neuropathy. *Neurol Neuroimmunol Neuroinflamm* 2019;6:e603.
24. Cortese A, Devaux JJ, Zardini E, Manso C, Taieb G, Carra Dallière C, et al. Neurofascin-155 as a putative antigen in combined central and peripheral demyelination. *Neurol Neuroimmunol Neuroinflamm* 2016;3:e238.
25. Koike H, Kadoya M, Kaida KI, Ikeda S, Kawagashira Y, Iijima M, et al. Paranodal dissection in chronic inflammatory demyelinating polyneuropathy with anti-neurofascin-155 and anti-contactin-1 antibodies. *J Neurol Neurosurg Psychiatry* 2017;88:465-473.