Clinical and Laboratory Features in Anti-NF155 Autoimmune Nodopathy

Lorena Martín-Aguilar, MD, PhD,* Cinta Lleixà, MSc,* Elba Pascual-Goñi, MD, PhD, Marta Caballero-Ávila, MD, Laura Martínez-Martínez, MD, PhD, Jordi Díez-Manera, MD, PhD, Ricard Rojas-García, MD, PhD, Elena Cortés-Vicente, MD, PhD, Janina Turon-Sans, MD, Noemi de Luna, PhD, Xavier Suárez-Calvet, PhD, Eduard Gallardo, PhD, Yusuf Rajabally, MD, Sangeeta Scotton, MD, Bart C. Jacobs, MD, PhD, Adája Baars, MD, Andrea Cortese, MD, PhD, Elisa Vegezzi, MD, Romana Höftberger, MD, Fritz Zimprich, MD, Cornelia Roesler, MD, Eduardo Nobile-Orazio, MD, PhD, Giuseppe Liberatore, MD, Nicolau Ortiz, MD, PhD, Manuel Bartolomé, MD, Özgür Duman, MD, Vera Bril, MD, Darwin Segura-Chávez, MD, Kalliopi Pitarokoili, MD, Elena Cortés-Vicente, MD, PhD, Fabian Márquez, MD, Julio Pardo-Fernández, MD, PhD, Laura Muñoz-Delgado, MD, Macarena Cabrera-Serrano, MD, PhD, Isabel Illa, MD, PhD, and Luis Querol, MD, PhD

Neurol Neuroimmunol Neuroinflamm 2022;9:e1098. doi:10.1212/NXI.0000000000001098

Abstract

Background and Objectives
To study the clinical and laboratory features of antineurofascin-155 (NF155)—positive autoimmune nodopathy (AN).

Methods
Patients with anti-NF155 antibodies detected on routine immunologic testing were included. Clinical characteristics, treatment response, and functional scales (modified Rankin Scale [mRS] and Inflammatory Rasch-built Overall Disability Scale [I-RODS]) were retrospectively collected at baseline and at the follow-up. Autoantibody and neurofilament light (NfL) chain levels were analyzed at baseline and at the follow-up.

Results
Forty NF155+ patients with AN were included. Mean age at onset was 42.4 years. Patients presented with a progressive (75%), sensory motor (87.5%), and symmetric distal-predominant weakness in upper (97.2%) and lower extremities (94.5%), with tremor and ataxia (75%). Patients received a median of 3 (2–4) different treatments in 46 months of median follow-up. Response to IV immunoglobulin (86.8%) or steroids (72.2%) was poor in most patients, whereas 77.3% responded to rituximab. HLA-DRB1*15 was detected in 91.3% of patients. IgG4 anti-NF155 antibodies were predominant in all patients; anti-NF155 titers correlated with mRS within the same patient (r = 0.41, p = 0.004). Serum NfL (sNfL) levels were higher in anti-NF155+ AN than in healthy controls (36.47 vs 7.56 pg/mL, p < 0.001) and correlated with anti-NF155 titers (r = 0.43, p = 0.001), with I-RODS at baseline (r = −0.88, p < 0.001) and with maximum I-RODS achieved (r = −0.58, p = 0.01). Anti-NF155 titers and sNfL levels decreased in all rituximab-treated patients.

*These authors contributed equally to this work as co-first authors.

From the Neuromuscular Diseases Unit (L.M.-A., C.L., E.P.-G., M.C.-A., R.R.-G., E.C.-V., J.T.-S., E.N.-O., I.I., L.Q.), Department of Neurology, Hospital de La Santa Creu i Sant Pau, Universitat Autònoma de Barcelona; Biomedical Research Institute Sant Pau (IBB Sant Pau) (L.M.-A., C.L., E.P.-G., M.C.-A., J.D.-M., E.C.-V., X.S.-C., E.G.); Immunology Department (L.M.-M.), Hospital de La Santa Creu i Sant Pau, Universitat Autònoma de Barcelona; Spain; Centro para la Investigación Biomédica en Red en Enfermedades Raras (CIBERER) (J.D.-M., R.R.-G., E.C.-V., N.L., X.S.-C., E.G., I.I., L.Q.); University Hospital Birmingham (Y.S., S.S.), UK; Erasmus Medical Center (B.C.J., A.B.), Rotterdam, the Netherlands; IRCCS Mondino Foundation (Andrea Cortese, E.V.), Pavia, Italy; Department of Neurology (R.H., F.Z.), Medical University of Vienna; Paracelsus Medical University (C.R.), Salzburg, Austria; IRCCS Humanitas Research Hospital (G.L.), Milan University, Rozzano, Italy; Kuala Lumpur General Hospital (F.L.H.), Kuala Lumpur, Malaysia; Hospital Universitari Germans Trias i Pujol (A.M.-P.), Badalona; Hospital Universitario Virgen de las Nieves (Alejandra Carvajal), Granada, Spain; Hospital Universitario Clínico San Cecilio (R.P.-M.), Granada; Hospital Son Llàtzer (M.U.-M.), Palma de Mallorca; Hospital San Jorge (O.A.), Huesca, España; Hospital San Pedro (M.A.L.-P.), Logroño; Hospital Universitari Josep Trueta (F.M.), Girona; Hospital Clínic Universitari de Santiago (J.P.-F.), Santiago de Compostela; Hospital Universitario Virgen del Rocio (L.M.-O., M.C.-S.), Seville; Hospital Universitari Sant Joan (N.O.), Reus; Complejo Asistencial de Avilés (M.B.), Avilés, Spain; Alcaldía University (O.D.), Antalya, Turkey; Toronto General Hospital (K.P.), Ruhr University Bochum; and Sant Joseph Hospital (E.S.), Berlin, Germany.

Go to Neurology.org/NXI for full disclosures. Funding information is provided at the end of the article.

The Article Processing Charge was funded by authors.

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives License 4.0 (CC BY-NC-ND), which permits downloading and sharing the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.
Glossary

CBA = cell-based assay; CIDP = chronic inflammatory demyelinating polyradiculoneuropathy; CMAP = compound muscle action potential; CNTN1 = contactin-1; EMG = electromyography; GBS = Guillain-Barré syndrome; HC = Healthy control; HLA = human leukocyte antigen; ICC = immunocytochemistry; I-RODS = Inflammatory Rasch-built Overall Disability Scale; IVlg = IV immunoglobulin; mRS = modified Rankin Scale; NCS = nerve conduction study; NF140 = neurofascin-140; NF155 = neurofascin-155; NF186 = neurofascin-186; OD = optical density; PLEX = plasma exchange; sNfL = serum neurofilament light chain.

Discussion

Anti-NF155 AN presents a distinct clinical profile and good response to rituximab. Autoantibody titers and sNfL are useful to monitor disease status in these patients. The use of untagged-NF155 plasmids minimizes the detection of false anti-NF155+ cases.

Classification of Evidence

This study provides Class IV evidence that anti-NF155 antibodies associate with a specific phenotype and response to rituximab.

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is a clinically and pathologically diverse autoimmune syndrome of the peripheral nervous system, causing significant disability. Disease-specific antibodies targeting proteins at the node and paranode of Ranvier, such as neurofascin 155 (NF155), nodal neurofascins (NF186 and NF140), contactin-1 (CNTN1), or CNTN-1/caspr-1 have been described in small subsets of patients with CIDP sharing immunopathologic mechanisms, clinical features, and treatment response and differing from those of typical CIDP. This has led to the appearance of the autoimmune nodopathy (AN) diagnostic category in the recent update of the European Academy of Neurology/Peripheral Nerve Society CIDP diagnostic guidelines.

Previous case series describe the association of anti-NF155 antibodies with predominately distal motor involvement, ataxia and low-frequency tremor with cerebellar features, marked nerve conduction abnormalities, and DRB1*15 human leukocyte antigen (HLA) Class II alleles. Moreover, these patients respond poorly to IV immunoglobulin (IVIg) and usually well to rituximab. Anti-NF155 antibodies, almost always of the IgG4 isotype, are pathogenic according to passive transfer experiments in animal models and pathologic studies detecting IgG4 deposition and axoglial junction dissection at the paranode. Recently, high serum neurofilament light chain (sNfL) levels were described in a subset of patients with anti-NF155+ AN.

Our work describes the clinical, immunologic, biomarker, treatment response and prognostic features of the largest anti-NF155+ AN cohort so far.

Methods

Protocol Approvals, Registrations, and Patient Consents

In this multicenter retrospective observational study, we included all sera reacting against NF155 transfected cells and identified during routine testing for nodal/paranodal antibodies. The samples were obtained between May 2010 and December 2020. These patients were selected for further characterization between May 2020 and December 2020. Demographic and clinical data at onset and during follow-up were collected in a coded database. This study was conducted according to a protocol approved by the Ethics Committee of the Hospital de la Santa Creu i Sant Pau. All patients gave written informed consent to participate in the study.

Data and Sample Collection

Data were collected retrospectively by patients’ neurologists in 24 different centers by chart review. European Academy of Neurology/Peripheral Nerve Society diagnostic criteria for CIDP were assessed, and patients were classified as having definite, probable, or possible CIDP. Demographic data (age and gender) and clinical features (initial diagnosis, time to nadir, the presence of weakness or sensory deficits, presence of ataxia, and tremor) were collected. Clinical presentation was defined as sensorimotor, pure motor, or pure sensory/ataxic. The results of routine nerve conduction studies (NCS), CSF examination, and treatments were also collected. As an electrophysiologic marker of axonal damage, we used the lowest (left or right) median nerve compound muscle action potential (CMAP) negative peak amplitude and, when available, the presence of spontaneous activity in the electromyography (EMG) at the tibialis anterior muscle. CSF protein levels higher than 0.45 g/L were considered relevant. Disability scores were collected at nadir and at the follow-up, including the modified Rankin Scale (mRS) and the Inflammatory Rasch-built Overall Disability Scale (I-RODS) scores (from 0 to 100; 100 indicating no disability), when available. Response to therapy was defined as a good response, partial response, or no response as classified by their primary neurologists after chart review of the neurologic examination. For rituximab-treated patients, mRS was prospectively collected pretreatment and, at least, once posttreatment; infusion protocol and adverse events (infection reactions and infections) were also collected. Serum
samples were obtained at diverse time points during routine autoantibody testing and stored at –80°C until needed.

**Anti-NF155 Antibody Detection and Titration**

Serum antibodies against NF155 were analyzed in the same laboratory using a cell-based assay (CBA) with human recombinant NF155-transfected HEK293 cells as previously described.24 The DDK-myc-tagged RC228652 NF155 plasmid (OriGene, Rockville, MD) was used for initial anti-NF155 detection, and the untagged EX-Z7183-M02 NF155 plasmid (GeneCopoeia, Rockville, MD) was used for false positive detection in those patients with discrepant results in the CBA and the ELISA. ELISA was used as a confirmatory test and for isotype identification and titration, as previously described.5 Optical density (OD) was measured at 450 nm with a Multiskan ELISA reader. Blank OD was subtracted to NF155 OD to control for unspecific background signal. The samples were considered positive by ELISA when they had a ΔOD higher than average healthy control (HC) ΔOD plus 2 SD. Titer variation within the same patient was expressed as the percentage of titer change compared with pretreatment levels. All samples were tested under the same conditions.

**Serum NfL Measurements**

sNfL levels were measured in all available anti-NF155 AN patient samples and compared with 78 HCs, using the Simoa NF-light kit in the SR-X Immunoassay Simoa analyzer (Quanterix Corp, Boston, MA), as previously described.24 The samples were analyzed in duplicates following the manufacturer’s instructions and standard procedures. All NfL values were within the linear ranges of the assay. The intra-assay and interassay coefficients of variation at intermediate level (15.25 pg/mL) were 3.9% and 9.5%, respectively.

**HLA Genotyping**

Genomic DNA from the peripheral blood from patients with anti-NF155+ with AN was extracted following standard protocols. HLA-DRB1 and HLA-DQB1 genotypes were analyzed as previously described.13

**Statistical Analysis**

A descriptive data analysis was performed. Descriptive statistics are shown as mean (±SD) or median (inter-quartile range) in continuous variables and as frequencies (percentages) in categorical variables. Comparisons between patients with anti-NF155+ AN and HC were performed by the Wilcoxon rank-sum test. The Kruskal-Wallis test was used to compare groups. Wilcoxon-Matched Pairs Signed Rank test was used to compare baseline anti-NF155 titers and sNfL levels at different time points. We used the Spearman coefficient to assess correlation between variables.

Statistical significance for all analyses was set at 0.05 (2-sided). All statistical analyses were performed with GraphPad Prism v8 and SPSS Statistics version 23 (IBM Corp.).

**Data Availability**

Anonymized data not published within this article will be made available by request from any qualified investigator.

**Results**

**Anti-NF155 Autoantibody Screening**

We detected 44 sera with a positive staining in the screening NF155 CBA and negative staining in the NF140/NF186 CBA. After performing a confirmatory study with anti-NF155 ELISA, 40 patients were confirmed true positives with ELISA and were selected for further characterization. The other 4 patients were classified as false positives in the CBA (9.1%). We used an untagged neurofascin-155 plasmid and confirmed that those 4 patients were negative when the myc-DDK tag was removed (eFigure 1, links.lww.com/NXI/A641).

**Clinical Features of Anti-NF155 Patients With AN**

Thirty-nine patients with anti-NF155+ fulfilled the CIDP diagnostic criteria; in 1 patient, antibodies were detected postmortem (supplementary results, links.lww.com/NXI/A641). Nine patients were previously reported in other series.3,14,15,25,26 The initial diagnosis was CIDP for most patients (80%), but 5 patients were initially diagnosed with Guillain-Barré syndrome (GBS). Patients with anti-NF155+ AN had a median age at onset of 42.4 years and were predominantly men (72.5%). The most frequent clinical presentation was sensory motor (87.5%), and most patients had a progressive (75%) and chronic (67.5%) clinical course. Most patients had a symmetric weakness with distal predominance in upper (97.2%) and lower extremities (94.5%). The sensory deficit was symmetric and more frequent in lower (97.5%) than in upper extremities (67.5%). Seventy-five percent of patients had tremor and ataxia (of which, 5 had only ataxia, 5 tremor, and 25 a combination of both). Tremor was classified as intention tremor or action tremor in 18 patients (60%). Thirty percent of patients had cranial nerve involvement: bilateral facial palsy was the most frequent (70%), and 2 patients had bilateral optic neuritis confirmed by evoked potentials27 with normal brain and spine MRI and negative MOG and anti-aquaporin-4 antibodies. Further information about disease characteristics is detailed in Table 1.

Regarding nerve conduction studies, 38 patients fulfilled definite electrodiagnostic European Academy of Neurology/Peripheral Nerve Society criteria for CIDP,19 1 patient was defined as possible CIDP, and 1 patient did not have nerve conduction studies performed because diagnosis was confirmed postmortem. We collected 33 (82.5%) NCS in which only 26 (65%) had needle EMG available. Median amplitude of distal CMAPs of different nerves are shown in eTable 1 (links.lww.com/NXI/A641). Seventeen of 26 patients (65.4%) had spontaneous activity on EMG. CSF was examined in 37 (92.5%) patients; most patients had less than 5 cells in CSF (72.2%), and all patients had high CSF protein levels with a median of 2 g/L (0.95–3.67).
Treatment Response and Clinical Follow-up

The median number of treatments received was 3 (2–4). Most patients were treated with IVIg (95%) and/or corticosteroids (90%), and approximately half of patients (46.2%) were treated with plasma exchange (PLEX) with a median number of sessions of 6 (5–9). Twenty-three patients (57.5%) were treated with rituximab, and 1 patient was included in a blinded clinical trial of rituximab vs placebo. Of those patients treated with rituximab (n = 23), 13 were also treated with plasma exchange before starting rituximab, and 10 patients were treated with rituximab alone. Nine patients were treated with azathioprine, and 8 patients received other...
Table 2 Treatment and Clinical Response

| Treatment       | No. of patients (n, %) | Response (n, %) | Dose/Protocol |
|-----------------|------------------------|----------------|--------------|
| IVIg            | 38 (95%)               | Yes: 5 (13.1%) | 2g/kg per course |
| Steroids        | 36 (90%)               | Yes: 10 (27.8%) | 1 mg/kg/d: 23 (63.9%) |
| PLEX            | 18 (46.2%)             | Yes: 7 (38.9%) | No: 5 (27.8%)  |
| Rituximab       | 23 (57.5%)             | Yes: 17 (73.3%) | 4 + 2: 8 (36.4%) |
| Azathioprine    | 9 (22.5%)              | Yes: 1 (11.1%) | No: 5 (27.8%)  |
| Mycophenolate   | 3 (7.5%)               | Partial: 1     | No: 2 (66.7%)  |
| Methotrexate    | 3 (7.5%)               | Partial: 1     | No: 2 (66.7%)  |
| Cyclosporine    | 1 (2.5%)               | No: 1 (100%)   |              |
| Interferon beta1a | 1 (2.5%)            | No: 1 (100%)   |              |

Abbreviations: IVIg = IV immunoglobulin; MP = methylprednisolone; PLEX = plasma exchange.

|                | (n, %) | Dose/Protocol |
|----------------|--------|---------------|
| MP iv pulse:   | 4 (11.1%) |               |
| MP iv pulse + mg/kg/d: | 5 (13.9%) |               |
| Others:        | 4 (11.1%) |  |

A One patient included in a blinded clinical trial of rituximab vs placebo.

B Improvement in mRS after rituximab treatment is detailed in eTable 1 (links.lww.com/NXI/A641).

Of 23 (56.5%) patients have an improvement of ≥2 points in mRS after rituximab treatment. Rituximab-treated patients in which mRS remained stable had lower median follow-up time, although differences were not statistically significant (eTable 2, links.lww.com/NXI/A641). Of the 4 rituximab-treated patients without detectable improvement in the mRS score, 2 patients were classified as nonresponders by their primary physicians (median follow-up time of 37 months) and 2 patients were classified as partial responders (median follow-up time of 6 months). Most frequent infusion protocol (36.4%) was 4 weekly + 2 monthly 375 mg/m² doses, followed by 1 + 1 (separated 2 weeks) 1,000 mg doses (27.3%) and 4 weekly 375 mg/m² doses (27.3%). Five (21.7%) patients had a relapse, a median of 21 (4.5–59.5) months after induction with rituximab; 11 (47.8%) patients received rituximab infusions. Four (17%) patients had adverse effects related to rituximab: 2 mild infusion reactions, 1 pneumonia, and 1 disseminated varicella infection. Treatment frequencies, doses, and responses to treatment are further detailed in Table 2.

The clinical scales at baseline, at nadir, and after treatment are described in Table 1. The median follow-up time was 46 (20–81) months. Patients with facial diplegia had lower maximum and final I-RODS than patients who did not have facial involvement (median maximum I-RODS 22 vs 47, p = 0.003 and median final I-RODS 43 vs 61, p = 0.035 (eTable 3, links.lww.com/NXI/A641). Three patients died during follow-up: 1 because of CIDP disease course, 1 because of aspiration pneumonia, and 1 because of a disseminated varicella infection. Patients who received rituximab had higher median mRS and lower I-RODS at nadir, although differences were not statistically significant (4 [3–4] vs 3 [2–4], p = 0.5; 40 [29–49] vs 47 [9–77], p = 0.78; Table 3). They received a higher number of previous treatments than those patients who did not received rituximab (4 [3–5] vs 2 [2–3], p = 0.03), including PLEX, but they did not differ at the final mRS or I-RODS from those patients not treated with rituximab despite being more drug resistant (Table 3). There were no differences between patients treated with PLEX and rituximab (n = 13) or with rituximab alone (n = 10), regarding response treatment, relapses, or infusions needed.

Baseline Immunologic Characteristics

All sera with an anti-NF155+ CBA were also positive by ELISA; anti-NF155 titers ranged from 1:300 to 1:72,300. Autoantibodies were predominantly of the IgG4 subclass in all patients. In addition, we evaluated NF155 positivity in 4 CSF from patients with anti-NF155+ AN and 3 of them tested positive for NF155 antibodies. We were able to perform subclass analysis and titration in 2 CSF samples: both were IgG4 and their titers significantly lower than in sera (1:160 in both CSF samples and 1:24,300 and 1:72,300 in sera).

Regarding the HLA genotyping, DRB1*15 alleles (DRB1*15: 01 or DRB1*15:02) were present in 21 of 23 patients with anti-NF155+ AN (91.3%). Most frequent allele was DRB1*15:01 or DRB1*15:02) were present in 21 of 23 patients with anti-NF155+ AN (91.3%). Most frequent allele was DRB1*15:01 and DRB1*15:02, except for a trend to younger age in patients with DRB1*15:02 (45.2 ± 20.5 vs 30.6 ± 14.6, p = 0.14). In contrast, HLA-DRB1*15 is found in 17% of Spanish population, 12% of North Italy population, 25% of Southern France population, and 20% of English population.

Baseline Serum NfL Levels

Serum NfL levels were determined in all samples available (36/40) at baseline. Anti-NF155 + AN patients had treatments (mycophenolate, methotrexate, cyclosporine, or interferon beta1a).

Only 5 of 38 (13.1%) patients had a good response to IVIg. 10 of 36 (27.8%) patients had a good response to steroids, and 7 of 18 (38.9%) had a good response to PLEX. On the contrary, 17 of 23 (77.3%) patients had a good response to rituximab and 13 of 23 (56.5%) patients have an improvement of ≥2 points in mRS after rituximab treatment. Rituximab-treated patients in which mRS remained stable had lower median follow-up time, although differences were not statistically significant (eTable 2, links.lww.com/NXI/A641). Of the 4 rituximab-treated patients without detectable improvement in the mRS score, 2 patients were classified as nonresponders by their primary physicians (median follow-up time of 37 months) and 2 patients were classified as partial responders (median follow-up time of 6 months). Most frequent infusion protocol (36.4%) was 4 weekly + 2 monthly 375 mg/m² doses, followed by 1 + 1 (separated 2 weeks) 1,000 mg doses (27.3%) and 4 weekly 375 mg/m² doses (27.3%). Five (21.7%) patients had a relapse, a median of 21 (4.5–59.5) months after induction with rituximab; 11 (47.8%) patients received rituximab infusions. Four (17%) patients had adverse effects related to rituximab: 2 mild infusion reactions, 1 pneumonia, and 1 disseminated varicella infection. Treatment frequencies, doses, and responses to treatment are further detailed in Table 2.

The clinical scales at baseline, at nadir, and after treatment are described in Table 1. The median follow-up time was 46 (20–81) months. Patients with facial diplegia had lower maximum and final I-RODS than patients who did not have facial involvement (median maximum I-RODS 22 vs 47, p = 0.003 and median final I-RODS 43 vs 61, p = 0.035 (eTable 3, links.lww.com/NXI/A641). Three patients died during follow-up: 1 because of CIDP disease course, 1 because of aspiration pneumonia, and 1 because of a disseminated varicella infection. Patients who received rituximab had higher median mRS and lower I-RODS at nadir, although differences were not statistically significant (4 [3–4] vs 3 [2–4], p = 0.5; 40 [29–49] vs 47 [9–77], p = 0.78; Table 3). They received a higher number of previous treatments than those patients who did not received rituximab (4 [3–5] vs 2 [2–3], p = 0.03), including PLEX, but they did not differ at the final mRS or I-RODS from those patients not treated with rituximab despite being more drug resistant (Table 3). There were no differences between patients treated with PLEX and rituximab (n = 13) or with rituximab alone (n = 10), regarding response treatment, relapses, or infusions needed.

Baseline Immunologic Characteristics

All sera with an anti-NF155+ CBA were also positive by ELISA; anti-NF155 titers ranged from 1:300 to 1:72,300. Autoantibodies were predominantly of the IgG4 subclass in all patients. In addition, we evaluated NF155 positivity in 4 CSF from patients with anti-NF155+ AN and 3 of them tested positive for NF155 antibodies. We were able to perform subclass analysis and titration in 2 CSF samples: both were IgG4 and their titers significantly lower than in sera (1:160 in both CSF samples and 1:24,300 and 1:72,300 in sera).

Regarding the HLA genotyping, DRB1*15 alleles (DRB1*15: 01 or DRB1*15:02) were present in 21 of 23 patients with anti-NF155+ AN (91.3%). Most frequent allele was DRB1*15:01 or DRB1*15:02 (n = 13; 72.2%). No clinical differences were observed between patients with DRB1*15:01 and DRB1*15:02, except for a trend to younger age in patients with DRB1*15:02 (45.2 ± 20.5 vs 30.6 ± 14.6, p = 0.14). In contrast, HLA-DRB1*15 is found in 17% of Spanish population, 12% of North Italy population, 25% of Southern France population, and 20% of English population.

Baseline Serum NfL Levels

Serum NfL levels were determined in all samples available (36/40) at baseline. Anti-NF155 + AN patients had...
significantly higher sNfL levels than HC (36.47 pg/mL vs 7.56 pg/mL, \( p < 0.001 \), Figure 1 and Table 4) at baseline. sNfL levels correlated with age in HC (\( r = 0.73, p < 0.001 \)) but not in patients with anti-NF155 + AN (\( r = 0.26, p = 0.12 \)). The samples collected pretreatment (\( n = 12 \)) have higher sNfL levels than those collected after treatment had been started (\( n = 24 \)) (65.84 vs 18.41 pg/mL; \( p = 0.002 \)).

### Relationship Between NF155 Titers, sNfL Levels, and Clinical Status

Absolute anti-NF155 titers did not correlate with clinical status across patients, but they did when we evaluated follow-up NF155 titers using baseline titers as the reference (\( r = 0.41, p = 0.004 \); eFigures 2 and 3, links.lww.com/NXI/A641). Baseline sNfL levels negatively correlated with I-RODS at blood sampling (\( r = -0.88, p < 0.001 \)) and with maximum I-RODS achieved (\( r = -0.58, p = 0.01 \)) (eFigure 4, links.lww.com/NXI/A641). However, correlation between the sNfL levels and the final I-RODS (\( r = -0.36; p = 0.1 \)) did not reach statistical significance. sNfL levels correlated with NF155 titers at baseline (\( n = 36; r = 0.43, p = 0.001 \)) and at every time point available (\( n = 105; r = 0.34, p < 0.001 \)).

Baseline sNfL levels did not correlate with lowest CMAP in nerve conduction studies in any of the nerves tested. Although patients showing spontaneous activity in the needle EMG of the tibialis anterior showed higher sNfL levels than patients without spontaneous activity (67.33 vs 25.12 pg/mL, \( p = 0.1 \)), the differences were not statistically significant.

### Relationship Between NF155 Titers, sNfL Levels, and Treatment Response to Rituximab: Kinetics

In rituximab-treated patients with anti-NF155+ AN in which follow-up samples at regular time points were available (\( n = 7 \)), antibody titers decreased during follow-up. This decline was significant as early as 3 months after administration of rituximab (mean decrease of 66.7\%, Figure 2). At 1 year, a mean titer reduction of 98.6\% in rituximab-treated patients was achieved. In patients not treated with rituximab in which follow-up sample at 1 year (\( n = 6 \)) was available, no significant decrease of antibodies was observed (2 patients had a median decrease of 94\%, 2 patients remained stable, and 2 patients increased their NF155 titers) (Figure 3). sNfL levels were higher in rituximab-treated patients compared with those not treated with rituximab (47.69 vs 14.43 pg/mL, \( p = 0.08 \), Table 3), but differences were not statistically significant. sNfL levels decreased at 1 year in rituximab-treated patients (median of 37.98 pg/mL at baseline vs 11.72 pg/mL at 1 year, \( p = 0.04 \)). In patients not treated with rituximab, median baseline sNfL levels were normal and no changes were observed at 1 year (7.62 vs 6.95 pg/mL, \( p = 0.16 \)). Clinical status improved at 1 year in both groups, but only the rituximab-treated group improved significantly (median of mRS 4 [3–4] at baseline vs 2 [1–2] at the 1-year follow-up,

### Table 3 Rituximab Treatmenta

| Value                      | Patients treated with rituximab (\( n = 23 \)) | Patients not treated with rituximab (\( n = 16 \)) | \( p \) Value |
|----------------------------|-----------------------------------------------|--------------------------------------------------|--------------|
| Age at onset (mean ± SD)    | 44.1 ± 20.7                                   | 39.25 ± 18.6                                    | 0.51         |
| Age at diagnosis (mean ± SD)| 45.2 ± 20.7                                   | 39.8 ± 18.12                                    | 0.44         |
| Sex (male; n, %)            | 17 (77.3%)                                    | 11 (68.8%)                                      | 0.41         |
| Baseline NF155 levels (median, IQR) (\( n = 36 \)) | 47.69 (18.87-154.29) | 14.43 (7.58-64.68) | 0.08         |
| NF155 titers (median, IQR)  | 1/24,300 (1/8,100-1/24,300)                    | 1/8,100 (1/2,700-1/24,300)                       | 0.19         |
| No. of previous treatments (median, IQR) | 4 (3–5)                                    | 2 (2–3)                                          | 0.03         |
| PLEX (n, %)                 | 14 (63.6%)                                    | 4 (25%)                                          | 0.02         |
| mRS (median, IQR)           |                                               |                                                  |              |
| Baseline (\( n = 27 \))     | 3 (2–4)                                       | 3 (1–4)                                          | 0.94         |
| Maximum (\( n = 37 \))      | 4 (3–4)                                       | 3 (2–4)                                          | 0.53         |
| Final (\( n = 37 \))        | 2 (1–2)                                       | 2 (1–3)                                          | 0.62         |
| R-ODS (median, IQR)         |                                               |                                                  |              |
| Baseline (\( n = 13 \))     | 45 (40–60)                                    | 61 (18–86)                                       | 0.83         |
| Maximum (\( n = 16 \))      | 40 (29–49)                                    | 47 (9–77)                                        | 0.78         |
| Final (\( n = 21 \))        | 58 (51–88)                                    | 60 (55–88)                                       | 0.69         |

Abbreviations: IQR = interquartile range; I-RODS = Inflammatory Rasch-built Overall Disability Scale; MP = methylprednisolone; mRS = modified Rankin Scale; NF155 = neurofascin-155; PLEX = plasma exchange.

*aWe exclude 1 patient included in a blinded clinical trial of rituximab vs placebo.*
Discussion

Our study describes the clinical, laboratory, treatment response and prognostic features of the largest anti-NF155+ AN cohort published so far.3,4,15,29-31 It confirms that patients with AN with autoantibodies against NF155 present at a younger age (including a significant proportion of patients below 30 years)5 with a specific clinical phenotype with distal weakness, tremor, and ataxia. The presence of these features in a patient fulfilling the CIDP criteria should immediately prompt anti-NF155 antibody testing, as recommended in the recently published revision of the EAN/PNS CIDP diagnostic guidelines.10 Other associated features, which may suggest the presence of anti-NF155 AN and prompt antinodal/paranodal autoantibody testing, are the presence of cranial nerve palsies, particularly facial palsy, high CSF protein content, and poor response to IVIg. An important implication of our study for the testing recommendations in diagnostic guidelines is that almost 10% of the patients testing positive for anti-NF155 in CBA performed with the myc-DDK tagged NF155 plasmid are false positives. This agrees with our previous observation that demonstrated that a positive test in the NF155 CBA could be due to antibodies targeting the myc-DDK tag and not NF155 itself.32 This implies that untagged-NF155 plasmids should be preferentially used and that a second test (ELISA or teased-nerve immunohistochemistry) is always recommended.

Previous case series and systematic reviews suggested that patients with anti-NF155+ AN respond poorly to IVIg or that IVIg response is less frequent than in seronegative CIDP.3,30,31,33 This has been described in other IgG4-mediated diseases such as anti-muscle-specific tyrosine kinase-positive myasthenia gravis.34 There are different hypotheses on why this happens in IgG4-mediated diseases, although none has been validated. On the one hand, complement and cell-mediated cytotoxicity do not happen in IgG4 diseases, and thus, any effect that IVIg may have over complement effector mechanisms or cytotoxic cells may be lost. On the other hand, IgG4 is secreted exclusively by IL10+ regulatory B-cells, and these cells, interestingly, have significantly lower expression of the inhibitory immunoglobulin receptor FCGRIIb on their surface (and this could decrease the ability of IgG4-producing cells to be inhibited by IgG).35 Our study has also found that most patients with anti-NF155+ AN do not respond appropriately to IVIg (or, to a lower extent, corticosteroids) according to their physicians. On the contrary, most patients respond to rituximab even when they are refractory to IVIg and corticosteroid therapy (this also happens in other IgG4-mediated diseases36,37). More than 50% of patients in our cohort were treated with rituximab after a poor response to other therapies, and more than 75% had a good response. This improvement agrees with prospectively collected follow-up mRS scores that show that most patients improved at least 1 point.

Figure 1 Baseline Serum NfL in Anti-NF155 + Patients With AN and Healthy Controls

Patients with anti-NF155 + AN had significantly higher sNfL levels than HC. The line in the center represents the median value, and the whiskers indicate the interquartile range. AN = autoimmune nodopathy; CIDP = chronic inflammatory demyelinating polyradiculoneuropathy; HC = healthy control; NF155 = neurofascin-155; sNfL = serum neurofilament light chain.
Anti-NF155 antibodies are pathogenic according to in vitro and in vivo models. As such, we hypothesized that their titers should correlate with disease severity. We found that IgG4 anti-NF155 antibody titers correlate with clinical status within the same patient, but not across patients. This is something that has been described in other IgG4 autoimmune diseases treated with rituximab, such as anti-muscle-specific tyrosine kinase myasthenia gravis, and in other polyneuropathies as IgM antinmyelin-associated glycoprotein neuropathy. Several factors may explain why autoantibody titers do not correlate with clinical activity across patients: autoantibody affinity for their target antigen and diverse biases arising from the retrospective nature of the study (diverse time points, diverse treatment regimens, and diverse baseline severities and ages) among others. However, our study proves that anti-NF155 antibody titers can be a good biomarker for disease activity and treatment response when assessed in individual patients and represented as changes relative to baseline levels. Indeed, in those patients treated with rituximab, IgG4 anti-NF155 decreased more than a 90% relative to baseline titers or even became negative in a few patients. This suggests that the reappearance or a significant increase in the pathogenic auto-antibody may precede a relapse and, thus, could guide treatment reinfusions. Again, this use of the autoantibodies needs to be validated prospectively, but the temporal evolution of the autoantibody titers, paralleling the sNfL levels and the clinical status in the few patients in which prospective follow-up was available, is promising.

We identified IgG4 anti-NF155 antibodies in the CSF of 3 of 4 patients in which a CSF sample was available. Intrathecal antipan neurofascin has been previously described, and anti-NF155 antibodies in CSF have been described in 2 patients with combined central and peripheral demyelination but not in anti-NF155 AN so far. The high protein content in CSF, the absence of oligoclonal bands, and the presence of higher anti-NF155 titers in serum than in CSF suggests that anti-NF155 antibodies appear in the CSF because of blood-brain barrier disruption and not because of intrathecal synthesis. The presence of these auto-antibodies in the CSF could help explaining the cerebellar features in patients with anti-NF155+ AN, but larger cohorts including patients with and without tremor in which CSF is analyzed are needed.

Our study also showed that sNfL levels were higher in patients with anti-NF155+ AN than in HC. High sNfL levels have also been recently described in CIDP, particularly in a small subset of patients with anti-NF155+ AN who showed higher sNfL levels than seronegative CIDP. In our study, we found a

### Table 4 Baseline Serum NfL in Anti-NF155 + Patients With AN and Healthy Controls

| Age at sampling, mean ± SD | 47.87 ± 20.16 | 48 ± 18.1 | 0.78 |
| Sex, n, % male | 28 (71.8%) | 31 (39.7%) | 0.001 |
| sNfL (pg/mL) | 36 | 78 | <0.001 |
| Min | 36.47 | 7.56 |
| Max | 536.64 | 56.82 |
| Abbreviations: AN = autoimmune nodopathy; HC = healthy control; NF155 = neurofascin-155; sNfL = serum neurofilament light chain. |
strong correlation between baseline sNfL levels and initial I-RODS and maximum I-RODS achieved, but not with final I-RODS, suggesting that the final outcomes are not completely determined by initial severity because effective therapies change the course of the disease and most patients improve significantly, regardless of the treatment used. These data differ from those found in GBS, a monophasic disorder in which initial events determine long-term outcomes, but nonetheless suggest that sNfL may be useful to monitor disease because it seems to happen in other peripheral neuropathies.

Our study was not designed to correlate sNfL levels with electrophysiologic parameters because EMG and sNfL levels were not performed at the same time points, but we explored potential correlations between CMAP amplitudes, the presence of spontaneous activity at distal, most affected, muscles, and sNfL levels. We failed to find strong associations. sNfL levels did not correlate with CMAP amplitudes, but they tended to be higher in patients with spontaneous activity. Thus, our results, although preliminary, support the ability of sNfL to monitor axonal damage. Altogether, the correlation of sNfL with disability scales and, less strongly, with the appearance of residual disability or spontaneous activity agrees with the relatively frequent presence of distal muscle atrophy because of secondary axonal damage that some of these patients display and would support the use of sNfL as an early marker of potential axonal damage that could guide treatment selection to prevent the appearance of this permanent damage.

sNfL levels and anti-NF155 antibody titers decreased in all patients in which prospective follow-up was performed on rituximab therapy, whereas neither sNfL or anti-N155 levels showed comparable changes with other treatments. The observation of the rituximab-treated prospectively followed subset of patients suggests, considering the caveats of clinical evaluation in monitoring disease activity in autoimmune neuropathies, that monitoring sNfL levels that inform about the tissue status and anti-NF155 titers that inform about the immunologic effector mechanism, at regular intervals after treatment, could be useful to guide treatment choices and detect suboptimal therapeutic responses. Hypothetically, an eventual increase in autoantibody titers or sNfL levels could herald a subsequent relapse and detecting the biomarker increase could help prevent it. However, the need of retreatment should be assessed individually based on patient’s clinical status and not only based on the laboratory data.

HLA loci are the group of genetic factors that has most frequently been associated with autoimmune diseases, including strong associations with other IgG4-mediated diseases. Previous studies have shown a strong association between a specific Class II allele, HLA-DRB1*15 (either 15:01 or 15:02), and patients with anti-NF155+ AN. Our study shows a stronger association than previously reported (91.3%), confirming that this HLA allele is a constitutive risk factor that, associated with unknown environmental factors, may be driving the appearance of the anti-NF155 autoantibodies. The study of this genetic association in conjunction with geographic distribution of the disorder, lifestyle, concomitant disorders, microbiome, or environmental triggers may yield interesting pathophysiologic insights but requires significantly larger cohorts of patients.

The main limitations of our study arise from the small number of patients and its retrospective nature, including the retrospective analysis of treatment efficacy using chart review. Furthermore, considering that patients were identified through routine diagnostic testing, it is likely that our cohort is enriched in patients with tremor or a lack of response to IVIg because of selection bias. However, since anti-NF155+ AN account for, approximately, 5% of all patients with CIDP, with 40 patients, our cohort provides the largest cohort in which a comprehensive clinical, serologic, and treatment response analysis has been performed.
In conclusion, our study confirms that anti-NF155+ AN constitutes a defined subset of patients with characteristic clinical, epidemiologic, and immunologic features that response to IVIg and steroids is often poor, whereas rituximab is an effective therapy for most patients and that anti-NF155 antibody titers and sNfL levels could be used in combination to monitor clinical activity, ongoing axonal damage, and treatment response.

**Acknowledgment**
The authors would like to acknowledge the Department of Medicine at the Universitat Autònoma de Barcelona. Several authors of this publication are members of the European Reference Network for rare neuromuscular diseases (EURO-NMD).

**Study Funding**
This work is supported by Fondo de Investigaciones Sanitarias (FIS), Instituto de Salud Carlos III, Spain and FEDER under grant FIS19/0140 and personal grant INT20/00080, personal grant GBS-CIDP Foundation to CL, personal grant Rio Hortega CM19/00042 to LMA and the ER20P3AC7624 project of the ACCI call of the CIBERER network, Madrid, Spain. XSC was supported by a “Sara Borrell” postdoctoral fellowship project “CD18/00195,” funded by Instituto de Salud Carlos III and co-funded by European Union (ERDF/ESF, “A way to make Europe”/“Investing in your future”). A.C. thanks the Medical Research Council (MR/T001712/1), the Fondazione CARIPLO (2019-1836), the Italian Ministry of Health-Ricerca Corrente, the Inherited Neuropathy Consortium (INC) and Fondazione Regionale per la Ricerca Biomedica for grant support.

**Disclosure**
L. Querol has provided expert testimony for Grifols, Sanofi-Genzyme, Novartis, UCB, Roche and CSL Behring and received research funds from Novartis Spain, Sanofi-Genzyme and Grifols. L. Martín-Agular has received speaking honoraria from Roche. E. Pascual-Goñi has received honoraria from Biogen for scientific translation works. K. Pitarokoili received travel grants to attend scientific meetings from CSL Behring and Kedrion. M. Cabrera-Serrano has received honoraria from Biogen for scientific translation works. K. Pitarokoili received travel grants and speakers’ honoraria from Novartis, Biogen idec, Teva, Bayer, Celgene, CSL Behring and Grifols, all not related to the manuscript. The other authors report no disclosures. Go to Neurology.org/NN for full disclosures.

**Publication History**
Received by Neurology: Neuroimmunology & Neuroinflammation March 2, 2021. Accepted in final form September 27, 2021.

---

**Appendix Authors**

| Name                        | Location                                      | Contribution                                      |
|-----------------------------|-----------------------------------------------|--------------------------------------------------|
| Lorena Martín-Agular, MD, PhD | Hospital de la Santa Creu i Sant Pau, IIB-Sant Pau Barcelona, Spain | Acquisition of data, performed the experiments, analyzed the data, drafted the manuscript for intellectual content |
| Cinta Lleixà, MSc           | Hospital de la Santa Creu i Sant Pau, IIB-Sant Pau Barcelona, Spain | Acquisition of data, performed the experiments, drafted and revised the manuscript for intellectual content |
| Elba Pascual-Goñi, MD, PhD  | Hospital de la Santa Creu i Sant Pau, IIB-Sant Pau Barcelona, Spain | Acquisition of data, revised the manuscript for intellectual content |
| Marta Caballero, MD         | Hospital de la Santa Creu i Sant Pau, Barcelona, Spain | Acquisition of data, revised the manuscript for intellectual content |
| Laura Martínez-Martínez, MD, PhD | Hospital de la Santa Creu i Sant Pau, Barcelona, Spain | Performed HLA experiments and analyzed the data, revised the manuscript for intellectual content |
| Jordi Díaz-Manera, MD, PhD  | Hospital de la Santa Creu i Sant Pau, Barcelona, Spain | Acquisition of samples and data. Revised the manuscript for intellectual content |
| Ricard Rojas-Garcia, MD, PhD | Hospital de la Santa Creu i Sant Pau, Barcelona, Spain | Acquisition of samples and data, revised the manuscript for intellectual content |
| Elena Cortés-Vicente, MD, PhD | Hospital de la Santa Creu i Sant Pau, IIB-Sant Pau Barcelona, Spain | Acquisition of samples and data, revised the manuscript for intellectual content |
| Janina Turón-Sans, MD       | Hospital de la Santa Creu i Sant Pau, Barcelona, Spain | Acquisition of samples and data, revised the manuscript for intellectual content |
| Noemi de Luna, PhD          | IIB-Sant Pau Barcelona, Spain                 | Revised the manuscript for intellectual content   |
| Xavier Suárez-Calvet, PhD   | IIB-Sant Pau Barcelona, Spain                 | Revised the manuscript for intellectual content   |
| Eduard Gallardo, PhD        | IIB-Sant Pau Barcelona, Spain                 | Revised the manuscript for intellectual content   |
| Yusuf Rajabally, MD         | University Hospital Birmingham, Birmingham, UK | Acquisition of samples and data, revised the manuscript for intellectual content |
| Sangeeta Scotton, MD        | University Hospital Birmingham, Birmingham, UK | Acquisition of samples and data, revised the manuscript for intellectual content |
| Bart C. Jacobs, MD, PhD     | Erasmus Medical Center, Rotterdam, The Netherlands | Acquisition of samples and data, revised the manuscript for intellectual content |
| Adája Baars, MD             | Erasmus Medical Center, Rotterdam, The Netherlands | Acquisition of samples and data, revised the manuscript for intellectual content |
## Appendix (continued)

| Name                        | Location                                           | Contribution                                                                 |
|-----------------------------|----------------------------------------------------|------------------------------------------------------------------------------|
| Andrea Cortese, MD, PhD     | IRCCS Mondino Foundation, Pavia, Italy             | Acquisition of samples and data, revised the manuscript for intellectual content |
| Elisa Vegezzi, MD           | IRCCS Mondino Foundation, Pavia, Italy             | Acquisition of samples and data, revised the manuscript for intellectual content |
| Romana Hoffberger, MD       | Medical University of Vienna, Vienna, Austria      | Acquisition of samples and data, revised the manuscript for intellectual content |
| Fritz Zimprich, MD          | Medical University of Vienna, Vienna, Austria      | Acquisition of samples and data, revised the manuscript for intellectual content |
| Cornelia Roesler, MD        | Paracelsus Medical University, Salzburg, Austria   | Acquisition of samples and data, revised the manuscript for intellectual content |
| Eduardo Nobile-Orazio, MD, PhD | Humanitas Clinical and Research Institute, Milan, Italy | Acquisition of samples and data, revised the manuscript for intellectual content |
| Giuseppe Liberatoro, MD     | Humanitas Clinical and Research Institute, Milan, Italy | Acquisition of samples and data, revised the manuscript for intellectual content |
| Hiew Fu Liong, MD           | Kuala Lumpur General Hospital, Jalan Pahang, Kuala Lumpur, Malaysia | Acquisition of samples and data, revised the manuscript for intellectual content |
| Alicia Martinez-Piñeiro, MD | Hospital Universitari Germans Trias i Pujol, Badalona, Spain | Acquisition of samples and data, revised the manuscript for intellectual content |
| Alejandra Carvajal, MD      | Hospital Universitario de Granada, Granada, Spain  | Acquisition of samples and data, revised the manuscript for intellectual content |
| Raquel Piñar-Morales, MD    | Hospital Universitario Clinico San Cecilio, Granada, Spain | Acquisition of samples and data, revised the manuscript for intellectual content |
| Mercedes Usón-Martin, MD    | Hospital Son Llàtzer, Palma de Mallorca, Spain     | Acquisition of samples and data, revised the manuscript for intellectual content |
| Olalla Alberti, MD          | Hospital San Jorge, Huesca, Spain                  | Acquisition of samples and data, revised the manuscript for intellectual content |
| Maria Ángeles López-Pérez, MD | Hospital San Pedro, Logroño, Spain                | Acquisition of samples and data, revised the manuscript for intellectual content |
| Fabián Márquez, MD          | Hospital Universitari Josep Trueta, Girona, Spain  | Acquisition of samples and data, revised the manuscript for intellectual content |
| Julio Pardo-Fernandez, MD, PhD | Hospital Clínico Universitario de Santiago, Santiago de Compostela, Spain | Acquisition of samples and data, revised the manuscript for intellectual content |
| Laura Muñoz-Delgado, MD     | Hospital Universitario Virgen del Rocio, Sevilla, Spain | Acquisition of samples and data, revised the manuscript for intellectual content |
| Macarena Cabrera-Serrano, MD, PhD | Hospital Universitario Virgen del Rocio, Sevilla, Spain | Acquisition of samples and data, revised the manuscript for intellectual content |
| Nicolau Ortiz, MD, PhD      | Hospital Universitari Sant Joan de Reus, Tarragona, Barcelona | Acquisition of samples and data, revised the manuscript for intellectual content |
| Manuel Bartolomé, MD        | Complejo Asistencial de Avila, Avila, Spain        | Acquisition of samples and data, revised the manuscript for intellectual content |
| Özgür Duman, MD             | Akdeniz University, Antalya, Turkey                | Acquisition of samples and data, revised the manuscript for intellectual content |
| Vera Bril, MD               | Toronto General Hospital, University Health Network, University of Toronto, Toronto, Canada | Acquisition of samples and data, revised the manuscript for intellectual content |
| Darwin Segura-Chavez, MD    | Instituto Nacional de Ciencias Neurologicas, Lima, Perú | Acquisition of samples and data, revised the manuscript for intellectual content |
| Kalliopi Pitarokoili, MD     | St. Josef-Hospital, Ruhr-University Bochum, Bochum, Germany | Acquisition of samples and data, revised the manuscript for intellectual content |
| Claudia Steen, MD           | Sant Joseph Hospital, Berlin, Germany              | Acquisition of samples and data, revised the manuscript for intellectual content |
| Isabel Illa, MD, PhD        | Hospital de la Santa Creu i Sant Pau, Barcelona, Spain | Revised the manuscript for intellectual content |
| Luis Querol, MD, PhD        | Hospital de la Santa Creu i Sant Pau, Barcelona, Spain | Design and conceptualized the study, interpreted the data; revised the manuscript for intellectual content |

## References

1. Lehmann HC, Burke D, Kuwahara S. Chronic inflammatory demyelinating polyneuropathy: update on diagnosis, immunopathogenesis and treatment. J Neurol Neurosurg Psychiatry. 2019;90(9):981-987.
2. Mathey EK, Park SB, Hughes RA, et al. Chronic inflammatory demyelinating polyradiculoneuropathy: from pathology to phenotype. J Neurol Neurosurg Psychiatry. 2015;86(9):973-985.
3. Querol L, Nogales-Gadea G, Rojas-Garcia R, et al. Neurofascin IgG4 antibodies in CIDP associate with disabling tremor and poor response to IVIg. Neurology. 2014; 82(10):879-886.
4. Delfont E, Manzo C, Querol L, et al. Autoantibodies to nodal isoforms of neurofascin in chronic inflammatory demyelinating polyneuropathy. Brain. 2017;140(7):1851-1858.
23. Querol L, Siles AM, Alba-Rovira R, et al. Antibodies to peripheral nerve antigens in chronic inflammatory demyelinating polyradiculoneuropathy. Brain. 2021;144(4):1183-1196.

24. Martín-Aguilar L, Querol L. Autoantibodies in chronic inflammatory demyelinating polyradiculoneuropathy. Curr Opin Neurol. 2019;32(5):651-657.

25. Querol L, Devaux J, Rojas-García R, Illa I. Autoantibodies in chronic inflammatory neuropathies: diagnostic and therapeutic implications. Nat Rev Neurol. 2017;13(9):533-547.

26. Van den Bergh PTK, Doom PA, Hadden RDM, 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. J Peripher Nerv Syst. 2021;26(3):242-268.

27. Painous C, López-Pérez MA, Illa I, Querol L. Head and voice tremor improving with immunotherapy in an anti-NF155 positive CIDP patient. Ann Clin Transl Neurol. 2018;5(4):499-501.

28. Kouton L, Boucrat J, Devaux J, et al. Electrophysiological features of chronic inflammatory demyelinating polyradiculoneuropathy associated with IgG4 antibodies targeting neurofascin 155 or contactin 1 glycoproteins. Clin Neurophysiol. 2020;131(4):921-927.

29. Martínez-Martínez L, Lehelí MC, Boera-Carnicero G, et al. Anti-NF155 chronic inflammatory demyelinating polyradiculoneuropathy strongly associates to HLA-DRB15. J Neurol. 2017;14(1):1-6.

30. Querol L, Rojas-García R, Diaz-Manera J, et al. Rituximab in treatment-resistant CIDP with antibodies against paranodal proteins. Neurol Neuroimmunol Neuroinflamm. 2015;2(5):e149.

31. Cortese A, Lombardi R, Briani C, et al. Antibodies to neurofascin, contactin-1, and contactin-associated protein 1 in CIDP: clinical relevance of IgG isotype. Neurol Neuroimmunol Neuroinflamm. 2020;7(1):e639.

32. Matoso C, Querol L, Lehelí C, et al. Anti-neurofascin-155 IgG4 antibodies prevent paranodal complex formation in vivo. J Clin Invest. 2019;129(6):2222-2236.

33. Koike H, Kadoya M, Kaida K, et al. Paranolal dissection in chronic inflammatory demyelinating polyneuropathy with anti-neurofascin-155 and anti-contactin-1 antibodies. J Neurol Neurosurg Psychiatry. 2017;88(6):465-473.

34. Fukami Y, Iijima M, Koike H, Yamada S, Hashnume A, Katsuno M. Association of serum neurofilament light chain levels with clinicopathology of chronic inflammatory demyelinating polyneuropathy, including NF155 reactive patients. J Neurol. 2021;268(10):3835-3844.

35. Van den Bergh PTK, Hadden RDM, Bouche P, et al. European Federation of Neurological Societies/Peripheral Nerve Society Guideline on management of chronic inflammatory demyelinating polyradiculoneuropathy: Report of a Joint Task Force of the European Federation of Neurological Societies and the Peripher. Eur J Neurol. 2010;17:356-363.

36. Breiner A, Bourque PR, Allen JA. Updated cerebrospinal fluid total protein reference values improve chronic inflammatory demyelinating polyneuropathy diagnosis. Muscle Nerv. 2019;60(9):180-183.

37. Quinn TJ, Dawson J, Walters MR, Lees KR. Functional outcome measures in chronic inflammatory demyelinating polyradiculoneuropathy: a systematic review and meta-analysis of acute antibodies for diagnosis and prognosis in patients with chronic inflammatory demyelinating Polyradiculoneuropathy. Front Neurol. 2021;15:637336.

38. Oh SJ, Morgan MB, Lu L, et al. Different characteristic phenotypes according to antibody in myasthenia gravis. J Clin Neuromuscul Dis. 2012;14(2):57-65.

39. Van De Veen W, Stanic B, Yaman G, et al. IgG4 production is confined to human IL-10-producing regulatory B cells that suppress antigen-specific immune responses. J Allergy Clin Immunol. 2013;131(4):1204-1212.

40. Joly P, Mousquet H, Roujeau J-C, et al. A single cycle of rituximab for the treatment of severe periphaphias. N Engl J Med. 2007;357(6):545-552.

41. Diaz-Manera J, Martínez-Hernández E, Querol L, et al. Long-lasting treatment effect of rituximab in MuSK myasthenia. Neurology. 2012;78(3):189-193.

42. Marino M, Basile U, Spagni G, et al. Long-Lasting rituximab-induced reduction of specific—but not total—IgG4 in MuSK-positive myasthenia gravis. Front Immunol. 2020;11:1-9.

43. Svalo J, Petrov P, Antoine JC, et al. Anti-MAG antibodies in 202 patients: clinicopathological and therapeutic features. J Neurol Neurosurg Psychiatry. 2018;89(5):499-505.

44. Dalakas MC, Rakocievic G, Salajegheh M, et al. Placebo-controlled trial of rituximab in IgGn anti-myelin-associated glycoprotein antibody demyelinating neuropathy. Ann Neurol. 2009;65(3):286-293.

45. Stengel H, Vural A, Brunder AM, et al. Anti-paran-neurofascin IgG3 as a marker of fulminating autoimmune neuropathy. Neurology Neuroimmunol Neuroinflamm. 2019;6(5):e603.

46. Kawamura N, Yamasaki R, Yonekawa T, et al. Anti-neurofascin antibody in patients with combined central and peripheral demyelination. Neurology. 2013;81(8):714-722.

47. Lieverloo GGA, Wieske L, Verhamme C, et al. Serum neurofilament light chain in chronic inflammatory demyelinating polyneuropathy. J Peripher Nerv Syst. 2019;24(2):187-194.

48. Sandelius Å, Zetterberg H, Blemow K, et al. Plasma neurofilament light chain concentration in the inherited peripheral neuropathies. Neurology. 2018;90(6):e518-e524.

49. Kapoor M, Foiani M, Heslegrave A, et al. Plasma neurofilament light chain concentration is increased and correlates with the severity of neuropathy in hereditary transthyretin amyloidosis. J Peripher Nerv Syst. 2019;24(4):314-319.

50. Nika EH, Kiks JBM, Roep BO, et al. Strong association of MuSK antibody-positive myasthenia gravis and HLA-DR14-DQ4. Neurology. 2006;66(11):1772-1774.

51. Huibers MG, Querol LA, Niki EH, et al. The expanding field of IgG4-mediated neurological autoimmune disorders. Eur J Neurol. 2015;22(8):1151-1161.

52. Kim TJ, Lee ST, Moon J, et al. Anti-LGI1 encephalitis is associated with unique HLA subtypes. Ann Neurol. 2017;81(2):183-192.
Clinical and Laboratory Features in Anti-NF155 Autoimmune Nodopathy
Lorena Martín-Aguilar, Cinta Lleixà, Elba Pascual-Goñi, et al.

Neurol Neuroimmunol Neuroinflamm 2022;9;
DOI 10.1212/NXI.0000000000001098

This information is current as of November 2, 2021
Clinical and Laboratory Features in Anti-NF155 Autoimmune Nodopathy

In the Article “Clinical and Laboratory Features in Anti-NF155 Autoimmune Nodopathy” by Martín-Aguilar et al., the affiliation for author Eduardo Nobile-Orazio should have been listed as “IRCCS Humanitas Research Hospital, Milan University, Rozzano, Italy.” The publisher regrets the error.

Reference
1. Martín-Aguilar L, Lleixà C, Pascual-Gotti E, et al. Clinical and laboratory features in anti-nf155 autoimmune nodopathy. Neurol Neuroimmunol Neuroinflamm. 2022;9(1):e1098. doi: 10.1212/NXI.0000000000001098.