Neurofascin-155 Immunoglobulin Subtypes: Clinicopathologic Associations and Neurologic Outcomes

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Abstract

**Background and Objective:** Multiple studies highlighting diagnostic utility of neurofascin 155 (NF155)-IgG4 in chronic demyelinating inflammatory polyradiculoneuropathy (CIDP) have been published. However, few studies comprehensively address the long-term outcomes, or clinical utility of NF155-IgM or NF155-IgG, in the absence of NF155-IgG4. In this study we evaluate phenotypic and histopathological specificity, and differences in outcomes between these NF155 antibody isotypes or IgG subclasses. We also compare NF155-IgG4 seropositive cases to other seropositive demyelinating neuropathies.

**Methods:** In this study, neuropathy patient sera seen at Mayo Clinic were tested for NF155-IgG4, NF155-IgG and NF155-IgM autoantibodies. Demographic and clinical data of all seropositive cases were reviewed.

**Results:** We identified 32 NF155 patients (25 NF155-IgG positive [20 NF155-IgG4 positive], 7 NF155-IgM seropositive). NF155-IgG4 seropositive patients clinically presented with distal more than proximal muscle weakness, positive sensory symptoms (prickling, asymmetric paresthesia, neuropathic pain) and gait ataxia. Cranial nerve involvement (11/20, 55%) and papilledema (4/12, 33%) occurred in many. Electrodiagnostic testing (EDX) demonstrated demyelinating polyradiculoneuropathy (19/20, 95%). Autonomic involvement occurred in 45% (n=9, median CASS score 3.5, range 1-7). Nerve biopsies from the NF155-IgG4 patients (n=11) demonstrated grouped segmental demyelination (50%), myelin reduplication (45%) and paranodal swellings (50%). Most patients needed 2nd and 3rd line immunosuppression but had favorable long-term outcomes (n=18). Among 14 patients with serial EDX over 2 years, all except one demonstrated improvement after treatment. NF155-IgG positive NF155-IgG4 negative (NF155-IgG positive) and NF155-IgM positive patients were phenotypically different from NF155-IgG4 seropositive patients. Sensory ataxia, neuropathic pain, cerebellar dysfunction and root/plexus MRI abnormalities were significantly more common in NF155-IgG4 positive compared to MAG-IgM neuropathy. Chronic immune sensory polyradiculopathy (CISP)/CISP-plus phenotype was more common among Contactin-1 neuropathies compared to NF155-IgG4 positive cases. NF155-IgG4 positive cases responded favorably to immunotherapy compared to MAG-IgM seropositive cases with distal acquired demyelinating symmetric neuropathy (p<0.001) and had better long-term clinical outcomes compared to contactin-1 IgG (p=0.04).

**Discussion:** We report long-term follow-up and clinical outcome of NF155-IgG4 patients. NF155-IgG4 but not IgM or IgG patients have unique clinical-electrodiagnostic signature.
We demonstrate NF155-IgG4 positive patients, unlike classical CIDP with neuropathic pain and dysautonomia common at presentation. Long-term outcomes were favorable.

**Classification of Evidence:** This study provides Class III evidence that NF155-IgG4 seropositive patients, compared to typical CIDP patients, present with distal more than proximal muscle weakness, positive sensory symptoms, and gait ataxia.
Introduction

Neurofascin-155 (NF155) autoantibodies are amongst the most common nodal and paranodal antibodies, comprising 4%\(^1\) to 18% of all chronic demyelinating polyradiculoneuropathy (CIDP) cases.\(^2\)-\(^9\) Despite the growing utilization of these antibodies in clinical practice, studies evaluating long-term outcomes and histopathological characterization are limited.\(^10\)

In this study, we determine frequency of NF155 autoantibodies in a large demyelinating neuropathy cohort. We evaluate phenotypic and histopathological specificity, and differences in outcomes between NF155-IgG4 seropositive, NF155 pan-IgG and NF155-IgM seropositive cases. We also compare phenotypic differences and outcomes in NF155-IgG4 positive cases to myelin associated glycoprotein (MAG)-IgM and Contactin-1 IgG associated demyelinating neuropathies.

Material and methods

Our primary research question was to evaluate the clinical utility of NF155-IgG4 and NF155-IgM or NF155-IgG (in the absence of NF155-IgG4) autoantibodies and assess phenotypic and histopathological differences in long-term outcomes amongst patients these autoantibodies.

Patient selection

We retrospectively reviewed Mayo Clinic Rochester database for diagnostic codes designating demyelinating neuropathies from January 1\(^{st}\), 1986 to January 1\(^{st}\), 2019. On review of electronic medical records (EMR) of the screened cases, 237 acute or chronic inflammatory demyelinating polyradiculoneuropathies (AIDP [n=23], CIDP [n=214]) were identified (Cohort 1). Additional 173 patients with stored sera identified during this initial screening with an alternative neuropathy etiology or clinical presentation not consistent with AIDP/CIDP/chronic immune sensory polyradiculopathy (CISP)/CISP-plus phenotype were utilized as disease controls (eFigure 1). Furthermore, peripheral nerve specialists (SS, DD, CJK, MM, SB, PJBD) prospectively sent samples for NF155 autoantibody evaluation among cases where nodal and paranodal antibody mediated neuropathy was suspected between January 1\(^{st}\), 2019 and March 31\(^{st}\), 2021 (Cohort 2).
**NF155 testing**

*Cohort 1:* Sera of all patients were tested on in-house flow cytometry-based assay that utilized a stable cell line co-expressing human NF155 and GFP using an approach previously described. Patient and control sera were tested at a 1:10 and 1:40 dilutions for NF155-IgG4 and NF155-IgG respectively. The median fluorescence intensity of Alexa Fluor 647–conjugated anti-human IgG4 or IgG was determined for both non-transfected and transfected cells. The ratio of median fluorescence intensity values for GFP+ and GFP− cells was calculated as IgG or IgG4 binding index. IgG binding index of ≥5, and IgG4 binding index ≥2, were considered positive.

*Cohort 2:* Prospectively collected patient sera were evaluated by flowcytometry for NF155-IgG4 in-house and/or for NF155 IgG4, pan IgG and IgM antibodies at the Washington University clinical service Neuromuscular Laboratory by western blot analysis.

**Nerve Histology**

Nerve biopsies from NF155 autoantibody positive cases were performed and processed in our peripheral nerve laboratory using standard histologic stains and immunohistochemistry stains (CD45, CD68) prepared on paraffin and epoxy sections. Teased fibers were prepared were graded by previously defined pathologic criteria. Morphometric analysis was performed on epoxy sections using our Imaging System for Nerve Morphometry.

**Clinical outcome**

INCAT disability scores and gait assistance (assessed at final neurological visit) were calculated for all patients. Favorable outcomes were defined by improvement ≥1 in INCAT disability scores calculated before and after immunotherapy. We defined disease relapse as >3 units increase in INCAT disability score after at least 3 months of disease stability, when follow-up data was available.

**Clinical comparison group**

NF155-IgG4 seropositive (NF155-IgG4 positive) cases were compared to Contactin-1-IgG and myelin associated glycoprotein (MAG)-IgM seropositive patients evaluated at Mayo Clinic within the study period. Contactin 1-IgG cases evaluated at mayo clinic between January 1, 1993, to March 31st 2021 (4 mayo patients previously published) were
included for clinical comparisons. Contactin-1 Euroimmun CBA was utilized for contactin-1 IgG and IgG4 testing\textsuperscript{17}. We searched the Mayo Clinic electronic database for patients seen in the neuromuscular and peripheral nerve specialty clinics between 2004 and 2018 with a distal acquired demyelinating symmetric (DADS) neuropathy phenotype in the setting of an IgM monoclonal gammopathy of uncertain significance (n=86). MAG IgM antibodies were measured using a clinically validated enzyme-linked immunosorbent assay (ELISA) from Buhlmann diagnostics. Positivity was defined using a cut-off of 1500 Buhlmann Titer Units (BTU).

**Statistical analysis**

For comparisons between groups, qualitative and continuous variables were analyzed using the Fisher exact test and Mann–Whitney U test, respectively.

**Standard Protocol Approvals, Registration, and Patient Consents**

The study was approved by the institutional review board of Mayo Clinic, Rochester, Minnesota (institutional review board number 08-006647). Permission to participate was obtained from the patients.

**Data availability**

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

**Results**

**Retrospective and prospective cohorts; classification of NF155 isotypes**

*Cohort 1:* Among 214 CIDP and 23 AIDP patients evaluated from the retrospective cohort, 14 CIDP were NF155-IgG4 positive (6.5%); none of the AIDP tested positive. Three patients were NF155-IgG positive and NF155-IgG4 negative (NF155-IgG positive). All 173 disease control sera tested for NF155-IgG4 by flowcytometry were negative; one patient was NF155-IgG positive.

*Cohort 2:* Fourteen patients NF155 autoantibody positive patients were evaluated prospectively seen by peripheral nerve specialists. Six patients were NF155-IgG4 positive. One patient was only NF155-IgG positive. An additional 7 patients were NF155-IgM positive on western blot but NF155-IgG and NF155-IgG4 negative.
Neuropathic pain, distal weakness, sensory ataxia, tremor, and cranial nerve involvement were common amongst NF155 IgG4 positive patients.

Demographic and clinical features for all NF155-IgG4 positive patients are shown in Table 1. Median age of symptom onset was 45.5 years, with 1 patient having symptom onset at 4 years of age. Nadir of symptoms severity occurred up to 12 months from symptom onset. Median time from symptom onset to demyelinating neuropathy diagnosis was 10 months (range 1 to 208 months). As a group, the most common clinical features were distal more than proximal muscle weakness (14, 70%). Majority of the patients had distal more than proximal weakness (14, 70%). Additionally, motor deficits involving lower extremities (18, 90%) were much more common than upper extremity predominant presentations. Positive sensory disturbances (including prickling, asymmetric paresthesia, and neuropathic pain) with sensory as well as cerebellar ataxia and tremor were (10, 50%) observed. The tremor was an action tremor affecting the distal extremities, most often the fingers and hands. Cranial nerve and bulbar symptoms were common 55% (11/20) and included one or more of the following: dysphagia or dysarthria (n=7), diplopia or ptosis (n=2), blurry vision (n=1) and unilateral facial numbness (n=2). Papilledema was also present (4/12, 33%). Neurological examination findings are shown in Table 1.

Evaluation of NF155 IgG4 seropositive patients revealed demyelinating polyradiculoneuropathy, frequently with autonomic dysfunction.

Nerve conduction studies (NCS) and needle electromyography examinations were performed in all patients. All NF155-IgG4 seropositive cases had electrodiagnostic features consistent with demyelinating polyradiculopathy with slowed motor conduction velocities or prolonged distal latencies. All 20 patients met the European Federation of Neurological Societies (EFNS) / Peripheral Nerve Society (PNS) demyelinating electrophysiological criteria for CIDP (18 definite, 1 probable and 1 possible). 18

Polyradiculoneuropathy with evidence of root and peripheral nerve involvement was the most common electrodiagnostic phenotype (n=19, 95%). More specifically, all patients had reduced or absent motor amplitudes (n=20, 100%); reduced or absent sensory amplitudes (n=19, 95%) and often prominent slowing of motor conduction velocities (n=18, 90%). F-wave latencies were prolonged (n=16) or absent (n=2) in 90% patients (n=18, 90%). Other features noted in minority of cases were temporal dispersion (n=4, 20%) and conduction block (n=4, 20%). Blink reflex studies were performed in 19 cases and were prolonged in majority of patients (84%, 16/19). Median R1 latency was 17.3 milliseconds
In nearly all cases fibrillation potentials were identified in proximal/paraspinal muscles supporting radicular localization (n=19, 95%).

Autonomic symptoms were present in 45% (9/20) patients and included: orthostatic intolerance (defined by clinical history of syncope or lightheadedness) and blood pressure changes (n=3), urinary incontinence and constipation (n=3), erectile dysfunction temporally associated with the date of symptom onset (n=2). Six patients demonstrated abnormal autonomic reflex screen (ARS) testing with median composite autonomic scoring scale (CASS) of 3.5 (range: 1-7) indicating a moderate autonomic neuropathy. Testing demonstrated sudomotor dysfunction (n=5) as well as cardiovascular adrenergic impairment (n=3).

CSF studies were available in 19 NF155-IgG4 positive patients. CSF protein was elevated in all patients with median CSF protein of 224 g/dL (range: 60-834 g/dL, normal <50 mg/dL). Nine patients had mild lymphocytic pleocytosis (median 5 cell/mm$^3$; range: 4-100 cell/mm$^3$).

**MRI showed diffuse symmetric enlargement, nerve root thickening and nerve root/plexus gadolinium enhancement amongst NF155-IgG4 seropositive patients.**

MRI images were available to review in 17 NF155 IgG4 (spine, n=13 and plexus, n=9) patients. Diffuse symmetric enlargement of the lumbosacral plexus or lumbosacral roots with marked T2 hyperintensity were a common finding in 82% (14/17) of patients. The most common abnormality identified on lumbar spine MRI was nerve root thickening (85%, 11/13) followed by nerve root gadolinium enhancement on axial images (46%, 6/13). In one patient, patchy, non-enhancing T2 hyperintensity was seen throughout the cervical spinal cord up to the brainstem. One patient had abnormal signal involving the oculomotor, trigeminal, facial, and vestibulocochlear nerves bilaterally on head MRI. Six patients had abnormal white matter changes that were considered as nonspecific white matter change presumed to be secondary to small vessel disease. Overall, there were no radiological findings supporting a concurrent central demyelinating disease in the 9 patients who underwent head MRI.

**Histopathological analysis of NF155-IgG4 seropositive patient showed active axonal degeneration, paranodal expansions and perineural inflammatory collections.**

Nerve biopsies from 11 NF155-IgG4 positive, 2 NF155-IgG positive paitents were performed at our institution. Median time from symptom to biopsy was 9 months (range: <1
The biopsies included: lumbar dorsal rootlet (n=1), fascicular sciatic (n=1) and distal cutaneous nerve biopsies (n=11). Electron microscopy (EM) was performed to better demonstrate ultrastructural changes in 1 patient who had proximal and distal biopsy.

Teased fiber preparations were available for review in 10 of 11 NF155-IgG4 positive biopsies and showed increased rates of segmental demyelination (n=5), highest in the fascicular sciatic biopsy (48%, Figure 1D) and lowest in distal cutaneous biopsies (mean 6%; range: 0-25%, normal <2%). Increased frequencies of myelin reduplication were common and observed in 50% (n=5) of biopsies, with areas of para-nodal swellings (areas of thickened myelin adjacent to the node of Ranvier) in 50% (n=5), Figure 1A-C, ranging in severity. Most severe in the proximal site (Figure 1C) to less severe areas distally (Figure 1A-B).

On the paraffin embedded sections, the main pathological abnormality was loss of large, myelinated nerve fibers seen in both distal and proximal biopsies (Figure 1A). Onion-bulb formations were not observed in any of the distal biopsies. Multifocal fiber loss was seen in 4/11 biopsies and sub-perineurial edema (Figure 2B) was present in 2 biopsies. Individual to small endoneurial and epineurial inflammatory collections were seen in 81% (9/11) of the distal nerve biopsies. In one patient (with severe sensory ataxia, tremor and pseudoathetosis) who had two biopsies a proximal fascicular sciatic biopsy and a sural nerve biopsy, large collections of epineurial mononuclear cells was seen in the proximal fascicular sciatic biopsy, Figure 2C-D with less inflammatory infiltrate in the distal sural site. Fascicular sciatic biopsy from another patient demonstrated multiple small endoneurial and epineurial inflammatory cell collections. The overall density of myelinated fibers ranged from normal to severely reduced.

**NF155-IgG4 seropositive cases were IVIG refractory, with favorable response to 2nd line immunosuppressive agents.**

All NF155-IgG4 positive patients were treated with immunotherapy. First-line immunotherapies included one or more of the following: intravenous immunoglobulin (IVIG, n=18) alone or in combination with intravenous methylprednisolone (IVMP, n=7) and plasmapheresis (PLEX, n=2). Most cases (12/18) had initially favorable responses to IVIG but later became IVIG refractory despite continued treatments. Six patients had worsening of their symptoms even with initial IVIG treatments.

Furthermore, a subset of these patients required secondary long-term immunosuppression (n=18, 90%): mycophenolate mofetil (n=7), rituximab (n=5), azathioprine (n=4) and cyclosporin (n=2). Eight cases needed a third immunotherapy:
corticosteroids (n=4), plasmapheresis (n=2), IVIG (n=2) while on immunosuppression medications. As a group, most patients improved at the time of last follow up (n=18).

Relapses were common in NF155-IgG4 seropositive patients and half of the patients required gait aid by 1 year, indicating high morbidity.

Median duration of follow up among NF155-IgG4 positive cases was 7 years (range: 5 to 411 months) measured from symptom onset to last follow up or death. Most of these cases had >3 years of follow up with repeated examinations (n=18, 90%). Despite refractoriness to IVIG, long-term outcomes in most cases were favorable (n=18, 90%). One patient stabilized and one continued to deteriorate despite IVMP and azathioprine treatment. Death was reported in 3 patients (12%) by the end of the study period. One (patient with fascicular sciatic biopsy) died from disease complication due to central port infection after plasmapheresis treatment, one from septic shock due to diverticulitis and cause of death was unclear in one patient who was lost to neurology follow up.

Median number of relapses per patient was 1 (range: 1 to 3 times). Median time to relapse was 58 months (range: 11 to 220 months). Nearly 50% of patients experienced relapses in the first 4 years from symptom onset and in the first 2 years from starting treatment, Figure 3A. There was a significant difference in inflammatory neuropathy cause and treatment (INCAT) disability scores comparing patients who had relapse versus patients who did not experience relapses in their disease course (p=0.02, Figure 3B).

Most patients were using gait aids at neurological presentation (n=15, 75%): cane (n=1), walker (n=5), wheelchair (n=9). At the time of last follow-up, seven patients who previously used gait aids were independently ambulatory. Of the remaining 8 patients 1 was using a cane, 3 using wheelchairs and 4 were using walkers at the time of last follow-up.

Neurological clinical outcomes measured at last neurology visit including needing assistance in daily tasks was markedly better after treatment (p<0.001, CI: 1-5). Time from symptom onset to maximal gait aid dependence was reached in the first year of the disease in half of patients, signifying disease nadir, Figure 4A. Electrophysiological testing with serial nerve conduction evaluations were available in 14 patients and the summated compound motor action potential (CMAP), a calculation in which CMAP amplitudes of all recurrent motor NCS are summated (a rough measure of axonal integrity) showed improvement after >24 months of treatment in NF155-IgG4 positive cases Figure 4B.
Clinical comparison nodo-paranodopathies to other seropositive demyelinating polyradiculoneuropathies

To further characterize the clinical phenotype and to identify distinguishing features we compared NF155-IgG4 positive patients to Contactin-1 IgG positive and MAG IgM seropositive demyelinating polyneuropathy. **Table 2.** NF155 IgG4 positive onset age was significantly younger compared to MAG IgM (p<0.001). Sensory ataxia, neuropathic pain, cerebellar dysfunction and root/plexus MRI abnormalities significantly more common in NF155-IgG4 positive compared to MAG IgM neuropathy. Of note, CISP/CISP-plus phenotype was more common among Contactin-1 neuropathies compared to NF155-IgG4 positive cases. INCAT disability scores at first encounter were significantly worse in the NF155IgG4 positive compared to MAG IgM groups (p<0.001). Additionally, improvement in INCAT disability score between first and last INCAT was significantly more in NF155-IgG4 positive patients versus the MAG-IgM patients **Figure 5.** Gait aid as last follow up improved in the NF155-IgG4 (from 75% to 40%) and worsened in the MAG IgM group (10% to 40%).

**NF155-IgG4 negative patients’ characteristics:**

**NF155 IgG positive or IgM positive patients were not clinically distinct.**

A total of 5 patients were NF155-IgG positive (NF155-IgG4 negative): 4 in retrospective cohort (1 disease control) and 1 in prospective cohort. The median age at diagnosis was 56.5 years (range: 30-66 years). Median time from symptom onset to diagnosis was 11 months (range: 4-61 months). Clinical presentations were consistent with motor predominant polyradiculoneuropathy (n=2), subacute motor polyradiculoneuropathy (n=1), length-dependent sensorimotor peripheral neuropathy (n=1), and length-dependent sensory neuropathy (n=1).

We identified 7 cases prospectively who were negative for NF55-IgG but NF55-IgM positive. The median age at presentation of this group was 54 years (range: 21-63 years). Clinically, they had various neurological presentations including motor predominant axonal polyradiculoneuropathy (n=2), sensory motor predominant axonal polyradiculoneuropathy (n=1), sensorimotor length-dependent axonal polyneuropathies (n=1), length-dependent sensory predominant axonal polyneuropathy (n=1), brachial plexopathy (n=1), facial numbness (n=1).
**NF155 IgG positive or IgM positive cases had no distinctive electrophysiological, CSF or imaging findings.**

**Electrodiagnostic**

Electrodiagnostic findings included: prolonged F-wave latency (n=1), reduced distal sensory and motor amplitudes (n=2), reduced motor amplitudes (n=2). Conduction velocity showed slowing (n=2) or was normal (n=3). Blink studies were abnormal in two of three patients tested.

Among the NF155-IgM positive patients, Electrodiagnostic finding were length-dependent axonal polyneuropathy (n=3), mixed axonal and demyelinating polyneuropathy (n=2), upper trunk brachial plexopathy (n=1) and normal (n=1). Blink studies were normal in all tested patients (n=5).

**CSF studies**

CSF studies in NF155-IgG positive patients were performed in four patients. CSF protein levels were elevated in 2 of the 4 patients, the median CSF protein levels was 200 g/dL (range: 43-496 g/dL). Among the NF155-IgM positive patients, CSF protein was only elevated in one patient, the median CSF protein levels were 43 g/dL (range: 22-190 g/dL).

**Imaging**

Two NF155-IgG positive patients with polyradiculoneuropathy had lumbar plexus MRIs, both showed enlarged proximal nerves and one also had increased T2 signal. MRI L-spine performed in three patients was unremarkable. Head MRI (n=4) showed non-specific T2/FLAIR hyperintensity suggestive of microvascular changes (n=2) or was normal (n=2).

Among all 5 NF155-IgM positive cases MRI L-spine was available for review. One patient showed non-enhancing T2 hyperintensity. MRI lumbosacral plexus was abnormal in 2 of the 4 patients showing T2 hyperintensities of the proximal nerves without gadolinium enhancement. Head MRI brain showed either nonspecific T2 hyperintensities (n=2) or was normal (n=2).

**NF155 IgG positive or IgM positive nerve biopsy findings were variable.**

Two sural nerve biopsies from NF155-IgG positive cases were performed. Teased fiber preparations did not show evidence of active demyelination, teased fiber preparations and semithin sections showed onion bulbs, figure 2G-H, and subperineurial edema (n=1). Small epineurial inflammation in one and absent in the other. The density of myelinated fibers was normal in one and borderline normal in other with normal fiber size distribution.
Two NF155-IgM positive patients underwent nerve biopsies. One patient had superficial radial nerve biopsy which showed severe axonal loss with no interstitial abnormalities. The other patient had a sural biopsy showing severely decreased density of myelinated fibers in a diffuse pattern with increased rate of axonal degeneration and multiple moderate perivascular epineurial mononuclear inflammatory cell collections. This was suggestive of inflammatory-immune process, which appeared to involve small vessel walls raising the possibility of a microvasculitis.

**NF155 IgG positive or IgM positive clinical outcomes were favorable, few did not require immune treatment**

Among the NF155-IgG positive cases, 4 patients were treated with immunotherapy, and one did not require treatment. First-line treatments included IVIG (n=4) and PLEX (n=1). Two patients needed additional long-term immunosuppression (azathioprine and mycophenolate mofetil).

Among NF155 IgM positive cases (n=7), 6 were treated with immunotherapy, one patient who had facial numbness and borderline-normal neurological examination was not treated. Treatment included IVIG (n=5) or IVMP (n=1).

Among the NF155-IgG positive cases median follow-up time was 7 years (range: 52-253 months). As a group all had favorable outcome, one patient was only treated for pain (diagnosis length depended large fiber sensory peripheral neuropathy). Gait aids were utilized at presentation in two patients (walker and wheelchair) and these two patients continued to require a walker at last follow-up.

Among the NF155-IgM positive cases, median follow-up time was 4 years (range: 2-128 months). Treatment response evaluation was available in 5 NF155-IgM positive cases who had neuromuscular clinic follow-ups. Four cases significantly improved with treatment. One case with brachial plexopathy did not demonstrate muscle strength improvement but his neuropathic pain significantly improved. Gait aids at presentation were needed in 4 patients (cane=3, wheelchair=1) and at last follow-up 2 patients still required a cane.

**Class of Evidence**

This study provides Class III evidence that NF155-IgG4 seropositive patients, compared to typical CIDP patients, present with distal more than proximal muscle weakness, positive sensory symptoms, and gait ataxia.
Discussion

The occurrence of NF155 IgG4-seropositivity in our US-based tertiary center for patients with immune mediated demyelinating neuropathies was 6.5%. This is similar to other studies which reported a frequency of 4-18%. Serologically, NF155 autoantibodies observed in this study were mainly IgG4 subtype with a distinct clinical pathological phenotype. Although a considerable proportion of NF155-IgM positive or NF155-IgG positive cases who were NF155-IgG4 negative had electrophysiological, radiological, and histopathological findings suggestive of an immune or inflammatory neuropathy, but no consistent clinical phenotype, histopathological findings or treatment response was observed (Table 2). More specifically, compared to NF155-IgG4 positive patients, there was significantly lower CSF protein (p=0.01) and INCAT score at presentation (p<0.001). This was also shown by other groups previously with few cases of chronic indolent idiopathic or genetic neuropathies patients testing positive for NF155-IgG/NF155-IgM antibodies. One hypothesis is that there is a transient IgM or IgG1-3 humoral response to NF155 antigens among neuropathies of varied etiologies may be secondary to paranodal damage and antigenic release.

Our study shows high frequency of neuropathic pain and autonomic symptoms (mainly sudomotor dysfunction, 45%) in NF155-IgG4 positive patients which clinically suggests small fiber involvement in this disease. Median CASS scores were higher than described in classic CIDP. Small fiber involvement was also a part of the pathological abnormalities seen on electron microscopy showing non-myelinating Schwann cells cytoplasm infiltrated by bundles of collagen fibers instead of axons, so called ‘collagen pockets’, Figure 1G. This indicates that in addition to more distal pattern of muscle weakness and sensory ataxia, autonomic involvement or pain as initial symptom should raise a concern for NF155-IgG4 positivity. Presence of papilledema and demyelinating features on electrodiagnostic testing with only a minority of studies demonstrating conduction block suggests that NF155-IgG4 testing should also be considered among patients clinically suspected to have POEMS syndrome.

Blink reflex latency measurements as a reflection of subclinical demyelination was recently reported to be prolonged in a small cohort of NF155-IgG4 positive patients. Our findings agree with this observation and we show that majority of our patients (84%) had prolonged blink responses. This can be used as a useful tool to detect proximal...
demyelination in the presence of severe axonal degeneration in distal nerves which is encountered in many NF155-IgG4 positive patients.

Fascicular sciatic biopsy taken from a severely affected patient with sensory ataxia and tremor demonstrated diffuse loss of myelinated fibers, thickened perineurium and a large degree of subperineurial edema similar to what has been previously shown in distal sensory NF155 nerves, Figure 2A. But what has not been previously shown were the high frequency of segmental demyelination (48%) and associated large epineurial perivascular inflammatory collections supportive of proximal inflammatory pathology Figure 2C. Pathologically, more severe neurologic involvement in a proximal fascicular sciatic biopsy than in distal cutaneous nerve biopsies of NF55-IgG4 positive patients is similar to what is seen in classical CIDP. We also show various degrees of paranodal swellings (myelin thickening) on teased nerve fibers from proximal and distal biopsies among NF55-IgG4 positive patients. The demyelination on NCS and hypertrophy of nerves on MRI made us expect biopsy specimens would show typical hypertrophic feature of onion bulb formation, however those were absent in NF155-IgG4 positive cases but present in a NF155-IgG positive patient, Figure 2H. Highlighting that the distinct histopathological changes may be limited to NF155-IgG4 positive cases, and NF155-IgG positive or NF155-IgM positive nerve biopsy findings may vary based on associated neuropathy phenotype.

Treatment response in our cohort confirms previous observations that NF155-IgG4 positive patients are IVIG refractory with most patients worsening after initial partial improvement. As a group, they require more extensive immunotherapy and show clinical improvement after 2nd or 3rd line immunotherapies are added, comparable to what has been previously described. Time to clinical improvement was prolonged compared to classic CIDP and in most patients it was longer than 2 years from symptom onset. Similarly, electrophysiological improvement in the form of summated CMAP was slow and was typically not seen until 12 months after treatment initiation Figure 4B. The requirement of more aggressive and prolonged immunotherapy course to bring about significant improvement is likely secondary to early axonal loss as shown by histopathological preparation and electrodiagnostic studies.

Relapse rates in NF155 nodo/paranodopathies are not well described, with several reports describing clinical declines only when immune treatment was stopped. In our study, the number of patients with relapsing course were high (45%), and the relapses commonly occurred in the first 2 years after diagnosis, Figure 3A. Furthermore, we found that patients with longer time from symptom onset to treatment and more neuropathic
disability at initial assessment had more relapses. Suggesting that early recognition and appropriate treatment is important factor in outcome.

Both NF155 and contactin-1 proteins play a role in the formation and stability of sodium channel clusters located at nodes of Ranvier. Antibodies against these proteins effect the conduction probably by disturbing axoglial contacts and myelin insulation. Supported by in vitro studies we speculate the mechanism of nerve injury are secondary to channel dysfunction, eventually causing axonal damage. This is also supported by our pathological studies demonstrating myelin swelling and thickening in the paranodal areas with multiple focal demyelinating changes. Figure 1C.

We compared the clinical features of other seropositive demyelinating polyradiculoneuropathies to NF155-IgG4 positive patients, Table 2. Younger age of neuropathy onset, sensory ataxia, cerebellar signs and neuropathic pain at onset were more common among NF155-IgG4 positive patients in comparison to MAG-IgM positive distal neuropathy patients. Presenting features sensory ataxia and neuropathic pain were common among NF155-IgG4 and contactin-1 IgG seropositive patients making clinical distinction between two conditions during initial presentation difficult. However, 4 of the 9 contactin-1 cases had a CISP or CISP-plus phenotype and two of the nine cases had membranous glomerulonephropathy but none of the NF155-IgG4 positive patients. Disease progression among NF155-IgG4 and contactin-1 IgG tends to be more rapid than MAG-IgM patients which have an insidious progression. Furthermore, both NF155-IgG4 and contactin-1 IgG patients were more immunotherapy responsive in comparison to MAG-IgM associated neuropathy (Figure 5). Comparing neurological outcomes between NF155-IgG4 and contactin-1 IgG seropositive patients showed that latter had a trend towards a more aggressive clinical course.

Limitation of our study include its retrospective nature. Additionally, the data collected is not population based therefore the frequency NF155 maybe skewed. Evaluation of assay clinical specificity during assay validation is critical; this data is not readily available for antibody evaluations performed at outside laboratory. As has been demonstrated in the past for other cell surface antibodies enzyme linked immunosorbent assays may generate higher number of false positive results. Therefore, multicenter studies comparing assay metrics of the different testing methodologies utilized for detection of NF155 autoantibodies should be performed.

In summary, NF155-IgG4 is a highly specific biomarker of clinically, electrophysiologically and histopathologically distinct demyelinating polyradiculoneuropathy. However, the clinical utility of NF155-IgM or NF155-IgG without co-existing NF155-IgG4
remains unclear. Therefore, NF155-IgG positive/NF155-IgM positive patients should be managed only on the basis of their clinical and electrodiagnostic phenotype. The clinical course and outcome are different from typical CIDP, with most patients requiring long term immune treatment (<2 years) and the utilization of more aggressive immunotherapy.

Table 1: Demographic Clinical characteristics of Neurofascin 155-IgG4 seropositive patients.

<table>
<thead>
<tr>
<th>Category</th>
<th>NF155-IgG4 (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender Male, n (%)</td>
<td>11 (55)</td>
</tr>
<tr>
<td>Age symptoms onset, median (range in years)</td>
<td>45.5(4-72)</td>
</tr>
<tr>
<td>Mean follow up months (range)</td>
<td>85 (5-411)</td>
</tr>
<tr>
<td>Median time to diagnosis months (range)</td>
<td>10.5(&lt;1-208)</td>
</tr>
<tr>
<td>Sensory prickling or parasthesia, n (%)</td>
<td>17 (85)</td>
</tr>
<tr>
<td>Neuropathic pain at onset, n (%)</td>
<td>9 (45)</td>
</tr>
<tr>
<td>Cerebellar features, n (%)</td>
<td>4 (20)</td>
</tr>
<tr>
<td>Autonomic symptoms, n (%)</td>
<td>9 (45)</td>
</tr>
<tr>
<td>Sensory ataxia on examination, n (%)</td>
<td>18 (90)</td>
</tr>
<tr>
<td>CN involvement on examination, n (%)</td>
<td>11 (55)</td>
</tr>
<tr>
<td>Tremor or pseudoathetosis, n (%)</td>
<td>10 (50)</td>
</tr>
<tr>
<td>Large fiber sensory loss on exam, n (%)</td>
<td>18 (90)</td>
</tr>
<tr>
<td>Small fiber sensory loss on exam, n (%)</td>
<td>18 (90)</td>
</tr>
<tr>
<td>Muscle weakness on exam, n (%)</td>
<td>19 (95)</td>
</tr>
<tr>
<td>Loss of deep tendon reflexes on exam, n (%)</td>
<td>18 (90)</td>
</tr>
<tr>
<td>Papilledema €, n (%)</td>
<td>4 (33)</td>
</tr>
<tr>
<td>Median CSF protein mg/dL (range)</td>
<td>224 (60-834)</td>
</tr>
<tr>
<td>Demyelinating features by EFNS*, n (%)</td>
<td>20(100)</td>
</tr>
<tr>
<td>Nerve root/plexus enhancement on MRI*, n (%)</td>
<td>14 (82)</td>
</tr>
<tr>
<td>Gait aid dependent at first follow-up, n (%)</td>
<td>15 (75)</td>
</tr>
<tr>
<td>Gait aid dependent at last follow-up, n (%)</td>
<td>8 (40)</td>
</tr>
</tbody>
</table>

*17 patients had MRI imaging available to review
€12 patients had funduscopic examination

Key: CN=cranial nerves, CSF=cerebrospinal fluid

*Initial EMG/NCV data utilized18
Table 2: Demographic and Clinical comparison of NF-155, CNTN1 and IgM MAG patients

<table>
<thead>
<tr>
<th>Category</th>
<th>NF155-IgG4 (n=20)</th>
<th>Contactin-1 IgG (n=9)</th>
<th>P value</th>
<th>MAG-IgM (n=44)</th>
<th>P value</th>
<th>NF155-IgM (n=7)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, Male</td>
<td>11 (55%)</td>
<td>5 (55%)</td>
<td>0.97</td>
<td>33 (75%)</td>
<td>0.1</td>
<td>5 (71%)</td>
<td>0.44</td>
</tr>
<tr>
<td>Mean onset age, years</td>
<td>45.5</td>
<td>63</td>
<td>0.18</td>
<td>62.3</td>
<td>&lt;0.00</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Mean follow up, months</td>
<td>85</td>
<td>92</td>
<td>0.13</td>
<td>117.2</td>
<td>0.64</td>
<td>45</td>
<td>0.1</td>
</tr>
<tr>
<td>Sensory ataxia, n</td>
<td>18 (90%)</td>
<td>7 (78%)</td>
<td>0.37</td>
<td>28 (64.5%)</td>
<td>0.08</td>
<td>0</td>
<td>----</td>
</tr>
<tr>
<td>Cerebellar ataxia, n</td>
<td>4 (80%)</td>
<td>0</td>
<td>0.14</td>
<td>1 (2%)</td>
<td>&lt;0.01</td>
<td>0</td>
<td>----</td>
</tr>
<tr>
<td>Tremor, n</td>
<td>10 (50%)</td>
<td>3 (33%)</td>
<td>0.4</td>
<td>14 (31%)</td>
<td>0.16</td>
<td>0</td>
<td>----</td>
</tr>
<tr>
<td>CISP/CISP+ phenotype</td>
<td>0</td>
<td>4 (44%)</td>
<td>0.005</td>
<td>0</td>
<td>----</td>
<td>0</td>
<td>----</td>
</tr>
<tr>
<td>Neuropathic pain, n</td>
<td>9 (45%)</td>
<td>4 (44%)</td>
<td>0.97</td>
<td>17 (56%)</td>
<td>&lt;0.00</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Monoclonal protein, n</td>
<td>1 (5%)</td>
<td>1 (11%)</td>
<td>0.34</td>
<td>48 (100%)</td>
<td>&lt;0.00</td>
<td>0</td>
<td>----</td>
</tr>
<tr>
<td>Glomerulonephritis, n</td>
<td>0</td>
<td>2 (22%)</td>
<td>0.08</td>
<td>0</td>
<td>----</td>
<td>0</td>
<td>----</td>
</tr>
<tr>
<td>CSF protein, median (range)</td>
<td>224(60-834)</td>
<td>87.5(50-960)</td>
<td>0.31</td>
<td>68 (44-152)</td>
<td>0.01</td>
<td>43(22-190)</td>
<td>0.01</td>
</tr>
<tr>
<td>Root enhancement on MRI, n a</td>
<td>14 (82%)</td>
<td>4 (50%)</td>
<td>0.09</td>
<td>3 (27%)</td>
<td>&lt;0.00</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Treated with IVIG, n</td>
<td>18 (90%)</td>
<td>8 (89%)</td>
<td>0.92</td>
<td>8 (18%)</td>
<td>&lt;0.00</td>
<td>5</td>
<td>0.26</td>
</tr>
<tr>
<td>Treated with Rituximab, n</td>
<td>5 (25%)</td>
<td>4 (44%)</td>
<td>0.29</td>
<td>4(9%)</td>
<td>0.08</td>
<td>0</td>
<td>----</td>
</tr>
<tr>
<td>Initial response to IVIG</td>
<td>14 (70%)</td>
<td>6 (75%)</td>
<td>0.66</td>
<td>0</td>
<td>&lt;0.00</td>
<td>3</td>
<td>0.2</td>
</tr>
<tr>
<td>Response to Rituximab</td>
<td>4 (80%)</td>
<td>3 (75%)</td>
<td>0.95</td>
<td>0</td>
<td>&lt;0.00</td>
<td>0</td>
<td>----</td>
</tr>
<tr>
<td>INCAT 1st visit median (range)</td>
<td>5 (1-8)</td>
<td>2 (2-9)</td>
<td>0.11</td>
<td>1 (0-3)</td>
<td>&lt;0.00</td>
<td>3(0-3)</td>
<td>&lt;0.00</td>
</tr>
<tr>
<td>INCAT last visit, median (range)</td>
<td>2.5 (1-7)</td>
<td>3 (0-9)</td>
<td>0.04</td>
<td>3 (0-4)</td>
<td>0.51</td>
<td>2.5(1-3)</td>
<td>0.48</td>
</tr>
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</table>
One additional CNTN1 patient was treated with IVMP

MRS >=1, INCAT >=1 for longer than 3 months

Two patients were stable one IVIG and one was stable with rituximab

All 9 patients were seen at Mayo Clinic, 7 with serum available were Contactin-1 IgG4 positive.

Imaging were available in NF155 IgG4 (n=17), CNTN1 IgG (n=8), MAG IgM (n=11)

Treatment response was available in 3/5 patients with IVIG treatment.

Abbreviations: NF155=neurofascin 155; CNTN1=contactin 1; MAG=myelin associated glycoprotein; MRI=magnetic resonance imaging; IVIG=intravenous immunoglobulin’s; INCAT=Inflammatory Neuropathy Cause and Treatment; IVMP=Intravenous methylprednisolone; MRS=modified Rankin score; CISP=chronic immune sensory polyradiculopathy; CSF=cerebrospinal fluid

Legends

Figure 1: Neuropathic histologic changes in NF155 IgG4 positive patients

Teased fiber preparations from four patients, taken from the sural (A, B) and the sciatic (C, D) nerves. Shown are variable degrees of paranodal separation and myelin swelling (thickening) from least (A) to most involved (C) in the fascicular proximal sciatic biopsy. Also seen in the fascicular sciatic biopsy is frank segmental demyelination (D) where segments are void of osmium staining (light regions). Electron micrographs show myelin separation within the paranodal region (E) and the internodal areas (F). Additionally observed were Schwann cell cytoplasm around sites of prior unmyelinated fibers now filled with collagen forming collagen pockets (G) indicative of small fiber involvements.
Figure 2: Interstitial histologic alternations in NF155 IgG4 positive and NF155 IgG positive (IgG4 negative) patients

Representative photomicrographs from cases with NF155 IgG4 (A-F) and NF155 IgG (G-H). Semithin epoxy section (methylene blue) from a sural nerve biopsy showing myelinated nerve fiber loss, active axonal degeneration and slight multifocality. Section B-F are taken from a targeted fascicular sciatic nerve biopsy of a 53 year old man, NF155 IgG4 positive, with rapid onset of numbness, sensory and cerebellar ataxia, cranial nerve involvement, dysarthric speech, tremor and pseudoataxia who was refractory to IVIg treatment. However, with prolonged ongoing (several times per week) plasma exchange, he had dramatic recovery and regained independence and ability to ambulate. Semithin epoxy section (methylene blue) (B) shows subperineural edema, reduced density of myelinated nerve fibers with degenerating profiles (mild to moderate degree). Serial paraffin cross sections (C-F) show a large perineurial inflammatory cell collection on H&E (C), on CD-45 (D) that was polyclonal for T cells (CD3) (E) and B cells (CD20) (F). In contrast, photomicrographs G and H come from a 35-year-old man with progressive CIDP; progressive onset of proximal more than distal weakness with falls who was NF155-IgG positive (NF155-IgG 4 negative). He was initially was very responsive to IVIG but over 3 years required increasing IVIg doses and was not helped with rituximab, and even worsened with plasma exchange. Panel G are teased nerve fiber preparations showing chronic de- and remyelination with onion bulbs formations (arrows) and tomaculae (myelin reduplication, Asterix) as well as active axonal degeneration (arrow heads). Panel H (methylene blue epoxy section) shows the mix pattern of onion bulbs (moderate sized onion bulbs intersperse among myelinated fibers without onion bulb) the typical pattern seen in inflammatory demyelinating neuropathies (CIDP). These findings show the different pathological pattern seen in NF155-IgG4 (no onion bulbs) compared to non NF155-IgG4 disease (frequent onion bulb formations).

Abbreviations: NF155=neurofascin 155, CD=cluster of differentiation. Ig=immunoglobulins
Figure 3: Relapses versus time from diagnosis in Neurofascin 155 IgG4 positive patients

Survival analysis comparison showing time to relapse from symptoms onset compared between two para/nodal antigens contactin-1 (CNTN1) and neurofascin 155 (NF155) IgG4 positive patients. We demonstrate 50% relapses occur in the first year from symptoms onset. Broken line stands for the median for each group (A). Whisker box plot comparison of Inflammatory Neuropathy Cause and Treatment (INCAT) scores at first neuromuscular visit shows higher score (more deficits) in those who relapses (p=0.02) (B). Abbreviations: NF155=neurofascin 155, Ig=immunoglobulins
Figure 4: Electrophysiological and clinical outcomes NF155-IgG4 and contactin-1 IgG cohorts

Time to maximal gait aid needed from symptoms onset comparing neurofascin 155 (NF155) and contactin 1 (CNTN1) positive patients (A). Demonstrating first 6 months 50% of patients will reach disease nadir. Compound CMAP comparison with 4 intervals of time showing return to base line more than 2 years after symptoms onset evaluated at our EMG laboratory (B). Abbreviations: CMAP=compound motor action potential.
Figure 5: Functional outcome NF155 IgG4 cases, in comparison to other seropositive demyelinating neuropathies

Functional neurological Inflammatory Neuropathy Cause and Treatment (INCAT) scores compared between first and last follow up among 3 groups of patients all with distal predominant presentation. Neurofascin 155 IgG4 positive and contactin-1 IgG positive patients showed improvement in INCAT scores compared to IgM MAG neuropathy patients. Abbreviations: NF155=neurofascin 155, Ig=immunoglobulins, Inflammatory Neuropathy Cause and Treatment score (INCAT score)

Neurofascin-155 Immunoglobulin Subtypes: Clinicopathologic Associations and Neurologic Outcomes
Shahar Shelly, Christopher Klein, P. James B. Dyck, et al.
Neurology published online October 11, 2021
DOI 10.1212/WNL.0000000000012932

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