

# Semiquantitative assessment of preganglionic nerves for chronic immune-mediated neuropathies using brachial plexus magnetic resonance imaging

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**Background:** Brachial plexus magnetic resonance imaging (MRI) is an important noninvasive supplementary diagnostic method of chronic immune peripheral neuropathies, but few MRI studies on the preganglionic nerves have been conducted. This retrospective cross-sectional study aimed to establish a reliable assessment for brachial plexus preganglionic nerve thickness and to use this method to assess and compare nerve characteristics in various types of peripheral neuropathies.

Methods: Hospitalized patients diagnosed as positive for anti-neurofascin-155 (NF155)-positive autoimmune nodopathy (AN) (NF155'), chronic inflammatory demyelinating polyneuropathy (CIDP), or multifocal motor neuropathy (MMN) at Huashan Hospital of Fudan University in Shanghai, China, who underwent brachial plexus MRI between October 2011 and August 2023 were consecutively recruited for this study. We also recruited participants who underwent brachial plexus MRI during this period with no history of trauma, inflammation, tumors, compression, or degenerative conditions as healthy controls. According to our self-developed semiquantitative assessment of preganglionic nerves, we assessed the bilateral preganglionic C5–C8 nerves individually and scored the enlargement degree from 0 to 4 points. Furthermore, a sum score ≥20 was defined as definite enlargement.

**Results:** A total of 122 participants were enrolled, including 28 with NF155<sup>+</sup>, 40 with CIDP, 15 with MMN, and 39 healthy controls. In the comparison of the single-nerve scores, we found that there was a significant difference distribution among the four groups ( $\chi^2$  test; P<0.001), with the patients with NF155<sup>+</sup> exhibiting the highest scores in each of the bilateral C5–C8 nerves. In the comparison of the sum scores, a descending tendency was observed in patients NF155<sup>+</sup>, CIDP, and MMN, with median scores of 11, 4, and 0 points, respectively (Kruskal-Wallis test; P=0.003, P<0.001, and P=0.005, respectively for NF155<sup>+</sup> vs. CIDP, NF155<sup>+</sup> vs. MMN, and CIDP vs. MMN). The proportion of definite enlargement in those with NF155<sup>+</sup> was greater than that in healthy controls (21% vs. 0%;  $\chi^2$  test; P=0.004), and the sum score at 0 points was lower in the NF155<sup>+</sup> group than in CIDP, MMN, and healthy control groups (7% vs. 37%, 87%, and 41%, respectively;  $\chi^2$  test; P<0.001).

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**Conclusions:** This semiquantitative assessment can be a valuable tool for measuring preganglionic nerve enlargement, which was found to be decreased, respectively, in those with NF155\*, CIDP, and MMN. Presence of definite enlargement could be a strong indicator of NF155\* in clinic.

**Keywords:** Brachial plexus; autoimmune nodopathy (AN); chronic inflammatory demyelinating polyneuropathy (CIDP); multifocal motor neuropathy (MMN); magnetic resonance imaging (MRI)

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### Introduction

Chronic immune-mediated peripheral neuropathies are disorders caused by autoimmune responses against peripheral nerves. Chronic inflammatory demyelinating polyneuropathy (CIDP) and multifocal motor neuropathy (MMN) are representative subtypes (1,2). According to the latest update of the European Academy of Neurology/ Peripheral Nerve Society (EAN/PNS) CIDP diagnostic guideline, patients with anti-neurofascin-155 (NF155)positive autoimmune nodopathy (AN) (NF155<sup>+</sup>) have been identified as a distinct cohort independent of CIDP due to characteristic pathologic changes and clinical manifestations (3). Because treatment methods differ, it is critical to diagnose and differentiate these various subtypes. The diagnosis depends on typical clinical manifestations, specific nerve conduction studies (NCSs), and laboratory features (3-5). However, assessment of NCS in the proximal areas of the brachial plexus may not always be accurate. Furthermore, laboratory examinations such as cerebrospinal fluid (CSF) analysis and nerve biopsy can cause trauma.

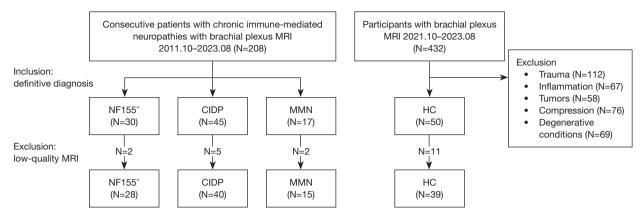
Brachial plexus magnetic resonance imaging (MRI) can be used to provide supporting diagnostic criteria, especially for those without evident NCS abnormalities (3,5). In studies of postganglionic nerves, features such as nerve root hypertrophy, increased signal intensity on the T2-weighted (T2W) sequence, and nerve tissue function detected on diffusion tensor imaging (DTI) have been found to be important supplementary evidence for identifying variant subtypes (6-9). The preganglionic part of the brachial plexus nerve is critical to the functional integrity of the upper extremity. Compared to the postganglionic nerves, the preganglionic nerves are delicate and immersed in CSF. However, to the best of our knowledge, few studies have focused on preganglionic nerves and no assessment standards for preganglionic nerve thickening. Therefore, the aim of our study was to develop a feasible and

repeatable semiquantitative assessment of enlargement of the brachial plexus preganglionic nerves and to investigate the differences in preganglionic nerve root thickening among patients with NF155<sup>+</sup>, CIDP, and MMN and healthy controls. We present this article in accordance with the STROBE reporting checklist (available at https://qims.amegroups.com/article/view/10.21037/qims-23-1473/rc).

### **Methods**

### Recruitment of patients and controls

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the ethics committee of Huashan Hospital of Fudan University (No. 2022-140). Informed consent was obtained from each patient. We retrospectively collected the data of consecutive patients who were diagnosed with NF155<sup>+</sup>, CIDP, or MMN and who underwent brachial plexus MR examination at Huashan Hospital Fudan University between October 2011 and August 2023. CIDP and MMN were diagnosed according to the European Federation of Neurological Societies (EFNS)/PNS and EAN/PNS criteria (3,5). As described in a previous study, the diagnosis of NF155+ was clinically and serologically confirmed. Anti-NF155 antibodies in the serum samples were detected with cell-based assays (CBAs) and confirmed by immunofluorescence tissue-based assays (TBAs) (10). We reviewed all participants who underwent brachial plexus MRI during this period and excluded those with a history of trauma, inflammation, tumors, compression, or degenerative conditions. The remaining participants, without a history of additional conditions, were included as healthy controls. The exclusion criteria were inadequate image quality caused by motion, CSF flow, and significant cervical disc herniation. Figure 1 shows the flowchart of the study.



**Figure 1** Flowchart of study with inclusion and exclusion criteria and the number of participants. MRI, magnetic resonance imaging; NF155\*, anti-neurofascin-155-antibody-positive autoimmune nodopathy; CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; MMN, multifocal motor neuropathy; HC, healthy control.

### MRI protocol

MRI was performed with a 3.0 T Discovery MR750 (GE HealthCare, Milwaukee, WI, USA) or a 3.0 T MAGNETOM Verio device (Siemens Healthineers, Erlangen, Germany) and use of a neck and body coil. The technical parameters for the MRI were as follows: (I) a three-dimensional (3D) fast imaging employing steady-state acquisition (FIESTA), with repetition time/echo time =4.3/1.7 ms, pixel bandwidth =244 kHz, slice thickness =1.0 mm, field of view =26×26 cm², matrix =260×260, and echo chain length =1; and (II) coronal T2W sampling perfection with application-optimized contrast using different flip angle evolutions (SPACE) sequence, with repetition time/echo time =1,500/223 ms, pixel bandwidth =488 kHz, slice thickness =2.0 mm, field of view =18×18 cm², matrix =320×309, and echo chain length =107.

### MRI analysis

In this study, the C5–C8 preganglionic nerves were analyzed. T1 nerve was not included in the analysis because it is vulnerable to gas artifacts of the lung apex. Two experienced radiologists, both with more than 10 years of experience in neuromuscular imaging, underwent 3 months of specialized training for the newly proposed semiquantitative assessment. They were blinded to the clinical data of patients, reviewed 3D-FIESTA and T2W-SPACE images, and evaluated the grade of preganglionic thickening. The degree of preganglionic enlargement was defined semiquantitatively as follows: 0 points, normal; 1 point, fascicular thickening; 2 points, adhesive thickening less than half of the length of

the longitudinal axis; 3 points, adhesive thickening more than half and less than the full length of the longitudinal axis; and 4 points, adhesive thickening in the full length of the longitudinal axis (*Figure 2*). Both ventral and dorsal nerve roots were assessed. Any discrepancies between the two radiologists were resolved by discussion. The sum score of both sides ranged from 0 to 32, and definite enlargement was defined as a sum score  $\geq 20$ .

## Statistical analysis

We used the Shapiro-Wilk test to assess the normality of continuous variables. Continuous variables are presented as the median with the interquartile range and categorical variables as numbers with percentages. The Kruskal-Wallis test was used to ascertain the differences between multiple groups of independent continuous variables or ordinal categorical variables. Pearson  $\chi^2$  test or Fisher exact test was used to analyze dichotomous variables. A two-sided P value <0.05 was considered significant. For multiple comparisons (six pairs for four groups), the significance level was defined as a P value of 0.008 after Bonferroni correction. Given that the grade of preganglionic thickening was an ordinal categorical variables, the kappa (κ) coefficient was used to assess inter- and intraobserver agreement. Statistical analyses of inter- and intraobserver agreements were interpreted by the Landis and Koch interpretation as follows: fair, 0.21-0.40; moderate, 0.41-0.60; substantial, 0.61–0.80; and almost perfect,  $\geq$ 0.81 (11). All statistical analyses were performed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA).

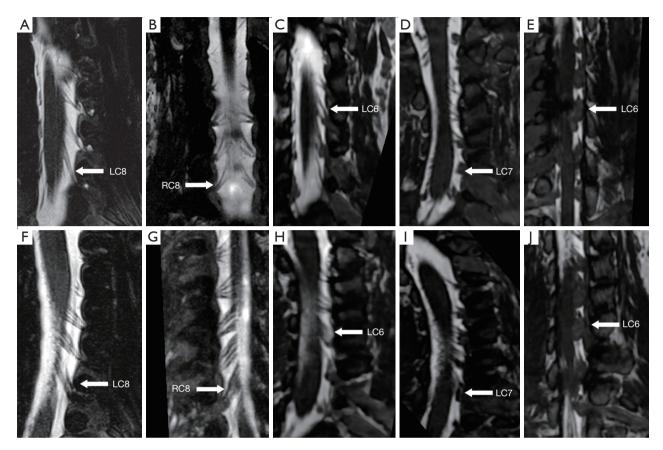


Figure 2 The scores of semiquantitative assessment of preganglionic nerves. (A-E) One side of the C5–C8 ventral preganglionic nerve roots visible on the plane parallel to the longitudinal axis. (F-J) One side of the C5–C8 dorsal preganglionic nerve roots visible on the plane parallel to the longitudinal axis. (A,F) A healthy control case with an LC8 score of 0. (B,G) A case of chronic inflammatory demyelinating polyradiculoneuropathy case with an RC8 scored of 1 and nerve fascicular thickening. (C,H) A chronic inflammatory demyelinating polyradiculoneuropathy case, with an LC6 score of 2 and showing adhesive thickening of less than half the length of the nerve. (D,I) A case of NF155<sup>+</sup> with an LC7 score of 3 showing adhesive thickening of more than half the length of the nerve. (E,J) A case of NF155<sup>+</sup> with an LC6 score of 4 showing adhesive thickening in the full length of nerve and complete nonvisibility of normal nerve structures. L, left; R, right; NF155<sup>+</sup>, anti-neurofascin-155-antibody-positive autoimmune nodopathy.

### Results

## Demographic characteristics of patients and controls

In this study, a total of 83 patients and 39 healthy controls were included. Of these, 28 patients had NF155<sup>+</sup>, 40 had CIDP, and 15 had MMN. The sample consisted of 84 men and 38 women, with a median age of 41 years and an age range of 11 to 78 years. The demographic features are summarized in *Table 1*. After the Shapiro-Wilk test, we found that the ages of those with NF155<sup>+</sup> did not follow a normal distribution. Moreover, these patients were younger than those with CIDP or MMN patients and healthy controls (Kruskal-Wallis test; P<0.001, P=0.008,

and P<0.001, respectively), while there was no significant difference in the mean age between the other three groups. In addition, the proportion of males in patients with NF155<sup>+</sup> was higher than that in those with CIDP (89% vs.~58%;  $\chi^2$  test; P=0.02), whereas there was no significant difference in the proportion of males and females in the other groups.

# Comparison of bilateral C5–C8 preganglionic single-nerve scores among groups

Based on the above semiquantitative assessment of the preganglionic nerves, we assessed the bilateral C5–C8

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Demographic characteristics	NF155+ (n=28)	CIDP (n=40)	MMN (n=15)	HC (n=39)	P value
Age (years)	22.5 [16–36]	46 [26.5–54]	39 [34–57]	46 [31–55]	<0.001
Sex					0.02
Female	3 [11]	17 [43]	3 [20]	15 [38]	
Male	25 [89]	23 [58]	12 [80]	24 [62]	

Table 1 Demographic characteristics of the NF155+, CIDP, MMN, and HC groups

Values are presented as the median [interquartile range] or number [%]. NF155<sup>+</sup>, anti-neurofascin-155-antibody-positive autoimmune nodopathy; CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; MMN, multifocal motor neuropathy; HC, healthy control.

in each sample individually. First, there was a significant difference in single-nerve score distribution among the four groups ( $\chi^2$  test; P<0.001). Second, the bilateral C5–C8 scores of the NF155<sup>+</sup>, CIDP, and MMN groups were significantly different from each other, representing a gradated decrease in a single-nerve score from NF155<sup>+</sup> to CIDP to MMN. Finally, there was no significant difference between patients with MMN and healthy controls in the bilateral C5–C8 and also no significant difference in the scores between patients with CIDP and healthy controls except for in the RC7 and RC8 (*Figure 3*, Table S1).

# Comparison of bilateral C5–C8 preganglionic nerve sum scores among the groups

The median of the sum scores was 11 in patients with NF155<sup>+</sup> (range, 0-32), 4 in those with CIDP (range, 0-22), 0 in those with MMN (range, 0-4), and 2 in healthy controls (range, 0-11). The NF155+ group had higher sum scores than did the CIDP, MMN, and healthy control groups (Kruskal-Wallis test, P=0.003, P<0.001, and P<0.001, respectively). In addition, the sum score in patients with CIDP was higher than that in patients with MMN (Kruskal-Wallis test; P=0.005). Six patients with NF155<sup>+</sup> (21%) and two of those with CIDP (5%) were considered to have definite enlargement (Figure 4). The proportion of those with definite enlargement of preganglionic nerves was higher in the NF155<sup>+</sup> group than in the healthy controls (21% vs. 0%,  $\chi^2$  test, P=0.004), and the proportion of sum score at 0 points was lower in NF155+ patients than CIDP, MMN, and healthy controls (7% vs. 37%, 87%, and 41%;  $\chi^2$  test; P<0.001) (*Table 2*). Furthermore, we found that of the 488 pairs of preganglionic nerves in the 122 samples, 441 pairs (90%) had the same left- and right-side scores.

# Inter- and intraobserver agreement in the semiquantitative assessment of preganglionic nerve enlargement

For intraobserver agreement, the  $\kappa$  values for the eight preganglionic nerves (bilateral C5–C8) ranged from 0.68 to 0.76, indicating a substantial agreement among repeated measurements by the same observer. In terms of interobserver agreement, the  $\kappa$  values were lower, ranging from 0.53 to 0.64, which indicated moderate to substantial agreement between different observers (*Table 3*).

#### **Discussion**

In this study, we evaluated a novel semiquantitative assessment for brachial plexus preganglionic nerve enlargement. We observed a pronounced enlargement of the preganglionic nerve in patients with NF155<sup>+</sup>, and a descending order of sum scores was apparent in patients with NF155<sup>+</sup>, CIDP, and MMN. Whereas, no significant differences in single-nerve scores or sum scores were observed between patients with MMN patients and healthy controls. In addition, the proportion of definite enlargement was higher in patients with NF155<sup>+</sup> than in healthy controls, and the proportion of those with a sum score of 0 was lower in those with NF155<sup>+</sup> than in the other three groups.

MRI techniques, such as FIESTA, SPACE, and volumetric isotropic turbo spin echo acquisition (VISTA) sequences, can provide a dark signal for nerve root contrast via a significantly high signal for CSF and can enable high-resolution isotropic 3D acquisitions for multiplanar reconstruction (12). These sequences facilitate the systematic evaluation of preganglionic nerve morphology. Prior to our study, there were a limited number of studies on the MRI characterization of the preganglionic nerves in immune-mediated neuropathies. A few studies (13-15)

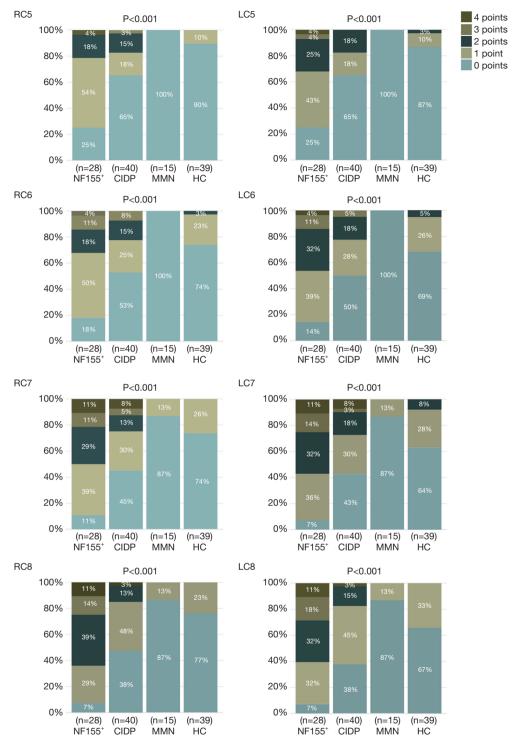
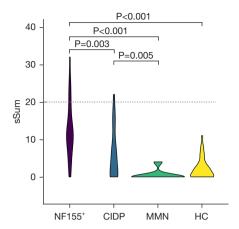


Figure 3 Preganglionic nerve scores for each ganglion in patients with NF155\*, CIDP, and MMN and healthy controls. The P values were calculated using Bonferroni correction. L, left; R, right; NF155\*, anti-neurofascin-155-antibody-positive autoimmune nodopathy; CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; MMN, multifocal motor neuropathy; HC, healthy control.



**Figure 4** sSums of patients with NF155\*, CIDP, MMN patients and healthy controls. NF155\*, anti-neurofascin-155-antibody-positive autoimmune nodopathy; CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; MMN, multifocal motor neuropathy; HC, healthy control; sSum, sum score.

highlighted the thickening of the preganglionic nerve in patients with Guillain-Barré syndrome (GBS). In addition, a recent study investigated the characterization of preganglionic nerves in chronic inflammatory neuropathies by measuring the diameter of nerves in the transversal plane (16). Given that such intricate anatomical structures require quantitative measurements in which the impact of human factors cannot be overlooked, we developed a semiquantitative method that is both reproducible and reliable.

Earlier studies focusing on postganglionic nerve root demonstrated that patients with NF155+ have significantly greater symmetrical enlargement in the postganglionic nerve root compared to patients with CIDP (17,18). Moreover, the extent of nerve swelling is greater in CIDP than in MMN (6), and the postganglionic nerves of those with MMN patients tend to show asymmetric enlargement (19). Nerve enlargement can be attributed to nerve root hypertrophy and Schwann cell proliferation, which result from repeated demyelination and remyelination (20). Histologic examination of biopsied sural nerves in patients with NF155<sup>+</sup>, in contrast to those with CIDP, show subperineurial edema and occasional paranodal demyelination without vasculitis, inflammatory cell infiltration, or onion bulbs. Loss of myelin fibers is minimal, even years after the onset of the disease (21,22).

Few studies have performed quantitative analyses of the

preganglionic nerves. A study by van Rosmalen et al. (16) reported the thickening of preganglionic nerves in chronic immune neuropathies, particularly noting that the ventral nerve roots in patients with MMN and CIDP with a motor phenotype were thicker than those in CIDP with a sensory-motor phenotype. However, our study observed almost no thickening in the preganglionic nerves of those with MMN. This discrepancy might be attributed to a few factors. The relatively small sample size of MMN cases in our study compared to that of Jongbloed et al. (15 vs. 27) and the uneven distribution of MMN lesions also need to be considered (19). Unlike postganglionic nerves, the preganglionic nerves are immersed in the CSF and are affected by its proteins and inflammatory factors. Notably, there are significant differences in CSF protein levels among these three diseases, with these levels being markedly higher in patients with NF155+ than in those with CIDP and MMN tending to be in the normal range (1,17,21). The correlation between CSF proteins and preganglionic nerve enlargement needs to be investigated in further studies. Besides extremely high levels of CSF protein, upregulation of both T helper type 1 (Th1) and Th2 cytokines is characteristic of NF155+, which causes inflammation at the spinal roots, resulting in nerve root hypertrophy (23). In this study, although not differences were statistically significant difference, there was a tendency that definite enlargement was more likely to be present in the NF155<sup>+</sup> group than in the other groups. Thus, the measurement of anti-NF155 antibodies is recommended in those with definite enlargement. In addition, a few nerve roots in healthy controls were scored as 1 or 2 points, possibly due to minor edema of the preganglionic nerves induced by the herniated disc compression.

There are several limitations to this study which should be mentioned. First, the sample size of the study was relatively small, and the demographic and disease conditions of the samples were not harmonized. Second, the assessment of the preganglionic nerve combined the motor ventral roots and sensory dorsal roots. Finally, the effectiveness of semiquantitative assessment is limited by the subjective nature of the assessment and requires specialized professional training. In future research, we will expand the sample size and improve the study methodology, including evaluating ventral and dorsal roots separately to improve the robustness and precision of the findings in characterizing peripheral neuropathy.

Table 2 Proportion of different extents of nerve enlargement in the NF155\*, CIDP, MMN, and HC groups

Extent of enlargement	NF155+ (n=28)	CIDP (n=40)	MMN (n=15)	HC (n=39)	P value
Enlargement					0.004
Nondefinite	22 [79]	38 [95]	15 [100]	39 [100]	
Definite	6 [21]	2 [5]	0 [0]	0 [0]	
sSum					<0.001
0 points	2 [7]	15 [37]	13 [87]	16 [41]	
>0 points	26 [93]	25 [63]	2 [13]	23 [59]	

Values are presented as number [%]. Definite enlargement was defined as a sSum ≥20. NF155<sup>+</sup>, anti-neurofascin-155-antibody-positive autoimmune nodopathy; CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; MMN, multifocal motor neuropathy; HC, healthy control; sSum, sum score.

**Table 3** Inter- and intraobserver agreement in the semiquantitative assessment of preganglionic nerve enlargement

assessment of preganglionic nerve enlargement						
Assessment	κ value	95% CI				
Intraobserver						
RC5	0.69	0.57-0.81				
RC6	0.72	0.61-0.82				
RC7	0.68	0.57-0.78				
RC8	0.76	0.66-0.85				
LC5	0.71	0.60-0.81				
LC6	0.69	0.58-0.79				
LC7	0.72	0.62-0.82				
LC8	0.73	0.64-0.83				
Interobserver						
RC5	0.57	0.44-0.70				
RC6	0.61	0.48-0.73				
RC7	0.53	0.41-0.65				
RC8	0.59	0.48-0.71				
LC5	0.59	0.46-0.71				
LC6	0.64	0.53-0.76				
LC7	0.60	0.48-0.71				
LC8	0.55	0.43-0.67				

κ, kappa; CI, confidence interval; R, right; L, left.

### **Conclusions**

Our novel semiquantitative assessment of the brachial plexus preganglionic nerve may be useful in brachial plexus MRI analysis. The single-nerve scores and sum scores decreased, respectively, in patients with NF155<sup>+</sup>, CIDP, and MMN, but there was no significant difference between patients with MMN and healthy controls. When a brachial plexus MRI reveals a definite enlargement of the preganglionic nerve, NF155<sup>+</sup> should be considered in the clinical diagnosis.

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### **Footnote**

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://qims.amegroups.com/article/view/10.21037/qims-23-1473/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-23-1473/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and approved by the ethics committee of Huashan Hospital of Fudan University (No. 2022-140). Informed consent was obtained from each patient.

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