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**Title:**

Electrophysiological features of **Chronic Inflammatory Demyelinating Polyradiculoneuropathy** associated with IgG4 antibodies targeting Neurofascin 155 or Contactin1 glycoproteins

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**Abstract:**

**Objective:** Chronic inflammatory demyelinating polyradiculoneuropathies (CIDP) with antibodies against neurofascin 155 (Nfasc155) or contactin-1 (CNTN1) have distinctive clinical features. Knowledge on their electrophysiological characteristics is still scarce. In this study, we are investigating whether these patients have specific electrophysiological characteristics.

**Methods:** The electrophysiological data from 13 patients with anti-Nfasc155 IgG4 antibodies, 9 with anti-CNTN1 IgG4 antibodies were compared with those of 40 consecutive CIDP patients without antibodies.

**Results:** All the patients with antibodies against Nfasc155 or CNTN1 fulfilled the EFNS/PNS electrodiagnostic criteria for definite CIDP. There was no electrophysiological difference between patients with anti-CNTN1 and anti-Nfasc155 antibodies. Nerve conduction abnormalities were heterogeneously distributed along nerves trunks and roots. They were more pronounced than in CIDP without antibodies. Motor conduction velocity on median nerve  $< 24\text{m/s}$  or motor velocity on ulnar nerve  $< 26\text{m/s}$  or motor distal latency on ulnar nerve  $> 7.4\text{ms}$  were predictive of positive antibodies against the node of Ranvier with a sensitivity of 59% and a specificity of 93%.

**Conclusions:** Marked conduction abnormalities may suggest the presence of positive antibodies against the node of Ranvier.

**Significance:** Anti-Nfasc155 and anti-CNTN1 antibodies target the the paranodal axo-glial domain but are associated with nerve conduction abnormalities mimicking a “demyelinating” neuropathy.

### **Highlights**

Patients with antibodies against the node of Ranvier fulfil electrodiagnostic criteria for definite CIDP

Patients with anti-CNTN1 and anti-NfascC155 antibodies have similar electrophysiological patterns

Electrophysiological abnormalities are more marked in patients with antibodies

### **Keywords:**

Neurofascin 155; Contactin 1; CIDP; electrophysiology

### **Conflict of Interest Statement**

None of the authors have potential conflicts of interest to be disclosed

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## Introduction:

Chronic inflammatory demyelinating polyradiculoneuropathies (CIDP) are chronic auto-immune neuropathies. They have, since their description, been defined by myelin damage resulting in disorders of the nerve conduction and of the nerve excitability (Joint Task Force of the EFNS and the PNS 2010). The precise antigenic target of the disease remains unknown in most cases, making it difficult to correlate electrophysiological finding with the pathophysiology of the disease and the clinical pattern.

Recently, IgG4 antibodies against the node of Ranvier or paranodes have been associated with subgroups of CIDP. These antibodies target neurofascin 155 (Nfasc155), neurofascin 186 (Nfasc186), contactin 1 (CNTN1) or contactin-associated protein 1 (Caspr1) (Ng et al. 2012; Querol et al. 2013; Doppler et al. 2016; Delmont et al. 2017). The CIDP patients with anti-CNTN1 antibodies have usually an acute disease course, sometimes misdiagnosed as Guillain-Barré syndrome (GBS), are older and may be associated with nephrotic syndrome (Querol et al. 2013; Miura et al. 2015; Hashimoto et al. 2018; Taieb et al. 2018). CIDP patients with anti-Nfasc155 antibodies are younger, have most often distal motor weakness, sensory ataxia, postural tremor and may have combined central and peripheral nervous system involvement (Querol et al. 2014; Ogata et al. 2015; Devaux et al. 2016; Kadoya et al. 2016). Intravenous immunoglobulins are mostly ineffective in CIDP with antibodies against paranodal proteins (Querol et al. 2013; Devaux et al. 2016).

The clinical phenotype of CIDP with antibodies against CNTN1 and Nfasc155 tends to be **better** understood. However, knowledge on the electrophysiological characteristics is still scarce in these patients. CIDP patients with anti-CNTN1 were first described to present mixed axonal and demyelinating features (Querol et al. 2013) although, only demyelinating features were described in another study (Miura et al. 2015). Few studies provided detailed electrophysiological data on patients with anti Nfasc155 antibodies, showing delayed distal motor latencies and prolonged F-waves latencies (Ogata et al. 2015; Vallat et al. 2017).

The objective of this study was to detail the nerve conduction studies of patients with anti-CNTN1 or anti-Nfasc155 antibodies and to compare these electrophysiological studies to those of CIDP without known antibodies.

## **Methods**

Patients with available electrophysiological data and positive IgG4 antibodies against Nfasc155 or CNTN1 were included in this study. Antibodies were tested in the Aix-Marseille University of Medicine, France. One thousand sera of patients from neurological departments from France, Belgium and Switzerland were screened for this study. A cohort of 40 consecutive CIDP patients without antibodies against the node of Ranvier was enrolled for comparison. These seronegative patients fulfilled the definite CIDP diagnostic criteria according to the EFNS/PNS (Joint Task Force of the EFNS and the PNS 2010) and were followed in the Referral Centre of Neuromuscular Diseases and ALS of Marseille, France. Data were obtained from available records. Assessments were part of routine evaluation. Patients did not undergo any additional electrophysiological tests, imaging or cerebrospinal fluid examinations as part of the current care. The study was approved by the the ethic committee of the Assistance Publique des Hôpitaux de Marseille (Agreement number PADS19-365).

Epidemiological, clinical and biological data were retrospectively collected: age, sex, clinical impairment, efficacy of IVIg treatment, Overall Neuropathy Limitations Scale (ONLS) (Graham and Hughes 2006), and cerebrospinal fluid (CSF) protein level. Good response to IVIg was defined as an improvement of at least one point on the ONLS scale.

Nerve conduction studies were performed bilaterally on the median, ulnar, tibial and fibular nerves at presentation. The following parameters were considered: distal motor latency (DML), distal compound muscle action potential (CMAP) amplitude, distal CMAP duration, sum of the distal CMAP amplitudes

(CMAP sum score), motor conduction velocity at the forearm or at the leg, F-waves latencies. Motor conduction block was defined by a  $\geq 50\%$  amplitude reduction of the proximal negative peak of the CMAP relative to the distal negative peak. Temporal dispersion was defined by a  $>30\%$  duration increase between the proximal and the distal negative peak of the CMAP (Joint Task Force of the EFNS and the PNS 2010). Terminal latency index (TLI) were calculated for median and ulnar nerves using the formula:  $\text{distal distance in millimetre} / \text{forearm conduction velocity} / \text{DML}$ .  $\text{TLI} < 0.25$  was indicative of excessive distal conduction slowing (Attarian et al. 2001). Modified F ratio (MFR) was calculated using the formula:  $(\text{F-wave latency} + \text{DML} - 2 * \text{PML} - 1) / (2 * \text{DML})$ , where PML is proximal motor latency measured at the elbow.  $\text{MFR} > 2.5$  for median nerve and  $>3.25$  for ulnar nerve were indicative of prominently proximal conduction slowing (Attarian et al. 2001). Distal CMAP duration thresholds were 8ms, 9ms, 9.1ms and 8.7ms for the median, ulnar, fibular and tibial nerves respectively (Rajabally et al. 2012). Sensory nerve action potentials (SNAP) amplitudes and sensory conduction velocities were recorded bilaterally on median, ulnar and sural nerves. SNAP sum core was obtained by adding the SNAP amplitude of median, ulnar and sural nerves.

Antibodies against Nfasc155 and CNTN1 were detected with a cell-binding assay or a flow cytometry technique using HEK cells transfected with the respective plasmid of interest (Miura et al. 2015; Devaux et al. 2016). IgG4 isotype was determined using a secondary antibody targeting IgG4 human IgG.

Quantitative data were expressed in mean (standard deviation). Quantitative data were compared using a Mann-Whitney test or an ANOVA test with Bonferroni post-test in case of multiple comparisons. Qualitative data were compared with a Fisher's exact test. Statistical and receiver operating characteristic (ROC) analysis were performed using IBM SPSS statistics software (version 20) and GraphPad Prism 5 (California, USA). Statistical significance was set for a two-sided p-value  $< 0.05$ .



## Results:

Thirteen CIDP with IgG4 antibodies against Nfasc155, 9 CIDP with IgG4 antibodies against CNTN1 and 40 CIDP negative for these antibodies were enrolled in this study. All fulfilled the EFNS/PNS diagnostic criteria for definite CIDP (Joint Task Force of the EFNS and the PNS 2010). Clinical characteristics are given in table 1. Eleven patients with antibodies against the node of Ranvier and 34 seronegative patients received IVIg treatment before inclusion in this study. CIDP patients with antibodies against paranodal proteins had more frequently sub-acute onset, higher ONLS score and were resistant to IVIg treatment (table1). CIDP with antibodies against CNTN1 had shorter disease duration. CIDP with antibodies against Nfasc155 were more prone to have a postural tremor. Central nervous system involvement was not present in this cohort.

Sural nerve biopsies were performed in 2 patients with antibodies against Nfasc155 and in one patient with antibodies against CNTN1. Semi-thin sections showed a loss of myelinated fibres without inflammatory cells infiltration. Some myelinated axons presented thin myelin sheaths suggestive of a demyelinating process. Electron microscopy showed a selective loss of the septate-like junctions at the paranodes in the patient with antibodies against CNTN1 (Figure 1).

### 1. Electrophysiological features of patients with IgG4 antibodies against Nfasc155 or CNTN1

Electrophysiological examination fulfilled the EFNS/PNS electrodiagnostic criteria for definite CIDP (Joint Task Force of the EFNS and the PNS 2010) in all patients. Abnormalities were symmetric and bilateral and heterogeneously distributed along the nerves. Conduction defects were: prolonged F-waves latencies, delayed distal motor latencies, reduced conduction velocities, conduction blocks, temporal dispersion, prolonged distal CMAP duration and normal sural with abnormal median SNAP amplitudes (table2).

### 2. Comparison of electrophysiological features of patients with antibodies against Nfasc155 or CNTN1 and seronegative patients:

There was no statistical difference when comparing electrophysiological data from patients with antibodies against Nfasc155 and patients with antibodies against CNTN1 (table 2). However, by comparison to seronegative patients, patients with antibodies against paranodal proteins had more prolonged motor distal latencies on median, ulnar and fibular nerves, more prolonged F-waves latencies on median nerves and motor and more reduced conduction velocities on median and ulnar nerves (table 2 and figure 2). The number of patients with conduction blocks was similar in CIDP with or without associated antibodies. CMAP amplitudes were comparable in both groups but SNAP amplitudes were lower in patients with antibodies namely on median and ulnar nerves.

As nerve conduction analyses were similar between patients with antibodies against Nfasc155 and anti CNTN1, the electrophysiological data of the 22 reactive patients were combined for comparison with the 40 seronegative patients. ROC analyses were performed to determine if electrophysiological data permitted to distinguish CIDP patients with and without antibodies (figure 2). Best discrimination was assessed with minimum motor velocity on median nerve (AUC = 0.76,  $p < 0.001$ ), minimum motor velocity on ulnar nerve (AUC = 0.80,  $p < 0.001$ ) and maximum motor distal latency on ulnar nerve (AUC = 0.76,  $p < 0.001$ ). Motor conduction velocity for median nerve  $< 24\text{m/s}$  or motor velocity for ulnar nerve  $< 26\text{m/s}$  or motor distal latency on ulnar nerve  $> 7.4\text{ms}$  were predictive of positive antibodies against paranodal proteins with a sensitivity of 59% and a specificity of 93%.

## **Discussion**

We report 13 patients with anti-Nfasc155 antibodies and 9 patients with anti-CNTN1 antibodies. These patients presented with similar clinical characteristics as those previously described: subacute onset, severe disability, resistance to IVIg treatment and postural tremor for patients with anti-Nfasc155 antibodies (Ng et al. 2012; Querol et al. 2013; Miura et al. 2015; Devaux et al. 2016).

All the patients with anti-CNTN1 or anti-Nfasc155 antibodies had abnormal nerve conduction features that fulfilled the EFNS/PNS electrodiagnostic criteria for definite CIDP. Electrophysiological data were similar between patients with anti Nfasc155 antibodies and anti-CNTN1 antibodies. Analysis of TLI and MFR did not reveal a predominantly distal or proximal pattern. The defects of nerve conduction had a heterogeneous distribution along nerves trunks and roots as in classical CIDP (Attarian et al. 2001). Abnormal electrophysiological features included conduction blocks and temporal dispersions, delayed distal motor latencies, delayed F-waves latencies, reduced conduction velocities and increased distal CMAP duration. Normal sural with abnormal median SNAP amplitudes, which is a supportive criterion for CIDP (Joint Task Force of the EFNS and the PNS 2010), was found in 5 patients. Decreased CMAP amplitudes were observed in most patients, due to axonal degeneration or distal conduction blocks.

Few studies have analysed electrophysiological data from patients with anti-Nfasc155 and CNTN1 antibodies. Anti-CNTN1 antibodies has been associated with an early axonal involvement in 3 patients (Querol et al. 2013) and with conduction blocks in 12 other patients (Miura et al. 2015). A detailed investigation of 21 Japanese patients with anti-Nfasc155 antibodies (Ogata et al. 2015), showed nerve conduction abnormalities in the same range as in our study. TLI were not in favour of a distal process: mean TLI was 0.32 for median nerves and 0.42 for ulnar nerves, compared to 0.30 and 0.38 respectively in our study. Alteration of nerve excitability has been reported in only one patient with anti-Nfasc155 antibodies, it showed an increase in the depolarization threshold and abnormalities compatible with a paranodal dysfunction (Garg et al. 2017). We compared the electrophysiological data of patients with antibodies against CNTN1 or Nfasc155 with those of seronegative CIDP patients. Conduction blocks and chronic denervation were observed in the same proportion. Axonal involvement can be analysed through CMAP and SNAP sum scores (Delmont et al. 2016). The motor component was comparable in patients with and without antibodies but axonal loss was greater for sensory nerves in patients with antibodies against paranodal proteins.

One study (Ogata et al. 2015) showed that patients with anti-Nfasc155 antibodies had more marked nerve conduction abnormalities than CIDP patients without antibodies. Our study found that both patients with anti-CNTN1 antibodies and patients with anti-Nfasc155 antibodies have more prominent nerve conduction abnormalities, notably for the distal motor latencies and motor conduction velocities in the median and ulnar nerves. Considering distal motor latency on the ulnar nerves and motor conduction velocities on the median and ulnar nerves, electrophysiology appears valuable to discriminate between patients with and without antibodies against CNTN1 or Nfasc155 with a sensitivity of 59% and a specificity of 93%.

Nfasc155 is expressed by the Schwann cell and CNTN1 by the axon, and both help maintaining the cohesion between the myelin sheath and the axon in the paranodal region and maintaining the segregation of the potassium channels of the juxtaparanodal region and the sodium channels of the nodal region. Several studies argue in favour of a pathogenic role for anti-Nfasc155 and CNTN1 antibodies: (Ng et al. 2012; Doppler et al. 2015; Manso et al. 2016, 2019; Koike et al. 2017; Vallat et al. 2017). Acute motor axonal neuropathies (AMAN) are related to anti-GM1 antibodies that target the node of Ranvier (Susuki et al. 2007). In these neuropathies, the nerve conduction studies show axonal abnormalities in the form of transient conduction block and decreased amplitudes of the distal CMAP (Uncini et al. 2013). One would expect that the anti-CNTN1 and Nfasc155 antibodies, that also bind the node of Ranvier, would give the same abnormalities. However, CIDP patients with antibodies against the node of Ranvier have clear nerve conduction abnormalities as seen in demyelinating neuropathies (Miura et al. 2015; Ogata et al. 2015; Doppler et al. 2016; Delmont et al. 2017). Nerve biopsies help to interpret this result. Nerve biopsies of CIDP patients with antibodies against Nfasc155 or CNTN1 show too thin myelin sheaths around some axons (figure 1), but no inflammatory infiltration nor onion bulb formations (Doppler et al. 2015; Ogata et al. 2015; Koike et al. 2017; Vallat et al. 2017). Electron microscopy examination shows a selective loss of the septate-like junctions at the paranodes (figure 1)

and a detachment of the paranodal myelin loops from the axon (Koike et al. 2017; Vallat et al. 2017). The detachment of the paranode leads to a widening of the node of Ranvier, to an alteration of the internode distance and to a loss of the segregation of the sodium and potassium channels (Boyle et al. 2001; Sherman et al. 2005). This disorganization of the nodes of Ranvier disrupts the saltatory conduction of the nerve impulses and causes nerve conduction abnormalities which may be interpreted as a "demyelinating" process, whereas the nerve biopsies do not display major demyelinating features.

This study shows that patients with anti-CNTN1 and anti-Nfasc155 antibodies have abnormal nerve conduction which fulfil the EFNS/PNS electrodiagnostic criteria for CIDP. Electrophysiological abnormalities seem more marked in patients with antibodies than in patients without antibodies against the node of Ranvier and have a propensity to demonstrate greater motor slowing at the forearm for upper limb nerves and greater distal latency prolongation at the wrist for the ulnar nerve. The limitations of this study are that it is a retrospective **analysis**, that disease durations were different between seronegative patients and CIDP with anti-CNTN1 antibodies and that most of conduction studies were performed on IVIg-treated patients. Our results need thus to be confirmed in a larger and prospective cohort.

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