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ORIGINAL COMMUNICATION

Antibodies against the node of Ranvier: a real-life evaluation of incidence, clinical features and response to treatment based on a prospective analysis of 1500 sera

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Abstract

Introduction IgG4 antibodies against neurofascin (Nfasc155 and Nfasc140/186), contactin (CNTN1) and contactin-associated protein (Caspr1) are described in specific subtypes of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). Our objective was to assess, in a real-life practice, the incidence, the clinical features and the response to treatment of these forms of CIDP.

Methods 1500 sera of patients suspected of having CIDP from France, Belgium and Switzerland were prospectively tested using a flow cytometry technique. The characteristics of patients with antibodies against the node of Ranvier were compared to 100 seronegative CIDP from our department.

Results IgG4 antibodies against Nfasc155, CNTN1, and Caspr1 were, respectively, detected in 15 (prevalence 1%), 10 (0.7%) and 2 (0.2%) sera. Antibodies specific of the Nfasc140/186 were not detected.

All subjects with antibodies against the node of Ranvier fulfilled diagnostic criteria for CIDP.

CIDP with anti-Nfasc155 were younger, had more sensory ataxia and postural tremor than seronegative CIDP. CIDP with anti-CNTN1 had more frequent subacute onset and facial paralysis, commoner renal involvement with membranous glomerulonephritis and greater disability, than seronegative CIDP. CIDP with anti-Caspr1 had more frequent respiratory failure and cranial nerve involvement but not more neuropathic pain than seronegative CIDP. Intravenous immunoglobulins were ineffective in most seropositive patients. Rituximab produced dramatic improvement in disability and decreased antibodies titres in 13 seropositive patients (8 with anti-Nfasc155 and 5 with anti-CNTN1 antibodies).

Conclusions Although rare, anti-paranodal antibodies are clinically valuable, because they are associated with specific phenotypes and therapeutic response.

Keywords Neurofascin 155 · Neurofascin 140/186 · Contactin · Caspr1 · Node of Ranvier · CIDP

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Introduction

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is a heterogeneous chronic auto-immune neuropathy [1]. Recently, IgG4 isotypes antibodies against the node of Ranvier have been described in some patients. They target glycoproteins of the node and of the paranode: neurofascin 155 (Nfasc155), neurofascin 140/186, contactin-1 (CNTN1) and contactin related protein 1 (Caspr1) [2–5]. They are all expressed on the membrane of the axon, except the Nfasc155 which is located on the Schwann cells. They maintain the cohesion between the myelin sheath and the axon in the paranodal region and preserve the segregation of the potassium channels of the juxtaparanodal region and the sodium channels of the nodal region. Nerve biopsies from patients with antibodies anti-CNTN1 or Nfasc155 display a specific pattern with selective loss of the septate-like junctions at the paranodes and a detachment of the paranodal myelin loops from the axon [6, 7]. Several elements argue in favour of a pathogenic role for these antibodies: anti-CNTN1 and Caspr1 antibodies block the interaction between Nfasc155 and CNTN1/Caspr1 complex, passive transfer of autoantibodies dismantles the paranodal specialization and enhance induced neuritis in rodents [3, 8–10].

These antibodies against the node of Ranvier are rare, but their detection is clinically of importance, because they are associated with severe forms of CIDP, unresponsive to intravenous immunoglobulins (IVIg). In previous studies, these antibodies were screened from banks of sera of particular CIDP patients [10–18]. Since 2016, we have prospectively tested 1500 sera of patients suspected of having CIDP, sent by neuromuscular referral centres from France, Belgium and Switzerland. Our objective is to describe in a real-life clinical practice, the incidence and clinical characteristics of CIDP associated with antibodies against the node of Ranvier.

Methods

We performed systematic search for IgG4 antibodies against the node of Ranvier from sera of 1500 consecutive subjects with a clinical diagnosis of "possible CIDP", as per EFNS/PNS Guidelines [1]. Tested sera came from Neurological departments from France, Belgium and Switzerland.

All patients with IgG4 antibodies against the node of Ranvier detected between August 2016 and March 2020 in the in the Aix-Marseille University of Medicine, France, were included. A cohort of 100 consecutive CIDP patients without antibodies against the node of Ranvier, or gangliosides or myelin associated glycoprotein (MAG) was enrolled for comparison ("seronegative CIDP"). These seronegative patients fulfilled the diagnostic criteria for "definite CIDP" according to the EFNS/PNS [1] 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 (CSF) examinations as part of the current care. The study was approved by the Ethics committee of the Assistance Publique des Hôpitaux de Marseille (Agreement number PADS19-365).

Demographic data, clinical and laboratory data and regarding response to treatment were retrospectively obtained from records. Disability was assessed though the overall neuropathy limitation scale (ONLS) and the modified Rankin score [19, 20].

Antibodies against Nfasc155, CNTN1, Nfasc186 and Casp1 were detected with a flow cytometry technique using human embryonic kidney (HEK) cells transfected with the respective plasmid of interest [3, 13, 21]. All the sera were first screened for IgG4 isotype antibodies against the node of Ranvier. If positive, others isotypes of antibodies were searched using a secondary antibody targeting IgG1, IgG2, IgG3, IgA or IgM human immunoglobulins. Results were expressed in median fluorescence intensity (MFI) which was the difference of the median fluorescence of the transfected cells and of the non-transfected cells. HEK cells were maintained in Dulbecco/Vogt modified Eagle's minimal essential medium (DMEM) supplemented with 10% fetal bovine serum (FBS), 1% of L-glutamine and 1% of penicillin/streptomycin. Cells were plated in 6-well plates at a density of 300,000 cells/wells. The day after, cells were transfected with plasmids encoding Nfasc155, Nfasc186 or CNTN1 and Caspr1associated with plasmid tdTomato using the transfection reagent JetPEI (Polyplus transfection). For antibodies detection, co-transfections were realized with 0.3 µg of plasmid of tdTomato and 1.5 µg of plasmids of interest diluted with 100 µL of NaCl 150 mM. Optimal cells expression was observed 48 h after the transfection. Patient sera were incubated at a 1/100 dilution with approximately 200,000 HEK cells in a volume of 100 µL of PBS (phosphate buffered saline)-1% FBS-0.02% Sodium Azide. Cells were then washed and incubated for 30 min in a solution containing FITC (Fluorescein isothiocyanate) conjugated mouse anti-human immunoglobulins monoclonal antibodies. After a new wash, cells were re-suspended in PBS solution containing 1% FBS, 0.02% Sodium Azide and 2% paraformaldehyde (PFA). Data were analysed on a cytometer FACSCantoII (Becton Dickinson) using the software FACSDiva. Transfected cells were differentiated from non-transfected cells according to red fluorescence. Positive thresholds were determined on the sera of healthy blood donors.

Quantitative data were expressed in median (interquartile range). Quantitative data were compared using a Mann–Whitney test or an ANOVA test. Qualitative data

were compared with a Fisher's exact test or a Khi2 test depending on the distribution of the data. Bonferroni post-test was asses in case of multiple comparisons. Statistical analysis, Spearman correlation, linear regression and graph constructions were performed using Graph Pad Prism 5 (GraphPad Software, San Diego, CA, USA) and IBM SPSS statistics, version 20 (IBM SPSS Inc, Chicago, IL, United States). A two-sided p value < 0.05 was considered as significant.

Results

Fifteen sera were positive for IgG4 antibodies anti-Nfasc155 (prevalence 1%), from our total cohort of 1500 tested sera. Among these sera the antibodies were also of other isotypes: IgG1 in 3 sera, IgG2 in 1, IgG3 in 7, IgA in 3 and IgM in 14 (Fig. 1).

Ten sera were positive for IgG4 antibodies anti-CNTN1 (prevalence 0.7%). Among these sera the antibodies were also of other isotypes: IgG1 in 1, IgG2 in 1, IgG3 in 3, IgA in 1 and IgM in 2 (Fig. 1).

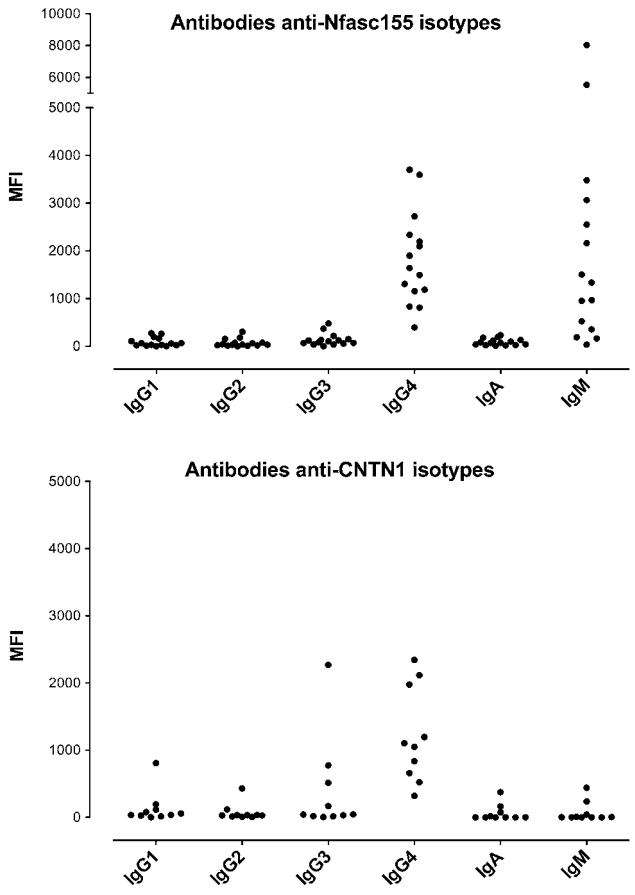

Fig. 1 Isotype of the antibodies against neurofascin 155 (Nfasc155) and contactin (CNTN1). *MFI* median fluorescence intensity, *Ig* immunoglobulin

Two sera were positive for IgG4 antibodies anti-Caspr1 (prevalence 0.2%). Both were of IgG3 and IgG4 isotypes.

None of the sera were positive for IgG4 anti-Nfas140/186 antibodies.

Clinical features are detailed in Table 1 and Fig. 2. Compared to seronegative CIDP, patients with IgG4 antibodies against the node of Ranvier had a subacute onset and were resistant to IVIg therapy.

Compared to seronegative CIDP, patients especially with IgG4 anti-Nfasc155 were younger, had greater lower limb disability and were more likely to have postural tremor and sensory ataxia. In two patients with antibodies against Nfasc155, the neuropathy was preceded by an infectious disease due to Epstein-Barr virus and Mycoplasma pneumoniae.

Compared to seronegative CIDP, patients with IgG4 anti-CNTN1, had more frequent facial paralysis, membranous glomerulonephritis and greater disability. Of note, these IgG4 anti-CNTN1 subjects had a more frequent acute or subacute onset, cranial nerve involvement and were more disabled than those with IgG4 anti Nfasc155 antibodies. A membranous glomerulonephritis was present in 6 patients with antibodies against CNTN1. The nephropathy appeared in the same time or a few weeks before the CIDP, except in one patient who had a lupus nephritis which appeared several years before the neuropathy. Antibodies against phospholipase A2 receptor (PLA2R) were negative in the 4 tested patients.

Compared to seronegative CIDP, patients with IgG4 anti-Caspr1, had more frequent cranial nerve involvement and respiratory failure. Pain was not more frequent than in seronegative CIDP.

All subjects with CIDP harbouring antibodies against the node of Ranvier had raised cerebrospinal fluid (CSF) protein levels. Mean CSF protein level was higher in patients with anti-Nfasc155 and anti-Caspr1 antibodies compared to seronegative CIDP. They also all had demyelinating features on nerve conduction studies, fulfilling the CIDP diagnostic criteria of EFNS/PNS for definite CIDP [1]. Distal motor latencies, nerve conduction velocities, F-waves latencies, number of conduction blocks, terminal latency index, modified F-ratio, motor and sensory nerve action potential amplitudes were comparable in CIDP with IgG4 against Nfasc155 and CNTN1.

Disability, assessed by the ONLS score, was greater in patients with antibodies against the node of Ranvier compared to seronegative CIDP, and was worse in patients with IgG4 anti-CNTN1 (Fig. 3 and Table 1). Two patients with IgG4 anti-CNTN1 died because of a severe nephropathy and neuropathy, compared to none in the other subgroups. The

Table 1 Clinical features of CIDP patients with or without antibodies against the node of Ranvier

	IgG4 anti-Nfasc155	IgG4 anti-CNTN1	IgG4 anti-Caspr1	Seronegative CIDP
Number	15	10	2	100
Age (years)	54 (47–64)$^{£}$	63 (55–75)	53 and 68	66 (55–72)
Female/male	8/7	2/8	0/2	43/57
Sub-acute onset	6 (40%)$^{£££}$	9 (90%)*,$^{£££}$	2 (100%)$^{£££}$	4 (4%)
Muscle weakness	12 (80%)	8 (80%)	2 (100%)	85 (85%)
Sensory deficiency	15 (100%)	10 (100%)	2 (100%)	94 (94%)
Sensory ataxia	15 (100%)$^{£££}$	9 (90%)	1 (50%)	53 (53%)
Postural tremor	10 (67%)$^{££}$	4 (40%)	0	22 (22%)
Cranial nerve involvement	2 (13%)	6 (60%)*,$^{£££}$	2 (100%)$^{£££}$	15 (15%)
Pain	4 (28%)	5 (50%)	1 (50%)	33 (33%)
Respiratory failure	0	2 (20%)	2 (100%)$^{££}$	14 (14%)
Membranous glomerulonephritis	0	6 (60%)***,$^{£££}$	0	0
ONLS				
Total	6 (4–7)	10 (7–12)**,$^{££}$	10 and 5	3 (2–4)
Arm	2 (1–3)	4 (4–5)**,$^{££}$	4 and 2	1 (0–2)
Leg	4 (2–4)$^{££}$	6 (5–7)**,$^{£££}$	6 and 3	2 (1–3)
Rankin	4 (2–4)	4.5 (4–5)$^{£££}$	5 and 4	2 (1–3)
CSF protein level (g/l)	2.82 (1.7–4.3)$^{£}$	1.9 (1.1–2.4)	12 and 2.5$^{£}$	0.6 (0.5–0.9)
Good response to				
IVIg	3/15 (20%)$^{£££}$	1/10 (10%)$^{£££}$	0/2$^{£££}$	67/84 (80%)
Steroids	8/13 (62%)	4/8 (50%)	0/1	26/38 (68%)
Plasma exchange	5/9 (56%)	2/6 (33%)	0/1	4/6 (67%)
Rituximab	8/8 (100%)	5/6 (83%)		5/5 (100%)

Quantitative data are expressed in median (interquartile range)

Comparison with seronegative CIDP. p values: $^{£££}p<0.001$, $^{££}p<0.01$, $^{£}p<0.05$

Comparison between CIDP with antibodies against CNTN1 and Nfasc155: $***p<0.001$, $**p<0.01$, $*p<0.05$

ONLS overall neuropathy limitation scale, *CSF* cerebrospinal fluid, *IVIg* intravenous immunoglobulins

ONLS values and the Rankin scores were correlated with the age at the diagnosis, respectively, $r=0.6$ $p=0.001$ and $r=0.6$ $p=0.002$ (Fig. 3). There were no association with diagnostic delay, sex, CSF protein level, electrophysiological data and titres of the antibodies.

Treatment with IVIg was not effective in CIDP with antibodies against the node of Ranvier (Table 1 and Fig. 2). One patient with IgG4 antibodies anti Nfasc155 had a 1 year remission after receiving a combination of steroids and plasma exchanges. Efficacy of plasma exchanges and steroids was initially good, but usually transient in all treated patients.

Eight patients with IgG4 anti Nfasc155 and 6 with IgG4 anti CNTN1 were resistant to first-line CIDP treatments (IVIg, steroids and plasma exchange) and received rituximab. Median duration of the disease before infusions was 10 months (6–36). One bedridden patient with anti-CNTN1 and membranous glomerulonephritis shortly died after the first rituximab injection. Efficacy was obtained in the remaining 13 patients, and was significant after 6 months (Fig. 4). All but one of these patients received an additional infusion of 1 g of rituximab after 6 months. Re-test of the antibody titres was available in 4 subjects with CIDP and IgG4 anti-Nfasc155 and in 3 CIDP and IgG4 anti-CNTN1, with a median follow-up of 24 months after the first rituximab infusion. These titres were dramatically decreased in all the patients with a median reduction of 93% (94 vs 1677 MFI) in patients with anti-Nfasc155 and of 96% (22 vs 659 MFI) in patients with anti-CNTN1 (Fig. 4).

Antibody titres and isotypes did not correlate with demographic or clinical features, electrophysiological data or response to treatment with one exception: patients with only IgG4 antibodies against Nfasc155 were younger than patients with IgG4 and other IgG isotypes antibodies against Nfasc155, median 44 years (42–47) vs 60 years (54–67) $p=0.006$. Positive IgM or IgA isotype antibodies were not associated with specific features.

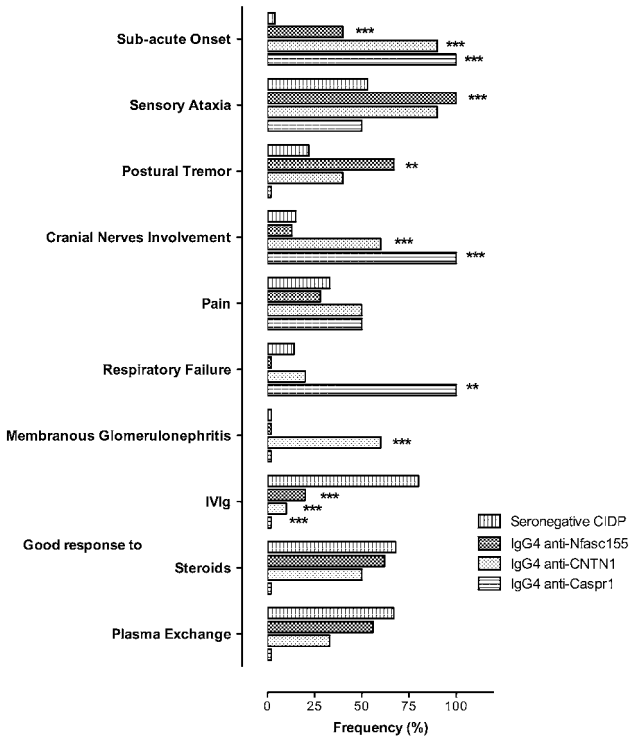

Fig. 2 comparison of the clinical features of CIDP patients with or without antibodies against the node of Ranvier. Comparison with seronegative CIDP. *p* value ***$p<0.001$, **$p<0.01$. *IVIg* intravenous immunoglobulins

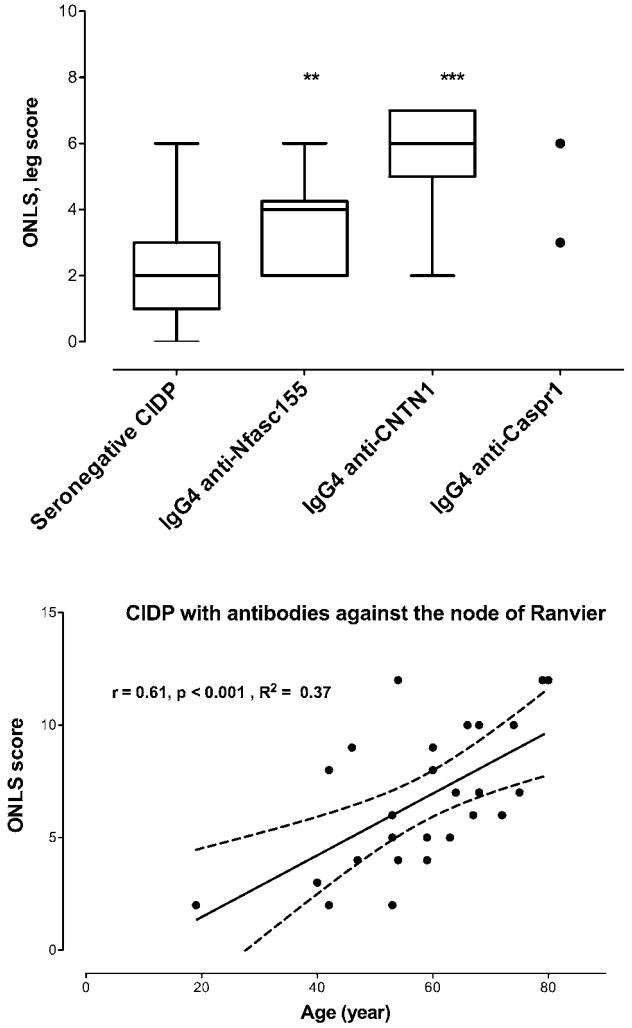

Fig. 3 Upper panel: box blot representing the disability of the CIDP with and without antibodies against the node of Ranvier. Comparison with seronegative CIDP. *p* value ***$p<0.001$, **$p<0.01$. Lower panel: linear regression between disability and age in patients with antibodies against the node of Ranvier. Graphs show best-fit line, 95% confidence band of best-fit line (dotted line), Spearman's correlation coefficient (*r*) and *R* square (R^2). *ONLS* overall neuropathy limitation scale

Discussion

In this study, we prospectively searched IgG4 antibodies against the node of Ranvier in a large cohort of possible CIDP patients. Several techniques are used to detect antibodies against the node of Ranvier. The enzyme-linked immunosorbent assay (ELISA) can be performed in almost any laboratory and the result can be quantified. The problem is that the presentation of the antigen is not physiological, because the proteins are coated on polystyrene plates. The presentation of the antigen is more natural when the protein is expressed by a transfected cell as in cell-based assays (CBA) and flow cytometry. The results of CBA are not quantified and interpretation of the test may be subjective for some "grey area" sera. We have, therefore, decided to test all our samples using a flow cytometry technique that allows us to screen a large number of samples at the same time in a quantified manner with cellular expression of the protein.

Incidence of IgG4 anti Nfasc155, CNTN1 and Caspr1 was, respectively, 1%, 0.7% and 0.2%. None of the tested patients had antibodies against Nfasc140/186. These incidence rates are lower than those previously reported. Frequency of IgG4 anti Nfasc155 was estimated at 3.7%, 5%, 7%, 8% and 18% in much smaller cohorts than ours, consisting, respectively, of 53, 55, 533, 191 and 50 patients [12–16]. The frequency of IgG4 anti CNTN1 was estimated at 2.4%, 6.5% and 7.5% in similarly smaller cohorts of, respectively, 533, 46 and 53 patients [2, 11, 12]. Frequency of IgG4 anti caspr1was estimated at 2.9% in one cohort of 35 subjects with CIDP [4]

These discrepancies may be due to several factors. Firstly, the studied populations were different. Previous studies were done on sera from banks of highly selected CIDP patients, whereas we prospectively tested a very large cohort of patients suspected of having a CIDP, as would be observed in routine clinical practice. Secondly, there may be geographical and ethnic differences resulting

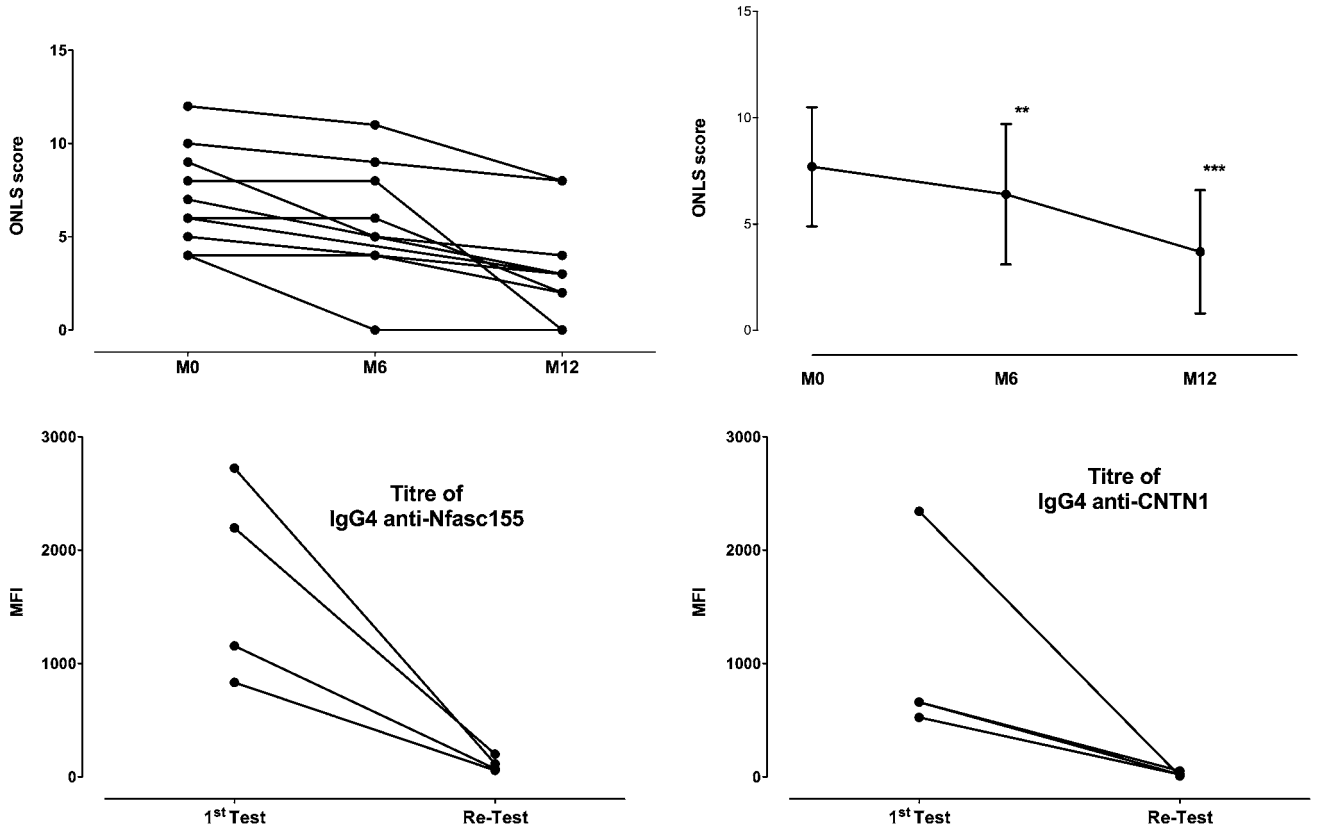

Fig. 4 Follow-up after rituximab treatment. Upper panel: on the left, evolution of the ONLS scores of 8 CIDP with IgG4 anti-Nfasc155 and 6 CIDP with IgG4 anti-CNTN1. On the right, mean with standard deviation of the ONLS score of the 14 patients. Comparison with the ONLS score at M0: ***p value < 0.01, **p value < 0.01. Lower panel: re-test of the antibodies measurement in 4 CIDP with IgG4 anti-Nfasc155 and in 3 CIDP with IgG4 anti-CNTN1, median follow-up of 24 months after the first rituximab infusion. *M* month, *ONLS* overall neuropathy limitation scale, *MFI* median fluorescence intensity

in the incidence of antibodies against Nfasc155 being possibly higher in Japan than in Europe [14]. In that regard, it is noteworthy that in an Italian cohort of 342 patients, the respective incidence of antibodies against Nfasc155, CNTN1 and Caspr1 was 2%, 0.8% and 0.8%, i.e., closer to our results. IgG4 antibodies against Nfasc140/186 are very rare and have so far been described in only 4 patients [5]. We found no subjects harbouring these antibodies in our current analysis.

Patients with antibodies against the node of Ranvier have bilateral and symmetrical, non-length-dependent motor and sensory deficits typical of polyradiculoneuropathy. Compare to seronegative CIDP, they more frequently have a subacute onset and are resistant to IVIg therapy. IgG4 anti-Nfasc155 are associated with younger onset, postural tremor and sensory ataxia [13–16]. Similar to others studying European populations [10, 16–18], we did not find associated central nervous system demyelination as described in Japanese cohorts.

Neuropathy associated with anti-caspr1 was initially said to be painful [4], but our patients, similar to others reported from Italy [10], did not have more neuropathic pain than seronegative CIDP. Of note, 2 of our patients with IgG4 anti Caspr1 antibodies had cranial nerve involvement and respiratory failure. However, antibodies against Caspr1 have been reported in only 6 CIDP patients and larger studies are, therefore, needed to ascertain the specific features associated with these antibodies.

CIDP associated with IgG4 anti-CNTN1 antibodies have a more frequent acute or subacute onset than those associated with IgG4 anti-Nfasc155. Postural tremor was present in 4/10 of our patients and reported in 3/4 patients in a previous study [12], but this seems less disabling than that reported in CIDP associated with IgG4 anti–Nfasc155 [22, 23]. Our patients with anti-CNTN1 antibodies had frequent bifacial palsy. Their neuropathy was severe with respiratory failure and marked disability demonstrated by high Rankin and ONLS scores. Death has been reported in 2 previous patients and 2 of our patients also passed away [12, 24]. The severity of anti CNTN1 syndrome might be due to the association of neuropathy and nephropathy. A membranous glomerulonephritis was present in 6/10 of our patients of and

previously reported in 1/3 and 1/4 CIDP with anti-CNTN1 antibodies, respectively [10, 12]. Renal biopsies show granular deposits of IgG4 along the glomerular basement membrane [25, 26]. Antibodies to anti PLA2R which are involved in most of primary membranous glomerulonephritis [27] were negative in these cases. Usually, nephritis and CIDP are concurrent and immunomodulatory treatment is effective for both. Membranous glomerulonephritis has also been associated with IgG4 anti Nfas140/186 [5]. The glycoproteins CNTN1 and Nfasc are expressed in the nervous system and in the kidney [28, 29] and these common antigens may explain that both organs could be involved by the same autoimmune process. Of note, it is interesting to notice that the combination of nephrotic syndrome and neuropathy has also been reported in Charcot-Marie-Tooth disease with mutation of inverted formin 2 (INF2), which, coincidentally is co-expressed in nerve and kidney, in podocytes and in Schwann cells [30].

CIDP associated with IgG4 antibodies against the node of Ranvier do not respond to IVIg therapy. Steroids and plasma exchanges can be effective, particularly when combined, but efficacy is often transient. We as others, found that rituximab is well-tolerated and effective in patients with IgG4 anti Nfasc155 or anti-CNTN1. Antibody levels became nearly undetectable and clinical improvement was observed at 6 months after the first infusion (Fig. 4). A previous study [24], based on 3 patients, suggested that treatment with rituximab should be administrated precociously to be effective, but in our cohort 6 patients were improved although the infusions were performed 2 years, or more, after the first symptoms of the CIDP.

Antibodies against the node of Ranvier are mainly of IgG4 isotypes. In some patients the antibodies also consist of other immunoglobulin isotypes. In the current study, occurrence of IgM, IgA or other IgG isotypes did not correlate with clinical features or treatment response. In one previous report, anti-Nfasc155 antibody level variations correlated with clinical and the electrophysiological changes [31]. We were unable to find any such correlations, nor with disease severity. The value of determining other isotypes and IgG4 titres needs to be further investigated. We just considered IgG4 antibodies in the first screen, because IgG4 is the only isotype clearly associated with specific subtype of CIDP. IgM anti-CNTN1 have not been described and IgM anti-Nfasc155 can be detected in Guillain-Barré syndrome, Charcot Marie Tooth disease, idiopathic neuropathies and healthy subjects [18, 32]. Other IgG isotypes are exceptionally detected in very rare inflammatory neuropathies [33]. Their incidence and specificity need to be determined in further studies.

In conclusion, it appears advisable to test for antibodies against the node of Ranvier in subjects with CIDP with acute or subacute onset, postural tremor, nephrotic syndrome or resistance to IVIg. In a large cohort of subjects with possible CIDP, which to our knowledge is the largest reported to date, we found that antibodies against the node of Ranvier are detected in less than 2% of patients. Although rare, these antibodies appear, however, of important diagnostic value, because they are associated with specific clinical features and a different response to treatment.

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Compliance with ethical standards

Conflicts of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

Ethics approval This study has been approved by the ethics committee of Assistance Publique des Hôpitaux de Marseille (Agreement Number PADS19-365) and have been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments

Consent to participate All persons involved in this study gave inform consent for participation and publication

Availability of data and material Data are available on demands.

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