Neurochemistry International 130 (2019) 104360

Contents lists available at ScienceDirect

Neurochemistry International

journal homepage: www.elsevier.com/locate/neuint

Anti-neurofascin autoantibody and demyelination

Jun-ichi Kira*, Ryo Yamasaki, Hidenori Ogata

Department of Neurology, Neurological Institute, Graduate School of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka, 812-8582, Japan

ARTICLE INFO

Keywords:
Chronic inflammatory demyelinating polyradiculoneuropathy
Combined central and peripheral demyelination
Multiple sclerosis
Neurofascin 155
Node of Ranvier
Paranode

ABSTRACT

Demyelination diseases involving the central and peripheral nervous systems are etiologically heterogeneous with both cell-mediated and humoral immunities playing pathogenic roles. Recently, autoantibodies against nodal and paranodal proteins, such as neurofascin186 (NF186), neurofascin155 (NF155), contactin-1 (CNTN1), contactin-associated protein 1 (CASPR1) and gliomedin, have been discovered in not only chronic demyelinating conditions, such as multiple sclerosis (MS) and chronic inflammatory demyelinating polyradiculoneuropathy, but also in acute demyelinating conditions, such as Guillain-Barré syndrome. Only a minority of these patients harbor anti-nodal/paranodal protein antibodies; however, these autoantibodies, especially IgG4 subclass autoantibodies to paranodal proteins, are associated with unique features and these conditions are collectively termed nodopathy or paranodopathy. Establishing a concept of IgG4-related nodopathy/paranodopathy contributes to diagnosis and treatment strategy because IgG4 autoantibody-related neurological diseases are often refractory to conventional immunotherapies. IgG4 does not fix complements, or internalize the target antigens, because IgG4 exists in a monovalent bispecific form *in vivo*. IgG4 autoantibodies can bock protein-protein interaction. Thus, the primary role of IgG4 anti-paranodal protein antibodies may be blockade of interactions between NF155 and CNTN1/CASPR1, leading to conduction failure, which is consistent with the sural nerve pathology presenting paranodal terminal loop detachment from axons with intact internodes in the absence of inflammation. However, it still remains to be elucidated how these autoantibodies belonging to the same IgG4 subclass can cause each IgG4 autoantibody-specific manifestation. Another important issue is to clarify the mechanism by which IgG4 antibodies to nodal/paranodal proteins emerge. IgG4 antibodies develop on chronic antigenic stimulation and can block antibodies that alleviate allergic inflammation by interfering with the binding of allergen-specific IgE to allergens. Thus, environmental antigens cross-reacting with nodal and paranodal proteins may warrant future study.

1. Introduction

Inflammatory demyelination affecting the central nervous system (CNS) and peripheral nervous system (PNS) has heterogeneous mechanisms with both cell-mediated and humoral immunities playing pathogenic roles. In chronic demyelinating conditions, such as multiple sclerosis (MS) and chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), autoantibodies against nodal and paranodal proteins, such as neurofascin186 (NF186) (Mathey et al., 2007), neurofascin155 (NF155) (Mathey et al., 2007; Ng et al., 2012; Kawamura et al., 2013; Querol et al., 2014; Ogata et al., 2015; Devaux et al., 2016; Kadoya et al., 2016), contactin-1 (CNTN1) (Querol et al., 2013; Doppler et al., 2015; Miura et al., 2015), and contactin-associated protein 1 (CASPR1) (Doppler et al., 2016), have been discovered and much studied. Even in acute demyelinating disease, such as Guillain-Barré syndrome, antibodies against nodal proteins, such as NF186, gliomedin and contactin, were detected in a minority of patients (Devaux et al., 2012). Demyelinating diseases associated with these autoantibodies are now recognized as nodopathies or paranodopathies (Fig. 1). Among these autoantibodies, anti-NF186 and -NF155 antibodies have been found in both CNS and PNS demyelinating disorders (Mathey et al., 2007; Kawamura et al., 2013; Ogata et al., 2015). Thus, knowledge of anti-neurofascin (NF), antibodies is increasingly important. In this review, we describe clinical and immunological features of anti-NF antibody-associated demyelinating diseases, with special focus on combined central and peripheral demyelination (CCPD) and CIDP.

2. Neurofascins

Among nodal and paranodal proteins, NF, a cell adhesion molecule, is critical for the formation and maintenance of the nodes of Ranvier. By

* Corresponding author.
E-mail address: kira@neuro.med.kyushu-u.ac.jp (J.-i. Kira).

https://doi.org/10.1016/j.neuint.2018.12.011
Received 25 August 2018; Received in revised form 30 November 2018; Accepted 21 December 2018
Available online 22 December 2018

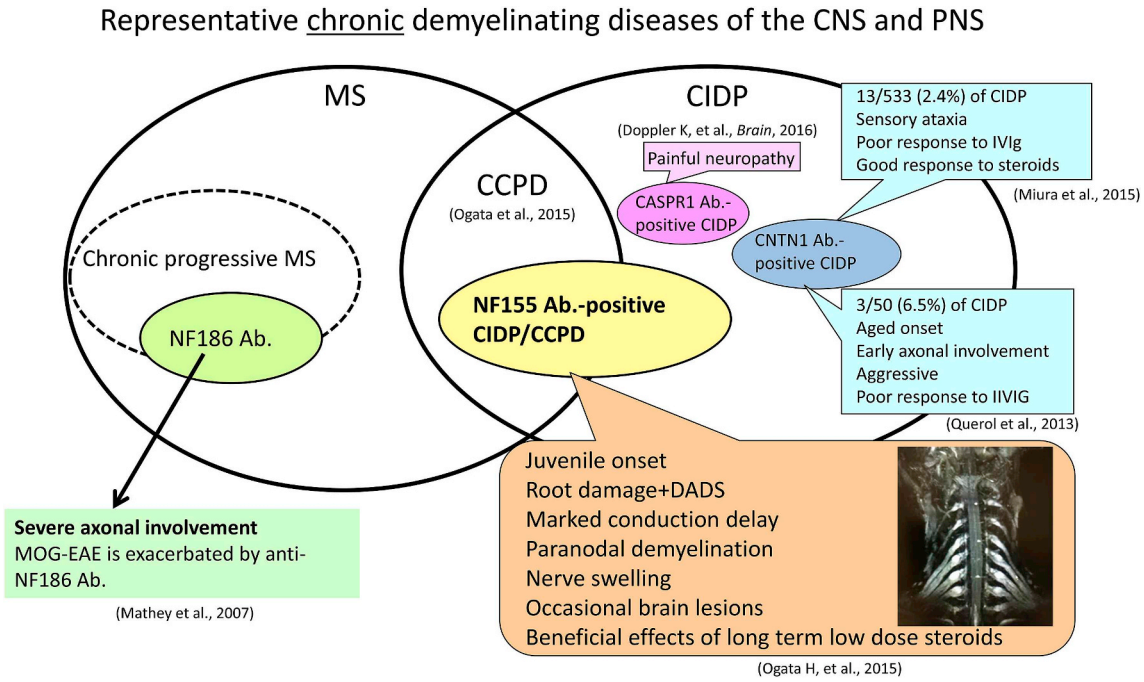

Fig. 1. Chronic demyelinating diseases targeting axo-glial junction are termed nodopathy or paranodopathy. Autoantibodies against NF186, gliomedin and contactin were reported in a minority of patients with Guillain-Barré syndrome, an acute demyelinating disease of the PNS (Devaux et al., 2012). The disease entity and the exact positioning of CCPD in the demyelinating diseases have not been established. In our previous study on seven CCPD cases (Kawamura et al., 2013), all seven CCPD cases fulfilled the EFNS/PNS criteria for CIDP (Guidelines PNSC, 2010) and six cases met the McDonald criteria (2011) for MS (Polman et al., 2011). In the first nationwide survey on CCPD (Ogata et al., 2016), 67.5% (27/40) of the CCPD patients met the McDonald criteria for MS, while 87.5% (35/40) fulfilled the EFNS/PNS definite criteria for CIDP. Ab. = antibody; CASPR1 = contactin-associated protein 1; CCPD = combined central and peripheral demyelination; CIDP = chronic inflammatory demyelinating polyradiculoneuropathy; CNTN1 = contactin-1; DADS = distal acquired demyelinating symmetric neuropathy; EAE = experimental autoimmune encephalomyelitis; IVIg = intravenous immunoglobulin; MOG = myelin oligodendrocyte glycoprotein; MS = multiple sclerosis; NF = neurofascin.

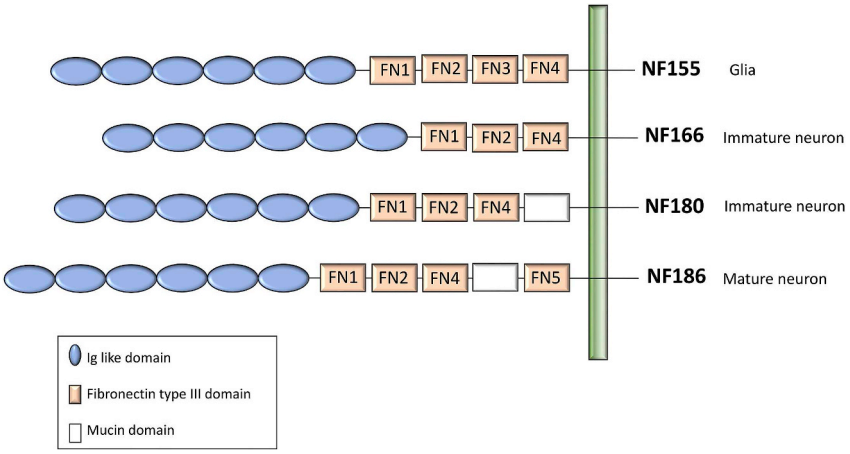

Fig. 2. Schematic diagram of different neurofascin isoforms.

alternative splicing, four major NF polypeptides are produced and expressed in nervous tissues; NF186, NF180, NF166 and NF155 (Fig. 2) (Kriebel et al., 2012). These polypeptides principally consist of six immunoglobulin-like domains, up to five fibronectin type III (FN) domains, a transmembrane domain, and a short cytoplasmic domain. NF180 and NF166 are immature neuronal proteins. In the mature nervous system, neuronal isoform NF186 and glial isoform NF155 are predominant (Kriebel et al., 2012). NF155 and NF186 are distinct in their extracellular domains; NF155 carries FN3 while NF186 lacks this domain, and instead has a mucin domain between FN4 and FN5.

Axonal NF186 interacts with ankyrin-G to cluster sodium channels at the nodes of Ranvier (Davis et al., 1996) (Fig. 3). In the PNS, NF186 interacts with gliomedin in the matrix and in Schwann cell microvilli to promote axon-Schwann cell microvilli attachment (Stathopoulos et al., 2015). In the CNS, several extracellular matrix proteins may play similar roles to gliomedin (Stathopoulos et al., 2015). Genetic ablation of NF186 results in loss of neuronal cell adhesion molecule (NrCAM), another axonal adhesion molecule that binds to ankyrin, and the Schwann cell adhesion molecule, gliomedin, leading to unclustering of sodium channels (Na_v) and ankyrin-G at nodes in the CNS and PNS, which is accompanied by invasion of paranodal loops to the nodal region (Thaxton et al., 2011). This indicates that NF186-dependent assembly of the nodal complex acts as a molecular boundary to restrict the migration of paranodal loops into nodal areas.

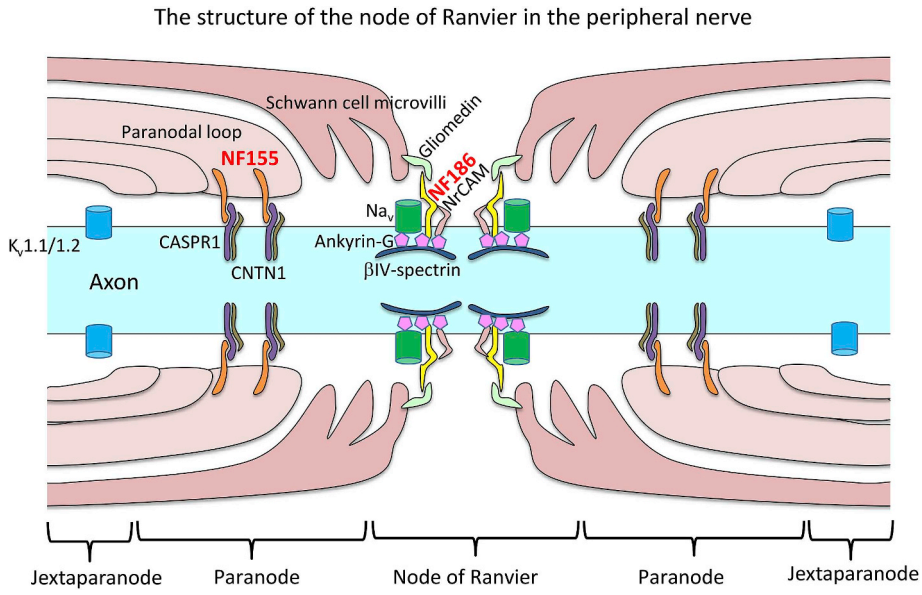

Fig. 3. Schematic illustration of the node of Ranvier in the PNS. CASPR1 = contactin-associated protein 1; CNTN1 = contactin-1; Kv = potassium channel; Na_v = sodium channel; NF = neurofascin; NrCAM = Neuronal cell adhesion molecule.

Glial NF155 is expressed at the paranodal loops of oligodendrocytes in the CNS (Tait et al., 2000) and in Schwann cells in the PNS (Sherman et al., 2005). Glial NF155 interacts with axonal CNTN1 and CASPR1 (Pedraza et al., 2001). In NF-null mice, transgenic expression of NF155 in the myelinating glia recruits CNTN1 and CASPR1, restoring the axon-glial adhesion complex at the paranodes. However, clustering of sodium channel and NrCAM at the nodes was not recovered (Sherman et al., 2005), suggesting a crucial role of NF186 in assembling the nodal complexes. Glial NF155 forms septate-like transverse bands between terminal loops and axons together with axonal CNTN1 and CASPR1 to maintain the ion channel clustering at nodes of Ranvier (Sherman et al., 2005). Myelinating glia-specific ablation of NF155 caused marked reduction of nerve conduction velocity together with migration of paranodal CASPR1 and juxtaparanodal potassium channels (Kv1.1) toward the nodal region (Pillai et al., 2009), suggesting that NF155 is indispensable for separating nodal voltage-gated sodium channels from juxtaparanodal potassium channels. As loss of NF155 and CNTN1 in genetically modified mice leads to disruption of septate-like junctions, leaving a large gap between the axolemma and Schwann cell terminal loops, which decreases nerve conduction velocity (Boyle et al., 2001; Sherman et al., 2005; Pillai et al., 2009), these molecules are regarded fundamental to maintain saltatory conduction.

3. Multiple sclerosis

MS is a demyelinating disease of the CNS while disability progression is determined by gray mater atrophy and widespread neuroaxonal injury that is not confined to demyelinating lesions (Li et al., 2006; Fisniku et al., 2008). A recent study provided evidence of early and persisting neuro-axonal degeneration throughout the entire course of MS (Azevedo et al., 2018). In autopsied MS brains, early alteration of paranodal structures was detected in actively demyelinating lesions, where NF155 is lost and potassium channels (Kv1.2) invade the NF186-positive nodes (Howell et al., 2006). In the remyelinating shadow plaques, the restoration of NF155 at the paranodes as well as clustering of sodium channels and NF186 at the nodes occurred (Howell et al., 2006).

Mathey et al. (2007) first reported the presence of autoantibodies recognizing the extracellular domain of both NF155 and NF186 in about a third of MS patients. Anti-NF antibodies were more frequently found in chronic progressive MS than relapsing remitting MS (RRMS). Passive transfer of anti-NF antibodies exacerbated experimental autoimmune encephalomyelitis (EAE), an animal model of MS, induced by adoptive transfer of myelin oligodendrocyte glycoprotein (MOG)-specific T cells in rats (Mathey et al., 2007). In this model, anti-NF antibodies deposited at the node of Ranvier *in vivo* together with complement, resulted in axonal injury. These observations suggest that anti-NF antibodies facilitate axonal pathology in MS, especially chronic progressive MS. Alternatively, it was reported that anti-NF antibodies were secondarily produced by inter-molecular antigenic epitope spreading in a MOG-induced but not a myelin basic protein-induced rat EAE model (Flytzani et al., 2015). However, caution should be observed because even in the original article (Mathey et al., 2007), patients with other inflammatory neurological diseases also had anti-NF antibodies at a similar frequency to RRMS, and another report described no difference in the prevalence of anti-NF seropositivity between patients with primary progressive MS (4.8%) or RRMS (0.6%) and healthy controls (2.0%) (Stich et al., 2016).

4. Combined central and peripheral demyelination

Demyelinating diseases usually affect either the CNS or PNS, possibly because the relevant autoantigens exist in only the CNS or PNS. However, patients with demyelination in the CNS or PNS occasionally exhibit demyelination in the other nervous system (Fig. 1). Autoantigens commonly present in both CNS and PNS are suggested to be recognized in these patients. Such a condition has various diagnostic names; not only CCPD but also CIDP with CNS involvement and CIDP with multifocal CNS demyelination (Kamm and Zettl, 2012). Because only case reports or a small series of studies of such cases exist in the literature, in 2012 we conducted the first nationwide survey in Japan to uncover the demographic features of CCPD (Ogata et al., 2016).

4.1. The nationwide survey results of CCPD

Definition: We defined CCPD as fulfilling the following criteria (Ogata et al., 2016):

1. CNS involvement criterion: T2 high-signal intensity lesions in the brain, optic nerves, or spinal cord upon MRI, or abnormalities on visual-evoked potentials (VEPs).
2. PNS involvement criterion: conduction delay, conduction block,

temporal dispersion or F-wave abnormalities, suggesting peripheral demyelinating neuropathy according to nerve conduction studies (NCS).

Demographic features: CCPD is a rare condition; likely less than 0.52% of MS and 2.8% of CIDP patients in Japan, based on the nationwide survey. The mean age at onset was 32 years (range; 8–59 years). The male to female ratio was 1:2.6. The mode of onset was acute in 19.4%, subacute in 45.2%, and chronic in 35.5%. Clinical courses were monophasic in 26.3%, relapsing remitting in 52.6%, and chronic progressive in 21.1%.

Neurological manifestations: Onset with CNS symptoms, such as visual disturbance, hemiplegia, and hemibody sensory disturbance, was observed in about 40%, onset with PNS manifestations, such as weakness and sensory disturbance of the four extremities, in around 40%, and onset with both CNS and PNS manifestations in about 20%. The most common symptom/sign during the entire course was sensory disturbance (94.9%), the second most common symptom/sign was motor weakness (92.5%), and the third was gait disturbance (79.5%). Cranial nerves were affected in 75.0%, and optic nerves were the most commonly affected (63.3%) with approximately 50% exhibiting bilateral involvement. Hyporeflexia and hyperreflexia were seen in 65.0% and 22.5%, respectively, and pathological reflexes were found in 45.0%. Sphincter disturbance was present in 47.4%. Muscle atrophy and cerebellar ataxia were detected in about 25%. Mental disturbance, seizure, and respiratory disturbance were occasionally observed.

Laboratory findings: Few patients had common autoantibodies and anti-aquaporin 4 (AQP4) antibodies were detected in none of the patients. Cerebrospinal fluid (CSF) protein levels were increased in 82.5% while pleocytosis was present in only 27.5%, indicating albuminocytological dissociation in 57.5%. The CSF oligoclonal IgG bands (OBs) were positive only in 7.4%, and the IgG index was elevated in 18.5%.

Magnetic resonance imaging (MRI) and electrophysiological findings: On MRI, cerebral, cerebellar, brainstem, and optic nerve lesions were found in 75.0%, 15.0%, 32.5% and 17.5%, respectively. Extensive lesions (>3 cm in diameter) were observed in 25.0% while gadolinium (Gd)-enhanced lesions were found in only 17.5%. Spinal cord lesions were detected in 75.0%, of which 36.7% were Gd-enhanced. Longitudinally extensive spinal cord lesions (LESCLs), extending three or more vertebral segments, were present in 7.5%. Visual-evoked potentials (VEPs) were abnormal in 71.4%, with bilateral observation of these in 53.3%. In motor nerve conduction studies (NCS), decreased motor nerve conduction velocity (MCV) and prolonged F-wave latency were the most common findings, which were recognized in 77.5% and 70.0%, respectively. Abnormal compound muscle action potential amplitude, prolonged distal latency, and decreased F-wave occurrence were detected in approximately half of the patients. Conduction block and temporal dispersion were detected in 27.5% and 40.0%, respectively. In sensory NCS, decreased or absent sensory nerve action potential was observed in as many as 87.5%, while decreased sensory nerve conduction velocity was present in 42.5%.

Treatment response: CCPD patients were most commonly treated with either intravenous or oral corticosteroids, followed by intravenous immunoglobulins, resulting in 83.3%, 75.0%, and 66.7% improvement, respectively. Plasmapheresis was performed in a small fraction of CCPD patients, of whom 87.5% improved. By contrast, interferon-beta (IFN-β) was effective in only 10.0%, and even exacerbated the disease in 30.0%. At the illness peak, 40.0% of CCPD patients had severe disability (≥ 4 Hughes functional scale score) with some requiring artificial ventilation, whereas after treatment 65.0% had no or only mild disabilities (≤ 1 Hughes functional scale score).

4.2. Characteristic features of CCPD with anti-NF155 antibodies

Kawamura et al. (2013) first described high frequencies of anti-NF155 antibodies in CCPD patients. According to the nationwide survey of CCPD in Japan, anti-NF155 antibodies were found in 45% of cases (Ogata et al., 2016). However, positivity rates of anti-NF155 antibodies in CCPD varies among studies, possibly reflecting the assay methods and antigen species used. As mentioned in the following section, CNS demyelinating lesions were observed in 8% of anti-NF155 antibody-positive CIDP patients, in which anti-NF155 antibodies similarly targeted the CNS and PNS paranodes (Devaux et al., 2016). The characteristic features of CCPD patients with anti-NF155 antibodies are as follows (Kawamura et al., 2013; Ogata et al., 2016). (1) CNS and PNS involvement occur either simultaneously or sequentially with a short or long interval. (2) NCS shows diffuse conduction slowing with focal conduction failure, which is indistinguishable from CIDP. (3) CNS involvement is mostly typical for MS, in which spinal cord lesions and Gd-enhancement of the lesions can develop, but is occasionally atypical, demonstrating diffuse cerebral white matter lesions. (4) CSF OBs are negative in most cases but CSF protein amounts show variable degrees of increase. (5) Combined immunotherapies including corticosteroids, IVIg, and plasma are beneficial for both CNS and PNS lesions. These findings suggest that autoantibodies against NF at the paranodes and nodes, but not compacted myelin, may disrupt axo-glial integrity, leading to inflammatory demyelination in both the CNS and PNS.

5. Chronic inflammatory demyelinating polyradiculoneuropathy

5.1. Prevalence of anti-paranode antibodies in CIDP and other inflammatory neuropathies

CIDP is an acquired immune-mediated disease affecting the peripheral nerves. As CIDP encompasses etiologically heterogeneous conditions, the precise mechanisms of CIDP remain to be elucidated. However, both cell-mediated and humoral immunities are supposed to play pathogenic roles in CIDP. Recently, a fraction of CIDP patients were demonstrated to have autoantibodies against paranodal proteins, such as NF155 (Ng et al., 2012; Querol et al., 2014; Ogata et al., 2015; Devaux et al., 2016; Kadoya et al., 2016), CNTN1 (Querol et al., 2013; Doppler et al., 2015; Miura et al., 2015), and CASPR1 (Doppler et al., 2016). Each of these autoantibodies is associated with unique features.

Anti-CNTN1 antibodies were detected in 6% of CIDP patients, who commonly showed advanced age, predominant motor involvement, aggressive symptom onset, and early axonal involvement (Querol et al., 2013; Doppler et al., 2015; Miura et al., 2015). Doppler et al. (2016) reported a CIDP case with anti-CASPR1 antibodies presenting a painful neuropathy. The sera from this case bound not only the paranodes but also some posterior ganglion neurons, suggesting anti-CASPR1 antibodies may cause painful neuropathy via impairment of small posterior ganglion neurons conveying pain sensation (Doppler et al., 2016). However, these findings should be confirmed by larger scale studies.

Contradictory results were reported for the presence of anti-NF186 antibodies in CIDP. One study showed a 12% positivity rate (Devaux et al., 2012), and others 0% (Ng et al., 2012; Ogata et al., 2015). Measurement of anti-NF155 antibodies by enzyme-linked immunosorbent assays in two studies revealed low positivity rates to human NF155, 2.5% (Ng et al., 2012) and 3.8% (Querol et al., 2014) although 22% positivity to rat NF155 was reported (Yan et al., 2014). We developed a more specific antibody assay using human NF155 and flow cytometry, and found that positivity rates for anti-NF155 antibodies among patients with CIDP, MS, and other neuropathies, and healthy controls were 18% (9/50), 0% (0/32), 2.5% (1/40), and 0% (0/30), respectively (Ogata et al., 2015). All CIDP cases had predominantly IgG4 subclass ani-NF155 antibodies while one positive case with Guillain-Barré syndrome had IgG1 subclass anti-NF155 antibodies (Ogata et al., 2015). Therefore, IgG4 subclass anti-NF155 antibodies seem to be specific for a subset of CIDP.

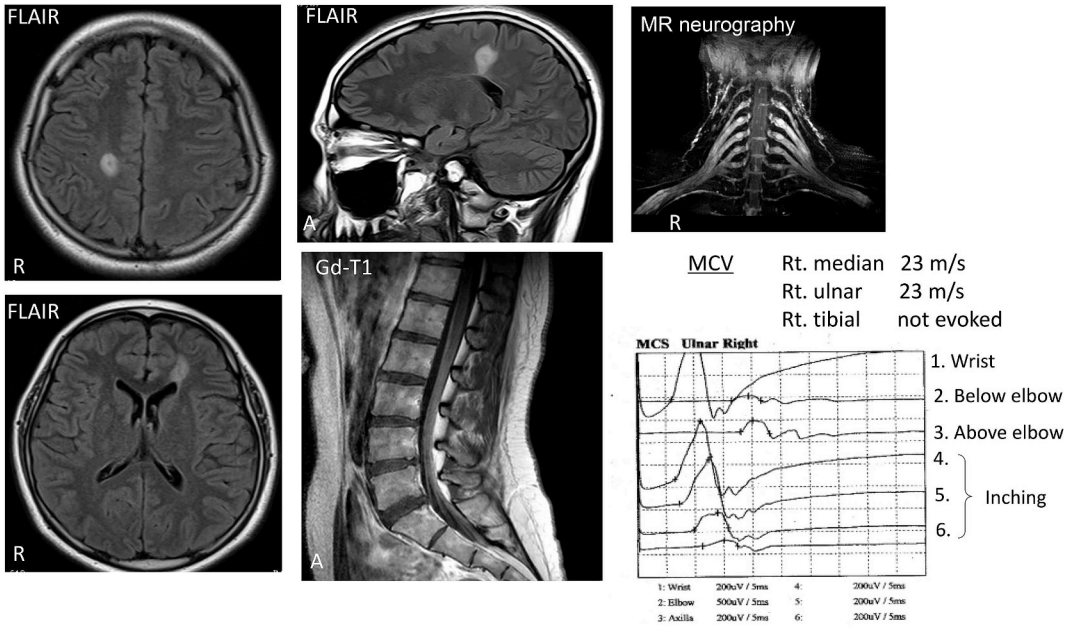

Fig. 4. MRI and electrophysiological findings suggesting CNS and PNS demyelination in a case with IgG4 anti-NF155 antibodies and CCPD. A 16-year-old female patient with IgG4 anti-neurofascin antibody experienced acute left hemiparesis (due to MS-like lesion in the right periventricular ovoid lesion, arrow) and four months later gradually developed distal dominant motor and sensory neuropathy (Kawamura et al., 2013). She was successfully treated with combined therapy of IVIg, corticosteroids and azathioprine. After gradual tapering of low dose corticosteroids and azathioprine, she became free of any drug but was left with muscle weakness and atrophy of distal parts of the four limbs eight years later. CCPD = combined central and peripheral demyelination.

5.2. Clinical aspects of IgG4 anti-NF155 antibody-positive CIDP

The characteristic features of IgG4 anti-NF155 antibody-positive CIDP compared with anti-NF155 antibody-negative CIDP are as follows: younger onset age (25.2 ± 10.7 vs. 47.9 ± 17.0 years, mean ± SD), higher frequencies of drop foot, gait disturbance, tremor and distal acquired demyelinating symmetric (DADS) neuropathy phenotype, higher CSF protein levels (317.0 ± 141.1 vs. 103.8 ± 75.8 mg/dl), and more pronounced prolongation of distal (7.7 ± 1.4 vs. 6.7 ± 3.3 ms) and F-wave latencies (53.7 ± 16.3 vs. 42.4 ± 11.4 ms) (Ogata et al., 2015).

We developed a new MRI neurography method with three-dimensional nerve-SHeath signal increased with INKed rest-tissue rapid acquisition with relaxation Enhancement Imaging (3D SHINKEI) of spinal roots and plexuses, and revealed that all seven cases with IgG4 anti-NF155 antibodies uniformly demonstrated marked cervical and lumbar spinal root hypertrophy. The largest root diameters among bilateral C5–C8 roots were significantly greater in anti-NF155 antibody-positive patients than in anti-NF155 antibody-negative patients (7.7 ± 1.3 vs. 4.9 ± 2.0 mm) (Fig. 5) (Ogata et al., 2015; Hiwatashi et al., 2017). Even proximal cranial nerves such as oculomotor and trigeminal nerves also show hypertrophy and is termed Moustache sign (Franques et al., 2017). These findings suggest that the emergence of IgG4 anti-NF155 antibodies are not confined to the DADS phenotype showing distal dominant motor and sensory polyneuropathy but are associated with proximal nerve involvement presenting the typical CIDP phenotype. In addition, IgG4 anti-NF155 antibody-positive patients occasionally develop CNS lesions suggestive of demyelination (CCPD) (Fig. 4) (Kawamura et al., 2013; Ogata et al., 2015, 2016; Devaux et al., 2016).

Anti-NF155 antibodies were originally found in a fraction of CIDP patients refractory to IVIg (Querol et al., 2014). Our results also suggest that IVIg alone is not sufficient to improve the disabilities of such patients (Ogata et al., 2015). Corticosteroids combined with IVIg is more beneficial than IVIg alone (Ogata et al., 2015), which is compatible with the fact that corticosteroids are widely used to treat diseases related to disease-specific IgG4 autoantibodies, such as pemphigus (Hertl et al., 2015) and thrombotic thrombocytopenic purpura (Scully et al., 2012). For sustained improvement, long-term immunosuppression by daily oral corticosteroids and/or immunosuppressants is more efficacious than repeated IVIg in IgG4 anti-NF155 antibody-positive CIDP. Importantly, a long-term observational study disclosed that anti-NF155 antibody levels varied in parallel with the clinical and electrophysiological changes, or even preceded them (Fujita et al., 2018), suggesting a pathogenic role of IgG4 anti-NF155 antibody itself. Restoration of nerve conduction by plasma exchanges with decreasing anti-NF155 antibody titers is also compatible with a pathogenic role of IgG4 anti-NF155 antibodies (Fujita et al., 2018). In a small case series

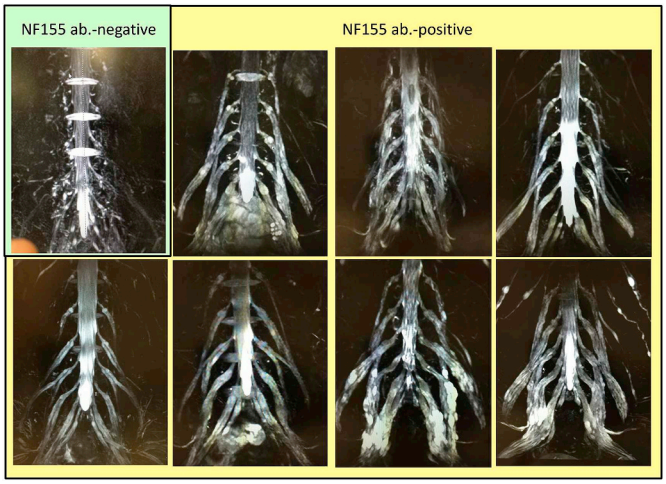

Fig. 5. Hypertrophy of the lumbar nerve roots in anti-NF155 antibody-positive CIDP. MRI neurography with 3D SHINKEI imaging of lumbosacral spinal roots and plexuses in IgG4 anti-NF155 antibody-positive CIDP patients together with an antibody-negative CIDP patient is shown (Ogata et al., 2015; Hiwatashi et al., 2017). All anti-NF155 antibody-positive CIDP cases so far examined had nerve root hypertrophy, which is thus supposed to be a characteristic feature of this condition.

with anti-NF155 antibody-positive CIDP refractory to conventional immunotherapies, rituximab, an anti-CD20 monoclonal antibody targeting B cells, was reported to be useful for long-term relief (Querol et al., 2015).

5.3. Neuropathology of anti-NF155 antibody-positive CIDP

There has been no autopsied case with anti-NF155 antibody-positive CIDP; however, by histopathological examination of biopsied sural nerves, we first revealed subperineurial edema and occasional paranodal demyelination, but no vasculitis, inflammatory cell infiltrates, or onion bulbs. Myelinated fiber loss was mild even if years after the disease onset (Ogata et al., 2015). Detachment of terminal Schwann cell loops from axons at the paranodes disrupting septate-like transverse bands was characteristically observed by electron microscopy in anti-NF155 antibody-positive patients but not seronegative CIDP patients (Koike et al., 2017; Kuwahara et al., 2018).

5.4. Mechanism of IgG4 anti-NF155 antibody-positive CIDP

Sera from anti-NF155 antibody-positive CIDP patients bind specifically to paranodal regions of peripheral nerves, suggesting the paranodes are primary targets. These sera do not react with neuronal isoform, NF186 (Ogata et al., 2015), indicating that antigenic epitopes should exist around the extracellular FN3 domain, which is unique to NF155 (Fig. 2). IgG4 subclass anti-NF155 antibodies predominate in all CIDP patients we have examined (Ogata et al., 2015). IgG4 has a compact structure because of trans heavy chain CH1−CH2 domain interaction, resulting in no accessibility for complements to the CH2 domain which fix complements. Thus, IgG4 cannot activate complement because it is unable to bind C1q (Huijbers et al., 2015). Moreover, *in vivo*, IgG4 exists monovalent bispecific because of half molecular exchange, following inter-chain disulfide bond disruption by protein disulfide isomerase expressed on immunocytes and endothelial cells. As a result, IgG4 does not internalize the target antigens (Huijbers et al., 2015). Physiologically, IgG4 is produced by chronic antigenic stimulation and IgG4 blocks binding of allergen-specific IgE to allergens, thereby reducing allergic inflammation. Therefore, IgG4 autoantibodies can also just bock protein-protein interaction (Huijbers et al., 2015). Collectively, these observations suggest the primary role of IgG4 anti-NF155 antibodies may be blockade of interactions between NF155 and CNTN1/CASPR1, leading to conduction failure, which is consistent with the sural nerve pathology in IgG4 anti-NF155 antibody-positive CIDP, presenting only paranodal terminal loop detachment with intact internodes in the absence of inflammation (Ogata et al., 2015; Koike et al., 2017; Kuwahara et al., 2018). Restoration of nerve conduction by plasma exchanges with decreasing anti-NF155 antibody titers is also compatible with action of IgG4 as a blocking antibody (Fujita et al., 2018).

6. Conclusion and future perspectives

By discovery of autoantibodies against nodal and paranodal proteins in a minority of patients with MS, CCPD, and CIDP, a concept of nodopathy or paranodopathy is emerging. Although the significance of anti-NF antibodies in chronic progressive MS needs further large scale studies, IgG4 autoantibodies against paranodal proteins in CIDP are associated with unique features specific for each condition. Establishment of IgG4-related demyelinating conditions contributes to diagnosis and treatment strategy, because IgG4 autoantibody-related neurological diseases are often refractory to conventional immunotherapies, such as IVIg.

The mechanism by which autoantibodies belonging to the same IgG4 subclass can cause each IgG4 antibody-specific feature remains to be elucidated. For example, extensive spinal root hypertrophy and pronounced elevation of CSF protein seen only in IgG4 anti-NF155 antibody-positive CIDP, but not other paranodopathies, such as anti-CNTN1 and anti-CASPR1 antibody-positive CIDP, suggest severe inflammation of the nerve roots (Ogata et al., 2015), which cannot be adequately explained by IgG4 antibody functions. We found increased CFS cell counts and proinflammatory cytokines in IgG4 anti-NF155 antibody-positive CIDP patients (submitted for publication); therefore, NF155-specific T cells may be involved in spinal root and CNS inflammation. As a distinct association of HLA class II alleles with anti-NF155 antibody-positive CIDP was reported in Europeans (Martinez-Marinez et al., 2017), future studies on HLA class II antigen-restricted T cells are called for to decipher the mechanism of this condition.

Another important issue is the mechanism by which IgG4 antibodies to nodal and paranodal proteins emerge. IgG4 antibodies can block antibodies that alleviate allergic inflammation by interfering with the binding of allergen-specific IgE to allergens. IgG4 class switch requires help from type 2 follicular helper T cells producing IL-4, IL-10 and IL-13. Thus, environmental antigens cross-reacting with nodal and paranodal proteins may be important to study in future.

Acknowledgments

This study was supported by a Health and Labour Sciences Research Grant on Intractable Diseases [H29-Nanchitou (Nan)-Ippan-043] from the Ministry of Health, Labour, and Welfare, Japan, by the “Practical Research Project for Rare/Intractable Diseases” from the Japan Agency for Medical Research and Development (AMED, 17ek0109115h0003), Japan, by a research grant from the Japanese Multiple Sclerosis Society, by a research grant from the Japan Intractable Disease Research Foundation, by “Glial Assembly” Grants-in-Aid for Scientific Research on Innovative Areas (MEXT KAKENHI Grant Number 25117012) from the Ministry of Education, Culture, Sports, Science and Technology of Japan, and by a Grant-in-Aid for Scientific Research (A) (JSPS KAKENHI Grant Number 16H02657) from the Japan Society for the Promotion of Science, Japan. We thank Jeremy Allen, PhD, from Edanz Group (www.edanzediting.com/ac) for editing a draft of this manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neuint.2018.12.011.

References

Azevedo, C.J., Cen, S.Y., Khadka, S., Liu, S., Kornak, J., Shi, Y., Zheng, L., Hauser, S.L., Pelletier, D., 2018. Thalamic atrophy in multiple sclerosis: a magnetic resonance imaging marker of neurodegeneration throughout disease. Ann. Neurol. 83, 223–234.

Boyle, M.E.T., Berglund, E.O., Murai, K.K., Weber, L., Peles, E., Ranscht, B., 2001. Contactin orchestrates assembly of the septate-like junctions at the paranode in myelinated peripheral nerve. Neuron 30, 385–397.

Davis, J.Q., Lambert, S., Bennett, V., 1996. Molecular composition of the node of Ranvier: identification of ankyrin-binding cell adhesion molecules neurofascin (mucin+/third FNIII domain-) and NrCAM at nodal axon segments. J. Cell Biol. 135, 1355–1367.

Devaux, J.J., Odaka, M., Yuki, N., 2012. Nodal proteins are target antigens in Guillain-Barré syndrome. J. Peripher. Nerv. Syst. 17, 62–71.

Devaux, J.J., Miura, Y., Fukami, Y., Inoue, T., Manso, C., Belghazi, M., Sekiguchi, K., Kokubun, N., Ichikawa, H., Wong, A.H.Y., Yuki, N., 2016. Neurofascin-155 IgG4 in chronic inflammatory demyelinating polyneuropathy. Neurology 86, 800–807.

Doppler, K., Appeltshauser, L., Wilhelmi, K., Villmann, C., Dib-Hajj, S.D., Waxman, S.G., Mäurer, M., Weishaupt, A., Sommer, C., 2015. Destruction of paranodal architecture in inflammatory neuropathy with anti-contactin-1 autoantibodies. J. Neurol. Neurosurg. Psychiatry 86, 720–728.

Doppler, K., Appeltshauser, L., Villmann, C., Martin, C., Peles, E., Krämer, H.H., Haarmann, A., Buttmann, M., Sommer, C., 2016. Auto-antibodies to contactin-associated protein 1 (Caspr) in two patients with painful inflammatory neuropathy. Brain 139, 2617–2630.

Franques, J., Chapon, F., Devaux, J., Mathis, S., 2017. Teaching Neuro*Images*: cranial nerve hypertrophy in IgG4 anti-neurofascin 155 antibody-positive polyneuropathy. Neurology 88, e52. https://doi.org/10.1212/WNL.0000000000003616.

Fisniku, L.K., Brex, P.A.P., Altmann, D.R., Miszkiel, K.A., Benton, C.E.C., Lanyon, R., Thompson, A.J., Miller, D.H., 2008. Disability and T2 MRI lesions: a 20-year follow-up of patients with relapse onset of multiple sclerosis. Brain 131, 808–817.

Flytzani, S., Guerreiro-Cacais, A.O., N'diaye, M., Lindner, M., Linington, C., Meinl, E., Stridh, P., Jagodic, M., Olsson, T., 2015. MOG-induced experimental autoimmune encepahlomyelitis in the rat species triggers anti-neurofascin antibody response that is genetically regulated. J. Neuroimflamm. 12, 194. https://doi.org/10.1186/s12974-012-0417-2.

Fujita, A., Ogata, H., Yamasaki, R., Matsushita, T., Kira, J., 2018. Parallel Fluctuation of anti-neurofascin 155 antibody levels with clinico-electorophysilological findings in patients with chronic inflammatory demyelinating polyradiculoneuropathy. J. Neurol. Sci. 384, 107–112.

Guidelines, P.N.S.C., 2010. European federation of neurological societies/peripheral nerve society guideline on management of chronic inflammatory demyelinating polyradiculoneuropathy: report of a joint task force of the european federation of neurological societies and the peripher. J. Peripher. Nerv. Syst. 15, 1–9.

Hertl, M., Jedlickova, H., Karpati, S., Marinovic, B., Uzun, S., Yayli, S., Mimouni, D., Borradori, L., Feliciani, C., Ioannides, D., Joly, P., Kowalewski, C., Zambruno, G., Zillikens, D., Jonkman, M.F., 2015. Pemphigus. S2 guideline for diagnosis and treatment - guided by the european dermatology forum (EDF) in cooperation with the european academy of dermatology and venereology (EADV). J. Eur. Acad. Dermatol. Venereol. 29, 405–414.

Howell, O.W., Palser, A., Polito, A., Melrose, S., Zonta, B., Scheiermann, C., Vora, A.J., Brophy, P.J., Reynolds, R., 2006. Disruption of neurofascin localization reveals early changes preceding demyelination and remyelination in multiple sclerosis. Brain 129, 3173–3185.

Huijbers, M.G., Querol, L.A., Niks, E.H., Plomp, J.J., van der Maarel, S.M., Graus, F., Dalmau, J., Illa, I., Verschuuren, J.J., 2015. The expanding field of IgG4-mediated neurological autoimmune disorders. Eur. J. Neurol. 22, 1151–1161.

Hiwatashi, A., Togao, O., Yamashita, K., Kikuchi, K., Ogata, H., Yoneyama, M., Kira, J., Honda, H., 2017. Evaluation of chronic inflammatory demyelinating polyneuropathy: 3D nerve-sheath signal increased with inked rest-tissue rapid acquisition of relaxation enhancement imaging (3D SHINKEI). Eur. Radiol. 27, 447–453.

Kadoya, M., Kaida, K., Koike, H., Takazaki, H., Ogata, H., Moriguchi, K., Shimizu, J., Nagata, E., Takizawa, S., Chiba, A., Yamasaki, R., Kira, J., Sobue, G., Ikewaki, K., 2016. IgG4 anti-neurofascin155 antibodies in chronic inflammatory demyelinating polyradiculoneuropathy: clinical significance and diagnostic utility of a conventional assay. J. Neuroimmunol. 301, 16–22.

Kamm, C., Zettl, U.K., 2012. Autoimmune disorders affecting both the central and peripheral nervous system. Autoimmun. Rev. 11, 196–202.

Kawamura, N., Yamasaki, R., Yonekawa, T., Matsushita, T., Kusunoki, S., Nagayama, S., Fukuda, Y., Ogata, H., Matsuse, D., Murai, H., Kira, J., 2013. Anti-neurofascin antibody in patients with combined central and peripheral demyelination. Neurology 81, 714–722.

Koike, H., Kadoya, M., Kaida, K., Ikeda, S., Kawagashira, Y., Iijima, M., Kato, D., Ogata, H., Yamasaki, R., Matsukawa, N., Kira, J., Katsuno, M., Sobue, G., 2017. Paranodal dissection in chronic inflammatory demyelinating polyneuropathy with anti-neurofascin-155 and anti-contactin-1 antibodies. J. Neurol. Neurosurg. Psychiatry 88, 465–473.

Kriebel, M., Wuchter, J., Trinks, S., Volkmer, H., 2012. Neurofascin: a switch between neuronal plasticity and stability. Int. J. Biochem. Cell Biol. 44, 694–697.

Kuwahara, M., Suzuki, H., Oka, N., Ogata, H., Yanagimoto, S., Sadakane, S., Fukumoto, Y., Yamana, M., Yuhara, Y., Yoshikawa, K., Morikawa, M., Kawai, S., Okazaki, M., Tsujimoto, T., Kira, J., Kusunoki, S., 2018. Electron microscopic abnormality and therapeutic efficacy in chronic inflammatory demyelinating polyneuropathy with anti-neurofascin 155 immunoglobulin G4 antibody. Muscle Nerve 57, 498–502.

Li, D.K., Held, U., Petkau, J., Daumer, M., Barkhof, F., Fazekas, F., Frank, J.A., Kappos, L., Miller, D.H., Simon, J.H., Wolinsky, J.S., Filippi, M., Sylvia Lawry Centre for MS Research., 2006. MRI T2 lesion burden in multiple sclerosis: a plateauing relationship with clinical disability. Neurology 66, 1384–1389.

Martinez-Marinez, L., Cinta Lleixà, M., Boera-Carnicero, G., Cortese, A., Devaux, J., Siles, A., Rajabally, Y., Martinez-Piñeiro, A., Carvajal, A., Pardo, J., Delmont, E., Attarian, S., Diaz-Manera, J., Callegari, I., Marchioni, E., Franciotta, D., Benedetti, L., Lauria, G., de la Calle Martin, O., Juárez, C., Illa, I., Querol, L., 2017. Anti-NF155 chronic inflammatory demyelinating polyradiculoneuropathy strongly associates to HLA-DRB15. J. Neuroinflammation 14, 224. https://doi.org/10.1186/s12974-017-0996-1.

Mathey, E.K., Derfuss, T., Storch, M.K., Williams, K.R., Hales, K., Woolley, D.R., Al-Hayani, A., Davies, S.N., Rasband, M.N., Olsson, T., Moldenhauer, A., Velhin, S., Hohlfeld, R., Meiml, E., Linington, C., 2007. Neurofascin as a novel target for autoantibody-mediated axonal injury. J. Exp. Med. 204, 2363–2372.

Miura, Y., Devaux, J.J., Fukami, Y., Manso, C., Belghazi, M., Wong, A.H.Y., Yuki, N., 2015. Contactin 1 IgG4 associates to chronic inflammatory demyelinating polyneuropathy with sensory ataxia. Brain 138, 1484–1491.

Ng, J.K.M., Malotka, J., Kawakami, N., Derfuss, T., Khademi, M., Olsson, T., Linington, C., Odaka, M., Tackenberg, B., Prüss, H., Schwab, J.M., Harms, Harms, L.H., Sommer, C., Rasband, M.N., Eshed-Eisenbach, Y., Peles, E., Hohlfeld, R., Yuki, N., Dornmair, K., Meinl, E., 2012. Neurofascin as a target for autoantibodies in peripheral neuropathies. Neurology 79, 2241–2248.

Ogata, H., Yamasaki, R., Hiwatashi, A., Oka, N., Kawamura, N., Matsuse, D., Kuwahara, M., Suzuki, H., Kusunoki, S., Fujimoto, Y., Ikezoe, K., Kishida, H., Tanaka, F., Matsushita, T., Murai, H., Kira, J., 2015. Characterization of IgG4 anti-neurofascin 155 antibody-positive polyneuropathy. Ann. Clin. Transl. Neurol. 2, 960–971.

Ogata, H., Matsuse, D., Yamasaki, R., Kawamura, N., Matsushita, T., Yonekawa, T., Hirotani, M., Murai, H., Kira, J., 2016. A nationwide survey of combined central and peripheral demyelination in Japan. J. Neurol. Neurosurg. Psychiatry 87, 29–36.

Pedraza, L., Huang, J.K., Colman, D.R., 2001. Organizing principles of the axoglial apparatus. Neuron 30, 335–344.

Pillai, A.M., Thaxton, C., Pribisko, A.L., Cheng Jr., G., Dupree, J.L., Bhat, M.A., 2009. Spatiotemporal ablation of myelinating glia-specific Neurofascin (NfasNF155) in mice reveals gradual loss of paranodal axoglial junctions and concomitant disorganization of axonal domains. J. Neurosci. Res. 87, 1773–1793.

Polman, C.H., Reingold, S.C., Banwell, B., Clanet, M., Cohen, J.A., Filippi, M., Fujihara, K., Havrdova, E., Hutchinson, M., Kappos, L., Lublin, F.D., Montalban, X., O'Connor, P., Sandberg-Wollheim, M., Thompson, A.J., Waubant, E., Weinshenker, B., Wolinsky, J.S., 2011. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. Ann. Neurol. 69, 292–302.

Querol, L., Nogales-Gadea, G., Rojas-Garcia, R., Martinez-Hernandez, E., Diaz-Manera, J., Suárez-Calvet, X., Navas, M., Araque, J., Gallardo, E., Illa, I., 2013. Antibodies to contactin-1 in chronic inflammatory demyelinating polyneuropathy. Ann. Neurol. 73, 370–380.

Querol, L., Nogales-Gadea, G., Rojas-Garcia, R., Diaz-Manera, J., Pardo, J., Ortega-Moreno, A., Sedano, M.J., Gallardo, E., Berciano, J., Blesa, R., Dalmau, J., Illa, I., 2014. Neurofascin IgG4 antibodies in CIDP associate with disabling tremor and poor response to IVIg. Neurology 82, 879–886.

Querol, L., Rojas-García, R., Diaz-Manera, J., Barcena, J., Pardo, J., Ortega-Moreno, A., Sedano, M.J., Seró-Ballesteros, L., Carvajal, A., Ortiz, N., Gallardo, E., Illa, I., 2015. Rituximab in treatment-resistant CIDP with antibodies against paranodal proteins. Neurol. Neuroimmunol. Neuroinflammation 2, e149.

Scully, M., Hunt, B.J., Benjamin, S., Liesner, R., Rose, P., Peyvandi, F., Cheung, B., Machin, S.J., British Committee for Standards in Haematology, 2012. Guidelines on the diagnosis and management of thrombotic thrombocytopenic purpura and other thrombotic microangiopathies. Br. J. Haematol. 158, 323–335.

Sherman, D.L., Tait, S., Melrose, S., Melrose, S., Johnson, R., Zonta, B., Court, F.A., Macklin, W.B., Meek, S., Smith, A.J.H., Cottrell, D.F., Brophy, P.J., 2005. Neurofascins are required to establish axonal domains for saltatory conduction. Neuron 48, 737–742.

Stathopoulos, P., Alexopoulos, H., Dalakas, M.C., 2015. Autoimmune antigenic targets at the node of Ranvier in demyelinating disorders. Nat. Rev. Neurol. 11, 143–156.

Stich, O., Perera, S., Berger, B., Jarius, S., Wildemann, B., Baumgartner, A., Rauer, S., 2016. Prevalence of neurofascin-155 antibodies in patients with multiple sclerosis. J. Neurol. Sci. 364, 29–32.

Tait, S., Gunn-Moore, F., Collinson, J.M., Huang, J., Lubetzki, C., Pedraza, L., Sherman, D.L., Colman, D.R., Brophy, P.J., 2000. An oligodendrocyte cell adhesion molecule at the site of assembly of the paranodal axo-glial junction. J. Cell Biol. 150, 657–666.

Thaxton, C., Pillai, A.M., Pribisko, A.L., Dupree, J.L., Bhat, M., 2011. Nodes of Ranvier act as barriers to restrict invasion of flanking paranodal domains in myelinated axons. Neuron 69, 244–257.

Yan, W., Nguyen, T., Yuki, N., Ji, Q., Yiannikas, C., Pollard, J.D., Mathey, E.K., 2014. Antibodies to neurofascin exacerbate adoptive transfer experimental autoimmune neuritis. J. Neuroimmunol. 277, 13–17.