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REVIEW

Pathophysiology of Chronic Inflammatory Demyelinating Polyneuropathy: Insights into Classification and Therapeutic Strategy

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ABSTRACT

Chronic inflammatory demyelinating polyneuropathy (CIDP) is classically defined as polyneuropathy with symmetric involvement of the proximal and distal portions of the limbs. In addition to this "typical CIDP", the currently prevailing diagnostic criteria proposed by the European Federation of Neurological Societies and Peripheral Nerve Society (EFNS/PNS) define "atypical CIDP" as encompassing the multifocal acquired demyelinating sensory and motor (MADSAM), distal acquired demyelinating symmetric (DADS), pure sensory, pure motor, and focal subtypes. Although macrophage-induced demyelination is considered pivotal to the pathogenesis of CIDP, recent studies have indicated the presence of distinctive mechanisms initiated by autoantibodies against paranodal junction proteins, such as neurofascin 155 and contactin 1. These findings led to the emergence of the concept of nodopathy or paranodopathy. Patients with these antibodies tend to show clinical features compatible with typical CIDP or DADS, particularly the latter. In contrast, classical macrophage-induced demyelination is commonly found in some patients in each major subtype, including the typical CIDP, DADS, MADSAM, and pure sensory subtypes. Differences in the distribution of lesions and the repair processes underlying demyelination by Schwann cells may determine the differences among subtypes. In particular, the preferential involvement of proximal and distal nerve segments has been suggested to occur in typical CIDP, whereas the involvement of the middle nerve segments is conspicuous in MADSAM. These findings suggest that humoral rather than cellular immunity predominates in the former because nerve roots and neuromuscular junctions lack blood–nerve barriers. Treatment for CIDP consists of intravenous immunoglobulin (IVIg) therapy, steroids, and plasma exchange, either alone or in combination. However, patients with anti-neurofascin 155 and contactin 1 antibodies are refractory to IVIg. It has been suggested that rituximab, a monoclonal antibody to CD20, could have efficacy in these patients. Further studies are needed to validate the CIDP subtypes defined by the EFNS/PNS from the viewpoint of pathogenesis and establish therapeutic strategies based on the pathophysiologies specific to each subtype.

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Paranode; Pathogenesis; Pathology; Schwann cell; Treatment; Ultrastructure

Key Summary Points

Chronic inflammatory demyelinating polyneuropathy (CIDP) is an acquired immune-mediated neuropathy characterized by heterogeneous clinical manifestations.

Although CIDP is clinically divided into six subtypes, including the typical CIDP, multifocal acquired demyelinating sensory and motor (MADSAM), distal acquired demyelinating symmetric (DADS), pure sensory, pure motor, and focal forms, no biomarkers specific to each clinical subtype have been identified.

Demyelination induced by macrophages is commonly found in some patients in each major subtype, including the typical CIDP, DADS, MADSAM, and pure sensory subtypes.

Recent studies revealed that some patients with typical CIDP and DADS have mechanisms of neuropathy distinct from classical macrophage-induced demyelination through IgG4 autoantibodies against nodal or paranodal components, such as neurofascin 155 and contactin 1.

Further studies are needed to validate the CIDP subtypes from the viewpoint of pathogenesis and establish therapeutic strategies based on the pathophysiologies specific to each subtype.

INTRODUCTION

Chronic inflammatory demyelinating polyneuropathy (CIDP) is a chronic neuropathy that has classically been characterized by demyelination resulting from immune-mediated processes [1–11]. Since recurrent polyneuropathy responsive to corticosteroid treatment was first reported in 1958 [12], the number of reports describing patients with chronic, immune-mediated neuropathy has increased over time. An entity of CIDP was established in 1975 in a study that assessed 53 patients [1]. These patients were characterized by steady or stepwise progression or recurrence of neuropathy, symmetric involvement of the proximal and distal portions of the limbs, and slowing of nerve conduction velocity. The authors described macrophage-induced segmental demyelination as the pathological characteristic of the peripheral nervous system. Since then, the role of macrophages in the pathogenesis of CIDP has attracted attention. In response to this trend, the presence of demyelination assessed by either electron microscopy or teased-fiber study became mandatory for a definitive diagnosis based on the research criteria proposed by the Ad Hoc Subcommittee of the American Academy of Neurology AIDS Task Force in 1991 [13]. More recent criteria proposed by the European Federation of Neurological Societies and Peripheral Nerve Society (EFNS/PNS) regard this feature as a supportive criterion [14]. The characteristics of the EFNS/PNS criteria encompass cases presenting as “atypical CIDP” based on anecdotal reports of cases showing atypical clinical manifestations [14]. Although the clinical spectrum of CIDP has expanded from the viewpoint of symptomatology, no biomarkers of these clinical subtypes have been identified. In contrast, recent studies revealed that IgG4 autoantibodies to paranodal junction proteins, such as neurofascin 155 and contactin 1, were present in approximately 5–10% of patients diagnosed with CIDP [15–23]. The pathological characteristic that defines these patients is the absence of classical macrophage-induced demyelination in mechanisms resulting in aberrant nerve conduction [23]. Therefore, from a pathophysiological viewpoint, there are at least two distinctive forms of CIDP.

In this article, we explored the relationship between the symptomatology and pathophysiology of CIDP to gain insights into its classification and potential therapeutic strategies. This article is based on previously conducted studies

and does not contain any studies with human participants or animals performed by any of the authors.

CURRENT CLASSIFICATION OF CIDP

As described above, CIDP was initially defined as neuropathy with diffuse weakness of the limbs [1, 13]. In the EFNS/PNS criteria, which are now frequently used in clinical practice, this classical form of CIDP was designated "typical CIDP" [14]. Typical CIDP is defined as the development of neuropathy with chronically progressive, stepwise, or recurrent symmetrical proximal and distal weakness and sensory dysfunction over at least 2 months [14]. In addition to typical CIDP, the EFNS/PNS criteria define five forms of "atypical CIDP", including the multifocal acquired demyelinating sensory and motor (MADSAM), distal acquired demyelinating symmetric (DADS), pure sensory, pure motor, and focal subtypes [14]. Patients with these variable subtypes of CIDP, as defined in the EFNS/PNS criteria, are diagnosed comprehensively on the basis of symptoms/signs, electrodiagnostic criteria, and other supportive criteria. Nevertheless, a recent development in neuroimaging techniques enabled the discovery of patients suspected of having chronic inflammation of the peripheral nerve similar to that observed in CIDP but that did not fulfill its EFNS/PNS electrodiagnostic criteria [11, 24]. In addition, some patients with CIDP initially manifest an acute, but not chronic, disease onset mimicking Guillain–Barré syndrome (GBS) [25].

The definitions of these subtypes, as defined in the EFNS/PNS criteria, are based only on the distribution and relative involvement of weakness and sensory deficits and not on biomarkers specific to each subtype. It has been shown that patients with anti-neurofascin 155 and contactin 1 antibodies manifest either typical CIDP or DADS, particularly the latter [16, 19–23]. Recent studies reported that antibodies to LM1 and LM1-containing ganglioside complexes that are abundant in myelin have also been found in some patients with typical CIDP [26–28]. However, these antibody-positive cases represent a minority of patients with CIDP, even among those with typical CIDP and DADS [29].

In a recent study of 106 consecutive patients with CIDP who fulfilled the EFNS/PNS diagnostic criteria but were negative for anti-neurofascin 155, contactin 1, or LM1 antibodies, 55 (52%) patients were classified as having typical CIDP. Regarding atypical CIDP, the MADSAM (n = 15, 14%), DADS (n = 16, 15%), and pure sensory (n = 15, 14%) forms were the major subtypes, while the pure motor (n = 4, 4%) and focal (n = 1, 1%) forms were rare [29]. Some studies have suggested that patients show a similar proportion of CIDP subtypes, although antibody-positive patients were not excluded in these studies [30, 31], whereas others have indicated that the frequencies of typical CIDP, MADSAM, or pure sensory subtypes were higher [32–34]. An Italian study that registered 460 patients suggested that conversion from atypical CIDP to typical CIDP occurred during the disease course [31]. In contrast, a patient with neurofascin 155 antibody-positive typical CIDP who evolved to DADS has also been reported [35]. These findings indicate that the mechanisms leading to these clinical subtypes may overlap to some extent. From this viewpoint, deciphering the mechanisms that determine these clinical subtypes is important to validating their definitions.

TWO DISTINCTIVE MECHANISMS OF CIDP

Macrophage-Induced Demyelination: A Classical Concept

Demyelination resulting from phagocytosis of myelin by macrophages has been proposed to play an important role in the pathogenesis of CIDP [1, 5, 7, 9, 36–38]. A recent study revealed that this so-called macrophage-induced demyelination was found not only in typical CIDP but also in major atypical CIDP subtypes, including the MADSAM, DADS, and pure sensory subtypes, although it was not found in all patients [29]. In teased-fiber preparations of

sural nerve biopsy specimens obtained from these patients, segments devoid of myelin as a result of phagocytosis by macrophages were observed (Fig. 1a). Additionally, macrophages surrounding myelinated fibers were observed on cross sections of epoxy-resin-embedded specimens (Fig. 1b). Electron microscopy studies revealed that these macrophages were located within the tubes of the basement membrane that normally surrounds myelinated fibers and contained myelin debris in their cytoplasm (Fig. 1c). The layers of myelin lamellae that were

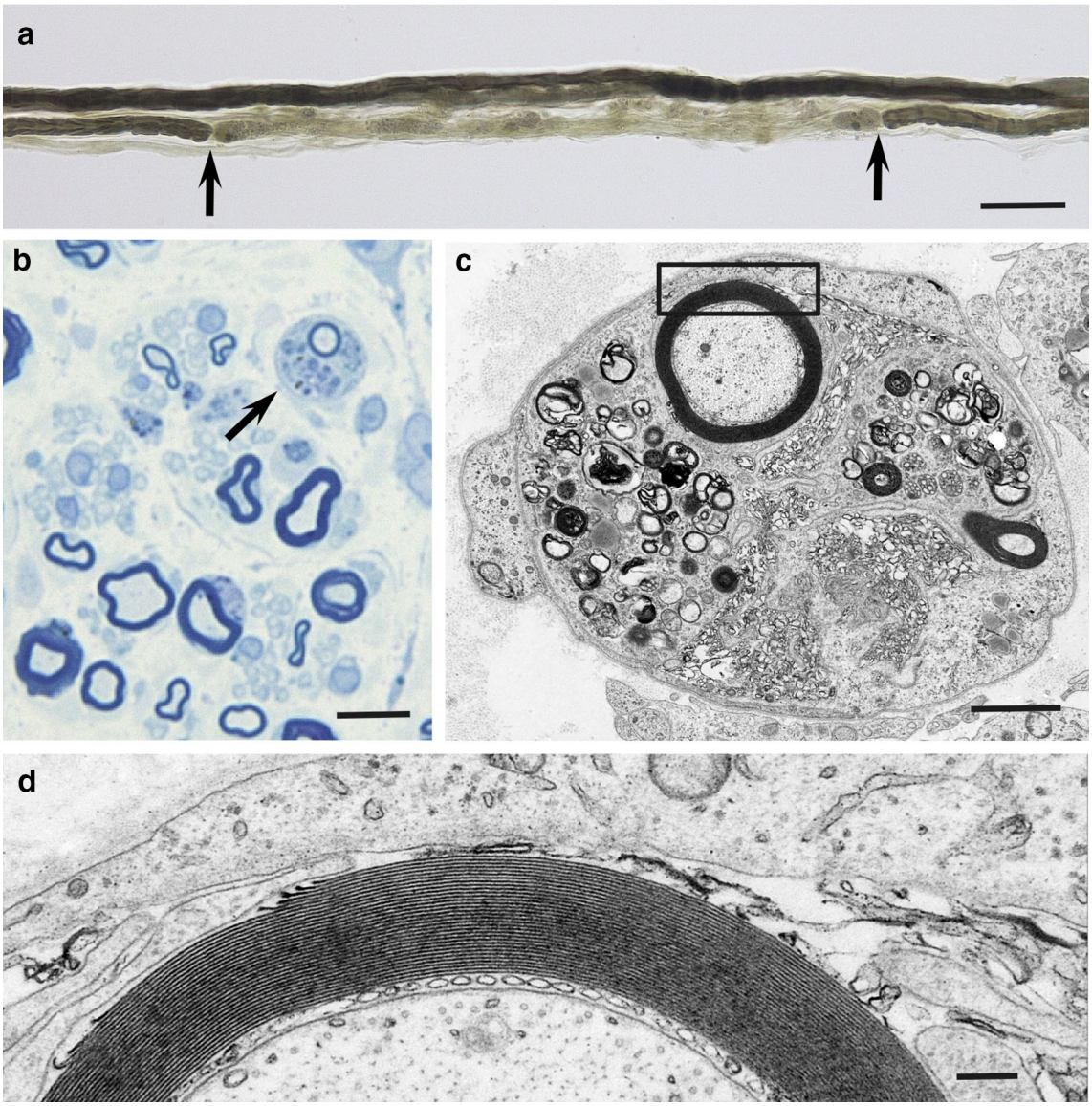

Fig. 1 Representative photographs of macrophage-induced demyelination. Sural nerve biopsy specimens obtained from a patient with typical CIDP. **a** Teased-fiber preparations showing segments devoid of myelin (indicated by arrows) as a result of phagocytosis by macrophages. **b** Cross sections of epoxy-resin-embedded specimens showing macrophages surrounding myelinated fibers (arrow). **c** Electron microscopy showing that these macrophages contain myelin debris in their cytoplasm. A high-powered view of the region shown in the box in **c** is shown in **d**. **d** Layers of myelin lamellae apposed to the cytoplasm of macrophages become fuzzy as a result of the disruption of myelin lamellae. Osmium stain (**a**), toluidine blue stain (**b**), and uranyl acetate and lead citrate stain (**c**, **d**). Scale bars 50 μm (**a**), 10 μm (**b**), 2 μm (**c**), and 0.2 μm (**d**)

apposed to the cytoplasm of these macrophages become fuzzy as a result of the disruption of the myelin lamellae (Fig. 1d). The macrophages seemed to be melting the myelin, indicating that proteases secreted by these macrophages may be involved in the formation of these lesions, as was suggested in previous animal studies [39]. In addition, the stripping of myelin lamellae by the thin cytoplasmic processes of macrophages may also be observed in association with macrophage-induced demyelinating processes [9, 36]. The cytoplasmic processes of these macrophages extend through the intraperiod line between adjacent major dense lines [9]. Notably, macrophages seem to be able to destroy structurally normal myelin lamellae [9, 36]. In contrast, axolemma remains intact even when closely apposed to the cytoplasmic membranes of macrophages. In addition, the cytoplasm of Schwann cells located at the outermost layer of myelinated fibers seems to be safe from phagocytosis by macrophages [9]. Therefore, remnants of Schwann cell cytoplasm were observed within the basement membrane even though macrophages were able to escape from the basement membrane tube after they completely phagocytosed the myelin [9].

The factors that trigger the phagocytosis of myelin by macrophages have not been identified. In a recent electron microscopy study of longitudinal sections of sural nerve biopsy specimens obtained from patients with CIDP, macrophages seemed to act at specific sites on myelinated fibers [9]. The site at which macrophages initiate invasion of the inner space of the basement membrane tube surrounding myelinated fibers was the area around the node of Ranvier in some of the patients but the internode in others. This finding may indicate that specific components distinguish nodal regions, such as the nodes of Ranvier and paranodes, from internodes may play a pivotal role in the mechanisms triggering macrophage-induced demyelination. Therefore, the deposition of some undiscovered autoantibodies at peripheral nerve components may trigger the phagocytosis of myelin by macrophages via the recognition of immunoglobulin Fc portions or complements triggered by autoantibodies. Macrophage-induced demyelination was reported in a patient with antibodies to LM1, a major human peripheral nerve glycolipid [28]. In that patient, the deposition of complement C9 neoantigen on myelin was also demonstrated [28].

A recent electron microscopy study of sural nerve biopsy specimens obtained from patients with the demyelinating form of GBS (i.e., acute inflammatory demyelinating polyneuropathy; AIDP) demonstrated macrophage-induced demyelination, which was morphologically indistinguishable from the demyelination observed in CIDP [40]. The concept that molecular mimicry by foreign epitopes in infectious agents of self epitopes in the peripheral nervous system could lead to the production of autoantibodies has been established in the axonal form of GBS (i.e., acute motor axonal neuropathy; AMAN) [41]. The deposition of autoantibodies at the nodal axolemma of motor fibers results in the activation of complement cascades, leading to axonal damage [42]. The deposition of complements has also been demonstrated in patients with AIDP [40, 43]. A similar mechanism may be the initial step of the immunological cascade in a subpopulation of patients with CIDP, particularly in those manifesting acute progression mimicking GBS [25]. However, studies of CIDP have not yet revealed a direct association between autoantibodies and the phagocytosis of myelin by macrophages except in the previously mentioned patient with anti-LM1 antibodies [28]. Another possible first step may be triggered by resident macrophages in the peripheral nervous system that may act as antigen-presenting cells [44]. The abnormal recognition of some myelin epitopes by these macrophages may act as the initial trigger in the pathogenesis of CIDP [44].

Nodo-Paranodopathy Caused by IgG4 Autoantibodies: Another Emerging Concept

Recent studies have suggested that autoantibodies against components present at the nodes of Ranvier and paranodes may be present in some of the patients diagnosed with typical CIDP and DADS [9, 23, 45–49]. In particular,

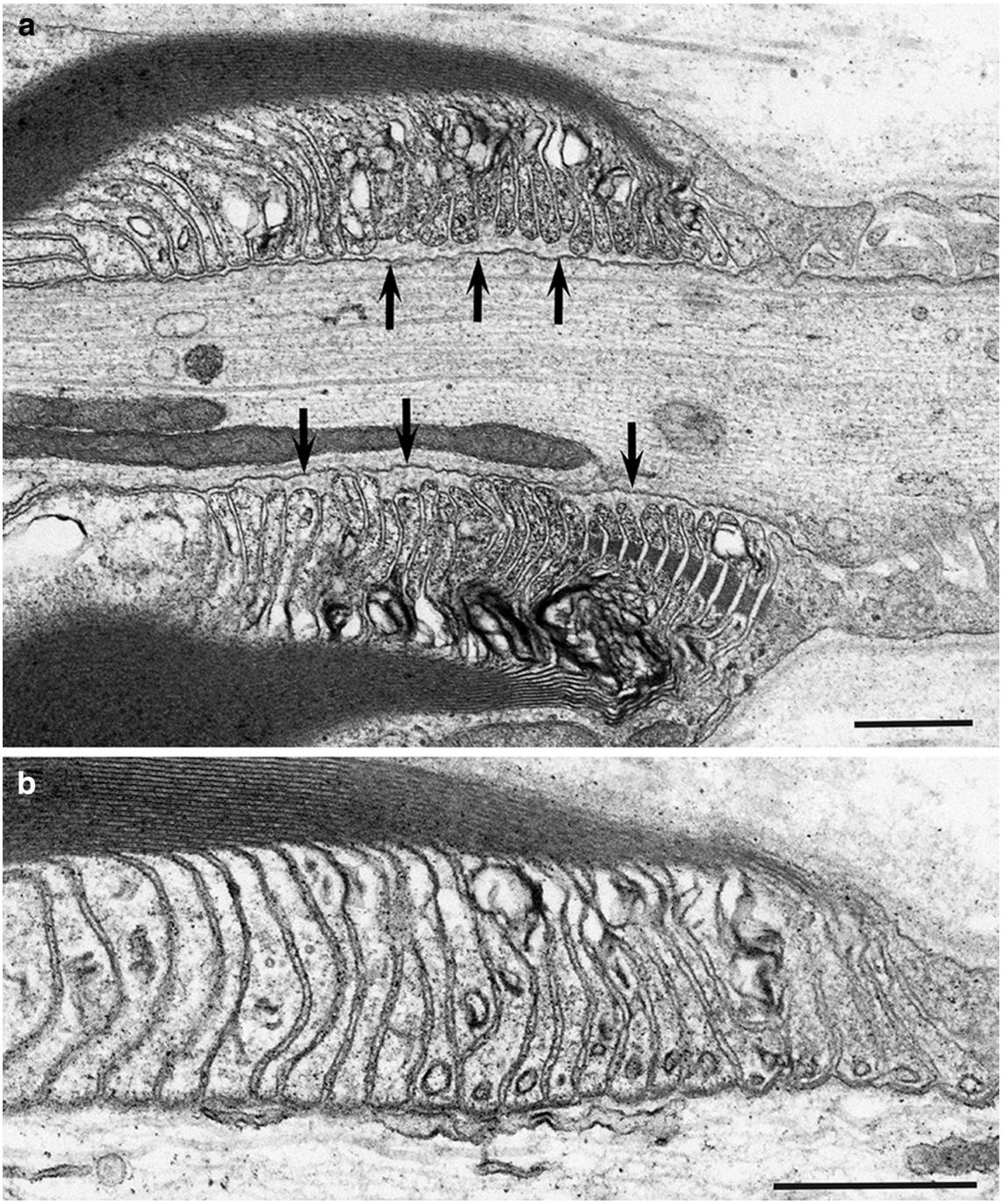

Fig. 2 Representative electron microscopy photograph of paranodal dissection. Sural nerve biopsy specimens obtained from a patient with anti-neurofascin 155 antibodies (**a**) and a control subject (**b**). Longitudinal sections. **a** Clear spaces are shown between the myelin terminal loops and axolemma (arrows). **b** Normally, the terminal loops of myelin are closely apposed to the axolemma at paranodes. Uranyl acetate and lead citrate stain. Scale bars 0.5 μm

IgG4 antibodies, such as anti-neurofascin 155 and anti-contactin 1 antibodies, against components at the paranodal junctions between myelin terminal loops and axolemma have attracted attention by researchers [15–23]. Patients with these antibodies show characteristic clinical features, such as sensory ataxia, tremor, and unresponsiveness to intravenous immunoglobulin (IVIg) therapy [9, 16, 17, 19–22]. Other reports have suggested that other IgG4 antibodies, such as those against paranodal contactin-associated protein 1 and nodal neurofascin 140/186, may be potential target antigens in patients with CIDP [47, 50].

The typical pathological features observed on cross sections of sural nerve biopsy specimens obtained from patients with anti-neurofascin 155 and anti-contactin 1 antibodies were summarized as including conspicuous endoneurial edema, a slight reduction of myelinated fiber density due to axonal degeneration, the absence of inflammatory cellular infiltration including macrophages responsible for demyelination, and no onion bulb formation [23]. An important point suggested by these observations is that the mechanisms underlying the neuropathy caused by these antibodies are distinct from the classical concept of macrophage-induced demyelination that has so far been considered to be the pathogenesis of CIDP. Because the immunoglobulin subclass of anti-neurofascin 155 and anti-contactin 1 antibodies is IgG4 [17, 19–23], the deposition of these antibodies does not provoke inflammatory processes [23]. Immunofluorescent studies of sural nerve biopsy specimens obtained from patients with anti-neurofascin 155 and anti-contactin 1 antibodies revealed that the deposition of complements was not observed at the paranodes at which IgG4 deposition was detected [23]. However, electron microscopy studies on longitudinal sections revealed the detachment of paranodal myelin terminal loops from the axolemma [9, 23, 51], a process that was called paranodal dissection (Fig. 2) [23]. Hence, the deposition of IgG4 and the subsequent morphological changes observed at paranodal junctions may result in nerve conduction abnormalities unrelated to classical macrophage-induced demyelination in patients with anti-neurofascin 155 and anti-contactin 1 antibodies [23]. Based on these findings, the concept of nodopathy or paranodopathy has recently been proposed for patients with IgG4 antibodies to nodal and paranodal components [46, 49].

WHAT DETERMINES CLINICAL SUBTYPE?

As described earlier, CIDP is clinically divided into six subtypes, including the typical CIDP, MADSAM, DADS, pure sensory, pure motor, and focal forms, according to the EFNS/PNS criteria [14]. Although these six subtypes of CIDP share common electrodiagnostic features that are suggestive of demyelination, the mechanisms that govern their differential clinical manifestations have not been clarified. In an early report describing patients with typical CIDP, macrophage-induced demyelination, as mentioned earlier, was designated as a characteristic feature [1]. According to a study that assessed sural nerve biopsy specimens obtained from patients with major clinical subtypes (i.e., typical CIDP, MADSAM, DADS, and pure sensory forms), macrophage-induced demyelination was commonly observed in some of the patients in each major subtype [29]. Other reports that explored MADSAM [52, 53], DADS [54], and pure sensory forms [55] also suggested the presence of active demyelination with or without onion bulb formation that likely resulted from the phagocytosis of myelin by macrophages. These findings indicate that at least some of the patients in individual major clinical subtypes share common mechanisms associated with macrophage-induced demyelination.

The clinical manifestations of CIDP may be determined by the distribution of lesions in the peripheral nervous system. For example, electrophysiological findings have suggested that the distribution of lesions in the peripheral nervous system determines the manifestations of typical CIDP and MADSAM [29, 34]. Compared to patients with MADSAM, in patients with typical CIDP, abnormalities in electrophysiological indices representing the

conduction of distal nerve segments, such as distal motor latencies and sensory nerve conduction velocities, were more conspicuous than conduction slowing in the middle nerve segments, such as motor conduction velocities The prolongation of F-wave latencies, which include conduction at proximal nerve segments, was also more conspicuous in patients with typical CIDP than in patients with MADSAM. These findings may indicate that compared to MADSAM, typical CIDP exhibits preferential involvement of the proximal and distal nerve segments, particularly nerve roots and neuromuscular junctions. Because blood–nerve barriers are deficient in nerve roots and neuromuscular junctions, humoral factors, such as autoantibodies to myelin components, may play an important role in the mechanisms that induce neuropathy in typical CIDP [56]. In support of this view, the increase in cerebrospinal fluid protein levels, which indicates the presence of lesions at proximal nerve segments, was more conspicuous in patients with typical CIDP than in patients with MADSAM [29]. In addition, in patients with anti-neurofascin 155 antibodies, serum IgG4 plays a pivotal role in the pathogenesis of neuropathy [23], and these patients also showed more marked electrophysiological abnormalities at the proximal and distal nerve segments than were observed in patients with CIDP without these antibodies [20]. In contrast, lesions in the middle nerve segments may characterize the electrophysiological features in MADSAM [29, 34]. In accordance with these findings, studies using ultrasonography or magnetic resonance imaging (MRI) demonstrated patchy swelling of the nerve trunk in patients with MADSAM, whereas these imaging techniques revealed hypertrophy predominantly in the nerve roots in patients with typical CIDP and anti-neurofascin 155 antibody-positive patients [20, 57, 58].

From the viewpoint of pathology of the sural nerve, a recent study demonstrated that variation in myelinated fiber density among fascicles tended to be absent or only mild in patients with typical CIDP even when macrophage-induced demyelination was observed [29]. In contrast, marked variation in myelinated fiber density among fascicles was observed in some of the patients with major atypical CIDP subtypes, including those with the MADSAM, DADS, and pure sensory subtypes (Fig. 3a), particularly in patients with findings suggestive of macrophage-induced demyelination [29]. The loss of myelinated fibers due to axonal degeneration and mild onion bulb formation has been observed in areas of reduced myelinated fiber density in patients with MADSAM (Fig. 3b), whereas the reduction of myelinated fiber density seemed to result from an enlargement of the cross-sectional area due to marked onion bulb formation in patients with DADS and pure sensory subtype (Fig. 3c) [29]. An autopsy study of patients with MADSAM also reported that multifocal lesions were observed in the nerve trunk of these patients, consistent with the patchy distribution of myelinated fiber loss [59]. Another report of a fascicular biopsy obtained at the brachial plexus where marked swelling was detected by MRI revealed extensive onion bulb formation in a patient with MADSAM [53]. As the formation of onion bulbs is deeply related to macrophage-induced demyelination [9], it could be hypothesized that some patients with both typical CIDP and major atypical CIDPs (i.e., MADSAM, DADS, and pure sensory) share common mechanisms associated with the phagocytosis of myelin by macrophages. Taken together, these results further suggest the hypothesis that differences in the distributions of lesions (i.e., proximal, middle, and distal nerve segments) and the repair processes underlying demyelination by Schwann cells determine the clinicopathological differences between typical CIDP and atypical CIDP, particularly MADSAM. Although both humoral and cellular immunities are thought to participate in the mechanisms underlying CIDP [6], compared to MADSAM, in typical CIDP the former may predominate.

INSIGHTS INTO CLASSIFICATION AND THERAPEUTIC STRATEGIES

As described earlier, patients with IgG4 antibodies to paranodal neurofascin 155 and contactin 1 exhibit neuropathy mechanisms distinct from those observed in classical

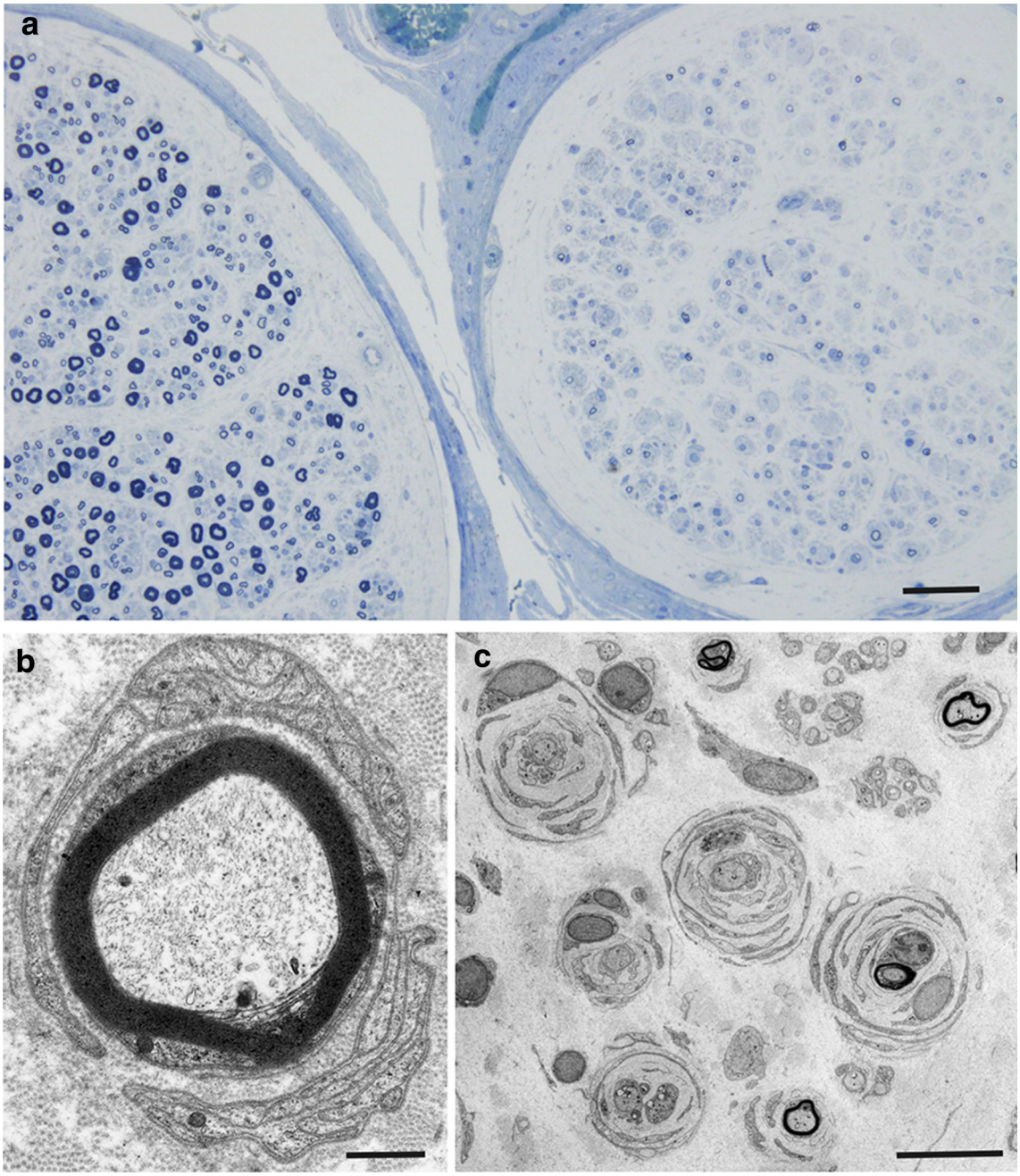

Fig. 3 Representative pathological findings in patients with atypical CIDP. Sural nerve biopsy specimens obtained from patients with pure sensory (**a**, **c**) and MADSAM (multifocal acquired demyelinating sensory and motor) (**b**). Transverse sections. **a** Conspicuous variation in myelinated fiber density among fascicles. **b** Mild onion bulb formation in areas of reduced myelinated fiber density in a patient with MADSAM. **c** In a patient with pure sensory subtype, the reduction in myelinated fiber density seemed to result from an enlargement of the cross-sectional area due to marked onion bulb formation. Toluidine blue staining (**a**) and uranyl acetate and lead citrate staining (**b**, **c**). Scale bars 50 µm (**a**), 1 µm (**b**), and 10 µm (**c**)

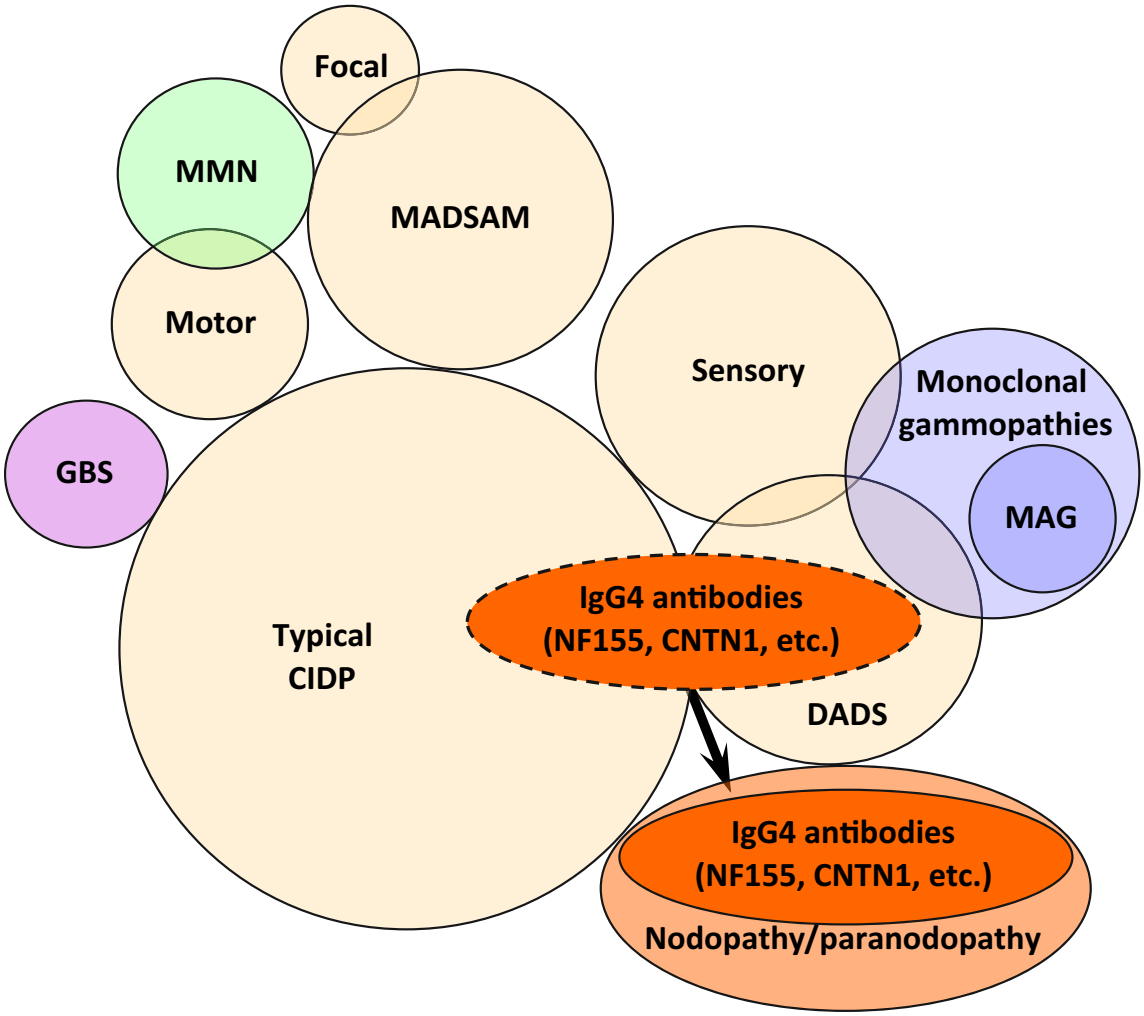

Fig. 4 A correlation diagram of CIDP subtypes defined in the EFNS/PNS criteria and their related diseases. Patients with IgG4 antibodies to paranodal neurofascin 155 and contactin 1 show mechanisms of neuropathy distinct from those observed in classical macrophage-induced demyelination, indicating that specific therapeutic strategies are involved in these two groups of patients. In particular, the concept of nodopathy or paranodopathy has recently been proposed for patients with IgG4 antibodies to nodal and paranodal components. Hence, clarifying whether the classification of this group of patients as "CIDP" is appropriate is a challenge for the future. CNTN1 contactin 1, DADS distal acquired demyelinating symmetric, GBS Guillain–Barré syndrome, MADSAM multifocal acquired demyelinating sensory and motor, MAG myelin-associated glycoprotein, MMN multifocal motor neuropathy, Motor pure motor, NF155 neurofascin 155, Sensory pure sensory

macrophage-induced demyelination, indicating that specific therapeutic strategies are needed for these two groups of patients. In particular, the concept of nodopathy or paranodopathy has recently been proposed for patients with IgG4 antibodies to nodal and paranodal components [46, 49]. Hence, clarifying whether the classification of this group of patients as "CIDP" is appropriate is a challenge for the future (Fig. 4).

Treatment for CIDP consists of IVIg, steroids, and plasma exchange, either alone or in combination [10, 11]. However, some patients, particularly those with findings suggestive of axonal damage, may show refractoriness to these therapies [60, 61]. Although evidence for

these treatments had already been accumulating before the publication of the EFNS/PNS criteria [62–64], the response of patients with atypical CIDP to these treatments has not been fully explored. A previous report suggested that compared to patients with typical CIDP, patients with MADSAM show a lower response rate to IVIg, steroids, and plasmapheresis [34]. Another study also showed that responses to IVIg were less frequent in patients with MADSAM and DADS than in patients with typical CIDP [31]. In addition, patients with the pure motor subtype showed unresponsiveness to or even exacerbation by steroid therapy [65, 66]. As the disease duration in patients with atypical CIDP tends to be longer than that observed in patients with typical CIDP [29], the accumulation of irreversible axonal damage may lead to refractoriness to immunotherapies in these patients. Alternatively, the differences in therapeutic response may suggest that there are differences in the pathogenic mechanisms underlying these subtypes.

It should be noted that a therapeutic strategy different from a conventional approach is needed for patients with anti-neurofascin 155 and anti-contactin 1 antibodies. In these patients, the most important issue is refractoriness to IVIg [9, 16, 17, 19–22]. As IgG4 is a main immunoglobulin subclass of anti-neurofascin 155 and anti-contactin 1 antibodies, a low capacity to bind Fc receptors and an inability to activate complements of this subclass of immunoglobulin may explain the poor response to IVIg observed in patients with these antibodies [10, 11]. In addition, immunoadsorption plasmapheresis should be avoided in these patients because it does not eliminate IgG4 [67]. It has been suggested that rituximab, a chimeric monoclonal antibody that binds to CD20, could have efficacy in patients with anti-neurofascin 155 and anti-contactin 1 antibodies [68]. A strategy aimed at using rituximab to reduce the production of autoantibodies is reasonable in conditions under which autoantibodies play a pivotal role in the pathogenesis of neuropathy. Currently, a randomized controlled trial of rituximab in patients with anti-neurofascin 155-positive CIDP is ongoing [69]. Rituximab may also be effective in some patients without these antibodies, especially intractable cases [70].

Unlike the disease process induced by IgG4 autoantibodies, IVIg seems to be effective in macrophage-mediated disease processes [71]. The mechanism underlying the efficacy of IVIg in CIDP seems to be complex and involves the neutralization of autoantibodies, the inhibition and abrogation of activated complements, the alteration of Fc receptor expression, and the modification of cytokine profiles [10]. Higher levels of expression of the activating Fc gamma I receptors on monocytes and lower levels of expression of the inhibitory Fc gamma IIb receptors on naïve and memory B cells as well as on monocytes have been reported in blood samples obtained from patients with CIDP before IVIg treatment, and these effects were partly restored after IVIg [72]. These findings indicate that the recognition of the Fc portion of immunoglobulin by Fc gamma receptors on the surface of immune cells plays an important role in the mechanisms underlying macrophage-induced demyelination.

Regarding other therapeutic options, the efficacy of eculizumab, a humanized monoclonal antibody that specifically binds to complement component 5 and inhibits the activation of complements, was reported in patients with GBS, including those with AIDP [73]. To support the efficacy of eculizumab in patients with AIDP, a recent study of sural nerve biopsy specimens obtained from patients with AIDP demonstrated the deposition of complements [40]. The activation of complements has also been reported in some patients with CIDP [28, 74–76]. As described earlier, humoral immunity may be more predominant in typical CIDP than in atypical CIDP, and complement inhibition might be another therapeutic option in a subpopulation of patients with CIDP. It is possible that complements do not play a role in the mechanisms underlying neuropathy in patients with anti-neurofascin 155 and anti-contactin 1 antibodies because IgG4 is the main immunoglobulin subclass of these antibodies [23]. Considering the complexity and heterogeneity of the mechanisms involved in CIDP, the efficacy of therapies that target specific sites of the immune system may vary among patients.

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Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

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