Diagnostic insights into chronic-inflammatory demyelinating polyneuropathies

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Abstract: Chronic inflammatory demyelinating polyneuropathy (CIDP) is a rare immune-mediated neuropathy with demyelination of nerve fibers as leading morphological feature. The course of disease can be chronic progressive or remitting relapsing. Whereas for acute immune-mediated neuropathies several serological markers have been identified and used successfully in clinical routine, the serological diagnosis of chronic variants such as CIDP has not yet been evolved satisfactory. The typical CIDP and its various atypical variants are characterized by a certain diversity of clinical phenotype and response to treatment. Thus, diagnostic markers could aid in the differential diagnosis of CIDP variants and stratification of patients for a better treatment response. Most patients respond well to a causal therapy including steroids, intravenous immunoglobulins and plasmapheresis. Apart from electrophysiological and morphological markers, several autoantibodies have been reported as candidate markers for CIDP, including antibodies against glycolipids or paranodal/nodal molecules. The present review provides a summary of the progress in autoantibody testing in CIDP and its possible implication on the stratification of the CIDP variants and treatment response.

Keywords: Chronic inflammatory demyelinating polyneuropathy (CIDP); antiganglioside antibody; antisulfatide antibody; antinodal/paranodal antibody

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Introduction

There has been remarkable progress in the clinical and electrophysiological categorization of acute and chronic immune-mediated neuropathies recently. However, the serological diagnosis of chronic inflammatory demyelinating polyneuropathies (CIDP) is still inconsistent and the search for useful serological markers is ongoing (1,2). CIDP represents a rare disabling autoimmune disorder of peripheral nervous system, with poorly understood etiopathogenesis. Various incidences have been reported, ranging from 0.8 to 8.9 per 100,000 individuals per year depending on geographical origin of the patient cohorts investigated (3). Nevertheless, along with acute polyneuropathies classified as the Guillain-Barré syndrome (GBS) CIDP accounts for the majority of immune mediated polyneuropathies (4).

Once correctly diagnosed, several causal treatment...
Pathophysiology of CIDP

The leading pathogenic process in CIDP is the multifocal demyelination of nerve cells affecting nerve roots, plexus and fibers as well as conditions mimicking this process (19-21). The latter refer to an emerging concept based on electrophysiological and experimental findings demonstrating a conduction failure with typical “axonal” damage characteristics which, however, can rapidly recover (reversible conduction failure) (20).

Experimental evidence on passive and active animal transfer models, active immunization with nerve components and response to immunosuppressive treatment, IVIg as well as plasmapheresis, suggest that dysfunctional acquired immune responses may play a pivotal role in the pathogenesis of CIDP (22-26). In this context, the heterogeneous clinical manifestation of CIDP may hint at pathophysiological processes involving humoral autoimmune responses against differing nerve fiber components. As a fact, IgG and IgM as well as complement deposits were demonstrated in patients with chronic inflammatory neuropathies (27). Moreover, compared to normal controls, one study reported increased serum levels of anaphylatoxin C5a and terminal complement complex (C5b9) in serum and cerebrospinal fluid (CSF) of CIDP patients (28). Autoreactive T-cell responses against myelin epitopes have also been reported, which lends further evidence to a certain role of a tolerance break to distinct components of the peripheral nerve system (26,29). Furthermore, CD4+ and particularly CD8+ T cells were identified in inflammatory infiltrates of patients with CIDP (30,31). Last but not least, elevated levels of inflammatory cytokines such as interleukin 2, interleukin 6, tumor necrosis factor alpha and B-cell activating factor were reported in serum and CSF of CIDP patients (32-35).

Altogether, there is mounting evidence that an autoimmune attack against distinct components of peripheral nerves particularly of the node and paranode regions is very likely as leading pathogenic mechanism. Likely, this autoimmune attack is triggered by microbial molecular mimicry (36). Hence, it is not surprising that multiple novel autoAbs identified recently have been proposed as potential biomarkers for CIDP (2,37-39). Nevertheless, it should be mentioned that no serum marker is recognized to be diagnostic currently despite the clear correlation of certain autoAbs with distinct peripheral
neuropathy variants (40,41).

Diagnostic options in CIDP

The diagnosis of CIPD relies on observation of neurological clinical symptoms of demyelination and detection of demyelinating electrophysiological features, as well as elevated CSF protein levels (8,42,43). New conduction studies may aid in the discrimination of demyelination (conduction block or reduced conduction velocity) and axonal impairment (diminished compound muscle action potential amplitude). The latter is, in general, accompanied with poor prognosis, but may rapidly recover. This is seen in patients with nodo-paranodopathies, a new concept in the diagnosis of autoimmune mediated polyneuropathies (21).

Clinical impairment is recommended to be assessed by the Medical Research Council (MRC) (44) and the inflammatory neuropathy cause and treatment (INCAT) disability score (45). Furthermore, disease activity may be ascertained by the Clinical Disease Activity Status (CDAS) with the classification in unstable and stable stages (46).

When a diagnosis cannot be established by the former features, biopsy of the nerve affected with assessment of inflammatory infiltrates may provide additional helpful information. However, inflammatory infiltrates may not be detectable at all, or only occasionally, which mirrors the heterogeneous clinical picture of CIDP (47). Thus, characteristic signatures of de- (thin myelin sheath around large axons) or re-myelination (onion bulbs) and endoneuronal edema should be considered as further biopsy characteristics (48).

Recently, non-invasive imaging techniques such as magnet resonance imaging of nerve roots and fibers or sonography have been successfully utilized in clinical studies as additional diagnostic options to support a diagnosis of CIDP (49-51). Furthermore, interesting diagnostic results have been achieved by corneal confocal microscopy due to the association of CIDP with small fiber damage (52,53). These findings sparked the intensive search for the corresponding targets responsible for specific autoAb binding. Hence, the diagnostic role of autoAbs to distinct targets related to the node of Ranvier and adjacent regions as well as to non-regional related components reported in CIDP so far (Table 1) and their corresponding detection techniques should be in the focus of this review.

AutoAbs to specific nerve fiber regions

AutoAbs to nodal targets

Potential nodal autoantigenic targets investigated in CIDP have been neurofascin (NF) 186, moesin, and gliomedin (67,68) (Table 1). Gliomedin is a microvilli cell adhesion molecule of Schwann cells interacting with NF186 of the
Table 1 Autoantigenic targets in chronic inflammatory demyelinating polyneuropathy (CIDP) and relevance of corresponding autoantibodies

<table>
<thead>
<tr>
<th>Location</th>
<th>Autoantigenic target</th>
<th>Relevance for CIDP</th>
<th>Regional association</th>
</tr>
</thead>
<tbody>
<tr>
<td>Node of Ranvier</td>
<td>Neurofascin 186 (NF186)</td>
<td>Anecdotal evidence/specific*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Neurofascin 140 (NF140)</td>
<td>Specific* (NF140/186), often IgG4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Moesin</td>
<td>Non-specific</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gliomedin</td>
<td>Non-specific</td>
<td></td>
</tr>
<tr>
<td>Paranode</td>
<td>Neurofascin 155 (NF155)</td>
<td>Specific*, often IgG4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Contactin-1</td>
<td>Specific*, often IgG4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Contactin-associated protein 1 (Caspr1)</td>
<td>Anecdotal evidence, neuropathic pain</td>
<td></td>
</tr>
<tr>
<td>Juxtaparanode</td>
<td>Contactin-2/transient axonal glycoprotein 1</td>
<td>Non-specific</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Contactin-associated protein 2 (Caspr2)</td>
<td>Non-specific</td>
<td></td>
</tr>
<tr>
<td>Myelin</td>
<td>Myelin protein zero</td>
<td>Non-specific</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Peripheral myelin protein 2</td>
<td>Non-specific</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Peripheral myelin protein 22</td>
<td>Non-specific</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Connexin 1</td>
<td>Non-specific</td>
<td></td>
</tr>
<tr>
<td>Axon + myelin</td>
<td>Sulfatide</td>
<td>Non-specific, predominantly IgM</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ganglioside GM1</td>
<td>Non-specific, predominantly IgM</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Glycolipid complexes</td>
<td>Non-specific</td>
<td></td>
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</table>

*, distinct CIDP subsets (“IgG4-mediated nodo/paranodopathies”): patients with autoantibodies (autoAbs) to neurofascin 155 (NF155) and contactin-1 present with rapid severe onset and tend to show distal limb involvement, sensory ataxia, tremor, and a poor response to intravenous immunoglobulin (IVIg). In contrast, patients with autoAbs to NF140/186 antibodies show a subacute-onset with clinical manifestations that include sensory ataxia, conduction block and cranial nerve involvement and may have a better response to IVIg.

In turn, NF 186 is linked along with other molecules to the voltage-gated sodium channels enriched in the nodal region and responsible for inward current of action and saltatory conduction finally (69). Consequently, the lack of NF186 interferes with axonal conduction, as elegantly demonstrated in NF186 null mice (70). Remarkably, autoAbs against the nodal neurofascin NF186 have been found in CIDP (66). Recently, autoAbs to NF140/186 (mainly IgG4) targeting epitopes different from autoAbs against NF155 and specific for a subset of CIDP showing subacute-onset and include sensory ataxia, conduction block and cranial nerve involvement have been found (39). Nevertheless, autoAbs to paranodal targets, in particular of the IgG4 isotype, seem to be more frequent in CIDP and may help in stratifying patients with CIDP variants (4).

**AutoAbs to paranodal targets**

Paranodes fence the internodal region and prevent the diffusion of nodal molecules like NF186 and voltage-gated sodium channels to that region (71). Furthermore, the integrity of the paranode is important to prevent interruption by juxtaparanodal voltage-gated potassium channels (72,73). Paranodal autoAbs against NF155 have been found consistently in CIDP patients with combined central and peripheral demyelination (CCPD) (74,75) and in a subset of CIDP patients with distinct clinical features (76) (*Table 1*). Out of the other molecules forming septate-like junctions in the paranodal region such as contactin-1 (CNTN1) and contactin-associated protein (Caspr), CNTN1 seems to be another relevant autoantigenic target in CIDP (65). The presence of particularly IgG4 to CNTN1 and NF155 was confirmed by several other clinical evaluations recently demonstrating an aggressive disease onset and poor responsiveness to IVIgs (68,77-80). Furthermore, Querol and coworkers found only paranodal autoAbs against NF155 and CNTN1 to be specific markers in CIDP (2). Both autoAbs seem to be
pathogenic by interfering with NF155/CNTN1 complex in a complement-independent manner, which has also implications for treatment decisions (68).

**AutoAbs to juxtaparanodal targets**

The potential role of autoAbs to juxtaparanodal targets such as CNTN2 also referred to as transient axonal glycoprotein 1 (TAG1) and Caspr2 interfering with the stability of the voltage-gated potassium channel complex is an emerging hypothesis (4,81). Loss of tolerance against these potential targets has not been conclusively reported so far. Interestingly, an association of distinct single nucleotide polymorphisms of *TAG1* with the responsiveness of CIDP patients to IVIg therapy is discussed controversially (82,83).

**AutoAbs to non-regional related components**

**AutoAbs to myelin proteins**

Despite extensive studies on the potential role of myelin proteins (i.e., myelin protein zero, peripheral myelin protein 2 or 22, and connexin 1) as autoimmune targets in CIDP, no significant associations of corresponding autoAbs with CIDP could be established (2,29,84-86) (Table 1). This was confirmed by a compelling study using indirect immunofluorescence on various cellular substrates and immunoprecipitation (2). In contrast, autoAbs to MAG were reported in patients with DADS (16).

**AutoAbs to gangliosides/sulfatide**

Unlike acute immune-mediated neuropathies, the value of autoAb testing to gangliosides and sulfatide has been still illusive in chronic immune-mediated polyneuropathies, and only established for a minority of them (Table 1). Thus, IgM autoAbs against disialosyl epitopes, particularly to GD1b, were found in chronic sensory ataxic neuropathy demonstrating often similar clinical features of CIDP (17). Furthermore, patients suffering from the CANOMAD syndrome demonstrated IgM autoAbs to the disialosyl gangliosides GD1b, GD3, GT1b, and GQ1b (17). Most patients with IgM autoAbs against GD1b profited from IVIg therapy or biologicals (87,88). These IgM autoAbs appeared to be pathogenic in terms of sensory ataxia, which can also be observed in CIDP.

Furthermore, autoAbs to sulfatide, which is predominantly expressed within the non-compact myelin, were associated with different subtypes of peripheral neuropathy, most of them axonal (60,89). However, a demyelinating type with a lower prevalence was also described (90). In acute polyneuropathies, a particular strong association of pathogenic autoAbs with distinct clinical variants [such as autoAbs against GQ1b to the Miller-Fisher syndrome (MFS), a subtype of the GBS], could be ascertained (37,91,92). Conversely, in terms of chronic immune-mediated neuropathies, IgM autoAbs against GM1 were reported in up to 60% of patients with multifocal motor neuropathy (MMN), a progressively worsening pure motor polyneuropathy (93-95). Of note, increased titers of IgM autoAbs to sulfatide were detected in patients with neuropathy, where they are often associated with a concomitant reactivity to the MAG (96). In contrast, Giannotta and coworkers reported reactivity to sulfatide in only 1% of CIDP patients (97). Furthermore, a recent retrospective analysis found IgM autoAbs to GM1 in 46% of patients with MMN but in only 3% of CIDP patients (93).

In a recent study, an elevated frequency of at least one IgM autoAb to GM1, GD1b and, sulfatide in patients suffering from CIDP was reported (98). Remarkably, patients positive for autoAbs to sulfatide were younger and showed typical manifestations of clinical symptoms of CIDP but no association with axonal degeneration and neither any association with monoclonal IgM gammopathy nor with positivity of autoAbs to MAG reported earlier (90,96,97,99). Of note, cerebrosides sulfotransferase-deficient mice demonstrated paranodal disruption by juxtaparanodal voltage-gated potassium channel invasion which underscores the role of sulfatide in stabilizing the paranodal junctions (100). Furthermore, autoAbs to sulfatide-ganglioside complexes detected by a combinatorial glycoarray methodology accounted for the largest group of antiglycolipid autoAbs in patients with GBS (60). Thus, the assay technique used for the analysis of such autoAbs appears to play a pivotal role. Thin-layer chromatography is supposed to be the gold-standard assay technique for the assessment of antiglycolipid autoAbs, though it is not applicable for routine use (63). Methods such as the LIA or the combinatorial glycoarray may be a good alternative for the multiplex assessment of autoAbs to gangliosides and sulfatide due to an optimal autoantigenic epitope-preserving binding on hydrophobic polyvinylidene difluoride membranes (64,101). The hydrophobic solid phase has already proven its usefulness for the specific analysis of auto/Abs to amphipathic molecules like lipopolysaccharides and phospholipids exhibiting similar physicochemical
characteristics (102-105). In the context of antiphospholipid antibody testing, hydrophobic membranes appear to result in a better assay performance than for instance solid phases used in enzyme-linked immunosorbent assays (106-108). Altogether, differences in assay techniques could be the reason for differing reports on the frequency of autoAbs to gangliosides and sulfatide (97). Thus, higher frequencies of IgM autoAbs to GM1 (16%) detected by LIA were found in CIDP and MMN patients in contrast to the glycoarray (7%), where IgM to glycolipid complexes containing GM1 and sulfatide were the most frequently observed autoAbs in CIDP patients (98,109). Interestingly, the patients of both studies demonstrated motor disturbances more frequently than autoAb-negative ones did. Moreover, patients with positivity of autoAbs to sulfatide showed a higher rate of conduction blocks in nerve conduction studies (98). These findings add further evidence to the assumption that impairment of primarily motor functions in CIDP may be explained by depletion of sulfatide and myelin proteins such as neurofascin 155 especially in the paranodal region (89). Furthermore, the ganglioside GM1 is highly expressed on the membranes of motor nerves and on the surface of Schwann cells. Binding of autoAbs to these targets on the axon at the nodes of Ranvier or on Schwann cells (see Figure 1) may cause complement activation and disruption of sodium channel clusters resulting in conduction abnormalities (57,110).

**Clinical relevance of autoAbs against paranodal proteins**

Since its first description in 1958 (111) results of numerous studies, case series and case reports indicate that CIDP is not a defined disease entity but rather a spectrum of related chronic neuromuscular disorders. The phenotypic variability and response to therapy may be driven by different pathomechanisms that are associated with autoantigenic targets of immune responses (19). Therefore, autoAbs specific for defined CIDP subtypes may be helpful in their early diagnosis leading to the most effective therapy. Although numerous autoAbs have been described in CIDP, only IgG4 autoAbs against paranodal proteins (i.e., neurofascin 155, contactin 1, Caspr1) determined by cell-based assays or ELISA using human native autoantigens showed a very high specificity for a defined clinical phenotype named “autoimmune nodo-paranodopathy” (2,15,112).

AutoAbs against neurofascin 155: summarizing the 12 studies which tested autoAbs against NF155 by using native human NF155, the overall frequency was 6.4% (90/1,404), with predominant IgG4 response in CIDP patients (66). The frequency differs between the studies from 4% to 18% (38,73,75,76,79,113-115). These studies, along with that of Siles et al. (116), showed a very high diagnostic specificity (>99–100%) by testing of more than 200 blood donors and 1,109 patients with other neurological diseases including GBS, MFS, multiple sclerosis (MS), MMN, paraneoplastic neurological syndromes, MAG antibody-positive and genetic neuropathies. Only some GBS patients (frequency <1%) were found positive with a predominant IgG1 or IgM response (38,73,75,76,79,113,115). Although the

![Figure 1](https://example.com/figure1.png)
clinical picture may vary slightly among studies, a specific clinical phenotype that differs from the autoAb-negative CIDP has been described, which includes a younger age of onset, a subacute and more severe onset, disabling tremor, sensory and cerebellar ataxia, distal dominant weakness, and poor response to IVIg (75,76,79,113). Furthermore, an association of NF155 autoAb with CCPD has been described in Japanese but not in Caucasian patients (66,73).

AutoAbs to CNTN1 with predominant IgG4 isotype were found in 3–8% of CIDP patients, with a diagnostic specificity of 100% vs. blood donors, GBS, and MMN (38,66,78). Patients with autoAbs to CNTN1 show a special clinical phenotype, including a more advanced age of onset compared to autoAb negative CIDP, an aggressive and GBS-like subacute onset of weakness, a very high ratio of sensory ataxia, early axonal involvement, and poor response to IVIg (66).

AutoAbs against Caspr1: up to now, autoAbs against Caspr1 were described in two studies only, showing a cumulative frequency in CIDP patients of about 1% (3/281) and a high diagnostic specificity (66). These were only detectable in one out of 48 GBS patients, but none of 52 MS patients, 32 patients with Charcot-Marie-Tooth disease, 34 patients with possible or definite paraneoplastic neurological syndromes and 78 blood donors (38,116,117). Whilst the GBS patient had IgG3 autoAb, the autoAb to Caspr1 of the CIDP patient in the study of Doppler et al. was of the IgG4 isotype. This patient had a subacute, severe, motor dominant onset, severe pain, reversible conduction block, was unresponsive to IVIg and corticosteroids, but showed a good response to B cell depletion (117).

Taken together, CIDP positive for autoAbs against the paranodal proteins NF155, CNTN1, and Caspr1 represent a different CIDP subtype (autoimmune nodo-paranodopathy) compared to seronegative CIDP with poor response to IVIG therapy, but partial favorable steroid and plasmapheresis responses (66). Therefore, IVIG is not a primary therapeutic option, especially in patients with autoAbs to NF155. First studies demonstrated that most seropositive CIDP patients had a good response to rituximab, a B cell depleting therapy (66,115,117,118). In conclusion, autoAbs against paranodal proteins should be determined for an early diagnosis of autoimmune nodo-paranodopathies indicating the treatment with rituximab.

**Summary**

The diagnosis of CIDP and its variants is based on clinical and electrophysiological features. Emerging autoAbs, especially against paranodal cell-adhesion molecules such as NF155, CNTN1, and Caspr1 as well as to glycolipids (gangliosides and sulfatide) appear to be good marker candidates for CIDP subentities, i.e., may aid in discriminating the diverse clinical variants and/or the response to treatment. AutoAbs to NF155 and Caspr1 of the immunoglobulin subtype IgG4 appear to be associated with a poor response to IVIg therapy, but good response to B cell depletion. On the other side, autoAbs to NF140/186 may be associated with a better response to IVIg.

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**Footnote**

**Conflicts of Interest:** D Roggenbuck has a management role and is a shareholder of GA Generic Assays GmbH and Medipan GmbH. Both companies are diagnostic manufacturers. The other authors have no conflicts of interest to declare.

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