


# Evolving Immunologic Perspectives in Chronic Inflammatory Demyelinating Polyneuropathy

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**Abstract:** Chronic inflammatory demyelinating polyneuropathy (CIPD) is the commonest chronic idiopathic dysimmune neuropathy. Pathophysiologic processes involve both cellular and humoral immunity. There are various known forms of CIPD, likely caused by varying mechanisms. CIPD in its different forms is a treatable disorder in the majority of patients. The diagnosis of CIPD is clinical, supported routinely by electrophysiology. Cerebrospinal fluid analysis may be helpful. Routine immunology currently rarely adds to the diagnostic process but may contribute to the identification of an associated monoclonal gammopathy with or without hematologic malignancy and the consideration of alternative diagnoses, such as POEMS syndrome, anti-myelin associated glycoprotein (MAG) neuropathy or chronic ataxic neuropathy, with ophthalmoplegia, M-protein, cold agglutinins and disialosyl antibodies (CANOMAD). The search for antibodies specific to CIPD has been unsuccessful for many years. Recently, antibodies to paranodal proteins have been identified in a minority of patients with severe CIPD phenotypes, often unresponsive to first-line therapies. In conjunction with reports of high rates of antibody responses to neural structures in CIPD, this entertains the hope that more discoveries are to come. Although still arguably for only a small minority of patients, in view of current knowledge, such progress will enable earlier accurate diagnosis with direct management implications but only if the important, unfortunately and infrequently discussed issues of immunologic technique, test reliability and reproducibility are adequately tackled.

**Keywords:** chronic inflammatory demyelinating polyneuropathy, dysimmune, immunologic, inflammatory, nodal, paranodal

## Introduction

Chronic inflammatory demyelinating polyneuropathy (CIPD) is a rare dysimmune peripheral nerve disorder of relatively recent description.<sup>1</sup> It however represents the most common chronic immune-mediated neuropathy with a prevalence of about 3 per 100,000 worldwide,<sup>2</sup> but widely variable reported figures, likely due to different criteria used for case ascertainment.<sup>3</sup> CIPD has a potential for effective treatment in the majority of affected individuals. The spectrum of the disorder has considerably expanded over the past few decades. In its classical form, also known as “typical CIPD”, patients present with symmetric weakness of proximal and distal muscles of the four limbs together with reduced sensation for proprioceptive modalities and absent or reduced reflexes.<sup>4</sup> Several other CIPD subtypes have been described. These include focal, multifocal asymmetrical, distal, pure motor as well as pure sensory forms.<sup>4</sup> A minority of subjects may present with cranial nerve involvement and an even smaller proportion, with respiratory muscle

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weakness. CIDP, by current definitions, evolves over at least 8 weeks of continuous deterioration, with a relapsing or progressive course, as opposed to Guillain-Barré syndrome (GBS), which plateaus within 4 weeks. However, there are acute-onset forms of CIDP which in the early stages, may be difficult to separate from GBS. Despite similarities, CIDP otherwise differs from GBS as only seldom causes respiratory difficulties or facial weakness, while more commonly causing impairment of sensation, in particular, of proprioception.<sup>5</sup> The diagnosis of CIDP relies on thorough history taking and neurological examination to ascertain the key features of the disorder. The main useful investigative procedure is electrophysiology, with in particular nerve conduction studies. These have the ability to establish electrical signs of demyelination of nerve fibers, by showing reduced conduction velocities along nerve segments, evaluating the presence of focal dysfunction of impulse transmission through conduction block and that of differential slowing in between fibers, through temporal dispersion.<sup>1</sup> Due to the pathology affecting proximal nerve roots, study of the cerebrospinal fluid (CSF) may be supportive of the diagnosis by revealing elevated protein content, although consideration of cut-offs used in relation to age and co-morbidities are essential as is awareness of poor specificity.<sup>6</sup> Nerve imaging has been extensively studied in CIDP in recent years through magnetic resonance and ultrasonography (US). A number of issues, starting with their uncertain specificity versus CIDP mimics as well as their highly operator-dependent nature, however currently limit their utility in clinical practice, particularly with regard to MRI.<sup>7</sup> Basic blood tests are done for incident cases of CIDP routinely and include blood count, electrolytes, renal and liver function, inflammatory markers, glycosylated haemoglobin (HbA1C) and HIV serology. Immunologic tests are frequently restricted to serum protein electrophoresis although immunofixation is preferable to identify low-level monoclonal proteins. Antibodies to anti-myelin associated glycoprotein (MAG) are commonly requested in presence of a monoclonal gammopathy of IgM subtype, but generally not done, otherwise.<sup>8</sup> Search for antinuclear antibodies, antibodies to extractable nuclear antigens and antineuronal antibodies are done, especially when the clinical picture may suggest concurrent autoimmune disease or malignancy.<sup>9</sup> Although not characteristically associated with CIDP, antiganglioside antibodies are often systematically requested in neuromuscular centers, less so in general neurologic practice. These immunologic tests, considered by many, as

superfluous especially in typical presentations, may arguably all lead to revising a diagnosis of CIDP, and more importantly still, have important consequences on further management and therapeutic decisions. For example, the presence of IgG anti-GM1 antibodies in a patient with GBS and successive re-deteriorations after treatment in the first 2 months makes the alternative and often considered diagnosis of acute-onset CIDP, most unlikely. Antibody positivity in this setting is clearly helpful in the diagnosis of GBS with “treatment-related fluctuations” vs that of CIDP, the latter, potentially leading to consideration of inappropriate and unnecessary but prolonged, treatments. More recently, and in support of this view, the discovery of antibodies to paranodal proteins, albeit in a small proportion of individuals with CIDP, has resulted in considerable interest.<sup>10</sup> The detection of these antibodies described in presence of atypical phenotypes and treatment refractoriness to first-line agents has contributed to enhancing the immunologic interest of CIDP, from a new, clinically directly relevant, perspective and opening new avenues to the dysimmune aspect of CIDP as optimal diagnostic marker in the future.

We attempt in this review, to discuss in greater detail the immunologic aspects of CIDP and their potential current, as well as future relevance within the clinical arena.

## Pathophysiologic Aspects of CIDP

CIDP results from aberrant immune responses to peripheral nerve antigens. Synergy between cell-mediated and humoral immunity directed against antigens within peripheral nerve structures represents the likely underlying basis for the triggering of the pathophysiologic processes.<sup>11</sup> These, in turn, lead to conduction dysfunction within the efferent and afferent components of the peripheral nervous system, with consequent motor and sensory impairments, ultimately resulting in neurologic disability. The evidence for a dysimmune process is supported by the efficacy of immune treatments and by the presence of features of inflammatory response in serum and nerve tissue of affected individuals.

Cellular immunity is implicated in CIDP pathogenesis as evidenced by inflammatory findings in peripheral nerves,<sup>12</sup> as well as alterations of T-cell populations and functions,<sup>13</sup> altered expression of cytokines and other inflammatory mediators.<sup>14</sup> The breakdown of the blood nerve barrier to activated T cells allows their passage but also results in increased permeability of the barrier itself to pro-inflammatory factors. Inflammation represents the

pathological hallmark, characterized by edema and macrophagic infiltration of the endoneurium, perivascular aggregation by T cells, increased cytokine expression and other inflammatory molecules. Demyelination of the peripheral nerve occurs through macrophagic and CD4+/CD8+ T cell presence.<sup>11</sup> How the process is actually initiated remains uncertain.

Efficacy of plasma exchange and of intravenous immunoglobulins (IVIg) favors the implication of humoral mechanisms in CIDP, as does the presence of immunoglobulin and complement in myelin structures of affected nerves.<sup>15</sup> It is possible that molecular mimicry resulting from cross-reactivity to microbial antigens resembling neural components may be involved. Although demonstrated in GBS through animal models,<sup>16</sup> this has however not been established in CIDP, although the concept may be supported by the association of CIDP with malignancies such as melanomas,<sup>17</sup> or infective or connective tissue disorders. Target antigens for specific antibodies in CIDP have remained however elusive despite extensive research in the field. Responses to various nerve antigens including myelin proteins P2, PMP22 and MPZ (P0) and glycolipids have been shown in small numbers of individuals with the disease, in few studies but not in others.<sup>10</sup> However, and importantly, there have been several reports of a significant proportion of subjects with CIDP harboring antibodies to neural components.<sup>10</sup> A number of case reports or small case series further illustrate this. For example, antiganglioside antibodies are described in multifocal motor neuropathy and GBS but have also been described, in albeit few patients with different CIDP subtypes including anti-GM1,<sup>18</sup> anti-GM2 and anti-GA1,<sup>19</sup> anti-LM1.<sup>20,21</sup> Anti-GD1b antibodies of IgM subtype were described in a series of patients with ataxic CIDP, responsive to IVIg.<sup>22</sup> Recently there have in addition, been reports of patients with anti-myelin associated glycoprotein (MAG) antibodies, with or without identifiable IgM monoclonal protein, presenting with a typical CIDP phenotype, instead of the supposedly usual phenotype associated with “anti-MAG neuropathy” which is one of distal demyelinating sensory and motor (“DADS”: “distal acquired demyelinating sensory and motor”) neuropathy.<sup>23</sup> In addition, the transition from DADS to typical CIDP may also occur in presence of anti-MAG positivity, which itself may pre-date the detection of an IgM monoclonal gammopathy.<sup>24</sup> Importantly, it is noteworthy that anti-MAG antibody testing methodology is in this regard, fundamental<sup>25</sup> and that low titers may

need considering with great caution.<sup>23</sup> Also, additional other antibodies such as those directed against the Human Natural Killer1 epitope (anti-HNK1 antibodies), may be of use in diagnosing anti-MAG neuropathy, and be associated with disease severity.<sup>26</sup>

The most compelling findings in support of the renewed immunologic research interests in CIDP of potential for direct clinical application have appeared in the last decade.<sup>10,11</sup> Nodal and paranodal structures have been discovered to harbor a number of antigens representing potential targets for immune attack in subjects with chronic dysimmune neuropathy. Ultrastructural disruption of the nodal/paranodal regions within the nerve sample of CIDP affected subjects was initially described nearly 10 years ago.<sup>27</sup> Since 2013, circulating antibodies to a number of antigenic structures within node and paranode, have been identified.<sup>10</sup> These are glycoproteins involved in maintaining cohesion between myelin and axonal structures in paranodal regions. Antibodies to these glycoproteins, namely neurofascin 155 (NF155),<sup>28</sup> contactin-1 (CNTN1),<sup>29</sup> contactin-related protein 1 (CASPR1),<sup>30</sup> neurofascin 186 (NF186) and neurofascin 140 (NF140)<sup>31</sup> have been described although only in a minority of patients with CIDP, accounting for <10%,<sup>32</sup> or possibly even <5% of all cases, as per our own, recently published, experience.<sup>33</sup> These antibodies have most frequently been discovered in circumstances different to those expected in typical or classical CIDP, with acute or sub-acute disease onset and with particularly severe clinical phenotypes as well as unresponsiveness to immunoglobulin therapy.<sup>10</sup>

## CIDP: Clinical Phenotypes and Immunology

The commonest form of CIDP, known as “typical CIDP”, presents with progressive onset over 8 weeks or more, of a symmetric polyradiculoneuropathy, involving proximal and distal limb regions, with weakness and large fiber sensory loss.<sup>4</sup> Although motor deficits may be as marked proximally as they are distally, a length-dependent process is also present, likely due to secondary axonal loss, and may in practice result in predominant distal deficits by the time of presentation.<sup>34</sup> Sensory deficits are similarly, frequently predominantly distal. In typical CIDP, immunologic studies may reveal the presence of a monoclonal gammopathy. When of IgG or IgA heavy chain, typical CIDP does not in the majority of cases differ from when the gammopathy

is absent, neither clinically, nor in treatment modalities or treatment response.<sup>8</sup> Particular attention is essential for IgM gammopathies, although, in typical presentations, CIDP is in that case too, similarly managed. Exclusion of a hematologic malignancy by multidisciplinary neuro-hematologic collaboration and the necessary investigations is mandatory in all, so as to confirm a Monoclonal Gammopathy of Uncertain Significance (MGUS), which still require periodic surveillance.<sup>8</sup> IgG/A gammopathies merit more concern when associated with a lambda rather than a kappa light chain. In such cases, presence of early distal axonal loss, atrophy and neuropathic pain may be suggestive of POEMS (Polyneuroneuropathy, Organomegaly, Endocrinopathy, M-protein, Skin) syndrome, which requires early diagnosis for appropriate treatment without which outcome is very poor. Although the other non-neuropathic features are expected, the syndrome is often incomplete. Measurement of serum VEGF (Vascular Endothelial Growth Factor), bone marrow studies and skeletal X-rays are useful for diagnostic confirmation, the monoclonal gammopathy being itself most often of low level.<sup>35</sup>

Atypical forms of CIDP represent a substantial minority of all cases, as described in different cohorts.<sup>36</sup> As demonstrated in large cohorts, such forms may also represent the initial phenotype which can however evolve over months to years to a typical CIDP, or, alternatively, remain unchanged.<sup>37</sup> The most common atypical form of CIDP is the multifocal asymmetric presentation, also known as “Lewis Sumner syndrome” (“LSS”), or “MADSAM” (“multifocal asymmetrical demyelinating sensory and motor”) neuropathy. Patients with LSS present with asymmetric deficits affecting two or more nerves. Upper limbs forms are more common.<sup>38</sup> Various hypotheses have been formulated with regards to the pathophysiologic differences between LSS and typical CIDP. Cellular immunity was proposed as of importance in LSS as opposed to typical CIDP.<sup>39</sup> This was based on electrophysiologic differences of demyelinating patterns, with a predominance of intermediate segment involvement and multifocal conduction block in LSS, possibly due to disruption of the blood nerve barrier by local activation of cell-adhesion molecules, cytokines and other inflammatory mediators. In contrast, in typical CIDP, demyelination was found predominantly distal and hypothesized to be caused by predominant humoral mechanisms. It is possible proximal as well as distal, rather than intermediate nerve segments are predominantly affected in typical CIDP as represent

areas of fragility of the blood nerve barrier. Differences in treatment response were also suggested as supporting this view, with good effect of steroids but not of IVIg in LSS.<sup>39</sup> However, this remains speculative, as other studies have found instead, poor response of LSS to steroids, or worse, deterioration with steroids, with, on the other hand, good response to IVIg.<sup>40</sup> In addition, the presence of antiganglioside antibodies in a minority of patients described with LSS casts further uncertainty on precise pathophysiologic mechanisms involved.<sup>38</sup> An overlap of LSS with multifocal motor neuropathy (MMN), which although a pure motor disorder may progressively involve sensory fibers, may be present. In presence of an MMN phenotype, sensory involvement may be secondary to more diffuse axonal loss and associated with disease severity, although remaining asymptomatic.<sup>41</sup> Motor CIDP although rare is heterogeneous with pure weakness clinically, but in some cases, both motor and sensory electrophysiologic involvement.<sup>42</sup> It presents with a symmetric picture affecting the four limbs proximally and distally, differentiating it from multifocal motor neuropathy which is asymmetric and upper limb-predominant. However, IgM anti-GM1 antibodies may occasionally be present in pure motor CIDP, as they are in about 50% of cases of MMN. Titers are similarly important and the relevance of low levels is uncertain. Avoidance of steroids is advised for motor CIDP as it is for MMN as there have been reports of deterioration, although it is possible that steroids may be safe and effective in the presence of sensory electrophysiologic abnormalities.<sup>37,42</sup> Pure sensory CIDP presents mainly with sensory ataxia as a result of impaired proprioception.<sup>4</sup> Motor function is preserved but this form of CIDP can be extremely disabling. The pure sensory form can also consist of an asymptomatic motor component illustrated by slowed motor conduction velocities. In addition, some patients have in addition to predominant sensory polyradiculopathy, some degree of sensory, postganglionic involvement.<sup>43</sup> Alternatively, electrophysiologic abnormalities may be exclusively sensory and there is also a rare form where no electrophysiologic defect is detected as a result of localized disease at the level of dorsal sensory rootlets. This form has become known as “chronic immune sensory polyradiculopathy” (“CISP”), and rare forms with concurrent motor root involvement have also recently been reported.<sup>44</sup> CISP, or its variants, are not to date known to be associated with a specific antibody.



Recently discovered anti-paranodal antibodies are associated with atypical CIDP phenotypes, expanding beyond the above-mentioned subtypes. The overwhelming majority of these antibodies are of IgG4 subtype, which are produced by regulatory B cells, and cannot fix complement or bind to immunoglobulin receptors. IgG4 antibodies, as a result, impair the function of their target antigens without involving inflammatory processes and, in the case of peripheral nerve disease, without causing demyelination.<sup>10</sup> Patients with anti-NF155 antibodies have been described with predominant distal weakness, ataxia and atypical, invalidating low-frequency and high-amplitude tremor.<sup>28</sup> Those with anti-CNTN1 antibodies have been reported with severe, predominantly motor disease of acute-onset<sup>30</sup> with recent reports in addition to describing associated glomerulonephropathy.<sup>45</sup> The few patients with anti-CASPR1 antibodies or antibodies to the CNTN1/CASPR1 complex have been described with acute GBS-like disease or with CIDP.<sup>10</sup> The main common denominator in these patients was, in all reports, their poor response to conventional treatment, in particular intravenous immunoglobulins. There have been several reports of the favorable effects of rituximab in this setting however,<sup>46</sup> as confirmed in our own experience, making prompt diagnosis offering a better chance of recovery, highly desirable.

## Future Perspectives

The discovery of antibodies to paranodal proteins offers the prospect that the dysimmune nature of CIDP may in future be proven early and directly. This would, it may be argued, reduce reliance on other indirect investigations, principally electrophysiology, the sensitivity and specificity of which, although appreciable, remains suboptimal.

However, it is apparent that only very few patients with a clinico-electrophysiological phenotype of CIDP are found to harbor these antibodies. It remains that previous studies considering other candidate antibodies have been in the setting of CIDP have been inconclusive. This leaves clinicians with little practical help from immunologic investigations at the current time, in diagnosis and management of subjects with clinically diagnosed, and electrophysiologically confirmed (or not), CIDP. The issue of testing for other antibodies in the setting of CIDP is otherwise one of the differential diagnoses, to exclude anti-MAG activity, POEMS syndrome, disialosyl antibodies in CANOMAD, Sjogren's syndrome or SLE, or a paraneoplastic syndrome. This is clearly different from

contributing directly to management within the CIDP spectrum itself.

It has been suggested that nearly half of patients with CIDP have antibodies against peripheral nerve myelin components. Although not contributing meaningfully to the management of the overwhelming majority of patients with CIDP to date, it may be hoped that this indicates the potential for future important advances in the field which may help tailor treatment to individual needs. In this regard, similar to antiparanodal antibodies appearing to suggest severe refractory disease, it is plausible other antibodies may similarly be discovered with other phenotypes including in the substantial proportion of patients with milder, treatment-responsive as well as remitting disease. This would prove invaluable to optimize management, reduce unnecessary and toxic therapies and their duration, as well as, importantly, provide optimistic prognostication for patients and families early in the disease course. For this to become reality, however, the technical aspects of immunologic testing will be of paramount importance to ensure consistency, reliability and reproducibility in between laboratories. Yet another technically unreliable test is certainly not what is needed, given existing high misdiagnosis rates,<sup>47</sup> however promising immunology may appear for CIDP. Finally, it has to be kept in mind, that despite extensive research, it is perfectly defensible to argue that antibodies identified so far, are clearly very rare and with little practical impact on patients' management and thus, remain of academic interest.<sup>48</sup> The modest progress made in the field despite decades of research provides little genuine hope for substantial major breakthrough findings in the near future. Improvement of patient care for dysimmune neuropathies may therefore not be as dependent on discoveries to come in neuroimmunology.

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