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Insight into the prognostic factors of chronic inflammatory demyelinating polyneuropathy

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Chronic inflammatory demyelinating polyneuropathy (CIDP) is an immune-mediated neuropathy with heterogeneous features. Appropriate treatment will produce a favorable outcome, but a poor treatment response and severe disability have also been reported. The roles of the clinical phenotypes and electrophysiological features of CIDP as well as of autoantibodies against nodal and paranodal proteins have been highlighted previously due to their association with the treatment response and long-term prognosis. This review addresses the diverse factors associated with the prognosis of CIDP.

Key words: Autoantibody; Chronic inflammatory demyelinating polyneuropathy; Clinical phenotype; Electrodiagnosis; Prognosis; Treatment

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INTRODUCTION

Chronic inflammatory demyelinating polyneuropathy (CIDP) is an immune-mediated neuropathy whose estimated prevalence ranges from 1 to 8.9 cases per 100,000.[1-5] CIDP is clinically important since it is a treatable neuropathy, with corticosteroids, intravenous immunoglobulin (IVIG), and plasma exchange being the most widely used first-line treatments. CIDP treatment should be initiated in the early phases of the disease to avoid the progression of demyelinating and secondary axonal degeneration. Most patients with CIDP respond successfully to standard treatment modalities. However, a poor treatment response and severe disability have been reported as long-term outcomes in certain patients. Reportedly 13-24% of patients with CIDP demonstrate severe disability despite treatment, while approximately 40% of them require continuous immunosuppressant therapy.[6-8]

CIDP is a heterogeneous disease with a wide range of clinical phenotypes and electrophysiological and immunological features. These heterogeneities could be responsible

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for the diversity of prognoses and treatment responses. This review addresses the numerous factors associated with the prognosis of CIDP and its response to treatment.

CLINICAL PHENOTYPES

Half of CIDP patients classically present as a chronic, progressive, symmetric neuropathy with proximal and distal weakness.[8,9] The remaining patients present with atypical manifestations such as asymmetry, distal predominance, and pure motor or pure sensory dysfunction. Based on the diagnostic criteria developed by the Joint Task Force of the European Federation of Neurological Societies and the Peripheral Nerve Society (EFNS/PNS), CIDP is categorized into 'typical' and 'atypical' phenotypes.[10] Typical CIDP, which is also described as classical CIDP, develops over a period of at least 2 months. It is characterized by symmetric motor and sensory neuropathy in both proximal and distal segments. Clinical manifestations of atypical CIDP include 1) multifocal acquired demyelinating sensory and motor neuropathy (MADSAM) or Lewis-Sumner syndrome, which shows an asymmetric pattern of involvement; 2) distal acquired demyelinating symmetric polyneuropathy (DADS), which predominantly involves a distal distribution; 3) pure sensory CIDP presenting with predominantly sensory symptoms; and 4) pure motor CIDP presenting with only motor symptoms and signs.

The response to treatment and prognosis of CIDP can vary with the clinical phenotype. CIDP has generally been reported to have a favorable treatment response and long-term outcome. However, atypical CIDP is characterized by a less-favorable response to treatment and a higher incidence of long-term disability. Previous studies have produced evidence of a poor response to treatment and long-term disability in patients with MADSAM compared to those with typical CIDP.[11-13] Typically 23-33% of patients with MADSAM showed no response to the first-line therapy,[11-13] and demonstrated a much worse response to IVIG compared to patients with typical CIDP.[11,13] Meanwhile, 40-50% of patients with MADSAM had severe disability associated with long-term prognosis, only 3-22% of those with typical CIDP exhibited severe disability.[11,12]

Previous studies have produced inconsistent results pertaining to the treatment response and prognosis in patients with DADS. Some studies found an improvement in the neurological deterioration (sensation or motor weakness) after treatment in these patients.[14,15] However, the response to treatment has been reported to be a less favorable in DADS than in typical CIDP. While 36-71% of patients with DADS displayed a poor overall response to treatment, only 13-16% of those with typical CIDP showed a compromised treatment response.[13,16] However, the disability score was lower in patients with DADS than in those with typical CIDP.[13] The treatment response of pure motor or pure sensory CIDP has also been reported for a single study that demonstrated favorable response rates of 88% and 90%, respectively, in patients affected by each of these conditions.[13] It is noteworthy that the response rate to IVIG was higher than that to corticosteroid therapy in pure motor and sensory CIDP (82% vs. 43% and 86% vs. 67%, respectively).[13]

The exact cause for the diversity in treatment responses and prognoses of CIDP based on clinical phenotypes is unknown. It can be hypothesized that this is attributable to different underlying disease pathomechanisms. Staudt et al.[17] reported stronger peripheral myelin antigen-specific T-cell responses with altered CD4+ memory subsets in atypical than typical CIDP. These differences in the immune responses between typical and atypical CIDP probably underlie the differences in treatment responses and prognoses. Kuwabara et al.[18] suggested that areas where the blood–nerve barrier is deficient are primarily prone to immune attack in typical CIDP. However, those authors pointed out that multiple-sclerosis-like cellular immunity with a breakdown of the blood–nerve barrier is the primary pathomechanism of MADSAM. It is likely that the difference in pathomechanisms between typical CIDP and MADSAM are related to differences in their phenotypes and electrophysiological features, producing differences in their treatment responses. However, the pathomechanisms underlying other phenotypes of CIDP are unclear. Further studies are essential to elucidate the primary pathomechanisms governing the various clinical phenotypes.

ELECTROPHYSIOLOGICAL FEATURES

Electrodiagnostic studies are essential for diagnosing CIDP.

Electrodiagnostic data can be used for both diagnosing and predicting the prognosis of these conditions. Electrodiagnostic data can also provide information regarding the degree of demyelination in CIDP, which in turn is likely to be related to the treatment response. Abraham et al.[19] reported that a higher fulfilment of the electrodiagnostic criteria is associated with higher treatment response rates in CIDP. CIDP patients with diabetes mellitus (DM) demonstrated higher treatment response rates when they fulfilled two or more EFNS/PNS electrodiagnostic criteria (89% vs. 36%, $p = 0.01$). Those findings highlight the role of the EFNS/PNS criteria as a favorable predictor of a treatment response in CIDP patients with DM (odds ratio = 3.73, $p = 0.01$). In addition, a change in the number of demyelination findings in serial electrodiagnostic studies is probably associated with clinical relapse.[20] Chin et al.[20] reported than an increase in the total number of demyelinating features or the development of four or more new demyelinating features is indicative of a high risk of relapse after the discontinuation of IVIG therapy. Furthermore, the absence of new demyelinating features in follow-up electrophysiological studies is suggestive of a reduced risk of subsequent relapse.[20]

Electrophysiological characteristics suggesting axonal dysfunction in peripheral nerves could be indicative of a poor treatment response in CIDP. Iijima et al.[21] demonstrated that a decreased compound muscle action potential (CMAP) amplitude is more prominent in non-responders to IVIG treatment, which is likely to be associated with axonal degeneration. On the other hand, electrophysiological features reflecting demyelination such as conduction block were associated with a more-favorable treatment response.[21] In contrast, a recent study using electrophysiological data-driven clustering analysis found that a decreased CMAP amplitude might not be indicative of a poor prognosis in CIDP.[22] A patient with a reduced CMAP accompanied by prominent demyelination-associated findings might have a favorable prognosis, thereby mandating active treatment.

Electrodiagnostic measurements could be useful predictors of the prognosis in CIDP. Previous studies have found that electrodiagnostic measurements are strongly correlated with clinical outcomes. It is noteworthy that CMAP amplitudes are associated with different clinical measures, including an overall adjusted inflammatory neuropathy cause and treatment disability score, Medical Research Council sum score, and dominant-hand grip power.[23] It is particularly interesting that the changes in CMAP amplitudes from baseline are correlated with changes in clinical outcome measures.[23] Furthermore, Rajabally and Narasimhan[24] reported that the CMAP amplitude is correlated with the degree of weakness and functional score in patients with CIDP. They suggested that the amelioration of the CMAP and normalization of the nerve conduction velocity can represent prognostic markers of clinical improvement in CIDP.[24] Therefore, electrophysiological measurements are likely to play an essential role as predictors of the treatment response and long-term disability.

IMMUNOLOGICAL FEATURES OF CIDP

There are recent reports of CIDP patients carrying autoantibodies against nodal and paranodal proteins. The absence of macrophage-mediated demyelination and relatively higher frequencies of axoglial dysfunction are characteristic features in CIDP patients with these autoantibodies.[25] The autoantibodies are generated against the cell adhesion molecules that play a role in the formation of septate-like junction in the axons, including neurofascin-155 (NF155), contactin-1 (CNTN1), and contactin-associated protein-1 (CASPR1).

NF155 is localized in the paranodal junctions and is essential for paranodal junction formation. Anti-NF155 has reportedly been detected in 4-18% of patients with CIDP.[26-32] These patients were characterized by a young age at onset, tremors, ataxia, and a poor response to IVIG.[26,28,31] CNTN1 is an axial adhesion molecule that plays an essential role in the formation of the node of Ranvier. It interacts with CASPR1 on the axon and NF155 on the glial side (glial counterpart of CNTN1). Anti-CNTN1 was detected in 2-7% of patients with CIDP.[32-34] While CNTN1-positive CIDP patients showed poor responses to IVIG treatment, they demonstrated favorable responses to corticosteroids.[26,33] Autoantibodies against CASPR1 were reported in two patients with inflammatory neuropathy: one with CIDP and one with Guillain-Barré syndrome.[35] CIDP patients with CASPR1 showed poor responses to IVIG and corticosteroids. Together these findings suggest that the presence of autoantibodies against NF155, CNTN1, or CASPR1 is predictive of a poor response to treatment in CIDP patients. Recent studies found that rituximab was ef-

fective in patients with refractory CIDP who tested positive for autoantibodies against nodal and paranodal proteins.[29,36]

CONCLUSION

CIDP is a chronic immune-mediated demyelinating polyneuropathy with diverse clinical manifestations. It has a favorable outcome with the appropriate treatment. The treatment response and prognosis vary with the clinical, electrophysiological, and immunological features in particular CIDP patients, and hence several factors need to be considered when treating this condition.

Conflicts of Interest

The author declares no conflicts of interest relevant to this article.

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