Progress in diagnosis and treatment of chronic inflammatory demyelinating polyradiculoneuropathy

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Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is a rare and heterogeneous but treatable immune-mediated neuropathy. Nerve conduction studies are considered essential for a definite diagnosis, but poor performance and misinterpretation of the results frequently leads to misdiagnosis. Nerve ultrasound and MRI could be helpful in diagnosis. Whereas typical CIDP is relatively easy to diagnose, atypical variants with distinct phenotypes can be a diagnostic challenge. Intravenous or subcutaneous immunoglobulin, corticosteroids, and plasma exchange are effective treatments, but maintenance treatments are often required for years, and treatment regimens require careful and regular adjustments to avoid undertreatment or overtreatment. Patients who do not improve, or insufficiently improve after treatment, might have specific characteristics related to a distinct disease mechanism caused by immunoglobulin G4 antibodies to nodal or paranodal proteins, and could require alternative treatments. Future studies should focus on curative and individualised treatment regimens to improve the patient's condition and to prevent further nerve damage.

Introduction

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is an immune-mediated neuropathy, with reported prevalence ranging 0·67–10·3 cases per 100 000 people and reported incidence ranging 0·15–10·6 cases per 100 000 person-years.[1] Epidemiological studies show a male predominance with increasing incidence and prevalence with age. Risk factors are as of yet unknown.[1,2] CIDP is clinically and immunologically more heterogeneous than previously thought, which has resulted in an extended group of CIDP variants, including distal predominant and asymmetric variants.[2–8] The diagnosis of CIDP can be difficult, especially in patients who do not show a typical progressive or relapsing sensory-motor polyneuropathy with involvement of proximal muscles. CIDP is a treatable condition, and thus avoiding diagnostic delay is important, but misdiagnosis of CIDP is common.[9–12] The diagnosis can be challenging because the demyelinating features fulfilling the European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS) 2010 electrodiagnostic criteria[4] for CIDP are not always present in patients who clinically are suspected to have CIDP.[10] In these patients, nerve imaging, either with ultrasound or MRI, can show proximal median nerve or nerve root enlargement indicating the presence of an immune-mediated polyneuropathy.[13–16] An important new development in the diagnostic investigations in patients with a clinical phenotype of CIPD is the identification of immunoglobulin G4 (IgG4) antibodies against nodal and paranodal proteins.[3,17–34] Patients with CIDP can be treated with intravenous or subcutaneous immunoglobulin, corticosteroids, or plasma exchange.[35–39] Patients with the IgG4 subclass antibodies might not sufficiently respond to the standard CIDP treatments, but can show remarkable improvement after treatment with rituximab, a monoclonal anti-CD20 antibody that depletes B cells.[17,19,21,24,27,40] In this Review, we provide an update on clinical phenotypes, diagnosis, and treatment of CIDP, including CIDP variants; on patients with IgG4 antibodies against nodal and paranodal proteins; on imaging techniques to help diagnose CIDP; and finally on possible future treatments.

Clinical phenotypes

The hallmark of typical CIDP is a chronic progressive, monophasic, or recurrent demyelinating polyradiculoneuropathy with a progressive phase of weakness that exceeds 2 months, often with sensory dysfunction and absent or reduced tendon reflexes.[4] Some patients with CIDP have had more rapidly progressive symptoms or treatment-related fluctuations that initially suggested Guillain-Barré Syndrome.[3,41]

Typical CIDP and atypical CIDP variants

A variety of clinical phenotypes are referred to as CIDP, but whether these are all atypical CIDP variants, or CIDP-like diseases with a different pathogenesis, which seems to be the case in patients with IgG4 antibodies against nodal and paranodal proteins, is unclear.[2–7,42] An overview of the phenotypes of typical CIDP and atypical CIDP variants is provided (table 1, figure). Because of the absence of unambiguous definitions, the reported frequencies of typical CIDP and atypical CIDP variants vary between studies.[2–7,42] The typical symmetric, sensory-motor CIDP phenotype with a progressive phase of at least 2 months accounts for at least 50% of patients.[2–4,6,7] However, up to 18% of patients with CIDP have a more acute disease onset, also known as acute-onset CIDP (A-CIDP).[4,6,41] These patients reach a clinical nadir within 2 months, after which there are relapses or further disease progression. This clinical course needs to be distinguished from subacute inflammatory demyelinating polyneuropathy, which is a monophasic disease with a nadir between 4–8 weeks, followed by clinical improvement.

Atypical CIDP variants include patients with asymmetric or a focal distribution of weakness.[2–7] Another atypical CIDP variant includes patients with predominant distal motor and sensory involvement, also labeled as

	Epidemiology	Clinical symptoms	Distribution of symptoms	Treatment response	Mimics and additional information
Typical CIDP					
Sensory-motor[2-4,6,7]	>50%	Chronic onset; motor and sensory	Symmetric; usually proximal rather than distal	Intravenous immunoglobulins, corticosteroids, and plasma exchange effective	Other more common sensory-motor neuropathies (eg, paraproteinemic or hereditary neuropathy)
Acute onset[4,6,41]	Around 18%	Subacute onset; motor and sensory	Symmetric; proximal and distal	Intravenous immunoglobulins, corticosteroids, and plasma exchange effective	Guillain-Barré Syndrome; might resemble patients with NF155 and CNTN1 antibodies
Atypical CIDP variants					
Asymmetric*[2-7]	8–15%	Chronic onset; motor and sensory	Asymmetric; distal rather than proximal; upper rather than lower limbs	Intravenous immunoglobulins, corticosteroids, and plasma exchange effective	MMN; HNLPP; vasculitis; neuralgic amyotrophy, spinal muscular atrophy
Focal†[3-7]	Around 1%	Chronic onset; slow disease progression; motor and sensory	Brachial or lumbosacral plexus or one or more peripheral nerves in one limb; proximal and distal; upper and lower limbs	Intravenous immunoglobulins, corticosteroids, and plasma exchange effective	MMN; HNLPP; vasculitis; neuralgic amyotrophy; spinal muscular atrophy; somatosensory evoked potential can show proximal demyelination
Distal predominant‡[2-7]	2–10%	Chronic onset; sensory more than motor	Symmetric; distal rather than proximal	Intravenous immunoglobulins, corticosteroids, and plasma exchange effective (if MAG antibodies not present)	IgM-MGUS with MAG antibodies; might resemble patients with NF155 antibodies; other common forms of neuropathies (eg, diabetic, CIAP)
Motor predominant[2-7]	4–10%	Chronic onset; motor more than sensory	Symmetric; proximal and distal	Intravenous immunoglobulins effective; patients' condition might deteriorate after corticosteroids	Guillain-Barré Syndrome; motor neuropathies; motor neuron disease; might resemble patients with CNTN1 antibodies
Sensory predominant[2-7,42] (including CISP)	4–35%	Chronic onset; sensory more than motor; sensory ataxia (in CISP)	Symmetric; distal rather than proximal; upper rather than lower limbs	Intravenous immunoglobulins, corticosteroids, and plasma exchange effective	Paraneoplastic polyneuropathy; paraproteinemic neuropathy; connective tissue disease; ataxic neuropathies (CISP mimic); CISP: normal nerve conduction studies but somatosensory evoked potential can show proximal demyelination
Phenotype with IgG4 antibodies against nodal and paranodal proteins					
NF155[17-19,23,24,28,30,43]	4–18%	Subacute severe onset at around age 25 years; motor more than sensory; sensory ataxia; tremor	Symmetric; distal rather than proximal	Poor response to intravenous immunoglobulins; partial response to corticosteroids; potentially good response to rituximab and plasma exchange	Detected in other peripheral nervous system disorders (eg, Guillain-Barré Syndrome, genetic neuropathies); NF155 antibodies are associated with HLA-DRB15 alleles[44]
NF140 and NF186[17,18]	2–5%	Subacute onset; motor and sensory; sensory ataxia; cranial nerve deficits can occur	Symmetric	Partial response to intravenous immunoglobulins and corticosteroids; potentially good response to rituximab	Ataxic neuropathies; concomitant autoimmune diseases[18]
CNTN1[21,26,27,31,43]	1–7%	Subacute severe onset at around age 25 years; motor more than sensory; sensory ataxia; tremor	Symmetric; proximal and distal	Poor response to intravenous immunoglobulins; partial response to corticosteroids; potentially good response to rituximab	Guillain-Barré Syndrome; motor neuropathies; motor neuron disease; nerve conduction study can show early signs of axonal involvement
CASPR1[18,20]	1–3%	Subacute severe onset; motor more than sensory; neuropathic pain	Symmetric; distal rather than proximal	Poor response to intravenous immunoglobulins; potentially good response to rituximab	Painful neuropathies (eg, vasculitis)

CIDP=chronic inflammatory demyelinating polyradiculoneuropathy. NF=neurofascin. CNTN=contactin. MMN=multifocal motor neuropathy. HNLPP=hereditary neuropathy with liability to pressure palsies. Ig=immunoglobulin. MGUS=monoclonal gammopathy of undetermined significance. MAG=myelin-associated glycoprotein. CIAP=chronic idiopathic axonal polyneuropathy. CISP=chronic immune sensory polyradiculopathy. HLA=human leucocyte antigen. CASPR=contactin-associated protein. *Additionally termed multifocal acquired demyelinating sensory and motor neuropathy or Lewis-Sumner Syndrome. †Involvement of only the brachial or lumbosacral plexus or one or more peripheral nerves in one limb.[4] ‡Additionally termed distal acquired demyelinating symmetric polyneuropathy.

Table 1: **Clinical characteristics of typical CIDP and atypical variants**

distal acquired demyelinating symmetric polyneuropathy. These patients might have an IgG, IgA, or IgM isotype of monoclonal gammopathy of undetermined significance (MGUS). Approximately half of the patients with an IgM MGUS have antibodies against myelin-associated glycoprotein (MAG).[45] IgM anti-MAG-associated neuropathy has a different disease mechanism to CIDP.[4,45] However, patients with an IgM MGUS without anti-MAG antibodies, who have a CIDP-like disease course, are generally considered atypical CIDP variants and can have treatment responses similar to those with typical CIDP.[45] In some patients with a chronic polyneuropathy, an IgG, IgA, or IgM isotype of monoclonal gammopathy is associated with a haematological malignancy.

The boundaries of the atypical CIDP variants are not yet clearly defined, and phenotypes can change over time

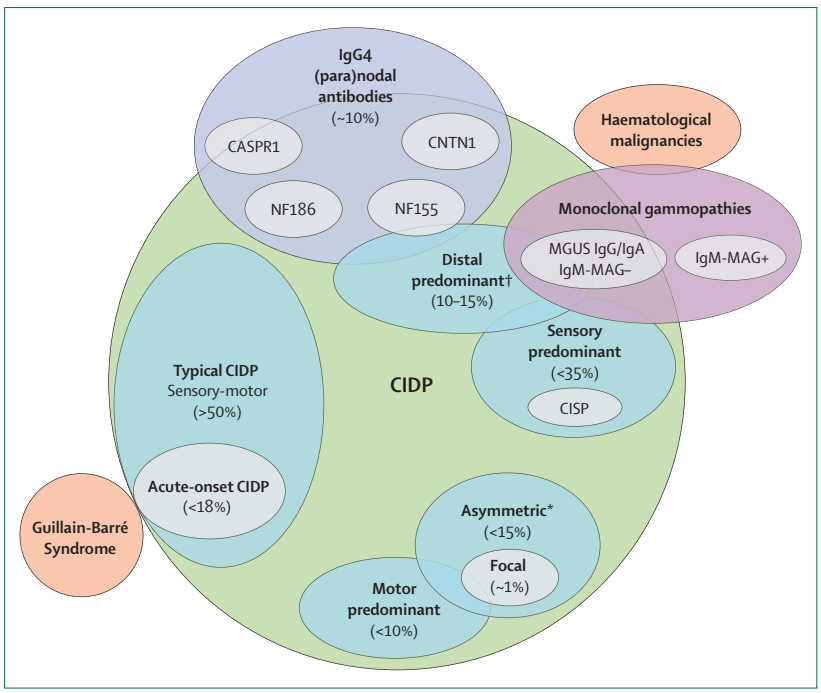

Figure: **Clinical phenotypes of CIDP**
Phenotypes can be classified into typical CIDP and atypical CIDP variants. CASPR=contactin-associated protein. CIDP=chronic inflammatory demyelinating polyradiculoneuropathy. CISP=chronic immune sensory polyradiculopathy. CNTN=contactin. Ig=immunoglobulin. MAG=myelin-associated glycoprotein. IgM-MAG–=IgM monoclonal gammopathy without MAG antibodies. IgM-MAG+=IgM monoclonal gammopathy with MAG antibodies. MGUS=monoclonal gammopathy of undetermined significance.NF=neurofascin. *Additionally termed multifocal acquired demyelinating sensory and motor neuropathy or Lewis-Sumner Syndrome. †Additionally termed distal acquired demyelinating symmetric polyneuropathy.

See Online for appendix

(eg, asymmetric variants could develop into a more typical symmetric phenotype).[7]

Patients with IgG4 antibodies to nodal and paranodal proteins

Over the past 6 years, autoantibodies against nodal and paranodal proteins were reported in about 10% (range 1–18) of patients diagnosed with CIDP, who have atypical clinical phenotypes and impaired response to the standard CIDP treatments (table 1).[29,34] These antibodies are considered pathogenic and are directed to various cell adhesion proteins located at or near the node of Ranvier, including the paranodal proteins neurofascin isoform 155 (NF155), contactin-1 (CNTN1), contactin-associated protein-1 (CASPR1),[19,20,27,31] and to the nodal proteins neurofascin isoforms 140 and 186 (NF140 and NF186) (appendix).[17,18]

NF155 is a transmembrane adhesion molecule expressed by glial cells located at the paranodes, connecting the myelin sheath to the axon via binding of CNTN1 and CASPR1 by the formation of axoglial junctions in the paranodal loops of myelinated fibres. Anti-NF155 antibodies have been reported in 4–18% of patients with CIDP.[17,19,24,28,30,43] The high variation in the proportion of patients with NF155 antibodies might be because of study heterogeneity regarding patient selection and methods for antibody detection. These antibodies are associated with a distal predominant phenotype with tremor, ataxia, and a poor response to intravenous immunoglobulin treatment.[17,19,23,24,28,30] The nodal isoforms of neurofascin, NF140 and NF186, are both axonal membrane proteins expressed at the node of Ranvier, are involved in clustering of sodium channels, and interact with gliomedin and neuronal cell adhesion molecules.[17,18,24] In contrast to NF155 antibody-positive patients, tremor can be absent in NF140 and NF186 antibody-positive patients, and the response to intravenous immunoglobulin seems better.[17,18]

Antibodies against CNTN1, CASPR1, and the CNTN1-CASPR1 complex can be found in 1–7% of patients with CIDP.[20,21,27,31,43] The clinical phenotype can include a subacute and aggressive disease onset similar to Guillain-Barré Syndrome, early signs of axonal involvement in nerve conduction studies, and poor or partial response to intravenous immunoglobulin treatment, with a slightly better response reported to corticosteroid treatment.[21,26,27,31]

Diagnosis

Because no biomarker exists for CIDP, nerve conduction studies that show features of a demyelinating polyneuropathy are considered essential for the definite diagnosis of CIDP.[4] At least 15 different diagnostic criteria have been developed for CIDP that are useful for research purposes, but might not identify all patients with a clinical suspicion of CIDP.[46] The most frequently used CIDP criteria in clinical practice and research are the revised European Federation of Neurological Societies/Peripheral Nerve Society 2010 criteria,[4,47] which include both clinical and electrodiagnostic criteria (appendix). The clinical criteria are divided into typical and atypical, and electrodiagnostic criteria into definite, probable, and possible.[4] The electrodiagnostic criteria are based on the presence of features suggestive of acquired demyelination (partial conduction block, prolonged distal and F-wave latencies, slow conduction velocities, and abnormal temporal dispersion) in one or more motor nerves.[4] To avoid misinterpretation of nerve conduction studies, limb temperature should be at least 33°C at the palm and 30°C at the external malleolus, otherwise the limbs need to be preheated. Distal compound muscle action potential amplitude should be sufficiently large before conclusions can be made regarding the presence of conduction slowing (usually at least 0·5 mV) or conduction blocks (usually at least 1 mV).[4] Laboratory testing is important to exclude other diagnoses such as diabetes mellitus and haematological malignancies associated with a monoclonal gammopathy, and should include assessment of fasting glucose, haemoglobin A_{1c}, complete blood count, electrolytes, liver function, renal function, thyroid function, vitamin B12, and screening for the presence of a monoclonal gammopathy in serum and urine (including electrophoresis, immunofixation, and free light chain analysis). Skeletal surveys (x-ray or scintigraphy) can be ordered to detect plasmacytoma or myeloma. Additional

laboratory tests can be done and might include testing for HIV, neuroborreliosis, and anti-nuclear antibodies.[4] Eliminating the possibility of a genetic neuropathy (eg, Charcot-Marie-Tooth disease type-1A and transthyretin familial amyloid polyneuropathy) is important because clinical and diagnostic findings could resemble CIDP findings and are important for prognosis and treatment strategies.[48] Supportive criteria of CIDP include elevated CSF protein concentration with normal leukocyte count. Enlarged nerves or nerve roots on MRI or nerve ultrasound, and clinical improvement following immunomodulatory treatment indicated by disease-specific quantitative outcome measures (such as muscle or grip strength, disability scales, or quality of life scales) would further support the diagnosis.[4,49,50] Questions about an accurate diagnosis of CIDP should arise in the presence of weakness of respiratory muscles, clear asymmetric distribution of weakness, severe tremor, ataxia or muscle atrophy at disease onset, painless injuries, autonomic dysfunction, prominent pain, and no improvement after one or more proven effective treatment regimens. In these situations, the diagnosis of CIDP should be reconsidered.

The diagnosis of CIDP can be made when patients fulfil a set of clinical, electrodiagnostic, and laboratory criteria.[4,46] However, the diagnosis can be difficult, in part because of the extensive list of differential diagnoses that mimic CIDP.[51] Poorly performed nerve conduction studies, misinterpretation of their findings, and non-adherence to electrodiagnostic criteria commonly lead to misdiagnosis.[4,5,10,11,51] An incorrect diagnosis can also occur in patients reporting subjective improvement after treatment, or when minor elevation of the CSF protein concentration (probably not exceeding 1 g/L) is considered clinically relevant by the treating neurologist.[9–11,52,53] Misdiagnosed cases of CIDP are reported in 15–89% of patients, with the lowest proportion occurring when diagnosis was made with the use of CIDP diagnostic criteria or by a neuromuscular specialist.[9,10,12,37,53] These studies show that acceptance of and compliance with international CIDP guidelines seems suboptimal in general neurological practice, confirmed by an international audit performed on compliance of the EFNS/PNS 2010 guidelines[4] on CIDP and multifocal motor neuropathy in daily neurological practice.[54]

Nerve imaging

Results of MRI and nerve ultrasound assist in the diagnosis of CIDP and might be particularly useful in patients with suspected CIDP, who do not fulfil the electrodiagnostic criteria (appendix).[4,49] MRI can identify hypertrophy or contrast enhancement of the cervical nerve roots, brachial or lumbosacral plexuses, and cauda equina.[14] Previous MRI studies have mainly focused on imaging of the brachial plexuses, with reported abnormalities (ie, nerve enlargement or signal hyperintensity, or both) in 44–82% of patients with CIDP.[16,55–57] Variation could be attributed to study differences in patient selection, imaging techniques, and the use of different cutoff values for nerve measurements. Most studies did not find an association between the presence or extent of abnormalities on MRI and clinical disease severity or duration.[16,56,57] A Japanese study that investigated whole-body MR neurography in 13 patients with CIDP and 12 healthy controls reported a positive correlation between disease duration and nerve volume, but this was a small and heterogenous study population, and results require confirmation.[58] Nerve MRI might be a helpful tool in supporting the diagnosis of CIDP, but is expensive, time consuming, and requires radiological expertise and standardised protocols with definitions of normal and abnormal values. Nerve ultrasounds are less expensive and time consuming than MRI and can measure nerves more proximally, especially in the upper limbs.

A Dutch comparative study in 23 treatment-naive patients with CIDP and 28 patients with multifocal motor neuropathy showed a comparable diagnostic performance of MRI and nerve ultrasound in the detection of abnormalities of the brachial plexus.[15] This could suggest the possibility of a relevant role for nerve ultrasound testing in the diagnosis of CIDP. A prospective Dutch case-control study on the diagnostic value of nerve ultrasound in chronic inflammatory neuropathies (53 patients with CIDP, 22 with motor neuropathies, 50 with axonal neuropathies, and 20 patients with amyotrophic lateral sclerosis) reported that nerve enlargement, especially in proximal median nerve segments and the brachial plexus, can reliably distinguish inflammatory neuropathies from axonal neuropathies and motor neuron disease.[13] Nerve enlargement has been reported in up to 90% of patients with CIDP, but available data are inconclusive concerning possible correlations with clinical characteristics (eg, disease duration, disease severity, or response to treatment).[13,49,59–62] Many studies on nerve imaging do not include the most relevant disease controls for the differential diagnosis of CIDP (eg, other immune-mediated or genetic neuropathies such as polyneuropathy related to monoclonal gammopathy or Charcot-Marie-Tooth type 1A); therefore, sensitivity and specificity in CIDP and CIDP-like disorders are nowadays difficult to establish.[13–15,49,55,56,58–62] Additional studies that use larger populations, include clinically relevant control groups, ensure repeated nerve measurements over time, include analysis on clinical and electrodiagnostic correlations, and provide comparisons with nerve conduction studies, could help to identify the precise utility of ultrasound in the diagnostics of CIDP, and the possible use of ultrasound as a biomarker for disease severity or treatment response.

Pathophysiology

CIDP is considered an immune-mediated disorder, although the pathogenesis remains to be elucidated. Evidence for involvement of auto-reactive T cells, B cells, soluble factors in nerve tissue including inflammatory cytokines and chemokines, antibodies against various nerve glycolipid and glycoprotein structures, and increased

concentrations of complement factors (eg, C5a, soluble terminal complement complex) have been found in patients with CIDP.[8,34,44,63–65] A Swiss case-control study on skin biopsies in 20 patients with CIDP and 17 healthy controls found a significant change in the expression of genes involved in immune and chemokine regulation in patients with CIDP.[66] Increased expression levels of the activating FcγI-receptors on monocytes and a reduced expression level of the inhibitory FcγIIb-receptors on naive and memory B cells, as well as on monocytes, has been found in the blood of treatment-naive patients with CIDP.[64] This disturbed Fcγ receptor regulatory system in patients with CIDP was partly restored after intravenous immunoglobulin therapy.[64,67] Improvement after intravenous immunoglobulin, corticosteroids, and plasma exchange additionally supports an underlying immune-mediated mechanism in patients with CIDP.[8,64,67]

The finding of IgG4 autoantibodies to nodal and paranodal proteins in a group of patients with a CIDP-like phenotype further indicates a pathogenic diversity.[17–21,23,24,27,28,30,31,40,43] These antibodies are usually—but not exclusively—of the IgG4 subclass.[17,20,21,27,28,30] IgG4 antibodies have a low capacity to bind to FcγIIb-receptors, cannot activate complement, and are considered anti-inflammatory. An increasing number of conditions have been identified in which IgG4 antibodies directly contribute to neural injury by binding to neural targets and interfering with their function, including myasthenia gravis, for which IgG4 antibodies against muscle-specific kinase are found,[68] parasomnia with antibodies against IgLON5,[69] limbic encephalitis with antibodies against leucine-rich glioma inactivated-1,[70,71] neuromyotonia, Morvan's syndrome, and limbic encephalitis with antibodies against CASPR2.[72,73] In addition to the finding of IgG4 NF155 antibodies in patients diagnosed with CIDP, these antibodies are also reported in some patients with Guillain-Barré Syndrome, and genetic or idiopathic neuropathies.[17,18]

The clinical relevance of these antibodies in disorders other than CIDP is not yet known and requires further investigation. Two studies screened a combined cohort of 199 patients with inflammatory neuropathies, patients with genetic neuropathies, disease controls, and healthy controls and reported the presence of IgM antibodies against NF155 and NF186 in some patients with CIDP and transient presence in some patients with Guillain-Barré Syndrome.[17,22] Further research is needed to determine the full range and specificity of nodal and paranodal antibodies, their clinical relevance, and their pathogenic role.[17,22] The term nodo-paranodopathy is proposed for patients with IgG4 antibodies. These patients might have distal predominant weakness with tremor and ataxia, or a subacute and severe disease course, but not the pathological features that are usually reported in patients with typical CIDP.[26,28,29,31,32,44,74] The strong association between NF155 IgG4-antibody positive patients and human leucocyte antigen DRB15 provides genetic evidence that the presence of these antibodies determines a specific subgroup of patients.[44] Although the proportion of these IgG4-antibody positive patients within the CIDP phenotype is relatively small (around 10% of CIDP patients), their detection has changed the understanding of pathogenesis and heterogeneity within the field of peripheral neuropathies, specifically in CIDP. Detection of these antibodies is helpful for diagnostic purposes and treatment strategies. The concept of nodo-paranodopathy is based on the observation that in acute axonal motor neuropathy, a subtype of Guillain-Barré Syndrome, motor nerve conduction slowing and conduction blocks occur because specific antibodies bind at the node and paranode, resulting in disorganisation of sodium channels and myelin detachment.[74] If the autoimmune process continues, axonal degeneration occurs but often the progress is aborted, and the nerve conduction abnormalities can be reversible, as shown by serial nerve conduction studies.[75] Electrodiagnostic findings in patients with IgG4 antibodies have shown signs of early axonal degeneration, especially in (but not exclusively in) patients with CNTN1 antibodies.[21,26,31] Pathological studies in patients with IgG4 antibodies do not show the typical demyelinating features (eg, onion bulbs, inflammation, or macrophage-mediated demyelination) as can be seen in patients with typical CIDP.[12,17–19,58,72,76] By contrast, widened nodes, detached myelin loops, and axonal degeneration without signs of regeneration are reported in patients with IgG4 antibodies.[21,26,32,33,43] Therefore, the term CIDP for neuropathies associated with nodal or paranodal IgG4 antibodies might not be appropriate since they are neither demyelinating nor inflammatory. Rather, they possibly should be classified as CIDP-like chronic nodoparanodopathies.[32,34,74]

Treatment

CIDP treatment can be divided into induction and maintenance treatment. Corticosteroids, plasma exchange, intravenous and now subcutaneous immunoglobins are proven effective treatments for CIDP (table 2).[36,37,39,82] Low-dose methotrexate and fingolimod were not efficacious in two placebo-controlled randomised controlled trials in patients with CIDP who received intravenous immunoglobulin or corticosteroid maintenance treatment.[39,83,84] The methotrexate trial investigated whether intravenous immunoglobulin or corticosteroid doses could be reduced when methotrexate or placebo were administered as add-on treatments. The fingolimod trial was done in a cohort of patients with CIDP treated with intravenous immunoglobulin or corticosteroids. Following the initiation of fingolimod or placebo, intravenous immunoglobulin was discontinued and corticosteroids were stopped after tapering. This trial was discontinued because of futility. Possible reasons for these results include ineffectivity of the drugs, study design issues (eg, low number of randomised patients, use of relatively low doses of treatment, discontinuation instead of treatment withdrawal),

	Administration	Costs	Side-effects	Response	Suggested treatment regimen
Intravenous immunoglobulins	Intravenous, at home or in hospital	Expensive*	Often headache, influenza-like symptoms, skin rash; rarely venous thrombosis, haemolytic anaemia, anaphylaxis[39]	Fast†	Initiation: 2 g/kg;[4,77,78,79] maintenance: 0·4–1·2 g/kg (usually no more than 80 g per day), every 2–6 weeks;[77–80] 15% of patients with CIDP require only 1–2 courses to reach remission[81]
Subcutaneous immunoglobulins	Subcutaneous, at home	Expensive*	Often local swelling and erythema at injection site, infections[35]	Probably fast†	Same maintenance dosage as for intravenous immunoglobulins;[35] injections could be given at multiple sites, or more frequently
Corticosteroids	Oral or intravenous, at home or in hospital	Inexpensive‡	Hypertension, glucose intolerance, mental and ocular disturbances, weight gain, osteoporosis, susceptibility to infections[37,39]	Can be fast, but usually slow§	Initiation: oral 60 mg prednisolone daily; maintenance: oral slowly tapering over weeks; pulsed oral high-dose dexamethasone 40 mg 4 days per month; methylprednisolone infusions, various regimens[37,39]
Plasma exchange	Intravenous, in hospital	Expensive*	Vasovagal reactions, complications because of venous access, citrate toxicity, infections[39,82]	Fast†	Initiation: usually 5–10 sessions in 2–4 weeks on alternate days; maintenance: 1 session every 2–6 weeks[39]

CIDP=chronic inflammatory demyelinating polyradiculoneuropathy. *Highly variable because of differences in intravenous and subcutaneous immunoglobulin or plasma exchange regimens, but can range from about €10 000 up to more than €60 000 per year. †Fast response is usually within 1 or 2 weeks. ‡Variable because of differences in corticosteroid regimens, including prophylaxis drugs for osteoporosis and opportunistic infections (eg, pneumocystis pneumonia), can cost from about €200 to €500 per year. §Slow response is usually within several weeks or months.

Table 2: **Treatment approaches for patients with CIDP**

and the unexpected proportion of patients who likely had inactive CIDP.[83] A Cochrane review[84] concluded that several types and regimens of different drugs, including rituximab, cyclophosphamide, etanercept, eculizumab, alemtuzumab, natalizumab, and haematopoietic stem cell transplantation seem to be effective in case reports or small studies in patients with CIDP (sample size ranging from 1–32 patients), but larger randomised controlled trials are required to confirm efficacy. Results from previous clinical trials have shown that it is important to include only patients with active disease (eg, by including a washout period to determine treatment dependency) and to use disease-specific objective outcome measures (eg, grip strength and measures of disability and quality of life).[50,85]

Acute phase

Induction treatment of CIDP with the most effective dose and regimen is important to improve the patient's condition and to prevent secondary axonal degeneration. Intravenous immunoglobulin is usually given at a dose of 2 g/kg bodyweight over 2–5 days.[4,36] Some patients only need one or two courses of intravenous immunoglobulin (2 g/kg) to induce remission.[81] Other patients require at least two intravenous immunoglobulin courses to show initial improvement.[77] Subcutaneous immunoglobulin (given at a weekly dose of 0·4 g/kg bodyweight for 5 weeks, applying 2–3 infusions per week) can possibly also be administered as treatment in the acute phase of disease.[86] If treatment is initiated with corticosteroids, a number of regimens are available and seem equally effective:[87] oral prednisolone (usually starting with 60 mg/day), pulsed high-dose dexamethasone (usually starting with 40 mg for 4 days every 4 weeks), or intravenous methylprednisolone (starting with 1000 mg weekly or monthly). No specific corticosteroid treatment is proven to be most effective, but pulsed oral and intravenous corticosteroid treatments possibly have fewer steroid-associated side-effects.[37,87] Plasma exchange can also be considered, especially in patients with CIDP not responding to intravenous immunoglobulin or corticosteroids, or in patients with severe symptoms. A plasma exchange course of 5–10 sessions within 2–4 weeks on alternate days is commonly used.[39,82] The likelihood of improvement after treatment with intravenous immunoglobulin, corticosteroids, or plasma exchange is about 50–80%.[36,37,39,81,82,87] A common question is whether to give intravenous immunoglobulin or corticosteroids as first line treatment. Side-effects are generally minor after treatment with intravenous immunoglobulin and potentially more frequent and severe after long-term use of corticosteroids.[36,37] Additionally, patients can have a more rapid response to intravenous immunoglobulin treatment than observed with corticosteroids.[36] Two studies have shown limited evidence for higher remission rates at 6 months following pulsed high-dose corticosteroid treatment than for intravenous immunoglobulin or oral prednisolone daily, but comparative data on long-term remission rates are not available.[37,88]

When a patient does not improve after the first treatment regimen, the diagnosis should be reconsidered because misdiagnosis is common.[9,10] A multicentre retrospective study in treatment-naive patients with CIDP showed that 214 (76%) of 281 patients responded to intravenous immunoglobulin treatment.[81] 58 of the 67 intravenous immunoglobulin non-responders were assigned to subsequent treatment with either plasma exchange or corticosteroids. 16 (67%) of 24 patients responded to plasma exchange, and 20 (59%) of 34 responded to corticosteroid treatment. A subsequent third treatment method was started in the non-responders of the plasma exchange and corticosteroid treatment groups. Six (75%) of the eight plasma exchange non-responders responded to corticosteroid treatment, and of the four corticosteroid non-responders that had plasma exchange, three (75%) responded.[81] Therefore, patients with CIDP can still improve using another proven effective treatment if the

first-line treatment or subsequent type of treatment is ineffective.

Chronic phase

About 85% of patients with CIDP that initially respond to intravenous immunoglobins require maintenance treatment, some patients requiring it for as long as 30 years.[81,78,80] An important and clinically relevant question is when maintenance treatment needs to be started. From a clinical point of view, intravenous immunoglobulin maintenance treatment should be started in patients who deteriorate after initial improvement following induction treatment with one or two courses of intravenous immunoglobulin.[36,78,79] This strategy might be similar for subcutaneous immunoglobulin treatment.[35,86] The most effective intravenous immunoglobulin maintenance dosing and frequency remain unknown, but intravenous immunoglobulin is usually administered in a regimen of 0·4–1·2 g/kg per day (usually no more than 80 g per day), once every 2–6 weeks, but dosage needs to be tailored for each individual patient. A Dutch study in 14 patients with CIDP and one with multifocal motor neuropathy, all in a stable clinical condition, found that IgG pharmacokinetic parameters, including half-life, were constant during subsequent intravenous immunoglobulin courses in the same patient, but varied considerably between patients.[76] The study suggested that immunoglobulin concentration one week after infusion correlated with grip strength. Whether serum IgG concentrations and clinical response are associated, and whether changes in serum IgG concentrations can be used to optimise intravenous immunoglobulin treatment requires further investigation.[76] Studies should preferally be longitudinal and in large groups of patients in various clinial and non-stable conditions.

Studies have also shown that subcutaneous immunoglobulin is an effective maintenance treatment.[35,89] For example, an international randomised controlled trial (PATH study)[35] comparing two different subcutaneous immunoglobulin dosages (0·2 g/kg and 0·4 g/kg given for 24 weeks) with placebo treatment in 173 patients with CIDP previously treated with intravenous immunoglobulin showed that both subcutaneous immunoglobulin doses are efficacious and well tolerated. This confirmed previous results from a Danish randomised controlled trial,[89] which compared subcutaneous immunoglobulin treatment with placebo in 30 patients with CIDP that were previously administered intravenous immunoglobulin maintenance treatment. However, the exact clinical role of subcutaneous immunoglobulin as a maintenance treatment in CIDP remains unknown and requires further research. Subcutaneous immunoglobulin might be a good option for patients with difficult venous access, those who have had substantial side-effects associated with use of intravenous immunoglobulin (such as headache), those living far away from infusion centres, or patients who largely incorporate travel into their lifestyle.[86,89]

Corticosteroids have been given as maintenance treatment, in the form of high-dose daily oral prednisolone, pulsed high-dose dexamethasone, or intravenous methylprednisolone. The treatments are effective and seem relatively safe when used for 6 months in pulsed high dose regimens and for up to 15 months with a regimen of oral prednisolone.[87,90] Randomised controlled trials investigating corticosteroid treatment had a short follow-up period of 6–12 months, so the known long-term side-effects of corticosteroid treatment might be underestimated.[36,91] If pulsed high-dose corticosteroids can increase the probability of remission, this would be a great advantage over the use of intravenous immunoglobulin treatment (which might only suppress disease activity) but confirmation in additional long-term follow-up studies is required.[36,37,88] Plasma exchange is rarely used given the relatively invasive nature of the procedure, practical issues of venous access, and limited availability of plasma exchange facilities.[36,82]

Randomised clinical trials have not shown that other immunosuppressive drugs are effective in the treatment of CIDP, including methotrexate, azathioprine, and ciclosporin.[84] However, the use of immunomodulatory treatments (eg, azathioprine, rituximab, and methotrexate) can have positive effects in individual patients, especially as add-on treatments or to reduce high doses of corticosteroids or intravenous immunoglobulin.[39,84] Chronic long-term treatment is often needed, but tailoring treatments to the lowest possible dose is important to reduce side-effects and associated costs, with recommended attempts at least yearly (because remission might have been reached).[78,79] The CIDP disease activity status helps assess the disease and treatment status of patients with CIDP, and might also be useful as a selection tool for the tailoring or withdrawal of treatment.[92]

Patients with IgG4 antibodies to nodal and paranodal proteins

A common feature in patients with IgG4 antibodies is a poor response or no response to intravenous immunoglobulin treatment, which could possibly be explained by the low capacity to bind with FcγIIb-receptors and inability to activate complement.[34,40] Treatment with corticosteroids and plasma exchange seems partly effective.[38,39,82,91] Treatment-refractory patients with CIDP and IgG4 antibodies showed variable responses to rituximab, from no response (mainly in patients with long disease duration and severe axonal damage) to remarkably good responses with clinical recovery and depletion of IgG4 antibodies.[17,18,23,27,30,39,40] Future prospective clinical trials on the efficacy of rituximab in patients with CIDP and IgG4 antibodies are needed.

Conclusions and future directions

CIDP is a disabling immune-mediated polyradiculoneuropathy with a typical phenotype and atypical variants. An early and accurate diagnosis is important to initiate

Search strategy and selection criteria

We searched MEDLINE, Embase, and the Cochrane database for articles published between Jan 1, 2013, and Oct 31, 2018. We used the search terms "CIDP" or "chronic inflammatory demyelinating polyradiculoneuropathy" or "auto-immune polyneuropathy" or "chronic acquired demyelinating polyneuropathy". No language restrictions were applied. We also used previously published articles (when more recent papers with comparable scientific relevance were unavailable) and articles present in our own files, when appropriate. The final reference list was generated on the basis of relevance to the topics covered in this Review.

treatment and to prevent further nerve damage.[9–11] The diagnostic investigations in patients suspected of having CIDP could be facilitated by use of nerve ultrasound and MRI, particularly in patients who do not meet electrodiagnostic CIDP criteria.[49] The clinical and immunological heterogeneity of CIDP is emphasised by the discovery of specific IgG4 antibodies against nodal and paranodal proteins that are found in a subgroup of patients.[17–21,23,24,27,28,30,31,40,43] These antibodies seem to be associated with particular clinical phenotypes and response to treatment.[17–21,23,24,27,28,30,31,34,40,43] Future studies are required to further unravel the pathogenesis of CIDP. The ongoing prospective International CIDP Outcome Study[93] and the Inflammatory Neuropathy Consortium based outcome study[94] aim to collect data from thousands of CIDP cases and biosamples and could help in the process of further understanding the mechanisms underlying CIDP.

CIDP treatment mainly consists of corticosteroids, intravenous immunoglobulin, and subcutaneous immunoglobulin, but long-term treatment with corticosteroids can have severe side-effects, and intravenous immunoglobulin and subcutaneous immunoglobulin are expensive.[35–37,39] Plasma exchange, although effective, is invasive and impractical for most patients.[38,39] Not all patients improve with the treatments available (or improve insufficiently) and many patients require long-term maintenance treatment. CIDP is a condition that presents a high unmet medical need for new treatments. Several ongoing studies are using standard treatments but in novel ways. These include an intravenous immunoglobulin dose-finding cross-over trial (DRIP trial, NTR 3705),[95] a maintenance intravenous immunoglobulin dose-finding trial (PROCID trial, NCT02638207),[96] and a trial comparing a combination of intravenous immunoglobulin and intravenous methylprednisolone treatments with intravenous immunoglobulin and placebo (OPTIC trial, ISRCTN15893334). Several agents in development might alter immune modulatory pathways to treat patients with CIDP. These include FcRn blockers, immunoabsorption,[97] complement inhibitors, and the IgG degrading enzyme of *Streptococcus pyogenes*.[98] Additionally, trials investigating long-term cures are being considered, for example, the B-cell depleting drugs rituximab and ocrelizumab are being investigated. These new studies are eagerly awaited and provide hope for the future.

Contributors

CB contributed to the literature search and writing of the manuscript, including the composition of the tables and figures. PAvD contributed to reviewing the literature search, writing the review synopsis, writing the manuscript, composition of tables and figures, and critically reviewing and revising the paper. BCJ contributed to writing the manuscript, and in critically reviewing and revising the paper. PYKVdB contributed to writing the manuscript, critically reviewed, and revised the paper. DRC contributed to writing the manuscript, and in critically reviewing and revising the paper. All authors read and approved the final manuscript before submission.

Declaration of interests

PAvD reports grants from Sanquin, Prinses Beatrix Spierfonds, Baxalta, Grifols. He is on the trial steering committee of Octapharma and is a consultant for Kedrion, CSL Behring, and Hansa, outside of the submitted work. BCJ receives grants from Baxalta, Grifols, CSL-Behring, Annexon, Prinses-Beatrix Spierfonds, and GBS-CIDP Foundation International, and is on the Global Medical Advisory Board of the GBS CIDP Foundation International. PYKVdB is a consultant for Pfizer, Genzyme, CSL Behring, LFB France, Natus, UCB Pharma and Alnylam. DRC is a consultant for Annexon Biosciences, Argenx BVBA, Biotest Pharmaceuticals, Inc, Cigna Health Management, CSL Behring, DP Clinical, Inc., Grifols SA, Hansa Medical, Merrimack Pharmaceuticals, Neurocrine Biosciences, Octapharma AG, Pharnext SAS, Sun Pharmaceuticals, and Syntimmune. He sits on Data Safety Monitoring Boards for Momenta Pharma, Pfizer, PledPharma, Technology Licensing for the Total Neuropathy Score to AstraZeneca Pharmaceuticals, Calithera Biosciences, Genentech, Neurocrine Biosciences, Merrimack Pharmaceuticals, and Seattle Genetics. He is on the Global Medical Advisory Board of the GBS CIDP Foundation International. He is Editor-in-Chief of the *Journal of the Peripheral Nervous System*. CB declares no competing interests.

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