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UPDATE

Diagnostic challenges in chronic inflammatory demyelinating polyradiculoneuropathy

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Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) consists of a spectrum of autoimmune diseases of the peripheral nerves, causing weakness and sensory symptoms. Diagnosis often is challenging, because of the heterogeneous presentation and both mis- and underdiagnosis are common. Nerve conduction study (NCS) abnormalities suggestive of demyelination are mandatory to fulfil the diagnostic criteria. On the one hand, performance and interpretation of NCS can be difficult and none of these demyelinating findings are specific for CIDP. On the other hand, not all patients will be detected despite the relatively high sensitivity of NCS abnormalities. The electrodiagnostic criteria can be supplemented with additional diagnostic tests such as CSF examination, MRI, nerve biopsy, and somatosensory evoked potentials. However, the evidence for each of these additional diagnostic tests is limited. Studies are often small without the use of a clinically relevant control group. None of the findings are specific for CIDP, meaning that the results of the diagnostic tests should be carefully interpreted. In this update we will discuss the pitfalls in diagnosing CIDP and the value of newly introduced diagnostic tests such as nerve ultrasound and testing for autoantibodies, which are not yet part of the guidelines.

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Abbreviations: CIDP = chronic inflammatory demyelinating polyradiculoneuropathy; CMAP = compound muscle action potential; EFNS/PNS = European Federation of Neurological Societies/Peripheral Nerve Society; NCS = nerve conduction studies; SSEP = somatosensory evoked potential

Introduction

Chronic inflammatory demyelinating polyradiculoneuropathies (CIDPs) consists of a spectrum of immune-mediated neuropathies, causing weakness and sensory symptoms in a progressive, relapsing-remitting or monophasic fashion (Van den Bergh *et al.*, 2010). Early diagnosis is important, as induction of treatment can prevent axonal damage and

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permanent disability (Bouchard *et al.*, 1999; Eftimov *et al.*, 2013; Mehndiratta *et al.*, 2015; Hughes *et al.*, 2017). Diagnosis is often challenging, because of the heterogeneous presentation. Clinical presentation and nerve conduction studies (NCS) play a major role in diagnosing CIDP, supplemented with diagnostic tests such as CSF examination, MRI, nerve biopsy and somatosensory evoked potentials (SSEP) (Van den Bergh *et al.*, 2010). Recently, nerve ultrasound and testing for autoantibodies were introduced (Goedee *et al.*, 2017*b*; Vural *et al.*, 2018). Despite diagnostic guidelines, in clinical practice both mis- and underdiagnosis are common. Misdiagnosis is a major problem, leading to the inappropriate use of expensive and potentially harmful treatment; underdiagnosis means that patients may not get effective treatment (Boukhris *et al.*, 2004; Ayrignac *et al.*, 2013; Allen and Lewis, 2015; Lucke *et al.*, 2019*a*). In this update we will discuss the frequent pitfalls in diagnosing CIDP and the value of newly introduced diagnostic tests such as nerve ultrasound and testing for autoantibodies.

Clinical signs and symptoms

Typical CIDP is defined as proximal and distal weakness and sensory dysfunction of all extremities, with absent or reduced tendon reflexes in all four limbs, with a progressive, relapsing-remitting or monophasic course, typically progressing over months. Atypical CIDP may be divided, based on clinical presentation, in the asymmetric, focal, distal, pure motor and pure sensory variants (Van den Bergh *et al.*, 2010). Misdiagnosis is common and is reported in up to 50% of patients referred with a CIDP diagnosis, mainly in patients with an atypical presentation (Allen and Lewis, 2015). In patients with a typical presentation of proximal and distal weakness, diagnosing CIDP is often straightforward. It was even suggested to base diagnosis on a typical presentation without further investigations (Koski *et al.*, 2009). However, none of the typical findings are specific for CIDP.

Diagnostic criteria sets

Consensus on the diagnostic criteria for CIDP has proven difficult, which led to many different sets throughout the years. One North American study (Breiner and Brannagan, 2014) compared 15 diagnostic criteria sets, including the revised European Federation of Neurological Societies/Peripheral Nerve Society (PNS/PNS) criteria (Van den Bergh *et al.*, 2010), the van den Bergh and Piéret criteria (2004), the American Academy of Neurology (AAN) criteria (American Academy of Neurology, 1991) and the Koski criteria (Koski *et al.*, 2009) in 57 CIDP patients and 37 patients with diabetic neuropathy and 39 patients with amyotrophic lateral sclerosis as control subjects (Table 1). The EFNS/PNS criteria had the highest sensitivities, with good specificities. Another European study (Rajabally *et al.*, 2009) investigated the specific electrodiagnostic criteria, including the 2006 EFNS/PNS criteria (Hughes *et al.*, 2006), the van den Bergh and Piéret criteria (2004), the AAN criteria (American Academy of Neurology, 1991) and the Koski criteria (Koski *et al.*, 2009) in 151 CIDP patients and 162 patients with axonal neuropathies as control subjects. The EFNS/PNS electrodiagnostic criteria had the highest sensitivity of 81% for definite or probable CIDP, with specificities ranging from 79% to 96%, depending on the extent of the NCS. The specificity of the criteria sets are likely overestimated, as all studies used control patients with clear clinical phenotypes of axonal neuropathies or motor neuron diseases instead of the ideal control population with initially suspected CIDP with alternative diagnosis. As the EFNS/PNS 2010 criteria seem the most accurate and widely used set of criteria, this review will further mainly focus on this set (Rajabally *et al.*, 2014). All diagnostic tests have their pitfalls and should be interpreted in the clinical context, including considering alternative causes of a demyelinating neuropathy (Table 2).

Table 1 Sensitivities and specificities of different diagnostic criteria sets

Criteria	Sensitivity	Specificity
EFNS/PNS, 2010		
Definite	73% (59.7–84.2%)	88% (78.7–94.4%)
Probable	77% (63.6–87.0%)	84% (74.0–91.6%)
Possible	91% (80.4–97.0%)	65% (54.0–76.3%)
Van den Bergh and Piéret		
Definite	63% (48.5–75.1%)	86% (77.1–93.5%)
Probable	66% (52.2–78.2%)	78% (68.1–87.5%)
AAN		
Definite	4% (0.4–12.3%)	100% (95.3–100%)
Probable	13% (5.2–24.1%)	100% (95.3–100%)
Possible	25% (14.4–38.4%)	100% (95.3–100%)
Koski	50% (36.3–63.7%)	84% (74.0–91.6%)

AAN = American Academy of Neurology; EFNS/PNS = European Federation of Neurological Societies/Peripheral Nerve Society. Adapted from Breiner and Brannagan (2014).

Diagnostic tests

Nerve conduction studies

The diagnosis of CIDP relies heavily on identification of demyelinating features on motor NCS. The electrophysiological demyelinating features are not equivalent to classical demyelination as found in nerve biopsy, but rather are markers for functional disruption or slowing of the saltatory conduction of the myelinated axons. Based on the amount and certainty of demyelinating features, this will lead to a definite, probable or possible electrodiagnosis according to the EFNS/PNS 2010 criteria (Van den Bergh *et al.*, 2010). A definite electrodiagnostic diagnosis requires at least two demyelinating features in two different nerves. A probable diagnosis requires two probable blocks or a probable block and one other demyelinating feature in a different nerve, while a possible diagnosis requires one demyelinating feature in one nerve. Recent studies highlighted the importance of

Table 2 Diagnostic pitfalls

Diagnostic test		Pitfall
Nerve conduction studies	Misdiagnosis	Other diseases that can meet electrodiagnostic criteria
		MMN
		Hereditary neuropathies with demyelinating features - CMT (demyelinating and intermediate types)
		HNLPP
		IgM monoclonal gammopathy associated with anti-MAG antibodies
		POEMS syndrome
		Amyloidosis
		Vasculitic neuropathy
		Lumbosacral radiculoplexus neuropathy
		Neurolymphomatosis
		Misinterpretation
		Increased distal latencies and slowed velocities due to severe axonal loss (low CMAP amplitudes), especially for the fibular nerve
		Demyelinating signs over segments prone to compression [median nerve (carpal tunnel), ulnar nerve (elbow), fibular nerve (fibular head)]
		interpreting CMAP reduction (abductor digiti minimi muscle) in forearm as a conduction block, without excluding Martin-Gruber anastomosis
		Uncertainties in determination of motor conduction block in segment axilla to Erb's point
		Absence of F-waves
		Distal CMAP duration prolongation with improper cut-off values
		Non-stringent interpretation of proximal CMAP amplitude reductions and temporal dispersion in the legs, especially for the tibial nerve
	Underdiagnosi	Testing too few (proximal arm) nerve segments
		Proximal leg nerves, including lumbosacral plexus, and partly brachial plexus are not accessible
		Criteria mainly based on motor nerves
Lumbar puncture	Misdiagnosis	Elevated CSF protein also found in diabetes mellitus and CMT
		CSF protein can increase with age
	Underdiagnosis	Normal CSF protein in atypical CIDP variants
Imaging	Misdiagnosis	Enlarged nerves also found in diseases such as vasculitis, diabetes mellitus, amyotrophic neuralgia, demyelinating and intermediate CMT
		Cut-off values for enlargement need critical attention
		High inter- and intra-observer variability of qualitative MRI assessment
	Underdiagnosis	Sensitivity of MRI is unknown
		High inter- and intra-observer variability of qualitative MRI assessment
Evoked potentials	Misdiagnosis	Prolonged SSEP not specific for CIDP
	Underdiagnosis	Sensitivity of SSEPs is unknown
Nerve biopsy	Misdiagnosis	Biopsy findings do not differentiate between CIDP and differential diagnoses such as axonal neuropathies or vasculitis
	Underdiagnosis	Demyelination is often not seen in biopsy
Autoantibodies	Misdiagnosis	Autoantibodies are regarded as specific; however, better standardization of techniques and estimates of the diagnostic accuracy are warranted
	Underdiagnosis	Sensitivity is currently low

CMT = Charcot-Marie-Tooth disease; HNLPP = hereditary neuropathy with liability to pressure palsy; MMN = multifocal motor neuropathy; POEMS = polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes.

correct interpretation of NCS and electrodiagnostic criteria, as this often led to misdiagnosis (Allen and Lewis, 2015; Allen *et al.*, 2018). A pitfall is that the electrophysiological criteria are sensitive to diagnose a demyelinating neuropathy, but they are also fulfilled in other diseases (Table 2).

Another frequent pitfall is severe axonal loss that can have a profound influence on nerve conduction velocity if the largest, fastest conducting axons are involved. For this reason, several criteria have additional fulfilments for the compound muscle action potential (CMAP) amplitude (Van den Bergh *et al.*, 2010). In general, demyelinating features should be identified with caution in measurements with CMAP amplitudes <1 mV, with particular focus on the clinical context (Van Asseldonk *et al.*, 2005). Recordings of more proximal muscles, such as the flexor carpi radial muscle to test the median nerve, can sometimes be of added value in case of profound distal axonal loss.

Demyelinating features in segments prone to compression or entrapment should not be considered as supportive for CIDP. The most important reason is that compression or entrapment itself can give demyelinating features. More severe demyelination was not observed at entrapment sites as compared with that observed at other nerve segments in CIDP (Padua *et al.*, 2004; Rajabally and Narasimhan, 2011*b*).

Interpretation of CMAP amplitude reductions as conduction blocks should be done with care in trajectories of nerves that are adjacent to each other, as co-stimulation and co-registration may occur. Moreover, physiological anastomoses, such as the Martin-Gruber anastomosis, have to be considered. These reasons should be ruled out prior to concluding that (apparent) CMAP reductions are due to conduction blocks, especially in the lower arm segment of the median or the ulnar nerve.

Both severely lengthened minimal F-wave latencies and absent F-waves may be classified as demyelinating features, but these findings are not specific, especially in case of the fibular nerve (Puksa *et al.*, 2003; Argyriou *et al.*, 2006; Pastore-Olmedo *et al.*, 2009). However, F-wave analysis may be of diagnostic utility when more distal NCS are found normal in presence of clinical features suggestive of the diagnosis (Rajabally and Varanasi, 2013).

The distal CMAP duration criterion in the guideline has been debated as it does not take differences in filter settings between centres into account (Isose *et al.*, 2009), which can greatly influence the duration (Rajabally *et al.*, 2012; Mitsuma *et al.*, 2015). However, when cut-off values are adjusted based on the filter settings used in the individual centre, it is a useful criterion that can aid diagnosis with limited testing.

Sensory NCS are not included in the electrodiagnostic criteria but can support sensory involvement and may be of value as one of the supportive criteria in the ENFS/PNS guidelines. Currently, a normal sural with abnormal median (excluding median neuropathy at the wrist from carpal tunnel syndrome) or radial sensory nerve action potential (SNAP) and/or a conduction velocity of $<80\%$ of lower limit of normal ($<70\%$ if SNAP amplitude $<80\%$ of lower limit of normal) are included as supportive criteria (Van den Bergh *et al.*, 2010). Additional review of the literature does not justify a more prominent position for sensory NCS in the guidelines and suggests that the evidence for the currently included supportive criteria, is limited with particularly low sensitivity levels (Kimura *et al.*, 1986; Kincaid *et al.*, 1988; Tamura *et al.*, 2005; Rajabally and Narasimhan, 2007; Bragg and Benatar, 2008; Rajabally and Samarasekera, 2010). Patients with clinically pure sensory involvement often also have motor abnormalities at NCS that can lead to the diagnosis of CIDP. However, an uncertain proportion of these patients with pure sensory involvement do not fulfil the electrophysiological criteria for at least possible CIDP, as these are based on motor NCS (Van den Bergh *et al.*, 2010). Some studies have proposed alternative diagnostic criteria for this specific CIDP phenotype (Ayrignac *et al.*, 2013).

In clinical practice the order and extensiveness of NCS vary widely. If too few nerve segments are tested, this may lead to underdiagnosis. The guideline advises to first test the median and ulnar nerve at one forearm and the fibular and tibial nerve of one lower leg (Van den Bergh *et al.*, 2010). However, in case of CIDP suspicion, there are arguments to initiate the study with the median and the ulnar nerves up to Erb's point, including F-waves, as demyelinating features may more often be found in the arms, including the more proximal (above) elbow to axilla and axilla to Erb's point segments, than in the legs (Rajabally *et al.*, 2005; Rajabally and Narasimhan, 2011*a*; Lucke *et al.*, 2019*b*). CMAP amplitudes of distal leg muscles are often too low for proper interpretation, while the proximal parts of the leg nerves are not accessible for NCS. Moreover, proximal CMAP amplitude reductions and temporal dispersion in the legs should be interpreted more stringently, taking into account physiological phenomena, especially in the tibial nerve. One study demonstrated that conduction blocks at the axilla and Erb's point were highly specific for CIDP and that proximal investigations improved the sensitivity of the diagnostic criteria (Rajabally and Jacob, 2006). This study defined a block at Erb's point as an amplitude reduction of $>50\%$ between wrist and Erb's point (Rajabally and Jacob, 2006). However, determining a block at Erb's point may be challenging, with a higher risk of submaximal stimulation at Erb's point due to the depth of the nerves, and no more proximal sites to verify CMAP amplitude reduction. Optimal stimulation at Erb's point is especially of importance, as CMAP amplitude reductions in normal control subjects may be substantial over longer arm nerve trajectories due to physiological temporal dispersion (Johnsen *et al.*, 2006).

CSF examination

Elevated protein in the CSF with normal leucocytes is found in up to 90% of patients with typical CIDP and is thought to be one of the hallmark features of the disease (Dyck *et al.*, 1975; Prineas and McLeod, 1976; McCombe *et al.*, 1987). In atypical CIDP variants such as the asymmetric subtype, protein elevation might be less pronounced, or absent (Rajabally and Chavada, 2009). Elevation of the CSF protein is not specific for CIDP and especially patients with diabetes mellitus or hereditary demyelinating neuropathies (CMT1) can have slightly elevated protein levels (Bouche *et al.*, 1983; Kobessho *et al.*, 2008). To prevent misdiagnosis, it was recently suggested to increase the cut-off value for CSF protein to 0.6 g/l in patients older than 50 (Breiner *et al.*, 2019). If an elevated leucocyte count ($>10/mm^3$) is found, infections or malignancies should be considered. However, slightly elevated leucocyte counts (>10 mm^3) have been reported in up to 11% of CIDP patients (van Doorn *et al.*, 1991; Press *et al.*, 2003; Lucke *et al.*, 2018), meaning that this does not automatically exclude the diagnosis. One study found that 8 of 14 (57%) patients with elevated leucocytes (>10 mm^3) had a (sub)acute onset of disease and that leucocytes spontaneously decreased over time (Lucke *et al.*, 2018).

Imaging

MRI and nerve ultrasound can be a valuable addition in the diagnostic work-up, as proximal segments such as the proximal part of the brachial plexus and the lumbosacral plexus

can be assessed, while NCS cannot study these regions. In both techniques, one of the main parameters is nerve hypertrophy. It is noteworthy that this is not an exclusive phenomenon for acquired inflammatory neuropathies such as CIDP and may be seen in other relatively prevalent diseases such as diabetes mellitus, hereditary demyelinating neuropathies and neuralgic amyotrophy (Breiner *et al.*, 2017; Padua *et al.*, 2018; van Rosmalen *et al.*, 2019).

Multiple studies were carried out to evaluate MRI in CIDP with widely varying results: nerve hypertrophy was found in 37–100% of cases (Tazawa *et al.*, 2008; Sinclair *et al.*, 2011; Lozeron *et al.*, 2016; Goedee *et al.*, 2017*a*; Jongbloed *et al.*, 2017), hyperintensity ranged from 56–100% (Adachi *et al.*, 2011; Sinclair *et al.*, 2011; Shibuya *et al.*, 2015; Goedee *et al.*, 2017*a*; Jongbloed *et al.*, 2017) and enhancement after gadolinium administration was reported in 0–69% (Midroni *et al.*, 1999; Adachi *et al.*, 2011; Goedee *et al.*, 2017*a*). Most cohorts had small sample sizes and consisted of prevalent cases with a typical presentation, who met the electrophysiological criteria for definite CIDP. Only few studies included a clinically relevant control group, leading to less generalizable results for the daily practice where distinguishing CIDP from its differential diagnoses is often difficult. A recent study has evaluated the diagnostic performance of MRI in differentiating CIDP and multifocal motor neuropathy from disease controls (segmental spinal muscular atrophy) and healthy control subjects (Oudeman *et al.*, 2020). In that study, intra- and inter-observer agreement for qualitative assessment of nerve hypertrophy and hyperintensity as scored on STIR varied widely. This was also the case for qualitative scoring on magnetic resonance neurography, a newer sequence technique.

Several studies showed changes in diffusion tensor imaging in CIDP, a technique that enables quantitative measurements of water diffusivity within nerve tissue, but the diagnostic contrast seems relatively small and may not be useful in clinical practice (Kakuda *et al.*, 2011; Markvardsen *et al.*, 2016; Kronlage *et al.*, 2017; Oudeman *et al.*, 2020). Given the rapid development of MRI techniques, the aim may be to develop other preferably quantitative measures suited to peripheral nerve tissue in health and disease.

Increases in nerve cross-sectional area on nerve ultrasound have been reported in several studies. Nerve enlargement was found in 69–100% of CIDP patients (Matsuoka *et al.*, 2004; Zaidman *et al.*, 2009; Sugimoto *et al.*, 2013). Studies showed that the CSA of the brachial plexus and the median nerve were the most adequate measurements to distinguish between CIDP and axonal neuropathy (Grimm *et al.*, 2014; Goedee *et al.*, 2017*b*). A recent single centre study provided cut-off values based on the upper limits for axonal neuropathies and found a 100% specificity for enlargement of one or more segments of the median nerve or the cervical trunci/roots (Goedee *et al.*, 2017*b*). However, also in this study, only patient controls with a clear-cut diagnosis of axonal neuropathy or amyotrophic lateral sclerosis were studied. A more recent single centre study that included 100 patients clinically suspected of an acquired inflammatory neuropathy found a high sensitivity (97%) for nerve ultrasound, but the specificity was lower than previously reported (69%) (Herraets *et al.*, 2020). In addition, ultrasound identified patients that responded to treatment but did not meet the electrodiagnostic criteria (Herraets *et al.*, 2020).

A good inter-observer variability of the nerve ultrasound was shown in a multicentre study, including acquired inflammatory neuropathies (Telleman *et al.*, 2019). An advantage of nerve ultrasound over MRI is that nerve ultrasound is a relatively easy, quick, patient-friendly tool.

Evoked potentials

SSEP and triple stimulation technique (TST) may be of help in diagnosing CIDP. SSEPs are used to assess the functioning of the whole sensory pathway, including the nerve roots. The evidence that supports the use of SSEP in diagnosing CIDP is limited. Proximal sensory nerve involvement as investigated with SSEP was found in 38–100% of CIDP cases (Pineda *et al.*, 2007; Yiannikas and Vucic, 2008; Tsukamoto *et al.*, 2010; Salhi *et al.*, 2014). Sample sizes of these studies were often small. None of the studies investigated the diagnostic utility of SSEP in treatment-naïve patients or with the use of SSEP as a primary investigation. The role of the SSEP in diagnosing CIDP is clearly limited if the electrodiagnostic criteria are met. However, studies showed that in up to 100% of patients with a pure sensory presentation, who did not meet the electrophysiological criteria, SSEP showed involvement of the nerve roots (Sinnreich *et al.*, 2004; Ayrignac *et al.*, 2013). In clinical practice, SSEP should be considered in patients with predominant sensory ataxia and areflexia, if the electrodiagnostic criteria are not fulfilled.

Another potential method to overcome the challenges of assessing demyelination in proximal parts might be motor evoked potentials. Several explorative studies using motor evoked potentials in CIDP showed (very) prolonged peripheral conduction times and, less often, changes in central conduction times, but formal diagnostic accuracy studies have not been performed (Takada and Ravnborg, 2000; Pineda *et al.*, 2007). TST is a specialized diagnostic tool to examine the nerve roots proximal of Erb's point, and includes the use of motor evoked potentials. It may demonstrate proximal motor conduction blocks, even if patients do not meet the electrodiagnostic criteria (Attarian *et al.*, 2015; Cao *et al.*, 2018), indicating that TST can probably increase sensitivity. However, specificity is yet unknown and there is very limited experience with this technique.

Nerve biopsy

Whether nerve biopsy has additional value in diagnosing CIDP has long been a matter of debate. Usually, the nerve selected for biopsy is the sural nerve, as it is easily accessible. The pathological findings are segmental demyelination and

remyelination, onion bulb formation and inflammatory infiltrates (Krendel *et al.*, 1989). These findings were reported in 48–71% of the biopsies in patients that met diagnostic criteria (Barohn *et al.*, 1989; Krendel *et al.*, 1989; Molenaar *et al.*, 1998; Bouchard *et al.*, 1999). However, sample sizes of the studies were small and few studies compared biopsy results from CIDP patients with disease controls. One study suggested that none of the biopsy findings were specific for CIDP, as these findings were also found in vasculitis, axonal and demyelinating hereditary neuropathies and monoclonal gammopathies (Krendel *et al.*, 1989). Other studies also showed that nerve biopsies failed to differentiate between CIDP and axonal neuropathies or diabetic neuropathies (Molenaar *et al.*, 1998; Uncini *et al.*, 1999; Bosboom *et al.*, 2001). Some studies suggested that there might be some value in atypical CIDP cases (Vallat *et al.*, 2003; Ayrignac *et al.*, 2013). The recent discovery of specific nodal and paranodal abnormalities in the ultrastructural analysis of the nerve in patients with antibodies against node of Ranvier cell adhesion molecules may have diagnostic utility in specific patients (Koike *et al.*, 2017; Vallat *et al.*, 2017; Uncini and Vallat, 2018). Nerve biopsy is considered invasive and will lead to persisting sensory loss in most patients, while persisting pain, infections and dysaesthesias have also been reported in a minority of patients (Gabriel *et al.*, 2000; Ruth *et al.*, 2005).

Autoantibodies

Autoantibody search has been an important topic of research in CIDP in the last decades, but just recently, subgroups of CIDP patients with antibodies targeting the nodes of Ranvier and paranodal regions have been described (Querol *et al.*, 2017*a*; Vural *et al.*, 2018). The discovery of these antibodies, associating with antibody-specific clinical features, boosted interest in the role of antibodies as diagnostic and prognostic biomarkers. Up to 25% of patients with CIDP show evidence of circulating autoantibodies targeting antigens of the peripheral nerve structures, including nodal and paranodal regions (Querol *et al.*, 2017*b*; Vural *et al.*, 2018; Broers *et al.*, 2019). Autoantibodies specifically targeting the nodal and paranodal regions are found in ~10% of CIDP patients. Antibodies to neurofascin 155 (NF155) are the most frequent, while antibodies to neurofascin 140 (NF140) and neurofascin 186 (NF186), contactin-1 (CNTN1) and contactin-associated protein 1 (CASPR1) are less common (Querol *et al.*, 2017*a*; Vural *et al.*, 2018; Bunschoten *et al.*, 2019). Most are of the IgG4 isotype. A systematic review reported a very low sensitivity of these autoantibodies but specificities of 100% in CIDP (Hu *et al.*, 2018). Specific clinical phenotypes have been described in patients with autoantibodies to the nodes and paranodes (Table 3). In general, antibodies to nodal and paranodal proteins, regardless of the autoantibody, associate with a subacute onset and more progressive CIDP phenotypes, initially often classified as Guillain-Barré syndrome, and poorer responses to immunoglobulins than patients without these autoantibodies (Hu *et al.*, 2018; Vural *et al.*, 2018). The clinical significance of antibodies other than those targeting nodal and paranodal proteins is unclear.

Table 3 Characteristics of patients with autoantibodies in CIDP

	Characteristics
Neurofascin 155 (NF155) (Querol *et al.*, 2014; Devaux *et al.*, 2016)	Subacute onset, fast progression Younger age Distal motor involvement Ataxia Prominent, low-frequency tremor
Neurofascin 140 and 186 (NF140 and NF186) (Delmont *et al.*, 2017; Stengel *et al.*, 2019)	Subacute onset, fast progression Cranial nerve deficits Ataxia
Contactin-1 (CNTN1) (Querol *et al.*, 2013; Miura *et al.*, 2015)	Subacute onset, fast progression Axonal involvement at onset Ataxia
Contactin-associated protein 1 (CASPR1) (Doppler *et al.*, 2016)	Severe pain

The optimal technical approach to test for nodal/paranodal antibodies is currently under investigation. However, most published studies use cell-based assays (either immunocytochemistry or flow-cytometry) performed with HEK293 cells transfected with the human recombinant protein target of the antibodies, ELISAs using human recombinant proteins as the protein substrate or immunohistochemistry on teased-nerve fibres to detect the typical nodal or paranodal staining. Considering that the detection of these autoantibodies usually leads to the use of therapeutic algorithms that includes therapies (e.g. rituximab) that are not first line therapies in CIDP, it seems reasonable to try to confirm the detected antibodies with at least two different techniques to increase diagnostic specificity (Martín-Aguilar *et al.*, 2020).

Two independent series, in which in a total of 113 patients were included, described six patients fulfilling the diagnostic criteria for CIDP, in which anti-MAG antibodies were detected in the absence of IgM paraproteinaemia. These patients presented and progressed similar to anti-MAG-positive patients with IgM paraproteinaemia (Sakamoto *et al.*, 2017; Pascual-Goñi *et al.*, 2019) and two of them developed detectable paraproteinaemia years after disease-onset, suggesting that a subset of patients classified as distal CIDP could indeed be patients with early anti-MAG-positive monoclonal gammopathy of undetermined significance related polyneuropathy (MGUSP) (Allen and Lewis, 2015). It is important to take this into account to avoid misdiagnosis, especially in patients with the distal phenotype.

Testing for antibodies should be considered in treatment unresponsive patients, especially in the presence of atypical symptoms such as a subacute onset, severe ataxia, pain or a tremor. In case of the distal phenotype and treatment unresponsiveness, M-protein reanalysis and anti-MAG antibodies may be considered. International, multicentric studies are currently underway, which focus on standardization of

measuring autoantibodies, but also on providing better estimates of the diagnostic accuracy of autoantibody testing in patients suspected of CIDP. If autoantibody testing is shown to be widely reliable and reproducible, it can be introduced for standard clinical practice.

Discussion

CIDP has a very heterogeneous presentation, and consists of a spectrum of autoimmune diseases of the peripheral nerves based on presumed breach of tolerance leading to autoimmunity against nerve antigens. Different pathophysiological mechanisms have been identified, often sharing clinical features, which makes diagnosis challenging.

The term CIDP was introduced in 1982 describing some of the most common features of the disease in four different domains, namely time of onset, pathophysiology, tissue component involved and anatomical distribution. However, the use of this term has evolved over time to try to incorporate other patients with primary chronic immune-mediated neuropathies susceptible to disease-modifying therapies that share but do not necessarily include all of the original features. More importantly, as our knowledge of the disease deepens, it has become increasingly difficult to unite all clinical presentations and pathophysiological mechanisms under this term, some even contradicting the original terminology. First, CIDP may have an acute onset, that initially resembles Guillain-Barré syndrome (Vural *et al.*, 2018). Also, some neuropathies meet various supportive criteria, including treatment response, but not the electrophysiological criteria (Lucke *et al.*, 2019*a*; Herraets *et al.*, 2020). However, the best examples are the recently discovered nodal and paranodal neuropathies that are caused by autoantibodies. Some are autoantibodies to axonal nodal structures, such as CNTN1, so that it became clear that autoimmunity can be primarily directed to axonal antigens, and not only to myelin antigens. In case of anti-CNTN1, electron microscopy examination showed a selective loss of the septate-like junctions at the paranodes and a detachment of the paranodal myelin loops from the axon, but there was an absence of inflammation and classical macrophage-induced demyelination (Kouton *et al.*, 2020). Importantly, this disorganization of the nodes of Ranvier disrupts the saltatory conduction, which leads to electrophysiological findings that are traditionally interpreted as demyelinating features. The electrophysiological criteria for CIDP were originally intended to be able to detect the physiological substrate of demyelination, as this was the only known underlying pathology. However, in essence they are markers for functional disruption or slowing of the saltatory conduction of myelinated axons. In the context of CIDP, conduction block can result from paranodal abnormalities of the myelin sheath, but also from primary dysfunction of the axon at the nodes of Ranvier. Considering that inflammation and demyelination as core features are not present in all CIDP patients, while an autoimmune aetiology is presumed in all patients, the umbrella term 'chronic autoimmune neuropathies' may fit

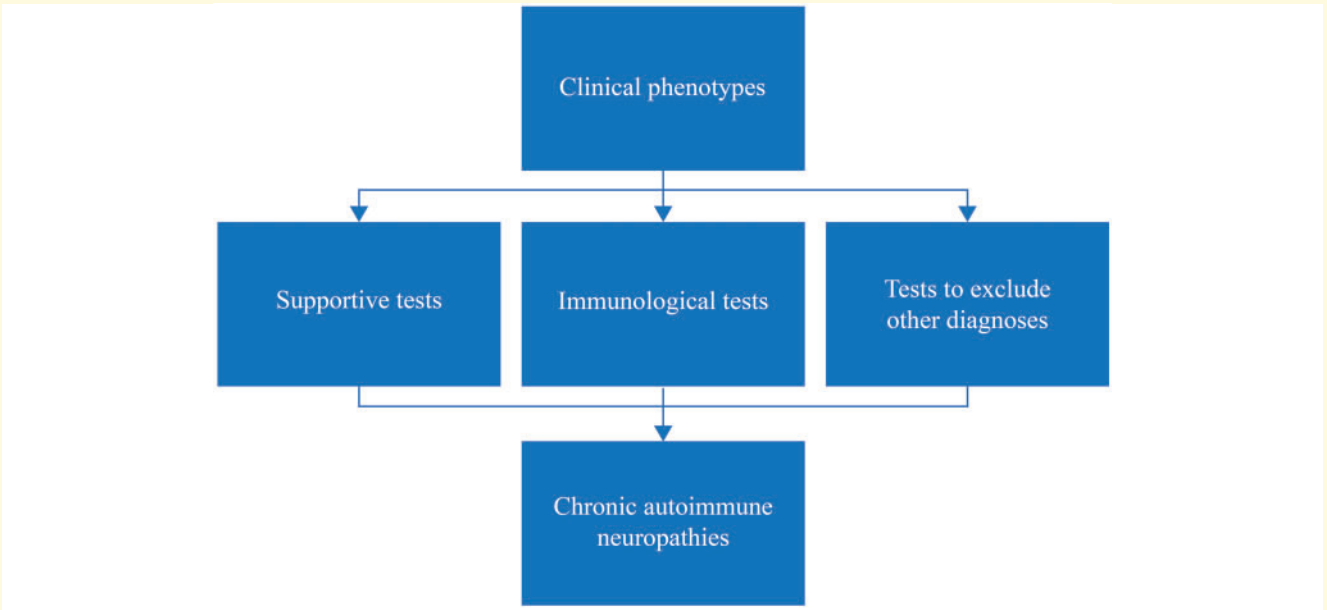

Figure 1 A conceptual framework for a diagnostic work-up in chronic autoimmune neuropathies. A conceptual framework for a diagnostic work-up in chronic auto-immune neuropathies, assuming future emphasis on immunological tests with high specificity to show evidence for autoimmunity. Combinations and number of tests required for diagnosis depend on specificity of clinical phenotypes, of immunological tests and of supportive tests, such as nerve conduction studies, imaging, CSF examination, pathology and response to treatment. NCS currently have the best diagnostic accuracy.

better (Fig. 1). Further discussion will be needed on whether to include other entities such as multifocal motor neuropathy and anti-MAG neuropathy within this term. Recent studies suggested that anti-MAG antibodies can be present in few patients with CIDP without the presence of IgM paraproteinaemia. However, in an overwhelming majority of patients there is also IgM paraproteinaemia, suggesting that the underlying pathomechanism is plasma cell dyscrasia rather than breach of tolerance. Moreover, further studies are needed to determine the diagnostic cut-off of anti-MAG antibodies in those patients without IgM paraproteins as these can also be found in low quantities in other conditions.

Regardless of the nomenclature, if we consider the autoimmune aetiology as the hallmark of the disease, in the future we should also probably focus more on introducing specific immunological tests in our diagnostic work-up. This would be in line with the diagnostic approaches of other, similarly heterogeneous, autoimmune diseases, in which access to tissue is difficult, such as autoimmune encephalopathies (Graus *et al.*, 2016). Unfortunately, despite recent progress, finding proof of autoimmunity is currently difficult as antibodies in blood/CSF are only found in a minority of patients, while unambiguous pathology results from nerve biopsy supporting an autoimmune origin are uncommon. However, other autoantibody reactivities or markers of autoimmunity, including immunity-related genes, may be identified in the future (Nevo *et al.*, 2013; Staudt *et al.*, 2017).

Despite desirable future advances to prove autoimmunity in more patients, the diagnosis of CIDP currently remains a clinical one, with greater complexity and concurrently increased uncertainty for atypical versus typical forms. The absence of a golden standard challenges proper evaluation of diagnostic accuracy of tests. Still, taking surrogate standards, such as fulfilment of consensus criteria and treatment response, partially overcomes this problem. Recognizing the technical difficulties and caveats as outlined in this review, will hopefully reduce the number of patients with misdiagnosis and underdiagnosis, particularly in non-expert environments. Currently, in the majority of patients, the diagnosis is supported by electrophysiological evidence of impaired saltatory conduction, so that NCS still are the most reliable and widely available diagnostic test to support the diagnosis of CIDP. A slightly elevated CSF protein level has a poor specificity, while normal protein levels do not exclude the diagnosis. If imaging is required, nerve ultrasound is probably preferred as it is quicker, easier and has a higher diagnostic accuracy compared to MRI, but further multicentre studies are needed. The role of evoked potentials and nerve biopsy is very limited in most patients and should be reserved for selected cases. Finally, progression should be made in standardized detection of currently available autoantibodies, of new autoantibodies and of other evidence for autoimmunity to improve diagnostic accuracy, so that these tests may become more useful in standard clinical practice. With the last update of the guidelines almost 10 years ago and the introduction of the nerve ultrasound and the discovery of autoantibodies in CIDP, the update of the EAN/PNS diagnostic guidelines is much awaited.

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