Journal of Autoimmunity 102 (2019) 8–37

Contents lists available at ScienceDirect

Journal of Autoimmunity

journal homepage: www.elsevier.com/locate/jautimm

Chronic inflammatory demyelinating polyneuropathy as an autoimmune disease

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ARTICLE INFO

Keywords:
Autoimmune disease
Autoimmune tautology
Chronic inflammatory demyelinating polyradiculoneuropathy
Guillain-Barré syndrome
Autoimmune ecology
Molecular mimicry
Polyautoimmunity

ABSTRACT

Chronic inflammatory demyelinating polyneuropathy (CIDP) is an autoimmune disease characterized by neurological symptoms and signs of progressive weakness, paresthesias, and sensory dysfunction. Other symptoms include reduced or absent tendon reflexes, cranial nerve involvement, autonomic symptoms, ataxia, and neuropathic pain. Unlike other autoimmune diseases, CIDP generally affects older individuals and has a male predominance. The onset is generally insidious and can take up to 8 weeks with a relapsing-recovery pattern. Like all autoimmune diseases, the etiology is multifactorial, with both genetic and environmental factors contributing to it. Case reports of CIDP have found associations with multiple pathogenic organisms including Hepatitis B and C viruses, *Bartonella henselae*, *Mycoplasma pneumoniae*, Human immunodeficiency virus, Cytomegalovirus and Epstein-Barr virus. Possible antigenic self-targets include myelin protein 0, myelin protein 2, peripheral myelin protein 22, Connexin 32, and myelin basic protein. Antibodies targeting the Ranvier node proteins such as contactin-1, contactin-associated protein 1, and neurofascin 155 have been described. CIDP is treated with rehabilitation and pharmacological modalities. Pharmacological treatments target autoimmune dysfunction and include corticosteroids, intravenous immunoglobulin, subcutaneous immunoglobulin, plasma exchange, immunosuppressive and immunomodulatory agents such as methotrexate, cyclophosphamide, rituximab, and mycophenolate mofetil. Although there are few observational studies and randomized clinical trials with limited evidence supporting the use of immunosuppressive drugs, they are widely used in clinical practice. A comprehensive review of CIDP is presented herein in light of the autoimmune tautology.

Abbreviations: AD(s), Autoimmune disease(s); AIDP, Acute inflammatory demyelinating polyneuropathy; ANA, Antinuclear antibodies; Anti ds-DNA, Anti-double stranded DNA antibodies; Anti Tg, Anti-thyroglobulin antibody; Anti-GAD65, Anti-glutamic acid decarboxylase antibody; Anti-HBc, Anti-hepatitis B core antibody; Anti-TPO, Anti-thyroid peroxidase antibody; Anti-TrAb, Anti-TSH receptor antibody; APC, Antigen presenting cells; B. henselae, Bartonella henselae; C. jejuni, Campylobacter jejuni; Ca 19-9, Cancer antigen 19-9; CAD, Cytoalbuminologic dissociation; CASPR1, Contactin-associated protein-1; CEA, Carcinoembryonic antigen; CIDP, Chronic inflammatory demyelinating polyradiculoneuropathy; CMT, Charcot-Marie-Tooth; CMV, Cytomegalovirus; CNS, Central nervous system; CNTN1, Contactin-1; CSF, Cerebrospinal fluid; CX32, Connexin 32; CT, Computerized tomography; DADSN, Distal acquired demyelinating symmetric neuropathy; EAN, Experimental autoimmune neuritis; EBV, Epstein-Barr virus; ELISA, Enzyme-Linked ImmunoSorbent Assay; EMG, Electromyography; GBS, Guillain-Barré syndrome; HBe-Ab, Hepatitis B "e" antigen antibodies; HBe-Ag, Hepatitis B "e" antigen; HBsAg, Hepatitis B surface antigen; HBV, Hepatitis B virus; HCV, Hepatitis C virus; HIV, Human immunodeficiency virus; HTLV-I, HumanT-cell lymphotropic virus type I; IVIg, Intravenous immunoglobulin; LSS, Lewis-Sumner syndrome; M. pneumoniae, Mycoplasma pneumoniae; MBP, Myelin basic protein; MG, Myasthenia gravis; MHC, Major histocompatibility complex; MMN, Multifocal motor neuropathy; MRI, Magnetic resonance imaging; MS, Multiple sclerosis; NF155, Neurofascin splice variant 155; NF186, Neurofascin splice variant 186; P0, myelin protein0; P2, myelin protein 2; PE, Plasma exchange; PMP, Peripheral myelin protein; PNS, Peripheral nervous system; RA, Rheumatoid arthritis; RT-PCR, Reverse transcription polymerase chain reaction; SCIg, Subcutaneous immunoglobulin; SLE, Systemic lupus erythematosus; SS, Sjögren's syndrome; T1D, Type 1 Diabetes; TST, Triple stimulation technique; VGKC, Voltage gated potassium channel-complex; ZIKV, Zika virus

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https://doi.org/10.1016/j.jaut.2019.04.021
Received 28 January 2019; Received in revised form 13 April 2019; Accepted 23 April 2019
Available online 06 May 2019
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1. Introduction

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is a neurological disorder associated with an immune-mediated response directed primarily against the peripheral nervous system (PNS) [1]. The prevalence of this disorder is variable, and it is affected by environmental and genetic factors as is the case for other autoimmune diseases (ADs) [2,3]. Clinically, CIDP presents as a chronic and insidious neurological disorder associated with relapses and recurrences lasting more than 8 weeks. It is also characterized by symmetric paresthesias, weakness, and sensory dysfunction in extremities. CIDP can also present with areflexia, cranial nerve involvement, autonomic symptoms, and neuropathic pain although these symptoms are less common [4]. The presence of multifocal demyelination is common. The pathogenesis of CIDP involves an inflammatory cell infiltrate, segmental demyelination, especially in the paranodal region, followed by remyelination by Schwann cells. The result of this process is defective nodal segments with sheaths of thinner myelin [1]. This process of demyelination-remyelination helps explain the irregular clinical course of the disease.

The management of CIDP patients is divided into pharmacological and non-pharmacological intervention. Rehabilitation is the central axis of non-pharmacological management. Pharmacological management with immunosuppressive therapy targets the immunological mechanism underlying this neuropathy [1]. The prognosis of CIDP is generally favorable, but factors exist that can influence the clinical outcome. These risk factors include the initial clinical presentation, electrodiagnostic patterns, treatment response, and associated comorbidities [4,5].

2. Epidemiology

CIDP is dependent on genetics and environmental triggers. It is more frequent in men than in women [6–9]. According to Iijima et al. [9] still “there is not a clear understanding about the background mechanism underlying this gender related difference”. The prevalence and incidence of the disease vary based on geography and the age of the patient. Studies show an increased incidence of the disease with age which reaches a peak in prevalence around the eighth decade [3]. The prevalence in Europe ranges between 1.0 and 7.7 per 100,000 people [3,8,10,11] while in Japan, it is between 0.8 and 1.6 per 100,000 [12,13], in Australia is 1.9 per 100,000 [7], and in the United States is 8.9 per 100,000 [9].

3. Autoimmune ecology

Despite the paucity of cohort studies, there is information regarding the role of infections as the main trigger for CIDP (Table 1) [6,14–33]. Multiple immunological mechanisms associated with infections have been described which explain how an infection may cause an immune response that results in an autoimmune process. Antigen-presenting cells (APC) such as dendritic cells process and present antigens throughout the major histocompatibility complex (MHC) to T cells. Thereafter, T cells release mediators such as cytokines, which activate macrophages, T cells, and B cells thus initiating a humoral response.

Four different mechanisms may contribute to the development of CIDP when triggered by an immune stimulus such as an infection or a vaccine. These are 1. molecular mimicry, 2. epitope spreading, 3. bystander activation, and, 4. cryptic antigens. The mechanism described as molecular mimicry is characterized by the presence of cross-reactivity between external and self epitopes. This mechanism has been widely described in Guillain-Barré syndrome (GBS) [34]. The epitopes identified as foreign are processed and presented to T cells by APCs, thus triggering an autoimmune response through the release of cytokines and the activation of cellular and humoral immune responses. Macrophages also contribute to this mechanism and work in concert with $CD8^+$ T cells to perpetuate the release of autoantigens and sustain the autoimmune response [35]. Epitope spreading is associated with a persistent immune response that results from the inability to completely eradicate a pathogen which leads to tissue damage, the processing of antigens by APCs, and subsequent ongoing activation of the autoimmune response [35]. Bystander activation is characterized by a non-specific and imprecise immune response against pathogens that leads to tissue damage. Cryptic antigens are molecules “unknown” to the host immune system. During cellular injury, proteases process and release cryptic antigens, present them to $CD8^+$ T cells and trigger an immune response in the corresponding tissue [35].

4. Genetic factors

As with other ADs, CIDP only occurs when genetic and environmental factors converge. The identification of genetic factors that contribute to the disease is crucial for understanding the pathogenesis and also for personalized medicine. Family studies are important for identifying common genes leading to CIDP. Korn-Lubetzki et al. described a family of Jewish origin in which the father and 2 daughters were diagnosed with inflammatory demyelinating polyneuropathy. The father and one daughter had the CIDP form and the other had acute inflammatory demyelinating polyneuropathy (AIDP). A deletion in the PMP22 gene (OMIM 601097.0004) typical of Hereditary Neuropathy with liability to Pressure Palsies (HNPP) was identified. Screening for the HNPP deletion in patients with recurrent, chronic, or familial inflammatory demyelinating polyneuropathy is suggested in this case report. However, to date there have been no studies that identify specific genes associated with CIDP [36].

Despite these limitations, several population studies have identified HLA genes and non-HLA genes that seem to confer susceptibility to CIDP (Tables 2 and 3) [14,37–51].

With regard to non-HLA genes, a polymorphism of the Fc-γRIIB promoter has been found to be overrepresented in CIDP [38]. Fc receptors are able to bind to immunoglobulin when immune complexes are formed, an ability which is fundamental to the pathophysiology of demyelinating neuropathies such as CIDP. Another polymorphism associated with CIDP is located at the *SH2D2A* gene [39]. The protein encoded by this gene is essential for signal transduction in T and natural killer cells [52]. Reduced expression of this protein has been found in other ADs [53].

α1-antitrypsin inhibits proteases in immune cells thereby conferring anti-inflammatory properties. One study identified a large number of CIDP patients that preferentially express the M3 allele at *SERPINA1*, which is associated with functional alterations of this molecule [40].

5. Polyautoimmunity

CIDP may co-exist with other ADs (Table 4) [21,54–93], especially neurological ADs such as multiple sclerosis (MS) and myasthenia gravis (MG). Having one AD increases the risk of developing another [94], and the polyautoimmunity phenomenon occurring in CIDP reinforces the theory that this disease has an important immunological component. Certain HLA loci confer greater risk of CIDP and other ADs. This is the case in MS [95], MG [96], rheumatoid arthritis (RA) [94], systemic lupus erythematosus (SLE) [97], and Sjögren's syndrome (SS) [98]. It is common for patients with CIDP to concomitantly or at a later time present with another AD or to develop CIDP in the context of another AD.

6. Pathogenesis

The immune mechanisms in CIDP involve defects in both the innate and adaptive immune systems (Fig. 1). CIDP is consistent with an autoimmune pathogenesis based on the presence of a genetic predisposition, an environmental trigger, an abberant innate immune response, a

Table 1
Data on infections and Chronic Inflammatory Demyelinating Polyradiculoneuropathy.

Agent	Geographic location	Publication date	Study type	Number of cases	Gender	Neurological manifestations	Cerebrospinal fluid results	Electrodiagnosis	Infection confirmation	Sural nerve biopsy	Observations	Ref
Bacterial infections												
Bartonella henselae	Netherlands	2000	Case report	1	Male	Symmetric distal muscle weakness in all limbs, sensory ataxia, diminished tendon reflexes over a course of a further 8 weeks	CAD	Nerve conduction showed decrease in motor nerve conduction velocities in all limbs and no response in sensory conduction EMG normal	*B.henselae* (ELISA) IgG: > 850 U/l (+) IgM: > 250U/l (+)	Demyelinated axons and signs of early remyelination Electron microscopy showed demyelination associated with macrophages	CIDP was identified after six weeks after identification of cat scratch disease	[25]
Campylobacter jejuni	United Kingdom	1996	Case and control	4/40	–	All patients fulfilled criteria for CIDP [177]	All patients fulfilled criteria for CIDP [177]	All patients fulfilled criteria for CIDP [177]	Serological evidence of recent *C.jejuni* infection	–	–	[27]
	United Kingdom	2004	Case report	1	Male	Progressive weakness of proximal limbs, numbness. Motor and sensory involvement was observed over the next month. Reflexes were absent, right abducens palsy	CAD	Findings met the requirements of the American Academy of Neurology for a diagnosis of CIDP [177]	*C.jejuni* IgG: < 80 (−) IgM: 320 (+)	Axonal degeneration with severe loss of myelinated fibers, without features of demyelination, remyelination, or presence of inflammatory cells	–	[28]
Mycoplasma pneumoniae	United Kingdom	2007	Case report	1	Female	progressive distal weakness, paresthesias, distal sensory loss	CAD	Nerve conduction showed a conduction block for all tested motor nerves, with moderately reduced motor nerve conduction velocity and an absent F wave response in the lower limbs	*M.pneumoniae* (immunofluorescent assay) IgA: (+) IgM: (+)	–	The patient was treated with IVIg (400 mg/kg daily for 5 days) and improved within a week. After 2 months of stability, she reworsened with similar features.	[29]
Viral infections												
Hepatitis B virus	Japan	1994	Case report	1	Male	Muscle weakness, tingling and numbness in the distal portion of all limbs	–	–	–	Presence of a band that reacts with anti-HBs antibody in the sural nerve in western blotting	–	[30]
	Japan	1998	Case report	1	Female	Weakness and dysesthesia in limbs, diminished deep tendon reflexes, distal sensory loss	CAD	Nerve conduction studies showed an increase in proportion of typical polyphasic motor unit potentials and decreased interference pattern	Serum HBsAg (ELISA): 20 COI Anti HBV Antibody: 100.0 HBV DNA: 21 cpm	Demyelinated and remyelinated fibers, onion bulb Immunohistochemical findings show deposition of HBsAg, IgG, and C3 in the same portion of the blood vessel wall in the endoneurium	Immune complexes composed of HBsAg, IgG, and complement is deposited in vessel walls in the endoneurium	[31]

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Table 1 (*continued*)

Bacterial infections												
Agent	Geographic location	Publication date	Study type	Number of cases	Gender	Neurological manifestations	Cerebrospinal fluid results	Electrodiagnosis	Infection confirmation	Sural nerve biopsy	Observations	Ref
	Turkey	2015	Case report	1	Male	Muscle weakness and difficulty in walking. The loss of strength progressed despite treatment with IVIg	Proteins: 129 mg/dl	EMG was compatible with sensorimotor demyelinating polyneuropathy in the subacute phase	HBe-Ag: (−) HBV-DNA: (+) HBs-Ag: (+) HBe-Ab (+)	–	–	[32]
	Romania	2017	Case report	1	Male	Progressive paresthesias, muscle weakness in upper limbs	CAD	EMG showed multifocal chronic demyelinating polyneuropathy with predominant upper limb involvement	HBsAg: (+) Anti-HBc (+)	–	Predominantly upper limb CIDP	[33]
Hepatitis C virus	France	2004	Case report	1	Male	3-month history of distal limb weakness and absent deep tendon reflexes	CAD	Nerve conduction showed a decrease in motor nerve conduction associated with low compound muscle action potential at the four limbs without conduction block EMG showed a diffuse denervation without spontaneous activity, both proximally and distally at the four limbs	HCV (PCR) Serum: (+) Virus genotype was 2a/2c	–	–	[15]
	Turkey	2006	Case report	1	Male	Symmetric weakness of proximal and distal limbs, absence of tendon reflexes and bilateral facial palsy	CAD	Nerve conduction showed reduced motor and sensory conduction velocities in the nerves examined.	HCV-RNA (+) anti-HBc-IgM (+) HBV-DNA (+)	–	CIDP may have been due to interferon-α, HCV, or HBV infection	[16]
	France	2006	Case series	2	Female	Case 1: Chronic progressive distal motor weakness and sensory disturbances Case 2: Bilateral plantar hypoesthesia and distal weakness in the lower limbs, tendon reflexes were normal except for ankle reflexes	Case 1: Normal Case 2: CAD	Case 1: Nerve conduction showed velocities moderately slowed in three nerves associated with low compound muscle action potential in the lower limbs EMG showed mixed axonal and demyelinating sensorimotor polyneuropathy Case 2: Nerve conduction showed axonal and demyelinating sensorimotor polyneuropathy in the lower limbs	Case 1: HCV (PCR): 3.140.000 IU/ml (+) Case 2: HCV (PCR): 3.311.220 IU/ml (+)	Case 1: Significant loss of myelinated fibers whose myelin sheaths were thin with respect to axonal diameters. There were signs of regeneration indicative of concurrent axonal impairment Case 2: Large myelinated fibers, typical onion-bulb formations and perivascular inflammatory infiltrates around epineurial vessels with vessel wall invasion without necrosis	Presence of cryoglobulinemia	[17]

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Table 1 (*continued*)

Bacterial infections												
Agent	Geographic location	Publication date	Study type	Number of cases	Gender	Neurological manifestations	Cerebrospinal fluid results	Electrodiagnosis	Infection confirmation	Sural nerve biopsy	Observations	Ref
	Japan	2018	Case report	1	Male	Muscle weakness in upper extremities, but patient recovered completely without any treatment. However, three months later, patient experienced a recurrence of muscle weakness and dysesthesia of the upper extremities	CAD	Nerve conduction showed a motor and sensory polyneuropathy with demyelinating features, including motor conduction blocks, decreased conduction velocities, and prolonged minimum F-wave latencies EMG showed chronic denervation with high amplitude motor unit potentials and slightly decreased recruitment with no abnormal spontaneous activity	Medical history of hepatitis caused by HCV genotype 1b	–	–	[18]
Human immunodeficiency virus	France	2000	Case report	1	Male	Distal paresthesias of limbs, which had appeared progressively 3 months earlier, generalized areflexia, superficial sensory loss	Raised protein level with mild lymphocytic pleocytosis	Nerve conduction showed that velocities in the median nerves were slow, with increased distal latencies and low amplitude of the compound muscle action potentials. The compound muscle action potentials were absent following distal stimulation of the tibial and peroneal nerves. The sensory nerve action potentials were absent following stimulation of the median and sural nerves	HIV-1: (+)	A perivascular lymphocytic infiltrate is present in the epineurium. Several clusters of regenerating myelinated fibers and prominent onion bulb formations	Patient have presented as asymptomatic Charcot-Marie-Tooth 1A	[14]
	India	2014	Case report	1	Female	Three months after treatment with tenofovir, lamivudine and nevirapiner, patient presented with areflexia, quadriparesis with bilateral facial palsy	Lymphocytic pleocytosis with mild protein elevation	Primary demyelinating polyneuropathy involving all nerves in upper and lower limbs	CD4 count of 86, oral candidiasis and other opportunistic infections	–	"The probable explanation is that CIDP in this case occurred as IRIS as evidenced by the improved BMI and CD4 count at the time of presentation"	[19]

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Table 1 (*continued*)

Bacterial infections												
Agent	Geographic location	Publication date	Study type	Number of cases	Gender	Neurological manifestations	Cerebrospinal fluid results	Electrodiagnosis	Infection confirmation	Sural nerve biopsy	Observations	Ref
Cytomegalovirus	Australia	1986	Case series	10	–	All patients fulfilled criteria for CIDP	All patients fulfilled criteria for CIDP	All patients fulfilled criteria for CIDP	CMV (Enzyme immunoassay): > 1:4 (+)	–	–	[6]
	Netherlands	1999	Case report	1	Male	Progressive diminished strength in limbs	CAD CMV IgG antibodies (+)	–	CMV (pp65 antigenemia assay): (+) IgG: (+) IgM: (+)	–	Patient received a renal transplant from a donor that was seropositive for CMV	[20]
	Japan	2006	Case report	1	Female	Cranial nerve involvement, weakness of distal limbs	CAD	Nerve conduction showed prolonged distal motor latencies and F-wave latencies in the median and ulnar nerves, and sensory nerve action potentials were absent in median, ulnar, and sural nerve studies	CMV ELISA IgG 95.7(+) IgM: 2.72 (+)	–	Patient concomitantly developed CIDP and MG following CMV infection	[21]
Epstein-Barr virus	United States	2002	Case report	1	Female	Bilateral lower extremity weakness, hypoesthesia, areflexia	CAD	Nerve conduction showed demyelinating polyneuropathy whit secondary axonal degeneration, a reduced motor nerve conduction velocities, partial conduction block, prolonged distal latencies and absent F-wave latencies	EBV capsid antigen IgG (+) IgM (−) EBV Early antigen: (+) EBV antinuclear antigen: (+)	Segmental demyelination and dense inflammatory T cell and macrophage infiltrate	The EBV infection was also associated with a lymphoproliferative disease	
	Germany	2010	Case and control	34	–	The modified AAN [175] and the EFNS criteria were used for the diagnosis of CIDP [170]	The modified AAN [175] and the EFNS criteria were used for the diagnosis of CIDP [170]	The modified AAN [175] and the EFNS criteria were used for the diagnosis of CIDP [170]	EBV- IgG (+) and the disease was associated with a moderately enhanced IgG reactivity to EBV-encoded antigens expressed during both B cell transformation and productive viral replication. Moreover, cellular EBV copy numbers were increase 3-fold in patients with CIDP	–	Host–pathogen interactions during chronic EBV infection are dysregulated in treatment-naïve patients with CIDP	[22]
Hantavirus	South Korea	2016	Case report	1	Male	After eight months of initial presentation, developed quadriplegia and hypoesthesia. The patient presented with a second relapse 2 months after he was discharged	CAD	Nerve conduction showed no response or delayed latency in all 4 extremities	Hantavirus (IFI) IgM: (+)	No infiltration of inflammatory cells and no evidence of atrophy or degeneration	Coinfection with hepatitis B	[23]

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Table 1 (*continued*)

Bacterial infections												
Agent	Geographic location	Publication date	Study type	Number of cases	Gender	Neurological manifestations	Cerebrospinal fluid results	Electrodiagnosis	Infection confirmation	Sural nerve biopsy	Observations	Ref
Human T-cell lymphotropic virus type I	Japan	1990	Case report	1	Female	Progressing symmetrical weakness of the lower limbs over one month, associated with areflexia. Atrophy of the upper limbs and trunk also appeared a month after onset	CAD	Nerve conduction showed prolonged distal latencies and slowing of F-wave recorded from the thenar muscles EMG showed denervation of the anterior tibial and gastrocnemius muscles.	HTLV-I (Particle agglutination Method): serum and CSF: (+) (Western blot) Serum and CSF IgG: (+)	No demyelination or perivascular and endoneurial infiltrates of mononuclear cells	–	[24]
Zika virus	Netherlands	2017	Case report	1	Male	Progressive weakness of legs starting in the right leg, leading to flaccid paraparesis with absent reflexes. The patient showed a deterioration of symptoms 6 weeks after start of initial symptoms	CAD	Nerve conduction showed slightly prolonged distal motor latencies of the peroneal and tibial nerves, mildly prolonged F-wave latencies of the ulnar and tibial nerves and a low amplitude of the sural nerve, compatible with a polyradiculoneuropathy	ZIKV RT-PCR (−) (ELISA): IgM (+), IgG (+)	–	–	[26]

CIDP: Chronic inflammatory demyelinating polyradiculoneuropathy, MG: Myasthenia gravis, IVIg: Intravenous immunoglobulin, EMG: Electromyography CSF: Cerebrospinal fluid, CAD: Cytoalbuminologic dissociation, *B.henselae: Bartonella henselae C.jejuni: Campylobacter jejuni*, *M.pneumoniae: Mycoplasma pneumoniae*, HCV: Hepatitis C virus, HBV: Hepatitis B virus, HBsAg: Hepatitis B surface antigen, HBe-Ag: Hepatitis B "e" antigen, HBe-Ab: Hepatitis B "e" antigen antibodies, Anti-HBc: Anti-hepatitis B core antibodies, HIV: Human immunodeficiency virus, CMV: Cytomegalovirus, EBV: Epstein-Barr virus, HTLV-I: Human T-cell lymphotropic virus type I, ZIKV: Zika virus, RT-PCR: Reverse transcription polymerase chain reaction, ELISA: Enzyme-Linked ImmunoSorbent Assay, AAN: American Academy of Neurology, EFNS: European Federation of Neurological Societies.

Table 2
Studies of HLA genes associated with Chronic Inflammatory Demyelinating Polyneuropathy.
Modified from Blum et al., [225].

Genes	Population	Association	Reference
HLA-A	Australia	Increased HLA A Aw30	[37]
	Australia	Increased HLA-A3	[46]
	United Kingdom	No association	[44]
	United Kingdom	No association	[45]
HLA-B	Australia	Increased HLA-B7	[46]
	The Netherlands	No association	[48]
	United Kingdom	Increased HLA-B8	[46]
	United Kingdom	Increased HLA-B7	[44]
HLA-C	The Netherlands	No association	[48]
	United Kingdom	Increased HLA-Cw7	[45]
HLA-DPB1	United Kingdom	No association	[45]
HLA-DQA1	Australia	No association	[49]
HLA-DQB1	Australia	No association	[49]
	The Netherlands	No association	[48]
	Tunisia	No association	[47]
	United Kingdom	No association	[45]
HLA-DR2	Australia	Increased HLA-DR2	[46]
	Australia	Increased HLA-DR2 in females	[49]
HLA-DR3	Australia	Increased HLA-Dw3	[37]
	United Kingdom	Increased HLA-Dw3	[44]
HLA-DRB1	Greece	No association	[50]
	Spain	Association between HLA-DRB1*15 and anti-NF155 antibodies	[51]
	The Netherlands	No association	[48]
	Tunisia	Increased HLA-DRB1*13	[47]
	United Kingdom	No association	[45]

Table 3
Studies on Non-HLA genes associated with Chronic Inflammatory Demyelinating Polyneuropathy.

Genes	Protein	Population	Chromosome location	Reference
SERPINA1	Alpha1 antitrypsin	Australia	14q32.1	[40]
CNTN2	Contactin 2	Japan	1q32.1	[41]
FCGR2B	Fcgamma receptor IIb	Germany	1q23	[38]
CD59	CD59	Israel	11p13	[42]
SH2D2A	T cell specific adaptor protein	Italy	1q21	[39]
PMP22	Peripheral myelin protein 22	France United Kingdom	17p12	[14,43]

Modified from Blum et al., [225].

cellular and humoral adaptive immune response to specific self-antigens, and a clinical response to immunomodulatory treatments. Histologically, the immune response occurs primarily at the level of spinal roots and the proximal region of peripheral nerves. The main pathological changes described are demyelination, remyelination, edema, formation of onion bulbs [99], and infiltration of macrophages and T cells at the perivascular and endoneurial levels associated with axonal degeneration (Fig. 1) [100–102]. Changes in the immune activity of subsets of T cells have been observed in the blood and in the cerebrospinal fluid (CSF) of patients with CIDP [103–106]. These cellular changes have been associated with altered cytokine production [107,108]. Furthermore, the immune response is prolonged by the production of TNF-α, INF-γ, and IL-2 [109], and macrophages that not only activate the immune response [102], but also participate in the final stage of the demyelination process [110]. Moreover, although the information is limited, it seems that the actions of intravenous immunoglobulin (IVIg) on the TNFR1 pathway have been documented, and a mechanism involving TLRs in the pathophysiology of CIDP has been associated with the response to this treatment [111].

6.1. Adaptive immune response - cellular response

CIDP is associated with the overexpression of MHC class II (Fig. 1) [100] and co-stimulatory molecules B7.1 and B7.2 [112,113]. A $CD4^+$ T cell response is crucial to generating a disruption in the blood-brain barrier through the over-expression of adhesion molecules generated by the production of proinflammatory interleukins (Fig. 1) [114].

Most studies have demonstrated a greater proportion and higher activity of $CD8^+$ T cells in comparison with $CD4^+$ T cells in CIDP [115,116]. In addition, although it has not been possible to identify the autoantigens targeted by MCH class I, there is histological evidence showing the presence of $CD8^+$ T cell clones in the sural nerve in all patients with CIDP [115]. This is associated with an overexpression of MHC I by Schwann cells [117]. The MHC I overexpression allows an overstimulation of $CD8^+$ T cells and, thus, facilitates a possible cytotoxic response.

The number of Treg $CD4^+$ $CD25^{high}$ Foxp3+ has been observed to be markedly reduced in CIDP [118]. Functionally, Treg cells in CIDP are less effective in controlling the proliferative response of effector cells during the progressive or relapsing phases of CIDP [118,119].

6.2. Adaptive immune response - humoral response

The presence of autoantibodies against myelin antigens supports the hypothesis that CIDP is an AD (Table 5) [27,119–135]. The presence of complement and immunoglobulin on the surface of Schwann cells in the sural nerve has been described in CIDP [136,137]. Using indirect immunofluorescence, serum was shown to bind to normal nerve sections thus leading to demyelination and a reduction in conduction velocity [138,139]. Recently, a series of documented myelin antigens have been described as targets of the autoantibodies found in CIDP. Among the most important is the myelin protein 0 (P0) [133]. Other potential myelin antigens are protein 2 (P2) [131], the peripheral myelin protein (PMP) −22 [123], and connexin (Fig. 1) [128]. Autoantibodies have been demonstrated in animal models, especially in experimental autoimmune neuritis (EAN) in which the autoimmune response is directed against P0, P2 (Fig. 1) [140], and PMP-22 (Fig. 1) [123]. The presence of all these autoantibodies has not been demonstrated in all patients with CIDP, and currently, the only antigen that has been shown to be related to the pathogenesis of the disease in *in vivo* models is P0 [139,141].

In CIDP, a humoral immune response against myelin antigens located in the Ranvier node has been reported (Table 6) [142–150]. Clinically, this is important because different autoantibodies can be associated with distinctive clinical courses. Myelinated fibers at the Ranvier node are of critical importance in determining the efficiency of a nerve impulse [151]. This structure consists of four compartments, the internode, the node, the paranode, and the juxtaparanode [152]. One of the compartments that has been most studied in CIDP is the paranodal region where the myelin sheath is in tight contact with the axon through septate junctions known as transverse bands [153]. The best-described adhesion molecules in this zone are contactin-1 (CNTN1), contactin-associated protein-1 (CASPR1), and neurofascin splice variant 155 (NF155). CNTN1 and CASPR1 form a complex which binds to NF155 thus allowing the compartmentalization of voltage-gated potassium channel (Kv1.1/1.2/1.4/1.6) at the juxtaparanodes and voltage-gated sodium channels (Nav1.6) at the nodes [148,154].

Querol et al., evaluated four patients with CIDP for a humoral response against neuronal antigens using immunoprecipitation and mass spectrometry, and identified antibodies against the CNTN1-CASPR1 complex in 3 of the 4 patients [149]. These results were verified in *in vitro* models. CNTN1 IgG4 antibodies were shown to alter the junction between the CNTN1-CASPR1 complex and NF155 [155]. In animal models, the passive transmission of CNTN1 IgG4 antibodies from EAN to naive recipients confirmed the pathogenicity of these autoantibodies [147]. CNTN1 IgG4 antibodies targeted the paranodal region and

Table 4
Autoimmune diseases associated with Chronic Inflammatory Demyelinating Polyneuropathy.

Autoimmune disease	Geographic location	Publication date	Study type	Number of cases	Gender	Neurological manifestations	Cerebrospinal fluid results	Electrodiagnosis	Autoimmune disease characteristics	Sural nerve biopsy	Observations	Ref
Systemic lupus erythematosus	United States	1984	Case series	2	Female	Case 1: Progressive paresthesias, limb weakness and areflexia over five months. Bilateral facial weakness after seven months of neurological symptoms onset Case 2: Progressive bilateral arm weakness and paresthesias for 5 weeks, associated with areflexia	Case 1: CAD Case 2: CAD	Case 1: Nerve conduction showed that sural and median sensory potential were reduced in both amplitude and velocity. Ulnar and radial sensory potentials were absent. Peroneal, median, and ulnar motor distal latencies were prolonged. Conduction velocities were slow with abnormal F-wave Latency. EMG showed positive waves in leg muscles. Motor unit potentials had increased polyphasia and rare long durations with reduced numbers. Case 2: Nerve conduction showed decreased sural amplitude, prolonged posterior tibial distal latency, reduced motor conduction velocities in median and ulnar nerves. Posterior tibial and ulnar F waves and bilateral H reflexes were absent. EMG was normal	Case 1: Hemoglobin of 10.2 g/dl Proteinuria ANA: 1:640 ds-DNA: (−) Anti-Sm (+) Anti-RNP (+) Renal biopsy showed moderate thickening of glomerular capillary loops without hypercellularity with granular capillary loop staining for IgG and C3. Case 2: ANA: 1:640 ds-DNA: 1:20 Anti-Sm (+) Anti-RNP (+) C3: 62 mgld C4: 8.2 mg/d	Case 1: A mild reduction in the number of myelinated fibers	–	[54]
	United States	1986	Case report	1	Female	Three episodes separated by approximately 2 years of progressive ascending weakness associated with paresthesias and areflexia. Bilateral facial palsy	CAD	Nerve conduction showed low amplitude in motor and sensory responses associated with prolonged distal latencies	ANA: 1:2000 Anti DNA: (+) Anti-RNP (+) Anti-Sm (+) Right-side pleural effusion 24-hour protein collection: 0.26g	–	CIDP may be the first clinical manifestation of SLE	[65]
	Switzerland	1991	Case report	1	Male	A clinical course of relapsing moderate proximal and distal weakness of all limbs, hypoesthesia, areflexia, ataxia, dysarthria	CAD	Nerve conduction showed prolonged median and tibial distal motor latency and slow nerve conduction velocities. F-wave latency to muscle adductor polticis brevis was abnormal and sural and median sensory potentials were absent. EMG revealed positive sharp waves in m. tibialis anterior. Motor unit potentials were polyphasic.	Malar rash C4 reduced ANA: 1:480 ds-DNA: 39 IE/ml anti-Sm: (+)	–	CIDP may be the first clinical manifestation of SLE	[76]

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Table 4 (*continued*)

Autoimmune disease	Geographic location	Publication date	Study type	Number of cases	Gender	Neurological manifestations	Cerebrospinal fluid results	Electrodiagnosis	Autoimmune disease characteristics	Sural nerve biopsy	Observations	Ref
	United States	2003	Case report	1	Female	Progressive proximal and distal weakness and areflexia for four months. After three weeks, the patient was readmitted to the hospital for similar neurological symptoms	CAD	Nerve conduction: sural responses were absent; amplitude of the median sensory response was low. The motor responses were abnormal throughout, conduction block in the median forearm segment. The F waves were absent throughout. EMG showed active denervation in the leg, with no recruitment of motor units in the gastrocnemius muscle.	ANA: 1:80	Accumulation of chronic inflammatory cells, mainly lymphocytes and occasional plasma cells. Myelin sheaths were virtually absent from most of the fascicles, some fascicles were devoid of myelinated fibers. Other fascicles were less badly damaged, showing axonal degeneration as well as demyelination. The teased-nerve preparation did not disclose evidence of either segmental demyelination or remyelination. There was also early onion-bulb formation.	Pediatric case, SLE seems to be supported by the patient's sex, the abnormal titer of ANA, the relatively high incidence of the disease, and the well-described association of lupus with CIDP.	[87]
	United States	2005	Case series	6	Female	All patients presented with progressive generalized weakness associated with areflexia		All patients showed slow motor conduction velocity with prolonged latency, with prolonged sensory responses and decreased amplitude	SLE cases were identified from the referral practice database of over 1000 SLE patients from a single rheumatologist specializing in the diagnosis and treatment of SLE	–	The presence of antibodies associated with SLE all appear to predict a good response to IVIg.	[89]
	Mexico	2010	Case report	1	Male	Recovery relapse of progressive generalized weakness	CAD	Nerve conduction showed a predominantly demyelinating pattern and motor polyradiculoneuropathy.	Malar rash proteinuria ANA: 1:80 Anti-dsDNA: (+) anticardiolipin IgM: (+) anti-β2glycoprotein 1 IgG and IgM: (+)	–	Pediatric case	[90]
	Belgium	2010	Case report	1	Female	Two episodes of progressive generalized weakness with areflexia associated with dysautonomia, ophthalmoplegia and mechanical	CAD	Nerve conduction showed prolonged distal latencies, absent F-waves, and normal conduction velocities. Distal compound muscle action potential amplitudes were markedly reduced. EMG showed evidence of	Malar rash Proteinuria ANA; 1:160 Anti-dsDNA: (+) anticardiolipin: (+)	–	–	[91]

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Table 4 (*continued*)

Autoimmune disease	Geographic location	Publication date	Study type	Number of cases	Gender	Neurological manifestations	Cerebrospinal fluid results	Electrodiagnosis	Autoimmune disease characteristics	Sural nerve biopsy	Observations	Ref
						ventilation requirement		ongoing denervation in distal muscles and absent recruitment in all muscles examined.				
	Argentina	2012	Case report	1	Female	Two episodes of recovery-relapse of progressive muscular weakness in upper and lower limbs associated to areflexia	CAD	Nerve conduction showed decreased velocity on motor nerve conduction, motor conduction block, prolonged F wave, prolonged distal latency, decreased amplitude.	Leukopenia Proteinuria Renal biopsy: stage II membranous lupus glomerulonephritis ANA: 1:160 Anti-dsDNA: (+)	–	CIDP and SLE arising after diagnosis of autoimmune thyroiditis and rubella vaccination. Sixteen months later is diagnosed with Sjögren's syndrome. Patient responded to rituximab treatment	[92]
	Malaysia	2012	Case report	1	Male	Facial weakness associated with progressive limb weakness and areflexia over 3 months	CAD	Nerve conduction showed inexcitable motor and sensory nerves EMG showed axonal denervation changes in the distal muscles.	Malar rash Leukopenia Lymphopaenia ANA: 1:5120 Anti-ds-DNA: (+) Low C3-C4 Anti-RNP (+) Anti-Sm (+) discoid lupus	–	Patient responded to cyclophosphamide treatment	[93]
	United States	2017	Case report	1	Female	Three-month history of progressive limb weakness associated with areflexia and sensory symptoms	Normal	Nerve conduction showed abnormal peroneal distal latency with very low amplitude and disappearance of F waves consistent with CIDP	Low C4 leukopenia anemia	–	–	[55]
	Netherlands	2017	Case series	6	3/Male 3/Female	All patients presented with progressive generalized weakness associated with areflexia	Five patients were diagnosed with CIDP and one patient with possible CIDP	Five patients were diagnosed with CIDP and one patient with possible CIDP	–	–	All patients presented with cutaneous lupus erythematosus after immunoglobulin treatment for CIDP	[56]
Myasthenia gravis	United States	1986	Case report	1	Male	Two separate episodes of progressive generalized weakness and areflexia	CAD	Nerve conduction showed slowing in all motor nerves in the lower extremities. All sensory nerve potentials in the upper and lower limbs had diminished amplitudes and velocities	Bilateral ptosis, limited extraocular movements. Edrophoniurn test: (+) Anti-acetylcholine receptor: (+)	–	Patient presented with vitiligo	[57]
	United States	1996	Case report	1	Male	Six month history of progressive weakness and areflexia	CAD	Nerve conduction showed multifocal, demyelinating sensorimotor polyneuropathy with partial conduction block and temporal dispersion	Bilateral ptosis, diplopia, mild dysphagia	Anti-acetylcholine receptor: (+)	–	[58]
	Japan	1998	Case report	1	Female	Progressive generalized weakness, hypoesthesia and areflexia over a year	CAD	Nerve conduction showed high amplitude potentials with long duration and a reduction in the number of motor units.	Left-sided blepharoptosis, limited elevation in bilateral ocular movement	Marked decrease in myelinated fiber density with loss of large myelinated fibers and an	Pediatric case	[59]

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Table 4 (*continued*)

Autoimmune disease	Geographic location	Publication date	Study type	Number of cases	Gender	Neurological manifestations	Cerebrospinal fluid results	Electrodiagnosis	Autoimmune disease characteristics	Sural nerve biopsy	Observations	Ref
								Reduction in motor conduction velocity in left median nerve with a prolonged distal latency compound muscle action potential, attenuated, partial conduction block	Repetitive electrical stimulation of the ulnar nerve at 20 Hz showed an amplitude decrement in the compound muscle action potential Edrophoniurn test: (+) Anti-acetylcholine receptor: (+)	increase in unmyelinated fibers There was axonal sprouting and lymphocyte infiltration		
	United States	1999	Case report	1	Female	Acute onset of extremity weakness, areflexia. After 4 weeks, patient relapse with same neurological symptoms	CAD	Nerve conduction showed multifocal, demyelinating, sensorimotor polyneuropathy with conduction block consistent with a demyelinating process	Anti-acetylcholine receptor: (+)	–	Pediatric case	[60]
	Japan	2006	Case report	1	Female	Cranial nerve involvement, weakness of distal limbs.	CAD	Nerve conduction showed prolonged distal motor latencies and F-wave latencies in the median and ulnar nerves. Sensory nerve action potentials were absent in median, ulnar, and sural nerve studies	Left ptosis, abduction restriction of her left eye, bilateral sluggish light reflex Anti-acetylcholine receptor: (+)	–	Patient developed CIDP and myasthenia following CMV infection	[21]
	United kingdom	2011	Case report	1	Male	Two relapses of weakness and a 2-year course of progressive generalized weakness and areflexia	CAD	Nerve conduction showed prolonged distal motor latencies and slow motor conduction velocities with preserved compound muscle action potential amplitudes consistent with patchy demyelination	History of weakness, Anti-acetylcholine receptor: (+) and a response to pyridostigmine six years before	Occasional degenerating axons with no regeneration clusters. There were occasional large-diameter axons with thin myelin sheaths, which, in the absence of significant regeneration, raised the possibility of demyelination.	Patient presented additionally with Morvan syndrome antibodies, anti VGKC, neuropsychiatric syndrome, insomnia, autonomic dysfunction, and elevation of CEA and Ca 19-9. Patient responded to treatment with Rituximab	[61]
	Germany	2018	Case report	1	Male	Progressive, distal weakness of the lower extremities, ascending hypoesthesia, areflexia facial palsy. Three months after discharge patients presented with the same neurological symptoms	CAD	Nerve conduction showed proximal demyelinating sensorimotor polyneuropathy with active denervation, prolonged motor distal latency, and a reduction in motor conduction velocity	Dysphagia, and dysarthria Anti-acetylcholine receptor: (+) Anti-titin antibodies (+) Clinical response after pyridostigmine treatment	–	2 years later patient developed membranous glomerulonephritis (anti-phospholipase A2 receptor antibody)	[62]

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Autoimmune disease	Geographic location	Publication date	Study type	Number of cases	Gender	Neurological manifestations	Cerebrospinal fluid results	Electrodiagnosis	Autoimmune disease characteristics	Sural nerve biopsy	Observations	Ref
	China	2018	Case report	1	Male	Two episodes of progresive weakness of limbs and numbness of the feet. In the next two months, numbness spread to his thigh root, followed by weakness and numbness of his hands associated with areflexia	CAD	Nerve conduction showed F-wave latency was prolonged in the upper limbs and absent in the lower limbs	Dysphagia and dysarthria, bilateral ptosis, bilateral periphery facial paralysis Prostigmine test: positive Anti-acetylcholine receptor: (+)	–	–	[63]
Multiple sclerosis	United States	1987	Case series	6	4/Female 2/Male	Progressive extremity weakness, areflexia, distal sensory loss, and relapsing course.	CAD	Nerve conduction showed low motor and sensory conduction velocities.	MRI evidence of central nervous system demyelination lesions contiguous with the ventricle and the subcortical white matter of the temporal, parietal, and occipital lobes Prolonged visual evoked responses Transient optic neuritis and spinal fluid oligoclonal bands	–	–	[64]
	United Kingdom	1987	Case series	6	2/Female 4/Male	Progressive extremity weakness, areflexia, sensory loss associated with a recovery-relapsing course.	CAD	Nerve conduction showed evidence of denervation in affected muscles, reduced motor nerve conduction velocity, and increased distal motor latencies consistent with demyelination in one or more nerves. Sensory nerve action potentials were consistently absent or of reduced amplitude	Prolonged visual evoked potentials latencies The N9 component of somatosensory evoked potentials was absent or delayed Brainstem auditory evoked potentials showed abnormalities CT showed focal low density lesions in periventricular, cerebral hemisphere white matter and in the region of the lentiform nucleus MRI showed periventricular lesions and additional discrete lesions in the central white matter and occipital horns An oligoclonal IgG pattern was only obtained in two cases	Myelinated nerve fibre density was reduced. The surviving fibers possessed inappropriately thin myelin sheaths for axon diameter suggesting remyelination. Onion bulbs were present	–	[66]

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Table 4 (*continued*)

Autoimmune disease	Geographic location	Publication date	Study type	Number of cases	Gender	Neurological manifestations	Cerebrospinal fluid results	Electrodiagnosis	Autoimmune disease characteristics	Sural nerve biopsy	Observations	Ref
	United Kingdom	1990	Case series	14	7/Female 7/Male	All patients fulfilled the clinical criteria for the diagnosis of CIDP [226].	All patients fulfilled the clinical criteria for the diagnosis of CIDP [226].	All patients fulfilled the clinical criteria for the diagnosis of CIDP [226].	MRI showed multiple discrete white matter lesions and irregular periventricular lesions. Lesions within the cerebellar hemisphere Oligoclonal IgG bands were detected in the CSF in three cases	–	–	[67]
	Australia	2003	Case report	1	Female	Three-month history of progressive weakness, hyperreflexia, bilateral ankle clonus and positive Babinski responses. Three years later, patient presented with a 3–4-month history of slowly progressive lower limb weakness, areflexia	CAD	Nerve conduction showed a marked reduction of nerve conduction velocities with evidence of conduction block, temporal dispersion, and absent F waves	Spine MRI showed patchy abnormal cord signal at C3–C6 and T12–L1, a small syrinx at T6 and enhancement of the cauda equine Brain MRI showed patchy corpus callosal, abnormally high signal in deep cerebral and cerebellar white matter After 18 months, patient suffered two more relapses of her central demyelination, both confirmed by the presence of new active lesions on her MRI Oligoclonal bands were absent.	–	Pediatric case	[68]
	Japan	2005	Case report	1	Female	Relapsing-recovering course of progressive weakness, right facial palsy	CAD	Nerve conduction showed decreased motor conduction velocities and prolonged F wave latencies in several nerves	Left optic neuritis MRI revealed multiple areas of increased signal intensity on T2-weighted images in the periventricular white matter of the bilateral cerebral hemispheres representing small periventricular white matter lesions A spinal MRI also revealed high signal intensity lesions at the C7 level on the right side and at the T6-7 levels on T2-weighted images	–	Two months later IFN-1β treatment showed a progressive worsening of the numbness After discontinuing IFN-1β therapy and the start of oral prednisolone, weakness was resolved	[69]

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Autoimmune disease	Geographic location	Publication date	Study type	Number of cases	Gender	Neurological manifestations	Cerebrospinal fluid results	Electrodiagnosis	Autoimmune disease characteristics	Sural nerve biopsy	Observations	Ref
	Italy	2006	Case series	2	Female	Relapsing-recovering course of weakness, reduced reflexes and sensorial symptoms	CAD	Case 1: Nerve conduction showed slowed conduction velocity, absence of late responses (F responses and H reflex), presence of conduction blocks and temporal dispersion Case 2: Nerve conduction showed specific features of inflammatory demyelinating polyneuropathy.	Case 1: reduced extraocular movements of right eye, spastic-ataxia with dragging of left leg, cerebellar dysarthria CSF showed lymphocytic pleocytosis, mild elevation of protein and increase of IgG, oligoclonal bands MRI showed multiple focal areas of increased signal density in the brain and brainstem, some of them showing enhancement after gadolinium administration Case 2: brain MRI showed multiple focal areas of altered signals and CSF examination was positive for OCB.	–	–	[70]
	United States	2008	Case series	5	2/Female 3/Male	Disabling extremity weakness over two–six months period attributable to multiple root involvement with a decrease in the muscle mass and sensory symptoms.	An increase in mean CSF protein level	Nerve conduction showed diffuse peripheral demyelinating process involving both sensory and motor nerves	Optic neuritis, (internuclear ophthalmoplegia in all the patients; hemisensory impairment: patients 3–5) with spinal cord–related signs and symptoms. Lhermitte's sign and band-like pressure in the upper abdomen and thoracic dermatomes Spastic paraparesis, gait ataxia and positive oligoclonal bands	–	There may be a common antigenic target in central and peripheral nervous system in this subset of patients.	[71]
	Norway.	2016	Case report	1	Male	Flaccid paraparesis without wasting and areflexia, had symmetrical polyradiculopathy with progression over more than two months	–	Nerve conduction showed sensory-motor polyneuropathy of probable demyelinating type in the lower extremities with pronounced F-response abnormality	Relapsing remitting MS in 2005 Several bright periventricular and juxtacortical lesions as well as two hyperintense	–	Patient was treated for MS with referral for autologous hematopoietic stem cell therapy and One year after, patient is diagnosed with CIDP	[72]

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Autoimmune disease	Geographic location	Publication date	Study type	Number of cases	Gender	Neurological manifestations	Cerebrospinal fluid results	Electrodiagnosis	Autoimmune disease characteristics	Sural nerve biopsy	Observations	Ref
									lesions of more than 3 mm but less than two vertebral bodies Spastic paraparesis and there were a few new lesions in the spinal cord			
Sjögren's syndrome	Taiwan	2011	Case report	1	Female	Progressive limb weakness, predominantly in lower limbs, areflexia, sensory deficit of 2 months duration.	–	Nerve conduction showed prolonged distal latencies, reduced motor conduction velocity, and low amplitude of compound motor action potentials Sensory nerve testing showed moderately prolonged distal latencies, reduced conduction velocities, and low amplitude of sensory nerve action potentials F-wave latencies were prolonged in the ulnar, median, peroneal, and tibial nerves	Xerophthalmia, xerostomia ANA: 1: > 1280 anti-Ro/SSA: (+) anti-LA: (−) Schirmer's test: (+) Salivary gland scintigraphy: mild dysfunction	–	–	[73]
	United Kingdom	2012	Case report	1	Female	Progressive limb weakness	CAD	Nerve conduction showed a demyelinating neuropathy with predominant involvement of the upper limbs (where velocities were reduced and conduction blocks were present), and a degree of motor axonal loss in the lower limbs	Xerophthalmia, xerostomia anti-Ro/SSA: (+) biopsy: chronic sialoadenitis consistent		The presence of familial autoimmunity, including RA in maternal aunt and alopecia areata in sister. Also, patient presented with alopecia totalis	[74]
	Italy	2013	Case report	1	Female	Relapsing-recovering progressive limb weakness	–	Nerve conduction showed polyradiculoneuropathy with axonal demyelination	Xerophthalmia, Raynaud's phenomenon Schirmer's test: (+) ANA: (+) anti-Ro/SSA: (+) anti-LA: (+) RF (+)	–	Possible SLE indicated by presence of ANA: (+) pleural effusions nephropathy	[75]
Hashimoto's thyroiditis	Israel	1986	Case series	2	Female	A relapsing-recovering pattern of progressive limb weakness with bulbar involvement, hypoesthesia and areflexia	An increase in mean CSF protein level	Nerve conduction showed symmetric moderate reduction of the motor nerve conduction velocities. Sensory action potentials were of low amplitude	History of Hashimoto's thyroiditis	–	One patient presented T1D, Scleroderma, and MG	
	Greece	2008	Case report	1	Male	Two separate episodes of progressive weakness in the forearms and hands as	Mild protein elevation	Reduced motor conduction velocities, normal latencies, temporal dispersion of the compound muscle action	History of Hashimoto's thyroiditis.	–	–	[77]

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Autoimmune disease	Geographic location	Publication date	Study type	Number of cases	Gender	Neurological manifestations	Cerebrospinal fluid results	Electrodiagnosis	Autoimmune disease characteristics	Sural nerve biopsy	Observations	Ref
						well as dysesthesias of the dorsum of the left foot, hyporeflexia in the upper limbs and hypoesthesia in the ulnar nerve distribution		potential with proximal stimulation, and partial conduction block in sites that are not susceptible to pressure.	Anti-TPO: (+) Anti-Tg (+)			
	India	2009	Case report	1	Female	Progressive limb weakness, areflexia	CAD	Nerve conduction revealed sensori-motor demyelinating polyneuropathy with markedly prolonged distal latencies and reduced conduction velocities. CMAPs showed increased dispersion in nerves of both lower & upper limbs. F waves were absent in the lower limb and were prolonged in the upper limb nerves that were tested	Diffuse Thyromegaly, mild periorbital and pedal edema T4: 5.51 μg/dl (4.6–12 μg/dl) TSH > 100mIU/ml (0.27–4.2mIU/ml) anti-TPO (+) Fine needle aspiration cytology: lymphocytic thyroiditis CSF: Anti-TPO (AMA) was 72.7 mg/d and CSF-anti-Tg was more than 4000 mg/d.	–	Patient also developed a membranous nephropathy	[78]
Rheumatoid arthritis	Italy	1995	Case report	1	Female	Three month history of progressive limb weakness	CAD	Nerve conduction showed absent sensory response, reduced motor amplitudes, prolonged distal motor and F-wave latencies, and reduced motor nerve conduction velocities with partial conduction blocks	History of RA	Severe loss of myelinated fibers with early onion bulbs. Mononuclear inflammatory infiltrates with perivascular distribution in the epineurium	–	[79]
	United States	2010	Case series	2	1/Female 1/Male	Progressive limb weakness, numbness, sensory ataxia, areflexia	CAD	Case 1: Nerve conduction showed demyelination, including multiple conduction blocks, marked slowing of motor conduction velocities, prolonged minimal F-wave latencies, and absent H-reflexes. EMG showed fibrillation potentials with a marked decrease in motor unit recruitment, especially in distal muscles of the lower extremities. Case 2: Nerve conduction showed progressive demyelinating sensory and motor peripheral polyneuropathy	History of RA	–	Case 1: Patient was treated with etanercept for RA and 1 week after the second injection, she experienced neurological symptoms. She recovered after discontinuing etanercept Case 2: Patient was treated with infliximab for RA and 1 year later experienced neurological symptoms. Patient recovered after discontinuing infliximab	[80]

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Autoimmune disease	Geographic location	Publication date	Study type	Number of cases	Gender	Neurological manifestations	Cerebrospinal fluid results	Electrodiagnosis	Autoimmune disease characteristics	Sural nerve biopsy	Observations	Ref
								with marked slowing of the conduction velocities, multiple conduction blocks, and absent F-waves and H-reflexes EMG showed fibrillation potentials in the distal muscles of the lower extremities with a marked decrease in motor unit potential recruitment. Motor unit potentials were enlarged and polyphasic.				
Type 1 diabetes mellitus	United States	2005	Case series	2	1/Female 1/Male	Progressive bilateral lower extremity weakness over 2 months and mild sensory loss of the lower extremities, areflexia	Case 1: protein elevation Case 2: CAD	Case 1: EMG showed low amplitudes with prolonged distal latencies, a normal tibial F-wave, but a prolonged F-wave in the ulnar motor nerve. Case 2: EMG showed decreased amplitudes, prolonged distal latencies, absent F-waves, and multiple conduction blocks.	Polyuria, polydipsia, weight loss, hyperglycemia and ketoacidosis Case 1: DQB1*0301/0301 genotype Anti- GAD65 (+) Case 2: DQB1*0301/05 genotype Anti- GAD65 (+) Anti- IA-2: (+)	–	Pediatric case	[81]
	Brazil	2009	Case report	1	Male	A recovery-relapsing pattern of progressive paresthesia and a symmetric muscular weakness in both lower limbs, areflexia	Normal	Nerve conduction showed decreased conduction velocities with normal amplitude in the median, ulnar, left fibular and posterior tibial nerves but not in the deep right fibular nerve. The distal motor latencies of the median, left ulnar, superficial fibular and sural nerves were prolonged The F waves showed prolonged latencies in the ulnar and posterior tibial nerves	History of T1D	–	Pediatric case	[82]

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Autoimmune disease	Geographic location	Publication date	Study type	Number of cases	Gender	Neurological manifestations	Cerebrospinal fluid results	Electrodiagnosis	Autoimmune disease characteristics	Sural nerve biopsy	Observations	Ref
Vitiligo	United States	1996	Case series	2	Male	Progressive limb weakness, ascending leg numbness, areflexia over two months	CAD	Characteristic of an acquired demyelinating polyneuropathy	History of vitiligo	–	Both patients developed malignant melanoma	[83]
	Spain	2009	Case report	1	Male	Two separated episodes of progressive proximal limb weakness	CAD	Nerve conduction showed prolonged proximal motor latencies in the upper limbs, prolonged F-wave responses with normal sensitive conduction velocities and signs of active denervation EMG showed signs of denervation in upper limbs.	Several depigmented skin lesions clinically compatible with vitiligo	–	Patient developed a metastatic malignant melanoma Patient received interferon alpha-2b	[84]
Graves' Disease	United States	1999	Case report	1	Male	Progressive muscle weakness, numbness, and paresthesias, bilateral facial palsy	Normal	Nerve conduction showed decreased conduction velocities and low amplitudes for both sensory and motor nerves suggestive of a primary demyelinating neuropathy with secondary axonal injury.	Diarrhea, and weight loss T4, 13.2 μg/dl (normal, < 13 μg/dl) T3, 311 ng/ml (normal, < 230 ng/ml); TSH, < 0.1 μIU/ml (normal, > 0.5 μIU/ml); Anti-TPO: (+) Anti-TrAb: (+) Anti-Tg: (−)	Mononuclear inflammatory infiltrate surrounding the perineurial and endoneurial blood vessels without evidence of demyelination, remyelination, or significant loss of nerve fibers	Pediatric case. Patient developed Crohn's disease	[85]
Primary biliary cholangitis	Japan	2012	Case report	1	Female	Eighteen month history of progressive numbness, dysesthesia, mild weakness, hyporeflexia	CAD	Nerve conduction showed severe slowing in the median, ulnar, and tibial nerves, wave latencies were prolonged, conduction blocks were observed in the median, ulnar, and tibial nerves Sensory conduction studies showed slowing in the right median nerve Sensory nerve action potentials from the left median nerve and bilateral sural nerves were not detected	Alkaline phosphatase: (elevated) Anti-mitochondrial M2 (+) Biopsy showed reduced number of normal bile ducts, surrounded by infiltrates of lymphocytes and the presence of small atypical bile ducts with mild portal fibrosis	–	–	[86]

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Autoimmune disease	Geographic location	Publication date	Study type	Number of cases	Gender	Neurological manifestations	Cerebrospinal fluid results	Electrodiagnosis	Autoimmune disease characteristics	Sural nerve biopsy	Observations	Ref
Autoimmune Hepatitis	Portugal	2014	Case report	1	Female	Six month history of progressive distal muscle weakness and severe gait disturbance, paresthesia, areflexia	CAD	Nerve conduction showed slowed conduction and a prolonged distal latency with conduction block. Sensory nerve conduction studies in the left median and sural nerves were not evoked.	Liver enzymes: elevated high total bilirubin, elevated prothrombin and partial thromboplastin time ANA: 1:640 Anti-smooth muscle: (+) biopsy: revealing a dense mononuclear and plasma cell infiltration in the portal areas expanding to the liver lobule, destruction of the hepatocytes at the periphery of the lobule resembling an interface hepatitis, and connective tissue collapse with portal fibrosis and portal-portal septa.	–	Pediatric case	[88]

CIDP: Chronic inflammatory demyelinating polyradiculoneuropathy, PNS: Peripheral nervous system, MG: Myasthenia gravis, RA: Rheumatoid arthritis, SLE: Systemic lupus erythematosus, MS: Multiple sclerosis, T1D: Type 1 diabetes, CSF: Cerebrospinal fluid, CAD: Cytoalbuminologic dissociation, MRI: Magnetic resonance imaging, Anti ds-DNA: Anti-double stranded DNA, ANA: Antinuclear antibodies, VGKC: Voltage gated potassium channel-complex, CEA: Carcinoembryonic antigen, Ca 19-9: Cancer antigen 19-9, CT: Computerized tomography, Anti-TPO: Anti-thyroid peroxidase antibody, Anti Tg: Anti-thyroglobulin antibody, Anti-TrAb: Anti-TSH receptor antibody, Anti- GAD65: Glutamic acid decarboxylase antibody.

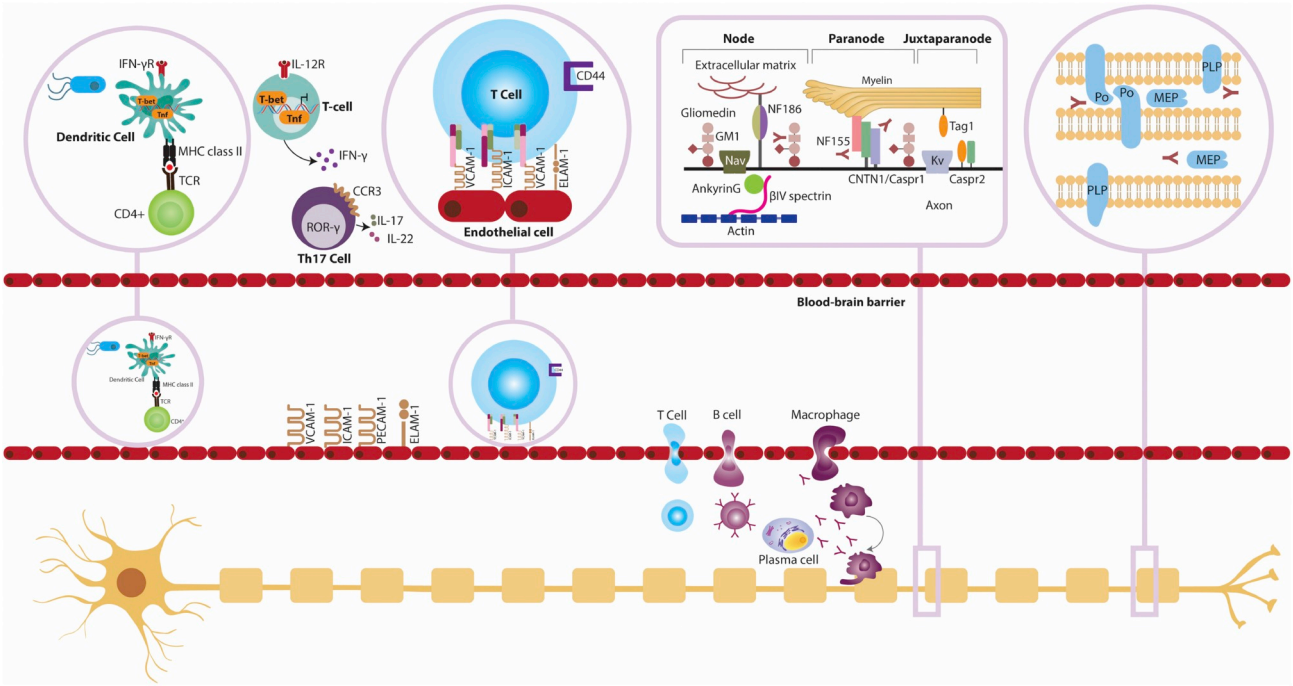

Fig. 1. Pathophysiology of chronic inflammatory demyelinating polyradiculoneuropathy. MHC: Major histocompatibility complex, NF155: Neurofascin splice variant 155, NF186: Neurofascin 186, CNTN1: Contactin-1, CASPR1: Contactin-associated protein-1, PLP: Proteolipid protein, P0: Myelin protein 0, MEP: Major excreted protein.

generated structural alterations and abnormalities in conduction nerve integrity [147]. In addition, chronic application of CNTN1 IgG4 antibodies to EAN worsened the clinical course and nerve conduction [147]. These findings were confirmed in *Cntn1* knockout models, where a loss of paranodal structures was associated with alterations in nerve conduction [148].

In the study by Querol et al., three patients with antibodies against CNTN1 had an aggressive clinical course with an acute onset and greater motor compromise associated with a poor response to IVIg. The poor response to IVIg [156] may be related to the presence of IgG4 isotype that does not activate complement or inflammatory cells efficiently [155]. This was later confirmed in a subgroup of Japanese patients with CIDP [157]. However, 8 out of 11 (73%) anti-CNTN1-positive patients had a good response to corticosteroids. Other reports have demonstrated a humoral immune response against neurofascin [158]. In murine models, the inoculation of neurofascin antibodies led to clinical deterioration [159].

A group of CIDP patients were found to have NF155 IgG4 antibodies [143]. These antibodies were later found to be directed against NF155 and other antigens [146]. Clinically, these patients presented with distal weakness, a demyelinating pattern on electromyography (EMG), a poor response to IVIg, and the presence of ataxia and other cerebellar symptoms [144]. A similar presentation was also seen in a cohort of 38 patients with anti-NF155 antibodies (IgG4 isotype) against the paranodal region [160]. These patients had cerebellar symptoms and a poor response to IVIg. Histologically, biopsies showed paranodal demyelination [161,162], and the loss of septate-like junctions in the paranodal region was seen on electron microscopy [163].

A diminished expression of CASPR1 [164] associated with elongated nodes and shorter internodes [165] has been described in CIDP. CASPR1 IgG3 antibodies have been detected in serum and biopsies associated with paranodal damage. Clinically, these patients presented with intense neuropathic pain, possibly due to antibodies against transient receptor potential cation channel subfamily V-positive and isolectin B4-positive small neurons located in the dorsal root ganglia [166]. Finally, in animal models, others have demonstrated demyelination after disruption of the neurofascin splice variant 186 (NF186) and gliomedin at Ranvier node [167].

Concerning regulatory B cells, their role in the pathophysiology of CIDP is poorly understood. However, in murine models that develop a spontaneous autoimmune polyneuropathy like CIDP, regulatory B cells control the immunopathogenesis and progression of autoimmune

Table 5
Myelin antigens identified in Chronic Inflammatory Demyelinating Polyradiculoneuropathy.
Modified from Mathey et al., [117], and Schafflick et al., [227].

Myelin Antigen	Population studied	Immunoglobulin Class	Method	Animal model	Animal model description	Reference
P0	40/276	IgG, IgA, IgM	Immunofluorescence, Western blot, ELISA	Lewis rat	CIDP-like relapsing	[27,120,121,128–135]
P2	26/150	IgG, IgM	ELISA	Lewis rat	CIDP-like relapsing	[122,129–131,134]
PMP22	19/70	IgG, IgM	ELISA, Western blot	Lewis rat	Mild EAN	[119,123–125]
Cx32	1/24	–	Western blot	–	–	[128]
MBP	2/40	IgG	ELISA	Lewis rat, Dark Agouti rat	CIDP-like relapsing	[27,126,127]

CIDP: Chronic inflammatory demyelinating polyradiculoneuropathy, PMP: Peripheral myelin protein, MBP: Myelin basic protein, ELISA: Enzyme-Linked ImmunoSorbent Assay, EAN: Experimental autoimmune neuritis.

Table 6
Paranodal antigens identified in Chronic Inflammatory Demyelinating Polyradiculoneuropathy.

Nodal/paranodal Antigen	Population studied	Immunoglobulin Class	Method	Animal model	Animal model description	Reference
NF155	13/210	IgG3, IgG4, IgA, IgM	ELISA, Cell-based assay	Nfasc-null mice65	–	[142–145]
NF186	1/167	IgG	ELISA, Cell-based assay	–	–	[143,146]
CNTN1	3/46	IgG	Cell-based assay	–	–	[147–149]
CASPR1		IgG, IgG4	Cell-based assay	–	–	[149,150]

NF155: Neurofascin splice variant 155, NF186: Neurofascin splice variant 186, CNTN1: Contactin-1, CASPR1: Contactin-associated protein-1, ELISA: Enzyme-Linked ImmunoSorbent Assay.
Modified from Mathey et al., [117].

polyneuropathy. This would make it possible to generate therapies aimed at the expansion of these cells for the management of autoimmune polyneuropathies such as CIDP [168].

7. Clinical features and diagnosis

The clinical spectrum of CIDP is similar to that of the AIDP subphenotype of GBS. However, AIDP is usually characterized by a single episode, acute onset, shorter clinical course, and lack of sequelae [1]. In CIDP, the onset and the clinical course is more insidious, and neurological symptoms are usually established over months and characterized by the presence of a relapsing-remitting course [1]. The appearance of AIDP is frequently associated with a previous infectious episode [34], whereas in CIDP, the presence of a previous infection is not always clear.

Like other inflammatory polyneuropathies, neurological symptoms in CIDP include limb weakness, paresthesias, sensory disorders, cerebellar symptoms, cranial nerve involvement, autonomic symptoms, and neuropathic pain. However, the clinical course of the disease suggests that there are two types of CIDP. Typical CIDP is characterized by the presence of progressive, chronic, and recurrent proximal or distal symmetrical weakness in the limbs associated with hypo or areflexia and sensory involvement. These symptoms develop over a period of 8 weeks. Atypical CIDP, or Lewis-Sumner syndrome [169], is characterized by asymmetrical distal limb weakness and either a pure motor or sensory pattern. Additionally, the presence of multifocal demyelinating motor and sensory neuropathy associated with a persistent conduction block is frequently observed and can be associated with antibodies against CASPR1 or NF155 [170].

In addition to these subphenotypes, a disease characterized by a sensory nerve root involvement (sensory ataxia) without weakness and numbness, but with normal nerve conduction studies has been described as another subtype of CIDP. As a result, there have been reports of erroneous CIPD diagnoses [171]. The use of electrodiagnostic criteria in conjunction with the clinical course may improve reliability in diagnosing CIDP. In electrodiagnostic studies, the presence of unequal multifocal demyelination is observed. This is due to prolonged F waves, slow conduction velocities, and prolonged distal latencies. In addition, a reduction in motor unit potential resulting from axonal loss is associated with an increase in duration.

In recent years, the European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS) has proposed criteria for diagnosing CIDP [170]. An evaluation of CSF is mandatory and characterized by the presence of cytoalbuminologic dissociation (CAD) (an elevated CSF protein level but no increase in white blood cell count) [172]. An increase in CSF protein, generally greater than 0.45 g/L, is found in more than 90% of the patients [173–175]. The proteins increased in the CSF include transferrin isoforms, α-1 glycoprotein acid 1 precursor, apolipoprotein-A IV, transthyretin, retinol-binding protein, and pro-apolipoprotein isoforms, whereas beta 8 integrin is diminished [176]. Less than 10 cells/μL are usually observed in the CSF of patients with CIDP [177].

In active CIDP, Th1 and Th17 cells are increased in CSF [178,179], as well as cathepsin B, CXCL10, CCL2, CCL3, CCL7, CCL19, CCL27, CXCL9, and CXCL12 In contrast, cystatin C is decreased [180–184]. . In addition, an increase in IL-6, IL-8, and IL-17 has been reported, while a decrease in the concentrations of IL-4, IL-5, and IL-7 has been observed [178]. There is also an increase in the adhesion molecules ICAM-1 and VCAM-1 [176,180].

Peripheral nerve ultrasounds are being used along with nerve conduction studies to distinguish CIDP from other chronic demyelinating diseases with similar clinical and electrophysiological findings such as M-protein associated neuropathy and Anti-MAG neuropathy [185]. Athanasopoulou et al. did a study of 39 patients and 27 controls using a peripheral nerve ultrasound and reported a substantial enlargement of nerves in CIDP patients [185].

The Triple Stimulation Technique (TST) is a method that makes possible to study the corticospinal tract as well as signs of demyelination. TST is superior to motor evoked potential since TST allows for quantification of the number of motor units activated through transcranial stimulation. TST has been used to study central motor conduction of the lower extremities and to diagnose MS and other neurologic disorders. Recently, it has been shown to be effective in evaluating motor neuron blocks in CIDP [186]. TST may be used when CIDP patients do not meet the diagnostic criteria or when nerve conduction study abnormalities are related to axonal loss. TST has successfully detected conduction blocks that are proximal to Erb's point. This is relevant as nerve conduction studies usually fail to show demyelination findings when conduction blocks are between the nerve root exit and Erb's point.

Somatosensory evoked potentials are another non-invasive method of studying the nerves of the CNS and PNS. They have been used as a complementary diagnostic tool in the diagnosis of CIDP [187]. Somatosensory evoked potentials evaluate a proximal section of sensory nerves that are not adequately assessed by routine nerve conduction studies.

Magnetic resonance neurography with 3-D reconstruction of demyelinated nerves can be helpful when the diagnosis of CIDP is inconclusive. This method uses magnetic resonance imaging (MRI) short tau inversion recovery images to show patterns of demyelination. For example, typical CIDP cases show symmetrical nerve enlargement and atypical cases show multifocal nerve enlargements while Charcot-Marie-Tooth cases reveal diffuse hypertrophy of the nerve. Overall, this method can help differentiate different variants of CIDP [188].

Corneal Confocal Microscopy is used to measure corneal nerve fiber loss and corneal nerve fiber length. A study done by Stettner et al., demonstrated corneal nerve fiber loss, density, and reduced length in CIDP. Moreover, this technique allows to detect a high number of cell infiltrates around the nerve which suggests early stages of CIDP. In addition, motor involvement in CIDP also correlates with an increased number of cell infiltrates [189].

8. Therapeutic strategies

CIDP is primarily treated with immunomodulation using glucocorticoids, IVIg, subcutaneous immunoglobulin (SCIg), plasmapheresis, and immunosuppressive drugs. Other therapeutic measures directed at treating associated symptoms of CIDP are also widely used [190].

Table 7
Classification criteria for autoimmune diseases in humans. Comparison among Chronic Inflammatory Demyelinating Polyneuropathy and some autoimmune rheumatic diseases.
Modified from Pinto et al., [224].

			Autoimmune diseases				Ref
			SLE	RA	SS	CIDP	
Direct proof	Antibody-mediated	Circulating antibodies altering function	+	+	+	+	[220]
		Localized autoantibodies	+	+	+	+	[220,221]
		Immune complexes located at the lesion	+	+	+	+	[154]
		Passive transference	+	+	+	+	[139]
	Cell-mediated	*in vitro* T-cell proliferation in response to autoantigen	+	+		+	[115]
		in vitro T-cell transference to immune-deficient mice	+	+		+	[222]
		in vitro T-cell cytotoxicity against target organ cells	+	+	+	+	[115]
Indirect proof		Disease reproduction (or induction) by experimental immunization	+	+	+	+	[105]
		Disease reproduction by idiotypes	+	+			–
		Spontaneous animal models	+	+	+	+	[121]
		Animal models produced by immune system deregulation	+	+	+	+	[105]
Circumstantial evidence		Autoantibodies	+	+	+	+	[221]
		Coexistence of other ADs	+	+	+	+	[21,54–93]
		HLA association	+	+	+	+	[37,44–51]
		Lymphocytic infiltration in target organ	+	+	+	+	[106]
		Good response to immune suppression	+	+	+	+	[223]

ADs: Autoimmune diseases, SLE: Systemic lupus erythematosus, RA: Rheumatoid arthritis, SS: Sjögren syndrome, CIDP: Chronic inflammatory demyelinating polyneuropathy.

The first studies that evaluated the effect of corticosteroids for the management of CIDP were initially done on few patients [191–193]. Subsequent larger studies have compared prednisone versus no treatment in 28 patients with CIDP for 3 months. One study revealed relative improvements in muscle strength and neurological symptoms in the treated group [194]. In another study, a group of 10 patients with CIDP underwent treatment with oral methylprednisolone weekly for 22 weeks with 6 patients showing improvement in disability scores and achievement of remission [195]. In 2010, Van Schaik et al., carried out a randomized clinical trial using 41 CIDP patients with two different corticosteroid management regimens. One group received 60 mg of prednisolone daily which they were gradually weaned off over a period of 32 weeks. The second group received oral dexamethasone which was administered at a daily dose of 40 mg for 4 days followed by placebo for 24 days repeated monthly for six months. This study revealed that the treated group with dexamethasone did not have a greater remission of neurological symptoms compared to the group managed with prednisolone [196].

In 2014, Boru et al., retrospectively analyzed 20 patients with CIDP, who initially received 1000 mg of methylprednisolone intravenously daily for 10 days and then, once monthly. This treatment regimen was continued for 5 years with additional follow-up for other 5 years. This study showed clinical improvement in 15 patients during the 5 years of treatment. However there were 6 relapses during the 5-year follow up period [197]. The use of corticosteroids as monotherapy or in high doses should not be considered for exclusive management of CIDP given the low quality of the studies that assessed their effect on CIDP and the potential long-term risk associated with the use of these medications.

Table 8
Autoimmune tautology. Focus on Chronic Inflammatory Demyelinating Polyneuropathy.

Autoimmune tautology premise	Definition	Chronic inflammatory demyelinating polyneuropathy
Female preponderance	Later presentation of AD is associated with a higher female predisposition	Epidemiological evidence currently available demonstrates a masculine predominance, as observed in GBS [224]
Shared subphenotypes	ADs share clinical signs and symptoms even though they have a heterogeneous spectrum and course that varies from patient to patient	CIDP shares signs and symptoms with GBS, at least at the onset of the disease, given the involvement of the PNS in both diseases. However, there are specific characteristics in the clinical course of CIDP not described in GBS.
Polyautoimmunity	The presence of two or more ADs in a single patient	The coexistence of CIDP with other ADs has been described (Table 4)
Coaggregation	Familial autoimmunity (i.e., diverse ADs in a nuclear family, coaggregation)	Not described
Age at onset influences severity	Severity of ADs is inversely related to the age at onset	Older patients disclose low scores for muscle strength and poor short-term prognosis
Similar pathophysiology	Although the target cells, affected organs, and clinical expression differ, similar immunopathological mechanisms have been established for ADs	CIDP shares similar pathophysiological mechanisms with GBS. In fact, both diseases share antigens that trigger humoral immune response
Autoimmune ecology	Similar environmental agents may influence ADs	Infectious agents associated with other ADs have also been described as triggers of CIDP (Table 3)
Ancestry	Amerindian ancestry influences the risk of acquiring ADs as well as its outcomes, which includes the development of polyautoimmunity	Not described
Common genetic factors	Combinations of common and disease-specific alleles in HLA and non-HLA genes in interaction with epigenetic and environmental factors over time will determine the final phenotype	HLA genes and alleles associated with CIDP have been described in other ADs
Similar treatment	Similar biological and non-biological therapies are used to treat diverse ADs	CIDP not only shares the same treatment with GBS, but also with other ADs where the use of immunomodulatory and even biological drugs have shown benefits

ADs: Autoimmune diseases, CIDP: Chronic inflammatory demyelinating polyneuropathy, GBS: Guillain-Barré syndrome.
Adapted from Anaya [228].

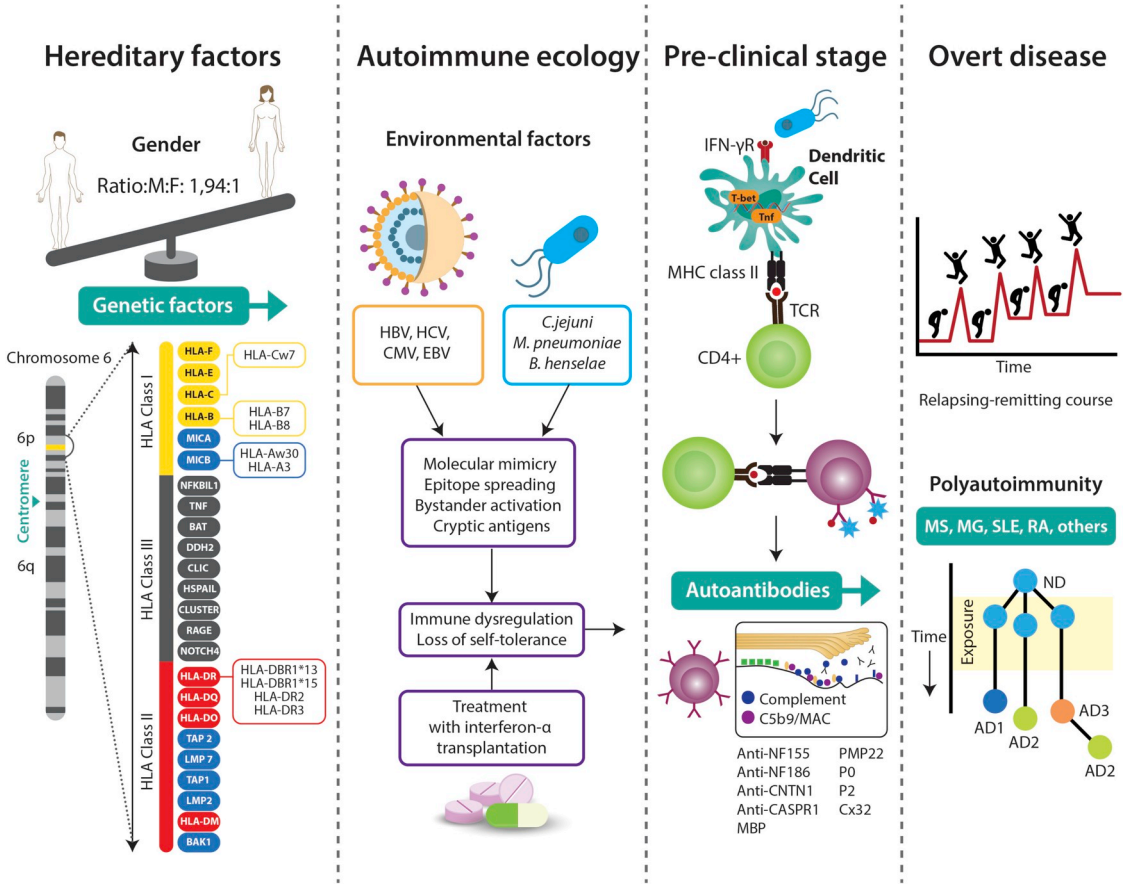

Fig. 2. Natural history of the CIDP. F155: Neurofascin splice variant 155, NF186: Neurofascin 186, CNTN1: Contactin-1, CASPR1: Contactin-associated protein-1, MBP: Myelin basic protein, MG: Myasthenia gravis, RA: Rheumatoid arthritis, SLE: Systemic lupus erythematosus, MS: Multiple sclerosis, *B.henselae: Bartonella henselae*, *C.jejuni: Campylobacter jejuni*, *M.pneumoniae: Mycoplasma pneumoniae,* HBV: Hepatitis B virus, HCV: Hepatitis C virus, Cytomegalovirus, EBV: Epstein-Barr virus, ND: no disease.

IVIg is frequently used for the management of CIDP based on its ability to interfere with complement activity, proinflammatory cytokine production, and signaling of phagocytes and B cells through Fcγ receptors [198,199]. In 2008, a clinical trial evaluated IVIg in 117 patients with CIDP. The clinical course and disability had improved after 24 weeks of IVIg treatment, and there was a low rate of relapse [200]. Other studies have confirmed these findings [200–205]. Recently, a group of researchers suggested the use of SCIg [206], especially for those who relapse and require maintenance therapy after initial therapy with IVIg [207].

It is necessary to individualize patients for IVIg management since there are different immunobiological and pharmacokinetic variables that can influence the response. Among the most important variables are the pharmacokinetic variability of IgG, the catabolic distribution rate of IgG, and the level of optimal IgG for clinical control [208]. A study by Allen et al. highlights the fact that strength impairment measured by dynamometry and disability measured with I-RODS (disability scale) can be helpful in documenting responses to IVIg treatment. Patients with autoantibodies against nodal and/or paranodal antigens, especially those of the IgG4 isotype, tend to benefit from IVIg [208].

The immunomodulatory effect of plasma exchange (PE) is based on the removal of autoantibodies, interleukins, and other proinflammatory molecules [198]. The first studies on PE demonstrated significant clinical improvement and favorable electromyographic changes [209]. Another study of 18 patients with CIDP also reported clinical responses to PE in approximately 80% of patients who completed the study [210–214].

Other immunomodulatory treatments have been used for the management of CIDP. These include azathioprine [215], methotrexate [216], interferon beta-1α [217], mycophenolate mofetil [218], and rituximab [219]. The effectiveness of these treatment modalities has not been clearly demonstrated, in part due to the quality of the studies. However, their use as adjuvant therapies in patients with a more aggressive clinical course is suggested.

9. Conclusions and perspectives

CIDP may be considered an AD and is consistent with the autoimmune tautology hypothesis (i.e., common mechanisms of ADs) (Tables 7 and 8) [21,37,44–51,54–93], [105,106,115,121,139,154,220–224]. The appearance of CIDP requires a genetic predisposition which, together with external triggers such as viruses, facilitates loss of immunological tolerance, a response against myelin, and a progressive clinical course characterized by the presence of remission and relapse (Fig. 2). However, research on CIDP is still in its infancy and large-scale studies are required to demonstrate an epidemiological link of infections and other environmental stimuli. At the same time, genetic mechanisms associated with this disease deserve much more attention.

Conflicts of interest

None.

Funding

This work was supported by Universidad del Rosario (ABN-011).

Acknowledgement

The authors would like to thank the CREA group for important contributions and fruitful discussions, and the anonymous reviewers for their valuable comments and suggestions to improve the quality of this work.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jaut.2019.04.021.

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