

A Review on Chronic Inflammation of Demyelinating Polyneuropathy

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ABSTRACT

Chronic inflammation of demyelinating polyneuropathy (CIDP) is a neurological disorder characterized by inflammation of the peripheral nerves, resulting in muscle weakness and sensory disturbances. The condition is caused by an abnormal immune response in which the immune system attacks the myelin sheath surrounding the nerves, leading to damage and dysfunction. CIDP is a chronic condition that can progress over time, and symptoms may vary in severity and duration. Treatment options include corticosteroids, immunosuppressive drugs, and intravenous immunoglobulin therapy. Early diagnosis and treatment are crucial in managing CIDP and preventing long-term disability. Further research is needed to fully understand the underlying mechanisms of the disorder and to develop more effective treatments. Chronic inflammation of demyelinating polyneuropathy (CIDP) is a neurological disorder characterized by inflammation and damage to the myelin sheath that surrounds nerve fibers. The exact cause of CIDP is unknown, but it is thought to be an autoimmune disorder, meaning that the body's immune system mistakenly attacks healthy tissue in the peripheral nervous system. This results in symptoms such as weakness, numbness, and tingling in the arms and legs, which can progress over time and lead to difficulty walking or performing daily activities. Treatment for CIDP typically involves immunosuppressive medications and/or plasma exchange therapy to reduce inflammation and improve nerve function. With proper management, many people with CIDP are able to control their symptoms and maintain a good quality of life.

Key words: Chronic inflammation of demyelinating polyneuropathy, immunosuppressive, corticosteroids

I. INTRODUCTION

Chronic inflammatory demyelinating polyneuropathies (CIDP) is a type of acquired

immune-mediated disorder that affects the peripheral nervous system. The first case was described by Eichhorst Burns in 1890.(1) Demyelination describes a pathological process of destruction in the myelin supporting cells, that is oligodendrocytes and schwann cells or myelin lamellae with relative preservation of the axon. The symptoms are slowly progressive over 2 months, symptoms like symmetric weakness of both muscles around the hip, shoulder, arms and feet (both proximal and distal muscles).(2) (CIDP) is the most common treatable chronic neuropathy worldwide, with a prevalence ranging from ~1 to 9 cases per 100 000.some do not respond or have lasting disability.(3)

Generally considered the chronic counterpart to Guillain-Barré syndrome (GBS), about 16% of the patients present with acute GBS, The long term nature of this condition leads to abnormalities in gait and impairments in both psychological and social functioning.(4-6) CIDP is difficult to diagnose, but early diagnosis can be crucial to prevent permanent nerve damage. Initial treatment options include corticosteroids, immunoglobulin given by intravenous administration, and therapeutic plasma exchange. (7)

Academic center data derived from more than 1000 cases in North America (The University of Kansas Medical Center and The University of Texas Southwestern) and 1034 cases from South America (Federal Fluminense University, Brazil) demonstrates a similar proportion of immune-mediated neuropathies ranging from 18 % to 20 %.(8)

Clinically CIDP is classified into 'typical' and 'atypical' cases; typical CIDP is a symmetrical polyneuropathy affecting proximal and distal muscles equally, whereas atypical CIDP includes 'distal acquired demyelinating symmetric' (DADS), and multifocal acquired demyelinating sensory and motor neuropathy (MADSAM, or Lewis-Sumner syndrome [LSS]).(9)

Diagnosis is based on cerebrospinal fluid protein, electromyography, nerve conduction velocity (NCV) test, peripheral nerve biopsy and electron micrograph of peripheral nerve.

ETIOLOGY:

CIDP could be due to an immune reaction, resulting in segmental and multifocal demyelination that may induce axonal loss with time.(10) It involves both T cell-mediated and humoral immune mechanisms by targeting the myelin of the peripheral nervous system.

Classical CIDP is idiopathic, but it has variants that can be seen in association with a neoplastic process, HIV infections, and chronic history of diabetes mellitus type II.(6)History of antecedent diseases have been commonly reported with AIDP/GBS; however, they are rare with CIDP.(1)25 patients, secondary causes could be found and included diabetes mellitus in 16, POEMS syndrome in two, MGUS in two, lymphoma in one, multiple myeloma in one, and gastrointestinal malignancy in one patient. Hypothyroidism was present as a part of POEMS in four, and was associated with diabetes in one and malignancy in two patients. In the remaining 40 patients, no cause could be established and these patients were included in the primary CIDP group. (11)

EPIDEMIOLOGY:

Reported prevalence of CIDP ranges from 0.7 to 10.3 cases per 100,000 people. (12)There is predominance in males, with a sex rate ratio ranging from 1.5 to 4. CIDP primarily affects adults and the incidence rises with advancing age. The median age of onset is not well established. No specific predisposing risk factors for CIDP have been clearly identified.(13)Prevalence is about 1/200,000 children and 1-7/100,000 adults, but it is generally accepted that the frequency is

underestimated.(10)Due to diverse clinical presentations and diagnostic criteria used worldwide, the incidence and prevalence rates also vary. CIDP predominantly affects males more than females, with a ratio of 2:1. (1)

PATHOLOGY

CIDP is primarily a T cell-mediated process. However, the response to plasmapheresis suggests a possible role of B cell-mediated immune functions.(14)At the microscopic level, demyelination and remyelination are the pathological hallmarks of CIDP. The demyelination and remyelination can be visualized on teased fibers analysis in 48% to 68% of the patients, while in 21% of patients, mixed demyelination and axonal changes are seen. (15)

The formation of 'onion bulbs' has also been described, which are made of concentrically oriented Schwann cell processes surrounding thinly myelinated fibers and sometimes, focally thickened myelin sheaths.(16)The classical CIDP is idiopathic, whereas the variants are linked to the antibodies directed against the myelin or proteins located at the node of Ranvier. Both T cell and B cell-mediated inflammation lead to neuronal damage and dysfunction. The activated T cells and macrophages act as antigen-presenting cells and bind directly to targeted structures to promote demyelination. (17)While many antibodies, such as GD1a, GD1b, GM1, and GQ1b, are associated with GBS, no particular antibody is associated with CIDP. Thus far, only a few autoantibodies have been identified in association with CIDP variants, such as perinodal proteins such as neurofascin 140In CIDP variants, such as DADS with Anti MAG Antibody, demyelination is seen along the large myelinated axons with separation of the myelin lamellae and depositions of IgM and C3d on myelin sheaths. (16)

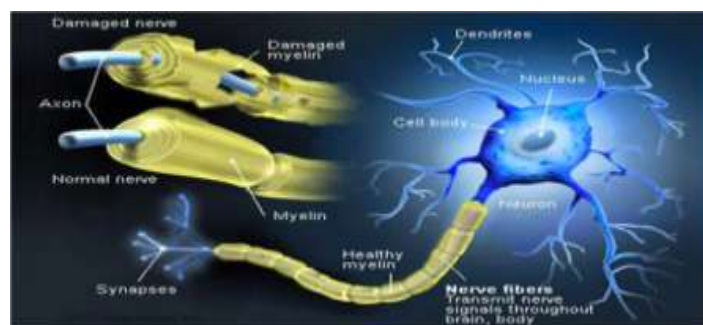


Figure 1: Chronic inflammation of demyelinating polyneuropathy Pathophysiology

PATHOGENESIS

Immunologic basis — although the cause of CIDP and its variants is unknown, there is evidence to support the hypothesis that the disorder(s) are immunologically mediated and can have multiple triggers. Both the cellular and humoral components of the adaptive immune system appear to be involved in the pathogenesis of CIDP and its variants.

a) Cellular immunity involvement is supported by evidence of T cell activation, crossing of the blood-

nerve barrier by activated T cells, and expression of cytokines, tumor necrosis factor, interferons, and interleukins.

b) Humoral immunity is implicated by the demonstration of immunoglobulin (Ig) and complement deposition on myelinated nerve fibers, and by passive transfer experiments that induce conduction block and demyelination by injecting serum or purified IgG from CIDP patients into rats.(18)

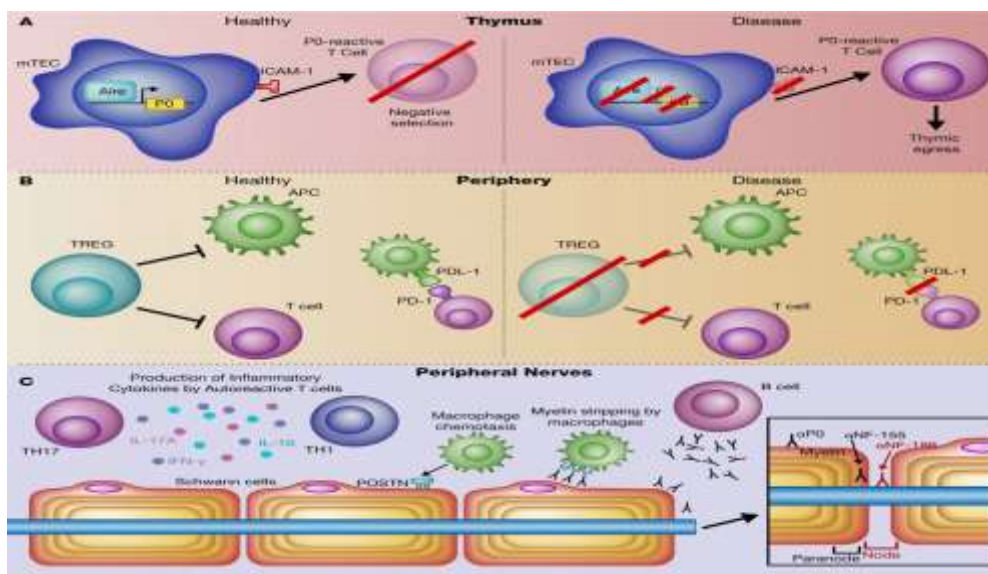


Figure 2: Chronic inflammation of demyelinating polyneuropathy Pathogenesis

CAUSES

The exact cause of CIDP is unknown but there are strong indications that CIDP is an autoimmune disorder. Recent studies have detected antibodies directed against constituents of peripheral nerve (neurofascin 155 and contactin 1) that cause rare variants of CIDP.(19)

Many people with CIDP don't have any identifiable risk factors. Among those who do, the most common risk factors include a history of:

- Guillain-Barré syndrome (GBS)
- cancer
- viral infection
- immunization(20)

The other factors (cancer, infection, immunization) may trigger an immune response that acts against myelin in the peripheral nervous system. (20)

A variety of medical conditions and other factors can cause polyneuropathy, including:

- Diabetes: This can be a significant risk factor, especially if blood glucose levels are poorly controlled. One study Trusted Source of more than 1,400 people with type 2 diabetes found that every fifth person had diabetic neuropathy.
- Alcohol abuse: Alcohol can damage nerve tissue, and alcohol abuse is often associated with nutritional deficiencies that contribute to neuropathy.
- Autoimmune conditions: The immune system attacks the body, causing damage to nerves and other areas. Conditions include Sjogren's syndrome, celiac disease, Guillain-Barré syndrome, rheumatoid arthritis, and lupus.
- Bacterial or viral infections: Certain infections can lead to neuropathy, including Lyme disease, shingles, hepatitis B, hepatitis C, and HIV.
- Physical trauma or injury: Repetitive motion

such as typing, accidents, or other injuries can damage peripheral nerves.(21)

CIDP may occur with other conditions, such as:

- Chronic hepatitis
- Campylobacter jejuni
- HIV/AIDS
- Immune system disorders due to cancer
- Inflammatory bowel disease
- Systemic lupus erythematosus
- Cancer of the lymph system
- Overactive thyroid
- Side effects of medicines to treat cancer or HIV(22-23)

SIGNS AND SYMPTOMS

Symptoms of chronic inflammatory demyelinating polyneuropathy are similar to those of Guillain-Barré syndrome: Weakness is more prominent than abnormal sensations (numbness and a pins-and-needles sensation). However, these symptoms worsen for more than 8 weeks. (In Guillain-Barré syndrome, weakness usually worsens over 3 or 4 weeks, then remains the same or starts to return to normal.)

Symptoms may slowly worsen or may lessen or disappear, then worsen or reappear. (24)CIDP causes weakness, paresthesia, and sensory deficits, usually with recurrent episodes. It affects both sides of the body — in a nearly but not perfectly symmetrical fashion. Symptoms usually develop slowly over a long period of time. (21)

This pattern of weakness, if caused by nerve damage, is highly suggestive of CIDP. Nerve signals become altered causing impairment in motor function and/or abnormal, or loss of, sensation. There are usually some alterations of sensation causing incoordination, numbness, tingling, or prickling sensations. (19)

Symptoms include any of the following:

- Problems walking due to weakness or lack of feeling in the feet.
- Trouble using the arms and hands or legs and feet due to weakness.
- Sensation changes, such as numbness or decreased sensation, pain, burning, tingling, or other abnormal sensations (usually affects the feet first, then the arms and hands)

Other symptoms that can occur with CIDP include:

- Abnormal or uncoordinated movement
- Problems breathing
- Fatigue
- Hoarseness or changing voice or slurred

speech.(22-23)

DIAGNOSIS

- To be diagnosed with CIDP, patients have to present a 2 month history of progression of demyelinating neuropathy (DN), some have a history of infection. CIDP may also appear more than 8 weeks after Guillain-Barré syndrome (GBS, so-called "acute CIDP"; see this term). Diagnosis is based primarily on clinical and electrophysiological findings. The need for CSF examination and nerve biopsy depends on the level of clinical diagnostic certainty (10)
- In addition, a doctor may order some tests to examine other parts of your body. A nerve conduction test can help differentiate between radiculopathy (pinched nerve), myopathy (muscle disease), CIDP, and other types of neuropathy (such as diabetic neuropathy).(20)
- **Electrodiagnosis** In patients with suspected CIDP, does the use of electrophysiology/electrodiagnosis (motor and sensory nerve conduction studies, somatosensory evoked potentials, root stimulation, triple stimulation technique, nerve excitability studies, and electromyography), compared to not using electrodiagnosis, influence diagnostic accuracy and patient outcome.
- **MRI or ultrasound**—in patients with suspected CIDP, does the use of imaging—MRI (thickening or abnormal enhancement of cervical/lumbar nerve roots or brachial/lumbar plexus) or nerve ultrasound (increased cross-sectional area of peripheral nerves or roots compared with normal values), compared to no imaging, influence diagnostic accuracy and patient outcome (treatment response).
- **CSF**—in patients with suspected CIDP, does the use of CSF examination compared to not using CSF examination, influence diagnostic accuracy and patient outcome? Are thresholds for raised protein different in children <16 years old or in any patient.
- **Nerve biopsy**—in patients with suspected CIDP, does nerve biopsy (looking for macrophage-associated demyelination, onion bulb formation, demyelinated and to a lesser extent remyelinated nerve fibres, endoneurial oedema, endoneurial mononuclear cell infiltration, loss of transverse bands or paranodal loop detachment, teased fibre analysis).

- Monoclonal gammopathies—In patient with suspected CIDP, does testing for the presence of IgG, IgA, IgM, or light chain monoclonal gammopathies, compared with not testing for monoclonal gammopathies.(25)
- Tests that can be of diagnostic help include nerve conduction testing and electromyography looking for very slow nerve conduction velocities, lumbar puncture looking for elevated spinal fluid protein without many inflammatory cells and MRI imaging of the nerve roots looking for enlargement and signs of inflammation.(19)

TREATMENT

Early treatment is key; it can help prevent nerve damage. That can help stop symptoms from becoming severe.

Treatment may include:

- **Corticosteroids:** These medications bring down inflammation and slow the immune system.
- **Immunotherapy.** These drugs interrupt your immune system to help stop it from attacking the myelin.
- **Intravenous immunoglobulin (IVIG):** Your doctor may give you injections of concentrated antibodies from healthy people to slow your body's immune response.
- **Stem cell transplant.** In rare cases, your doctor may inject healthy stem cells (either yours or donated by someone else) to "reset" your immune system
- **Plasma exchange (PE):** This treatment involves receiving a part of blood called plasma through an IV to slow down your immune system.(26)

A doctor may also prescribe medications called immunomodulators that are known to suppress the immune system and improve signs and symptoms of CIDP.

These drugs include:

- azathioprine
- cyclophosphamide
- cyclosporine
- methotrexate
- mycophenolate

These drugs can be given alongside the immunomodulators mentioned above. They include:

- carbamazepine
- gabapentin
- amitriptyline
- pregabalin
- duloxetine (27)

Approximately 25% of patients are refractory to first-line treatment. These patients require further investigations to evaluate for CIDP variants or other causes of acquired demyelinating chronic neuropathies. In such cases, targeted therapies such as rituximab and alemtuzumab can be used.

PREVENTION

Preventing polyneuropathy involves limiting the risk factors and managing underlying conditions. A person with polyneuropathy may not be able to avoid all risk factors, but some lifestyle choices may reduce the risk. These are:

- avoiding alcohol
- avoiding exposure to toxins, including cigarette smoke
- limiting factors that contribute to physical trauma or injury, such as repetitive actions and restrictive positions
- getting enough sleep and physical activity to support immune function
- eating a balanced diet rich in vitamins and minerals
- considering vitamin B-12 supplements if a vegan or vegetarian.(27)

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