Chronic Inflammatory Demyelinating Polyradiculoneuropathy: Post-Pandemic Review

Kronik İnflamatuvar Demiyelinizan Poliradikülonöropati: Pandemi Sonrası Gözden Geçirme

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ABSTRACT

Chronic inflammatory demyelinating poly(radiculo)neuropathy is an acquired and disabling peripheral nervous system disease in which the immune system plays a role in a chronic process. Although the disease has been known for many years, its first serious definition was made by James Austin in 1958 and it was reported that the disease progressed with recurrences, responded to corticosteroid therapy and that the underlying cause of this clinic may be segmental demyelination. In this article, in the light of the new information obtained about the pathophysiology and treatment of the disease, it is aimed to review the changes in treatment strategies after the coronavirus pandemic in 2019 (COVID-19) and the update of the electrophysiological diagnostic criteria of the European Academy of Neurology/Peripheral Nerve Society (EAN/PNS) in 2021.

Keywords: Chronic inflammatory demyelinating polyneuropathy; COVID-19; EAN/PNS.

Inflammatory demyelinating polyradiculopathies, which are an acquired and immune-mediated group of neuropathies, are examined in two groups as acute inflammatory demyelinating polyneuropathy (AIDP) or Guillain Barre syndrome (GBS) and chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) based on the clinical picture. In GBS, maximal deficit develops within days (maximum 28 days), then plateau period and subsequent improvement are observed. In the chronic form, slower progression (2 months or longer) or a pattern of recovery and relapse are observed. [1] In both diseases, the presence of high protein in the cerebrospinal fluid (CSF) and the absence of cells (albuminocytological dissociation) demyelinating type nerve conduction abnormalities and pathological features are common.
Although definitive evidence cannot be shown for both diseases, they are considered to be autoimmune-based. In addition to the temporal course, there are some clinical features that allow to distinguish GBS from CIDP. Involvement of the autonomic nervous system in GBS, cranial manifestations with facial involvement at the forefront, more pronounced weakness (e.g., loss of walking ability and need for mechanical ventilation), and precursor events in the history are important for differential diagnosis. Approximately 70–80% of patients diagnosed with AIDP have a history of infectious diseases, vaccination or surgical intervention 3–4 weeks before the onset of clinical symptoms of the disease. Despite this, 32% of CIDP patients reported precursor events prior to the disease. According to some authors, the term subacute inflammatory demyelinating polyneuropathy (SIDP) is used to refer to the disease condition that lasts between 4 and 8 weeks.

Clinical and Research Consequences

Definition

CIDP is an acquired, peripheral nervous system disease in which the immune system plays a role in a chronic process. In addition to affecting the peripheral nerves, the disease almost always involves the nerve roots in the medulla spinalis. As a reflection of nerve root involvement, proximal findings are also seen in addition to the distal findings observed in classical neuropathies; the disease is called radiculoneuropathy and causes an increase in protein in the CSF. Although the mechanism of disease formation has not been fully elucidated, there is strong evidence that the immune system is involved. The most important of this evidence is the use of immunomodulatory therapies in the current treatment of the disease. Although the disease has been known for many years, the first serious definition was made by James Austin in 1958, it was reported that the disease progressed with recurrences and responded to corticosteroid treatment, and precursor events in the history are important for differential diagnosis. Dyck et al. revealed it was also reported that the underlying cause of this clinic currences and responded to corticosteroid treatment, and in 1958, it was reported that the disease progressed with re-

Etiology

CIDP can be idiopathic or occur with certain diseases. These diseases have been implicated in the pathogenesis of CIDP. Osteosclerotic myeloma, Waldenström macroglobulinemia, lymphoma, monoclonal gammopathy, monoclonal gammopathy of undetermined significance (MGUS), myelin-associated glycoprotein (MAG) antibodies; chronic infections (human immunodeficiency virus [HIV], Hepatitis-C, and Ebstein-Barr virus); other autoimmune diseases (systemic lupus erythematosus, Sjogren’s, rheumatoid arthritis, and inflammatory bowel disease); systemic diseases (Diabetes Mellitus [DM], thyrotoxicosis, and chronic renal failure requiring dialysis); malignancies (hepatocellular carcinoma, melanoma, and colon adenocarcinoma); some drugs (interferon alfa, procainomide, and tacrolimus); vaccines; and organ transplants may also be associated with CIDP. Therefore, blood examinations including serum protein electrophoresis, immune electrophoresis, MAG and antibody tests against HIV in all patients, as well as skeletal examinations to investigate osteosclerotic myeloma and further hematologic evaluation of possible plasma cell dyscrasia in patients with monoclonal protein must be done. The relationship between DM and CIDP is controversial. In some publications, DM has been shown as a risk factor for CIDP, while in some publications, this risk has not been shown. Some DM patients may have demyelinating findings on their electromyogram (EMG); even increased protein can be detected in CSF findings. It is unclear whether these cases will be classified as CIDP in a DM patient or as a neuropathy complication of diabetes. The association of infection with CIDP is not very clear compared to the acute variant; however, it is still considered to be a relationship. Overall, infection association has been reported around 30% in published series (70% in GBS). Human coronavirus such as SARS-CoV-2 are known to cause a variety of neurological symptoms. GBS and CIDP have been described in patients with COVID-19 pneumonia.
Pathogenesis

Both cellular and humoral components of the immune system play a role in the pathogenesis of CIDP and its variants. While the presence of activated T cells, cytokines, interferon, and interleukins in inflammation on pathological examinations is evidence of the involvement of the cellular immune system, the presence of complement and immunoglobulin on myelinated nerve fibers is also interpreted as the effect of humoral immunity.\[16\] Other important elements activated in inflammation are macrophages and act by major histocompatibility complex Class 2 regulation. It has been suggested that demyelination is caused by myelin phagocytosis of macrophages.\[17\] A recent study found that macrophage-induced demyelination is present not only in typical CIDP, but also in major atypical CIDP subtypes, including multifocal acquired demyelinating sensory and motor neuropathy (MADSAM), distal acquired demyelinating symmetric neuropathy (DADS), and pure sensory subtypes, but not in all patients.\[6\]

In recent years, it has been shown that IgG autoantibodies such as anti-neurofascin-155 (NF-155) and anti-contactin-1 antibodies may be present against components found in Ranvier nodes and paranodes in some patients with typical CIDP and DADS diagnoses. Patients with these antibodies show characteristic clinical features, such as sensory ataxia, tremor, and non-response to intravenous immunoglobulin (IVIg) therapy. Since the immunoglobulin subclass of antibodies anti-NF-155 and anti-contactin-1 is IgG4, the accumulation of these antibodies does not provoke inflammatory processes, the appearance of onion peel does not occur as a result of the absence of inflammatory cellular infiltration, including macrophages responsible for demyelination. Some reports have been able to show potential antigens such as Contactin-associated protein 1 (CASPR1) and nodal NF140/186. Autoantibodies specifically targeting the nodal and paranodal regions are found in 10% of CIDP patients. Antibodies to NF 155 (NF155) are the most frequent, while antibodies to NF 140 (NF140) and NF 186 (NF186), contactin-1 (CNTN1), and CASPR1 are less common.\[18,19\] Due to their clinical and therapeutic differences, authors have proposed to call this group of diseases “auto immune nodopathies.”

Although there are various studies showing that there is a relationship with human leukocyte antigen types, no significant genetic predisposition has been detected.\[13,20\] As a genetic relationship, repeat of polymorphic GA in the T-cell adaptor protein SH2D2A, which is involved in the negative control of T cell activation and variations related to the protease inhibitor Type M3 allele has been shown.\[2,21\] Treatment of tumor necrosis factor alpha inhibitors has also been shown to cause CIDP.\[22\]

Clinical Features

The disease usually starts from the feet. Patients complain of difficulty walking, difficulty climbing stairs, and getting up from a chair, staggering and falling. Both proximal and distal muscles are involved, involvement is usually symmetrical. Due to upper limb involvement, they have difficulty using tools or grasping objects. Deep tendon reflexes are unbearable or weak. The most basic clinical feature of CIDP is proximal weakness; this distinguishes CIDP from other common neuropathies.\[23\] The disease may also begin with a clinic similar to GBS. In the acute period, it is impossible to understand whether the disease is GBS or the onset of CIDP.\[3\] Since 20–40% of children have acute or subacute CIDP, the distinction between GBS and acute onset of CIDP may be even more difficult.\[24\]

Loss of large-scale sensory fibers (sense of touch, vibration, and position) is more frequent than small-scale fiber loss (pain and sensation of heat).\[12\] Sensory involvement is evident in the distal as opposed to motor involvement. Weakness in the involved muscles without atrophy indicates that neuropathy is more demyelinating than axonal.\[13\] While severe pain is present in only a small proportion of CIDP patients, pain interferes with activities of daily living in more than 1/3 of patients.\[25\] Back pain may occur.\[3\] The Romberg find is often present. Severe bulbar and respiratory weakness are not frequent.\[12\] Autonomic changes are rare. Change in micturition (voiding difficulty or urgency), constipation, Horner’s syndrome can be seen. If there is hypertrophy in the nerve roots, symptoms of lumbar stenosis and cauda equina syndrome may occur.\[26\] Nerve hypertrophy can sometimes be observed in the cranial nerves. Nerve hypertrophy is more common in patients with a relapsing remitting course and prolonged disease duration.\[2,27\] Cranial nerve involvement is rare and occurs in 10–20% of patients. Also cranial nerve involvement is mild and symmetrical involvement is seen. Most often cranial nerves 7 (facial nerve), 10 (vagal nerve), 12 (hypoglossal nerve) are affected. Moderate facial weakness, diplopia secondary to ophthalmoplegia, dysarthria, and dysphagia can be seen.\[28\] Dropped head may develop with involvement of neck extensor muscles.\[29\] Tremor may be a hampering symptom in CIDP and has been reported in more than half of patients.\[30\] An approximately 40% higher incidence has been reported
for restless legs syndrome in patients with CIDP compared to normal controls. Fatigue may be the main complaint in CIDP patients and may be severe in up to 3/4 of the patients. Regardless of fatigue, about half of patients may also experience activity-induced weakness.

**Classification**

Chronic acquired demyelinating neuropathies are divided into two groups as symmetrical and asymmetrical according to their involvement.

Symmetrical features are classical CIDP, DADS, CANOMAD (chronic inflammatory sensory polyradiculopathy, chronic ataxic neuropathy, ophthalmoplegia, M paraproteinemia, Agglutin, Disialosly antibody) pure motor, and pure sensory CIDP. Asymmetrical features are MADSAM and focal CIDP. Although CIDP is clinically divided into several subtypes, no biomarker specific to clinical subtypes has been identified. According to the criteria revised in 2021, the previous term “atypical CIDP” was replaced by “CIDP variants” because these are well characterized entities (multifocal, focal, distal, motor, or sensory CIDP).

**DADS Polyneuropathy**

Pure sensory loss and pain are observed in the limb distals. The muscle strength of the limb is usually normal or minimal weakness in the tibialis anterior muscle may be observed. It is very slow progressive compared to classical CIDP. About 80% of the patients are male patients over the 6th decade. About 70% of patients have anti-MAG antibodies. Since the risk of developing lymphoproliferative disease is high in this group, annual hematology control is recommended. About 2/3 of patients with the DADS phenotype have IgM paraprotein and are called DADS-M. Those without IgM paraproteinemia are called DADS-I. Although associated with or without anti-MAG, DADS-M is generally thought to be different from CIDP in that it tends to be resistant to standard immunomodulatory therapy for CIDP.

**Pure Sensory CIDP**

This is probably the most frequent CIDP variant. It accounts for 5–8% of CIDP cases. In the clinic, sensory involvement in all senses and distal pain is seen. Motor exposure may either not occur or there may be minimal weakness in the distal. Prednisolone or IVIG is used in treatment, but the response to treatment is poor.

**Pure Motor CIDP**

It is rare. There are cases where the arms are affected first. Clinically and electrophysiologically, sensory nerves are not affected. Forms of atrophy, dysarthria, and bulbar symptoms have been reported in the tongue resembling motor neuron disease. IVIG and plasma exchange are administered in treatment, and cases of worsening of motor symptoms have been reported with steroid therapy.

**MADSAM**

MADSAM, also known as Lewis-Sumner Syndrome, was described by Lewis et al. in two patients with conduction blocks. In these patients, sensory insufficiency and muscle weakness have a multifocal distribution that matches one or more peripheral nerve distributions. It can be confused with multifocal motor neuropathy. It follows a slow progressive course. The average age of the disease is 28–58 years. The weakness is asymmetrical, the limb is more pronounced in the distal than proximal and the arms are held more than the legs. There may be atrophy, fasciculation, and cramping in the muscles. Unlike CIDP and other variants, cranial nerve involvement is quite common during the course of the disease and occurs in approximately 25% of patients.

**Focal CIDP**

Focal CIDP is defined as involvement of one or more peripheral nerves in the brachial or lumbosacral plexus or an upper or lower extremity. This is a rare phenotype, with an incidence of 1% in a large retrospective cohort of CIDP.

**Diagnosis**

After clinical evaluation and examination in the diagnosis, EMG and lumbar puncture are performed primarily. Nerve biopsy, contrast-enhanced brachial and lumbosacral plexus magnetic resonance imaging (MRI), somatosensory evoked potential, and serum qualitative immunofixation are the methods used as adjunct to diagnosis.

**EMG**

Electrophysiological diagnostic criteria were determined by European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS) in 2010 and revised by EAN/PNS in 2021. The levels of diagnostic certainty were reduced from three (definite, probable, and possible CIDP) to only two (CIDP and possible CIDP), because the diagnostic accu-
racy of criteria for probable and definite CIDP did not significantly differ. Good practice points were formulated for supportive criteria; such as “IVIg should be considered as first-line treatment in motor CIDP” and investigations to be considered to diagnose CIDP. The EFNS/PNS criteria had the highest sensitivities, with good specificities.

Lumbar Puncture

High protein levels (albuminocytological dissociation) in CSF without increased leukocytes are an important criterion for diagnosis. In 95% of patients, CSF protein levels are above 45 mg/dL and often above 100 mg/dL. If the number of leukocytes in CSF is more than 10 cells/mm³, other diagnoses should be investigated rather than CIDP.

Imaging

MRI and nerve ultrasound can be a valuable addition in the diagnostic work-up, as proximal segments such as the proximal part of the brachial plexus and the lumbar-sacral plexus can be assessed, while NCS (nerve conduction studies) cannot study these regions. While the clinical incidence of nerve hypertrophy is <10%, gadolinium involvement is detected in approximately 50% of nerve roots and lumbar-brachial plexus by MRI. Nerve hypertrophy can also be seen in other inflammatory neuropathies. MRI results can be a guide in determining the nerve to choose for biopsy.

Nerve Biopsy

Nerve biopsy is especially helpful if the demyelination criteria in the nerve conduction study have not been fully met and other studies have failed to clearly diagnose CIDP. However, since it is a disease with segmental demyelination, the biopsy sample may not show demyelination, furthermore, the inflammatory component of CIDP may not be evident and may not be shown on biopsy. Despite these problems, it can help to distinguish between other diseases that may mimic CIDP (amyloidosis, sarcoidosis, and vasculitis).

Therapy

In line with the accepted immunopathogenesis in the formation of the disease; plasmapheresis, IVIG, steroids are first choice in the treatment of CIDP. Response can be observed by applying pulsed methylprednisolone in the form of 1 g IV × 5 days/month for 3–6 months. IVIG 2 g/kg loading dose followed by IVIG 1 g/kg maintenance therapy is given for 4–6 weeks. Considering patient response and clinical necessity, plasmapheresis can be applied 5 times with an interval of 1 day. The use of immunosuppressive drugs becomes necessary if patients; have frequent attacks, do not respond to these treatments (single or combined) or experienced significant side effects in first-line treatments. These treatments include azathiopurine, mycophenolate mofetil, cyclosporine-A, cyclophosphamide, rituximab, interferon alpha, etanercept, tacrolimus, and alemtuzumab.

Rehabilitation can be applied to patients with significant disabilities. Patients should also be questioned in terms of neuropathic pain and appropriate treatments should be started when necessary.

For patients with anti-neurofascin-155 and anti-contact 1 antibodies, a different therapeutic strategy is needed than the traditional approach. IVIG response is low in these patients. In addition, immunoadsorption plasmapheresis should be avoided in these patients because it does not eliminate IgG4.

It has been suggested that rituximab, a monoclonal antibody that binds to CD20, may be efficacy in patients with anti-neurofascin-155 and anti-contact 1 antibodies. Although the treatment of CIDP varies according to the clinic and the types of the disease, there has been a need to change the treatment algorithm with the pandemic. As a result of the non-preference of corticosteroids, immunoglobulins as the first preference and plasma exchange as the second preference have started to be widely applied.

New studies have shown that complement inhibition, such as eculizumab, a humanized monoclonal antibody specifically linked to complement 5, may be beneficial in GBS. Additional studies are needed for the efficacy of eculizumab in CIDP subtypes with complement activation.

Conclusion

CIDP is a disease that shows heterogeneity in its etiopathogenesis. Although there are various diagnostic criteria, the clinical and electrophysiological criteria established by EFNS/PNS give the most reliable results. EFNS/PNS criteria were revised in 2021. The previous term “atypical CIDP” was replaced by “CIDP variants” because these are well characterized entities (multifocal, focal, distal, motor, or sensory CIDP). The levels of diagnostic certainty were reduced from...
three (definite, probable, and possible CIDP) to only two (CIDP and possible CIDP), because the diagnostic accuracy of criteria for probable and definite CIDP did not significantly differ. Good practice points were formulated for supportive criteria and investigations to be considered to diagnose CIDP were highlighted. IVIG, corticosteroids, plasma exchange, and other immunosuppressant therapies can be used successfully in the treatment. IVIG should be considered as first-line treatment in motor CIDP (Good Practice Point). Cases of CIDP after COVID-19 infection have been reported and, in this case, it is recommended not to prefer corticosteroids in treatment. Autoantibodies specifically targeting the nodal and paranodal regions are found in 10% of CIDP patients. Due to their clinical and therapeutic differences, authors have proposed to call this group of diseases “auto immune nodopathies.” Difficulties in diagnosis, confusion with other diseases or lack of biomarker sufficiency are reasons that may disrupt treatment. Considering the variants of CIDP, more comprehensive research is needed that can reveal pathogenesis and biomarkers to reach an effective therapeutic approach.

Disclosures

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