CHRONIC INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY (CIDP): CURRENT PERSPECTIVES

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INTRODUCTION
Peripheral neuropathy has diverse etiologies and a de novo presentation without any known association presents difficult diagnostic problem. We at Armed forces Medical College and Command Hospital (SC) Pune systematically studied 35 such cases of peripheral neuropathy between 2006-2008 and in the final analysis Chronic Inflammatory Demyelinating Neuropathy emerged as a single large group (20 out of 35). In this communication I will be discussing various features of this important neuropathy interspersed with our own observations as compared to world literature wherever applicable.

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is an acquired multifocal neuropathy that commonly has symmetric, proximal, and distal limb weakness, distal sensory loss that progresses over more than 2 months. Clinical and immunopathological studies suggest an aberrant immune mechanism and CIDP can be treated with immunomodulatory medications. Whether CIDP is a disease or a syndrome remains controversial. The following neuropathies all have chronicity, demyelination, inflammation, or immune-mediation in common: Multifocal motor neuropathy with conduction block (MMNCB), Lewis-Sumner Syndrome (Multifocal acquired sensory and motor neuropathy -MADSAN) and Distal acquired symmetric demyelinating neuropathy (DADS) and many more associated with various diseases.

EPIDEMIOLOGY
The reported prevalence is between 1-1.9 per 100000 populations and incidence is 0.15 per 100000. The mean age of onset in most studies is 47.6y. A relapsing remitting course is encountered in approximately 51% cases. The ALS phenotype may have upto 1.6% cases of MMNCB. In AFMC study the predominant age group is between 20-30 y (11/35) and 51-60y 11/35 (Table 1). Eighty percent of our cases were males (Fig 1).

Table 1: 35 cases of peripheral Neuropathy (AFMC Study)
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Most commonly CIDP is idiopathic but it may be associated with other diseases. Most common associations are seen with Diabetes Mellitus, Paraproteinemias and Monoclonal Gammopathy of Unknown Origin (MUGS). Other notable associations are HIV infection, Hepatitis C Infection, Sjogren’s syndrome, Lymphoma and Melanoma.

CIDP occurs both with type-1 and type-2 DM and may be more common than idiopathic variety. When CIDP occurs in the setting of DM the disease is more severe with fewer relapses and a better response to IVIG.

CIDP associated with hematologic malignancies characteristically involves plasma cells such as plasmacytoma or osteosclerotic myeloma.

**PATHOGENESIS**

Both cell-mediated and humoral immunity-related abnormalities are implicated in pathogenesis. Cellular immunity involvement is supported by evidence of T-cell activation, crossing of the blood-nerve barrier by activated T-cells, and by expression of cytokines, tumor necrosis factor, interferons, and interleukins. Humoral immunity is implicated by the demonstration of immunoglobulin and complement deposition on myelinated nerve fibers.

**PATHOPHYSIOLOGY**

The characteristic pathologic features of CIDP include segmental demyelination and remyelination, and onion bulb formation. Some degree of axonal degeneration is usually present. Varying degrees of interstitial edema and endoneurial inflammatory cell infiltrates, including lymphocytes and macrophages, are additional pathologic features of CIDP.

Electrophysiology — Peripheral nerve demyelination underlies the characteristic electrophysiologic features of CIDP, which are as follows: Partial conduction block Conduction velocity slowing, prolonged distal motor latencies, Delay or disappearance of F waves and Dispersion and distance dependent reduction of compound motor action potential (CMAP) amplitude.

**CLINICAL FEATURES**

There is a temporal continuum between acute inflammatory demyelinating polyneuropathy (AIDP), the demyelinating form of Guillain-Barré syndrome, and CIDP. AIDP is a monophasic subacute illness that reaches its nadir within three to four weeks CIDP continues to progress or has relapses for greater than eight weeks Subacute inflammatory demyelinating polyneuropathy (SIDP) is the term used by some authors for disease that reaches its nadir between four and eight weeks

In the classic form of CIDP, motor involvement is greater than sensory, and neurologic deficits are fairly symmetric. Weakness is present in both proximal and distal muscles. Most patients have globally diminished or absent reflexes.

Sensory impairment in CIDPs is usually greater for vibration and position sense than for pain and temperature sense, reflecting the involvement of larger myelinated fibers. Unlike the motor involvement, the sensory involvement tends to follow a distal to proximal gradient, although finger involvement is frequently seen as early as toe and foot involvement. Painful dysesthesias can occur in some patients. Cranial nerve and bulbar involvement occur in a minority. The clinical course of CIDP is slowly progressive in a majority of patients, but a relapsing-remitting course is noted in at least one-third.

In AFMC study the study material of peripheral neuropathy in which CIDP formed a major group consisted of limb weakness and numbness in 71%, pain and numbness in 11%, numbness in 9%, pain alone in 6% and weakness by itself in 3% cases (Fig. 2).

Progressive weakness in proximal muscles and sensory symptoms distally over two months is the most frequent presentation. This contrasts with the distal weakness seen in axonal neuropathies. Distal predominance of motor and sensory features are seen in 17% of cases (DADS variant) and pure motor in 10% of cases (MMNCB). Subclinical cranial

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**Fig. 1**: Sex Distribution: 35 cases of Peripheral Neuropathy (AFMC study)

**Fig. 2**: Clinical Symptomatology: 35 cases of Peripheral Neuropathy (AFMC study)
nerve dysfunction may occur in 6-30% cases and presents as facial numbness, facial weakness, papilloedema and hypoglossal neuropathies.

**DIAGNOSIS**

The diagnosis of CIDP should be considered in patients with symmetric or asymmetric polyneuropathy who have a progressive or relapsing-remitting clinical course for more than two months, particularly if the clinical features include positive sensory symptoms, proximal weakness, areflexia without wasting, or selective loss of vibration or joint position sense. In our study of 35 cases of peripheral neuropathy the clinical syndromes included 74% (Symmetric Distal Motor Sensory Peripheral Neuropathy-SDMSNP), 11% (Symmetric Distal Sensory Polyneuropathy-SDSPN), Asymmetric sensory neuropathy 9% asymmetric motor peripheral neuropathy 3% and mononeuritis multiplex in 3% cases. (Fig 3) Both SDMSN and SDSPN accounted for all cases of CIDP and Unknown etiology. Our population may present more commonly with atypical features of CIDP or variants.

While the initial diagnosis of CIDP is clinical, the diagnosis is confirmed by evidence from electrodiagnostic studies, and in some cases by cerebrospinal fluid analysis, nerve biopsy findings, and other laboratory investigations. Peripheral nerve demyelination must be demonstrated by either electrodiagnostic findings or by nerve biopsy. The clinical features that distinguish CIDP from chronic length-dependent (ie, axonal) peripheral neuropathies are the prominence of muscle weakness and the involvement of upper extremity and proximal muscles, as well as distal muscles. In contrast, axonal neuropathies are characterized by predominantly distal weakness. Furthermore, deep tendon reflexes are globally reduced or absent in CIDP, whereas only the ankle reflexes are diminished in typical axonal polyneuropathies. The features of CIDP point to the multifocal or generalized nature of the disease even at early stages of the illness.

**DIAGNOSTIC CRITERIA**

1. Progression over at least two months.
2. Weakness more than sensory symptoms Symmetric involvement of arms and legs Proximal muscles involved along with distal muscles
3. Reduced deep tendon reflexes throughout
4. Increased cerebrospinal fluid protein without pleocytosis (the classic albuminocytologic dissociation is present in over 90 percent of patients with CIDP)
5. Nerve conduction evidence of a demyelinating neuropathy Nerve biopsy evidence of segmental demyelination with or without inflammation: The diagnostic utility of nerve biopsy (typically of the sural nerve) for suspected CIDP is controversial. Nerve biopsy can provide solid evidence of demyelination. In addition, biopsy occasionally reveals other neuropathies that mimic CIDP, such as those due to amyloidosis, sarcoidosis, and vasculitis. Supportive features for CIDP on nerve biopsy include the following: Endoneurial edema Macrophage-associated demyelination Demyelinated and remyelinated nerve fibers Onion bulb formation Endoneurial mononuclear cell infiltration Variation between fascicles
6. MRI — MRI with gadolinium of the spinal roots, cauda equina, brachial plexus, lumbar sacral plexus, and other nerve regions can be used to look for enlarged or enhancing nerves. MRI abnormalities are useful as supportive criteria for CIDP in the EFNS/PNS guideline
7. Other Laboratory studies — There are no blood tests that specifically point to CIDP. However, a number of studies are useful to look for disorders that are either associated with or mimic CIDP. These include: Fasting serum glucose and/or oral glucose tolerance test Glycated hemoglobin Thyroid function studies Hepatitis profiles HIV antibody Serum and urine immunofixation electrophoresis to detect paraprotein Complete blood count Renal function tests Liver function tests C reactive protein Antinuclear antibodies Extractable nuclear antigen antibodies Angiotensin converting enzyme Chest radiograph Skeletal survey, if a paraprotein is found.

There is still no gold standard set of diagnostic criteria for the electrophysiologic identification of demyelination, or for the clinical diagnosis of CIDP and its variants, even though at least eight sets of diagnostic criteria have been published since 1989. The current CIDP guideline from the European Federation of Neurological Societies and the Peripheral Nerve Society (EFNS/PNS) (show table 1) is the one most useful for clinical diagnosis. The EFNS/PNS guideline defines CIDP as typical (ie, classic) or atypical. Atypical CIDP encompasses variants of CIDP with predominantly distal weakness such as DADS, and variants with pure motor or pure sensory presentations. For definite CIDP, one must have a typical or atypical clinical picture with clear demyelinating electrodiagnostic changes.
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in two nerves, or probable demyelinating features in two nerves plus at least one supportive feature (from cerebrospinal fluid analysis, nerve biopsy, MRI, or treatment response to immunotherapy). The EFNS/PNS guidelines relegate CIDP with concomitant disease to a “possible” category. IgM paraprotein-related neuropathies with anti-MAG antibodies are considered as distinct from CIDP, but IgM disorders without anti-MAG are considered to be a CIDP variant.3 Our study showed features of both axonal and demyelinating features more commonly than pure demyelination features. Only seven out of 23 cases had pure features of demyelination and 16 cases showed electrophysiological findings of both axonopathy and demyelination (Fig 4).

**Evidence Based Medicine (EBM) point:**

*Which Electrophysiological Criteria Should Be Used for the Diagnosis of CIDP?*

After studying and analyzing eight different studies the following criteria are recommended for the diagnosis of CIDP:

In two or more nerves

a. Distal latency: >150% of Upper limit of Normal
b. Conduction velocity: >70% of Lower limit of Normal.
c. Conduction block: 30-50% loss of amplitude
d. F-response: >120%. Or absent f wave with CMAP>20% of normal amplitude.

e. Any single criteria is sufficient for the diagnosis of CIDP. If conduction block is demonstrated in one nerve another anyone nerve should show one other abnormality. The sensitivity is 75% and specificity is 100%.

The CSF examination was done in 20 out of 23 cases of CIDP and typical albumin-cytological dissociation was found in 18 cases (90%). Two cases with normal CSF were diagnosed by sural nerve biopsy findings. (Fig 5)

**EBM point:**

*What Is the Utility of Nerve Biopsy in the Diagnosis of CIDP?*

The issue is controversial. Elevated CSF protein, neurophysiological evidence for demyelination, and the absence of an alternative etiology for the neuropathy were the three factors that most strongly predicted the diagnosis of CIDP. The results of

Sural nerve biopsy was found to have no significant additional predictive value. The further advances consisting of a teased
fiber preparation and studies under electron microscope should give a correct answer.

In AFMC study sural nerve biopsy was performed in 32 out of 35 cases. The histopathology report showed changes suggestive of CIDP (Segmental demyelination) in 15 cases, vasculitis in one case, focal axonolysis in 3 cases. Normal histopathology findings were seen in 13 cases (Fig. 6, 7, 8) Sural nerve biopsy was carried out in 17 out of the 20 cases of CIDP. And it proved to be confirmatory in 15 out of 17 cases (88%)

TREATMENT

The mainstays of treatment for CIDP are intravenous immune globulin (IVIG), glucocorticoids, and plasma exchange. These treatments appear to be equally effective. IVIG and plasma exchange may lead to a more rapid improvement in CIDP than glucocorticoid therapy, but are less likely than glucocorticoids to produce a remission IVIG is expensive, and its supply is sometimes limited. Glucocorticoids are inexpensive, but chronic use is limited by common and clinically important side effects. Plasma exchange is expensive, invasive, and available only at specialized centers. The rate of disability improvement within one month after treatment was significantly higher with IVIG than with placebo (relative risk [RR] 2.4, 95% CI 1.72-3.36). To obtain improvement in one patient, the number needed to treat (NNT) was 3. Overall, IVIG improved disability for at least two to six weeks. The benefit of IVIG was similar to that of plasma exchange and oral prednisolone. ICE study confirmed evidence from earlier trials that IVIG is effective for the treatment of CIDP. In addition, the ICE results suggested that the benefit of IVIG extends to as long as 48 weeks with maintenance treatments of 1 g/kg every three weeks. While IVIG therapy can usually control CIDP, most patients require repeated expensive treatments every two to six weeks for many years, since IVIG monotherapy does not usually lead to remission. The initial dose of IVIG is 2 g/kg infused over two to five days (eg, 0.4 g/kg per day for five days). Many patients with CIDP require repeat IVIG maintenance dosing every two to six weeks. For patients who respond well to initial treatment and remain clinically stable, the maintenance dose can be tapered to 1.0 g/kg, or as low as 0.4 g/kg per dose, given over one to two days.

Substantial data from retrospective series suggest that oral glucocorticoids are beneficial for CIDP. The maximum benefit of glucocorticoid therapy in these studies was seen after one to six months of treatment. However, relapses were common, particularly when tapering the dose. Clinical experience suggests that glucocorticoid therapy is more likely to produce a clinical remission than either IVIG or plasma exchange. Although less well-studied, retrospective evidence suggests that weekly pulse methylprednisolone (500 mg once a week) is also an effective option for long-term treatment of CIDP. Refractory disease — For patients with severe CIDP who are refractory to treatment with IVIG, glucocorticoids, and plasma exchange, and are also refractory to glucocorticoids combined with IVIG or plasma exchange, alternative immunosuppressant treatment options include methotrexate, cyclosporine, azathioprine, mycophenolate, and cyclophosphamide. While the long-term prognosis of CIDP is generally favorable, data are limited, and up to 15 percent of patients are severely disabled despite treatment.

EBM point:

What Is the Evidence That Steroids Are of Benefit to Patients With CIDP?

Based on the results of a single randomized study (28 patients) as well as the data from the uncontrolled case series, the
conclusion seems to be that prednisolone leads to a small but significant improvement in disability in previously untreated patients with CIDP. The latency from the start of treatment to the onset of improvement is unclear, with the available data suggesting that the norm is 4–8 weeks, but that it may take as long as 5 months

Is Intravenous Immunoglobulin Effective in the Treatment of Patients with CIDP?

Available data suggest that IVIg is effective in the treatment of patients with CIDP, although fewer than one-half of patients treated with IVIg will show a significant improvement in their level of disability. Furthermore, the effect of IVIg is often not lasting in patients with relapsing-remitting disease, and these patients may require regular infusions in order to maintain a clinical response.

PROGNOSIS

At present approximately 70–75% of patients with CIDP will have only slight or no residual disability following appropriate therapy. Probable good prognostic factors: 1) Female gender 2) Younger age 3) Relapsing-remitting pattern 4) Electrophysiology studies suggesting pure demyelination without axonal loss.

CONCLUSION

On the basis of clinical examination, electrophysiological studies, relevant biochemical tests including CSF analysis, as well as histopathological report of the sural nerve biopsy, etiological factors found out for the peripheral neuropathy cases in which common secondary causes were already excluded were as follows: CIDP=20 (Includes variants like MUGS-1, CML-1), Vit B 12 deficiency=1, Vasculitis =1, Neuroacanthocytosis=1 and anterior horn cell disorder=1. The most CIDP (58%). Despite the thorough evaluation as per the protocol, in 11 cases (34%) the etiology could not be identified

REFERENCES