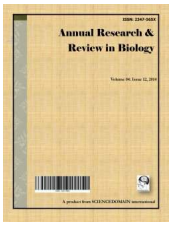

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Review: Current Diagnosis, Treatment and Management of Chronic Inflammatory Demyelinating Polyradiculoneuropathy

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Author's contribution

The sole author designed, analyzed and interpreted and prepared the manuscript.

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Review Article

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ABSTRACT

Polyradiculoneuropathy is a complex neuromuscular condition which has its etiology either acquired or inherited form. There are a number of neuromuscular conditions that can affect combinations of nerve root, junction, and peripheral nerve. Chronic demyelinating Polyradiculoneuropathy remains an important cause of radiculopathy in children and adults. There have been few studies involving the clinical management and diagnosis of this condition primarily as a result of its rare nature and difficulty in diagnosing, particularly at the onset of the disease. Failure to properly diagnose this condition can result in a prolonged and often protracted recovery process, which can limit a full recovery and lead to a severe functional disability. This review aims to provide proper diagnosis, treatment and management of chronic inflammatory polyradiculoneuropathy.

Keywords: Demyelination; electromyelogram; neuromuscular; polyradiculoneuropathy; weakness.

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1. INTRODUCTION

1.1 Background

Chronic inflammatory demyelinating polyneuropathy (CIDP) is a clinical disorder that describes a protracted course of chronic progressive or relapsing pattern of symmetrical muscle weakness in proximal and distal muscles both in upper and lower extremities. It is commonly found in adults (estimated to be between 1 and 2 per 100,000 population [1]) but is a rare entity in childhood, with hereditary neuropathies being more common than acquired causes in children. Its frequency is largely unknown, although a few large case series have suggested a higher incidence during the first decade with both sexes equally affected [1]. The condition is borne largely from its clinical response to treatment with absence of systemic disease that may cause demyelinating polyneuropathy. A preceding viral illness may or may not be present in the history [2].

However, prior history of immunization in children may be an important factor that must be closely ascertained. At some point in the course of neuropathy CSF protein becomes elevated, while nerve conduction studies are prolonged and slowed. It has been suggested that the inflammatory process involves both cellular and humoral immunologic mediated reaction which may play a role in nerve damage. The predominance of inflammatory infiltrates found in peripheral nerve biopsies, with abundance of T cells and macrophages, relate to this process of perivascular infiltration in both the endoneurium and epineurium with continued cycles of demyelination and remyelination [3]. Sural nerve biopsy may reveal demyelination and inflammatory infiltrates.

1.2 Clinical Features

The most common clinical presentation is generalized, symmetrical weakness due to proximal and distal muscle involvement, findings that are primarily neuropathic involvement. Difficulties with running or clumsiness in walking are signs of gait abnormalities resulting from significant weakness of the lower extremities [4]. In younger children frequent falls and instability in standing position are signs of generalized weakness. The presence of motor abnormalities and evidence of weakness are often the initial signs that first bring the patient to their doctor. However on examination, changes in deep tendon reflexes as evident by absent or markedly decrease stretch reflexes may be noted.

Sensory abnormalities are difficult to elicit in most children with CIDP. Accompanying symptoms of numbness and tingling sensation are reflective of the polyneuropathy nature of this disorder. The importance of finding out the presence of sensory deficit favors this diagnosis rather than a spinal muscular atrophy or myopathy [1].

Cranial nerves are commonly not involved [5]. Results of cranial nerve testing are often normal in patients and neurological abnormalities restricted to peripheral nerve(s) involvement. In few presenting cases facial weakness and ptosis with poor extra ocular muscle movements had been reported, with further neurological examination revealing CN III, IV, VI or VII involvement. Cranial nerve deterioration is not often the norm, while in GBS it is more commonly involved. Ventilatory support is rarely needed for children with CIDP. Though in some case series patients had signs of respiratory compromise marked by decrease, shallow pulmonary breathing. In one report, patient required mechanical ventilation and this presented with a rapid deterioration of functional status. This patient was on ventilation support for 24 hours following periods of cyanosis and pallor.

Bladder dysfunction is possible following the onset of lower extremity (LE) weakness[5]. Development of this autonomic dysfunction is characterized by loss of urine with spontaneous remission noted.

1.3 Clinical Course & History

The clinical course of CIDP is often variable depending on the number of relapses that may occur. Monophasic illness is a single episode of deterioration followed by improvement, while progressive form of CIDP has gradual deterioration with or without relapsing episode [5].

Chronic-relapsing CIDP patients [6] had an average age of 5 years. Half of them were related relapse most commonly secondary to corticosteroid therapy adjustment. Other relapses were uniformly less severe with most patients exhibiting weaknesses. These relapses were often short in duration with intervals between relapses averaging approximately 2 1/2 months. Almost all patients had a very short (< 6 months)

period of initial progression of illness. The institution of treatment resulted in quick reversal of progression and dramatic improvement was often the norm. Rapid weakness and deterioration occurring during periods of relapse characterize chronic progressive course in CIDP that does not rapidly respond even with active therapy. Their deterioration is not related to treatment variance, but reflects a more dynamic deterioration. After a short period of time following completion of treatment they often revert back to a relapsing state. Multiple drug therapy maybe needed to achieve improvement. Weekly regimen of IVIg or a combination therapy of prednisone and IVIg allowed remission from progressive weakness.

There is a great variability in the natural history especially in children, not only in its clinical course- with some patient having a self-limited course while others having a more progressive history- but even on the response to treatment as a whole. There have been few large center studies that have presented the natural history and treatment effects in CIDP. Ryan et al. [7] had a relatively large series (16 children) that described the course; treatment related outcomes on CIDP in children. Furthermore Simmons et al. [8,9] made a comparative study between children and adults with CIDP. These children often had a more rapid fluctuating course. Overall their response to treatment is excellent generally. Particularly when multiple drug regimens are employed there is increase effectiveness contributing to a shorter time to first recovery.

Children may continue to have demonstrable weakness even with certain type of medications that previously have showed excellent response [10-12] Previous retrospective studies to investigate the natural history and effects of treatment to children with CIDP showed that the most common initial clinical sign upon presentation was weakness of proximal and distal muscles in upper & lower extremities with symptoms of areflexia and gait disturbance being the more common features. This is in contrast to muscular dystrophy where weakness selectively affects proximal limb muscles before distal ones. The degree of disability upon admission can be moderately severe with significant difficulty walking and may require immediate assistance.

Differentiating CIDP from other more common polyneuropathies especially in children can be challenging. Like CIDP, GBS may also present with albumino-cytologic dissociation [13]. However, GBS has a more acute onset of clinical signs whereas CIDP has a more gradual, slower onset with the characteristic progressive, recurrent or monophasic course. The mean age of onset age is very similar with slightly older age distribution with CIDP s [13,14]. However, this is likely a result of lead time bias in diagnosing GBS since it is more commonly diagnosed and the overwhelming majority of CIDP patients typically present with chronic progressive course (Table 1). Cranial nerve involvement is also more common in GBS, with bulbar signs more common in GBS and rarely observed in CIDP. Hereditary neuropathies do not commonly present with a subacute onset and relapsing pattern of weakness.

2. DIAGNOSIS

2.1 Conduction Studies

Electrophysiological studies reveal findings of markedly slow conjunction velocities [8,9]. Motor and sensitivity involvement recorded in patients may show reduced amplitude and prolonged distal latencies. Absent peroneal motor response and reduced median nerve amplitudes were particularly evident resulting from variable involvement of different peripheral nerves. The conduction abnormalities ranged from reduced (10-20 m/s) to absent motor velocities, which may or may not be representative of classic proximal to distal multifocal conduction blocks.

Focal conduction abnormalities prolonged distal latencies, and low amplitude of CMAP with characteristic reduction in temporal summation may appear evident in cases resulting from distal conduction block or peripheral nerve demyelination. Variable presentations of conduction abnormalities are evidence of varying degrees of segmental demyelination with or without axonal degeneration [9,11]. Severe neuropathy suggested by severe reduction of conduction velocities and absent F waves has been noted resulting in a very poor recovery prognosis. Findings of axonal loss and multifocal conduction velocity changes provide a distinct difference between CIDP and other polyneuropathy such as Charcot-Marie-Tooth disease [11].

The American Academy of Neurology Ad Hoc Subcommittee in 1991 initially established the electrodiagnostic criteria for chronic inflammatory demyelinating polyneuropathy for research

purposes (Table 2) [16]. The AAN criteria require the presence of 3 of 4 criteria involving 2 or more nerves in support of CIDP diagnosis. Unfortunately, subsequent EMG studies using the AAN protocol has resulted in further confusion and controversy due to varying degrees of sensitivity and specificity [17].

2.2 CSF Studies

Cytoalbuminologic dissociation in the CSF with features of elevated protein and mild pleocytosis (cell count < 10 cells/mm^3) is a characteristic finding. Raised CSF protein level is often the norm, with average value of >78 mg/dl (range 16-217) noted in a case series. In one case the protein level on repeat measurements revealed an average value of 173 mg/dl. Levels these high are often associated with familial demyelinating neuropathy. This patient had paternal history of HSM I/II [18]. Increase of mononuclear cells may also be detected. In cases of marked increase in mononuclear cells with relatively normal glucose levels, a careful search for possible sub acute case of infectious origin should be ascertained. Normal myelin basic protein and absence of oligoclonal bands may indeed be found in patients following immunization history. Their CSF protein levels were noted to be much less than the average norm.

Inflammatory infiltrates found in CIDP are often non-specific and mild. A few lymphocytic infiltrates and other inflammatory cells are often the norm [8,15]. It is often difficult to ascertain the chronic nature of CIDP by the characteristic presence of non-specific inflammatory cells. In a few of these cases, macrophagic histiocytes were found which would effect a more active, chronic demyelination and remyelination process that are close characteristic features in CIDP.

2.3 Nerve Biopsy

Nerve biopsies are often obtained from the superficial, distal sural nerve. The most common feature found in nerve biopsy is demyelination with inflammatory cell infiltration. These lesions along with mild inflammatory cell infiltrates of lymphocytic cells and macrophages are commonly noted in acute phase reaction [12] that shows marked variability in fiber size & density, edema of perineurium, and macrophagic histiocytes that have been observed in close association with onion bulb formation suggestive of this disease. Demyelination of fiber density was most frequently observed (82.8%) following muscle fiber reduction. Onion bulb formation (28.3%) was also noted as a critical component of endoneurial inflammation in the relapsing-remitting variant [19].

Onion bulb formation is a characteristic feature in nerves resulting from continuous demyelination and remyelination process around the axons [12]. Furthermore, the presence of onion bulb formation strongly supports an active demyelination process, which can be suggestive of severe clinical symptomatology. Repeat biopsies may further reveal the chronicity and severity of disease process by noting the increase concentration of onion bulb formation [20].

Table 1. Contrast of CIDP and Guillain Barre Syndrome

Table 1	Guillain Barre syndrome [13,14]	CIDP [5,15]
Mean age onset	40-50 yrs old	40-60 yrs old
Sex distribution	Male > Female	Male > Female
Incidence	0.84-1.91/100,000/year	0.15-0.48/100,000/year
Bulbar signs	40% dysphagia, 5% ptosis	Rare

Table 2. American Academy of Neurology Ad Hoc Subcommittee [16]

Three of four criteria must be fulfilled
• Reduction in conduction velocity (MNCV) in two or motor nerves: • Prolonged distal latencies (DML) in two or more nerves: • Absent F-waves or prolonged minimum F-wave latencies in two or more motor nerves: • Partial conduction block (CB) in one or more motor nerves defined as <15% change in duration between proximal and distal sites and >20% drop in negative peak (−p) are or peak-to-peak (p–p) area or peak-to-peak (p–p) amplitude between proximal and distal sites.

Non-specific inflammatory changes are observed early on during the initial progressive phase. Histogram may reveal normal results with no detectable alterations during this phase. It should be noted that there are no prominent features of active muscle abnormalities or process of denervation on biopsies performed during the initial progressive phase of muscle weakness. The process of denervation involves axonal involvement which supports a more chronic phase of inflammatory response.

It should be noted that nerve biopsy in childhood CIDP is often atypical, non-specific, and less precise in their findings [20]. Any biopsies performed should be correlated with EMG findings particularly when performed during the initial, acute phase. Due to the predominance in proximal nerve involvement, nerve biopsy of sural nerve may often reveal normal results. No detectable alterations are observed in the majority of cases with distal nerve biopsies. Establishing clear diagnosis based on nerve biopsy should be supportive at best with strong correlation of clinical and conduction studies.

Histological findings would be better serve if used in relation to supporting or excluding children diagnosed with CIDP when electrophysiologic studies are not available. Marked presence of interstitial and perivascular infiltrates are suggestive of inflammatory neuropathy rather than hereditary polyneuropathies.

2.4 MRI Investigation

Neuroimaging studies have been conducted on a majority of patients. However, very few large patient studies have been done due to non-specific findings. Results of MRI studies can reveal diffuse nerve root involvement with increased IgG synthetic rate in the CSF. Recent advances in MRI techniques reveal thickening and hypertrophy of the spinal nerve roots [21]. This finding is useful in supportive diagnosis and as a clinical marker for CIDP. On a large MRI study involving 12 patients [22], there have been findings that disclosed extensive lesions of the thoracic cord in two patients with an overt spinal cord syndrome. Overall MRI studies can be helpful in identifying spinal cord lesions particularly in relapsing-remitting type due to chronic inflammatory exposure and these could serve as supportive findings for CIDP.

2.5 Other Tests

Thyroid function, autoimmune antibody, blood chemistry and serum protein electrophoresis are some of the other lab investigations that can be conducted which may show no apparent or significant abnormal changes.

3. TREATMENT

3.1 Immunoglobulin

Patients treated with IV immunoglobulin (IVIg) showed considerable dramatic improvement, rapid recovery of muscle strength [12]. The first sign of improvement can be noted within 5 days of the onset of treatment. Treatment effects are long lasting in the majority of patients with little or no relapses noted thereafter. Initial treatment of 1-2 gm/kg for 2-3 days was often the norm once CIDP diagnosis was ascertained. Two to three was the average number of treatments involved prior to achieving any significant, dramatic clinical response. The lowest effective dosage with the largest possible intervals without further deterioration of the patient was noted to be 1-2 gms/kg for 2-5 days [17,23,24]. IVIg treatment is mostly provided over consecutive days in hospital for the entire duration. Few patients may not require any maintenance medication of corticosteroid following their clinical recovery and hospitalization discharge. Maintenance treatment with IVIg is generally limited by costs considering it is much more expensive than conventional corticosteroid.

The response with IVIg treatment is generally good, although relapse in patients who had received treatment may require additional treatment modalities consisting of corticosteroid maintenance for the duration of the illness [25]. Additional treatment with immunoglobulin is strongly correlated with improvement afterwards. Reinstitution of IVIg treatment resulted in refractory course. Many of these patients who did not experienced significant functional relapses and weaknesses are dependent on intermittent infusions for a period of considerable amount of time [26]. These patients with chronic relapsing CIDP appears to derive temporary therapeutic benefits marked by short term improvement and return to similar degrees of weakness during bouts of relapse(s) [4]. These patients had an average of 5 relapses with significant disabilities and weakness of upper and lower extremities. Repeat electrophysiologic studies conducted revealed absent H reflexes and F waves prolongation as well as temporal dispersion.

Table 3. Treatments for CIDP

Types of treatment	Dosage	Reinfusion treatment	Maintenance treatment
Immunoglobulin (IVIg) [17,23,24]	1-2 grams x 2-5 days	Yes, if relapse occurs	No
Corticosteroid [17,29]	1 gram x 5 days	Yes, if relapse occurs	Yes, 60 to 100 mg/day
Plasmapharesis [29]	5 exchanges x 7-10 days	N/a	No
Azathioprine [17]	2-3 mg/kg/day, single dose	No	No
Cyclophosphamide [30]	200 mg/kg/day x 4 days	No	No

3.2 Corticosteroid Therapy

Patients on corticosteroid dependent treatment often required other treatment regimen, not only due to their side effects but also to improve their recovery rates following dose dependent relapses attributed to corticosteroid treatment. Repeated high dose corticosteroid treatment appears to induce remission and significant clinical improvement. Improvement can be gradual with no dramatic changes often noted. Oral prednisone at a dose of 60-100 mg per day [27] can be beneficial in decreasing the complication of the disease.

Patients who are treated with steroids as part of their maintenance treatment resulted in sustained improvement following initial therapy with IVIg. Relapses are common when changes or lowering of dose occurs. Any adjustment or changes in their drug regimen lead to series of relapses, ultimately requiring additional therapy and hospitalization. Increased fatigue involving lower extremities with further progression to involve the upper extremities may herald a relapsing episode from rapid or abrupt changes in corticosteroid medication. On one patient, prednisone medication was supplemented with IV immunoglobulin for more than a year (18 months) due to her persistent remissions of notable LE weakness after tapering her prednisone. This therapeutic regimen led to a progressive improvement. Most patients on steroid treatment have sustained improvement with little or no loss of strength noted. Repeated high dose corticosteroid treatment appears to induce remission and significant clinical improvement [27,28].

3.3 Other Treatments

Plasmapharesis, azathioprine, IV immunoglobulin therapy (Table 3) are effective in decreasing repeated relapses of weakness when weaning off corticosteroid treatment [9,11]. Sustained rapid response following these medications when used in conjunction with corticosteroid treatment led to improve recovery outcome characterized by return of significant strength in peripheral muscle groups. In patients with only corticosteroid medication their recovery response was slower with marked fluctuations in outcome, while taking longer to achieve significant progress and functional health status.

3.4 Adverse Effects

Major adverse effects from corticosteroids include nausea, vomiting, immunosuppression with susceptibility to infection, and weight gain from increase appetite. Repeated weakness of extremities and loss of strength are possible side effects as well. Multiple medication regimens brought considerable positive outcome during treatment. Their synergistic mechanism produces better, more sustainable progress in muscle strength and functional capacity.

4. SUMMARY AND CONCLUSIONS

Diagnosing CIDP especially in children is a difficult process that requires a strong suspicion and serial neurologic exam. The acute phase of the disease is particularly challenging due to similar elements of presentation from other polyneuropathies. These patients are often seen only after their generalized weakness has been present for a prolonged period of time or has been progressively worsening over time. Changes in daily activity and symptoms of weakness or easy fatigueability are events that parents may readily recall. The importance of diagnosis during the early progressive phase provides a favorable clinical outcome following institution of treatment, with most improvement occurring within 2 to 4 weeks. Future studies of CIDP should involve characterizing the immune-modulatory response considering the

autoimmune process of this condition. Anti-MAG neuropathy antibody and anti-sulfatide neuropathy antibody are antibodies that have been detected in other peripheral autoimmune neuropathy conditions. The need to find newer diagnostic lab test in determining CIDP may help in expanding the understanding of the natural course of this disease.

The availability of intravenous immunoglobulin (IVIg) provides the best treatment option not only in minimizing the progression but also in securing a favorable outcome with decrease protracted and intractable course. However, costs and availability are determining factors particularly in limited resource medical management. There are other treatment modalities that can be substituted to IVIg with variable efficacy in mitigating the progression of the disease in addition to more adverse effects which may be encountered. Further observations into the role of immunosuppressive agents (azathioprine, cyclophosphamide) should be determined as potential synergistic agents in reversing or preventing the relapse of this autoimmune condition.

Diagnosing CIDP involves not only a strong clinical suspicion and serial neurologic exam, but the use of diagnostic modalities including CSF analysis, nerve biopsy and electromyelographic studies. Each of these testing modalities has specific characteristics that can identify this disease. Although MRI studies provide an additional layer of diagnostic evidence, there are however no findings that may prove to be specific for CIDP. Future diagnostic studies should attempt to characterize the MRI findings in patients with this condition. One area that might prove to be important in elucidating this disease will be characterizing the spinal nerve roots with the use of MRI tractography images which can reveal the damage and discontinuity of the myelin sheath in peripheral nerve injury.

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COMPETING INTERESTS

Author has declared that no competing interests exist.

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