Original Article

Treatment of pediatric chronic inflammatory demyelinating polyneuropathy: Challenges, controversies and questions

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Abstract

Pediatric chronic inflammatory demyelinating polyneuropathy (CIDP) is an uncommon acquired disorder of unknown cause, presumed to have an immunological basis. We report 20 patients seen at Children's Hospital Los Angeles over a period of 10 years. The outcome of our patients was favorable in a vast majority with good response to various treatments instituted. However, residual neurologic deficit was common. The choice of treatment modality was empirical and selected by the treating neurologist. Intravenous immunoglobulin (IVIG) and corticosteroids were most commonly utilized for treatment. Plasmapheresis, mycophenolate mofetil, rituximab, cyclophosphamide, azathioprine, and abatacept were added if the patients were refractory to IVIG or became corticosteroid dependent. The spectrum of disease severity ranged from a single monophasic episode, to multiphasic with infrequent relapses with good response to IVIG, to progressive disease refractory to multiple therapies.

Key Words

Childhood, children, chronic inflammatory demyelinating polyneuropathy, CIDP, pediatric

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Ann Indian Acad Neurol 2015;18:327-330

Introduction

Chronic inflammatory demyelinating polyneuropathy (CIDP) is relatively uncommon in children.[1] It is an acquired disorder with an immunological basis. However, the underlying cause and the precise trigger of both initial episodes and relapses are unknown. Patients may initially be diagnosed with acute inflammatory demyelinating polyneuropathy (AIDP), but then go on to have relapses. Others may have a more chronic initial course, often with subtle onset of symptoms only recalled retrospectively, with clinical nadir reached beyond 8 weeks. Motor weakness is usually more prominent than sensory involvement and autonomic dysfunction may occur. Cerebrospinal fluid analysis generally reveals albumin-cytological dissociation. Electrodiagnostic studies show evidence of demyelination with slowed conduction velocities, prolonged distal latencies, temporal dispersion of compound muscle action potential (CMAP), and delayed or absent F waves. Nerve biopsy may show demyelination and/or remyelination, but is not necessary for diagnosis. Evidence of axonal damage may be seen in later stages. Magnetic resonance imaging (MRI) spine with gadolinium infusion may show enhancing and thickened nerve roots and plexuses, but is not a criterion to make a diagnosis and not always abnormal.[2] Children with CIDP are more likely to have an acute onset with severe symptoms and a relapsing course when compared to adults.[3] They also exhibit good response to therapy with better improvement and more favorable outcomes.[4] About one in five pediatric patients with CIDP may be refractory to several treatments and have a poor outcome.[5]

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DOI: 10.4103/0972-2327.160065

Materials and Methods

We reviewed charts of all patients with CIDP seen at our institution (Children's Hospital Los Angeles) between October 1, 2003 and September 30, 2013 and collected data. Outcome was assessed at last visit, last contact with patient, or as of March 31, 2014 whichever came earlier. Residual deficit was assessed using modified Rankin scale [Table 1] and overall outcome with the use of CIDP Disease Activity Status (CDAS) scale [Table 2].[2,3,6,7]

Table 1: Modified Rankin scale

0 = Asymptomatic
1 = Non-disabling symptoms that do not interfere with lifestyle
2 = Minor symptoms that lead to some restriction of lifestyle, but do not interfere with the patients' capacity to look after themselves
3 = Moderate symptoms that significantly interfere with lifestyle or prevent totally independent existence
4 = Moderately severe symptoms that clearly prevent independent existence, although patients do not need constant attention
5 = Severely disabled, totally dependent, requiring constant attention

Table 2: Chronic inflammatory demyelinating polyneuropathy Disease Activity Status scale (CDAS)

Cure: ≥5 years off treatment
Normal examination
Abnormal examination, stable/improving
Remission: <5 years off treatment
Normal examination
Abnormal examination, stable/improving
Stable active disease: ≥1 year, on treatment
Normal examination
Abnormal examination, stable/improving
Improvement: ≥3 months <1 year, on treatment
Normal examination
Abnormal examination, stable/improving
Unstable active disease: Abnormal examination with progressive or relapsing course
Treatment naive or <3 months
Off treatment
On treatment

Results

A total of 20 patients with pediatric CIDP were identified, 11 females and nine males [Table 3]. Diagnosis of CIDP was based on clinical diagnostic and supportive criteria as proposed by the joint task force of the European Federation of Neurological Societies and the Peripheral Nerve Society, and aided by electrodiagnostic studies.[8] Age of onset ranged from 10 months to 17 years. Six patients had a relapsing course after an initial diagnosis of AIDP, while 13 presented with progressive symptoms with clinical nadir beyond 8 weeks from onset. One had a relapsing course after initial presentation with weakness and diplopia that spontaneously improved without diagnosis. Subsequently, this patient had more typical relapses and was confirmed to have CIDP. Twelve patients had only motor involvement; seven had sensory-motor involvement with more predominant motor weakness; and one had predominant motor involvement with additional autonomic disturbance with unilaterally dilated unreactive pupil. One patient had bulbar muscle involvement requiring a gastrostomy tube, and another one had respiratory failure requiring tracheostomy and long-term ventilator support. Initial evaluation included lumbar puncture in all. Cerebrospinal fluid (CSF) protein levels were available for review in all patients except one and ranged from 40 to 653 mg/dl. CSF white blood cell counts were available in 16 patients, ranging from 0 to 4 cells/mm^2. Electrodiagnostic studies were done for 16 patients. The details were available for 11 of these and supported the diagnosis (prolonged distal latencies in 10, decreased conduction velocity in nine, delayed or absent F waves in nine, and temporal dispersion in seven). The details were not available for five (done at other institutions or reports not available), but the results were noted to be supportive of the diagnosis by the treating neurologist. One of the four patients who did not have electrodiagnostic studies underwent a nerve biopsy with results supporting the diagnosis. MRI of full spine or lumbar spine with gadolinium infusion was obtained in 11 patients and showed abnormal findings supportive of diagnosis in nine (enhancing and/or thickened/clumped lumbar/cervical roots; enlarged nerves in brachial/lumbosacral plexus). None of the patients had an identifiable underlying primary autoimmune diagnosis other than CIDP, and the only identifiable triggering events were minor viral illnesses. We did not perform genetic testing to rule out hereditary neuropathy as the clinical presentation and electrodiagnostic studies were not consistent with that diagnosis.

The choice of treatment modality was empirical, selected by the treating neurologist. Change of therapy or addition of other immunosuppressive agent was instituted either due to development of adverse effects, inability to wean from corticosteroids, or lack of response or relapse. Intravenous immunoglobulin (IVIG) was the most common initial choice of treatment with seven patients requiring no other therapies. It was well-tolerated other than minor adverse effects such as headache, itching, rash, and chills. Corticosteroids were used either as chronic oral prednisone or periodic pulse methylprednisolone. Adverse effects were those expected from high dose corticosteroids: Weight gain, development of Cushingoid facies, mood changes including depression, upper gastrointestinal discomfort, osteopenia, fracture, osteonecrosis, delayed puberty, short stature, acne, and poor wound healing. Plasmapheresis was used intermittently in three patients, all of whom had transient partial responses without complications. Ongoing continued use of plasmapheresis was considered to be impractical due to technical difficulties and incomplete response. Other treatments included mycophenolate mofetil, rituximab, cyclophosphamide, azathioprine, and abatacept. Mycophenolate mofetil was used in seven patients and thought to be partially effective in four. Rituximab was used in one patient, with no definitive benefit. Cyclophosphamide, azathioprine, and abatacept were used in one patient each with perceived partial response. In one, prolonged use of monthly abatacept allowed gradual reduction of multiple other agents including cyclophosphamide, bolus dose corticosteroids, and IVIG. However, he had a severe relapse when abatacept doses were reduced after 4 years of control. No major side effects were noted with the use of these immunomodulating agents. The duration of follow-up ranged from 5 months to 18 years. All patients but one had relatively favorable outcomes at final assessment based on CDAS. Please note that the single patient in the 5C category with unstable active disease at final evaluation at our institution had been treated with IVIG, steroids, plasmapheresis, and mycophenolate mofetil before insurance issues dictated transfer of care elsewhere.

Residual neurological deficit was assessed at final visit with modified Rankin score and was common. We did not have any patients that met the criteria for a cure based on chart review. However, ongoing contact with two patients previously

Table 3: Basic clinical characteristics, treatment, and outcome of our 20 patients

Age	Sex	Deficit	Duration	Treatment	CDAS at last visit	Modified Rankin scale at last visit
10	F	Motor> sensory	4	IVIG, steroids, and mycophenolate mofetil	3B	2
4	F	Motor	3	IVIG	2A	0
9	F	Motor	2	IVIG and steroids	2A	0
6	M	Motor	5	Steroids and azathioprine	3B	2
8	M	Motor > autonomic	2	IVIG	3A	0
5	M	Motor > sensory	6	IVIG, steroids, plasmapheresis, cyclophosphamide, mycophenolate mofetil, and abatacept	3B	4
9	M	Motor	1	IVIG	3B	1
16	M	Motor >sensory	11 months	IVIG, steroids, plasmapheresis, rituximab, and mycophenolate mofetil	4B	3
6	M	Motor > sensory	3	IVIG, steroids, and mycophenolate mofetil	3B	2
11	F	Motor	4	IVIG and steroids	3A	1
17	F	Motor > sensory	6 Months	IVIG, steroids, plasmapheresis, mycophenolate mofetil, rituximab	5C	4
9	M	Motor	11	IVIG, steroids, and mycophenolate mofetil	3B	2
6	M	Motor	14	IVIG and mycophenolate mofetil	3B	2
12	F	Motor	6	IVIG	2A	0
12	F	Motor	5	IVIG	4B	2
10 Months	F	Motor > sensory	18	IVIG	3B	2
8	F	Motor	8	IVIG and steroids	2A	0
8	M	Motor > sensory	4	IVIG	3B	2
10	F	Motor	1	Steroids	3B	2
13	F	Motor	5 months	IVIG and steroids	4B	2

CDAS = Chronic inflammatory demyelinating polyneuropathy Disease Activity Status scale, IVIG = Intravenous immunoglobulin. Age and duration are in years unless otherwise specified, F = Female, M = Male

discharged off therapy (and overage for our clinic) indicated that both continue in full remission, asymptomatic, and without ongoing therapy. A number of our patients may have been in complete remission, but once off treatment for several years, they were discharged from our clinic. Since this was a retrospective study, we could not contact patients who had been discharged or who had "aged out" of our clinic.

Discussion

Pediatric CIDP is generally a chronic condition, often requiring multiple modalities of treatment over time, and often leaving patients with residual deficits, even with successful treatment. A majority of patients do not have complete remission of their illness, and many need intermittent, if not continuous, immunomodulatory treatment.

Management of pediatric CIDP is challenging due to absence of definitive evidence of efficacy of the various agents in the literature, with complete lack of any randomized studies. This is due to the rarity of this condition. Riekhoff *et al*., noted in 2012 that only 136 pediatric CIDP cases had been described in the literature.[9] There is no clear consensus for initial choice of treatment nor for second-line therapies for patients in whom IVIG and corticosteroids fail, or for patients who become corticosteroid dependent. IVIG is considered to be the preferred initial treatment by many.[2,3,10] However, this is an off-label use in the USA for pediatric CIDP, with questions raised about cost and issues with reimbursement.[11] Moreover, it is well-known that the response to IVIG is not universal and can be partial. A trial of oral prednisone or periodic pulse methylprednisolone with slow taper after several months and addition of IVIG only in case of relapse have been proposed. Others have advocated plasmapheresis as a reasonable first-line therapy.[3] Long-term corticosteroid use is best avoided due to chronic adverse effects on growth and bone density. Adverse effects of plasmapheresis and technical difficulties of using it on an ongoing basis make it less practical in small children. Relapses are common upon withdrawal of corticosteroids and plasmapheresis.[12,13] Data for efficacy and tolerability of other immunomodulating agents such as azathioprine, cyclosporine A, mycophenolate mofetil, methotrexate, cyclophosphamide, and rituximab are anecdotal and mixed.[2,5,13-17]

Publications pertaining to pediatric CIDP over several decades continue to mention the lack of definitive evidence regarding treatment strategies. It is quite clear that there has been little progress over many years. Areas for further research include: What is the optimal initial treatment? What is the best second-line treatment option when initial therapy fails? What should be the outcome goals when assessing efficacy? When should a particular therapy be considered a failure? When does combination therapy become necessary? At what point should a therapy be reduced or withdrawn in a stable patient to assess for remission? Most importantly, what should be the strategies to avoid long-term corticosteroids and resultant adverse effects? Randomized control trials to test and compare efficacy and tolerability of various treatment options will help optimize management, especially for the cases which are refractory to first-line treatments; but may be impractical because of low

incidence of pediatric CIDP and varying severity of disease across the spectrum. Although, we are a quaternary level free standing children's hospital, our numbers are small. Hence, we are not able to make any specific recommendation based on our experience. Formation of a worldwide network of pediatric CIDP centers may be worth considering for research purposes and for eventual development of a consensus statement with guidance for treatment.

Funding

Desai and Ramos-Platt report receipt of no financial support for the research and/or authorship of this article; Mitchell has received research financial support for Neurology Division activities and/or for participation in multicenter clinical trials from Lundbeck (formerly Ovation) Pharmaceuticals, Eisai, UCB, Novartis, Questcor.

Ethical approval

Approval was obtained from our institutional review board.

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How to cite this article: Desai J, Ramos-Platt L, Mitchell WG. Treatment of pediatric chronic inflammatory demyelinating polyneuropathy: Challenges, controversies, and questions. Ann Indian Acad Neurol 2015;18:327-30.

Received: 04-03-15, **Revised:** 19-03-15, **Accepted:** 29-03-15

Source of Support: Nil, **Conflicts of Interest:** None declared.