



Childhood chronic inflammatory demyelinating polyradiculoneuropathy: Combined analysis of a large cohort and eleven published series

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Abstract

The clinical presentation, disease course, response to treatment, and long-term outcome of thirty childhood chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) patients are presented representing the largest cohort reported to date. Most children (60%) presented with chronic (>8-weeks) symptom-onset while a smaller proportion showed sub-acute (4–8 weeks) or acute (“GBS-like”; <4 weeks) onset of disease. No gender predilection was observed. The majority of patients had a relapsing (70%) versus a monophasic (30%) temporal profile. Most received initial IVIG monotherapy; 80% showing a good response. Long-term follow-up (mean = 3.8 years) was available for 23 patients; 45% were off all immunomodulatory medications, demonstrating no detectable (55%) or minimal (43%) clinical deficits. Our data were compared with 11 previously published childhood CIDP series providing a comprehensive review of 143 childhood CIDP cases. The combined initial or first-line treatment response across all studies was favourable for IVIG (79% patients) and corticosteroids (84% patients). Response to first-line plasma exchange was poor (only 14% patients improved) although it may offer some transient or partial benefit as an adjuvant or temporary therapy for selected patients. The combined long-term outcome of our cohort and the literature reveals a favourable prognosis for most patients. The combined modified Rankin scale decreased from 3.7 (at presentation) to 0.7 (at last follow-up). This review provides important data pertaining to clinical course, treatment response and long-term outcome of this relatively uncommon paediatric autoimmune disease.

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1. Introduction

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) may occur from infancy [1,2] to late-adulthood [3] with increasing disease prevalence seen with advancing age. Auto-reactive T-cells play a dominant role in the initial pathogenesis of CIDP, triggering an

inflammatory response within sensory and motor nerves and damaging Schwann cells and the peripheral nerve myelin [4]. Children present with slowly progressive or relapsing episodes of gait ataxia, distal symmetric weakness and paraesthesiae. Diagnostic criteria differentiate CIDP from its acute counterpart, Guillain–Barré syndrome, as well as hereditary and metabolic causes of childhood polyneuropathy [5–8].

Several case series of childhood chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) have been published in the literature. However, given the low prevalence of childhood CIDP (i.e. <0.5 per 100,000) [3], studies

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have offered conflicting information pertaining to gender ratio, treatment efficacy and long-term outcome of this disease [1,2,9–18]. This report represents the largest case series of childhood CIDP published to date. It includes a description of disease-onset, clinical features, response to treatment and long-term disease outcome for 30 childhood CIDP patients. Data from our cohort have been combined with data from 11 previous case series (1980–2009) to provide a comprehensive review of childhood CIDP.

2. Methods

Institutional research ethics board approval was obtained prior to the start of data collection. The medical records of all patients with CIDP seen at Boston Children's Hospital (BCH) from 1989 to 2009 were reviewed.

2.1. Inclusion/exclusion criteria

Inclusion criteria included: (1) age \leq 19.0 years old; (2) clinical history of progressive or relapsing motor and sensory polyneuropathy; (3) clinical evidence of diffuse hyporeflexia or areflexia; (4) cerebrospinal fluid white cell count $< 10 \text{ mm}^{-3}$; (5) electrophysiological studies consistent with an acquired demyelinating disorder in ≥ 2 nerves. AAN research criteria [5] were used to set the electrodiagnostic criteria for an acquired demyelinating neuropathy; nerve conduction studies must have demonstrated three of the four following features: (1) reduced conduction velocity (i.e. $< 80\%$ of the lower limit of normal (LLN) if the compound muscle action potential (CMAP) amplitude is $> 80\%$ LLN or $< 70\%$ LLN if the CMAP amplitude is $< 80\%$ LLN); (2) abnormal temporal dispersion or partial conduction block. Temporal dispersion was defined as excessive prolongation of the CMAP duration with proximal stimulation compared to distal stimulation reflecting non-uniform conduction slowing; a $> 20\%$ increase in proximal-to-distal CMAP duration of median, ulnar or peroneal nerves or $> 30\%$ for tibial nerves was defined as abnormal. Partial conduction block was defined as a $> 20\%$ drop in peak-to-peak amplitude between proximal and distal stimulation sites; (3) prolonged distal latency (i.e. $> 125\%$ upper limit of normal if amplitude was $> 80\%$ of LLN or $> 150\%$ upper limit of normal if amplitude was $< 80\%$ of LLN); (4) absent or prolonged F-waves (10 trials) (i.e. $> 120\%$ of the upper limit of normal if amplitude was $> 80\%$ of LLN or $> 150\%$ of the upper limit of normal if amplitude was $< 80\%$ of LLN). Published reference values for normal paediatric sensory and motor nerve conduction were used [19]. Nerve biopsies were not typically performed for patients meeting the above criteria.

Exclusion criteria included: (1) family or past medical history of an inherited polyneuropathy; (2) drug or toxin exposure; (3) clinical suspicion of an underlying metabolic disorder (i.e. retinitis pigmentosa, ichthyosis, hand or foot mutilation, developmental delay or regression); (4) sensory level; or (5) sphincter disturbance.

2.2. Clinical data

Patients' medical charts were reviewed to obtain the following information: (1) gender; (2) age of symptom onset; (3) time between symptom-onset and maximum disability; (4) maximum clinical deficit (using modified Rankin scale (MRS), see below); (5) clinical features at initial presentation (i.e. deep tendon reflex findings, limb/back pain, limb paraesthesiae); (6) disease course (i.e. monophasic or relapsing/polyphasic); (7) number of relapses; (8) choice and response to first-line immunomodulation therapy; (9) choice and response to all immunomodulation therapies (used at any stage of disease); (10) follow-up duration; and (11) MRS at last follow-up visit.

The modified Rankin scale (MRS) was used to quantify clinical deficit. MRS was devised as a reliable means of scoring clinical deficits after stroke [20] and has since been used to estimate clinical deficit in adult and childhood CIDP patients [9–11,13]. MRS functional scales are defined as: 0 = asymptomatic; 1 = mild symptoms that do not interfere with any work, school or extracurricular activity; 2 = slight disability (i.e. child has given up one or more activities) but is able to perform all age-appropriate personal care (i.e. dressing, eating) and complex tasks (i.e. handwriting, age-appropriate food preparation); 3 = moderate symptoms (i.e. child is still able to walk independently (may require cane or walker) but requires assistance for age-appropriate tasks (see above)); 4 = moderate-to-severe symptoms (i.e. child is unable to walk (carried by parent and/or wheelchair required) and unable to perform age-appropriate personal care); 5 = severe disability (i.e. patient is bed-ridden and requires constant nursing care), may require intubation and mechanical ventilation; 6 = death.

Cerebrospinal fluid leucocyte (WBC) count and protein were recorded for all patients. Results of magnetic resonance imaging (MRI) of the spine were recorded whenever available.

2.3. Outcomes

Clinical response to the immunomodulatory therapies (i.e. intravenous immunoglobulin (IVIG), plasma exchange (PE) or corticosteroids) was measured, both for first-line therapies and at subsequent stages of the disease. We defined a "good response" as clinical improvement to the point where the treating physician reported minimal-to-no functional impairment or limitation of activities. "Partial response" was defined as some degree of clinical improvement as judged by the treating physician; however, a change or addition of immunomodulatory treatment was necessary. "No response" was defined as either no apparent clinical improvement or clinical deterioration on a given treatment. Disease relapse was defined as a clinical deterioration not associated with weaning immunosuppressant medication and/or wearing-off effects of IVIG or plasma exchange therapy. In cases where patients could

not be weaned off a given medication and were started on a second immunomodulatory agent, they were classified as having a partial response to that drug.

2.4. Meta-analysis

Data from 11 previous case series published from 1980 to 2009 [1,2,9–18] were compiled and analysed with data from the current series.

3. Results

Of the 32 CIDP patients seen at BCH, 30/32 (94%) met inclusion/exclusion criteria for entry into the study. Two patients were excluded. The first was a $2\frac{1}{2}$ year old boy who met clinical and electrodiagnostic criteria for inclusion but had a CSF leucocyte count of 13 mm^{-3} . The second was a 15 month old female whose clinical course was consistent with relapsing CIDP but had equivocal electrodiagnostic test results.

The *gender* of the 30 eligible CIDP patients at our centre included 13 males and 17 females. Analysis of gender for all published CIDP patients ($N = 143$) reveals 73 males and 70 females indicating no gender predilection for childhood CIDP (see Table 1). The *mean age of symptom onset* at our centre was 7.6 years old (range: 1.5–19.0 years old), comparable to that published in other studies.

The *time between symptom-onset and maximum disability* varied considerably. Most CIDP patients (18/30; 60%) demonstrated a slow or insidious onset of their initial disease symptoms (i.e. >8 weeks from symptom-onset to maximum clinical deficit). The mean time between disease-onset and maximum clinical deficit was 7.9 months in these patients. There was a smaller proportion of CIDP patients (6/30; 20%) who showed an initial acute-onset disease (i.e. <4 weeks between symptom-onset and maximal clinical deficit). These patients were initially diagnosed with Guillain–Barré syndrome (i.e. acute inflammatory demyelinating polyradiculoneuropathy; AIDP) before later relapsing and/or showing an incomplete clinical recovery (>8 weeks). Four of these six patients showed a complete clinical recovery with a single IVIG treatment (1 g/kg; $\times 2$ days) only to clinically deteriorate 1–17 months later. A fifth patient ($2\frac{1}{2}$ year old female) initially presented with rapidly progressive weakness over several days, becoming quadriplegic and requiring intubation and mechanical ventilation. She demonstrated a partial response to IVIG therapy and required plasma and corticosteroids to attain disease remission. She later had 2 disease relapses which were eventually controlled with maintenance corticosteroids and azathioprine. Her long-term outcome was favourable, at her last follow up visit (4 years later) she was off treatment and had no restrictions to her daily activities. The sixth patient (8 years old female) initially presented with unilateral right ptosis, diplopia, proximal

muscle weakness and hyporeflexia. Her initial clinical examination, electrodiagnostic testing and CSF studies were consistent with AIDP. Her family declined treatment as she remained ambulatory and recovered spontaneously. Three years later she returned with a clinical relapse characterised by distal weakness and paraesthesiae without cranial nerve involvement. She responded well at the time of relapse to IVIG therapy. A similar, small proportion of children at our centre (6/30; 20%) showed subacute-onset disease (i.e. between 4 and 8 weeks from symptom-onset to maximum clinical deficit).

The *maximum clinical deficit* for our CIDP patients corresponded to a mean modified Rankin scale of 2.8, which was similar to four other studies where MRS data were available [9–12]; see Table 1). Although most CIDP patients at BCH reported some problems with gait (29/30; 97%), only a minority were non-ambulatory (7/30; 23%). Of the non-ambulatory patients (i.e. MRS 4 or higher), their initial symptom-onset ranged from acute (2 patients), sub-acute (2 patients) to chronic (3 patients). Patients with milder symptoms (i.e. MRS = 1–2) were more likely to have demonstrated a chronic-symptom onset (9/13; 69%).

Clinical features amongst our CIDP patients included deep tendon reflexes that were absent 24/30 (80%) or decreased 6/30 (20%). Pain was only reported in 6/30 (20%) patients including: back-ache (4/6) or leg discomfort (2/6). Sensory testing (pin-prick and vibration sense) was abnormal in 11/30 (37%) patients and normal in 5/30 (16%) patients. Reliable sensory testing was not possible in the majority of our CIDP patients given young age (<5 years old) and/or poor cooperation (14/30; 47%).

Disease course in most CIDP patients at BCH 21/30 (70%) demonstrated a relapsing or polyphasic disease course with the *number of relapses* ranging from 1 to 4. Relapsing disease was seen in patients with an initial chronic (9 patients), sub-acute (6 patients) or acute-onset (6 patients) disease. Only 9/30 (30%) children showed a monophasic disease course; all of whom had an initial chronic disease-onset. Information relating to CIDP disease course could be obtained from 9 other studies ($N = 129$; see Table 1) with more patients demonstrating a relapsing (61%) versus monophasic (39%) disease course.

Spinal fluid analysis was documented for all of our CIDP patients. Elevated CSF protein was noted in 26/30 (87%) patients with mean CSF protein 95.4 g/L (range 21–568.4 g/L; normal = 15–45 g/L). All patients (as per inclusion criteria) had CSF WBC < 10 mm^{-3} . *MRI of the spine* was performed in 21/30 (70%) of our CIDP patients; of whom 8/21 (38%) had evidence of diffuse nerve root thickening and gadolinium enhancement. One patient also showed MR evidence of a thickened cauda equina. There was no correlation between imaging findings and clinical parameters.

The *choice and response of first-line immunomodulation therapy* was recorded for our CIDP patients and compared to the responses in previous studies (Table 2). The majority of our CIDP patients received initial IVIG monotherapy,

Table 1
Childhood CIDP: clinical presentation and outcome.

Reference	# Patients (male:female)	Mean age onset (years)	Disease course	Modified Rankin score	
				Initial	Follow-up
Current series	30 (13M:17F)	7.6 (1.5–19)	21 Relapsing: 9 monophasic	2.8	0.5 ^a
Rosignol et al. [9]	13 (9M:4F)	9 (3–14)	10 Relapsing: 3 monophasic	3.0	1.3
Ryan et al. [10]	16 (5M:11F)	6.3 (2.2–13.8)	6 Relapsing: 10 monophasic ^b	3.4	0.25
Hattori et al. [11]	10 (6M:4F)	11 (2–16)	7 Relapsing : 3 monophasic	4.4	1.9
Simmons et al. [12]	15 (7M:8F)	11.5 (3–17)	10 Relapsing : 2 monophasic ^c	3.5	0.2 ^c
Korinthenberg [14]	21 (12M:9F)	8.6 (2–14)	9 Relapsing : 12 monophasic	NR ^d	NR ^d
Nevo et al. [2]	13 (8M:5F)	6.5 (1–16)	10 Relapsing : 3 monophasic	NR	NR
Vednarayanan et al. [15]	4 (1M:3F)	7.5 (7–9)	3 Relapsing : 1 monophasic	NR	NR
Rodriguez-Casero et al. [16]	5 (3M:2F)	8.0 (4.5–13.9)	0 Relapsing : 5 monophasic	NR	NR
Uncini et al. [17]	5 (1M:4F)	7 (6–11)	NR	NR	NR
Sladky et al. [1]	6 (5M:1F)	NR	NR	NR	NR
Colan et al. [18]	5 (3M:2F)	9.6 (5–17)	3 Relapsing ; 2 monophasic	NR	NR
Total	143 (73M:70F)		79 (61%) Relapsing ; 50 (39%) monophasic		

M, male; F, female; NR, not reported.

^a Long term follow-up available for 20/30 patients.

^b Monophasic and progressive were grouped together.

^c Long term follow-up and treatment data available for 12/15 patients.

^d Different functional scoring system was used.

Table 2
Childhood CIDP: treatment success with initial or first-line therapy.

Reference	# Patients	Patients showing GOOD response (%)		
		IVIG	PE	Corticosteroids
Current series	29 ^a	20/25 ^a (80%)	0/2 (0%)	Not used ^a
Rosignol et al. [9]	13	2/3 (67%)	Not used	8/10 (80%)
Ryan et al. [10]	16	3/4 (75%)	0/1 (0%)	7/11 (64%)
Hattori et al. [11]	10	1/2 (50%)	1/2 (50%)	4/6 (66%)
Simmons et al. [13]	12	5/6 (83%)	0/2 (0%)	4/4 (100%)
Korinthenberg [14]	21	10/12 (83%)	Not used	8/11 (73%)
Nevo et al. [2]	13	Not used	Not used	13/13 (100%)
Rodriguez-Casero et al. [16]	5 ^b	Not used	Not used	3/3 (100%) ^b
Uncini et al. [17]	5	Not used	Not used	4/5 (80%)
Sladky et al. [1]	6	Not used	Not used	6/6 (100%)
Colan et al. [18]	5	Not used	Not used	5/5 (100%)
Total	135	41/52 (79%)	1/7 (14%)	62/74(84%)

Note: Korinthenberg et al. [14]; 1 patient appears to have received combined initial IVIG and corticosteroids although this cannot be confirmed in the text.

^a Of 30 patients: 1 patient received no treatment at her initial presentation; 2 patients received combined initial IVIG and corticosteroids (therefore, not included in this table).

^b Of 5 patients: 2 patients received combined initial IVIG and corticosteroids (therefore, not included in this table).

with most patients (20/25; 80%) showing a good response to this treatment. No patient was started on initial corticosteroid therapy alone. Two patients were treated with both initial IVIG and corticosteroids as first-line agents demonstrating a good response and were excluded from the analysis of treatment success to first-line therapy since multiple immunomodulation therapies were used. One patient did not receive any treatment for her initial presentation. Two patients received initial plasma exchange therapy with limited benefit. One patient (9 year old female with chronic-onset disease who became non-ambulatory) showed no response to first-line plasma exchange. She was later treated with IVIG (partial response) and

eventually, combined IVIG and prednisone therapy with a good response. Another patient (13 year old female with mild symptoms and chronic-onset disease) showed a good clinical response to plasma exchange but could not continue with this therapy due to difficulty obtaining peripheral venous access. Corticosteroids have been commonly used as initial therapy in many published series (particularly in earlier case series) with good response (Table 2).

Of the 20 CIDP patients who showed a good response to first-line IVIG, 6/20 (30%) were eventually weaned completely off IVIG maintenance therapy with no evidence of disease relapse after a mean follow-up (off-therapy) of 3.1 years. A larger proportion; 12/20 (60%) of our CIDP

patients still required ongoing IVIG therapy and/or were in the process of weaning-off IVIG. This includes three children who had just relapsed at the time of their last follow-up visit. One patient (5%) who had demonstrated a good response to first-line IVIG later opted to switch to maintenance plasma exchange. He remained in disease remission with PE therapy. Another patient (5%) demonstrated a good response to first-line IVIG therapy, attained disease remission and was off-therapy for 9 months before CIDP relapse. This relapse was successfully treated with prednisone and she remains in remission after withdrawal of this medication.

Combining our data with that from other published series the overall treatment response of childhood CIDP to first-line IVIG or first-line corticosteroids appear similar (79% versus 84%) and superior to first-line plasma exchange (14% success; Table 2).

The choice and response of immunomodulation therapy at any stage of disease was recorded. All but one of our CIDP patients received IVIG at some point in their disease (Table 3) with 23/29 (68%) showing benefit with this therapy. Ten patients received corticosteroids at some time in their disease treatment which was beneficial in all (100%) cases (Table 3). Two patients were treated with both initial IVIG and corticosteroids as first-line agents. In other patients corticosteroid therapy was started as a result of an inadequate response to IVIG monotherapy (5 patients) or plasma exchange (1 patient). Two other patients were treated with corticosteroids at the time of a later disease relapse after they had been off-treatment. The duration of corticosteroid treatment ranged from months (i.e. pulse intravenous methylprednisone followed by tapering doses of oral prednisone) to several years of daily prednisone therapy. Data pertaining to side effects were not available for 2 patients who had only one visit at our centre, however for the remaining eight patients side effects included: weight gain (4 patients), hirsutism (2 patients), cushingoid facies (2 patients) and growth failure (1 patient).

Overall treatment response of childhood CIDP at any stage of disease appears similar between IVIG versus corticosteroids (77% versus 80% showing a good response) which were both superior to plasma exchange (45% showing good response; Table 3). Overall, plasma exchange is used less frequently and appears less efficacious in childhood CIDP (often due to issues surrounding vascular access). Nevertheless, several case series have emphasised that plasma exchange may still offer partial and/or transient benefit [2,13,15]. As such, there may still be a role for PE as an adjuvant or temporary measure for select children with CIDP. The data presented in Table 3 outline treatment success with each therapy when used at any stage of treatment (i.e. first-line, second-line, etc.). The treatment may have been used in isolation (i.e. monotherapy) or in combination with another immunomodulation or immunosuppressant therapy.

Adjuvant immunomodulating therapies were not commonly used at our centre. Three patients were treated with azathioprine and one with mycophenylate mofetil for steroid-sparing effects. One patient with Crohn's disease also received concomitant infliximab therapy.

Long-term follow-up data were available for most children (23/30; 77%) who were followed at BCH for their entire treatment. For these children, mean follow-up duration was 3.8 years (range: 5 months–13 years). Seven patients (23%) were seen at our institution on one or more occasions for the purpose of obtaining a second opinion regarding disease diagnosis and/or treatment recommendations. Long-term functional outcome (i.e. follow-up MRS score) was not available for these 7 children. Long-term outcome was favourable for most patients followed at our centre. Follow-up MRS score had improved for all but three children (who had just suffered disease relapse at the time of their most recent follow-up visit). The mean follow-up MRS score for the remaining 20/23 children at BCH was 0.5 at their last clinical assessment (improved from mean initial MRS score of 2.8). Nine children (9/20;

Table 3
Childhood CIDP: treatment success to therapies used at any stage of disease.

Reference	# Patients	Patients showing GOOD response (%)		
		IVIG	PE	Corticosteroids
Current series	30	23/29 (68%)	2/5 (16%)	10/10 (100%)
Rossignol et al. [9]	13	3/5 (60%)	1/2 (50%)	8/11 (73%)
Ryan et al. [10]	16	4/6 (67%)	1/4 (25%)	8/12 (67%)
Hattori et al. [11]	10	2/3 (66%)	2/3 (66%)	6/8 (75%)
Simmons et al. [13]	12	7/8 (88%)	2/4 (50%)	5/7 (71%)
Korinthenberg [14]	21	10/12 (83%)	3/5 (60%)	12/20 (60%)
Nevo et al. [2]	13	3/6 (50%)	1/3 (33%)	13/13 (100%)
Vedanarayanan et al. [15]	4	4/4 (100%)	1/3 (33%)	3/4 (75%)
Rodriguez-Casero et al. [16]	5			5/5 (100%)
Uncini et al. [17]	5			4/5 (80%)
Sladky et al. [1]	6			6/6 (100%)
Colan et al. [18]	5			5/5 (100%)
Total	140	56/73 (77%)	13/29 (45%)	85/105 (80%)

Note: These data include response to first-line (initial), second or third line treatments. Treatment can include monotherapy or combined therapies.

45%) were also off all immunosuppressant medication at the time of their last clinical follow-up. No clinical deficit was seen on the clinical examination of 11/20 (55%) patients. Minimal focal weakness, primarily distal, was observed in 9/20 (45%). None of these mild deficits was reported to cause any functional disability or restricted school or extracurricular activities (i.e. MRS = 1). Only one patient had residual clinical deficits causing restriction of activities (i.e. MRS = 2).

No long term follow-up data were available for the 7 CIDP patients who were evaluated on only 1 or 2 occasions for a second opinion. Most of these children (6/7) presented with a chronic onset disease. Their disability at initial presentation ranged from mild to moderately-severe (i.e. MRS = 2–4). Only 1 child with very mild disease at onset (MRS = 1) had not received treatment. Of the remaining six children, 4/6 had demonstrated a good clinical response to IVIG monotherapy (4/6). One showed a partial response to IVIG necessitating the addition of oral corticosteroids. The final child showed no improvement with IVIG only responding when corticosteroids were added. All treated children had demonstrated some clinical improvement (MRS = 0–2) by the time of our assessment.

Combined long-term outcome could be compared amongst CIDP patients at our centre with 4 prior case series [9–11,13]. The overall mean MRS score improved from 3.7 at presentation to 0.7 at follow-up (Table 1). Our series and two others [10,13] reported favourable long-term outcome with CIDP, whereas two other case series [9,11] showed mild-to-moderate clinical deficits at follow-up. An additional case series reported favourable long-term outcome for the majority of children with CIDP, although a different functional rating scale was used which was not directly comparable with the MRS [14].

4. Discussion

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is rare enough in childhood to present challenges for population-based studies and clinical trials. By providing the largest reported cohort of childhood CIDP and combining data from 11 prior case series, this study provides important information regarding the clinical presentation, disease course, response to treatment and long-term outcome of childhood CIDP.

The combined data from this and previous studies provide several key observations. First, no gender predilection was observed. Prior reports of male (9) or female (10) gender preponderance likely reflect sampling bias. Second, the disease course of childhood CIDP is more often relapsing or polyphasic (61%) than monophasic (39%). The data from our institution also indicate that a slow, chronic-onset of symptoms (i.e. >8 weeks) may be a more common presentation of childhood CIDP as this was observed in 60% of patients. However, like prior studies, some children with CIDP may demonstrate an initial subacute-onset (i.e. 4–8 weeks) [16] or acute “GBS-like” symptom onset before

their eventual relapse and diagnosis with CIDP [21]. Twenty percent of the children at our centre had an initial presentation that was indistinguishable from Guillain–Barré syndrome. Such patients illustrate the difficulty of differentiating patients with monophasic GBS who show transient fluctuations post-IVIG or post-PE as seen in 10% of adult GBS patients [22] from CIDP patients with abrupt symptom onset (i.e. “GBS-like presentation”) as seen in 16% of adult patients [21]. The ability to distinguish the two groups would be beneficial. For example, early differentiation could permit the use of corticosteroids in abrupt-onset CIDP patients (where it may be beneficial) and avoid corticosteroid use in GBS patients (where there is no benefit to the use of this medication) [23]. Recent adult studies have pointed to early clinical features that may differentiate GBS treatment-related fluctuations from those with an acute-onset CIDP [24,25]. Factors favouring CIDP have been reported to include; longer time to initial clinical nadir, longer time until first clinical deterioration and reduced likelihood of respiratory failure and mechanical ventilation [24,25]. Other factors favouring CIDP may include; more prominent initial sensory symptoms, lower incidence of autonomic involvement and/or facial weakness and maintaining the ability to walk independently [25]. Amongst our six patients with acute (“GBS-like”) onset of CIDP, only 1 showed definite, length-dependent abnormality on sensory examination. For the remaining five patients, sensory testing was not feasible given their young age (i.e. 2–4 years old). This serves as a reminder of how challenging it can be to extrapolate clinical data and predictive testing from adult studies to children with similar disorders. Although none of the six patients with acute-onset CIDP exhibited autonomic symptoms, two became non-ambulatory including one child who required mechanical ventilation.

Revised diagnostic criteria for childhood CIDP were created after an international workshop based upon available evidence and expert opinion [8]. The mandatory clinical criteria were revised to include progressive muscle weakness over at least 4 weeks (instead of 8 weeks) or in the case of rapid progression (i.e. GBS-like presentation) followed by relapse or protracted course >1 year. Areflexia or hyporeflexia was also required [8]. The required major electrodiagnostic criteria were similar to, but less stringent than, the American Academy of Neurology CIDP research criteria [5]. Nerve biopsy was excluded as mandatory laboratory criteria when other clinical, laboratory and electrodiagnostic criteria were met. The removal of nerve biopsy from diagnostic criteria more accurately reflects current clinical practice at many centres. Only 5/30 (16%) patients at our centre had a nerve biopsy performed. Nerve biopsies are most useful for children with an atypical clinical presentation or nerve conduction study results in order to properly consider CIDP-mimics such as vasculitis [4,8,26].

Evidence for nerve root thickening and/or enhancement on MRI of the lumbosacral spine can provide support for CIDP. However it is not part of diagnostic criteria [8].

Nerve root thickening is seen in about 60% of adult CIDP patients with a smaller proportion also demonstrating gadolinium enhancement of thickened roots [27]. MRI evidence of nerve root thickening does not appear to correlate with either disease activity, disease severity or any clinical or laboratory features [8]. Marked nerve root and cranial nerve thickening and enhancement have been documented in childhood CIDP [10,28]. Although the majority of children in our series did have an MRI of the lumbosacral spine, only 38% of those studies demonstrated evidence of nerve root thickening and enhancement. Our data suggest that nerve root thickening may be a less consistent finding in childhood CIDP and should not be relied upon alone to support the diagnosis. Rarely, nerve root thickening has been reported in Charcot–Marie–Tooth, type 1A [29] or malignant infiltration of nerve roots (S. Chan, personal communication to H.R. Jones).

Most children treated for CIDP at our centre demonstrated a good long-term clinical outcome. The improvement in mean MRS score from 2.8 to 0.5 was directly comparable to that observed in two prior studies [10,13] as well as a third which used a different functional rating scale [14]. Two other reports described a slightly worse long-term outcome [9,11]. This underscores the relatively good prognosis for most children with CIDP.

Adult CIDP patients respond well to intravenous immunoglobulin (IVIG), plasma exchange (PE) or corticosteroids. Five adult studies have demonstrated superiority of IVIG over placebo [30–34]. The efficacy of IVIG has been shown to be equivalent to that of PE [35] or corticosteroids [36] in adult CIDP. A recent Italian study reported better short-term tolerability of monthly IVIG compared to monthly intravenous methylprednisone [37]. At our institution, IVIG therapy was used first-line for most children with CIDP. Most children (80%) showed a good response to initial IVIG treatment. This finding was similar to that noted in the aggregate data from other paediatric centres [9–12,14] (Table 2). Most children are initially given 1 g/kg \times 2 days before being placed on maintenance therapy of IVIG 1–2 g/kg every 4 weeks (see [38] for review). After clinical recovery, IVIG is weaned by gradually increasing the dosing interval. IVIG is thought to exert its immunomodulatory effects by neutralizing pathogenic cytokines and auto-antibodies as well as inhibiting complement activity [39]. Most children tolerate IVIG therapy well, though infusion-related side effects can include headache, fever, nausea and vomiting. Severe side effects can include anaphylaxis, thromboembolism, aseptic meningitis, renal failure and congestive heart failure. Increased care must be taken in patients with renal or cardiac disease [40].

Corticosteroids have proven efficacy in adult CIDP [41] and are used at some paediatric centres as first-line therapy. Corticosteroid use was reported more frequently in older case series (i.e. prior to late 1990s). They are still used first-line in situations when access to IVIG is limited due to logistical or financial reasons [42]. Only two CIDP patients at our centre were treated with first line corticoste-

roids (in addition to concomitant IVIG) with good effect. Corticosteroids were used as second or third-line therapy for an additional 8 patients at our centre with good effect. Given the significant concern surrounding long-term side-effects associated with corticosteroid use (i.e. osteoporosis and increased risk of fractures, obesity, decreased linear growth velocity and reduced adult height attainment), this medication is typically used as a second or third-line therapy at our institution and added at the time of relapse and/or when a partial or absent response is seen with IVIG or PE therapy. Although no children with CIDP at our centre were treated with first-line corticosteroid monotherapy, all patients who received corticosteroids as a second or third-line agent showed a good response to this treatment, consistent with other case series. Comparing the data from all studies, IVIG and corticosteroids are both effective as first-line treatment (Table 2) or at any stage of disease treatment (Table 3) for childhood CIDP.

While plasma exchange (PE) is superior to placebo for adult CIDP patients [43,44] with comparable efficacy to IVIG [35], this therapy appears to be less useful for childhood CIDP. Peripheral venous access for PE can be technically challenging in younger children. Complications can include central line-related complications (infection, thrombosis), acute effects (hypotension, electrolyte imbalance) as well as effect of chronic therapy (iron deficient anaemia, hypogammaglobulinaemia). PE was used first-line in 2 patients at our centre and in 5 additional patients at other centres (Table 2). Only 14% patients showed a good response to PE as a first-line therapy suggesting that it is less efficacious than other standard treatments in childhood CIDP.

Data pertaining to the use of steroid-sparing immunosuppressant therapy are limited in childhood CIDP. Although case series have reported some observational evidence for a beneficial response of azathioprine for adult CIDP [21,45], the one controlled trial [46] failed to show any benefit. This trial had a short duration (9 months), which may not have been long enough to observe a clinical effect. [47] Azathioprine is the most commonly used immunosuppressant amongst childhood CIDP patients both at our institution and in prior published series [9,14]. A beneficial effect of azathioprine has been reported for some paediatric CIDP patients when combined with corticosteroids [1,9,14] although others experienced no benefit from this medication [10,14] and/or discontinued treatment due to adverse effects (i.e. hepatitis or persistent vomiting) [2,9,10]. Data pertaining to the overall effectiveness of azathioprine for childhood CIDP are lacking.

Other immunosuppressants have been used infrequently for childhood CIDP. Mycophenolate mofetil appeared beneficial in one CIDP patient at our centre. Infliximab was used for another patient at our centre who also had inflammatory bowel disease. Other series of childhood CIDP have reported some clinical improvement with methotrexate [2,10] or cyclophosphamide [9,10]. Cyclosporine showed no effect when used for patients in two series

[2,10]. Rituximab use was reported for one child with steroid-refractory CIDP with a partial response [9]. The effect of these drugs in adult CIDP has not been promising. Mycophenolate mofetil (inhibits lymphocyte proliferation) [48], intramuscular beta-interferon (potent inhibitors of T-cell proliferation) [49] and rituximab [50] have failed to demonstrate any convincing benefit in adult CIDP. There is insufficient evidence to offer any recommendations regarding the use of these agents in childhood CIDP.

Given the low prevalence of childhood CIDP, multi-centre clinical trials will be required to evaluate immunosuppressant drugs in order to sufficiently power clinical studies and evaluate the efficacy of various agents at inducing remission and improving long-term functional outcome.

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