Available online at www.sciencedirect.com

ScienceDirect

Neuromuscular Disorders 29 (2019) 684–692

www.elsevier.com/locate/nmd

Chronic inflammatory demyelinating polyneuropathy: Plasmapheresis or cyclosporine can be good treatment options in refractory cases

WooJoong Kim[a], Young Kyu Shim[a], Sun Ah Choi[c], Soo Yeon Kim[a], Hunmin Kim[c], Byung Chan Lim[a], Hee Hwang[c], Jieun Choi[b], Ki Joong Kim[a], Jong-Hee Chae[a,*]

[a] *Department of Pediatrics, Seoul National University College of Medicine, Pediatric Clinical Neuroscience Center, Seoul National University Children's Hospital, Seoul, Republic of Korea*

[b] *Department of Pediatrics, SMG-SNU Boramae Hospital, Seoul, Republic of Korea*

[c] *Department of Pediatrics, Seoul National University Bundang Hospital, Seoul, Republic of Korea*

Received 31 March 2019; received in revised form 13 June 2019; accepted 16 June 2019

Abstract

Childhood chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is a rare condition, and the optimal treatment strategy is not well established, especially in refractory cases. We analyzed the clinical features and treatment outcomes of 14 cases of childhood CIDP with more than 12 months of follow-up. Of the 14 cases, 10 cases were considered refractory to the conventional first-line treatment. In the monophasic group ($n=6$), plasmapheresis resulted in a better treatment response than did IVIG. Monophasic refractory cases ($n=4$) were especially responsive to plasmapheresis. In the polyphasic group ($n=8$), IVIG and plasmapheresis had comparable effects. Among them six polyphasic patients were refractory to the first-line treatment options and received additional immunosuppressants. Four treatment-refractory polyphasic patients received cyclosporine and achieved successful disease control. With regard to the long-term outcomes, six patients showed minimal symptoms and no relapse within 6 months. Our results suggest that early administration of plasmapheresis in a monophasic course and cyclosporine in a polyphasic course may be effective treatment options for refractory childhood CIDP.

Keywords: Childhood CIDP; Refractory CIDP; Treatment outcome; Plasmapheresis; Cyclosporine.

1. Introduction

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is an acquired immune-mediated disease of the peripheral nervous system. CIDP is traditionally described as progressive symmetric weakness of all limbs over the course of at least 8 weeks [1]. It is observed in patients of all ages but is much rarer in pediatric patients, with a prevalence of less than 0.5 per 100,000 [2,3]. CIDP is a clinical diagnosis, and there are many proposed diagnostic criteria [4]. Thus, CIDP can be seen as a group of heterogeneous polyneuropathies with a spectrum of clinical findings and numerous variants [5]. Childhood CIDP has several distinct clinical characteristics from adult CIDP, which have led to the establishment of separate diagnostic criteria at the 88th European Neuromuscular Center (ENMC) International Workshop [6]. Due to the rarity of childhood CIDP, the clinical findings and management outcomes are often conflicting between studies [7–11]. To date, there is no consensus regarding the optimal treatment of childhood CIDP. Corticosteroids, plasmapheresis and intravenous immunoglobulin are generally accepted as first-line therapies, but solid evidence supporting one treatment over the others is lacking [7,10]. There are even fewer studies to help clinicians treat refractory CIDP when the first-line treatments fail. This retrospective study aimed to analyze the treatment responses of childhood CIDP treated at a single tertiary center to propose an effective treatment strategy, with an emphasis on refractory cases. This is an extension of the previous case series report with an increased cohort size and longer follow-up period [12].

* Corresponding author.
E-mail address: chaeped1@snu.ac.kr (J.-H. Chae).

https://doi.org/10.1016/j.nmd.2019.06.010
0960-8966/

2. Patients and methods

2.1. Patient enrollment

Children with CIDP who were diagnosed and treated at Seoul National University Children's Hospital from 2004 to 2017 were enrolled in this study. The inclusion criteria for patient enrollment were (1) onset age ≤ 18.0 years, (2) a diagnosis of confirmed or probable CIDP according to the diagnostic criteria proposed by the ENMC [6] and (3) a minimum follow-up of 12 months. The exclusion criteria were patients with other underlying medical conditions and patients with suspected hereditary neuropathy.

2.2. Clinical data collection

The enrolled patients' medical records were retrospectively reviewed. Each patient's clinical course was classified as either monophasic or polyphasic [10,13]. A patient was classified as having a monophasic clinical course when a single episode of deterioration followed by sustained improvement was observed, and a patient was classified as having a polyphasic (relapse-remitting) clinical course when two separate episodes of relapse were observed, and each relapse was separated by at least one episode of sustained improvement. Sustained improvement was defined as a decrease of one or more in the Rankin score that was maintained for at least 1 month. The mode of onset was classified as subacute (less than 8 weeks) or chronic (more than 8 weeks).

Electrophysiological studies were performed in all patients at the time of diagnosis as described in previous case series [12]. Either the bilateral or unilateral side of the median, ulnar, common peroneal and tibial nerves for the motor nerve and the median, ulnar, superficial peroneal and sural nerves for the sensory nerve were tested for distal latency, conduction velocity and amplitude. The F-wave was measured at either bilateral or unilateral motor nerves, including the ulnar nerve at the abductor digiti minimi, the median nerve at the abductor pollicis brevis, and the tibial nerve at the abductor hallucis muscle. Cerebrospinal fluid (CSF) examination results and spinal MRI results were collected when available. An elevated CSF protein level was defined as being above 35 mg/dL [6,14].

The functional status of the patient was determined from the clinical reports and scored according to the modified Rankin Scale (MRS) [15]. The MRS categorizes the functional status as follows: 0: asymptomatic; 1: minimal symptoms that are not disabling and do not interfere with the patient's lifestyle; 2: minor disability symptoms causing some restriction of the patient's lifestyle but not impairing the patient's autonomy; 3: moderately disabling symptoms that significantly interfere with the patient's lifestyle or prevent a totally independent existence; 4: moderately disabling symptoms that clearly prevent an independent existence but without the need for constant attention; 5: severely disabling symptoms that require constant attention day and night; and 6: dead.

Each patient's clinical response to treatment was classified in one of three categories as previously described [12]. A good response was defined as an improvement in the MRS score of at least 2 points, and no additional treatment or change in treatment was necessary; a partial response was defined as an improvement in the MRS score of at least 1 point, but a change or addition of treatment was necessary; and no response was defined as no change or a worsening of the MRS score. Patients were considered to be refractory to treatment if they did not respond to at least two treatment modalities among the first-line treatments (IVIG, IV steroids or plasmapheresis) for at least 3 months.

The long-term treatment outcomes were grouped into 3 categories. Complete remission was defined as patients with minimal to no functional impairment (MRS 0 to 1) who had been off treatment for a minimum of 6 months; partial remission was defined as patients maintaining some degree of functional recovery (MRS 2 to 3) and/or who required regular treatment within the past 6 months to maintain function; and no response was defined as patients with significant functional disability (MRS 4 to 5) and/or no improvement despite treatment. The treatment effect of cyclosporine was determined by comparing the IVIG treatment requirements and the number of relapse events before and after the initiation of cyclosporine.

2.3. Treatment protocol

The treatment protocol was described in the previous case series [12]. The initial first-line treatment after the diagnosis of CIDP was either IVIG or IV steroids. The choice of which initial treatment was used was made by the physicians who treated the patient for the first time. IVIG was administered at 2 g/kg per cycle over 2 to 5 consecutive days. IV methylprednisolone was administered at 30 mg/kg/day (maximum dose of 1 g per day) for 3 days followed by oral prednisolone administered at 1–2 mg/kg/day (maximum of 60 mg per day) for a minimum duration of 4 weeks. When either IVIG or IV steroids were ineffective, plasmapheresis was initiated. When patients were still unresponsive to the above treatments, an additional immunosuppressant (either azathioprine or cyclosporine) was added. Patients needing plasmapheresis were admitted during the course of treatment. A central dual-lumen catheter was inserted with ultrasound guidance into the internal jugular vein for the treatment. Replacement fluid was either 5% albumin or fresh frozen plasma depending on the coagulation profiles determined before plasmapheresis. Plasmapheresis performed 7 times over 2 weeks was considered one treatment cycle. Azathioprine was administered at 2 mg/kg/day. Azathioprine treatment was continued for at least 6 months before determining the treatment efficacy.

Cyclosporine was administered at 3–5 mg/kg/day. Cyclosporine was started with an initial test dosage of 1 mg/kg/day that was gradually increased to 5 mg/kg/day

over a 2-month period. The dose was decreased to a maintenance dose of 4 mg/kg once there was some sign of clinical improvement, such as the prolongation of the relapse interval. The maintenance dosage was adjusted according to the clinical response, side effects and serum trough level. The target trough level was set between 50 ng/mL and 100 ng/mL.

2.4. Statistical analysis

Due to the small sample size, nonparametric tests were applied. Factors that may have affected the treatment outcome were analyzed. Continuous variables such as the age at disease onset, time from symptom onset to initial treatment and time from symptom onset to treatment for CIDP (defined as the addition of an additional treatment other than the initial treatment) were compared between the complete remission group and the partial remission group with the Mann-Whitney U test. Categorical variables such as disease course (monophasic or polyphasic) and onset mode (subacute or chronic) were compared between the complete remission group and the partial remission group with Fisher's exact test. The differences were considered statistically significant when the p value was below 0.05. SPSS version 21.0 was used for the statistical analyses.

3. Results

3.1. Clinical features

Fourteen patients (6 male and 8 female) met the inclusion criteria and did not meet the exclusion criteria (Table 1 and Table 2). One male patient out of the ten patients from the previously reported case series was excluded from this extension study due to the presence of other autoimmune diseases, including ulcerative colitis and ankylosing spondylosis, which resulted in the use of other various immune therapies. Five newly diagnosed patients were also enrolled in this follow-up extension study.

The mean age at disease onset was 8.6 ± 3.8 years (range 3–15 years). Ten patients (71.4%) had a subacute onset of symptoms and were initially treated under the diagnosis of Guillain–Barré syndrome (GBS). Antecedent upper respiratory infections occurred in 6 out of the 14 patients (42.9%). The time between the antecedent infection and the onset of symptoms ranged from 1 week to 2 months, with the most common interval being approximately 1 month.

The mean time between onset of symptom to maximal disability was 31.7 ± 36.8 days (range 1–120 days). Nine patients (64.3%) were initially treated in other centers before they were transferred to this center for further management. All patients had lower extremity weakness at presentation. Nine patients (64.3%) showed coexisting upper extremity weakness, and eleven patients (78.6%) reported having sensory changes. Two patients reported cranial nerve involvement (14.3%), presenting as dysarthria or facial paralysis. Two patients described symptoms of autonomic dysfunction (14.3%), such as nausea, vomiting and difficulty urinating. The mean peak MRS score was 4.1 ± 0.7 (range 3 to 5). Eight patients subsequently progressed to a polyphasic course (57.1%), while six patients followed a monophasic course (42.9%). The mean number of relapse events among polyphasic patients was 9.1 ± 8.4 (range 2 to 28). The disease phase that required treatment for monophasic patients ranged between 9 months to 4 years.

Table 1
Summary of clinical characteristics of the patients.

	Number of patients (%) ($n = 14$)	Range
Demographics		
Male: Female	6 (42.9%): 8 (57.1%)	
Mean age of onset	8.6 ± 3.8 years	3–15 years
Mean duration of follow up	47.7 ± 29.6 months	12–99 months
Presentation		
Infection history	6 (42.9%)	
Subacute onset	10 (71.4%)	
Mean duration from symptom onset to treatment	31.7 ± 36.8 days	1 – 120days
Elevated CSF protein	11 (78.6%)	
Mean CSF protein	86.1 ± 70.7 mg/dL	25–283 mg/dL
MRI nerve root enhancement	10 (71.4%)	
Neurological Symptoms		
Motor weakness	14 (100%)	
Sensory	11 (78.6%)	
Cranial nerve	2 (14.3%)	
Autonomic	2 (14.3%)	
Course		
Monophasic	6 (42.9%)	
Polyphasic	8 (57.1%)	
Mean number of relapses	9.1 ± 8.4	2–28
Mean maximum MRS	4.1 ± 0.7	3–5
Mean follow up MRS	0.9 ± 0.7	0–2
Treatment		
IVIG	14 (100%)	1–25 cycles
Plasmapheresis	9 (64.3%)	1–10 cycles
Steroids	10 (71.4%)	
Immunosuppressant	7 (50%)	

IVIG, Intravenous immunoglobulin; MRS, Modified Rankin Scale.

Among the fourteen patients, thirteen met the ENMC electrophysiologic criteria [6] for the diagnosis of CIDP (Table 3). One patient who did not meet the ENMC electrophysiologic criteria showed a predominant abnormal pattern in sensory nerve conduction, elevated CSF protein level and prominent lower limb weakness on a neurologic exam. All other patients showed increased distal latency and decreased conduction velocity, amplitude in the motor nerves. Conduction block was observed in 10 patients (71.4%) and temporal dispersion was observed in 6 patients (42.8%). CSF analysis was performed in all subjects, eleven (78.6%) of whom had elevated protein levels (mean: 86.1 ± 70.7 mg/dL, range 25–283 mg/dL, normal range < 35 mg/dL). Spinal MRI was performed in all patients, ten (71.4%) of whom showed lumbosacral nerve root enhancement.

3.2. Therapeutic response

The initial treatments were not standardized because the patients were managed in different centers. Eleven patients

Table 2
Clinical data of individual patients.

Patient/Dx	Sex/Onset age (yr)	Course/Relapse events	Max/Last MRS	1st line Tx	2nd line Tx	Follow up (mon)	CSF (mg/dl)	MRI II	NCS sensory/motor
1/2013	F/5	P/28	5/2	IVIG, PE, mPD	AZT CsA	47	98	(+)	S+M
2/2012	M/7	M/1	5/1	IVIG, PE		43	84	(+)	S+M
3/2012	F/3	P/13	3/1	IVIG, PE, mPD	CsA	59	40	(-)	S+M
4/2010	M/15	M/1	4/2	IVIG, PE, mPD		82	285	(+)	S+M
5/2010	F/7	M/1	5/2	IVIG, PE, mPD		81	30	(+)	M
6/2010	F/9	P/10	3/1	IVIG,PE mPD	AZT, CsA	85	61	(-)	S+M
7/2009	F/9	P/9	4/0	IVIG, PE, mPD	AZT	99	25	(-)	S+M
8/2014	M/8	P/2	4/1	IVIG		32	71	(+)	S+M
9/2004	F/12	M/1	5/0	IVIG, PE, mPD		26	30	(+)	S+M
10/2015	M/9	P/2	4/1	IVIG		12	76	(+)	S+M
11/2016	M/15	P/5	4/0	IVIG	AZT	21	39	(-)	S+M
12/2016	F/7	M/0	4/1	IVIG, m PD	AZT	17	185	(+)	S
13/2016	M/12	M/0	4/1	IVIG, PE, mPD		12	114	(+)	S+M
14/2013	F/3	P/4	4/0	IVIG, mPD	CsA	52	69	(+)	S+M

Dx: year diagnosed.
MRS: modified Rankin Scale.
Tx: treatment.
M: monophasic.
P: polyphasic.
IVIG, Intravenous immunoglobulin.
PE: plasmapheresis.
mPD: methylprednisolone.
AZT: azathioprine.
CsA: cyclosporine.
NCS, Nerve Conduction Studies.
S, Sensory.
M, Motor;.
D, Demyelinating neuropathy;.
A, Axonal neuropathy.

Table 3
Summary of NCS findings.

Case	Initial onset to test date	Prolonged DL	Slowed CV	Low Amp	F- wave	CB	TD	Abnormal Sensory NCS
1	1 week	(+) UE LE	(+)	(+)	(-)	(+)	No	(+)
2	1 month	(+) UE LE	(+)	(+)	(-)	(+)	(+)	(+)
3	1 month	(+) LE only	(+)	(+) LE	(-)	(+)	(+)	(+)
4	1 week	(+) UE LE	(+)	(+)	(-)	No	No	(+)
5	1 month	(+) UE LE	(+)	(+)	(-)	No	No	No
6	3 months	(+) UE LE	(+)	Normal	Normal	No	(+)	(+)
7	3 months	(+) UE LE	(+)	(+)	Normal	(+)	No	(+)
8	2 weeks	(+) UE LE	(+)	(+)	(-)	(+)	No	(+)
9	2 months	(+) LE only	(+)	(+) LE	(-)	(+)	(+)	(+)
10	1 week	(+) UE LE	(+)	(+)	(-)	(+)	No	(+)
11	3 months	(+) UE LE	(+)	(+)	(-)	(+)	(+)	(+)
12	1 week	(+) UE LE	Normal	Normal	(-)	No	No	(+)
13	4 months	(+) LE only	(+)	(+) LE	(-)	(+)	(+)	(+)
14	2years	(+) UE LE	(+)	(+)	(-)	(+)	No	(+)

DL, Distal Latency; CV, Conduction Velocity; Amp, Amplitude; CB, Conduction Block; TD, Temporal dispersion; NCS, Nerve Conduction Studies; UE, Upper extremity LE, Low Extremity.

(78.6%) received IVIG, and 3 patients (21.4%) received IV steroids. During the course of the disease, IVIG was used at least once in all patients, including IV steroids in 10 patients and plasmapheresis in 9 patients. Patients received averages of 8.6±7.5 cycles (range 1–25 cycles) of IVIG and 3.4±3.0 cycles (range 1–10 cycles) of plasmapheresis.

In the monophasic group, plasmapheresis resulted in a better treatment response (good 80%, partial 20%) than did IVIG (good 0%, partial 50%, none 50%) and steroids (good 0%, partial 40%, none 60%) (Table 4). Four patients (4/6, 66%) in the monophasic group were considered refractory to the first-line therapy due to their lack of improvement

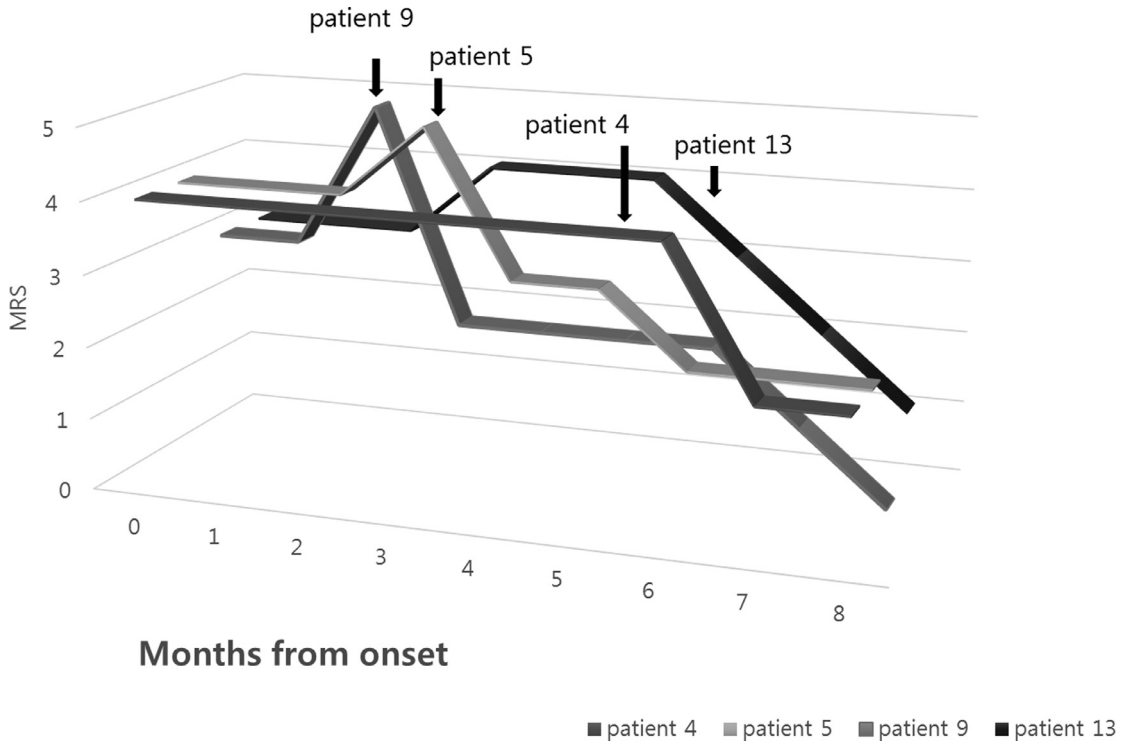

Fig. 1. Effect of plasmapheresis in severe monophasic course CIDP: Each line represents individual monophasic patients. Arrow depicts the point of initiation of plasmapheresis. Change of MRS score is plotted according to time.

Table 4
Treatment response to first line treatments.

Disease course	Treatment	Good response	Partial response	No response
Monophasic ($n=6$)	Steroid ($n=5$)	0/5 (0%)	2/5 (40%)	3/5 (60%)
	IVIG ($n=6$)	0/6 (0%)	3/6 (50%)	3/6 (50%)
	PE ($n=5$)	4/5 (80%)	1/5 (20%)	0/5 (0%)
Polyphasic ($n=8$)	Steroid ($n=5$)	0/5 (0%)	2/5 (40%)	3/5 (60%)
	IVIG ($n=8$)	2/8 (25%)	6/8(75%)	0/8 (0%)
	PE ($n=4$)	0/4 (0%)	4/4 (100%)	0/4 (0%)

in terms of the MRS score. The MRS score improved significantly only after initiating plasmapheresis in four treatment-refractory monophasic patients (Fig. 1). Patient 2 had relatively mild symptoms and improved after IVIG treatment, and patient 12 improved after steroids.

In the polyphasic group, IVIG (good 25% partial 75%, none 0%) and plasmapheresis (good 0%, partial 100%, none 0%) resulted in comparable treatment responses that were both better than the response to steroids (good 0%, partial 40%, none 60%) (Table 4). Six patients (6/8, 75%) in the polyphasic group were considered refractory to first-line therapy due to frequent relapses. These patients were started on additional immunosuppressants. Four patients (patient no. 1, 6, 7 and 11) were initially administered additional azathioprine. Patient 7 achieved complete remission through a combination of steroids and azathioprine, and patient 11 also achieved partial remission. However, patient 1 and patient 6 were switched to cyclosporine due to a lack of treatment response. Patients 3 and 14 were started on additional cyclosporine from beginning without trying azathioprine.

All patients who received cyclosporine (patients 1, 3, 6, 14) achieved significant disease control (Table 5). The mean number of IVIG treatments per year decreased from 6.2 ± 3.2 cycles per year (range 2.9 to 9) to 0.5 ± 2.0 cycles per year (range 0 to 4.5). The relapse rate decreased from 5.5 ± 4.4 times per year (range 2.7 to 12) to 1.7 ± 1.7 times per year (range 0.2 to 4) after adding cyclosporine.

There were few adverse events related to the treatment. Two patients treated with IVIG complained of headache and received mannitol during emergency department stay under the impression of aseptic meningitis. There were no significant side effects related to plasmapheresis other than minor pain and discomfort. In the group treated with cyclosporine, two patients had adverse events. One patient complained of hirsutism, and another had to stop cyclosporine temporarily due to abdominal discomfort but was able to continue with supportive care. Azathioprine was generally well tolerated without significant side effects.

3.3. Treatment outcome

The mean duration of follow-up was 47.7 ± 29.6 months (range 12–99 months). The mean MRS score was 0.9 ± 0.7 (range 0 to 2) at the last outpatient follow-up compared to the average MRS score of 4.1 ± 0.7 during the period of maximum functional deficit.

In the monophasic group, two patients (patients 2 and 9) achieved complete remission, and four patients (patients 4, 5, 12, and 13) achieved partial remission. Patient 4 and patient 5 were off treatment with only minimal foot drop present

Table 5
Treatment response of cyclosporine in refractory polyphasic group.

Patient No.	Period of CsA treatment (months)	Relapse free period (months)	Average IVIG cycles required before CsA (cycles/yr)	Average IVIG cycles required after CsA (cycles/yr)	Relapse rate before CsA (events/yr)	Relapse rate after CsA (events/yr)
1	27 m	4 m	9	4.5	12	4
3	39 m	14 m	9	1.5	4.6	1.8
6	36 m	23 m	3.9	0.2	2.7	0.2
8	17 m	15 m	2.9	0	2.9	0.7

CsA: cyclosporine.

at the last follow-up. Patient 13 showed a good response to plasmapheresis but was still undergoing treatment at the last follow-up.

In the polyphasic group, four patients (patients 6, 7, 8, and 10) achieved complete remission (50%), and four patients (patients 1, 3, 11, and 14) achieved partial remission (50%) after treatment. Patient 1 was administered cyclosporine, which has been shown to have a significant impact on disease course; however, the patient still has occasional relapses. Patient 3 had previously achieved remission with cyclosporine treatment but experienced relapses when cyclosporine was tapered. Patient 11 is responsive to IVIG but is currently trying azathioprine to achieve disease control. Patient 14 was able to achieve long-term remission after cyclosporine treatment but has yet to attempt tapering of the medication.

Overall, complete remission was observed in 6 patients (42.8%), and partial remission was observed in 8 patients (57.2%). Several factors were compared between the complete remission group and the partial remission group. The age at disease onset ($p=0.560$), time from symptom onset to initial treatment ($p=0.948$), time from symptom onset to treatment as CIDP ($p=0.4$), disease course (monophasic vs. polyphasic) ($p=0.627$), and onset mode (subacute vs. chronic) ($p=0.58$) were not significantly different between the two outcome groups.

4. Discussion

This retrospective study analyzed 14 children with CIDP from a single tertiary center in South Korea. The current study is an extension of a previous report with a longer follow-up duration and additional patients [12]. The cohort in the current study is unique because they represent relatively more severe cases of childhood CIDP due to our center's status as the final referral center in our country. The majority of the patients (9/14, 64.3%) were referred from other centers for further management because they failed to respond to initial treatment. Subsequent treatment response was observed in 10 patients (4 monophasic patients, 6 polyphasic patients) who were refractory to the first-line treatments.

Antecedent upper respiratory infections were common (42.9%), which was consistent with the findings of a previous case series, which reported antecedent infections in 23 to 56% of the patients [9,10,16–19]. The majority of the patients (71.4%) presented with subacute onset of symptoms, evolving in less than 2 months period. The pediatric group is already known to show subacute presentation more commonly compare to the adult group, hence the diagnostic criteria states the symptom evolution as 4 weeks [6]. Childhood CIDP is typically characterized by predominantly motor symptoms and a relative lack of sensory, cranial and autonomic symptoms [16,18–20]. Patients in the current study also presented with predominantly motor symptoms. However, sensory symptoms were present in 11 patients (78.6%). This is a higher proportion than those found in previous reports of childhood CIDP, which generally reported a range between 15–30% [16,18–20]. This may be due to the higher proportion of refractory cases in the current study cohort. Overall, polyphasic disease course seem to be more common than monophasic disease course, as revealed by a recent meta-analysis [11]. The proportion of patients experiencing a polyphasic course was also slightly higher (57%) than the proportion of patients experiencing a monophasic course in the current cohort.

CIDP does not have a definitive biologic diagnostic marker; its diagnosis is not always straightforward and can sometimes be very challenging. At least 15 sets of diagnostic criteria have been proposed for adult CIDP to date [4]. Most diagnostic sets rely on electrophysiologic data obtained from nerve conduction studies, and both overdiagnosis and diagnostic delay occur frequently in patients with CIDP [21]. The reliance of CIDP diagnosis on electrophysiologic data poses additional problems in pediatric populations due to the poor level of cooperation of the patients and lack of experience and data among clinicians [22]. It is important not to misdiagnose CIDP, as a delay in treatment administration results in permanent axonal damage [23]. Electrophysiology studies can miss CIDP either due to secondary axonal loss or in cases of the pure sensory form when motor nerve conduction is normal. Patient 12 in our cohort only initially tested positive for sensory nerve dysfunction despite having clinical motor weakness. The presentation of pediatric CIDP also frequently mimics that of GBS, confusing the diagnosis. Indeed, our cohort was frequently initially diagnosed with GBS because the disease in the majority of the patientsshowed subacute onset.

On the other hand, the reliance on electrophysiologic data also results in the overdiagnosis of CIDP. It is estimated that up to 50% of patients tested may be misdiagnosed with CIDP when they have an alternative diagnosis [21]. The diagnosis of childhood CIDP necessitates extra caution because many hereditary neuropathies or inborn errors of metabolism can

mimic CIDP [22]. The consideration of alternative diagnosis is especially important in cases refractory to conventional treatment options. Our study also excluded one patient from the previous study because of the patient was diagnosed with multiple autoimmune syndromes, including Crohn's disease, SLE and the presence of the HLA-B27 marker.

Compared to the many criteria proposed for the diagnosis of adult CIDP, the only diagnostic criteria for pediatric CIDP are those established at the 88th ENMC International Workshop. Not much is known regarding their sensitivity and specificity, but one study found the diagnostic criteria to have a sensitivity of 0.77 and specificity of 0.26 for childhood CIDP [24]. There is a need for better diagnostic methods for childhood CIDP to ensure delivery of the optimal treatment to the correct patient. Based on the findings from the current study, differentiating between monophasic disease and polyphasic disease may be of clinical importance. Differentiating between the two disease courses was relatively straightforward in the current study, as the follow-up period was generally much longer than 1 year. However, this can be much more challenging in newly diagnosed patients with short-term follow-up periods. Overall, a correct diagnosis of childhood CIDP can be difficult; patients may need to be followed for prolonged periods of time, and clinicians should exercise extra caution in both ruling out and confirming CIDP.

The optimal treatment for childhood CIDP is still under debate and has not been definitively established, and the current treatment is guided by experience gained from the treatment of adult CIDP, which includes corticosteroids, IVIG and plasmapheresis as first-line treatments [25]. In terms of treatment efficacy, all three treatments result in similar treatment responses in adult CIDP [26–28]. When available, IVIG is usually used first due to its favorable side-effect profile [29]. IVIG is even more likely to be used as the initial treatment for childhood CIDP, as children frequently present with GBS-like symptoms [17,19]. In children, corticosteroids are usually considered a second-line treatment when IVIG is not available, is ineffective or causes significant adverse events. Plasmapheresis is generally avoided due to the additional risk of central line complications [11,25]. Due to the lack of clear evidence, the choice of first-line treatment depends on many factors, such as patient age, socioeconomic settings and physician preference [29]. In line with the findings of previous studies, IVIG was the most common initial treatment in the current study. This is probably because most of the current study cohort had a subacute disease onset that imitated GBS.

When the initial treatment is not successful, which happens in about 20% of the patients, various immunosuppressive agents are used. These agents are also needed in situation where sparing of steroids or IVIG is required. The agents that were adopted include azathioprine, interferon beta-1a, cyclophosphamide, ciclosporin, methotrexate, etanercept, alemtuzumab, rituximab and the list continues to grow [30]. There is only four small randomized controlled trial using azathioprine, interferon beta-1a, methotrexate until date [31–34]. None have shown solid evidence of efficacy to date, and the evidence for use of other agents are descriptive. The evidence for immunosuppressive agents in the pediatric population is even more scarce compared to the adult population. As a result, immunomodulatory treatment guideline for the refractory pediatric cases is difficult to be established.

Interestingly, the results of our study suggest that treatment responses to individual therapies may differ depending on the type of disease progression, especially in refractory cases.

In the monophasic group, four patients (patients 4, 5, 10, and 13) were deemed refractory because neither IVIG nor steroids resulted in improvement. These patients showed an initial severe progressive course, and some patients required intubation, despite IVIG or IV steroids. However, they responded to plasmapheresis and significant improvement of functional status was achieved. Plasmapheresis necessitates relatively frequent hospital admissions and the insertion of a central lumen catheter, but it was successfully performed without any significant complications. Thus, the findings of the current study suggest that plasmapheresis could be considered early in selected monophasic patients with severe progression, in contrast to the current trend to use it later.

IVIG treatment was more effective in the polyphasic group than in the monophasic group. However, six polyphasic patients (75%) were treatment-dependent, meaning that they responded to IVIG treatment but presented with frequent relapses and required constant repetition of the IVIG treatments. These patients also did not show substantial responses when treated with steroids. Thus, polyphasic patients who still experienced relapse and required constant IVIG treatment were considered refractory to treatment.

These patients were administered with cyclosporine as an additional immunosuppressant. Cyclosporine was chosen among other immunosuppressive agents as it is a potent T-cell inhibitor, and CIDP association with dysfunctional T-cell function has long been suspected [35,36]. Thus, cyclosporine to have therapeutic effectiveness in CIDP is theoretically plausible. In addition it is easy to follow up its serum trough level, and was shown to be safe and effective in previous reports [37].

Patients achieved complete remission or at least a dramatic decrease in the reliance on IVIG after the addition of cyclosporine. Cycloporine showed promising efficacy in several adult studies, with response rates ranging from 40 – 90% [37–40]. Reports of cyclosporine use in children are much more scarce, with some studies showing positive effects and others showing a lack of significant efficacy [8,10,41–43]. Cyclosporine was often discontinued in adult CIDP patients due to nephrotoxicity or hypertension [44]. However, neither nephrotoxicity nor hypertension were observed in the current cohort, which was similar to the results of the previous pediatric study [42]. One patient had to temporarily stop cyclosporine due to abdominal pain, but the pain was dependent on the dosage and did not recur when the patient was restarted at a lower maintenance dosage (3 mg/kg/day).

Another patient had mild hirsutism which did not require specific intervention.

The mechanisms underlying the different treatment responses based on different disease progression modes need to be further elucidated. Many subtypes of CIDP have been reported, and whether they represent different underlying pathophysiologies is unknown. Indeed, different neuropathies, such as anti-MAG neuropathy and multifocal motor neuropathy (MMN), are now considered distinct entities that respond to treatment differently [45–47]. Similarly, the monophasic course and polyphasic course forms may be separate disease entities driven by currently unknown different pathophysiologies. However, the pathophysiology of CIDP needs to be better understood before addressing this question.

This study shares common limitations with most other childhood CIDP studies, including a small number of patients and uncontrolled treatment initiation. The patient numbers in previous childhood CIDP case series generally ranged between 10 and 20 patients; the largest study consisted of 31 patients [11,17]. Recently, McMillan et al. attempted to overcome this issue by performing a meta-analysis of the previously published case series. That meta-analysis demonstrated that the overall treatment responses of childhood CIDP to IVIG and corticosteroids are similar and that childhood CIDP is frequently less responsive to plasma exchange [11]. However, the study did not compare the efficacy of treatments according to the specific disease stage or course and gavelittle information about the treatment of refractory cases of childhood CIDP. Although the current study is clearly limited by the small number of patients, this is still one of the largest case series conducted in a single center, and patients received treatment according to relatively consistent standards. Most importantly, this study provides a new perspective on treatment-resistant patients, including the early administration of plasmapheresis to refractory monophasic patients and the use of cyclosporine in refractory polyphasic patients. Thus, in order to implement these treatments, early referral of refractory patients to centers experienced in plasmapheresis and immunomodulatory treatment may be important. Timely administration of appropriate treatment may prevent from missing the critical time before neuronal damage becomes irreversible. Further multinational and multicenter efforts to conduct larger randomized controlled trials with these treatments are needed to verify the observations in this study.

Acknowledgments

This research did not receive specific grants from funding agencies in the public, commercial or not-for-profit sectors.

References

[1] Dyck PJ, Lais AC, Ohta M, Bastron JA, Okazaki H, Groover RV. Chronic inflammatory polyradiculoneuropathy. Mayo Clin Proc 1975;50:621–37.

[2] Iijima M, Koike H, Hattori N, Tamakoshi A, Katsuno M, Tanaka F, et al. Prevalence and incidence rates of chronic inflammatory demyelinating polyneuropathy in the Japanese population. J Neurol Neurosurg Psychiatry 2008;79:1040–3. doi:10.1136/jnnp.2007.128132.

[3] McLeod JG, Pollard JD, Macaskill P, Mohamed A, Spring P, Khurana V. Prevalence of chronic inflammatory demyelinating polyneuropathy in New South Wales, Australia. Ann Neurol 1999;46:910–13.

[4] Breiner A, Brannagan TH. Comparison of sensitivity and specificity among 15 criteria for chronic inflammatory demyelinating polyneuropathy. Muscle Nerve 2014;50:40–6. doi:10.1002/mus.24088.

[5] Connolly AM. Chronic inflammatory demyelinating polyneuropathy in childhood. Pediatr Neurol 2001;24:177–82.

[6] Nevo Y, Topaloğlu H. 88th ENMC International Workshop: Childhood chronic inflammatory demyelinating polyneuropathy (including revised diagnostic criteria), Naarden, The Netherlands, December 810, 2000. Neuromuscul Disord. 2002;12:195–200. doi:10.1016/S0960-8966(01)00286-3.

[7] Korinthenberg R. Chronic inflammatory demyelinating polyradiculoneuropathy in children and their response to treatment. Neuropediatrics 1999;30:190–6. doi:10.1055/s-2007-973489.

[8] Nevo Y, Pestronk A, Kornberg AJ, Connolly AM, Yee WC, Iqbal I, et al. Childhood chronic inflammatory demyelinating neuropathies: clinical course and long-term follow-up. Neurology 1996;47:98–102.

[9] Rossignol E, D'Anjou G, Lapointe N, Haddad E, Vanasse M, D'Anjou G, et al. Evolution and treatment of childhood chronic inflammatory polyneuropathy. Pediatr Neurol 2007;36:88–94. doi:10.1016/j.pediatrneurol.2006.09.012.

[10] Ryan MM, Grattan-Smith PJ, Procopis PG, Morgan G, Ouvrier Ra. Childhood chronic inflammatory demyelinating polyneuropathy: clinical course and long-term outcome. Neuromuscul Disord 2000;10:398–406 doi:S0960-8966(00)00119-X [pii].

[11] McMillan HJ, Kang PB, Jones HR, Darras BT. Childhood chronic inflammatory demyelinating polyradiculoneuropathy: combined analysis of a large cohort and eleven published series. Neuromuscul Disord 2013;23:103–11. doi:10.1016/j.nmd.2012.09.008.

[12] Kim WJ, Choi S A, Kim S Y, Kim H, Lim B C, Hwang H, et al. Childhood onset chronic inflammatory demyelinating Polyneuropathy: treatment and outcome. J Korean Child Neurol Soc 2016;24:223–31.

[13] Viala K, Maisonobe T, Stojkovic T, Koutlidis R, Ayrignac X, Musset L, et al. A current view of the diagnosis, clinical variants, response to treatment and prognosis of chronic inflammatory demyelinating polyradiculoneuropathy. J Peripher Nerv Syst 2010;15:50–6. doi:10.1111/j.1529-8027.2010.00251.x.

[14] Wong M, Schlaggar BL, Buller RS, Storch GA, Landt M. Cerebrospinal fluid protein concentration in pediatric patients. Arch Pediatr Adolesc Med 2000;154:827. doi:10.1001/archpedi.154.8.827.

[15] Van Swieten JC, Koudstaal PJ, Visser MC, Schouten H, Van Gijn J. Interobserver agreement for the assessment of handicap in stroke patients. Stroke 1988. doi:10.1161/01.STR.19.5.604.

[16] Hattori N, Ichimura M, Aoki S-I, Nagamatsu M, Yasuda T, Kumazawa K, et al. Clinicopathological features of chronic inflammatory demyelinating polyradiculoneuropathy in childhood. J Neurol Sci 1998;154:66–71.

[17] Cabasson S, Tardieu M, Meunier A, Rouanet-Larriviere M-F, Boulay C, Pedespan J-M. Childhood CIDP: study of 31 patients and comparison between slow and rapid-onset groups. Brain Dev 2015;37:943–51. doi:10.1016/J.BRAINDEV.2015.04.001.

[18] Luan X, Zheng R, Chen B, Yuan Y. Childhood chronic inflammatory demyelinating polyneuropathy with nonuniform pathologic features. Pediatr Neurol 2010;43:103–9. doi:10.1016/j.pediatrneurol.2010.04.001.

[19] Harada Y, Herrmann DN, Logigian EL. Pediatric CIDP: clinical features and response to treatment. J Clin Neuromusc Dis 2017;19:57–65.

[20] Jo HY, Park M-G, Kim D-S, Nam S-O, Park K-H. Chronic inflammatory demyelinating polyradiculoneuropathy in children: characterized by subacute, predominantly motor dominant polyeuropathy with a favorable

response to the treatment. Acta Neurol Scand 2010;121:342–7. doi:10.1111/j.1600-0404.2009.01222.x.

[21] Allen JA, Lewis RA. CIDP diagnostic pitfalls and perception of treatment benefit. Neurology 2015;85:498–504. doi:10.1212/WNL.0000000000001833.

[22] Haliloğlu G, Yüksel D, Temuçin CM, Topaloğlu H. Challenges in pediatric chronic inflammatory demyelinating polyneuropathy. Neuromuscul Disord 2016;26:817–24. doi:10.1016/J.NMD.2016.09.016.

[23] Köller H, Kieseier BC, Jander S, Hartung H-P. Chronic inflammatory demyelinating polyneuropathy. N Engl J Med 2005;352:1343–56. doi:10.1056/NEJMra041347.

[24] Potulska-Chromik A, Ryniewicz B, Aragon-Gawinska K, Kabzinska D, Seroka A, Lipowska M, et al. Are electrophysiological criteria useful in distinguishing childhood demyelinating neuropathies? J Peripher Nerv Syst 2016;21:22–6. doi:10.1111/jns.12152.

[25] Sladky JT, Teasley JE. What is the best initial treatment for childhood chronic inflammatory demyelinating polyneuropathy: corticosteroids or intravenous immunoglobulin? Muscle Nerve 2008;38:1638–43. doi:10.1002/mus.21058.

[26] Hughes RA, Donofrio P, Bril V, Dalakas MC, Deng C, Hanna K, et al. Intravenous immune globulin (10% caprylate-chromatography purified) for the treatment of chronic inflammatory demyelinating polyradiculoneuropathy (ICE study): a randomised placebo-controlled trial. Lancet Neurol 2008;7:136–44. doi:10.1016/S1474-4422(07)70329-0.

[27] Nobile-Orazio E, Cocito D, Jann S, Uncini A, Beghi E, Messina P, et al. Intravenous immunoglobulin versus intravenous methylprednisolone for chronic inflammatory demyelinating polyradiculoneuropathy: a randomised controlled trial. Lancet Neurol 2012;11:493–502. doi:10.1016/S1474-4422(12)70093-5.

[28] Dyck PJ, Litchy WJ, Kratz KM, Suarez GA, Low PA, Pineda AA, et al. A plasma exchange versus immune globulin infusion trial in chronic inflammatory demyelinating polyradiculoneuropathy. Ann Neurol 1994;36:838–45. doi:10.1002/ana.410360607.

[29] Gorson KC. An update on the management of chronic inflammatory demyelinating polyneuropathy. Ther Adv Neurol Disord 2012. doi:10.1177/1756285612457215.

[30] Mahdi-Rogers M, Brassington R, Gunn AA, van Doorn PA, Hughes RA. Immunomodulatory treatment other than corticosteroids, immunoglobulin and plasma exchange for chronic inflammatory demyelinating polyradiculoneuropathy. Cochrane Database Syst Rev 2017;5:CD003280. doi:10.1002/14651858.CD003280.pub5.

[31] Dyck PJ, O'Brien P, Swanson C, Low P, Daube J. Combined azathioprine and prednisone in chronic inflammatory-demyelinating polyneuropathy. Neurology 1985;35:1173–6. doi:10.1212/wnl.35.8.1173.

[32] Hadden RD, Sharrack B, Bensa S, Soudain SE, Hughes RA. Randomized trial of interferon beta-1a in chronic inflammatory demyelinating polyradiculoneuropathy. Neurology 1999;53:57–61. doi:10.1212/wnl.53.1.57.

[33] Hughes RAC, Gorson KC, Cros D, Griffin J, Pollard J, Vallat J-M, et al. Intramuscular interferon beta-1a in chronic inflammatory demyelinating polyradiculoneuropathy. Neurology 2010;74:651–7. doi:10.1212/WNL.0b013e3181d1a862.

[34] RMC Trial Group Randomised controlled trial of methotrexate for chronic inflammatory demyelinating polyradiculoneuropathy (RMC trial): a pilot, multicentre study. Lancet Neurol 2009;8:158–64. doi:10.1016/S1474-4422(08)70299-0.

[35] Klehmet J, Goehler J, Ulm L, Kohler S, Meisel C, Meisel A, et al. Effective treatment with intravenous immunoglobulins reduces autoreactive T-cell response in patients with CIDP. J Neurol Neurosurg Psychiatry 2015;86:686–91. doi:10.1136/jnnp-2014-307708.

[36] Schneider-Hohendorf T, Schwab N, Uceyler N, Gobel K, Sommer C, Wiendl H. CD8+ T-cell immunity in chronic inflammatory demyelinating polyradiculoneuropathy. Neurology 2012;78:402–8. doi:10.1212/WNL.0b013e318245d250.

[37] Odaka M, Tatsumoto M, Susuki K, Hirata K, Yuki N. Intractable chronic inflammatory demyelinating polyneuropathy treated successfully with ciclosporin. J Neurol Neurosurg Psychiatry 2005;76:1115–20. doi:10.1136/jnnp.2003.035428.

[38] Matsuda M, Hoshi K, Gono T, Morita H, Ikeda S. Cyclosporin a in treatment of refractory patients with chronic inflammatory demyelinating polyradiculoneuropathy. J Neurol Sci 2004;224:29–35. doi:10.1016/J.JNS.2004.05.014.

[39] Barnett MH, Pollard JD, Davies L, McLeod JG. Cyclosporin a in resistant chronic inflammatory demyelinating polyradiculoneuropathy. Muscle Nerve 1998;21:454–60.

[40] Mahattanakul W, Crawford TO, Griffin JW, Goldstein JM, Cornblath DR. Treatment of chronic inflammatory demyelinating polyneuropathy with cyclosporin-A. J Neurol Neurosurg Psychiatry 1996;60:185–7.

[41] Sabatelli M, Madia F, Mignogna T, Lippi G, Quaranta L, Tonali P. Pure motor chronic inflammatory demyelinating polyneuropathy. J Neurol 2001;248:772–7. doi:10.1007/s004150170093.

[42] Visudtibhan A, Chiemchanya S, Visudhiphan P. Cyclosporine in chronic inflammatory demyelinating polyradiculoneuropathy. Pediatr Neurol 2005;33:368–72. doi:10.1016/j.pediatrneurol.2005.05.015.

[43] Rostasy KM, Diepold K, Buckard J, Brockmann K, Wilken B, Hanefeld F. Progressive muscle weakness after high-dose steroids in two children with CIDP. Pediatr Neurol 2003;29:236–8. doi:10.1016/S0887-8994(03)00222-4.

[44] Cocito D, Grimaldi S, Paolasso I, Falcone Y, Antonini G, Benedetti L, et al. Immunosuppressive treatment in refractory chronic inflammatory demyelinating polyradiculoneuropathy. A nationwide retrospective analysis. Eur J Neurol 2011;18:1417–21. doi:10.1111/j.1468-1331.2011.03495.x.

[45] Latov N, Sherman WH, Nemni R, Galassi G, Shyong JS, Penn AS, et al. Plasma-Cell dyscrasia and peripheral neuropathy with a monoclonal antibody to peripheral-nerve myelin. N Engl J Med 1980;303:618–21. doi:10.1056/NEJM198009113031105.

[46] Rowland LP, Defendini R, Sherman W, Hirano A, Olarte MR, Latov N, et al. Macroglobulinemia with peripheral neuropathy simulating motor neuron disease. Ann Neurol 1982;11:532–6. doi:10.1002/ana.410110515.

[47] Latov N. Diagnosis and treatment of chronic acquired demyelinating polyneuropathies. Nat Rev Neurol 2014;10:435–46. doi:10.1038/nrneurol.2014.117.