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Clinical characteristics and treatment outcome of childhood onset chronic inflammatory demyelinating polyneuropathy

소아 만성 염증성 탈수초성 다발성 신경병증의 임상양상 및 치료 효과

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The Department of Translational medicine

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by

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ABSTRACT

Introduction: Chronic inflammatory demyelinating polyneuropathy (CIDP) is a clinically heterogeneous group of sensory and motor peripheral neuropathy, presumed to occur due to immune related reactions. Because childhood CIDP is very rare, there are very few published studies to help clinicians in treating refractory cases. Aim of this study is to investigate the clinical features and treatment outcome of childhood CIDP.

Methods: Clinical features and treatment outcomes of 14 cases of childhood CIDP (mean age = 8.6 ± 3.8years old) followed up for more than a year (mean duration = 47.7±29.6 months)were analyzed. Patients were initially treated with either intravenous immunoglobulin (IVIG) (78.6%) or steroids (21.4%). Plasmapheresis was considered when both treatments were proven ineffective.

Results: In contrast to adult CIDP, which commonly showed insidious onset with monophasic courses, patients from this study manifested more frequently with subacute onset (n=10, 71.4%) and polyphasic course (n=8, 57.1%).

In the monophasic group (n=6, 42.9%), plasmapheresis (n=5) showed a better treatment response (good 80%, partial 20%, none 0%) compared to IVIG (n=6) (good 0%, partial 50%, none 50%) and steroids (n=5) (good 0%, partial 40%, none 60%), especially in progressive phases. In the polyphasic group (n=8), IVIG (n=8) (good 50%, partial 37.5%, none 12.5%) and plasmapheresis (n=4) (good 0%, partial 100%, none 0%) showed comparable treatment responses. Six polyphasic patients (75%) were refractory to first line treatment and received immunosuppressant; All four patients who received cyclosporine achieved significant disease control. The overall long-term outcomes were favorable, with 6 patients (42.8%) showing minimal symptoms and no relapse within 6 months.

Conclusions: This study results suggest that administration of plasmapheresis in progressive monophasic course and cyclosporine in refractory polyphasic course may be effective in childhood CIDP.

Key words: childhood CIDP; IVIG; treatment outcome; plasmapheresis; cyclosporine

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LIST OF ABBREVIATIONS

CIDP, Chronic inflammatory demyelinating polyneuropathy

GBS, Guillain–Barré syndrome

IVIG, Intravenous immunoglobulin

MRS, modified Rankin Scale

NCS, Nerve conduction study

EMG, Electromyography

AZT, Azathioprine

CsA, Cyclosporine

CSF, Cerebrospinal fluid

INTRODUCTION

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is a clinically heterogeneous group of peripheral neuropathies characterized by symmetric weakness and/or sensory deficit evolving over more than 8 weeks. CIDP is a rare disease, with a prevalence rate of 1 to 7.7 per 100,000 in adults(1). CIDP is best described as a spectrum of diseases with numerous variants and a variety of clinical presentations(2). There is no definitive biologic diagnostic marker and clinical and laboratory features show wide variety, which makes diagnosis of CIDP complicated in many cases (3, 4).

The usual clinical presentation includes symmetric proximal and distal muscle weakness, sensory loss, and decreased or absent deep tendon reflexes. Most commonly, the disease begins with paresthesia and weakness in the distal limbs as well as difficulty walking (5). Its presentation can be slowly progressive onset, but can also show subacute onset, making it difficult to distinguish from Guillain–Barré syndrome (GBS). CIDP patient can present acutely with the maximum severity of symptoms and signs reached within 4 weeks in up to 16% of patients, which is followed by a chronic

course (6, 7). The disease course can be steadily or stepwise progressive over at least 2 months often referred as being monophasic, but can also be relapsing, often referred as being polyphasic. In contrast to GBS, cranial nerves are rarely affected and respiratory or autonomic involvement is not common (8, 9).

The clinical spectrum of atypical CIDP is much wider than typical CIDP. Atypical CIDP include predominantly distal or proximal weakness, pure motor or sensory forms, and asymmetric or focal presentations. However, even if some clinical features are different from typical CIDP, atypical CIDP can be grouped under CIDP as they share the common pathogenic mechanism of inflammatory demyelination and response to immune therapy (4, 10).

There are several common diagnostic work up performed in CIDP to help the diagnosis. By definition CIDP is a primary demyelinating neuropathy, thus nerve conduction findings are mandatory for definitive diagnosis. Several variables are considered, including nerve conduction velocity slowing, distal motor latency prolongation, F wave latency prolongation or absence and partial conduction block (11, 12). Cerebrospinal fluid study shows increased protein level in most but not all patients, reports ranging 91%(13)–95%(14). MRI may demonstrate gadolinium enhancement and/or nerve root hypertrophy at the lumbosacral or cervical level(15).

Due to the heterogeneity of clinical spectrum of CIDP and lack of gold standard diagnosis, various diagnostic criteria have been proposed to accommodate the advancing understanding over last 20 years, each with different sensitivity and specificity(5, 16). The most recently proposed criteria based on an experts consensus of the European Federation of Neurological Societies and the Peripheral Nerve Society (EFNS/PNS) put emphasis on clinical and electrophysiological criteria, and suggest that the clinical definition of CIDP should include typical and atypical forms of CIDP(17). An elevated CSF protein count and demyelinating features on nerve biopsy are now considered as supportive but non-necessary criteria for diagnosis. Abnormalities of roots or plexuses on MRI and response to immunomodulatory treatment are also considered supportive criteria (18).

Childhood onset CIDP is much rarer than adult onset CIDP, with a prevalence rate of 0.15 to 0.48 per 100,000, and differs from adult onset CIDP in many important clinical aspects (19). Overall, childhood CIDP patients have a more rapid onset, greater disability at the peak of disease, and a more frequent polyphasic course, but they respond better to treatment and have a more favorable long term outcome(1). Due to its rarity, little is known about childhood CIDP, and the clinical findings and managements are often

conflicting (20-25).

Intravenous immunoglobulin, corticosteroids, and plasma exchange is considered the first line therapy in childhood CIDP (23, 26). In adult studies, approximately 60-80% of patients are able to control disease activity with conventional treatment(27). Childhood CIDP seems to respond better to treatments, but a significant proportion still becomes refractory (19). Various immunosuppressant therapies are being used in this group of patients, but the evidence of their efficacy has been controversial(28). There are very few published studies to help clinicians treat refractory cases, especially in children. This study reports retrospective analysis of treatment outcomes of childhood CIDP patients in a single tertiary center over ten years. We investigated the clinical features that distinguish childhood CIDP from adult CIDP, as well as the treatment responses and outcomes to the various therapeutic approaches according to the clinical courses.

PATIENTS AND METHODS

1. Patient enrollment

Children with a diagnosis of CIDP who were diagnosed and treated at Seoul National University Children's Hospital from 2001 to 2016 were enrolled in this study. The inclusion criteria for patient enrollment were (1) age ≤ 19.0 years old; (2) a diagnosis of probable or definite CIDP according to the European Federation of Neurological Society/Peripheral Nerve Society (EFNS/PNS) diagnostic criteria (18); (3) well documented and sufficient data of interest; and (4) a minimum follow up of at least 12 months. The EFNS/PNS diagnostic criteria mainly consist of a) progressive or relapsing motor and sensory dysfunction of more than 2 limbs of a peripheral nerve nature, developing over at least 2 months and b) electrophysiological evidence of acquired demyelination.

2. Clinical data collection

Patients' medical records were reviewed to obtain the following information: (1) gender; (2) age of symptom onset; (3) time of treatment initiation; (4) clinical features at presentation (i.e., motor, sensory, autonomic and cranial nerve); (5) disease course (i.e.,

monophasic or polyphasic); (6) number of relapses; (7) choice and response to each therapy; (8) follow up duration; and (9) treatment outcome at last follow up.

Each patient's clinical course was collected and classified as follows(19): monophasic CIDP, described as a single episode of deterioration followed by sustained improvement, or polyphasic (relapsing-remitting) CIDP, when at least two episodes of relapses were observed and were separated by at least one episode of improvement. Relapse was defined as rapid worsening, evidenced either symptomatically or by clinical examination and with or without treatment.

Electrophysiological findings at the time of CIDP diagnosis were collected in all patients. Motor and sensory nerve conduction studies (NCS) including the medial, ulnar, peroneal, tibial and sural nerves were performed. Cerebrospinal fluid (CSF) examination results, including white blood cell (WBC) count and protein level, were obtained whenever possible. Spinal MRI results were obtained whenever possible.

The functional status of the patient was determined from clinical reports according to the modified Rankin Scale (MRS)(29). The MRS was designed to reliably assess neurological deficits and has commonly been used to assess adult and childhood CIDP. MRS

scoring system for functional status is shown in table 1.

3. Treatment protocol

The first line of treatment was either IVIG or steroids when CIDP was first diagnosed. Choice of initial treatment was made by treating physician, according to clinical presentation. IVIG was considered when presentation was indistinguishable from GBS. If the patient was unresponsive to the initial treatment, another first line treatment was used or a combination of the two was tried. If both IVIG and steroids were ineffective, plasmapheresis was administered. If the patient was unresponsive to the initial treatment, another first line treatment was used or a combination of first line treatments was tried. If the patient was still refractory to these treatments, either azathioprine or cyclosporine was added. Patients were considered refractory when they showed no improvement in MRS score or required constant IVIG or plasmapheresis treatment to maintain function and presented with frequent relapses. A therapy was considered effective if the treatment produced an improvement of at least one point on the MRS.

IVIG was administered at 2 g/kg per cycle over 2 to 5 consecutive days. Methylprednisolone was given at 30 mg/kg/day for 3 days as

Table 1. Modified Rankin Scale(29)

Score	Description
0	No symptoms at all
1	No significant disability despite symptoms; able to carry out all usual duties and activities
2	Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
3	Moderate disability; requiring some help, but able to walk without assistance
4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention
6	Dead

pulse therapy and following oral prednisolone was administered at 1 mg-2 mg/kg/day for the initial 4 to 6 weeks and gradually tapered off according to the clinical response. Plasma exchange of 7 times given over 2 weeks was considered one cycle of plasmapheresis. Azathioprine was administered at 2 mg/kg/day. Azathioprine was used for at least 6 months and was then switched to second-line immunosuppressant if no improvement occurred. Cyclosporine was administered at 3-5 mg/kg/day. The cyclosporine dosage was adjusted according to the clinical response and serum trough level, with a target trough level between 60 and 100 μg/μL.

4. Outcome evaluation

Patients' clinical response to therapies was classified into 3 categories (Table 2): good response- significant clinical improvement (MRS improvement of at least 2 points) displaying minimal to no functional impairment or limitation of activities ; partial response- displaying some degree of functional improvement (MRS improvement of at least 1 point),however a change or addition of treatment was necessary; no response- either minimal functional improvement or clinical deterioration (no change or worsening of MRS score).

Table 2. Categorization of treatment response

Response	Description
Good response	significant clinical improvement (MRS improvement of at least 2 points)
Partial response	displaying some degree of functional improvement (MRS improvement of at least 1 point)
No response	either minimal functional improvement or clinical deterioration (no change or worsening of MRS score)

Long-term treatment outcomes were grouped into 3 categories based on the patient's last outpatient visit (Table 3): complete remission- patients displaying minimal to no functional impairment(MRS 0 to 1) who had been off treatment for more than 6months; partial remission- patients maintaining some degree of functional recovery (MRS 2 to 3) and/or required regular treatment within the past 6 months to maintain function; no response- patients with significant functional disability (MRS 4 to 5) and/or no improvement despite treatment. The treatment effect of cyclosporine was evaluated by comparing IVIG treatment requirements and relapse events before and after the initiation of cyclosporine.

5. Statistical Analysis

Due to the small number of sample, non-parametric tests were applied. Factors that may have effect on the treatment outcome was analyzed. Continuous variables such as age of disease onset, time from symptom onset to initial treatment, time from symptom onset to treatment as CIDP (defined as add on of additional treatment other than initial treatment) were compared between complete remission group and partial remission group using The Mann-

Table 3. Categorization of long term treatment outcome

Outcome	Description
Complete remission	patients displaying minimal to no functional impairment(MRS 0 to 1) and who had been off treatment for > 6months
Partial remission	patients maintaining some degree of functional recovery (MRS 2 to 3)and/ or required regular treatment within the past 6 months to maintain function
No response	patients with significant functional disability (MRS 4 to 5) and/or no improvement despite treatment

Whitney U test. Categorical variables such as disease course (monophasic or polyphasic) were compared between complete remission group and partial remission group using the Fisher's exact test. The differences were considered statistically significant when the p value was below 0.05. SPSS version 21.0 was used to perform the statistical analysis.

RESULTS

1. Clinical features

During the study period, a total of 14 CIDP cases (6 males and 8 female) met the inclusion criteria and were enrolled. Basic demographics are summarized in table 4. The mean age of onset was 8.6 ± 3.8 years (range 3–15 years). 10 patients (71.4%) presented with subacute symptom onset (less than 8 weeks) rather than chronic symptom onset (more than 8 weeks. The mean duration from onset of initial symptoms to the initiation of treatment was 31.7±36.8 days. 9 patients (64.3%) were transferred from other medical centers for further management.

The clinical presentation and treatment is summarized in table 5 and 6. Eight patients (57.1%) progressed to follow polyphasic course and 6 patients (42.9%) showed monophasic course. All patients had lower extremity weakness at presentation (100%). Nine patients also had upper extremity weakness (64.2%), and 11 patients reported sensory changes (78.6%). Cranial nerve involvement such as dysarthria and facial muscle weakness was observed in two patients (14.3%), and autonomic symptoms such as nausea, vomiting and urination difficulty were identified in two

Table 4. Demographic features

	Number of patients (%) (n=14)	Range
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
Mean duration from symptom onset to treatment	31.7±36.8 days	1 – 120days
Patients transferred from other center	9 (64.3%)	

Table 5. Summary of clinical characteristics of the patients

	Number of patients (%) (n=14)	Range
Presentation		
Infection history	6 (42.9%)	
Subacute onset	10 (71.4%)	
Mean duration from infection to onset (n=6)	27±18.0days	14-60days
Elevated CSF protein	10 (71.4%)	
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	9 (64.3%)	
Immunosuppressant	7 (50%)	

IVIG, Intravenous immunoglobulin; MRS, Modified Rankin Scale

Table 6. Clinical data of individual patients

Patient/ Dx*	Sex/ Onset age (yr)	Presenting symptoms	Course/ Relapse events	Max/Last MRS†	1st line Tx‡	2nd line Tx	Follow up (months)	CSF§ protein (mg/dl)	MRI ‖	Response to IVIG	Response to PD	Respons e to PE
1/2013	F/5	Weakness LL¶>UL**	P††/18	5/2	IVIG‡‡, PE§§, PD†††	AZT ‖‖, CsA¶¶	47	98	(+)§§§	Partial	None	Partial
2/2012	M/7	Weakness LL>UL	M***	5/1	IVIG, PE		43	84	(+)	Partial	N/A ‡‡‡	Partial
3/2012	F/3	Weakness LL>UL	P/9	3/1	IVIG, PE, PD	CsA	59	40	(-) ‖‖‖	Partial	None	Partial
4/2010	M/15	Weakness LL>UL , Dysarthria, Paresthesia	M	4/2	IVIG, PE, PD		82	285	(+)	None	None	Good
5/2010	F/7	Weakness LL, nausea	M	5/2	IVIG, PE, PD		81	30	(+)	Partial	None	Partial
6/2010	F/9	Weakness LL	P/10	3/0	IVIG,PE	AZT, CsA	85	61	(-)	Partial	N/A	Partial
7/2009	F/9	Weakness LL Paresthesia	P/9	4/0	IVIG, PE, PD	AZT	99	25	(-)	None	Partial	Partial
8/2014	M/8	Weakness LL>UL, Dysarthria	P/2	4/0	IVIG		32	71	(+)	Good	N/A	N/A

9/2004	F/12	Weakness LL, Paresthesia		M	5/0	IVIG, PE ,PD		26	30	(+)	Partial	None	Good
10/2015	M/9	Weakness LL		P/2	4/1	IVIG		12	76	(+)	Good	N/A	N/A
11/2016	M/15	Weakness LL>UL Paresthesia		P/5	4/0	IVIG	AZT	21	39	(-)	Good	N/A	N/A
12/2016	F/7	Weakness LL>UL Paresthesia		M	4/1	IVIG, PD	AZT	17	185	(+)	None	Partial	N/A
13/2016	M/12	Weakness LL>UL		M	4/1	IVIG,PE,PD		12	114	(+)	None	Partial	Good
14/2013	F/3	Weakness LL>UL		P/4	4/0	IVIG,PD	CsA	52	69	(+)	Good	None	N/A

*Dx: Year diagnosed, †MRS: modified Rankin Scale, ‡Tx: Treatment, §CSF: Cerebrospinal fluid, ‖MRI: Magnetic Resonance Imaging, ¶LL: lower limb, **UL: upper limb, †† P: polyphasic, ‡‡ IVIG: intravenous immunoglobulin, §§ PE: plasmapheresis, ‖‖AZT: azathioprine, ¶¶ CsA: cyclosporine, ***M: monophasic, †††PD: prednisolone, ‡‡‡ N/A: not available

patients (14.3%). The highest level of disability as estimated by the modified Rankin scale using the data collected from medical charts varied between 3 and 5 with mean score of 4.1±0.7.

NCS are mandatory for CIDP diagnosis and were performed in all patients and the results are summarized with EMG (electromyography) results in table 7. All patients showed abnormal motor conduction pattern in both lower limb and upper limb, and 13 patients (92.8%) showed abnormal conduction pattern in sensory nerves. 1 patient showed predominant sensory change in both clinical presentation and electrophysiological features. All patients showed features of demyelination and three patients also showed features of axonal damage. 1 patient showed predominant feature of axonal damage. No clear asymmetry between left or right side or upper limbs and lower limbs was seen.

Regarding other investigations, all patients received a CSF exam, and 10 patients (71.4%) showed increased CSF protein levels (normal range <40 mg/dL), with an average of 86.1 ±70.7 mg/dL (range 25−283 mg/dL). All patients had MRI performed, and 10 patients (71.4 %) showed root enhancement. The disease course was monophasic in 6 patients (42.9%), and polyphasic course was observed in 8 patients (57.1%), with a mean number of relapse events of 9.1± 8.4 (range 2 to 28).

Table 7. Nerve conduction study result of individual patients

Case/age of exam	Nerve	Motor NCS				Sensory NCS		EMG	Demyelinating /Axonal
		DL(ms)	Vel(m/s)	Amp(mV)	F-wave(ms)	PL(ms)	Amp(μV)	SA/IP (muscles)	
1/5y	median	6.45	26	1.8	NR	3.8	5.8	Normal/Normal (TA, GCM)	D
	ulnar	2.9	33.3	5.5	NR	3.05	8.6		
	peroneal	6.95	27.4	1.1					
	tibial	8.45	23.7	3.4	NR				
	S. peroneal					4.4	6.9		
	Sural					2.95	29.6		
2/7y	median	9.8	23	1.5	NR	NR	NR	Positive/Reduced (TA, VM)	D
	ulnar	6.7	22	1.3	NR	NR	NR		
	peroneal			1.3	NR				
	tibial				NR				
	S. peroneal					4.5	6		
	Sural					NR	NR		
3/3y	median	4.8	18.3	4.35	NR	3.3	7.3	Normal/Reduced (FDI, BB, TA)	D
	ulnar	3.2	18.9	6.64	NR	2.9	9.1		
	peroneal	5.8	12.6	1	NR				
	tibial	6.8	13.9	3.22	66				
	S. peroneal					2.5	5.5		
	Sural					2.7	8.9		

4/5y	median	36.9	29.4	0.71	NR	NR	NR	Positive/Reduced (FDI, FCR, BB)	D+A
	ulnar	30.1	13.3	2.27	NR	NR	NR		
	peroneal	34.5	34	0.8	NR				
	tibial	16	46	0.55	NR				
	S. peroneal					4.5	NR		
	Sural					4.3	NR		
5/8y	median	NR	NR	NR	NR	3.2	27.1	Positive/Reduced (FDI, TA, GCM)	D+A
	ulnar	NR	NR	NR	NR	2.9	18		
	peroneal	NR	NR	NR	NR				
	tibial	NR	NR	NR	NR				
	S. peroneal					1.1	19.5		
	Sural					2.4	19		
6/9y	median	14.4	20	5.5	30.9	3.4	14.6	Normal/Reduced (FCR,BB,TA, GCM)	D
	ulnar	9.8	22	7.4	41.6	3.1	14.7		
	peroneal	12.2	38	3.8	64.4				
	tibial	16.5	32	6.8	64.2				
	S. peroneal					9.6	4.9		
	Sural					2.2	45.2		
7/9y	median	16.55	22.3	2.6	51.03	NR	NR	Normal/Reduced (FCR, TA)	D
	ulnar	11.6	26.4	2.8		NR	NR		
	peroneal	16.6	51	1.4					

	tibial	17.1	34.6	1.9	80.42				
	S. peroneal					NR	NR		
	Sural					NR	NR		
8/8y	median	35.6	35.3	1.7	NR	NR	NR	Positive/Reduced (FDI, TA)	D
	ulnar	16.6	35.3	1.5		NR	NR		
	peroneal	8.35	15.6	0.4					
	tibial	NR	NR	NR	NR				
	S. peroneal					NR	NR		
	Sural					NR	NR		
9/12y	median	4.65	37.2	6	NR	NR	NR	Positive/Reduced (FDI, FCR, BB, TA)	D
	ulnar	6.4	43.6	6.3	NR	NR	NR		
	peroneal	10.9	20.4	1.2	NR				
	tibial	14.95	20	1.1	NR				
	S. peroneal					NR	NR		
	Sural					NR	NR		
10/8y	median	29.11	29.7	2	NR	6.15	2.3	Positive/Reduced (FCR, TA)	D
	ulnar	15.73	34.9	1.5	NR	10.16	5.3		
	peroneal	NR	NR	NR					
	tibial	NR	31.2	0.7	NR				
	S. peroneal					7.6	6.9		
	Sural					5.16	8.6		

11/14y	median	32.5	19.7	2.5	71.5	5.63	2.2	Normal/Reduced (FDI,FCR,BB, TA, GCM, VM)	D
	ulnar	47.29	31.2	1.7	NR	4.64	3.7		
	peroneal	NR	NR	NR					
	tibial	51.04	14.1	0.2	NR				
	S. peroneal					3.7	4.9		
	Sural					NR	NR		
12/8y	median	2.24	54.4	9.9	normal	2.6	37.5	Positive/Reduced (FDI,FCR,BB, TA, GCM, VM)	D+A (A>D)
	ulnar	2.5	60.9	10.4	normal	2.3	21.6		
	peroneal	3.23	42.3	3.8	NR				
	tibial	3.8	43.6	15.5	normal				
	S. peroneal					2.6	10.2		
	Sural					4.43	11.6		
13/14y	median	4.5	17.1	7	59.4	5.7	5.6	Positive/Reduced (FDI,BB,TA, GCM, VM)	D
	ulnar	3.5	21.9	4	56.7	7.14	17.2		
	peroneal	5.4	19.8	1.1	54.2				
	tibial	6.77	10.8	0.4	NR				
	S. peroneal					NR	NR		
	Sural					NR	NR		
14/5y	median	NR	NR	NR		NR	NR	Normal/Reduced (FDI,FCR,BB, TA, GCM, VM)	D
	ulnar	NR	NR	0.8	NR	NR	NR		
	peroneal	NR	NR	0.2					

	tibial	NR	NR	NR					
	S. peroneal					NR	NR		
	Sural					NR	NR		

NCS, Nerve Conduction Studies; DL, Distal Latency; Amp, Amplitude; PL, Peak Latency; S. peroneal, Superficial peroneal; Blank, no data; NR, No Response; EMG, Electromyography; SA, Spontaneous Activity: IP, Interference Pattern; FDI, First Digit Interosseous; FCR, Flexor Carpi Radialis; BB, Biceps Brevis; TA, Tibialis Anterior; GCM, Gastrocnemius; VM, Vastus Medialis; D, Demyelinating neuropathy; A, Axonal neuropathy (reference values: Motor DL <4.5ms, CV >48m/sec, Amp >5mV; Sensory PL<4.0ms, Amp upper limb 20 μV, Amp lower limb 6 μV)

2. Therapeutic response and progression

For the initial treatment, 11 patients received IVIG (78.6%) and 3 patients received steroids (21.4%). IVIG was often used initially because the initial presentation was frequently indistinguishable from GBS. IVIG treatment was administered in all patients (100%) at some point during the follow up. Either IV pulse steroid or oral steroid was administered in 9 patients (64.3%). Plasmapheresis was used in 9 patients (64.3%). Patients received an average of 8.6 ± 7.5 cycles (range 1−25 cycles) of IVIG and 3.4 ± 3.0 cycles (range 1−10 cycles) of plasmapheresis.

The overall treatment responses to first line treatment are as summarized in table 8. IVIG (n=14) showed good response in 28.5% (n=4), partial response in 42.9% (n=6) and no response in 28.5% (n=4) of the patients. Steroid (n=10) showed good response in 0%, partial response in 40% (n=4) and no response in 60% (n=6) of the patients. Plasmapheresis (n=9) showed good response in 44.4% (n=4), partial response in 55.6% (n=5) and no response in 0% of the patients.

In the monophasic group (n=6), plasmapheresis (n=5) showed a better treatment response (good 80%, partial 20%, none 0%) compared to IVIG (n=6) (good 0%, partial 50%, none 50%) and

Table 8. 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)	4/8 (50%)	3/8(37.5%)	1/8 (12.5%)
	PE (n=4)	0/4 (0%)	4/4 (100%)	0/4 (0%)

steroids (n=5) (good 0%, partial 40%, none 60%), especially in progressive phases. In the polyphasic group (n=8), IVIG (n=8) (good 50%, partial 37.5%, none 12.5%) and plasmapheresis (n=4) (good 0%, partial 100%, none 0%) showed comparable treatment responses, whereas steroids (n=5) showed slightly lower efficacy (good 0%, partial 40%, none 60%). Steroids showed a relatively lower response rate compared to IVIG and plasmapheresis.

The chronological changes in MRS scores before and after plasmapheresis in monophasic patients are shown in figure 1. Patient 2, who also had a monophasic disease course, suffered from relatively milder symptoms and showed a similar response to both IVIG and plasmapheresis, and was excluded from the graph.

A total of six patients in the polyphasic group (75%) who were considered refractory to conventional first line therapy received additional immunosuppressant therapy. Of these patients, four (patients 1, 6, 7 and 11) received azathioprine as the initial immunosuppressant and two (patients 3, 14) used cyclosporine as the initial immunosuppressant.

In the patient group who initially was put on azathioprine, patient 1 and patient 6 subsequently switched from azathioprine to cyclosporine due to ineffectiveness. Patient 7 achieved remission with combination of steroids and azathioprine. Patient 11 is still

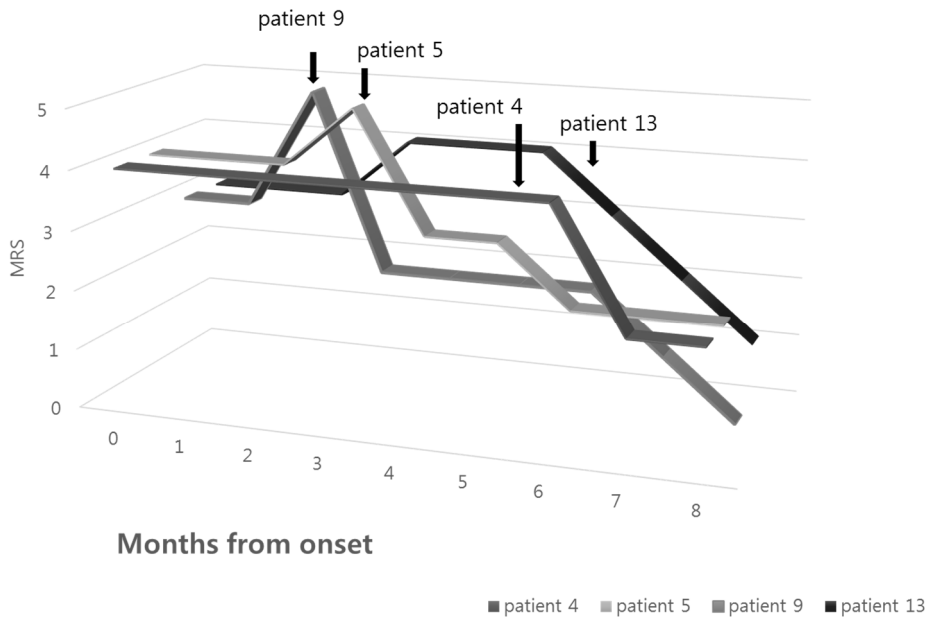


Figure 1. Effect of plasmapheresis in severe monophasic course.

Y-axis is MRS score and X-axis is number of months past symptom onset. Arrow indicates the point of plasmapheresis. Patients were not improving in their neurological status despite repeated IVIG treatment until plasmapheresis was done.

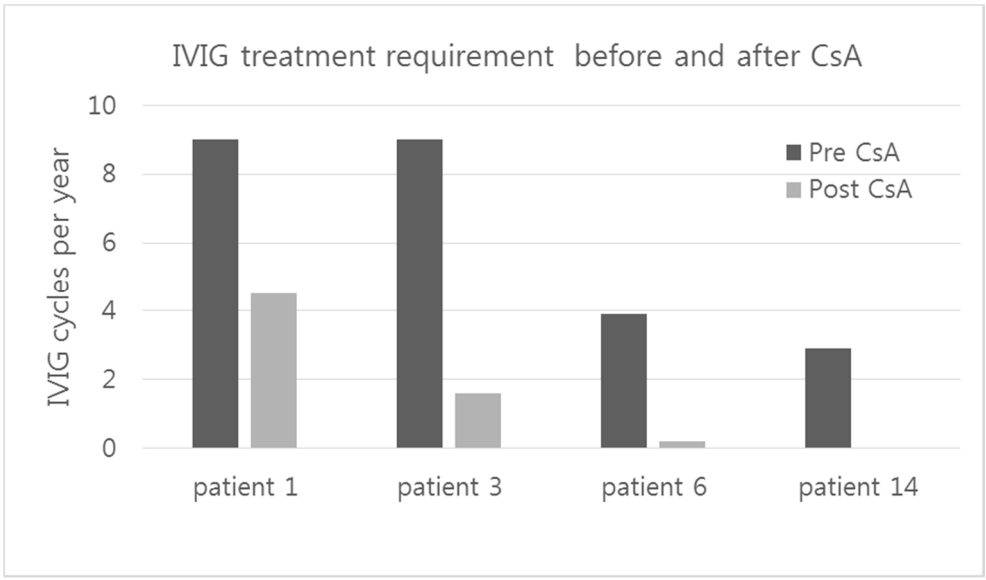
under observation for treatment response.

All four patients who used cyclosporine (patients 1, 3, 6, 14) reached significant disease control after adding cyclosporine as described in table 9 and figure 2. The need for IVIG treatment as well as relapse events dropped significantly in all four patients after they added cyclosporine, as shown in figure 2. On average, the required IVIG treatment per year decreased from 6.2 ±3.2 cycles per year to 1.5 ±2.0 cycles per year. The relapse rate also decreased more than half in all patients after adding cyclosporine. On average, the relapse rate decreased from 5.5 ±4.4 times per year to 1.7 ±1.7 times per year after adding cyclosporine.

There were few adverse effect related to the treatment. Two patients treated by IVIG complained of headache and required work up for aseptic meningitis. There was no significant side effect related to plasmapheresis other than minor pains and discomfort. In the group treated with cyclosporine, one patient complained of hirsutism and patient 1 had to stop cyclosporine due to abdominal discomfort. Azathioprine was generally well tolerated without significant side effect.

3. Long-term treatment outcome

The mean duration of follow up was 47.7±29.6 months (range



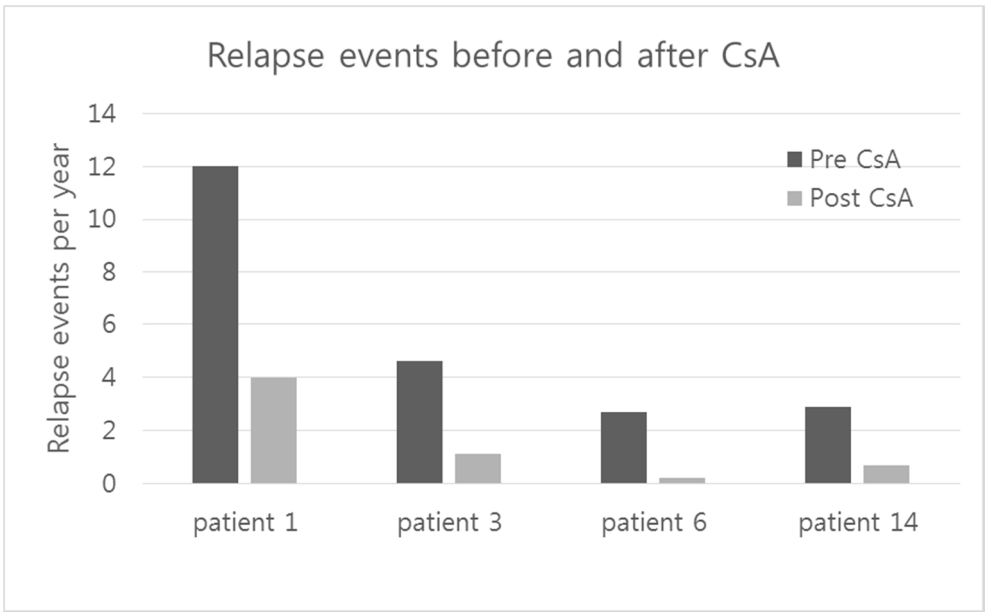


Figure 2. Effect of cyclosporine (CsA) on refractory polyphasic course

Cyclosporine was given to 4 treatment resistant polyphasic patients (Patient 1, 3, 6, 14). IVIG treatment requirement and relapse frequencies (X-axis) in each patients (Y-axis) were compared between the time period before and after adding cyclosporine.

Table 9. Treatment response of cyclosporine in refractory polyphasic group

	Total follow up	Period of CsA treatment	Relapse free period	Average IVIG cycles required before CSA (cycles/year)	Average IVIG cycles required after CSA (cycles/year)	Relapse rate before CsA (Incidence/year)	Relapses rate during CsA (Incidence/year)
1	47m	27m	4m	9	4.5	12	4
3	59m	39m	14m	9	1.5	4.6	1.8
6	85m	36m	23m	3.9	0.2	2.7	0.2
14	52m	17m	15m	2.9	0	2.9	0.7

CsA: cyclosporine

12 months to 99 months). The mean MRS score was 0.9±0.7 at the last outpatient follow up compared to the average maximum clinical deficit MRS score of 4.1±0.7.

In the monophasic group, two patients (patient 2, 9) achieved a complete remission (33.3%) after treatment, and four patients (patient 4, 5, 12, and 13) achieved partial remission (66.6%). Patient 4 and patient 5 were off treatment with only minimal foot drop present at the last follow up, and patient 13, although showing good response to plasmapheresis, were still in treatment. In the polyphasic group, four patients (patients 6, 7, 8, 10) showed a complete remission (50%), and four patients (patient 1, 3, 11, and 14) showed a partial remission (50%) to treatment. Patient 1 was put on cyclosporine and had already shown a significant impact on disease course, but the patient was recently taken off the medication due to abdominal pain. Patient 3 had previously achieved remission state with cyclosporine treatment, but experienced relapse with cyclosporine tapering. Patient 11 is responsive to IVIG but currently trying azathioprine to gain disease control. Patient 14 was able to achieve long term remission after cyclosporine treatment, but yet to try medication tapering. Overall, complete remission in the whole group was seen in 6 patients (42.8%), partial remission in 8 patients (57.2%).

Several factors were compared between the complete remission group and partial remission group. Age of 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) and disease course (p=0.627) were not different significantly between the two outcome groups. MRI nerve root thickening and high CSF protein level was also not different between the two groups (p=1.0).

DISCUSSION

This study showed important differences compared to adult CIDP in several characteristics. Childhood CIDP most often present with subacute onset (less than 8 weeks) of symptoms (20, 21, 24, 25). In accordance with the previous studies, a subacute onset of symptoms was common in this study. This often makes it difficult to distinguish between CIDP and GBS. As a result, patients from this study initially received IVIG on many occasions to target GBS, rather than therapy for CIDP. This is in contrast with adult CIDP, which often presents an insidious (63–84%) onset rather than a subacute onset (16–27%) (23). The relatively high incidence of prodromal infection events (42.9%) in this study was similar to previous reports (53–57%)(21, 24).

It has been suggested that polyphasic courses are more common in childhood CIDP (30). Similarly, polyphasic courses were more common (57.1%) in the current study. Motor symptoms are much more common and predominates the clinical presentation in childhood CIDP, whereas adult CIDP frequently shows coexisting sensory or autonomic symptoms. This was also observed in in this study, with most patients (92.8%) presenting with motor symptoms. Sensory symptoms were relatively common (78.6%) but cranial

nerve involvement (14.3%) or autonomic dysfunction (14.3%) was rare.

A higher proportion of adult CIDP is recognized to have underlying medical conditions such as neoplasia and autoimmune conditions, which is rarely observed in childhood CIDP (25). None of the patients from this study had associated significant comorbidities in line with previous reports, but three patients showed antibodies to ganglioside GM1.

Patients mostly showed good responses to initial treatment, similar to previous childhood CIDP series (30). However, current study found that the treatments responses to individual therapy differed between the monophasic group and the polyphasic group.

In the monophasic group, steroid therapy did not result in much clinical improvement. Plasmapheresis showed a better treatment response than IVIG in the monophasic group. IVIG was especially ineffective when the patient was in a progressive stage suffering from severe symptoms, ranging from MRS score of 4 and 5. In contrast, plasmapheresis was able to restore function when patients were suffering from severe exacerbations and were refractory to other treatments. This was demonstrated in patient 4, 5, 10 and 13 (Figure 1). In the polyphasic group, IVIG showed similar efficacy comparable to plasmapheresis, whereas steroids gained lesser

response in comparison. Six (patient 1, 3, 6, 7, 11, 14) of polyphasic course patients, who initially showed good response, eventually became treatment refractory or treatment dependent.

The high proportion of treatment refractory monophasic patients (n=4, 66.7%) and polyphasic patients (n=6, 75%) observed in this study is likely due to the characteristics of the studying center; as the national tertiary center, more severe cases are likely to have been referred to the center. Indeed, 9 patients had been transferred from other medical centers that found the patient care to be overwhelming. Thus, patients in this group were probably skewed, representing a more severe group of childhood CIDP cases.

Overall, childhood CIDP cases progress more favorably, with complete remission or minimal residual weakness in 70–100% of cases compared to the moderate to severe sequelae observed in 30–40% of adult CIDP patients (24). This study also showed relatively better long-term outcomes, with 6 patients (42.9%) showing minimal symptoms with no relapse within 6 months and rest of the patient maintaining functional status of MRS score of at most 2 with or without ongoing treatment.

There is ongoing debate regarding whether disease course, type of onset, or time from onset to treatment are predictive factors of outcomes or response to certain treatments. Some studies argue

that there are correlations, while others have found no differences in outcomes between these groups (21, 22, 25). In adult CIDP patients, younger patients with a rapid onset monophasic course are more likely to respond to treatment and recover completely (31, 32). This study considered predictors such as time lapse between symptom onset and treatment, symptom onset and addition of second treatment, onset age, and disease course were compared with treatment long term outcome. However none of these showed clear correlations.

Nerve root thickening observed in MRI and elevated CSF protein levels indicate the presence of CIDP, although these measures are not part of the diagnostic criteria. In previous studies, MRI based evidence of nerve root thickening and increased protein levels in CSF did not appear to be correlated with disease activity, disease severity or other clinical features(33) This study also did not show a significant association between CSF protein levels or MRI findings and disease severity.

The choice of first line treatment in childhood CIDP depends on several variables including initial disease severity, age, general health status, and potential contraindications (26). Many centers use IVIG as the initial treatment for CIDP, as it is generally effective and safe for use in children, and some believe that IVIG

has been established as the standard initial treatment when available(18). IVIG was the most often used first line treatment in this study as well. However, this was largely because most patients presented with acute onset polyneuropathy, which is difficult to distinguish from GBS. When the patients returned with recurrence, making CIDP the more likely diagnosis, IV steroids was tried to attain initial control of CIDP due to the past evidences and cost effectiveness. Thus, either IV steroids or IVIG was the first agent of choice. In addition, IVIG was used more often as initial treatment in patients diagnosed in recent years. This is probably due to increased availability of IVIG in Korea during recent years.

Although proven effective in adult CIDP, plasmapheresis is rarely considered for initial treatment in childhood CIDP due to issues of central vein access and the related complications(26). One meta-analysis published in 2013 reported that only 14% of childhood patients responded to plasmapheresis, suggesting that it was less effective in childhood CIDP than in adult CIDP patients(30). However, plasmapheresis was effective in controlling disease activity in progressive monophasic CIDP patients in this study. Patients 4, 5, 10 and 13 did not respond to either cyclic IVIG or steroid therapy and remained severely symptomatic until plasmapheresis was administered. Patients 5 and 10 had responded

to IVIG at other times when their symptoms were not as severe. All four patients now remain in remission state with only minimal symptoms or disability. This finding suggests that plasmapheresis can provide a better treatment option in severe progressive states of monophasic CIDP. Initial stabilization of CIDP is important in the acute active phase, as concomitant axonal loss follows the demyelination process (34). This is clinically significant, as the long-term prognosis of CIDP is suggested to depend on the magnitude of axonal loss rather than on demyelination(34). Thus, findings from this study suggest that plasmapheresis should be considered early, rather than late, in selected cases to reach initial control of disease activity.

Although first line therapy is very useful in controlling disease activity in the short term, it is not suitable for controlling disease activity in the long term (35). Corticosteroids have serious long-term side effects, such as hypertension, osteoporosis, diabetes mellitus and obesity, and both plasma exchange and IVIG are expensive, require hospitalization and have only short term benefits. It is estimated that up to 20% of CIDP patients eventually do not respond to treatment (36). Another challenging problem related to polyphasic CIDP is treatment dependence. One study reported that 55% of responders to IVIG, 23% to plasmapheresis and 18% of

those on prednisone eventually became dependent (4). The need for better long-term treatment options is becoming more evident.

A similar situation was observed in the current study, as six (75%) of the polyphasic patients became treatment refractory or treatment dependent. Most refractory polyphasic patients achieved control of disease activity only after adding cyclosporine treatment. The one exception was patient 7, who showed milder symptoms than the other refractory patients and improved after a combination of azathioprine and steroids. Cyclosporine had a dramatic effect in reducing relapse events, and patients were able to taper off of IVIG treatments.

Cyclosporine was administered in the current study based on previous reports suggesting its effectiveness in adult CIDP (35, 37-39). Cyclosporine is thought to be ideal for long-term treatment, due to its simplicity in adjusting doses and monitoring adverse effects (35). Promising results have been obtained with conventional doses (3-5 mg/kg per day) of cyclosporine in uncontrolled studies of severe refractory CIDP in adult populations(40). Response rates of cyclosporine treatment ranged from 40-90% with improvement usually occurring within 2-3 months of treatment initiation, and many succeeded in discontinuing prednisone without clinical deterioration (35, 38, 39). The use of

cyclosporine in childhood CIDP is much more rarely described in the literature. In two cases described by Visudtibhan *et al.*, cyclosporine was effective in both cases at 5 mg/kg/day (41). In the case series presented by Ryan *et al.*, one patient received 3 mg/kg/day, and in Sabatelli's report, one patient received 50 mg/day, both of which did not show a clear beneficial effect (24, 42).

However, one problem with cyclosporine in adult CIDP was the high incidence of side effects, often leading to discontinuation of the therapy (43). Adverse effects include abdominal pain, nausea, diarrhea, hepatitis, bone marrow suppression, hirsutism, and gingival hyperplasia. Serious potential side effects include nephrotoxicity, malignancy, and infections. However, nephrotoxicity, which was the main side effect resulting in discontinuation of the therapy, was not observed in childhood case(41). The patients generally tolerated cyclosporine, although one patient was taken off the treatment due to abdominal pain.

The underlying pathophysiology of CIDP is not completely understood, but T cells have been suspected to play a critical role for a long time. This speculation is based on reports of increased T cell infiltration in nerve biopsy specimens, impaired circulating regulatory T cell function and increased circulating Th17 cells during the active phase (44–46). Thus, cyclosporine as a method of

CIDP treatment is quite plausible, as it is a potent T cell inhibitor. Despite this plausibility, different case series have shown inconsistent effects of cyclosporine. These findings suggest that cyclosporine is beneficial in CIDP, but the evidence for using cyclosporine is still considered weak (28).

One explanation of the inconsistent results may be that CIDP is a heterogeneous group of diseases. Patients presenting with a different disease course and treatment may represent the presence of a different pathophysiology. Thus, cyclosporine may be an efficient treatment option only in a selected patient group that has a similar pathophysiology. Bernett *et al.* investigated 19 patients with refractory CIDP who were treated with cyclosporine and could not identify any clinical characteristics that would predict a positive response from cyclosporine therapy(39).

Another more likely reason for the inconsistent results is that the case series simply did not have a sufficient number of cases. Small number of patients due to the rarity of the disease is shared problem by most studies addressing CIDP. Literature review of the childhood CIDP shows that studies with more than 10 patients are very rare as shown in table 10. The dosage, treatment duration and point of treatment change would have differed in each center, and the number of patients was insufficient to represent the CIDP

Table10. Overview of childhood CIDP described in literature.

References	Country	Year published	Patients number	Mean age onset (years)	Disease course	Modified Rankin Scale	
						Maximum	Follow up
Chang et al(47)	Korea	2015	4 (2M: 2F)	9.7 (8-12)	4 polyphasic: 0 monophasic	3.0	NR
McMillan et al(30)	USA	2013	30 (13M: 17F)	7.6 (1.5-19)	21 polyphasic: 9 monophasic	2.8	0.5
Luan et al(48)	China	2010	12 (9M: 3F)	8.5 (2-17)	7 polyphasic: 5 monophasic	3.3	0.9
Jo et al(49)	Korea	2010	7 (No report)	9.1 (3-13)	2 polyphasic: 5 monophasic	4.0	0.3
Rossignol et al(23)	Canada	2007	13(9M:4F)	9 (3-14)	10 polyphasic: 3 monophasic	3.0	1.3
Rodriguez-Casero et al(50)	Australia	2005	5 (3M:2F)	8.0 (4.5–13.9)	0 Relapsing : 5 monophasic	NR	NR
Ryan et al(24)	Australia	2000	16 (5M: 11F)	6.3 (2.2-13.8)	6 polyphasic: 10 monophasic	3.4	0.25
Korinthenberg(20)	Germany	1999	21 (12M:9F)	8.6 (2–14)	9 Relapsing : 12 monophasic	NR	NR
Hattori et al(22)	Japan	1998	10 (6M:4F)	11 (2–16)	7 polyphasic: 3 monophasic	4.4	1.9
Simmons et al(25)	USA	1997	15 (7M:8F)	11.5 (3–17)	10 polyphasic: 2 monophasic	3.5	0.2
Nevo et al(21)	Australia	1996	13 (8M:5F)	6.5 (1–16)	10 Relapsing : 3 monophasic	NR	NR
Uncini et al(51)	USA	1991	5 (1M:4F)	7 (6–11)	NR	NR	NR
Sladky et al(52)	USA	1986	6 (5M:1F)	NR	NR	NR	NR
Colan et al(53)	USA	1980	5 (3M:2F)	9.6 (5–17)	3 Relapsing ; 2 monophasic	NR	NR

population as a whole. This limitation is also shared in this study.

In conclusion, this is one of the largest case series ever reported, and the largest group reported in Asia to the best of our knowledge. Although it may not be large enough to provide statistically significant evidence, it may provide important evidence for future management in childhood CIDP. This study finding suggests that cyclosporine can be an effective treatment option, especially in refractory polyphasic patients. Some agents such as azathioprine(54), methotrexate(55), and interferon beta-1a(56, 57) have been studied in larger randomized controlled trials and shown to be ineffective, but no large randomized controlled trials of cyclosporine have been conducted to date. This study supports a need for conducting randomized controlled study in a larger population in the future. This study also supports the early trial of plasmapheresis rather than late, in severe monophasic CIDP patient groups. Taken together, treatment pathway using either IVIG and/or IV steroids as initial treatment, and plasmapheresis as first add on treatment in monophasic patients, and cyclosporine in polyphasic patients is proposed (Figure 3).

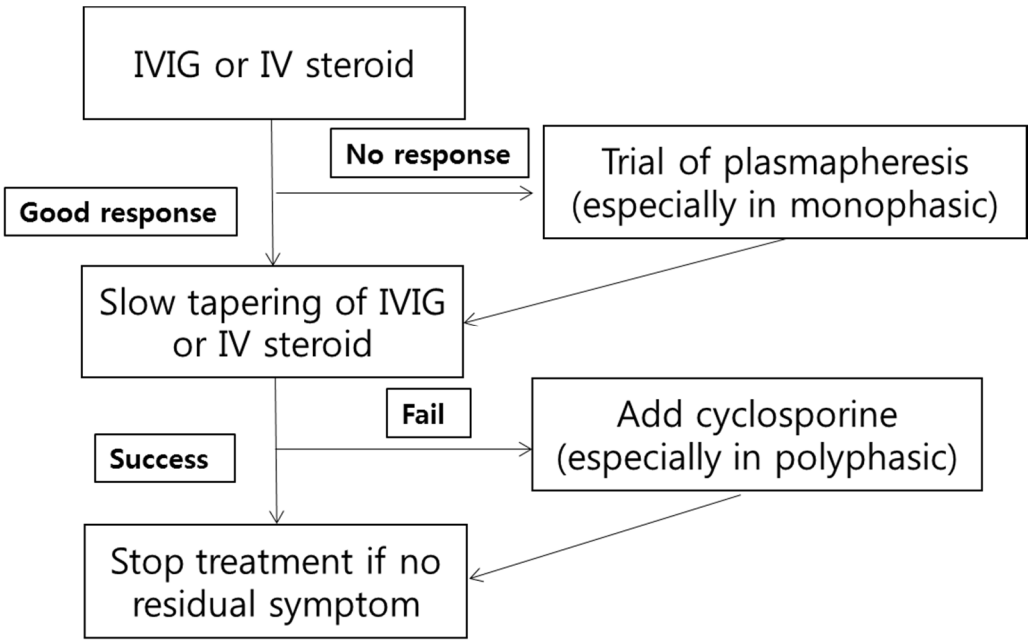


Figure 3. Treatment protocl proposed for chidhoold CIDP.

Patients are put on either IVIG or IV steroids as first treatment option. If the patient is treatment refractory monophasic, plasmapheresis is considered early. If the patient is treatment refractory polyphasic, cyclosporin trial is considered early.

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국문초록

소아 만성 염증성 탈수초성 다발성 신경병증의 치료 및 효과

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서론: 소아에서 발병하는 만성 염증성 탈수초성 다발성 신경병증은 임상적으로 다양하게 나타나는 말초 신경병증으로 면역기전에 의해 발생하는 것으로 알려져 있다. 소아 만성 염증성 탈수초성 다발성 신경병증은 굉장히 희귀한 질병이어서 치료 방법에 대한 연구가 부족한 바이다. 이에 소아 만성 염증성 탈수초성 다발성 신경병증 환자들의 임상양상과 치료효과를 연구 하였다.

방법: 본원에서 소아 만성 염증성 탈수초성 다발성 신경병으로 진단되어 추적관찰 중인 환자들 중 최소 1년이상(평균 기간 47.7±29.6 개월) 추적관찰 된 환아 14명 (평균 연령 8.6 ± 3.8세)을 대상으로 후향적 자료분석을 시행하였다. 환자들은 모두 정맥 면역글로불린 (78.6%) 이나 정맥 스테로이드(21.4%)로 초기치료를 받았다. 혈장 교환술은 이 두 치료방법을 모두 시도해보았으나 효과가 없을 때 사용되었다.

결과: 성인 발병 만성 염증성 탈수초성 다발성 신경병증의 보고된 임상

양상과 달리, 아급성 증상발현(n=10, 71.4%)과 재발성 임상경과 (n=8, 57.1%)를 보이는 경우가 더 많았다. 단발성 임상경과를 보인 그룹(n=6)에서는 혈장 교환술이 정맥 면역글로불린이나 정맥 스테로이드 보다 더 효과적이었고 이는 특히 질병이 진행형 일 때 돋보였다. 재발성 임상경과를 보인 그룹(n=8) 에서는 정맥 면역글로불린과 혈장 교환술이 비슷한 정도의 치료효과를 보였고 정맥스테로이드는 상대적으로 효과가 떨어졌다. 재발성 임상경과 그룹에서 6명 (75%)은 결국 위 치료들에 더 이상 반응하지 않아 면역 억제제 치료를 받았고 이 중 4명은 결국 cyclosporine 치료를 한 후에야 임상적 호전을 보였다. 종합적인 장기 예후는 성인에 비해 좋았으며, 전체 환자 중 6명 (42.8%)이 지난 6개월동안 재발 없이 완전 관해를 보였다.

결론: 소아 만성 염증성 탈수초성 다발성 신경병증에서 증상이 심한 단발성 형태의 임상양상을 보이면 혈장 교환술이 효과적일 수 있으며, 치료에 반응하지 않는 재발성 형태에서는 cyclosporine이 효과적인 치료방법일 수 있다.

주요어: 소아 만성 염증성 탈수초성 다발성 신경병증, 면역 글로불린, 혈장교환술, cyclosporine

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