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Childhood-onset demyelinating polyneuropathy: challenges in differentiating acquired from genetic disease

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Abstract

Childhood chronic inflammatory demyelinating polyneuropathy (CIDP) can be misdiagnosed for the more common genetic neuropathies such as Charcot-Marie-Tooth (CMT) disease. We present a case of childhood-onset demyelinating polyneuropathy who was initially diagnosed as CMT before a revised diagnosis of CIDP was made. A 14-year-old boy with bilateral pes cavus presented with progressive history of ataxic gait, generalized areflexia and proprioceptive sensory loss. Nerve conduction studies showed demyelinating features including markedly slow motor conduction velocities and prolonged distal motor latencies resembling CMT1. Despite the absence of a family history of genetic neuropathies, a diagnosis of CMT1 was considered most likely. The patient presented two years later with an acute onset of worsening instability and muscle weakness. A detailed history revealed functional improvement following the last presentation along with two separate episodes of exacerbations suggesting a relapsing-remitting form of neuropathy. Cerebrospinal fluid analysis showed cytoalbuminergic dissociation. Nerve ultrasound demonstrated enlarged peripheral nerves, particularly in the proximal and non-entrapment sites. Genetic testing was negative for known mutations in common CMT genes. A course of intravenous immunoglobulin resulted in clinically significant improvement. In conclusion, our patient highlights the diagnostic challenges in childhood-onset demyelinating neuropathies and the importance of not missing a potentially treatable immune-mediated neuropathy.

Keywords: Chronic inflammatory demyelinating polyneuropathy; Charcot-Marie-Tooth disease; childhood CIDP; pediatric CIDP; hereditary neuropathy; inherited neuropathy

INTRODUCTION

Childhood-onset chronic inflammatory demyelinating polyneuropathy (CIDP) is an immune-mediated disease of the peripheral nerves. It is characterized by a duration of progressive symmetrical weakness of at least 4 weeks or a rapidly progressing weakness with relapsing and prolonged course for more than a year.[1,2] Childhood CIDP is relatively rare with a prevalence of <0.5 per 100,000 and can potentially be misdiagnosed for the more common genetic neuropathies such as Charcot-Marie-Tooth (CMT) disease which has a higher prevalence of 82 per 100,000.[3,4] We present a case of childhood-onset demyelinating polyneuropathy, initially diagnosed as CMT before a revised diagnosis of CIDP was made. We highlight the diagnostic challenges in childhood-onset demyelinating neuropathies and discuss the features that may help to distinguish between inherited and immune-mediated forms of childhood-onset demyelinating neuropathies. Written informed consent for patient information and images to be published was provided by the patient and his guardian.

CASE REPORT

A 14-year-old Chinese boy presented to the neurology clinic at University Malaya Medical

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Centre, Kuala Lumpur with progressive gait difficulties. According to his family, the gait problems had started at the age of 6. He was the youngest of three siblings and there was no family history of neuromuscular diseases. He had normal developmental milestones, walking at the age of 15 months old. He also performed well in school but was never active in sports. On examination, he had an ataxic gait. There was bilateral pes cavus (Figure 1A) and mild muscle wasting of his limb extremities. Muscle power was intact but there was generalized areflexia. Sensory examination revealed loss of joint position sense over the distal feet and abnormal coordination with dysmetria on finger-nose and heel-shin tests. Nerve conduction study (NCS) was performed which showed demyelinating features including marked slowing of the motor conduction velocities (CVs) and prolonged distal motor latencies (DMLs) (Table 1). Due to the young age of onset and progressive history, he was diagnosed as CMT1 although at the time, genetic testing was not accessible. He was referred to the rehabilitation physicians for further management.

Two years later, he represented acutely with a 2-week history of peripheral numbness, progressive upper limb clumsiness, lower limb weakness and unsteadiness. Within the same period, he had also lost his ability to write and walk independently. Clinical examination revealed bilateral muscle weakness of finger abduction and hip flexion (Medical Research Council [MRC] grade 4). There were generalized areflexia, proprioceptive sensory loss. There was also truncal and gait ataxia (Video 1). Romberg's sign was positive.

A more detailed history was obtained, and it emerged that the patient had initially had symptoms of mild unsteadiness at the age of 6, which at the time was not functionally disabling and thus medical treatment was not sought. At the time, his symptoms had spontaneously improved over a period of a year. Similar disabling symptoms resurfaced at the age of 10 years old, which caused him to become progressively unsteady with frequent falls. He also described bilateral upper and lower limb numbness and had difficulties running and climbing stairs. During this period of deterioration, the family opted for intensive 'traditional Chinese medication' over several months. His symptoms gradually improved over a period of a year. Subsequently, he remained independent with some residual deficits until his first and second presentation to us at ages 14 and 16 respectively.

Following the second presentation, in view of the relapsing and remitting nature of his clinical presentation, the diagnosis was revised to CIDP. A lumbar puncture was performed and his cerebrospinal fluid (CSF) was acellular with

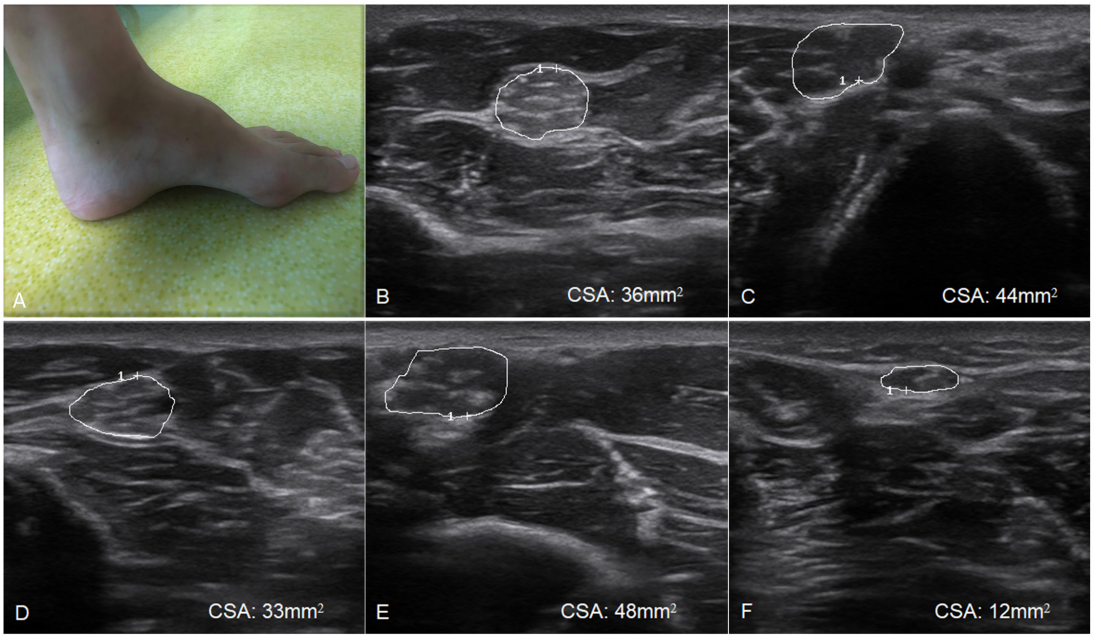

Figure 1. High arched foot in this patient suggesting chronicity of the underlying disease (A). Nerve ultrasound and cross-sectional area measurements for median nerve at forearm (B), median nerve at mid-arm (C), ulnar nerve at forearm (D), ulnar nerve at mid-arm (E), and sural nerve at mid-calf (F).

an elevated protein level of 4.35 g/L, consistent with cytoalbuminergic dissociation. A repeat NCS showed further reduction of the CMAP amplitudes with persistent demyelinating features (Table 1). Nerve ultrasound showed diffusely enlarged cross-sectional areas (CSAs) of the peripheral nerves particularly over the proximal regions and non-entrapment sites with increased intranerve CSA variability (Table 1) (Figure 1B-F). Following written informed consent from the parents, sequence analysis and deletion/duplication testing of 72 genes were performed, including *PMP22*, *MPZ, LITAF, EGR2, GDAP1, MTMR2* and *GJB1* which were negative.

He was treated with a five-day course of intravenous immunoglobulin (IVIG) at 2 g/kg. Over a period of two weeks, his ataxia gradually improved, regaining his ability to write and walk independently (Video 2). However, a repeat NCS did not show any significant changes compared to pre-IVIG study (Table 1). At follow-up six months after IVIG, he had regained close to normal function allowing him to return to school.

DISCUSSION

CMT1 and CIDP are both demyelinating forms of neuropathies. Distinguishing between the two conditions can be challenging especially in the setting of a childhood-onset and negative family history. Table 2 summarizes the distinguishing features between CMT1 and childhood-onset CIDP.[1, 5-7] The initial diagnosis of CMT1 was made based on the finding of bilateral pes cavus suggesting a pattern of muscle wasting that was present in the developmental stages of childhood. NCS demonstrated a uniformed pattern of demyelination involving all four limbs with markedly reduced CVs (< 5 m/s) and prolonged distal motor latencies. There was also an absence of conduction block or temporal dispersion, supporting a genetic rather than acquired form of neuropathy. Patients with demyelinating forms of CMT tend to demonstrate very slow mean CV when compared to inflammatory neuropathies such as CIDP.[2] In particular, the most common type of CMT, CMT1A, demonstrate very slow CV, typically < 15 m/s.[8]

The diagnosis of CMT was revisited when the patient demonstrated spontaneous improvement at follow-up and following his subsequent relapse, a diagnosis of CIDP was considered. This was supported by the presence of CSF cytoalbuminergic dissociation. Previous studies have reported both relapsing course of disease and markedly raised protein in childhood-onset CIDP, with up to 100% of patients having raised CSF protein.[9] In one review, a cut-off CSF protein of > 1 g/L was recommended as a marker to distinguish between inflammatory and genetic forms of neuropathy.[5] Foot deformities including pes cavus has commonly been associated with CMT[4,8] but it is not pathognomonic of CMT and is not an uncommon finding in the context of children with early onset of distal muscle weakness including CIDP.[10]

Despite the uniform pattern, our patient had NCS parameters that would fulfil the European Neuromuscular Center (ENMC) International Workshop criteria for childhood CIDP[1] and similar "very slow" CVs have been reported in other cases of childhood CIDP.[9] In adults, the most commonly referenced criteria for CIDP is the European Federation of Neurological Societies/ Peripheral Nerve Society (EFNS/PNS) in 2010. However, this criteria lack specificity in childhood CIDP, with 96% of hereditary neuropathy with liability to pressure palsies (HNPP) and 43% of CMT fulfilling this criteria.[2] Other useful NCS parameters include the presence of sural-sparing pattern and a 10 m/s CV difference in between nerves which reported have high specificity for childhood CIDP.[2] The presence of conduction block, and/or abnormal temporal dispersion can also be helpful, although both features have been described in genetic neuropathies.[2]

In recent years, there is an emerging role for the use of nerve ultrasound in peripheral neuropathies. Nerve ultrasound in both inflammatory and inherited demyelinating neuropathies has demonstrated enlarged CSAs. However, the patterns of nerve enlargement in inflammatory neuropathies, such as CIDP, tend to be patchy, involving the proximal and non-entrapment sites.[7] In contrast, nerve enlargement in demyelinating CMT is diffuse and in CMT1A, the nerve CSA is typically much larger, up to twice the size of healthy controls.[6] In the current case, we found increased intranerve CSA variability in the upper limbs especially in the ulnar nerve, in keeping with CIDP.

The most remarkable finding in the current case was the marked clinical improvement following treatment with IVIG therapy which would be in keeping with an immune-mediated neuropathy such as CIDP. In retrospect, the improvement in his condition following the onset at the age of 10 may have resulted from steroid exposure from traditional Chinese medication. Both IVIG and steroids are effective in childhood CIDP. Due to

Table 1: Nerve conduction studies and nerve ultrasound

Nerve Conduction Studies				
Nerve		**14 years old**	**16 years old**	
			Before IVIG	**After IVIG**
Median				
DML (ms)		26.35	34.11	28.59
CMAP (mV)	Wrist	3.5	1.6	0.9
	AF	2.2	NR	0.2
MCV (m/s)		4.8	NR	4.2
F-wave (ms)		NR	NR	NR
SNAP (μV)		NR	NR	NR
Ulnar				
DML (ms)		20.68	38.54	23.07
CMAP (mV)	Wrist	0.5	0.1	0.1
	BE	0.8	NR	NR
	AE	0.3	NR	NR
MCV (m/s)	Wrist-BE	3.4	NR	NR
	BE-AE	3.5	NR	NR
F-wave (ms)		NR	NR	NR
SNAP (μV)		NR	NR	NR
Peroneal		NR	NR	
Tibial				
DML (ms)		62.97	57.45	NR
CMAP (mV)	Ankle	0.3	NR	NR
	PF	0.1	NR	NR
MCV (m/s)		3.5	NR	NR
F-wave (ms)		NR	NR	NR
Sural				
SNAP (μV)		NR	NR	NR

Nerve Ultrasound			
Nerve	**Location**	**Cross-sectional area (mm²)**	**Reference value (mean±SD, mm²)[c]**
Median	Wrist	21	6.1±1.2
	Forearm	36	5.2±0.8
	Elbow	42	6.9±1.5
	Midarm	44	7.2±1.4
	Intranerve CSA variability[a]	2.10	-
Ulnar	Wrist	13	4.0±1.0
	Forearm	33	4.6±1.1
	BE	27	-
	Elbow	16	6.1±1.4
	AE	43	-
	Midarm	48	5.4±1.4
	Intranerve CSA variability[a]	3.69	-
Tibial	Ankle	28	11.8±2.4
	Knee	54	10.4±2.2
	Intranerve CSA variability[a]	1.93	-
Peroneal	FH	23	8.9±2.0
	Knee	33	7.5±1.7
	Intranerve CSA variability[a]	1.43	-
Sural	Mid-calf	12	1.6±0.9
	Internerve CSA variability[b]	2.58	-

DML: distal motor latency, CMAP: compound muscle action potential, MCV: motor conduction velocity, SNAP: sensory nerve action potential, SCV: sensory conduction velocity, AF: antecubital fossa, BE: below elbow, AE: above elbow, FH: fibular head, PF: popliteal fossa, NR: Not recordable

[a]maximal CSA/minimal CSA

[b]maximal/minimal intranerve CSA

[c]Normative data from our lab

Table 2: Distinguishing features between CMT1 and childhood CIDP

	CMT1	Childhood CIDP
Clinical		
Weakness	Symmetrical, distal	Symmetrical, proximal and distal
Progression	Slowly progressive	Progressive > 4 weeks or rapid with relapsing and prolonged course > 1 year
Ataxia	Rare	Common initial presentation
Pes cavus	Common	May be present if early onset of disease
Sensory symptoms	Negative symptoms	Positive symptoms
Electrophysiological		
Demyelinating	Yes, uniform, homogeneous	Yes, non-uniform, heterogeneous
Conduction block/temporal dispersion	Rarely	Yes, non-entrapment sites
Internerve motor CV slowing difference > 10 m/s	No	Yes
Motor CV	Typically very slow (< 15 m/s)	Slowing, < 75% of mean CV minus 2 SD for age
Sural sparing pattern	No	Yes
CSF protein	Normal or mildly elevated (< 1 g/L)	Elevated > 0.5-1 g/L
Imaging		
Ultrasound	Diffuse enlargement, up to twice the size of controls	Patchy, enlargement more prominent in proximal and non-entrapment sites
MRI nerve roots/plexus	Thickened nerve roots, rarely enhanced	Thickened and enhanced nerve roots
Histopathology (nerve biopsy)		
Demyelination: onion bulbs, loss of myelinated fibres	Yes	Yes
Inflammatory cells	No	Yes, macrophage induced demyelination
Response to immunotherapy (IVIG or steroids)	No response	Up to 2/3 with good response

CMT1: Charcot-Marie-Tooth 1, CIDP: chronic inflammatory demyelinating polyneuropathy, CV: conduction velocity, IVIG: intravenous immunoglobulin.

the side-effects associated with steroids, IVIG has been preferentially used with up to 80% of patients displaying good response.[1]

The possibility that our patient had both CMT and CIDP cannot be entirely excluded. Previous reports of dual pathology have been described in one review, with 23 patients ranging from 1.5 to 69 years old with genetically confirmed CMT1A co-existing with CIDP.[5] This group of patients had features of stepwise deteriorations, presence of conduction blocks on NCS, elevated CSF protein and inflammatory histological features, with up to 47% of patients showing some response to immunotherapy.[5] Aside from CMT1A, CIDP has also been reported to occur with other types of CMT including CMT1B, CMTX1 and CMT4J.[5] It is less clear as to why some patients can have both pathology but given that CMT is the most common form of inherited neuromuscular disorder, the findings may well be coincidental.[5] In the current case, the negative testing for mutations in common CMT genes along with the resolution of his symptoms with immunotherapy make a dual pathology less likely.

In conclusion, this report highlights the diagnostic challenges in childhood-onset demyelinating neuropathy and the characteristics that can help distinguish immune-mediated neuropathies that are amenable to treatment from genetic neuropathies, for which there is as yet no effective therapy.

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DISCLOSURE

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Conflict of Interests: None

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Video 1: This video demonstrates his gait instability and inability to walk without support. The high steppage gait with visual dependence suggests a marked proprioception loss resulting in sensory ataxia. Consent for publication was obtained from the patient and guardian.

Video 2: This video shows marked improvement in his gait stability and speed after treatment with IVIG. Consent for publication was obtained from the patient and guardian.