Neuroendocrinology Letters Volume 37 No. 4 2016
ISSN: 0172-780X; ISSN-L: 0172-780X; Electronic/Online ISSN: 2354-4716
Web of Knowledge / Web of Science: Neuroendocrinol Lett
Pub Med / Medline: Neuro Endocrinol Lett

Narcolepsy with cataplexy in a child with Charcot-Marie-Tooth disease

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Submitted: 2016-04-15 Accepted: 2016-05-12 Published online: 2016-09-30

Key words: **Charcot-Marie-Tooth Disease; Narcolepsy; child; genetic; pediatrics**

Neuroendocrinol Lett 2016; **37**(4):265–268 **PMID:** 27857041 NEL370416C01

Abstract

We report an 8-year-old boy diagnosed with both CMT1 and narcolepsy, which were not reported simultaneously presenting in one person. The boy presented with a history of increased suddenly falling frequency and excessive daytime sleepiness for 3 months. CMT1 was diagnosed by electrophysiology and genetic testing. Narcolepsy had not been diagnosed until the frequently falling caused by sudden and transient episodes of legs weakness triggered by emotion was found. Multiple sleep latency test showed multiple sleep onset REM periods with reduced sleep latency. When CMT1 and narcolepsy were coexist in an individual, the latter might be overlooked. Cataplexy caused by narcolepsy might be disregard as distal muscle weakness of CMT1. The daytime sleepiness might also be ignored. Therefore, we recommend that patients with sleep disorders should be queried about the symptoms of narcolepsy.

CASE REPORT

INTRODUCTION

Hereditary motor and sensory neuropathy, also known as Charcot-Marie-Tooth disease (CMT), is the most common inherited disease of the peripheral nervous system. CMT1, one of the main type of CMT, shows autosomal dominant inheritance and slow nerve conduction velocity (NCV) (Harding & Thomas 1980; Houlden & Reilly 2006). Patients with CMT1 exhibit a profound distal muscle weakness and sensory deficits, resulting in "steppage" gait and secondary foot deformities. The most frequent CMT1-causing mutation is the duplication of *PMP22* gene, which localize on chromosome 17p12. This kind of CMT1 is classified as CMT1A (Houlden & Reilly 2006).

There was approximate 1 person with narcolepsy in every 3000 people worldwide (Leschziner 2014). It is manifested as severe daytime sleepiness and/or cataplexy, which is defined as sudden episodes of muscle weakness triggered by emotions, such as laughing or joking. There was no previous report on the simultaneous presence of CMT1 and narcolepsy in one patient. Here, we reported an 8-year-old boy diagnosed with both CMT1 and narcolepsy.

CASE PRESENTATION

An 8-year-old boy was the first child of non-consanguineous Chinese parents. At the age of 14 months, he developed an abnormal gait, drop foot,

and frequent falling. It was difficult for him to stand up from a squatting position. However, the symptom was progressing slowly and ignored by his parents. In recent 3 months, he got balance lost and unusual frequent falling without any inducement factors. At the same time, excessive daytime sleepiness which occurred daily was observed in this patient. Moreover, excessive motion of legs and talking during sleep were found, but there were no hypnogogic hallucinations and sleep paralysis. The weight of the patient increased by 10 kg in recent 3 months. The neurologic examination revealed muscle tone was normal in four limbs. The muscle strength was grade 5 in upper extremities and grade 4 in lower extremities. The patient can not walk in heel and had pes cavus. His deep tendon reflexes were absent, and bilateral Babinski's sign was negative.

Nerve conduction velocity (NCV) study showed abnormal findings. Moreover, there were also abnormal results of NCV in the patient's father, though he didn't show any symptom of limb weakness. The NCV studies (Table 1) showed that motor nerve conduction velocities (MNCVs) of the bilateral median, peroneal and tibial nerves in the patient were between 8 m/s and 19.2 m/s. Sensory nerve action potentials (SNAPs) of the bilateral median sensory nerve and sural nerve were absent. The MNCVs of the bilateral median and peroneal nerves in the patient's father were between 22 m/s and 36 m/s. The SNAPs were all absent except the left median nerve of the father, and the sensory nerve conduction velocity (SNCV) was obviously below normal.

The boy and his father were both diagnosed with CMT1. During the hospitalization, it was found that the boy suffered from sudden and transient episodes of legs weakness triggered by emotion especially by laughing, which induced most of the falling. However, it was overlooked before.

Gene mutation analysis by next-generation sequencing was performed. The mutations were then verified using Sanger sequencing. A heterozygous mutation of c.49_54del and p.17_18del was detected in *PMP22* gene in the patient and his father (Figure 1). Although the mutation has not been reported before, the mutation was not multitude, so it may be a novel disease-causing mutation. The diagnosis of CMT1 was confirmed in the patient and his father, but CMT1 cannot be used to explain the excessive daytime sleepiness and cataplexy of the boy. Therefore, the multiple sleep latency test (MSLT) was performed and showed 3 sleep onset REM periods with reduced sleep latency (<5 min on average). In this way, he was finally confirmed to be diagnosed with narcolepsy with cataplexy. Then Concerta (Methylphenidate Hydrochloride Prolonged-Release tablets, ALZA, USA, 18 mg/day) was given. One week later, daytime sleepiness and the abnormal falling down diminished.

Tab. 1. Electrophysiological features of the patient and his father.

Patients	boy		father	
	Left	Right	Left	Right
Age at exam (years)	8		36	
Median nerve				
TL (ms)	9.2	10.4	7.2	8.2
MNCV (m/s)	15.6	19.2	35.9	36
Peroneal nerve				
TL (ms)	8.5	8	7.0	6.6
MNCV (m/s)	A	A	22	27.3
Tibial nerve				
TL (ms)	12.2	12.4		
MNCV (m/s)	A	A		
Median nerve				
SNCV (m/s)	A	A	27.8	A
Sural nerve				
SNCV (m/s)	A	A	A	A

A, absent potentials; TL, terminal latency; MNCV, motor nerve conduction velocity; SNCV, sensory nerve conduction velocity.

DISCUSSION

The most frequent CMT phenotype is characterized by progressive distal weakness and sensory loss appearing toward the second decade in clinical. Other patients develop a much more severe form of CMT with onset in infancy or early childhood and progress to disability within a few years. Electrophysiology is important for the differentiating of demyelinating CMT1 (motor conduction velocities (MCVs) of the median nerve <38 m/s) and axonal CMT2 (median nerve MCV > 38 m/s) (Harding & Thomas 1980). In the current case, the median motor nerve conduction velocity (MMNCV) was less than 38 m/s, and the heterozygous mutation of c.49_54del and p.17_18del in *PMP22* gene was detected by genetic test in the patient, which indicated that the patient was consistent with autosomal-dominant demyelinating neuropathy (CMT1A) diagnostic criteria (Harding & Thomas 1980; Houlden & Reilly 2006). Furthermore, the clinical manifestation of excessive daytime sleepiness for more than 3 months, sudden and transient episodes of legs weakness triggered by emotion, multiple sleep onset REM periods with reduced sleep latency in MSLT indicated that narcolepsy with cataplexy was also existent according to the diagnostic criteria for narcolepsy (International classification of sleep disorders: diagnostic and coding manual, 2005).

The narcoleptic tetrad (excessive daytime sleepiness, hypnogogic hallucinations, sleep paralysis, and cataplexy) only presents in 10–15% patients. The diagnostic symptoms of narcolepsy are usually less typical in children. In many child patients, excessive daytime sleepiness is not immediately recognized as abnormal until cataplexy appears (Guilleminault & Pelayo 1998;

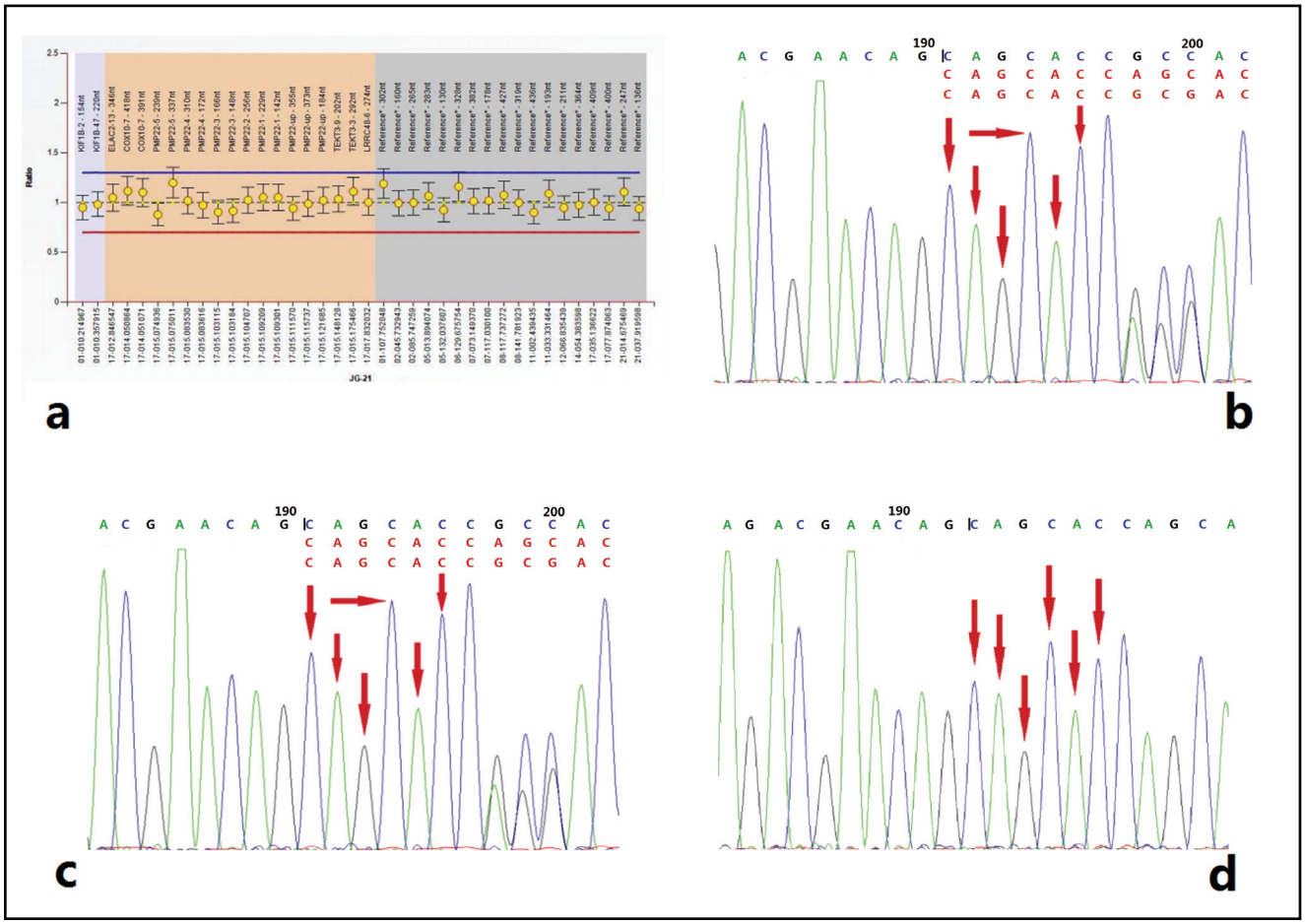

Fig. 1. Heterozygous mutation detected by Sanger sequencing in the patient and his father. **A**. Next generation sequencing showed heterozygous c.49_54del, p.17_18del mutation in PMP22 gene in the patient; **B.** The patient had heterozygous deletion mutation c.49_54del, p.17_18del; **C.** The father had heterozygous deletion mutation c.49_54del, p.17_18del; **D.** No mutation was found in the mother.

Nevsimalova 2014). Excessive daytime sleepiness which cannot be explained by CMT1 in this case, might be disregarded as hyporactive, inattentive, learning-disabled, or lazy (Walters *et al.* 2008; Nevsimalova 2014). In our case, cataplexy had not been suspected until we found out that the frequently falling was partly caused by sudden and transient episodes of legs weakness triggered by emotion rather than aggravated muscle weakness of lower extremity of CMT1. As narcolepsy is controllable, it is very important to recognize the main diagnostic characteristics between CMT1 and the narcolepsy to improve the quality of life of patient.

The most frequent CMT1-causing mutation is the duplication of the *PMP22* gene, which is responsible for 60–70% of the CMT1 and 50% of the total CMT patients. The known (*MPZ*, *LITAF*, *EGR2*, and *NEFL*) and unknown genes account for the remainder mutations (Houlden & Reilly 2006). Narcolepsy is a disorder of the central nervous system for which the reason of onset was still unknown, but a strong genetic component is indicated by family studies (Mignot 1998). Both CMT and narcolepsy are rare diseases, the former has an estimated prevalence of 1:2500 (Houlden & Reilly 2006) which was about 1:3000 for the latter (Leschziner 2014). The combined prevalence of the two disease was about 1.3 cases in every 10,000,000 individuals. The combined presence of CMT1 and narcolepsy have not been reported in one patient previously. Narcolepsy has been described in association with hereditary sensory autonomic neuropathy (HSAN), which is another major category of hereditary neuropathies. Moghadam *et al.* (2014) described that HSAN and narcolepsy could coexist in hereditary sensory and autonomic neuropathy with dementia and hearing loss type IE (HSAN IE). This is caused by mutation in the DNA methyl-transferase type 1 (*DNMT1*) gene, usually in exon 20, with the exception of a single family with a novel mutation in exon 21(Yuan *et al.* 2013). Mutations in exon 21 of *DNMT1* have been found in all cases of autosomal dominant cerebellar ataxia, deafness, and narcolepsy (Yuan *et al.* 2013). The finding of narcolepsy in *DNMT1*-related diseases suggests that impaired *DNMT1* activity could lead to the development of narcolepsy and HSAN. The impaired *DNMT1* activity establishes the relationship between hereditary neuropathies and narcolepsy up to now. However, we

have not found clear correlation factors between the CMT1 and narcolepsy in our patient. It is therefore very likely that the coexistence of CMT and narcolepsy in this case is casual.

In conclusion, CMT1 and narcolepsy can coexist in an individual. Narcolepsy may be overlooked because cataplexy may be disregard as distal muscle weakness of CMT1 and daytime sleepiness may be overlooked in childhood. As the diagnostic symptoms of narcolepsy are usually not typical in children, we recommend that child patients with sleep disorders should be queried about the symptoms of narcolepsy. In addition, the prompt diagnosis and treatment of narcolepsy may improve the quality of life of patient.

ACKNOWLEDGEMENTS

This paper is supported by the funding for FXZ from the item of Sci-research of The Second Affiliated Hospital & Yuying Children's Hospital of Wenzhou Medical University (NO:2011A004) in the decision to submit the manuscript for publication.

Consent: *Written informed consent was obtained from the patient's father for publication of this Case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.*

Competing interest: *The authors declare that they have no conflict of interest.*

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