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Adult-onset Krabbe disease manifesting as Charcot-Marie-Tooth disease

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Abstract

Krabbe disease (KD) is a progressive lysosomal storage disorder characterized by the deficiency of β-galactocerebrosidase (GALC). It mainly manifests as central nervous system involvement, but peripheral nervous system damage is also found. Although it can appear as a widespread neuropathy, it is very rare to manifest in a form similar to Charcot-Marie-Tooth disease (CMT). A 34-year-old woman presented with progressive gait disturbance and foot deformity. There were no other medical or family history of abnormalities. Nerve conduction studies showed demyelinating neuropathy, and brain MRI showed white matter hyperintensities. Sequencing of *PMP22* gene was normal, followed by next-generation sequencing (NGS). Potential compound heterozygous variants in the *GALC* gene were found; additionally a decrease in GALC enzymatic activity was confirmed, and KD was diagnosed. Although CMT has been previously diagnosed through a single genetic test, since the introduction of NGS, various genetic mutations have been identified in patients suspected of having CMT. In addition to the phenotypes mainly found in KD, other unusual phenotypes have also been found. In this case, we identified a unique clinical phenotype similar to CMT in a KD patient. We also confirmed the clinical usefulness of NGS by demonstrating in a KD patient diagnosed through NGS, who was not identified by conventional genetic mutation testing.

Keywords: Krabbe disease, *GALC* gene, CMT disease, β-galactosylcerebrosidase, neuropathy

INTRODUCTION

Krabbe disease (KD) is a progressive lysosomal storage disorder characterized by deficiency of β-galactocerebrosidase (GALC) in the nervous tissues, leading to widespread demyelination of the central and peripheral axons.[1-5] Symptoms or signs mainly occur with central nervous system involvement but also occur in the form of widespread peripheral neuropathy. Charcot-Marie-Tooth disease (CMT) is an important disease that should be a major differential diagnosis in a juvenile- or young adult-onset peripheral neuropathy.[6,7] CMT is diagnosed through genetic testing when a patient develops widespread uniform polyneuropathy in the hand or foot deformity Previously, *PMP22*, *MPZ*, *MFN2*, and *GJB1* were found to be major causative genes according to the neuropathy type; however, in recent years, with the development of next-generation sequencing (NGS), various causative genes and their phenotypes have been identified.[6,8] However, a *GALC* gene mutation expressed as a phenotype of CMT and diagnosed as KD is a very rare phenomenon. Herein, we report the case of a patient with KD who presented with diffuse demyelinating polyneuropathy and foot deformity and was initially misdiagnosed as CMT.

CASE REPORT

A 34-year-old woman had been suffering from slowly progressive gait disturbance for a few years. Her parents, brother, and son had no definite similar history. Neurological examination of the patient revealed subtle motor weakness in all extremities and distal hand paresthesia, but her hand and foot showed claw hand and high-arched foot (Figure 1). Deep tendon reflexes in the upper and lower extremities were normal. She showed normal cranial nerve and cerebellar functions. Gait examination revealed a subtly slowed gait speed

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Figure 1. Pictures showed high-arched foot and claw hand.

and mild disequilibrium, and the Romberg sign was equivocally positive. She reported mild word-finding difficulty for a few years, and cognitive tests were normal, except for mild verbal memory deficit. Biochemical and cerebrospinal fluid screening indicated that plasma electrolytes, liver function, calcium, phosphate, thyroid function, full blood count, vitamin B-12 and folate levels, syphilis serology, and autoantibody profile were all unremarkable. Brain magnetic resonance imaging showed multifocal patchy T2 hyperintensities involving both parieto-occipital WMs, both superior and inferior cerebellar peduncles, both cerebellum, and linear T2 hyperintensity in the splenium (Figure 2). Motor nerve conduction velocities in the median, ulnar, peroneal, and tibial nerves were reduced, distal latencies were prolonged, and compound muscle action potentials in the corresponding nerves were mostly reduced (Table 1, Figure 3). Sensory nerve conduction studies of the median, median, ulnar, peroneal, and sural nerves showed reduced sensory nerve conduction velocities and action potentials. No deletions or duplications were found in the *PMP22* gene using the multiple ligation probe application method conducted in a previous clinic. Whole-exome sequencing identified potential compound heterozygous variants with a pathogenic variant, c.136G>T (p.Asp46Tyr) and a variant of uncertain significance (c.1589T>C (p.Leu530Pro) in the *GALC* gene according to the American College of Medical Genetics and Genomics guideline (Figure 4). Additionally, GALC enzymatic activity using liquid chromatography-tandem mass spectrometry in leukocytes was decreased (0.8 nmol/16 h/mg protein) compared with 44.4 nmol/16 h/mg protein in an age-matched control (normal range: 24–82 nmol/16 h/mg protein). Therefore, providing evidence for phenotypic specificity (PP4) to be added to these two variants.

DISCUSSION

In CMT, not only new and rare genetic mutations were discovered in genetically negative cases through targeted NGS but also hereditary spastic paraplegia-related genes were discovered, confirming the involvement of the peripheral (PNS) and central (CNS) nervous system.[8] In this case, KD was among patients with leukodystrophy diseases, in which CNS and PNS involvement, as well as various neurological symptoms, occurred. In KD, peripheral neuropathy mainly manifest with uniform conduction slowing. Patchy demyelination is rarely found in KD as in other leukodystrophy or CMT. Patchy demyelinating

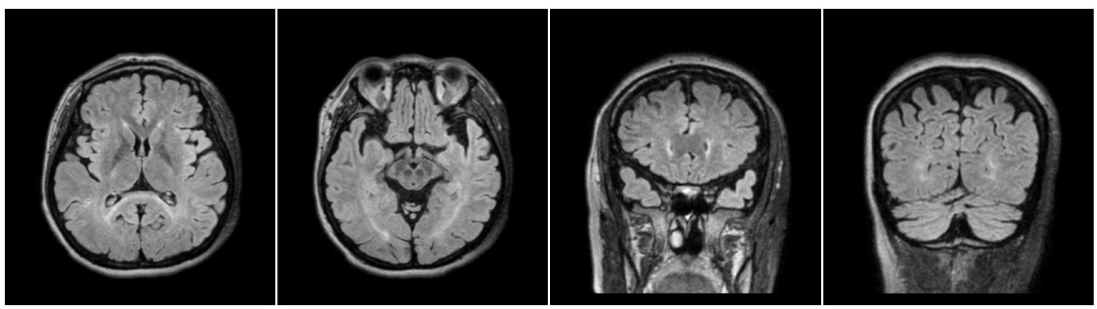

Figure 2. Brain magnetic resonance images showed multifocal T2 hyperintensities involving splenium of corpus callosum, both optic radiations, and both anterior and posterior lateral periventricular white matter

Table 1: Nerve conduction studies

Nerve sites	Lat (ms)	Amp (mV)	CV (m/s)
Motor NCS			
Median			
Wrist	**9.2/8.0**	**4.0/2.5**	
Elbow	18.7/17.3	**1.7/1.8**	**24.1/23.7**
Axilla	22.8/22.2	**1.4/1.6**	**32.9/26.5**
F-wave	**65.1/63.2**		
Ulnar			
Wrist	**4.6/5.2**	6.4/6.4	
Below elbow	11.8/11.6	6.1/5.1	**33.0/34.5**
Above elbow	13.9/14.2	6.0/**4.6**	**35.7/30.8**
Axilla	15.3/15.8	6.0/**3.6**	**48.6/37.5**
F-wave	**52.4/54.6**		
Peroneal			
Ankle	**9.1/9.8**	**2.8/2.9**	
Fibular head	27.0/28.4	**2.1/1.3**	**17.0/15.1**
F-wave	**130/126**		
Tibial			
Ankle	7.2/7.5	**4.6**/5.0	
Popliteal fossa	20.8/19.6	**2.2/1.5**	**26.0/31.0**
F-wave	**110/126**		
Sensory NCS			
Median			
Finger-wrist	**NP/NP**	**NP/NP**	**NP/NP**
Wrist-elbow	5.1/5.1	12.5/**6.7**	**38.0/40.5**
Elbow-axilla	2.1/3.0	15.5/**7.8**	**49.5/43.9**
Ulnar			
Finger-wrist	4.5/4.0	**1.3/0.9**	**23.0/22.3**
Wrist-elbow	4.2/4.8	11.3/10.6	51.6/49.5
Elbow-axilla	2.6/2.1	13.2/27.7	48.4/53.8
Superficial peroneal			
Lower leg	3.5/3.8	**3.5/1.7**	34.7/34.3
Sural			
Lower leg	3.1/3.0	**5.5**/9.6	34.7/**33.8**
H-reflex	**NP/NP**		

Data are values on the right/left sides. Bolded values are abnormal.
Lat, latency; Amp, amplitude; CV, conduction velocity; NCS, nerve conduction study; NP, no potential

is sometimes explained by the disease itself, but also by multifocal slowing due to different definitions of conduction block and important technical considerations rather than the disease itself. In this case, mostly motor slowing (<38 m/sec) and prolongation of distal terminal latency appeared, and although focal slowing appeared in some nerves, it can be seen as a demyelinating neuropathy that appeared as uniform slowing.

Electrophysiological findings of Krabbe disease could provide grounds for suspicion.

As juvenile- or adult-onset KD may show slower progression than infant-onset KD, it is not often detected in cases with a prominent form of peripheral neuropathy, unless there is a characteristic lesion in the brain magnetic resonance imaging.[9,10] In Brain MRI , KD also frequently shows lesions in the corticospinal tract, optic radiation, posterior lateral periventricular WMs, and corpus callosum.[5,10] Since the patient

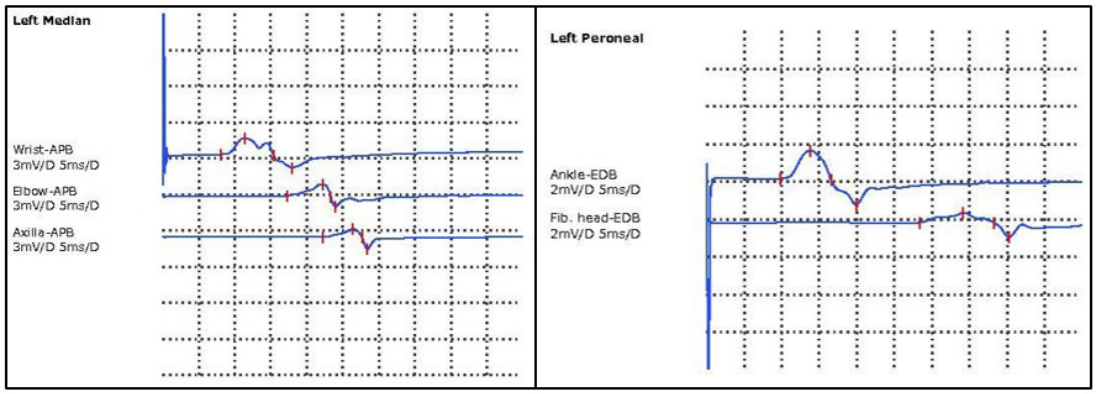

Figure 3. Motor nerve conduction studies in left median and peroneal nerves showed delayed distal motor latencies, slowed conduction velocities, and reduced compound muscle action potential amplitudes with conduction block, suggesting demyelinating neuropathy.

developed at a late age, corticospinal tract lesions may not be prominent, but some characteristic findings in KD were identified with mild degree lesions in optic radiation, corpus callosum, and periventricular WMs. Therefore, with these findings, leukodystrophy could be considered.

The coexistence of demyelinating features in CNS and PNS is a significant finding in KD, and electrodiagnostic studies and brain MRI confirmed the need for NGS and enzymatic activity tests for KD in addition to differential diagnosis of CMT.

Previously, it was not found well through Sanger sequencing tests of numerous genes, but the possibility of diagnosis can be increased through the discovery of genetic tests corresponding to white matter disorder or leukodystrophy. In patients with leukodystrophy diagnosed using these diagnostic technologies, heterogeneous clinical, electrophysiological, and neuroimaging manifestations have been frequently reported, and in the patient with KD, non-KD-specific CMT-like manifestations were confirmed in KD patients.

In conclusion, KD diagnosis was made through a decrease in GALC activity after a heterozygote *GALC* mutation was confirmed through NGS in a patient with suspected CMT and normal *PMP22* gene function. If no major mutation is found in patients with CMT, evaluation, including using NGS, for other diseases, including leukodystrophy, will be required to identify additional clues, including subtle CNS involvement.

DISCLOSURE

Ethics: This case was reviewed and approved by the Ethics Committees of the Inje University Busan Paik Hospital (IRB No. 2015-01-271). The need for informed consent was waived by the Board.

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Conflicts of interest: None

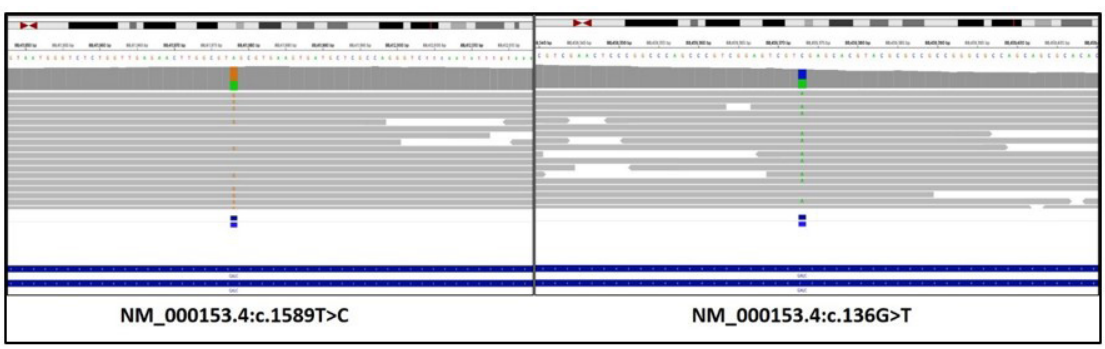

Figure 4. Integrative genomics viewer of the patient showed that two GALC variants are heterozygous for c.1589T>C and c.136G>T.

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