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Case Report

Pelizaeus-Merzbacher Disease with *PLP1* Exon 1 Duplication, Previously Misdiagnosed as Cerebral Palsy: a Case Report

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HIGHLIGHTS

- We present a case of Pelizaeus-Merzbacher disease (PMD) with proteolipid protein 1 gene mutation.
- This patient was previously misdiagnosed and regarded as cerebral palsy.
- PMD was later diagnosed via next-generation sequencing.

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Pelizaeus-Merzbacher Disease with *PLP1* Exon 1 Duplication, Previously Misdiagnosed as Cerebral Palsy: a Case Report

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ABSTRACT

Pelizaeus-Merzbacher disease (PMD) is a X-linked recessive disorder with dysmyelination in central nervous system caused by proteolipid protein 1 (*PLP1*) gene mutation. We report a case of PMD with *PLP1* exon 1 duplication, previously misdiagnosed as cerebral palsy (CP). A 25-year-old male previously diagnosed as CP visited our clinic with progressive weakness and spasticity of bilateral lower limbs. Next generation sequencing revealed hemizygous duplication of exon 1 in *PLP1*. Additionally, multiplex ligation-dependent probe amplification assay of the patient's mother showed the same mutation, which could finally confirm the diagnosis as PMD. This patient received comprehensive rehabilitation program, and helped the patient to achieve functional improvement. Proper diagnosis and therapeutic plan will be needed for the patients with PMD, before diagnosing CP rashly.

Keywords: Pelizaeus-Merzbacher Disease; Cerebral Palsy; Next Generation Sequencing

INTRODUCTION

Pelizaeus-Merzbacher disease (PMD) was first described in 1885 by a German physician, Friedrich Pelizaeus who reported a family with male individuals manifesting nystagmus, spasticity, ataxia and delayed development [1,2]. In 1910, thereafter, a German pathologist, Ludwig Merzbacher found a severe loss of myelin in the white matter by postmortem examination [3,4].

Genetic studies have identified mutations in the proteolipid protein 1 (*PLP1*) gene on X chromosome (Xq21-22) which encodes major myelin structural protein of central nervous system (CNS), is major cause of PMD [5]. The most common mutation is gene duplication followed in frequency by missense mutations, insertions, and deletions [4].

Conflict of Interest
The authors have no potential conflicts of interest to disclose.

PMD is clinically classified to connatal, classic, and X-linked spastic paraplegia type 2 (SPG2) [2]. Classic PMD is the most common type, and classic PMD patients presents hypotonia, nystagmus, and psychomotor developmental delay within the first year of life. Nystagmus often disappears and spasticity, ataxia, and choreoathetotic movements develop later. Connatal form of PMD is rare but presents the most severe course, including psychomotor developmental arrest, respiratory distress, and seizures. Most of connatal PMD patients die within the first decade of life because of respiratory problems. As SPG2 is a milder form of PMD, SPG2 patients show normal development until the first year of life, but progressive weakness and spasticity develop within a decade of life. SPG2 was at first established as a subgroup of spastic paraplegias, but further studies have shown it is allelic to PMD [2]. Adjuvant symptoms such as nystagmus, optic atrophy, ataxia, dysarthria and mental retardation are less prominent in SPG2 patients. Some SPG2 families show later onset spastic diplegia with no adjuvant symptoms and are categorized as the pure form of SPG2 [6].

Here, we report a case of classical PMD misdiagnosed as cerebral palsy (CP). A 25-year-old male who presented weakness and spasticity of both lower limbs was previously diagnosed as CP.

CASE REPORT

A 25-year-old male, who was previously diagnosed as CP spastic diplegia, visited our hospital to find a cause of progressive weakness and spasticity of both lower limbs on June 2019. He was born at 3.20 kg at 39 weeks of intrauterine period without remarkable perinatal history. In the developmental history, he was able to roll over alone at 5 months, sit alone at 6 months, and start crawling at 8 months. However, he could stand alone at 14 months; then, he first began to walk when he became 3 years old. From early childhood, he presented intellectual delay and mild dysarthria. At age of 11, he was diagnosed as CP based on the spasticity of both legs, equinus gait pattern and developmental history in the orthopedic hospital. He received both adductor tenotomy and hamstring release operation in 2005 and received both femur derotational osteotomy in 2008. Progressive weakness of both lower limbs worsened symmetrically since 2008 after the orthopedic operation, and he began to use an anterior walker for daily ambulation. From 2014, he only walked in indoor environments using the anterior walker. He began to use wheelchair in 2018. Bladder symptoms such as urinary frequency and urgency newly appeared on the same year. Motor weakness and spasticity of lower limbs did not show diurnal variation.

On the manual muscle test, hip flexors and adductors showed fair grades on both sides. Hip extensors and abductors showed poor grade on both sides. Knee flexors showed poor grade on right side and trace on left side. Knee extensors showed fair grade on both sides. Ankle dorsi-flexors and plantar-flexors showed fair grade on both sides. Muscle tone was increased in both lower limbs. Hyperactive patellar tendon reflex and ankle jerk reflex were noted on both sides. Sustained ankle clonus and positive Babinski signs were presented at both sides. Cranial nerve test showed no abnormal findings. Facial palsy or facial sensory change was not found from the patient. Neither nystagmus nor nystagmoid eye movement was noted. He presented mild dysarthria.

In brain magnetic resonance imaging (MRI), T1-weighted image exhibited no signal contrast between white matter and gray mater, but T2-weighted image revealed diffuse T2 high signal intensity in bilateral deep and subcortical white matter (Fig. 1). However, spinal cord MRI

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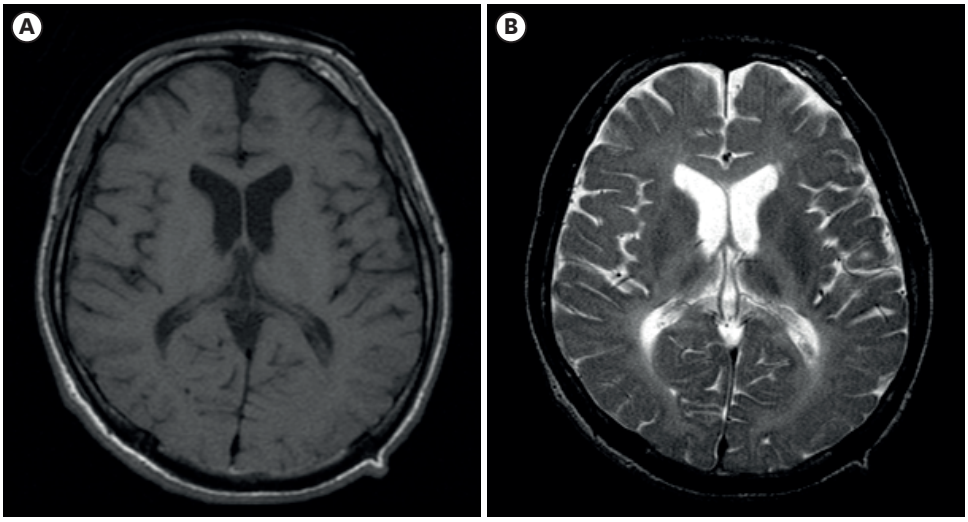

Fig. 1. Findings of brain MRI in this patient. T1-weighted MRI exhibits no signal contrast between white matter and gray mater (A), and T2-weighted MRI reveals diffuse T2 high signal intensity in bilateral deep and subcortical white matter (B).
MRI, magnetic resonance imaging.

showed no significant abnormality. Mini-Mental State Examination scored 24, showing mild cognitive impairment. In Korean Wechsler Adult Intelligence Scale-IV, his IQ scored 47, which was below 0.1 percentile. Seoul Neuropsychological Screening Battery also revealed global impairment of cognitive domains including language, memory, visuospatial function and frontal/executive function. In addition, electrodiagnostic studies such as H-reflex and F-wave revealed no evidence of peripheral demyelination.

When a familial history of the patient was carefully checked, his mother presented mild weakness of both lower limbs which had been never found, and the mother's father also had a sign of lower limbs' weakness (Fig. 2). She experienced mild spasticity of lower limbs while climbing stairs. On the manual muscle test for the patient's mother, hip extensors and abductors showed good grade on both sides. Ankle dorsi-flexor and foot evertor showed good grade on the right side. Other muscles showed normal grades.

At first, complicated hereditary spastic paraplegia including PMD was suspected for the following reasons: 1) progressive weakness and spasticity of both lower limbs, 2) familiar history

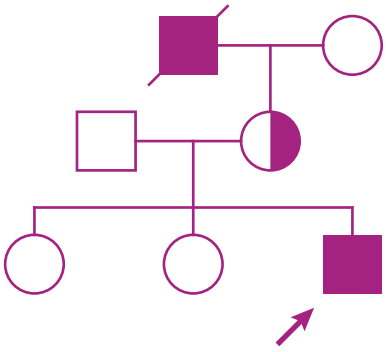

Fig. 2. Pedigree structure of the patient's family. The patient is indicated by an arrow. The patient's mother presented mild weakness of both lower limbs and difficulty in climbing stairs. The patient's grandfather presented paraplegia, and genetic evaluation was unavailable.

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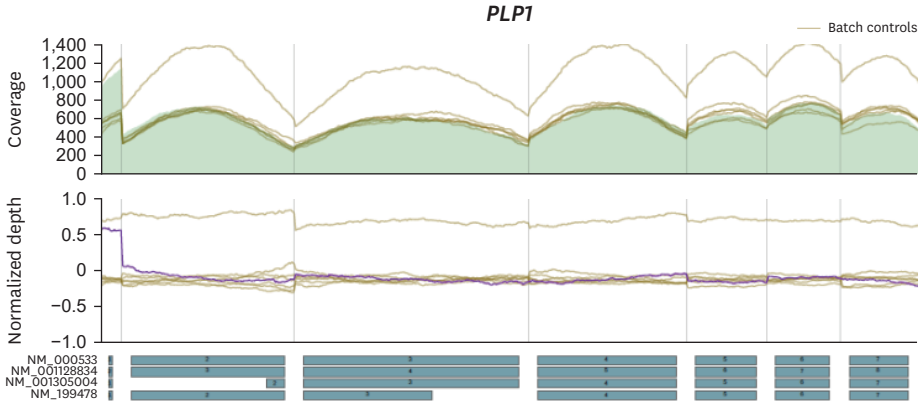

Fig. 3. Results of NGS in this patient. Hemizygous duplication of exon 1 in *PLP1* gene was identified in the NGS including 600 genes related to leukodystrophy panel.
PLP1, proteolipid protein 1; NGS, next-generation sequencing.

of paraplegia, 3) signs of leukodystrophy in brain MRI. Considering diagnosis of hereditary spastic paraplegia based on physical exams and diagnostic tests [7], next-generation sequencing (NGS) was performed, including 600 genes, by the NextSeq 550Dx system (Illumina, San Diego, CA, USA). The NGS results showed hemizygous mutations, including exon 1 duplication of *PLP1*, which was responsible for PMD (Fig. 3). Multiplex ligation-dependent probe amplification was conducted on the patient's mother, and we could find heterozygote exon 1 duplication of *PLP1*. Finally, the patient was diagnostically confirmed with PMD.

On the day of admission, modified Barthel index (MBI) scored 53 among maximum 100 score. After comprehensive rehabilitation program including strengthening exercise, standing balance training, gait training and occupational therapy for about 1 month, MBI improved to the score 72 at discharge. Approximately 1 year later, however, the score slightly decreased (Table 1). Among the items of MBI, dressing, bladder control, ambulation and chair/bed transfer showed improvement at discharge. In the item of dressing, he required minimal assistance for putting on clothes at the admission, but he could perform independently at the discharge. In the item of bladder control, he used diaper at first, but he became able to express to go to toilet and wait until the preparation. During the daytime, he used toilet instead of diaper. In the item of ambulation, he could not walk at the admission,

Table 1. Course of functional outcomes in this patient

MBI	On admission	At discharge (1 mon later)	About 1 yr later
Personal hygiene	4	4	4
Bathing self	3	3	3
Feeding	8	8	8
Toilet	8	8	8
Stair climbing	0	0	2
Dressing	8	10	8
Bowel control	10	10	10
Bladder control	0	2	5
Ambulation	0	12	8
Chair/bed transfer	12	15	12
Total	53	72	68

MBI on the day of admission, discharge and outpatient follow-up. On the day of admission, MBI scored 53 among maximum 100 score. After comprehensive rehabilitation program for about 1 month, MBI improved to the score 72 at discharge. Approximately 1 year later, however, the score slightly decreased.
MBI, Modified Barthel index.

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but he became able to walk with anterior rolling walker at the discharge. In the item of chair/bed transfer, he required one man assist for chair/bed transfer, while he could perform independently at the discharge. About 1 year later, ambulation and chair/bed transfer scores slightly decreased, because he required caregiver's assistance when moving along irregular ground and on chair/bed transfer for safety.

DISCUSSION

PMD is a X-linked recessive disorder with *PLP1* mutation, characterized by progressive spastic paraplegia, ataxia, psychomotor deterioration, and other neurological impairments. *PLP1* encodes proteolipid protein which is a major component of myelin protein of CNS and is responsible for stabilization of the myelin sheaths [8]. Thus, PMD is defined as a CNS dysmyelinating disorder, in which myelin is not formed properly [2]. Brain MRI is important in diagnosis of PMD. T1-weighted images reveal the lack of high-signal intensity in the white matter. Cortex and white matter tend to blend without demarcation. T2-weighted images show persistent high-signal intensity [4].

Various types of *PLP1* mutations such as genomic duplications, deletions and point mutations, have been reported [8,9]. Among patients with *PLP1* mutations, gene duplications are found in 60%–70% of patients and intragenic mutations are found in 15%–20% of patients [2,10]. The type of genetic mutation causes different phenotypes of PMD. The first mechanism is associated with loss of proteolipid protein function, which fails to accumulate proteolipid protein with relatively mild phenotype. The second mechanism makes a gain-of-toxic function. A point mutation leads to production of misfolded proteolipid protein, triggering increased oligodendrocyte cell death by apoptosis, with resultant dysmyelination. The third mechanism makes overexpression of proteolipid protein by duplication, consequently resulting in dysmyelination [5]. Duplication is the most common genetic mechanism, and the severity varies from classic PMD to connatal form. Duplication of *PLP1* can be divided into whole genome duplication and partial duplication. Partial duplication is rare, and shows milder clinical manifestations compared to whole genome duplication [11,12]. In this patient, we found partial duplication of *PLP1* gene, and the clinical presentation was relatively milder.

PMD is a dysmyelinating disease, but peripheral nervous system can be preserved since proteolipid protein constitutes a small proportion of the total myelin protein [13]. In our case, electrodiagnostic studies such as H-reflex and F-wave showed normal latencies representing preservation of peripheral nervous system, although previous study investigated that electrodiagnostic studies including visual evoked potentials were grossly abnormal in PMD patients [14].

For PMD patients, no definite curative treatment does not exist so far. Nevertheless, researches on gene therapy or cell therapy have been conducted to reduce expression of proteolipid protein through antisense gene therapy [5]. Researches on cell transplantation therapies using neural stem cells and glial progenitor cells are now underway [15]. However, such treatments have been not yet well established [16]. Furthermore, there are few studies about effectiveness of rehabilitation treatment on PMD patients; only a case report about rehabilitative management in an infant PMD patient was introduced [17]. From our case, we found comprehensive rehabilitation can achieve functional improvement in an adult with

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PMD previously misdiagnosed as CP despite late diagnosis and late intervention. However, our patient did not participate in rehabilitation after discharge and his MBI slightly declined. Therefore, this case report implies steady rehabilitative management and long-term follow-up should be necessary.

PMD can be easily misdiagnosed and regarded as CP. In a previous report, the patient presented similar symptoms such as progressive weakness of both legs, dysarthria, and mild mental retardation. The clinicians suspected PMD because the MRI showed demyelination patterns. Further evaluation of NGS demonstrated mutation (c.88G>C) in exon 1 of *PLP1* [18]. In our case, there are several reasons why the diagnosis was delayed. First, the patient first visited hospital at a relatively older age. Second, the clinician misdiagnosed as CP at first might conclude the diagnosis based on the spasticity of both legs and equinus gait pattern. Third, progressive weakness after the orthopedic surgery was regarded as post-operative deconditioning rather than the natural course of PMD.

Despite the similarity of clinical features of PMD and CP, a clinician's suspicion is essential because an accurate diagnosis can be made through a further genetic test nowadays. We should make correct diagnosis for appropriate treatment plans, as PMD, which has a different disease course, is essentially progressive but CP is not in nature. Although early diagnosis of PMD remains complicated, NGS rises as a key component in the diagnosis of PMD.

In conclusion, we presented a PMD patient with exon 1 duplication in *PLP1*, previously misdiagnosed as CP. Although the differential diagnosis of PMD and CP is difficult, it is important to correctly diagnose patients with spastic diplegia for proper management plan [7]. Before a clinician confirms the diagnosis as CP rashly, further considerations are required including family history, perinatal history, diurnal variation, presence of adjunctive symptoms, and brain imaging studies. If a patient previously diagnosed as CP shows a progressive course with other adjunctive neurological features, NGS should be concerned and it will be greatly helpful for early diagnosis.

REFERENCES

1. Pelizaeus F. Ueber eine eigenthümliche form spastischer lähmung mit cerebralerscheinungen auf hereditärer grundlage (multiple Sklerose). Arch Psychiatr Nervenkr (1970) 1885;16:698-710.
CROSSREF
2. Inoue K. PLP1-related inherited dysmyelinating disorders: Pelizaeus-Merzbacher disease and spastic paraplegia type 2. Neurogenetics 2005;6:1-16.
PUBMED | CROSSREF
3. Merzbacher L. Eine eigenartige familiär-hereditäre erkrankungsform (Aplasia axialis extracorticalis congenita). Zeitschr Ges Neurol Psychiat 1910;3:1-138.
CROSSREF
4. Koeppen AH, Robitaille Y. Pelizaeus-Merzbacher disease. J Neuropathol Exp Neurol 2002;61:747-759.
PUBMED | CROSSREF
5. Garbern J, Cambi F, Shy M, Kamholz J. The molecular pathogenesis of Pelizaeus-Merzbacher disease. Arch Neurol 1999;56:1210-1214.
PUBMED | CROSSREF
6. Cambi F, Tang XM, Cordray P, Fain PR, Keppen LD, Barker DF. Refined genetic mapping and proteolipid protein mutation analysis in X-linked pure hereditary spastic paraplegia. Neurology 1996;46:1112-1117.
PUBMED | CROSSREF
7. Huntsman R, Lemire E, Norton J, Dzus A, Blakley P, Hasal S. The differential diagnosis of spastic diplegia. Arch Dis Child 2015;100:500-504.
PUBMED | CROSSREF

8. Lo Giudice T, Lombardi F, Santorelli FM, Kawarai T, Orlacchio A. Hereditary spastic paraplegia: clinical-genetic characteristics and evolving molecular mechanisms. Exp Neurol 2014;261:518-539.
PUBMED | CROSSREF
9. Suzuki SO, Iwaki T, Arakawa K, Furuya H, Fujii N, Iwaki A. An autopsy case of adult-onset hereditary spastic paraplegia type 2 with a novel mutation in exon 7 of the proteolipid protein 1 gene. Acta Neuropathol 2011;122:775-781.
PUBMED | CROSSREF
10. Grossi S, Regis S, Biancheri R, Mort M, Lualdi S, Bertini E, Uziel G, Boespflug-Tanguy O, Simonati A, Corsolini F, Demir E, Marchiani V, Percesepe A, Stanzial F, Rossi A, Vaurs-Barrière C, Cooper DN, Filocamo M. Molecular genetic analysis of the *PLP1* gene in 38 families with *PLP1*-related disorders: identification and functional characterization of 11 novel *PLP1* mutations. Orphanet J Rare Dis 2011;6:40.
PUBMED | CROSSREF
11. Matsufuji M, Osaka H, Gotoh L, Shimbo H, Takashima S, Inoue K. Partial *PLP1* deletion causing X-linked dominant spastic paraplegia type 2. Pediatr Neurol 2013;49:477-481.
PUBMED | CROSSREF
12. Inoue K. Patient-derived iPS cells for unveiling the molecular pathology of Pelizaeus-Merzbacher disease: a commentary on 'Reduced *PLP1* expression in induced pluripotent stem cells derived from a Pelizaeus-Merzbacher disease patient with a partial *PLP1* duplication'. J Hum Genet 2012;57:553-554.
PUBMED | CROSSREF
13. Garbern JY, Cambi F, Tang XM, Sima AA, Vallat JM, Bosch EP, Lewis R, Shy M, Sohi J, Kraft G, Chen KL, Joshi I, Leonard DG, Johnson W, Raskind W, Dlouhy SR, Pratt V, Hodes ME, Bird T, Kamholz J. Proteolipid protein is necessary in peripheral as well as central myelin. Neuron 1997;19:205-218.
PUBMED | CROSSREF
14. Apkarian P, Koetsveld-Baart JC, Barth PG. Visual evoked potential characteristics and early diagnosis of Pelizaeus-Merzbacher disease. Arch Neurol 1993;50:981-985.
PUBMED | CROSSREF
15. Osorio MJ, Rowitch DH, Tesar P, Wernig M, Windrem MS, Goldman SA. Concise review: stem cell-based treatment of Pelizaeus-Merzbacher disease. Stem Cells 2017;35:311-315.
PUBMED | CROSSREF
16. Duncan ID, Grever WE, Zhang SC. Repair of myelin disease: strategies and progress in animal models. Mol Med Today 1997;3:554-561.
PUBMED | CROSSREF
17. Jang YC, Mun BR, Choi IS, Song MK. Rehabilitative management of an infant with Pelizaeus-Merzbacher disease: a case report. Medicine (Baltimore) 2020;99:e20110.
PUBMED | CROSSREF
18. Chen YC, Liang WC, Su YN, Jong YJ. Pelizaeus-Merzbacher disease, easily misdiagnosed as cerebral palsy: a report of a three-generation family. Pediatr Neonatol 2014;55:150-153.
PUBMED | CROSSREF