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CASE REPORT

Pelizaeus-Merzbacher Disease, Easily Misdiagnosed as Cerebral Palsy: A Report of a Three-generation Family

Yen-Chun Chen [a], Wen-Chen Liang [a,*], Yi-Ning Su [b,c], Yuh-Jyh Jong [a,d,e]

[a] *Department of Pediatrics, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan*
[b] *Department of Obstetrics and Gynecology, National Taiwan University Hospital, National Taiwan University, Taipei, Taiwan*
[c] *Department of Medical Genetics, National Taiwan University Hospital, National Taiwan University, Taipei, Taiwan*
[d] *Department of Laboratory Medicine, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan*
[e] *Graduate Institute of Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan*

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Pelizaeus-Merzbacher disease (PMD) is an X-linked recessive disorder affecting myelination of the central nervous system, and is caused by mutations of the proteolipid protein 1 (*PLP1*) gene. Clinical manifestations of PMD are variable and major features include progressive nystagmus, spasticity, tremor, ataxia, and psychomotor delay. We describe a classical PMD patient who had been misdiagnosed as cerebral palsy. He had nystagmus and psychomotor delay since infancy and tremor with ataxia developing gradually. Brain MRI revealed demyelination over white matter of the cerebral hemispheres and posterior limbs of the internal capsules. Positive family history led to subsequent mutation analysis, which identified a novel mutation (c.88G>C) in *PLP1* in the proband, as well as his affected brother and maternal uncle, and asymptomatic maternal grandmother, mother and two sisters. Therefore, PMD should be considered in a cerebral palsy-like patient with or without positive family history. Mutation analysis is crucial for early diagnosis and further genetic counseling.

* Corresponding author. 100 Tz-You First Road, Kaohsiung 807, Taiwan.
E-mail address: 880320@ms.kmuh.org.tw (W.-C. Liang).

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1. Introduction

Pelizaeus-Merzbacher disease (PMD) is a rare X-linked recessive demyelinating leukodystrophy in the central nervous system (CNS).[1] Major clinical features of PMD include progressive nystagmus, spasticity, tremor, hypotonia, ataxia, and psychomotor delay in infancy or early childhood. PMD is caused by mutations of the proteolipid protein 1 (*PLP1*) gene on X chromosome (Xq21-22).[1] The *PLP1* encodes the myelin proteolipid protein (PLP) and DM20, an alternatively splicing product of PLP. [2] PLP is the most abundant membrane protein of CNS myelin[2] and may be a mediator for membrane signaling.[3] More than 100 mutations of *PLP1* have been found in PMD, including duplications, point mutations, insertions and deletions.[1] Duplication is the most common type among these mutations.[4,5] Various mutations of *PLP1* lead to abnormal myelination, death of oligodendroglia in the CNS, secondary axonal loss, and have been implicated in a wide spectrum of neurologic diseases.[2,6]

PMD is clinically classified to connatal, classic, transitional, X-linked spastic paraplegia Type 2 (SPG2), and *PLP1* null syndrome.[1] The patients with connatal PMD show the most severe phenotype, including nystagmus, hypotonia, developing spasticity, respiratory distress, and seizures at birth or during the first week of life. Most connatal PMD patients die of aspiration problems before age 10 years. Classic PMD is the most common type of PMD. These patients develop the symptoms without respiratory involvement within the first year of life and can survive until the sixth decade of life. Transitional PMD patients have overlapping features between the connatal and classic forms. SPG2 is a milder form of PMD, presenting with the clinical features in the first 5 years of life. Only SPG2 patients can reproduce, in contrast to all other forms of PMD. *PLP1* null syndrome is caused by null mutation and presents in the first 5 years of life. *PLP1* null syndrome patients develop mild spastic quadriparesis, ataxia, and mild to moderate cognitive difficulties. No nystagmus is observed in *PLP1* null syndrome patients. Diagnosis of PMD depends on clinical features, brain magnetic resonance imaging (MRI), and genetic testing of *PLP1*. T2-weighted and FLAIR brain MRI shows diffuse or patchy high signal intensity in the white matter of the cerebrum, cerebellum, and brainstem, suggesting demyelination in these affected areas and allowing an accurate assessment.[7,8]

In this report, we describe a classical PMD patient who had been misdiagnosed as cerebral palsy. Mutation analysis revealed a novel mutation (c.88G>C) in Exon 1 of *PLP1*. Further screening of his three-generation family identified asymptomatic female carriers, which thus makes genetic counseling possible.

2. Case Report

The 29-year-old male patient had been diagnosed as cerebral palsy. He was brought to our outpatient department for counseling due to a positive family history of other family members. He was wheelchair-bound but could transfer himself with arms. He was aware of the surroundings and able to communicate with others although with dysarthria. Neurological examination revealed increased muscle tones and deep tendon reflexes, especially in lower extremities. Horizontal nystagmus and head tremor were also observed. Scoliosis and joint contractures in ankles were present. Tracing the patient's history, prenatal examinations were uneventful. He was born full term via smoothly spontaneous delivery. At age 3—4 months, poor head control and roving eye movements were observed. Progressive lower limb spasticity also developed gradually. He could not sit independently until age 5 years. He also had speech delay with dysarthria. Neither respiratory insufficiency nor seizure was noted during his growing up. His mental development was mildly retarded but he was socially interactive. As for the family history, he was the second child of non-consanguineous parents. His two sisters were healthy. His

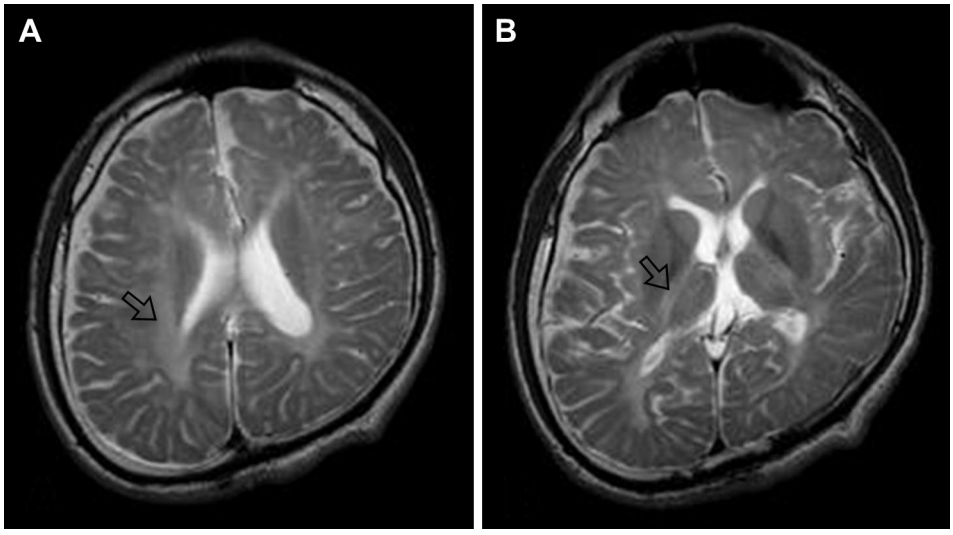

Figure 1 Brain MRI of the index case showed high signal intensity in the white matter of (A) the cerebral hemispheres and (B) the posterior limbs of the internal capsule. Axial MRI (TE: 101.088 ms, TR: 400 ms).

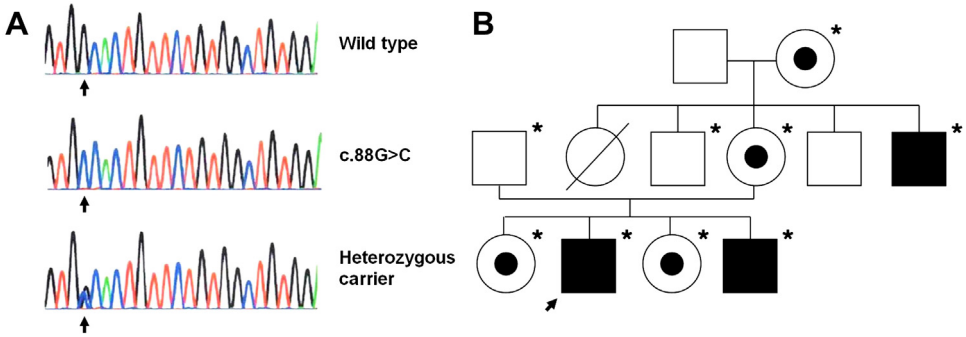

Figure 2 Mutation analysis of the three-generation pedigree of the family. (A) Sequence analysis of Exon 1 of the *PLP1* shows a c.88G>C missense mutation. (B) Pedigree of the three-generation pedigree indicates affected, carrier and unaffected individuals. ■ = affected male; ⊙ = carrier female; ↗ = proband; * = DNA obtained.

younger brother had similar but more severe symptoms. General muscle weakness was observed since birth. Then nystagmus, head tremor, dysarthria, seizures, spasticity in all extremities, and severe cognitive impairment gradually developed. He needed a wheelchair and had no self-care ability. His maternal uncle also had similar clinical features as the index patient. He developed nystagmus, lower extremity weakness, mild dysarthria, and slight mental retardation. He had used a wheelchair since age 9—10 and now lived independently. All were diagnosed as cerebral palsy. No associated neurophysiological tests had been performed.

Based on the findings above, we arranged for further brain images. T2-weighted brain MRI of the patient showed high signal intensity over the white matter of the cerebral hemispheres and posterior limbs of the internal capsules (Figure 1), indicating diffuse demyelination within these areas, which led to the diagnosis of PMD. Chromosomal and mutation analyses were subsequently done, which revealed male karyotype, 46, XY and a novel missense mutation c.88G>C in Exon 1 of the *PLP1* (p.Ala30Pro). We therefore screened the three-generation family of the proband for this mutation. c.88G>C in *PLP1* was identified in his symptomatic brother and uncle, as well as asymptomatic members including maternal grandmother, mother and two sisters, but not in his father or asymptomatic uncle (Figure 2).

Accordingly, the patient was finally diagnosed as classical PMD with a novel missense mutation (c.88G>C) in Exon 1 of the *PLP1*.

3. Discussion

As in the PMD patient in our report, this disease is often misdiagnosed as cerebral palsy because of the similar phenotypes in infancy or early childhood. To make a differential diagnosis between PMD and cerebral palsy is important for genetic counseling and outcome prediction. Cerebral palsy is characterized as a disorder of motor impairment with nonprogressive course due to an insult in the immature brain. As a result, the key characteristics to distinguish PMD from cerebral palsy include progressive pattern, a positive male-to-male family history and some uncommon features such as tremor and nystagmus. Brain MRI also plays an important role differentiating PMD and cerebral palsy. Brain MRI of cerebral palsy patients often shows white matter damage in periventricular areas and the basal ganglia.[9] In contrast, brain MRI of PMD may reveal leukodystrophy in the entire central white matter of the cerebrum, cerebellum, and brainstem. In addition to image study, mutation analysis of *PLP1* is also essential for early diagnosis of PMD.

PLP is a 276-residue integral membrane protein with four α-helix transmembrane domains. Point mutations of the transmembrane domains of PLP have been demonstrated to cause aberrant assembly of PLP and lead to PLP being retained in the endoplasmic reticulum.[10,11] Previous studies have also shown that PLP transmembrane domain mutations could trigger the unfolded protein response, oligodendrocyte apoptosis, and demyelination of the CNS.[12,13] Here, we report a novel missense mutation of G to C change at nucleotide 88 in the *PLP1*. The mutation results in an alanine to proline substitution in the first transmembrane domain of the PLP. Therefore, this PLP mutant is assumed to influence the stability of transmembrane structure, resulting in protein misfolding and accumulation in the endoplasmic reticulum, and leading to clinical disorders of PMD.

In conclusion, if a cerebral palsy-like patient presents with a progressive course and diffuse white matter involvement in brain MRI, PMD should be considered first whether this is a sporadic condition or there is a positive family history. Genetic analysis may be of great help for early diagnosis.

Conflicts of Interest

The authors have no conflicts of interest relevant to this article.

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