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A Rare Heterozygous Female Patient with X-Linked Recessive Pelizaeus-Merzbacher Disease: A Case Report

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Abstract

Pelizaeus-Merzbacher disease (PMD) is an X-linked disorder caused by mutations in the proteolipid protein-1 (PLP1) gene which results in central hypomyelination. As an X-linked condition, PMD were primarily reported in males, females were rarely affected. Herein we report a female sporadic PMD case with no relative family history, who presented with congenital and progressive ataxia..

Keywords: Pelizaeus-Merzbacher disease; Proteolipid protein-1; Ataxia; Female

Background

Pelizaeus-Merzbacher disease (PMD) is a rare, X-linked recessive genetic disorder caused by mutations in the proteolipid protein 1 (PLP1) gene on Xq22, which encodes the proteolipid protein of myelinating oligodendroglia [1]. As an X-linked condition, PMD were primarily reported in males [2-3]. The typical neurological impairments of PMD include nystagmus, hypotonia, tremors, titubation, spasticity, ataxia, and cognitive impairment and developmental retardation [4]. Patients with PMD have a diffuse pattern of hypomyelination on MRI: increased signal intensity on T2-weighted or FLAIR scans in the cerebral hemispheres, cerebellum, and brainstem [3,5].

Case Presentation

This patient was a 26-year-old female born as the second child of her healthy nonconsanguineous parents at full-term normal delivery. No genetic history was acquired from her family. There was no obvious abnormality in the delivery process, but it is noteworthy that at 28 weeks of gestation, the mother of the patient had been treated with insecticidal treatment for Ascaris infection, but the specific treatment medications are unknown. The patient presented with physical developmental retardation, unable to stand until 2 years old. From then on, the patient could walk slowly and unsteadily, confirmed as ataxia later.

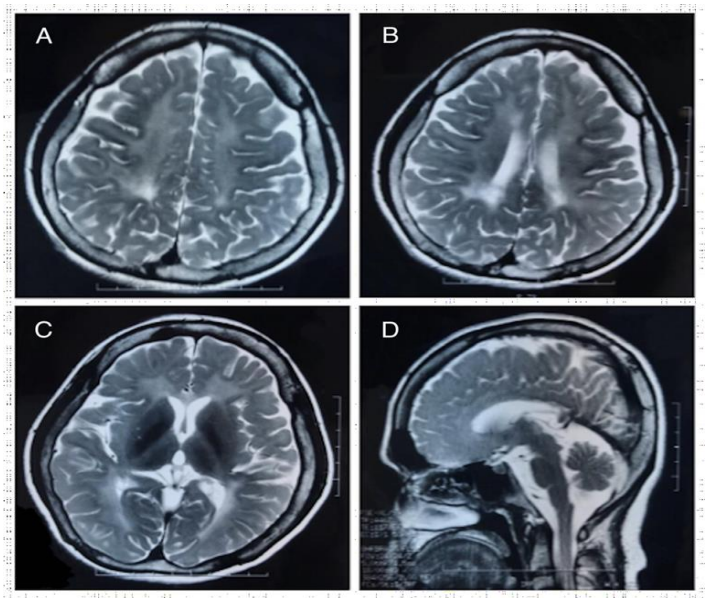

Figure 1: *Cranial magnetic resonance imaging (MRI) scans of the female patient. T2-weighted or FLAIR scans showed the high-intensity signals in the central white matter of the cerebral hemisphere.*

The patient did not seek medical treatment for family economic reasons until she was 26 years old when her ataxia symptoms became so severe that her self-care ability was impaired.

Neurologically she presented with spastic gait, dysmetria on finger-to-nose or heel-to-shin testing, increased knee and patellar reflexes, and bilateral Babinski signs. Her cognitive performance was mildly impaired, with neuropsychological testing below average level. Cranial magnetic resonance imaging (MRI) scan showed diffuse pattern of hypomyelination in both cerebral hemispheres, flattening of the corpus callosum and consideration of dysplasia (Figure 1).

A genetic study of second generation sequencing later confirmed a point mutation in PLP1 gene (c.353C>G, p.T118R, NM_000533, Figure 2) in the blood sample of patient. This analysis confirmed that this patient had heterozygous PMD with c.353C>G (p. T118R).

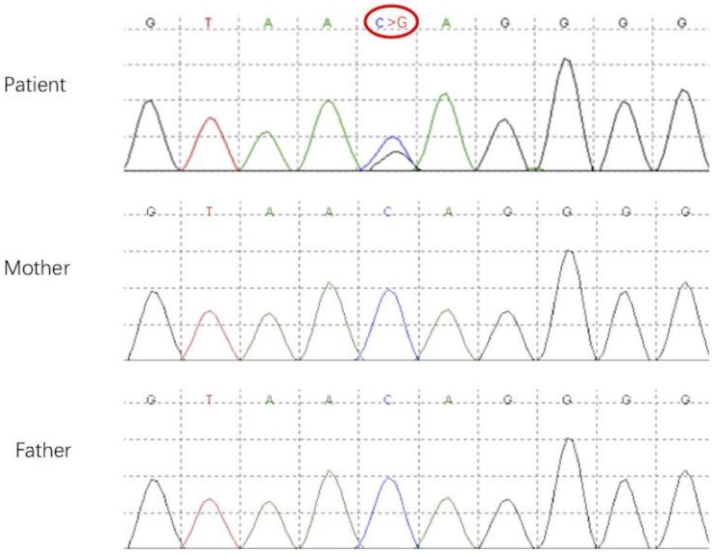

Figure 2: *The whole-exome sequencing of the female patient. A point mutation in PLP1 gene (c.353C>G, p.T118R, NM_000533) was confirmed in blood sample of patient, rather than her parents.*

Discussion and Conclusions

PMD was firstly reported by Friedrich Perezius in 1885 on five boys in a family with nystagmus, limb spasms and developmental retardation. In 1910, Ludwig Merzbacher independently found that all affected members of this family shared a common female ancestor. Pelizaeus and Merzbacher identified that PMD is characterized by X-linked inheritance, neonatal neurological deficits and a low myelin sheath pattern in central nervous system pathology. The prevalence of PMD in China or all over the world remains unknown, but according to a local epidemiological survey, the prevalence of PMD in Japan is estimated to be 1.45 in 100,000 live births [6].

As PMD is rare and mostly affects male, female PMD is hardly diagnosed in clinic. After a review of the literature, we only retrieved 8 cases of affected females with a genetic diagnosis of PMD [7-9]. The symptoms of PMD are usually unspecific, including nystagmus, hypotonia, tremors, titubation, spasticity, ataxia, cognitive impairment and developmental retardation [4]. The most prominent symptom of this female patient is ataxia, which had misled us into another disease “hereditary ataxia” at first. However, PMD patients usually have specific features in magnetic resonance imaging (MRI) characterized by diffusely low-intensity T1-weighted and high-intensity T2-weighted signals in the central white matter of the cerebral hemispheres, cerebellum, and brain stem [10], as we have observed in this patient. Final diagnosis of PMD depends on the detection of mutations in the PLP1 gene 1.

PLP1 is synthesized in the rough endoplasmic reticulum of oligodendrocyte and is subsequently transported to the cell membrane of these cells, where it is involved in myelin formation [11-12]. Mutations or alterations of the PLP1 gene cause a spectrum of X-linked dysmyelinating disorders of central nervous system, ranging from the most severe connatal form of Pelizaeus-Merzbacher disease to the mildest form of spastic paraplegia type 2 [13-14]. Chromosomal Xq22 microduplications involving PLP1 were observed in 60-70% of PMD patients. Point mutations, including missense, nonsense and splicing, have been detected in 10-25% of patients and deleterious mutations are rare [15].

Heterozygous females may be affected in one of two ways: 1. perturbed X-inactivation in brain cells, when the PLP1 mutation causes little or no oligodendrocyte apoptosis; 2. Heterozygous females may be affected by an X-linked recessive pattern through the gene deletion and skewed X chromosome inactivation [7-9]. The cause of PLP1 mutation in this female patient is unclear, and we cannot correlate the PLP1 mutation in this patient to the Ascaris treatment in her mother during pregnancy, as the specific drugs remains unknown. Unfortunately, there is no specific therapy for PMD patients with PMD. Currently, some new proofs indicated that neural stem cell and glial progenitor cell transplantation may be a potential treatment in the future [16].

Acknowledgments

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Contribution

Chen P and Peng Q contribute to this work equally.

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