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Case report

Mutations in the *PLP1* gene residue p. Gly198 as the molecular basis of Pelizeaus–Merzbacher phenotype

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Abstract

Pelizaeus–Merzbacher disease (PMD) and spastic paraplegia type 2 (SPG2) are rare X-linked allelic disorders caused by mutations in the *PLP1* gene, encoding the main component of myelin, proteolipid protein 1 (PLP1). Various types of mutations, acting through different molecular mechanism, cause the diseases.

Duplications of variable size at Xq22.2, containing the entire *PLP1*, are responsible for more than 50% of PMD cases. Other causes of PMD include point mutations, gene deletions and triplications. There is a spectrum of *PLP1*-related disorders with some correlation between the type of mutation and phenotype. Generally the missense mutations cause the more severe forms of the disease, the most common *PLP1* duplications, result in the classical PMD whereas deletions and null mutations in mild form of PMD and SPG2.

We present a patient with c.593G>A substitution in the exon 4 of the *PLP1* gene causing a *novel* missense mutation p.Gly198Asp, finally diagnosed as PMD but showing an atypical MRI picture.

Keywords: Pelizaeus–Merzbacher disease; *PLP1* gene; Missense mutation

1. Introduction

Pelizaeus–Merzbacher disease (PMD, MIM 312080) is a rare X-linked recessive hypo/dysmyelinating leukodystrophy. This disorder has been described in patients of Asian and Caucasian origin. It is probably the most common form of congenital hypomyelinating disorders in the central nervous system (CNS), but even the exact frequency of this group of diseases is currently unknown. According to Orhpanet data the prevalence of PMD is 1-9/1,000,000 (www.orpha.net). The incidence of this disease was reported as 0.13 in 100,000 live birds in Germany but ten times higher in Czech Republic [1].

PMD is caused by mutation in the *PLP1* gene (MIM 300401) encoding the main myelin component, proteolipid protein 1 (PLP1). Mutations in the same gene also cause spastic paraplegia type 2 (SPG2, MIM 312920), and both disorders encompass a spectrum of phenotypes generally call as *PLP1-related* disorders differing in age of onset, clinical picture, severity and rate of progression [2,3]. The phenotypes in this spectrum cannot be easily categorized into distinct syndromes however, according to the age of onset and its severity are classified as severe connatal (cnPMD), classical PMD (clPMD) and milder

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forms of PMD/SPG2 (the *PLP1*-null phenotype, complicated/pure SPG2) [1,6]. Because clinical cases combining features of connatal and classical PMD have been identified, transitional form of PMD is also described [3]. This phenotypic variability is due to different types of *PLP1* mutations acting through different cellular mechanisms [3,4]. Generally the missense mutations cause the more severe forms of the disease, the most common, *PLP1* duplications, result in the classical PMD whereas deletions and null mutations in mild form of PMD and SPG2 [3,5], but it should be pointed out that most of the SPG2-causing mutations are also missense substitutions. However there is correlation between localisation of the amino-acid missense substitution and disease severity. Mutations causing the most severe form of PMD are mainly localized in transmembrane segments of PLP1 and in the first extracellular loop of the protein [5].

We describe a patient carrying the novel *PLP1* missense mutation p.Gly198Asp. The patients was initially diagnosed as atypical PMD, however he was finally classified as having classical PMD, but showing not typical white matter abnormalities in MRI.

This is the second reported case of a patient with a missense variant at the PLP1 residue p.Gly198 [6]. If we consider phenotypes due to *PLP1* mutations p.Gly198Asp and p.Gly198Arg we believe that substitutions at this residue may give atypical features of the PMD phenotype.

2. Case report

2.1. Clinical characterization

The 17-year-old boy was born after an uncomplicated full term pregnancy (weight 3650 g, Apgar score 10), as the first child of non-consanguineous healthy Polish parents without significant family history. He was diagnosed in the first year of life with cerebral palsy. At 4 years of age he was noted to have horizontal nystagmus, which persisted. The patient was able to sit and walk with support at 18 and 30 months of age, respectively. Neurological examination at 6 years of age revealed significantly decreased muscle tone with mild ataxia on sitting. He presented also developmental delay with progressive deterioration of cognitive functions and regression of verbal functions. At 8 years of age, increased muscle tone was revealed with brisk deep tendon reflexes, positive Babinski reflexes, and positive ankle clonus. Within the next two years he developed severe spasticity, contractures in upper and lower limbs and scoliosis. He lost walking and sitting abilities. Rapid progression of dysphagia led to severe weight loss and gastrostomy feeding was introducing to improve nutrition.

Brain MRI at 14 years of age showed diffuse hyperintensity of the cerebral white matter on T2-weighted images, particularly in the parieto-occipital region and only can be explained by hypomyelination (Fig. 1). The parietal white matter was hypointense on T1-weighted sequences, whereas the remaining white matter was almost isointense with the cortex.

Findings of evoked potentials of brainstem performed at 13 years of age were abnormal. The first I response was obtain with decreased amplitude, and the next four II–V responses were absent.

Electrolytes, blood glucose, renal, liver, thyroid function tests, bone profile, VLFCA and white cell enzymes were normal. Metachromatic leukodystrophy was excluded, as well as, Krabbe and Schindler disease, due to normal lysosomal enzymes activity.

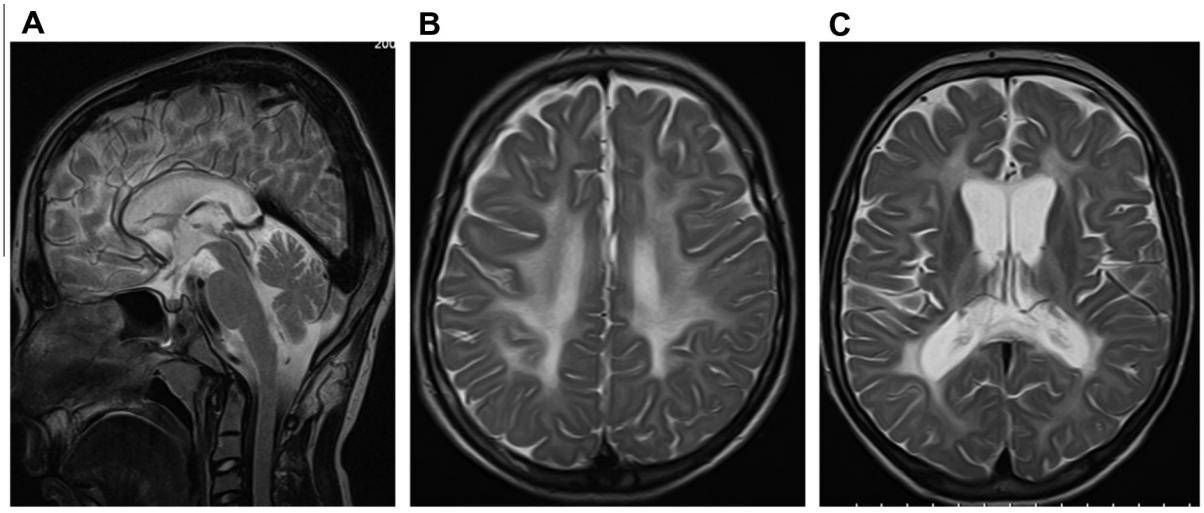

Fig. 1. Sagittal and axial T2-weighted brain MRI images of the proband at 14 years of age. (A) Note: the thin and unmyelinated corpus callosum. (B) Diffuse white matter hyperintensity of the centrum semiovale is seen. Lack of myelination of the corticospinal tracts. (C) The image at the level of basal ganglia. Abnormal, high signal of the internal and external capsules. The periventricular white matter is also involved. Enlarged lateral ventricles are seen.