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Case Report

Pelizaeus-Merzbacher disease-like disorder in an Indian girl with a missense variant in GJC2 gene

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ABSTRACT

Pelizaeus-Merzbacher-like disease 1 (PMLD1) is a slowly progressive leukodystrophy that typically presents during the neonatal or early infantile period with nystagmus, commonly associated with hypotonia, delayed acquisition of motor milestones, speech delay and dysarthria. We present a 7-year-old female born to a non-consanguineous marriage with developmental delay. On examination, she had 22 teeth, and nystagmus with pseudophakia. Neurological examination showed spasticity with increased deep tendon reflexes. On investigation, MRI of the brain done at 3 years showed hypomyelination. Targeted exome sequencing revealed a homozygous non-synonymous variation c.138C>G in exon 2 of the *GJC2* gene. Sanger sequencing was done which showed the presence of a variant in the heterozygous state in both parents. PMLD1 should be suspected in any child presenting with diffuse hypomyelination with abnormal eye movements, especially in a girl child with Pelizaeus-Merzbacher disease phenotype with hypomyelination in the pons.

Keywords: Pelizaeus-Merzbacher disease-like disease, *GJC2* gene, India

INTRODUCTION

Pelizaeus-Merzbacher-like disease (PMLD) (OMIM 608804) is like Pelizaeus-Merzbacher disease (PMD) except for mutation within the *PLP1* gene. PMLD is an autosomal recessive hypomyelinating leukodystrophy caused by mutations in the gap junction protein gamma-2 gene (*GJC2*) (OMIM 608803). It was previously known as *GJA12*. This gene encodes the connexin 47 protein (Cx47), a connexin family member and gap junction protein with critical function in astrocytes and oligodendrocytes.[1,2] Mutation of *GJC2* halts Cx47 to reach the membrane, which results in loss of function.[3] The prevalence is exactly not known and only few cases are reported. Here, we report the first case of genetically confirmed PMD-like disorder from India.

CASE REPORT

We present a 7-year-old female born to a non-consanguineous marriage with a history of delayed development of milestones. At present, she is walking with an ataxic gait, speaks in phrases with dysarthria and needs support for eating and putting on clothes. She underwent bilateral cataract surgery around 18 months of age. On examination, the head size of 48 cm (WHO Z: -1 to -2), the height of 110 cm (WHO Z: -1.98), the weight of 20 kg (WHO Z -0.74), 22 teeth, nystagmus, and pseudophakia were noted. Neurological examination showed pyramidal and cerebellar signs.

On investigation

Complete hemogram, liver function, renal function, arterial blood gas, serum ammonia, and lactate were all normal. MRI brain done at 3 years of age showed diffuse white matter hyperintensities in the subcortical and deep white matter in axial T2W images [Figure 1a-c] at the level of basal ganglia, corona radiata and pons shows diffuse white matter hyperintensities in the subcortical and deep white matter with relative sparing of the anterior limb of internal capsules. Pontine and bilateral dentate hilar hyperintensities are also noted. Axial T1W images [Figure 1d and e] are showing normal myelination in cerebral WM; however, pons shows a subtle hypointensity, and normal corpus callosum [Figure 1f]. The MRI findings are suggestive of diffuse hypomyelination including pons and cerebellum. Targeted exome sequencing showed a homozygous non-synonymous variation c.138C>G in exon 2 of the *GJC2* gene. Sanger sequencing showed the presence of variants in a heterozygous state in both parents.

DISCUSSION

In this report, we present a 7-year-old female with global developmental delay, microcephaly, nystagmus, cerebellar and pyramidal signs, cataracts and hypomyelination in an MRI of the brain. The child had been clinically suspected to have PMD-like disorder as the child had PMD features and was a female child. However, unusual features were the presence of cataracts. We also considered the following differentials such as hypomyelination with congenital cataract (HCC), hypomyelination with atrophy of basal ganglia and cerebellum (HABC), hypomyelination, hypogonadotropic hypogonadism and hypodontia (4H syndrome), fucosidosis and sialic acid storage disorder. As there were no basal ganglia changes or hypodontia or T1 hypointensities in deep white matter, HABC, 4H syndrome and HCC were ruled out, respectively. Dysmorphism, coarse facies and other features were not present, hence fucosidosis, and sialic acid storage disorder was ruled out.

Uhlenberg *et al*. reported a Turkish family, in which multiple members had the characteristic clinical features of PMD; 312080, in the early infancy.[1] It is like our case except that in the current report, the child also had a cataract. Bugiani *et al*. screened for GJA12 mutations in 10 PMLD families originating from Italy, Pakistan, and Saudi Arabia. Three novel homozygous GJA12 mutations were identified. The mutations segregated with the disease with respect to an autosomal recessive trait and showed one missense (G236S) and two non-sense (L281fs285X and P131fs144X) changes.[4]

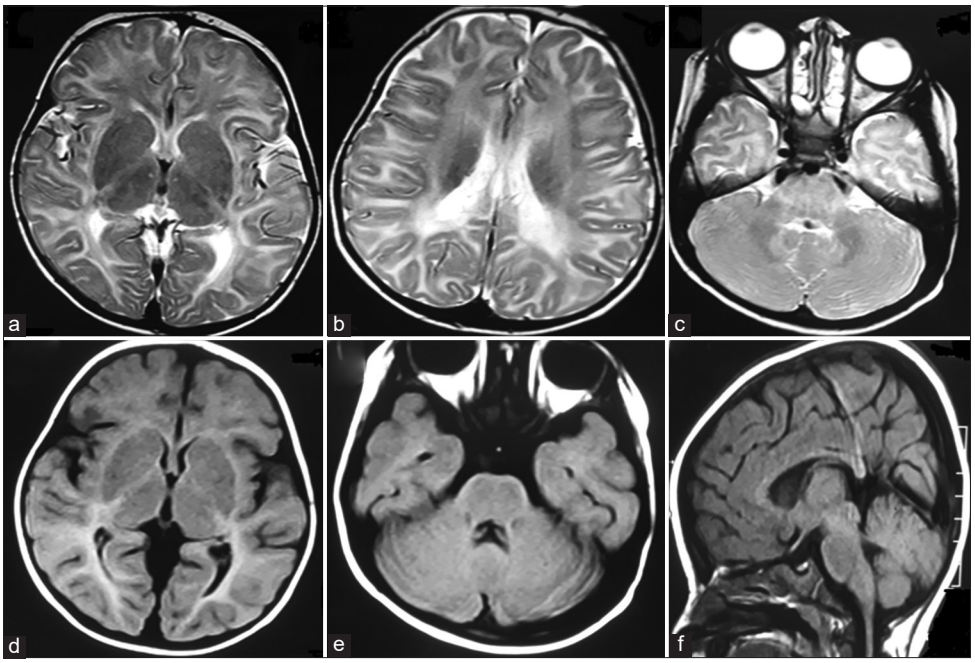

Figure 1: Axial T2W images (a-c) at the level of basal ganglia, corona radiata and pons show diffuse white matter hyperintensities in the subcortical and deep white matter with relative sparing of the anterior limb of internal capsules. Normal myelination-related hypointensity is also noted as tiny streaks in the middle aspect of the posterior limbs of internal capsules. Pontine and bilateral dentate hilar hyperintensities are also noted. Axial T1W images (d and e) are showing normal myelination in cerebral WM; however, pons shows a subtle hypointensity. Sagittal T1W image (f) shows similar findings with normal morphology of the corpus callosum. Findings are suggestive of diffuse hypomyelination.

PMLD1-associated *GJC2* pathogenic variants result in the loss of function of Cx47.[1,5,6] It either fails to properly localize to the cell surface or mislocalises to the endoplasmic reticulum.[7]

The variant was reported by Wang *et al*. in their report with patient two having a homozygous missense mutation at c.138C>G (p.I46M) causing PMD-like disease.[8] The clinical features reported in Patient 2 by Wang *et al*. like our case. According to ACMG criteria, the variant can be classified as pathogenic. This is a rare association of PMD-like disease having cataracts.

Gulati *et al*., in their series of leukodystrophies from North India, reported a radiologically diagnosed case of PMD-like disease in a 9-year-old female with no mutation in the PLP gene.[9] This is the first report of a genetically confirmed case of PMD a disease from the Indian sub-continent due to a mutation in the *GJC2* gene. No definite treatment exists for this disease and treatment is supportive.

CONCLUSION

Any child who presents with the predominant motor delay with nystagmus, cerebellar and pyramidal signs with hypomyelination and PMD-like disorder should be considered in addition to PMD especially when there is hypomyelination in the pons and cerebellum in a girl child.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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