A genetically proven case of Pelizaeus-Merzbacher disease: Clinicoradiological clues

Sir,

A 5-month-old boy presented with global developmental delay, generalized looseness of the body, and jerky, chaotic eye movements. There was no history of seizures, impaired hearing, swallowing difficulty, drooling of saliva, or impaired sensation. His family history, antenatal history, and neonatal history were

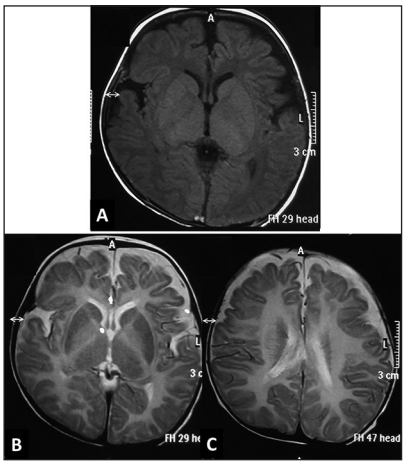

Figure 1: T1- (a) and T2 (b and c)-weighted axial MR images of the brain show diffuse hypomyelination of white matter appearing isointense on T1-weighted images and hyperintense on T2-weighted images. The internal capsule is unmyelinated (a and b) as well

unremarkable. Salient features on examination were impaired cognition, pendular nystagmus, axial and appendicular hypotonia with preserved antigravity movements, brisk-deep tendon reflexes, and bilateral upgoing plantars.

Magnetic resonance imaging (MRI) of the brain revealed diffuse hypomyelination [Figure 1]. In view of global developmental delay, central hypotonia and pendular nystagmus, the possibility of Pelizaeus-Merzbacher disease (PMD) was kept. A triplication in the proteolipid protein 1 (PLP1) gene at Xq22 confirmed the diagnosis.

PMD is an X-linked recessive hypomyelinating leukodystrophy, characterized by early-onset pendular nystagmus, global developmental delay, and central hypotonia. It is caused by mutations of the PLP1 gene.[1] The spectrum of PLP1-related disorders include the severe connatal PMD, intermediate classical PMD, which is less severe, and the milder phenotype of spastic paraplegia type 2 (SPG2).[2] Whereas the severe forms arise due to missense mutations, deletions and null mutations account for the milder variants such as SPG2. However, the most common mutations are duplications that lead to the classical intermediate form of PMD, as is the current case. Triplication mutations, as described in the current case, are extremely rare. The PLP1 gene encodes the PLP1 and its smaller, spliced form DM20. PLP1/DM20 is the major constituent of oligodendrocytes that forms myelin in the central nervous system and in addition, plays a pivotal role in stabilizing and sustaining the myelin sheath. Moreover, the PLP1/DM20 expression is not solely restricted to the oligodendrocytes. It is, as well, expressed in Schwann cells and neurons of the corticospinal tracts and the brainstem. The expression of this gene across multiple sites in the central nervous system is responsible for the wide spectrum of phenotypic expression of PLP1-related disorders.[3]

Leukodystrophies presenting in infancy can be either hypomyelinating or dysmyelinating.[2] PMD is a hypomyelinating leukoencephalopathy and close clinico-radiological differentials are Pelizaeus-Merzbacher-like disorder (PMLD) and Salla disease. Characteristic clinical features and radiological presence or absence of basal ganglia, cerebellum, and brainstem involvement helps in differentiating hypomyelinating disorders. This helps in choosing the right genetic-diagnostic test.[3] PMLD is characterized by cerebellar atrophy, whereas Salla disease has characteristic N-acetylaspartate (NAA) peak on magnetic resonance (MR) spectroscopy.[2,4] The genetic defects in PMLD affect the gap junction alpha-12 (GJA12) and sex-determining region Y (SRY)-box 10 (SOX10) gene that are responsible for the formation of oligodendrocytes in very early stages.[5] In Salla disease, the underlying pathogenic defect is in a lysosomal transporter protein for sialic acid. Dysmyelinating leukodystrophies such as Cockayne disease, metachromatic leukodystrophy, Krabbe disease, and Canavan disease can also present in infancy but characteristic clinical and radiological features differentiate these disorders from PMD.[2]

Recognition of these characteristic clinico-radiological patterns is imperative for appropriate genetic counselling and prognostication, as these disorders have a clinically rapid downhill course.

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Conflicts of interest
There are no conflicts of interest.

Lokesh Saini, Biswaroop Chakrabarty, Atin Kumar[1], Sheffali Gulati

Departments of Pediatrics and [1]Radiodiagnosis, All India Institute of Medical Sciences, New Delhi, India

For correspondence:
Dr. Sheffali Gulati, Department of Pediatrics, Division of Child Neurology, All India Institute of Medical Sciences, New Delhi - 110 029, India.
E-mail: sheffaligulati@gmail.com

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