

Pelizaeus-Merzbacher Disease: A Rare Cause of Spastic Paraplegia

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Abstract: Pelizaeus-Merzbacher disease is a rare hypomyelinating leukoencephalopathy disorder of central nervous system caused by mutations of the proteolipid protein 1 (PLP1) gene, and is inherited in X-linked recessive pattern. Clinical manifestations of PMD include progressive nystagmus, spasticity, tremor, ataxia, and psychomotor delay in variable proportions. Symptoms generally manifest early in the life in classical and connatal forms but may be delayed. Clinical diagnosis can be supplemented by magnetic resonance imaging and genetic studies. These patients may survive up to fourth or fifth decade provided good care is provided. We are presenting a case of 18 years girl with slowly progressive spastic paraparesis and leukodystrophy diagnosed with Pelizaeus-Merzbacher Disease.

Keywords: Pelizaeus-Merzbacher disease, leukodystrophy, spastic paraplegia, nystagmus.

I. Introduction

Pelizaeus-Merzbacher disease (PMD) is a leukoencephalopathy affecting the white matter of the brain. In 1885 Friedrich Pelizaeus described a large family in which the boys developed neurological symptoms at an early age. In 1910 Ludwig Merzbacher studied the same family and noted that while myelin, the white matter of the brain, was generally lacking in the brains of boys with the disease, the myelin which covered nerve fibres outside the brain was normal^[1]. Islands of myelin enveloped the blood vessels of the brain, producing a spotted (tigroid) white matter pattern. He also noted that the nerve cells in the brain showed no changes and that there were no signs of inflammation. We are presenting a case of 18 years girl with slowly progressive spastic paraparesis, tremors, nystagmus with evidence of hypomyelination in MRI brain.

II. Case Report

An 18 year old girl presented in medicine emergency department with complains of progressive ataxic gait and painless paraplegia without bladder or bowel involvement since 4 years of age. Her weakness was almost symmetric in onset, gradually progressive in nature and there was no diurnal variation, fever, trauma or seizures preceding the onset. She was unable to sit independently at the age of 6 years. She was wheel chair bound now. Her mother denies any bad perinatal history or any episode of birth asphyxia. She was born full term by normal vaginal delivery. Detailed developmental history could not be elicited; however, her mother remembers delayed speech. She has one elder sister who is healthy. No history of consanguineous marriage in family.

On examination patient was oriented to time place and person. She was able to communicate with mild dysarthria. Bilateral non fatigable horizontal nystagmus and head tremor were noted. She was mildly mentally retarded but was socially interactive. There was spastic hypertonia in both lower limbs; power was grade 2/5 in both lower limbs and grade 4/5 in upper limbs across all joints. Deep tendon reflexes were exaggerated in both lower limbs and bilateral Babinski sign was positive. Romberg sign could not be elicited as patient was unable to stand without support. No other cerebellar or sensory abnormality was detected on clinical examination.

Apart from mild anaemia (Hb 9.6 gm/dl), all routine investigations and TSH were normal. MRI brain showed well myelinated posterior limb of internal capsule on T1WI which is consistent with age. T2 weighted images showed periventricular and deep white matter symmetrical patchy areas of hyperintensities (tigroid pattern, fig 1a) suggestive of hypomyelination. Also peritrigonal significant sized T2 hyperintensities are noted [fig 1b]. The diagnosis of Pelizaeus-Merzbacher disease was carried forward in view of clinical features and supporting MRI findings.

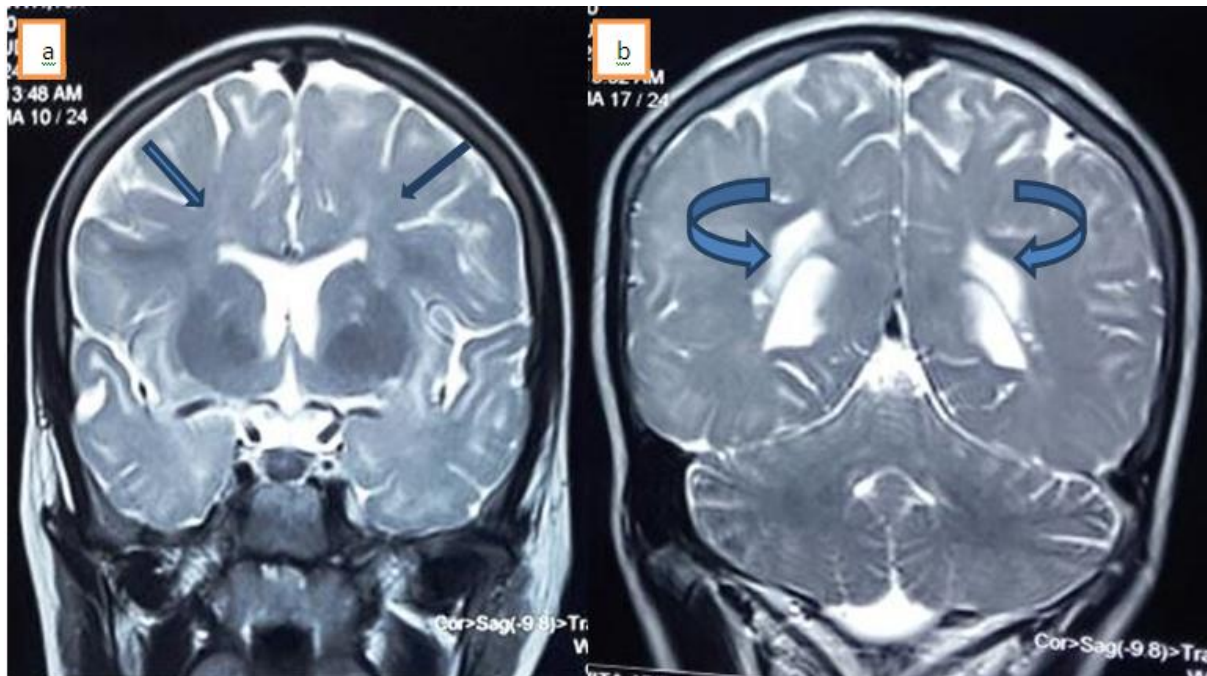


Figure1: [a] T2 weighted images showing periventricular and deep white matter symmetrical patchy areas of hyperintensities (tigroid pattern); [b] Peritrigonal significant sized T2 hyperintensities.

III. Discussion

Pelizaeus-Merzbacher Disease [PMD], a leukodystrophic disorder presenting as spastic paraplegia, ataxia, nystagmus, tremors and mental retardation^[2]. Disease is inherited in X-linked recessive pattern thus, male patients outnumber females. It is caused by mutations of the proteolipid protein 1 (PLP1) gene located on X chromosome (Xq21-22)^[2]. The PLP1 gene is responsible for production of the myelin proteolipid protein (PLP) and DM20, a splicing product of PLP^[3]. Being the most abundant membrane protein of CNS myelin, PLP may be a mediator for membrane signalling^[4]. More than 100 types of mutations of PLP1 have been found in PMD^[2]. However, it is estimated that 5 to 20 per cent of people with Pelizaeus-Merzbacher disease do not have identified mutations in the PLP1 gene. Pelizaeus-Merzbacher disease is divided into classic, connatal, transitional, X-linked spastic paraplegia Type 2 (SPG2), and PLP1 null syndrome types^[2].

Classic Pelizaeus-Merzbacher disease is the most common type. Within the first year of life, the affected child experiences hypotonia, nystagmus, and delayed development of motor skills such as crawling or walking. As the child gets older, nystagmus usually stops but other movement disorders, spasticity and ataxia develop. Connatal Pelizaeus-Merzbacher disease is the most severe type. Symptoms can begin at birth or during the first week of life. It includes difficulty in feeding, respiratory distress, progressive spasticity leading to contractures, nystagmus, hypotonia, and seizures. They show little development of motor skills and intellectual functions. Usually, they die within 10 years due to respiratory complications. In transitional PMD, symptoms of connatal and classic forms overlap. SPG2 is a milder form of PMD, presenting within the first 5 years of life. PLP1 null syndrome is caused by a null mutation. It usually presents in the first 5 years of life. These patients do not have nystagmus.

Diagnosis of PMD is based on clinical features, brain imaging, especially magnetic resonance imaging (MRI), and genetic testing of PLP1. Molecular diagnostic tests for mutations of the PLP1 gene are the definitive for the diagnosis of Pelizaeus-Merzbacher disease. Brain MRI is the most useful imaging study in Pelizaeus-Merzbacher disease. It typically demonstrates diffuse or patchy high signal intensity in the white matter of the cerebrum, cerebellum, and brainstem on T2 weighted and FLAIR images with partial sparing of the pyramidal tracts at the posterior limb of the internal capsules (PLIC)^[5,6]. T1 weighted images demonstrate normal or isointense white matter. Major differentials of disease include cerebral palsy, Cockayne syndrome, adrenoleukodystrophy and other leukodystrophies.

IV. Conclusion

Our patient presented with slowly progressive paraparesis, head tremor and nystagmus since childhood with mild mental retardation. Her MRI brain had periventricular and deep white matter symmetrical patchy areas of hyperintensities in a tigroid pattern with peritrigonal significant sized hyperintensities on T2 weighted imaging suggestive of hypomyelination, thus can be diagnosed as Pelizaeus-Merzbacher disease. We could not do

genetic studies because of its unavailability in our hospital. There is no definitive treatment for the disease at present therefore; symptomatic management viz. medication for seizures and spasticity, regular evaluations by physical medicine and rehabilitation, orthopaedic, developmental and neurologic specialists and a good nursing care could reduce the morbidity amongst these patients. The prognosis of Pelizaeus–Merzbacher disease is variable; the most severe form (connatal) usually not surviving to adolescence, but survival up to fifth or sixth decades is documented, especially with attentive care. Genetic counselling should be provided to the family of a child with PMD.

Though a rare cause of spastic paraparesis a clinician should be vigilant enough and keep Pelizaeus-Merzbacher disease amongst one of the differentials of spastic paraplegia.

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