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Pelizaeus-Merzbacher Disease: A Case Report

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ABSTRACT

Pelizaeus-Merzbacher Disease (PMD), as a rare genetically x-linked leukodystrophy, is a disorder of proteolipid protein expression in myelin formation. This disorder is clinically presented by neurodevelopmental delay and abnormal pendular eye movements. The responsible gene for this disorder is the proteolipid protein gene (PLP1). Our case was a one-year-old boy referred to the radiology department for evaluating the Central Nervous System (CNS) development by brain Magnetic Resonance Imaging (MRI). Clinically, he demonstrated neuro-developmental delay symptoms. The brain MRI results indicated a diffuse lack of normal white matter myelination. This case report should be considered about the possibility of PMD in the brain MRI of patients who present a diffuse arrest of normal white matter myelination.

Introduction

Pelizaeus-Merzbacher Disease (PMD) is a rare genetically x-linked disorder of proteolipid protein gene (PLP1) expression (locus at Xq22) in the Central Nervous System (CNS) myelin formation [1, 2]. The products of the gene (PLP1) significantly impact the development of oligodendrocytes in the CNS for the myelination process. The lack of normal white matter myelination is the significant pathology in PMD [3]. This disease clinically causes neurodevelopmental delay and progressive hypo-tonic-

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ity in infancy [4]. Symptoms initially begin before three months of age and gradually progress [1].

Brainstem auditory- and somatosensory-evoked potential tests are consistently abnormal in PMD [5]. Brain MRI findings are highly suggestive for diagnosis; they present a lack of normal white matter myelination in the pattern that the brain should be myelinated according to age. Additionally, there is a correlation between the stage of myelinated white matter and the clinical severity of the disease. MRI data suggested a low signal intensity of unmyelinated white matter structures on the T1 sequence and high signal intensity of these structures on the T2 sequence, associated with diffuse cerebral and cerebellar atrophy [3].

Case Presentation

A one-year-old boy was referred by a pediatrician to the radiology department for performing brain MRI to evaluate the developmental delay. Additionally, he had a history of recent head trauma. He was born from full-term pregnancy with natural vaginal delivery without significant birth problems. His birth weight was 2850 grams. He was normal until the age of three months. Then, he presented a lack of attention, progressive hypotonia, and abnormal pendular eye movements. His brain MRI result indicated diffuse abnormal signal intensity in the white matter (hyperintensity on T2, FLAIR, & iso signal intensity on T1 weighted sequences). It demonstrated a lack of normal white matter myelination according to the patient's age. This lack of normal myelination was observed diffusely in the cerebral and cerebellar white matter, brain stem, corpus callosum, basal ganglia, especially globus pallidus, and internal capsule. Additionally, the brain MRI data revealed bilateral subdural hematoma over frontoparietal lobes convexity probably, i.e. because of his recent head trauma (Figure 1).

Additionally, a subdural hematoma was observed; (C: Sagittal brain MRI). T2W sequence signifies diffuse white matter hypomyelination, involving supra and infratentorial white matter, and corpus callosum, as abnormal high signal intensity. Furthermore, a subdural hematoma was noted; coronal brain MRI (D). T2W sequence suggests diffuse hypomyelination, involving cerebral and cerebellar white matter as abnormal high signal intensity. Besides, a bilateral subdural hematoma was noted; axial brain MRI; T1W sequence presented diffuse bilateral isointense in the white matter. Eventually, a bilateral subdural hematoma was observed (E and F).

Discussion

Normal CNS white matter myelination occurs in a predictable pattern. When this process is arrested, it occurs under myelination or the lack of it. PMD is a rare hypo-myelination disorder caused by a mutation in the proteolipid protein (PLP1) gene locus at chromosome Xq22; this disorder is a progressive disease, resulting in death during early or mid-adulthood [1, 6]. The responsible gene encodes the main myelin components in the CNS, the two proteolipid proteins, as well as PLP and its spliced isoform, DM20. PLP is produced by mature oligodendrocytes, while DM20 is generated earlier in myelin development. The most frequent mutation of the PLP1 gene is duplication (70%), and the most common clinical phenotype of PMD, initiated by PLP1 duplication, corresponds to the classic form of PMD [7, 8].

PMD could be categorized into two subtypes, including classic and connatal (more rare and severe) [1, 2]. The classic type of PMD has an x-linked recessive inheritance and exclusively occurs in boys. This subtype remains symptomatic during late infancy and is more common than the connatal subtype. The connatal form could be autosomal or x-linked recessive; both genders are equally affected. This subtype is more severe and begins at birth or during early infancy. Both subtypes are presented with nystagmus, hypotonia, spasticity, and slow psychomotor development [6].

Histopathologically, PMD is characterized by patchy white mater myelin deficiency with the involvement of the subcortical "U" fibers. There are areas of persistent perivascular myelin resulting in a classic "tigroid" appearance. Indeed, a brain CT scan in PMD demonstrates diffuse abnormal low attenuation in the white matter with progressive brain atrophy. Brain MRI presents a diffuse lack of normal white matter myelination without white matter destruction; hypomyelination is progressive over time, and cerebellar atrophy may also happen [6].

MRI could be applied as the best imaging modality to evaluate myelination patterns [6]. Normal myelination causes shortening of relaxation times on T1 and T2 sequences; as white matter tracts become myelinated, they become more hyperintense on T1-weighted and more hypointense on T2-weighted images. In brain MRI, the T1W sequence is more valuable for evaluating the myelination pattern in children during the first year of life. Moreover, a healthy adult pattern of myelination on the T1 sequence occurs by one year of age. T2W sequence is more valuable after 10 months of age and normal complete myelination occurs at three years of age.

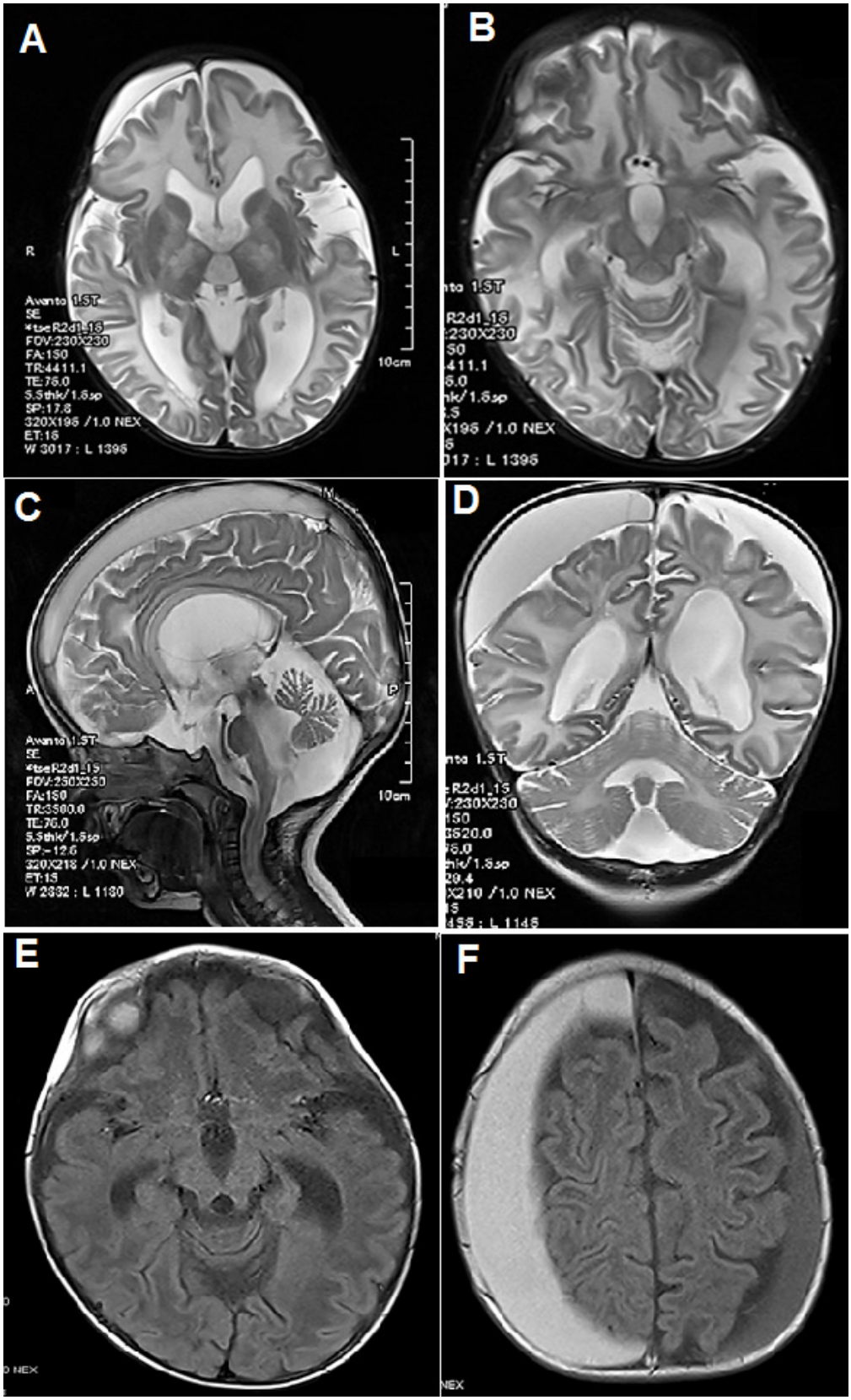

Figure 1. Brain MRI in Pelizaeus-Merzbacher disease

A and B: Axial brain MRI T2W sequence indicating diffuse brain atrophy and bilateral abnormal high signal intensity of periventricular, deep, subcortical white matter, internal capsule and both globus pallidus; C: Sagittal brain MRI; D: Coronal brain MRI; E and F: Axial brain MRI

Essential areas to assess the myelination are internal capsule, pyramidal tracts, optic radiations, and frontal lobes white matter [9]. Besides, the signal intensity of the brainstem and corticospinal tract of the internal capsule could be the points to suppose the clinical severity in PMD patients [10]. There is no standard treatment for PMD, and the disease is always fatal in all patients [10].

Conclusion

Radiologically, the possibility of PMD should be considered as a diagnosis in young children (especially in boys). Moreover, it should be assessed with brain MRI which indicates a diffuse lack of normal white matter myelination, delayed development, abnormal eye movements, and hypotonia in the patient's history. For diagnosing PMD, it is crucial to understand the regular myelination pattern of the brain.

Ethical Considerations

Compliance with ethical guidelines

All ethical principles were considered in this article.

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Conflict of interest

The authors declared no conflicts of interest.

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