CASO CLÍNICO/CASE REPORT

Pelizaeus-Merzbacher Disease: A Rare Cause of Nystagmus and Developmental Delay

Doença de Pelizaeus-Merzbacher: Uma Causa Rara de Nistagmo e Atraso do Desenvolvimento

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Abstract

Pelizaeus-Merzbacher disease (PMD) is an X-linked leukodystrophy of the central nervous system characterized by a developmental arrest in myelin formation. It is classified into five phenotypes, with different severity. The most common clinical features are nystagmus, spasticity, tremor, ataxia, and hypotonia.

A 11-month-old child was referred to the Neuropediatric Unit due to nystagmus, hypotonia, and developmental delay. Brain magnetic resonance imaging showed signs of diffuse hypomyelination (absence of the T2 low signal in the supratentorial white matter). Molecular analysis revealed a duplication in the *PLP1* gene, confirming the diagnosis of PMD.

PMD should be considered in infants with nystagmus, hypotonia, and cognitive impairment. Neuroimaging supports the diagnosis, and it should be confirmed by genetic testing. Since no definitive treatment is available, management of this disorder is mainly symptomatic and a multidisciplinary approach for these patients is essential for an improvement in their quality of life.

Resumo

A doença de Pelizaeus-Merzbacher (DPM) é uma leucodistrofia do sistema nervoso central ligada ao X caraterizada por um defeito na formação de mielina. É classificada em cinco fenótipos, com diferentes gravidades. As manifestações mais comuns incluem nistagmo, espasticidade, tremor, ataxia e hipotonia.

Um lactente de 11 meses foi referenciado à Unidade de Neuropediatria por nistagmo, hipotonia e atraso no desenvolvimento. A ressonância magnética cerebral mostrou sinais de hipomielinização difusa (ausência do hipossinal em T2 na substância branca supratentorial). A análise molecular revelou uma duplicação no gene *PLP1*, confirmando o diagnóstico de DPM.

A DPM deve ser considerada em lactentes com nistagmo, hipotonia e compromisso cognitivo. Os exames de neuroimagem auxiliam no diagnóstico, mas este deve ser confirmado geneticamente. Dado não existir tratamento definitivo, a abordagem desta patologia é principalmente de suporte, sendo essencial o apoio de uma equipa multidisciplinar para melhoria da qualidade de vida.

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Introduction

Pelizaeus-Merzbacher disease (PMD) is a rare X-linked disease of the central nervous system (CNS) characterized by hypomyelination and subsequent deterioration of coordination, motor abilities, and cognitive function. It is caused by mutations in the proteolipid protein 1 (*PLP1*) gene on the long arm of the X chromosome (Xq21-22), with males being primarily affected. Diagnosis relies on clinical features, brain magnetic resonance imaging (MRI), and genetic testing. This report presents an infant with transitional PMD with nystagmus, hypotonia, and developmental delay in the first weeks of life.

Case Report

An 11-month-old male was referred to the Neuropediatric Unit for a Neuropediatric consultation due to rotatory nystagmus, hypotonia, and developmental delay.

He was the second child of healthy unrelated parents, born at 39 weeks of gestational age, through eutocic delivery following an uneventful pregnancy. Birth weight was 2950 g and head circumference was 36 cm. Apgar scores were 9,10 and 10 at 1, 5, and 10 minutes, respectively. The first physical examination after birth was unremarkable. The mother reported concern about the infant's vision since the first days of life, as well as global hypotonia and feeding difficulties. There was no history of seizures. He had two male cousins with similar clinical manifestations, one of them with an identified defect in the *PLP1* gene. Due to these concerns, he was already having regular General Pediatrics and Ophthalmological appointments and was under physical and occupational therapies.

On physical examination at 11 months of age, he presented with rotational pendular nystagmus of both eyes (fine amplitude, moderate frequency, symmetrical and conjugated), axial hypotonia, poor head control with head lag during pull-to-sit, inability to sit without support, discoordination of upper limbs, and dyskinesias. Brain MRI performed at 6 and 15 months of age (**Fig. 1**) showed a pattern of diffuse hypomyelination, without the expected T2 low signal at the age of examination in the supratentorial white matter. Since these findings are characteristic of PMD, molecular analysis was requested, confirming the diagnosis of PMD with an identification of a hemizygous pathogenic variant with a duplication in the *PLP1* gene.

On his last appointment at 3 years of age, he seemed to show slight improvements in developmental delay. He has full head control, although he cannot sit without support, and can walk with a walking frame, showing some spasticity of the lower limbs. The rotational nystagmus has a higher frequency, with multiple jerk movements and oscillopsia. He also has low vision, without any eye globe abnormalities or refractive error, which can be explained by the level of nystagmus and neurologic pathology. Regarding cognitive skills, he understands instructions, recognizes colors, and uses some words. He is being periodically evaluated by a multidisciplinary team that evolves Neuropediatrics, Ophthalmology, Endocrinology (due to subclinical hypothyroidism), Gastroenterology (due to gastroesophageal reflux), and Pediatric Surgery (due to cryptorchidic testes). Brain auditory-evoked potentials were normal. He is also under speech, occupational and physical therapy.

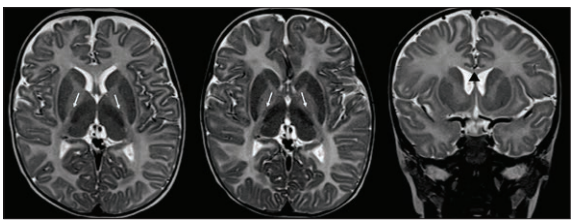
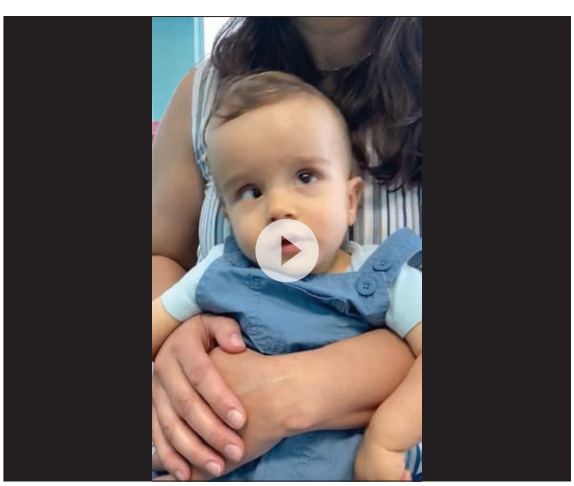


Figure 1. (A) and (B). T2/SE weighted images in the axial plane, at the level of the basal ganglia, at 6 and 15 months of age, respectively. (C) Coronal T2/TSE-weighted image at 15 months of age. Diffuse homogeneous and symmetrical hypersignal of the cerebral hemispheres white matter, inappropriate for age, reflecting marked hypomyelination. Additionally, there is no myelination progression between the 2 studies (9 months period). Tenuous foci of myelination in the posterior limbs of the internal capsules (white arrows in A and B) and absence of myelination of the corpus callosum (black arrowhead in C).



Video. Rotational pendular nystagmus of both eyes (fine amplitude, moderate frequency, symmetrical and conjugated) on physicial examination.

Discussion

Pelizaeus-Merzbacher disease (PMD) is an X-linked disease of the central nervous system (CNS) characterized by a developmental arrest in myelin formation. It is caused by mutations in the proteolipid protein 1 (*PLP1*)

gene on the long arm of the X chromosome (Xq21-22). This gene encodes the myelin proteolipid protein (PLP), the major constituent of CNS myelin.[1,2] PMD is relatively rare, accounting for 6.5% of all leukodystrophies, with an estimated worldwide prevalence of approximately 1:90 000 to 1:750 000 live births.[3] Since it is an X-linked recessive disorder, males are mostly affected but heterozygous females may manifest mild-to-moderate features. Based on the clinical symptoms and mutations PMD is commonly classified into five phenotypes, presenting with different clinical severity: connatal, classic, transitional, X-linked spastic paraplegia type 2 (SPG2), and PLP1 null syndrome. These phenotypes may present overlapping features. The most common clinical signs are nystagmus, spasticity, tremor, ataxia, and hypotonia.[4]

The most common type is classic PMD, with an onset during the first five years. It presents initially with nystagmus, head nodding, and delayed motor development, typically evolving into involuntary movements and spasticity, without any involvement of the respiratory system. Cognitive abilities are impaired, but less severely than in the connatal phenotype – language and speech usually develop and usually retain the ability to ambulate partially. These patients have an average lifespan of 30 to 60 years.[4-6] Connatal PMD is the most severe form, presenting with pendular nystagmus, hypotonia, and stridor at birth or during the first weeks of life. Patients have significantly impaired ambulation, speech, and cognition and may have optic atrophy and seizures.[6] Laryngeal stridor and pharyngeal weakness are common features, and most are deceased by the age of 10 due to pulmonary aspiration complications.[1] Patients with overlapping characteristics of the two previous syndromes are classified into the transitional type. SPG2 is a milder form of PMD and presents later in life with a delay in gross motor skills with independent walking abilities in most cases. Affected males can reproduce, in contrast to all other forms of PMD. PLP1 null syndrome can be distinguished from the other types by the presence of a mild multifocal demyelinating peripheral neuropathy and the absence of nystagmus.[6] Clinical features include mild spastic quadriparesis, ataxia, and moderate cognitive difficulties. Patients with SPG2 and PLP1 null syndrome have a normal life expectancy.

Hypomyelinating disorders are a heterogeneous group of diseases affecting myelin formation, defined by abnormal white matter T2 signal adapted to the age of myelin development and inadequate progression on two successive brain magnetic resonance imaging (MRI) scans carried out at least 6 months apart, one of them acquired after the age of 12 months.[1,7] PMD is the prototype hypomyelination disorder, with classic imaging findings of total or near total absence of the expected T2 low signal on the expected locations according to age in a male patient.[1,8] MRI is crucial in the diagnostic steps of PMD since the clinical presentation is mostly non-specific and brain imaging often raises the first clue to the diagnosis. Routine neuroradiological assessment should be performed for other intracranial abnormalities, namely atrophy of the basal ganglia and/or cerebellum.[7] Conducting this systematic evaluation is feasible and aids in achieving a short differential diagnosis.[8]

The next step in the diagnostic workup is molecular genetic testing which will confirm the diagnosis by demonstrating a heterozygous pathogenic variant in the *PLP1* gene. More than 60 point mutations in this gene have been identified but duplication of the *PLP1* gene is the most common defect, accounting for 60%-70% of the cases.[2]

Since no definitive treatment is available, management of this disorder is mainly symptomatic and supportive and should involve a multidisciplinary team.

In our case, the patient presented with the transitional type of PMD given the overlapping characteristics between the classic and connatal forms. Clinical features (rotational pendular nystagmus, hypotonia, and developmental delay) were present in the first weeks of life but were less severe than those seen in the connatal type. Moreover, he did not present with respiratory involvement or seizures. Also, he seems to be improving in some developmental fields, being able to walk and speak. Brain MRI showed the typical hypomyelination and genetic investigation identified the most common mutation in PMD.

The diagnosis of PMD should be considered in infants (particularly males) with nystagmus, hypotonia, and cognitive impairment. Neuroimaging may help support diagnosis through the identification of characteristic neuroimaging findings, but, whenever possible, it should be confirmed by genetic testing. A definitive diagnosis is important since genetic counseling represents the only possibility of preventing the disease. However, it must be taken into consideration that early intervention of these patients is crucial, even in the absence of a definitive diagnosis, since it may prevent complications and further neurologic deterioration as well as expand their life span. ■

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All authors have agreed to this final version of the paper being submitted to the journal.

All have contributed.

DA: Conceptualization; Bibliographic research; Writing –

original draft; Writing – review and editing

AA: Bibliographic research; Contributed with data; Writing – review and editing.

AFG and MAR: Contributed with data; Validation; Writing – review and editing.

MVR and FS: Validation; Writing – review and editing.

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