PLP1-related disorders (including pelizaeus-merzbacher disease [PMD])

Record Status
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Authors’ conclusions
PLP1-related disorders are hereditary conditions caused by duplications, deletions, or sequence variants involving the PLP1 (proteolipid protein 1) gene. They are neurodegenerative disorders that encompass a broad spectrum of disease phenotypes, including the severe Pelizaeus-Merzbacher disease (PMD) and the milder hereditary spastic paraplegia type 2 (SPG2). The precise prevalence of PLP1-related disorders has not been reported, although it is estimated that PMD occurs in up to 1 in 200,000 live births. The PLP1 gene, which encodes a protein that functions in the production of myelin (a protein sheath that insulates nerve cells), is located on the X chromosome at band q22.2. Consequently, PLP1-related disorders are inherited in an X-linked manner and primarily affect males (since they have only 1 copy of the PLP1 gene). Carrier females (with 1 normal copy of PLP1 and 1 with a duplication, deletion, or sequence variant) are typically unaffected, although some do exhibit PLP1-related symptoms. PLP1-related disorders are defined by clinical presentation and disease severity, although the various conditions represent a disease continuum with similar and overlapping features. The most severe PLP1-related disorder is connatal PMD, which results from variants involving critical PLP1 sequences, PLP1 duplications, or PLP1 triplications. Individuals with connatal PMD present at birth or in early infancy with nystagmus (abnormal eye movements) and hypotonia (low muscle tone), and develop severe spasticity (stiffness) of the limbs and other neurological complications. They have severe hypomyelination (decreased myelin) on brain imaging, are typically unable to speak or walk, may have severe cognitive impairment, and are likely to die in the first 2 decades of life. Classic PMD is the second most severe PLP1-related disorder and most often results from duplications of the PLP1 gene. Those with classic PMD present in infancy or early childhood with nystagmus and hypotonia, develop significant spasticity of the limbs, and exhibit cognitive impairment and severe hypomyelination. However, they may develop the ability to speak and may be able to walk with assistance (although this skill is frequently lost with disease regression). The PLP null phenotype results when there is an absence of PLP1 protein, most often the consequence of PLP1 gene deletion. Patients with the PLP null phenotype frequently exhibit developmental delays, mild to moderate cognitive impairment, leg spasticity, hypomyelination, and peripheral neuropathy (nerve dysfunction). They are typically able to speak and walk, although these skills may deteriorate as the disease progresses. SPG2 is the least severe of the PLP1-related disorders. Complex (or complicated) SPG2 is associated with nystagmus, leg spasticity, ataxia (loss of control of bodily movements), mild cognitive impairment, and mild changes in myelination; while pure (or uncomplicated) SPG2 is limited primarily to leg spasticity and weakness. Individuals with SPG2, who frequently carry milder sequence variants in the PLP1 gene, are able to speak and walk, although disease progression may lead to the need for a wheelchair or other assistive devices. There is no cure for PLP1-related disorders and no way to prevent or delay symptoms. Disease management is generally supportive and may include physical and occupational therapies, medications for spasticity and seizures, surgery for joint contractures or spinal curvature, and feeding tube placement for those with severe swallowing problems.

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