Pelizaeus-Merzbacher Disease: The Value of Natural History Studies in Understanding Neurogenetic Disorders

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More than a century ago, in 1885 Friedrich Pelizaeus, a German Physician first identified a genetic disorder in five boys in a single family with nystagmus, spasticity, and hypotonia of the limbs and developmental delay [1]. Twenty-five years later in 1910, Ludwig Merzbacher independently reexamined this family and described further the neuropathology of 14 affected individuals and found that all affected members shared a common ancestor [2]. Together, Pelizaeus and Merzbacher identified the exclusive X-linked inheritance that now characterizes this rare and heterogeneous CNS white matter disease.

Pelizaeus-Merzbacher disease (PMD) is caused by an extensive array of mutations affecting the proteolipid protein 1 gene (PLP1). Expression of PLP1 dominates in the CNS oligodendrocyte lineage and correlates with the onset of myelination that begins during the 3rd trimester of pregnancy in humans [3]. PLP1 encodes the most abundant CNS protein, proteolipid protein (PLP) a major structural protein in compact myelin [4-7]. Although it is evident that PLP plays a vital role in myelin assembly and maintenance, on a functional and molecular level, its precise role remains undefined. Today, more than 100 points mutations have been identified and described in the PLP1 coding region causing a wide spectrum of clinical heterogeneity. Although, the clinical description of PMD has been well studied in humans and animal models [8] the cellular and molecular pathogenesis across the clinical spectrum remains elusive.

The most severe form of PMD is caused by PLP point mutations and presents at birth or during the first few weeks of life with pernundal nystagmus, hypotonia, respiratory distress, pharyngeal weakness, stridor and cognitive impairment. Affected males later develop significant spasticity and have little voluntary muscle control.

Majority of cases responsible for PMD is caused by increased PLP1 gene dosage, usually a duplication of the region of the X chromosome surrounding and including the gene for PLP1 [9-11]. This form of the disease, often called the classical form of PMD, is mild to moderate in severity and associated by nystagmus, hypotonia, spasticity, ataxia and cognitive impairment which typically manifest in the first five years of life.

In contrast to increased PLP1 gene dosage, a relatively rare form of PMD, is the PLP1 null syndrome, in which PLP1 expression is absent (loss of function) as a result of a complete deletion or a truncation mutation [12]. The signs and symptoms of this disease are initially relatively mild, but in early adolescence progresses into a severe spastic quadriplegia associated with ataxia and cognitive impairment. Ultra structural examinations of myelin in both knockout mice and patients with a null syndrome have shown myelin to be physically unstable and fragile [7,13]. The absence of PLP paradoxically does not disrupt or affect the process of myelination. Garbern and coworkers [14] found a length-dependent axonal degeneration in both human and animals that can account for the progressive lower limb spasticity and thus the evolution of clinical signs and symptoms.

Irrespective to the location and type of PLP mutation and gene expression (i.e. loss or gain of function), PMD is described as a prototypical hypomyelinating disorder. Recent pathologic findings in a study to examine autopsy tissue from a small number of PMD patients exhibited a late-onset demyelinating phenomenon accompanied with remarkable axonal injury that is reminiscent of MS pathology (unpublished results). The examination of human tissue is required to fully appreciate the vast heterogeneity of PLP mutations that exists across the clinical spectrum.

Although, an array of PLP mutations in animals, both experimental and naturally occurring continue to provide significant contribution into the underlying disease pathogenesis, not all animals models will recapitulate the human condition in its vast heterogeneous forms that often accompany neurogenetic disorders. The immeasurable value of natural history studies combined with the dynamic and dissecting power of non-invasive MRI techniques are instrumental towards elucidating the mutation mechanism responsible for the disease pathogenesis and clinical severity. White matter atrophy has been found to be a likely cause of clinical disability in PMD [15], however this does not imply that the cellular and molecular mechanisms are the same for all type of PLP1 mutations. The different PLP1 mutation mechanisms impose different effects on oligodendrocyte viability, thereby resulting in an overall gross reduction and/or alteration to CNS myelin.

Inherited leukodystrophies, such as PMD represent a heterogeneous group of neurogenetic disorders that remain poorly understood. Natural history studies allowing patient’s to serve as their own baseline of clinical progression, non-invasive neuroimaging modalities, comprehensive genetic testing all play a collective role in dissecting the variables responsible for assessing the disease pathogenesis and severity. Furthermore, evaluating meaningful clinical change, monitoring the efficacy of new pharmacological...
therapies and response to stem cell therapies all require a multifaceted approach to achieve the desired clinical outcome.

References


