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, ataxia and cognitive impairment. In contrast to increased PLP1 gene dosage and presents at birth or during the first few weeks of life with pendular nystagmus, hypotonia, respiratory distress, pharyngeal weakness, stridor and cognitive impairment. Affected males later develop spastic quadriplegia, ataxia and cognitive impairment. The signs and symptoms of this disease are initially 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a late-onset demyelinating phenomenon accompanied with remarkable axonal injury that is reminiscent of MS pathology (unpublished results).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


