Pelizaeus-Merzbacher Disease

Pelizaeus-Merzbacher disease (PMD) is a rare and progressive condition affecting the central nervous system.\(^1\) It is one of a group of gene-linked disorders known as the leukodystrophies, which are all characterised by myelin sheath abnormalities. This is due to a mutation in the gene that controls the production of a myelin protein called proteolipid protein 1 (PLP1). The exact type of PLP1 mutation dictates the onset and severity of PMD. PMD can be classified into different types:

- Pelizaeus Merzbacher disease, PMD: an X-linked recessive disease with the mutation at Xq22.\(^2\)
- Pelizaeus Merzbacher disease, acute infantile type (perinatal sudanophilic leukodystrophy): inheritance uncertain, possibly heterogeneous but boys and girls are affected; probably autosomal recessive.\(^3\)
- Pelizaeus-Merzbacher-like disease, PMLD: autosomal recessive (PMLDAR) with mutation at 1q41-q42.\(^4\)

This article will concentrate on the first of these three diseases. Spastic paraplegia type 2 (SPG2)\(^5\) is another condition that arises due to a mutation at the same allele and so it would seem that the two diseases are at each end of a spectrum.\(^6\) There are four levels of severity described which, in order of decreasing severity are:

- Connatal PMD - the most severe type: involves delayed mental and physical development and severe neurological symptoms.
- Classic PMD - the early symptoms include muscle weakness, involuntary movements of the eyes (nystagmus) and delays in motor development within the first year of life.
- Complicated SPG2 - features motor development problems and brain involvement.
- Pure SPG2 - includes cases of PMD that do not have neurological complications.

Epidemiology\(^6\)

- This is a rare disease with an international incidence that is probably between 0.1 and 1 per 100,000 of the population.
- As an X-linked disease it would be natural to expect that males are affected and females are carriers but females do have features of the disease (see ‘Female carriers’, below).
- This disease affects all ethnic groups.

Female carriers

- Females have random inactivation of the X-chromosome and so a heterozygous female begins life with roughly half the oligodendrocytes manifesting the normal and half the mutated X chromosome.
- Females heterozygous for severe mutations show transient neurological abnormalities during childhood but symptoms regress (presumably as defective oligodendrocytes die and are replaced by healthy oligodendrocytes) and these individuals are neurologically normal as adults.
- Females heterozygous for less severe mutations that do not result in oligodendrocyte apoptosis (programmed cell death) continue to have oligodendrocytes that have the defective PLP1 and therefore will continue to have abnormal neurological signs.
- Carrier girls are usually asymptomatic but some develop a classical picture that then regresses and they are normal as adults. Female carriers of less severe variations are usually normal in childhood but may develop symptoms in adulthood, including dementia.
- Female carriers have a 1 in 2 chance of passing on the abnormal chromosome to a child, giving a 1 in 4 chance of having an affected son, a 1 in 4 chance of having a carrier daughter and a 1 in 2 chance of having a normal child, boy or girl. Molecular genetic analysis is the best technique for carrier detection.\(^7\)

Presentation

Generally, the clinical picture is one of:\(^2\)

- Nystagmus
- Spastic quadriplegia
Ataxia
Developmental delay

Typically, the disease begins in the first two months of life \[6\] but milder variations may not present until childhood.

- **Connatal PMD** - there is nystagmus from birth or the first few weeks of life. They often have stridor, respiratory difficulty and hypotonia. Seizures may occur. They have limited language, never walk and develop severe spasticity with little voluntary movement. They usually die in infancy or childhood.
- **Classical PMD** - boys present within the first 2 months of life. There is nystagmus and weakness, followed by development of ataxia, cognitive delay and spasticity. Titubation is described: this may mean either a staggering gait, tremor or shaking of the head, of cerebellar origin, but in this context it is more likely to be the latter as most never learn to walk properly. Those that do walk tend to be milder cases but lose the ability in adolescence. Most cases achieve some language skills but fluency is slow and may suggest a more severe degree of learning difficulty than is present. These patients may survive to the sixth decade of life or longer.
- **SPG2-like disease** - there is spastic paraplegia from childhood, mild cognitive impairment, ataxia and athetosis (continual slow movements, especially of the extremities). They usually live to the sixth decade or beyond. Neurological signs progress gradually with periods of relative stability. If they learn to walk they tend to lose it during adolescence (occasionally adulthood).

Other general observations may be made:

- Developmental milestones are either markedly delayed or never achieved (connatal PMD) and these individuals are small for age.
- Over 95% have nystagmus but the age of onset does not predict clinical severity. The nystagmus is usually pendular but can have horizontal or rotator components.
- Although the disease is associated with spasticity, there may be hypotonia in early life. In severe cases, the neonatal hypotonia may resemble spinal muscular atrophy but over 90% of cases develop spasticity, although possibly not until the second year of life. As the child grows and spasticity replaces hypotonia, head control remains poor.
- In more severe cases there may be convulsions.
- Milder cases may be able to walk but this is lost in adolescence, as the spasticity tends to be worse in the legs. There is gross spasticity, hyperreflexia and extensor plantar response. In severe cases, the child is unable to sit unsupported and is certainly unable to walk.
- Ataxia is evident once voluntary movements are acquired and affects virtually all patients. In milder cases, the ataxia affects their speech. Therefore, although there is cognitive delay, this may seem more severe than it is because of severe limitation of speech. Comprehension may be rather better than phonation. Voluntary movements are almost invariably complicated by ataxia.

**Differential diagnosis**

There are features similar to:

- Spinal muscular atrophy.
- Autosomal dominant cerebellar ataxia.
- Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL).
- Severe cerebral palsy.
- Chorea.
- Multiple sclerosis.

**Investigations**

- MRI scan is a very useful investigation as it shows poor myelination, although this may not be apparently abnormal until about 1 year of age. It also shows reduced brain volume. This is most marked in the connate variety and is not very obvious in SPG2.
- Nerve conduction studies show normal conduction in peripheral nerves whereas other leukodystrophies show a slowing of peripheral nerve conduction.
- Molecular diagnostic testing is the definitive test. \[8\] There will be some variation according to the type of mutation present.

**Management**\[6\]

There is no cure for the disease and, currently, there are no treatment options, \[1\] although work is being done in the field of stem cell culture as a possible solution to a range of paediatric disorders of myelin. Management is purely supportive and this can include:

- Genetic counselling and telling the parents the prognosis.
- Physiotherapy and orthotic inputs to help minimise the development of joint contractures, dislocations and kyphoscoliosis.
- Antispasmodics, eg clonazepam and baclofen.
- Regular physical and orthopaedic evaluations (surgery may be beneficial where there are severe contractures).

Severely affected individuals may additionally need attention to airway protection, management of gastro-oesophageal reflux disease and anticonvulsants.
Prognosis

- **Connatal PMD** - these individuals often die of respiratory complications during infancy or early childhood. If they get through this early period of life, they can live into their third decade of life.
- **Classic PMD** - if these individuals survive past adolescence, they may live into their 40s or 50s. This depends on the predominant phenotype - if this is predominantly spastic paraplegia, they can have a normal life expectancy.
- **SPG2** - these patients tend to have a normal lifespan.

There may appear to be periods of stability but the prognosis is for gradual deterioration.

Further reading & references

1. Pelizaeus-Merzbacher Disease, National Institute Neurological Disorders and Stroke
2. Pelizaeus-Merzbacher Disease; PMD, Online Mendelian Inheritance in Man (OMIM)
3. Pelizaeus-Merzbacher-Like Disease, Autosomal Recessive Type 2, Online Mendelian Inheritance in Man (OMIM)
4. Pelizaeus-Merzbacher-like Disease, Autosomal Recessive, Type 1, Online Mendelian Inheritance in Man (OMIM)
5. Spastic Paraplegia 2, x-linked; Spg2, Online Mendelian Inheritance in Man (OMIM), 2008
6. Garbern JY; Pelizaeus-Merzbacher Disease, eMedicine, Aug 2008

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