Pelizaeus Merzbacher Disease – What is PMD?

History

In 1885, a German physician named Pelizaeus described five boys in a single family with involuntary oscillatory eye movement, spasticity in the limbs, very limited head and trunk control, and delay in cognitive development. In 1910, another German physician named Merzbacher reexamined this family, which then included 14 affected individuals including two girls, and found that all affected family members shared a common female ancestor. In addition, he noted that the disease was passed exclusively through the female line without father-to-son transmission. Pathological analysis of brain tissue from one affected individual showed that most of the central white matter generally lacked histochemical staining for myelin, the fat and protein based substance that acts as an insulator for nerve conductors in the Central Nervous System (CNS). The description of this family provides the clinical, genetic and pathological basis for Pelizaeus-Merzbacher Disease (PMD): an X-linked disorder of myelin classically characterized by nystagmus, spastic quadriparesis, ataxia and cognitive delay in early childhood.

In Layman’s Terms

So you’re wondering about this thing called “myelin” and cannot visualize what this all means, and why a person with PMD has little hope of ever walking? Perhaps this will help you:

Here is a picture of a typical, healthy neuron:

Neurons are a type of cell in our brains and spinal cord that serve to transmit and receive electrical signals (impulses) throughout our central nervous system. In the picture above, the neuron’s nucleus can be found on the left as the blue-colored mass with the black spots. The short arms or branches hanging off the nucleus on the left are known as “dendrites”. Dendrites carry impulses
towards the nucleus. The long appendage to the right is an “axon”. Axons carry impulses away from the nucleus and towards the dendrite of another neuron. This axon is covered by five sections of “myelin”, which are colored green. You can see in the magnified box that the axon is a bundle of little fibers and the myelin is actually wrapped around it several times liked a rolled up carpet. Myelin serves some incredibly important functions. It protects the axon. It allows an impulse to get from one neuron to another, and it allows that impulse to move very, very fast.

Now, let’s say you have an idea in your head to move your right hand and pick up a pencil. That “idea” travels as an electrical impulse from your brain through your spinal cord (hopping neuron after neuron along the way), out to the peripheral nerves in your right arm and finally to your right hand, where motion finally occurs and you start to move your hand to grab the pencil.

So, what happens if there is little or no myelin as is the case with someone who has PMD?

Tragically, as the impulse tries to make its way across the axon, it leaks out where there is no myelin. (Click on the picture to the left for an animation of this activity.) This results in little, if any, impulse making it to the next neuron in the chain. And for a PMD patient, they’re lucky if they have neurons with even a little myelin. That’s what separates PMD from a disease like Multiple Sclerosis (MS). The PMD patient simply never forms any myelin on their axons, while the MS patient has healthy neurons but the immune system eventually attacks and destroys the myelin surrounding the axons.

**Clinical Features of PMD**

Pelizaeus-Merzbacher Disease is one of a class of neurological diseases known as leukodystrophies, disorders that affect the formation of the myelin sheath, the fat and protein covering—which acts as an insulator—on neural fibers (axons) in the central nervous system or CNS, which is the brain and spinal cord. It is a rare condition caused by mutations affecting the gene for the **proteolipid protein** (PLP). The PLP gene lies on the X chromosome so that most affected individuals are males who inherit the mutant or abnormal gene from their mothers. Rarely, females can have symptoms. Clinically, Pelizaeus-Merzbacher disease usually begins during infancy and signs of the disease may be present at birth or in the first few weeks of life. The first recognizable sign is a form of involuntary oscillatory movements of the eyes called **nystagmus**. Some infants
have **stridor** (labored and noisy breathing). Infants may show **hypotonia** (lack of muscle tone; floppiness) or eventually develop **spasticity** (a type of increased muscle tone or stiffness of the muscles and joints). Motor and intellectual milestones are delayed, however the intellectual delay is often more apparent than real, if care and time are taken to evaluate the children. Children are often non-verbal. Head and trunk control may be impaired and wavering or tremor of the upper body when sitting is commonly seen (titubation). Seizures occur only rarely in affected children. The clinical diagnosis generally includes the clinical findings listed above along with a family history consistent with X chromosome transmission (that is, being passed down by mothers, and never being passed from an affected father to his son). The most useful screening test after the neurologic examination and family history, is a brain magnetic resonance imaging (MRI) scan, which is a very sensitive test for leukodystrophies (diseases of the white matter), as long as it is done after one or two years of age (the times when the major white matter pathways in the brain are developing). The definitive test is demonstration of a pathologic mutation of the PLP gene.

**PMD Genetics**

PMD occurs due to genetic mutation. In the tens of thousands of gene pairs, sometimes one will be changed. The mutation may be inherited or may happen by itself. Sometimes a mutated gene will not cause problems. Other times, a gene with a mutation will cause the body not to work correctly, and that person will have a genetic condition such as PMD. Genes are carried on chromosomes and most individuals have 46 chromosomes in each cell in their body. The chromosomes come in 23 pairs with the first 22 pairs being identical in males and in females. The last pair is the sex chromosomes; females have two X chromosomes, while males have one X and one Y chromosome. The chromosome can be thought of like a bookcase and the gene as a book located on the bookcase. DNA (deoxyribonucleic acid – see Figure 1), which is the basic component of the gene, is like the letters in the book. Genetic information is stored, and passed down from generation to generation, in the form of the precise sequence of DNA letters or **bases**.

*Tightly coiled strands of DNA are packaged in units called chromosomes, housed in the cell’s nucleus. Working subunits of DNA are known as genes. The four types of bases are colored orange, pink, blue and green here. This and other figures are from “Understanding Gene Testing” from the National Cancer Institute.*

Since the gene for PMD is located on the X chromosome, the disease typically affects only boys or men in a family. Technically, this is called X linked inheritance. Remember that females have two X chromosomes
while males have one X and one Y chromosome. If there is a gene on the X chromosome that is not working properly, males will be affected more often than females. Females likely have a gene on the other X chromosome that does work properly and compensates for the defective X chromosome. Females who carry the gene for PMD therefore typically are not affected since the PLP gene on the other X chromosome is normal. Males with PMD are usually not able to have children. So, when it occurs in several generations, women act as the carriers for the PMD mutation and pass on the disease. Women who carry the PMD gene have a 50% or 1 in 2 chance of passing it on to their sons and their daughters. These odds are the same for every pregnancy. What happened in one pregnancy does not in any way influence the odds for the next pregnancy. Sons who inherit the gene would be affected, whereas daughters would be carriers. If a daughter did not inherit the PMD gene, then she would not pass PMD on to her children.

**PLP and Myelin**

The gene specific to PMD is called proteolipid protein (PLP) and it is located on the X chromosome. About 75% of myelin is made up of fats and cholesterol and the remaining 25% is protein. PLP constitutes about half of the protein of myelin and is its most abundant constituent other than the fatty lipids. Various mutations within this gene have been identified. The types of mutations that are known to cause PMD fall into two general categories: point mutations and duplications. A mutation (any alteration of the DNA) that affects only a single base (one letter) is called a point mutation. Other types of mutations can occur as well, including insertions (additions of DNA into a gene), deletions (removal of part of a gene), and duplications where entire genes are present in one or more additional copies.
This figure shows what the myelin made by a single myelin forming cell (called an oligodendrocyte) looks like. The myelin is shown in cross section. From the side it would look more like a rolled up carpet around each axon. A single oligodendrocyte can myelinate many different nerve fibers (also called axons). One postulated function for PLP is that it acts like a glue to keep the adjacent layers of cell membrane tightly stuck together. This figure shows that PLP crosses only two times through the cell membrane. Most people now believe that it crosses the membrane 4 times. The lower right hand figure shows an actual electron microscope picture of a cross section of myelin magnified thousands of times.

The point and other small mutations usually cause the substitution of one of the amino acids for another somewhere in the protein or prevent PLP from reaching its full length. This probably results in the protein being unable to fold into the correct shape or to interact with other myelin constituents. These mutant proteins are toxic to the octopus-like cells called oligodendrocytes (see Figure 2), whose job it is to make myelin, and prevent them from making normal myelin. These cells operate by actually myelinating several axons at once. They develop tentacle-like appendages that wrap around neighboring axons providing the insulation needed for proper nerve function. However, in just the past two years or so it has been discovered that most PMD cases are caused by duplications of the entire PLP gene accounting for 50-75% of the cases. This seems to be the case for PMD families around the world and we still do not understand why it occurs. We currently believe that the duplication results in too much otherwise normal proteolipid protein being made. This excessive PLP also appears to be toxic to oligodendrocytes.
We also know that in addition to the regions that code for protein, there are regions of genes that regulate their expression. In order for the right proteins to be made in the right organs and in the right amounts, there are many processes that have to be regulated very precisely. Mutations that change these regulatory sequences can have drastic affects on the gene, and might result in the protein being made in too high or too low an amount, or to be made in the wrong organ or at the wrong time of life.

**Current Outlook for PMD**

There is currently no cure for Pelizaeus-Merzbacher disease, nor is there a standard course of treatment. Treatment, which is symptomatic and supportive, may include medication for seizures and the stiffness or spasticity that most PMD patients have. Once a PLP gene mutation is identified in a family, it is possible to test family members for the mutation and to provide prenatal diagnosis for parents who have a risk of transmitting this disorder. The prognosis for those with Pelizaeus-Merzbacher Disease varies. Some mutations are more severe than others and may result in death during childhood, but some individuals can survive into their sixties. The course of the disorder is usually very slow, with some individuals reaching a plateau and remaining stable for years. However, some do worsen over time, for reasons to be investigated. A group of clinicians and researchers working on Pelizaeus-Merzbacher disease and PLP has recently been organized in the North America and in Europe to promote research to facilitate understanding of disease pathogenesis and development of specific treatments and, we hope, a cure.

[http://pmdfoundation.org/what-is-pmd/](http://pmdfoundation.org/what-is-pmd/)