PELIZAEUS-MERZBACHER DISEASE (PMD) is a X-linked disease that is transmitted from normal appearing carrier mothers to their sons. Each male born to these mothers has a 50/50 chance of being affected with PMD. Each female child born to them has a 50/50 chance of being a carrier herself. Having more than one affected child, with a disease that there is only 50/50 of, I know sounds impossible, but I did the same thing! You have to realize it's a 50/50 chance with every pregnancy. One way to possibly describe this is to take a deck of cards, remove all 4 aces. Let the 2 red ones represent females, the ace of hearts could represent a non-carrier female, the ace of diamonds could represent a carrier female. Let the 2 black ones represent males, the ace of clubs could represent a non-affected male, the ace of spades could represent an affected male. With each pregnancy you have a 1 in 4 chance of having an affected son. Turn the 4 cards face down and draw one, if it should be the ace of spades (affected male), you can't say, "I have already had my affected one", and exclude it from the next pregnancy. With each pregnancy you have to "draw" from all 4 "cards".

This disease affects the myelin sheath, that insulates the nerves of the central nervous system. These nerve fibers, called axons, carry impulses from the brain to other parts of the body. The axons are similar to an electrical wire, the myelin is like insulation that covers them. In males with PMD there is an inborn error that does not allow this "insulation" to form properly. As with the electrical wire, if the insulation is missing or worn through in some areas, the impulses don't reach their proper destination. The first symptom of PMD is usually a nystagmus, involuntary movement of the eyes, noticed between birth and six weeks of age. It is described as "shaking", "rocking", "dancing", etc. The next symptom is usually failure of the infant to gain normal head and trunk control (hypotonia). PMD patients may not gain weight or grow as quickly as other children. They also seem to be more susceptible to infections. Some other symptoms may be: smaller than normal head size, weak or unusual cry, difficulty sucking, head tremors (titubation), poor muscle reflexes, a rattling sound in the throat caused by the weak muscles, sometimes referred to as stridor and, in rare cases, seizures. Males with PMD may seem normal at birth and may reach some of the normal milestones other children do, and they may plateau as the normal child gets older. As the child with PMD gets older, usually the arms, and especially legs, become stiffer or spastic. He usually is also uncoordinated or ataxic. PMD is usually not a progressive disease. Males with this disease may seem to get worse as they grow older, but this is probably due to other things like: poor nutritional health, recurrent infections, skeletal abnormalities (scoliosis, etc.), growth, maturity and/or seizures.

If a male has nystagmus and a past history of this disease the diagnosis can usually be made in the first few weeks or months of life. A magnetic resonance imaging (MRI) scan of the brain is often very helpful and should show abnormal white matter (which is white because the myelin is concentrated there) throughout the brain. The MRI may also suggest other diseases of the white matter, such as adrenoleukodystrophy, which can be excluded by specialized blood, urine, and/or skin testing. In families with no past history of PMD the diagnosis is usually made after many other diseases have been ruled out, or when a second handicapped child is born into the family and further investigation is done.

Unfortunately, there is no specific treatment for PMD as yet, such as special diet, vitamins, therapy, medication, etc.. Treatment is symptomatic. Progression of physical deformities may be slowed by

appropriate physical and/or occupational therapy. Good nutritional health can be more difficult. Most PMD infants are able to take feedings by mouth, they sometimes have difficulty sucking due to their weak muscle tone and/or a high palate (roof of the mouth). They eventually enjoy eating and usually handle solids easier than liquids. Although they seem to take in adequate amounts of food and calories, they fail to gain weight appropriately. Some require nasogastric (NG) or gastrostomy tube (G-tube) feedings to supplement or provide nutrition when they cannot or will not eat properly. There are medications, such as Baclofen (Lioresal) or tizanidine (Zanaflex), that may be quite helpful in reducing the spasticity.

In the less severe cases, males speak in a slow drawn out manner. They may have a vocabulary of a few simple words or phrases to an extensive list of several thousand words. They may sit with minimal support, maneuver a manual and/or electric wheelchair, feed themselves finger foods or small pieces with a spoon or fork, handle a covered cup with a straw and be toilet trained. They usually never walk independently, but some mildly affected individuals learn to walk. In the most severe cases, males never develop any physical or self help skills, they are unable to sit without total support, and are unable to feed themselves or talk. They seem to understand words and concepts even though they are unable to speak. They are also more medically fragile.

Because of their limited physical abilities many PMD males are labeled severely retarded. Parents, and I, usually don't agree with this and feel their PMD sons understand much more than they are able to express. PMD males are often very amazing in their ability to use their limited and/or abnormal body movements to do things that seem impossible for them. Schooling varies from place to place. Some PMD males may learn colors, letters, words and numbers. If the teacher is receptive to having them in the classroom and he/she is creative they may do very well. In other cases the children are often lost in the shuffle and school is nothing more than a "babysitting" service. With computers and new technology these children may someday be able to show us all how intelligent they really are. Life expectancies seem to vary depending on how severe a male is physically affected. Some patients live only a few months or years, while others live into their sixties.

In families with a past family history of this disease, affected males are generally affected similarly in abilities and life expectancies. However, even within a family where we know that all the affected individuals have the same mutation, there can be quite noticeable variation in the severity of symptoms.

Thanks to advancements in medical care and medications everyone is living longer. So we cling to this and hope the same will be true for our PMD sons. At the present time, there is no 100 percent accurate test to tell if a male has PMD. In the past, the only way to know what was going on in the brain was by autopsy and the diagnosis was made by the clinical symptoms and in some cases a past family history of this disease. Today we have the MRI. If a male has the nystagmus type eye movements and his MRI indicates there is lack of myelin, without evidence of active myelin breakdown, PMD might be suspected. If you have a past family history of this disease and the MRI shows this lack of myelin, you can be pretty certain of the diagnosis. Current research focuses on the Proteolipid Protein (PLP), the chief component of myelin in the Central Nervous System. Research has found mutations in the PLP

gene. Some of these mutations are point mutations, where a specific part of the gene may be missing, or switched, thus causing PMD. They have also found mutations where a part of this gene is duplicated or doubled. It is believed this may be the most common cause of PMD. Research in genetics is progressing very quickly, but for those waiting for answers it seems very slow. We hope in the near future, they will be able to find the gene abnormalities or mutations for all PMD families. Then they will be able to diagnose these males accurately, tell if a female is a carrier before she has an affected child and determine prenatally if a child will be affected with or be a carrier of PMD. There is research being done that we hope will eventually lead to better treatments and even a cure for PMD, but this will probably be a long process and require research support from the government (National Institutes of Health) and private agencies, such as the United Leukodystrophy Foundation and the National Multiple Sclerosis Society. The way medical technology is advancing we don't know what the future may bring. If you have further questions about the genetic research being done you may contact : Dr. James Garbern at (313) 577-2648, at Wayne State University in Detroit. Dr. Garbern is doing clinical and basic neurologic research on PMD that we hope will help us understand PMD and then lead to better treatments. Dr M. E. Hodes did most of the genetic testing in the US for PMD for over a decade. Currently testing is done at Baylor College of Medicine and by Dr. Grace Hobson at Dupont Hospital for children.

For questions about the clinical and/or neurological aspects of PMD you may contact : Dr. Garbern at (313) 577-2648 or Dr Larry Walsh at Indiana University at 317-274-3292. For family support you may contact: Patti Daviau at 317-635-7359 or email pdaviau@clarian.org.

The late Dr. Hodes and other researchers, at the Indiana University Medical Center have spent many years researching PMD. They were first to identify the PLP mutation in connection with PMD in my family. Since then, Dr Hodes and other researchers, including Dr's Garbern, Marks and Hobson, have discovered mutations in several different PMD families. Although they have found many mutations, there have been many PMD patients that they have not been able to find a specific mutation for.

Patti Daviau