Duchenne Muscular Dystrophy

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Duchenne muscular dystrophy (DMD) is one of several types of muscular dystrophy, a group of inherited diseases characterized by defects in production of certain muscle proteins and the ensuing degeneration of skeletal/cardiac muscles. DMD involves mutations in the dystrophin protein. It is the most common, and also the most severe type of muscular dystrophy.

About 1 in 3500 boys is born with DMD, with this disease frequency being relatively constant across all ethnic groups. It is inherited in an X-linked recessive pattern and thus males account for nearly all of the cases of DMD. Since most males do not live to reproductive age, the incidence of DMD in females is extremely rare. The few cases of females with DMD have mostly been a result of random X-inactivation, and the symptoms are usually similar, but progress at a much slower rate. According to Haldane's rule, for a genetic lethal X-linked recessive disease like DMD, about one in every three cases is due to a new mutation. Haldane's theory is based on the idea that "if selection acts against deleterious alleles, it must be balanced by mutation pressure to generate observed allele frequencies in a population" (Nachman, 2004).

Unless a parent is aware of a family history, DMD is unlikely to be diagnosed before the child is two years old, and is usually diagnosed between three to six years of age. A child typically first presents with a delayed ability to walk, a waddled gait, difficulty standing up and hypertrophied calf muscles. This is seen because the first muscles that DMD affects are the muscles of the lower limb and pelvis. By the age of twelve, most children with DMD are no longer able to walk. As other skeletal muscles degenerate, symptoms such as scoliosis become common. Eventually, the patient's respiratory and cardiac muscles begin to degenerate. While some patients can be kept alive longer with ventilator care, most males with DMD do not live past twenty years. The average life expectancy according to one study was 17 years (Boland et al., 1996)

In the past, if a physician suspected that a child had DMD, the traditional test was a calf muscle biopsy that tested for high levels of creatine kinase. Creatine kinase is an enzyme involved in ATP metabolism which is normally present in muscle cells. Since the muscle cells in children with DMD are undergoing a fast rate of degeneration, a biopsy reveals elevated levels of creatine kinase in muscle serum. In recent years, the dystrophin gene has been mapped and a genetic test using polymerase chain reaction with primers for mutated sequences has been developed. This test uses a patient's blood sample and is less invasive and more accurate than the creatine kinase test. In addition, this test can also be used for carrier testing and prenatal testing (Flanigan et al., 2003).

For a family with a history of DMD, a pedigree can usually identify those females who are at risk for being carriers. Carrier testing is highly recommended for such women, especially before planning a family. Counseling a woman who carries the DMD mutation would require informing her about the risk to her children. Because DMD is an X-linked disorder, a female has a 50% chance of passing the disease to her sons, and her daughters have a 50% chance of being carriers. It would be important to inform her of these risks – that there is a ½ chance of having a completely normal child, but also a ¼ chance of having an affected son and a ¼ chance of having a daughter who will be a

carrier. She should also be told of the severity of the disease and that the prognosis is currently quite grim. It would also be necessary to inform her of the availability of prenatal testing for DMD, so that if she did decide to conceive, the fetus could be tested for the disease.

For a woman who tests positive for carrier status, it would also be important to inquire about whether other family members have been tested. Her sisters have a fifty percent chance of being carriers, and depending on the pedigree, other family members could also be it risk. If a woman has a son with DMD, it is important to remember that about one-third of all cases are due to new mutations. This could be determined by testing the mother. If the mother does not have the DMD mutation, then the child has most likely undergone a new mutation. In these cases, there would be no elevated risk for other family members, nor for additional children from the same parents.

As described previously, DMD results from a loss of individual muscle fibers and has been attributed to aberrations in the gene encoding the protein dystrophin. This gene is located upon the short arm of the X chromosome at Xp21. The dystrophin gene is extremely large consisting of 2.5 million base pairs, with approximately 70 exons. The gene product is a 14 kbp transcript resulting in the 427 kDa dystrophin protein. The gene is about 10 times larger than the next largest known gene. The gene's large size is thought to account for its high rate of mutation.

Dystrophin is a protein that is expressed primarily in the sarcolemma of smooth, cardiac, and striated muscle but is also expressed in cerebellar purkinje fibers and certain neurons of the cerebral cortex. In myocytes, dystrophin proteins are concentrated over the Z-bands, an integral structure involved in muscle movement. Despite the size of the gene and protein, both the sequence of the gene and the primary structure of the protein have been determined. The primary sequence of the dystrophin molecule reveals four structural domains that show significant homology with two cytoskeletal proteins, alpha actinin and beta spectrin.

Under normal conditions, dystrophin functions as a part of a glycoprotein complex. Multiple dystrophin molecules combine to form a chain. Parts of the chain connect to cytoplasmic actin while other parts attach to transmembrane proteins, dystrobrevin and syntrophins, which in turn form a link to the extracellular matrix. From these connections, dystrophin is able to transfer the force of the muscle fiber contraction to the connective tissue.

The ability to transfer force and stabilize the plasma membrane of the muscle fibers is the critical function that is lost in those with DMD. DMD differs from other muscular dystrophies in the fact that it results from a quantitative defect in the dystrophin gene, resulting in little to no viable dystrophin molecules synthesized. On the other hand, Becker Muscular Dystrophy is characterized by a qualitative defect in the dystrophin gene resulting in the production of abnormal dystrophin. The errors in the dystrophin gene that cause DMD have not been localized to a particular region. However, it is known that 65% of DMD patients have deletion mutations, which usually cause frameshift mutations, and 7% have duplication mutations within their dystrophin genes. Due to the large size of the gene no point mutations have been identified to cause DMD. Furthermore, there is no clear connection between the size of the deletion and the severity of the disorder.

The quantitative deficiency of dystrophin decreases the stability of the muscle fiber plasma membrane. Subsequently upon muscle contraction, the force causes transient plasma membrane holes to form. These pathologic openings in the plasma membrane allow creatine kinase and other intracellular enzymes to leave the cell while allowing large amounts of extracellular Ca^{2+} to enter. This influx of Ca^{2+} is the likely cause of necrosis of the dystrophin deficient muscle fibers.

Although much is understood about the mechanism of Duchenne's Muscular Dystropy, currently there are no known treatments. Clinical strategies are designed to ease symptoms and maximize the quality of life of the patient. Physical therapy is used to maintain muscle function and strength. Exercise is also encouraged to affected individuals. Often braces, canes, or wheelchairs are used to help mobility if they are needed. In addition mechanical ventilators are recommended if the disease exhibits respiratory symptoms. This is usually while the patient is asleep and is at risk for under-ventilation. However, they may become increasingly dependant on a mechanical ventilator as the disease progresses.

Duchenne's Muscular Dystrophy was initially described clinically in 1860 by the French neurologist Guillaume Benjamin Amand Duchenne. During his initial research of the disease he developed the use of electrical current to stimulate muscles for diagnostic and therapeutic purposes. Current research in the field looks toward gene therapy, pharmacology, and cell mediated treatments for the pathology of Duchenne's Muscular Dystrophy. Gene therapy aims to replace the defective dystrophin gene via introduction of exogenous DNA in plasmids, viral vectors, or oligonuclotides(zhang et al 2004). Alternative approaches include the upregulation of other dystrophin related proteins to compensate for the mutation. Studies have shown that in a mouse model of muscular dystrophy upregulation of utrophin can ameliorate muscle pathology (Hurst et al 2005). Myostatin inhibitors have also shown promise as a pharmacologic target. It is a negative regulator of muscle mass from the TGF-beta family (Whittemore et al 2003). In a mouse model the inhibitors of myostatin improved the pathophysiology and even enhanced muscle repair following injury(Whittemore et al 2003). Several groups have been studying the disease in a Golden Retriever dog model, which most accurately simulates the pathology of human DMD(Sampaolesi et al 2006). Skeletal muscle can be completely regenerated by precursor stem cells but that ability is lost in muscular dystrophy(Shi et al 2006). Recently, stem cell transplant in the dog model of DMD yielded exciting results. Transplantation of mesoangioblast stem cells eased many of the symptoms associated with muscular dystrophy in these animals (Sampaolesi et al 2006). These blood vessel precursor cells were able to migrate through the endothelial wall and to the muscle where they restored contractility and demonstrated expression of dystrophin. The mechanism of Duchenne's Muscular dystrophy has been well characterized through the collaborative efforts of many researchers. The diversity of research towards a cure for this devastating disease has much promise and there is certainly hope in the future.

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