Genetics in Special Education Series

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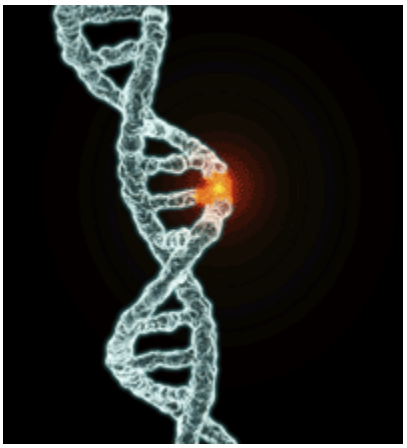

Genetic disorders presented in this issue:

Duchenne muscular dystrophy

What is Duchenne muscular dystrophy?

Duchenne muscular dystrophy (DMD) is a rapidly progressive form of muscular dystrophy that occurs primarily in boys. It is caused by an alteration (mutation) in a gene, called the DMD gene that can be inherited in families in an X-linked recessive fashion, but it often occurs in people from families without a known family history of the condition. Individuals who have DMD have progressive loss of muscle function and weakness, which begins in the lower limbs. The DMD gene is the second largest gene to date, which encodes the muscle protein, dystrophin. Boys with Duchenne muscular dystrophy do not make the dystrophin protein in their muscles.

Duchenne muscular dystrophy affects approximately 1 in 3500 male births worldwide. Because this is an inherited disorder, risks include a family history of Duchenne muscular dystrophy.

What are the symptoms of Duchenne muscular dystrophy?

The symptoms usually appear before age 6 and may appear as early as infancy. Typically, the first noticeable symptom is delay of motor milestones, including sitting and standing independently. The mean age for walking in boys with Duchenne muscular dystrophy is 18 months. There is progressive muscle weakness of the legs and pelvic muscles, which is

associated with a loss of muscle mass (wasting). This muscle weakness causes a waddling gait and difficulty climbing stairs. Muscle weakness also occurs in the arms, neck, and other areas, but not as severely or as early as in the lower half of the body.

Calf muscles initially enlarge and the enlarged muscle tissue is eventually replaced with fat and connective tissue (pseudohypertrophy). Muscle contractures occur in the legs, making the muscles unusable because the muscle fibers shorten and fibrosis occurs in connective tissue. Occasionally, there can be pain in the calves.

Symptoms usually appear in boys aged 1 to 6. There is a steady decline in muscle strength between the ages of 6 and 11 years. By age 10, braces may be required for walking, and by age 12, most boys are confined to a wheelchair. Bones develop abnormally, causing skeletal deformities of the spine and other areas.

Muscular weakness and skeletal deformities frequently contribute to breathing disorders. Cardiomyopathy (enlarged heart) occurs in almost all cases, beginning in the early teens in some, and in all after the age of 18 years. Intellectual impairment may occur, but it is not inevitable and does not worsen as the disorder progresses.

Few individuals with DMD live beyond their 30s. Breathing complications and cardiomyopathy are common causes of death.

How is Duchenne muscular dystrpohy diagnosed?

Duchenne muscular dystrophy is diagnosed in several ways. A clinical diagnosis may be made when a boy has progressive symmetrical muscle weakness. The symptoms present before age 5 years, and they often have extremely elevated creatine kinase blood levels (which are described below) . If untreated, the affected boys become wheelchair dependent before age 13 years.

A muscle biopsy (taking a sample of muscle) for dystrophin studies can be done to look for abnormal levels of dystrophin in the muscle. The dystrophin protein can be visualized by staining the muscle sample with a special dye that allows you to see the dystrophin protein. A muscle which has average amounts of dystrophin will appear with the staining technique as though there is caulking around the individual muscles cells and it is holding them together like window panes. A boy with Duchenne, on the other hand, will have an absence of dystrophin and appear to have an absence of the caulking around the muscle cells. Some individuals can be found to have an intermediate amount of the dystrophin protein. Often these boys are classified as having Becker muscular dystrophy.

Genetic testing (looking at the body's genetic instructions) on a blood sample for changes in the DMD gene can help establish the diagnosis of Duchenne muscular dystrophy without performing a muscle biopsy. Genetic testing is constantly changing, but the methods currently being used look for large changes in the gene (*deletion/duplication*) and another method, which looks at the letters that spell out the instructions found within the DMD gene (*sequencing*). Together these two methods can detect the disease causing changes in about 95% of patients. Those individuals who are not found to have a detected change in the DMD gene using this method, and who are diagnosed with DMD by biopsy, still have a change in their gene but it is in areas of the gene that are not examined using these methods. However, the results of genetic testing may not be

conclusive of a diagnosis of DMD, and only the muscle biopsy can tell the level of dystrophin protein for sure.

For the remaining individuals, a combination of clinical findings, family history, blood creatine kinase concentration and muscle biopsy with dystrophin studies confirms the diagnosis. Creatine kinase is an enzyme that is present normally in high concentrations in the muscle cells of our body. During the process of muscle degeneration or breakdown, the muscle cells are broken open and their contents find their way to the bloodstream. Therefore elevated levels of creatine kinase can be detected from a blood test and it is a measure of muscle damage. Elevated levels can be the result of multiple reasons including acute muscle injury, or chronic condition such as Duchenne muscular dystrophy.

What is the treatment for Duchenne muscular dystrophy?

Treatment for Duchenne muscular dystrophy is aimed at the symptoms. Aggressive management of dilated cardiomyopathy with anti-congestive medications is used, including cardiac transplantation in severe cases. Assistive devices for respiratory complications may be needed, especially at night. The medication prednisone — a steroid — is given to improve the strength and function of individuals with DMD. Prednisone has been shown to prolong the ability to walk by 2 to 5 years. However, the possible side effects of prednisone include weight gain, high blood pressure, behavior changes, and delayed growth. A synthetic form of prednisilone, called Deflazacort, is used in Europe and believed to have fewer side effects than prednisone. A medication called cyclosporine has been used and has improved clinical function in children, but its use is controversial due to cyclosporine-induced myopathy. Oxandrolone, a medication used in a research study, has similar effects to prednisone with fewer side effects. Several other therapies are also under investigation, including coenzyme Q10, glutamine, pentoxifylline, and PTC124 (see clinical research below).

Physical therapy is used to promote mobility and prevent contractures. Surgery may be needed for severe contractures and scoliosis.

Is Duchenne muscular dystrophy inherited?

Duchenne muscular dystrophy is inherited in an X-linked recessive pattern. Males have only one copy of the X chromosome from their mother and one copy of the Y chromosome from their father. If their X chromosome has a DMD gene mutation, they will have Duchenne muscular dystrophy. Females, on the other hand, have two copies of the X chromosomes.. Since females have two copies of this gene, if one copy does not work, they have a second back up copy to produce the dystrophin protein. A woman who has a genetic change in one of her two copies is said to be "a carrier" of Duchenne muscular dystrophy. Carriers do not have Duchenne muscular dystrophy and most are unaware that they even carry this change in their genetic material unless they have a family history. However, recent studies have shown that some carrier females (approximately 20 percent) will show symptoms of DMD, including muscle weakness and cardiac abnormalities.

With an X-linked recessive condition, the chance of passing on the changed (non-working) copy of the gene to a child is different for males and females.

Females who carry the changed copy of the gene have a 50 percent chance of passing it on with each pregnancy. Thus, there is a 25 percent chance of having a affected child with DMD (eg., 50 percent of boys have the chance of having DMD and 50 percent of girls will be carriers). The chance of a woman who has one affected son (and no family history) of being a carrier of the changed DMD gene is approximately 2/3. However, in the remaining third of individuals with DMD, the change in the dystrophin gene is a new genetic change, or *de novo change* and about 10 percent of new mutations are due to gonadal mosaicism. Gonadal mosaicism refers to a condition where an individual has two or more cell populations that differ in genetic makeup in their eggs or sperm.

Males who inherit or are born with a changed copy of the DMD gene will have DMD since they have a Y chromosome, and do not have back-up X chromosome. If a male with DMD were to have children, all of his daughters would be carriers and none of his sons would be affected.

Currently various reproductive options are available to families. The preconception options include MicroSort which is a technology that can separate sperm containing X chromosomes allowing for an increase in chances of having a female. The second reproductive option is preimplantation genetic diagnosis (PGD), which is a technique that can allow the cells of a fertilized egg to be tested to determine if it contains a change in the DMD gene and then implant those eggs which do not. The post conception options include Chorionic Villus Sampling (CVS) and amniocentesis which analyze sampled cells derived from the developing fetus.

Several of the prenatal testing options for pregnancies at increased risk are available when the DMD disease-causing mutation has been identified in a family member, or if informative, genetically-linked markers have been identified.

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Factor V Leiden thrombophilia

What is factor V Leiden thrombophilia?

Factor V Leiden thrombophilia is an inherited disorder of blood clotting. Factor V Leiden is the name of a specific mutation (genetic alteration) that results in thrombophilia, or an increased tendency to form abnormal blood clots in blood vessels. People who have the factor V Leiden mutation are at somewhat higher than average risk for a type of clot that forms in large veins in the legs (deep venous thrombosis, or DVT) or a clot that travels through the bloodstream and lodges in the lungs (pulmonary embolism, or PE).

Factor V Leiden is the most common inherited form of thrombophilia. Between 3 and 8 percent of the Caucasian (white) U.S. and European populations carry one copy of the factor V Leiden mutation, and about 1 in 5,000 people have two copies of the mutation. The mutation is less common in other populations.

A mutation in the factor V gene (F5) increases the risk of developing factor V Leiden thrombophilia. The protein made by F5 called factor V plays a critical role in the formation of

blood clots in response to injury. The Factor V protein is involved in a series of chemical reactions that hold blood clots together. A molecule called activated protein C (APC) prevents blood clots from growing too large by inactivating factor V. In people with the factor V Leiden mutation, APC is unable to inactivate factor V normally. As a result, the clotting process continues longer than usual, increasing the chance of developing abnormal blood clots.

Information courtesy of: Genetics Home Reference

What are the symptoms of factor V Leiden thrombophilia?

The symptoms of factor V Leiden vary among individuals. There are some individuals who have the F5 gene and who never develop thrombosis, while others have recurring thrombosis before the age of 30 years. This variability is influenced by the number of F5 gene mutations a person has, the presence of other gene alterations related to blood clotting, and circumstantial risk factors, such as surgery, use of oral contraceptives and pregnancy.

Symptoms of Factor V Leiden include:

- Having a first DVT or PE before 50 years of age.
- Having recurring DVT or PE.
- Having venous thrombosis in unusual sites in the body such as the brain or the liver.
- Having a DVT or PE during or right after pregnancy.
- Having a history of unexplained pregnancy loss in the second or third trimester.
- Having a DVT or PE and a strong family history of venous thromboembolism.

The use of hormones, such as oral contraceptive pills (OCPs) and hormone replacement therapy (HRT), including estrogen and estrogen-like drugs) taken after menopause, increases the risk of developing DVT and PE. Healthy women taking OCPs have a three- to four-fold increased risk of developing a DVT or PE compared with women who do not take OCP. Women with factor V Leiden who take OCPs have about a 35-fold increased risk of developing a DVT or PE compared with women without factor V Leiden and those who do not take OCPs. Likewise, postmenopausal women taking HRT have a two- to three-fold higher risk of developing a DVT or PE than women who do not take HRT, and women with factor V Leiden who take HRT have a 15-fold higher risk. Women with heterozygous factor V Leiden who are making decisions about OCP or HRT use should take these statistics into consideration when weighing the risks and benefits of treatment.

Information courtesy of: The American Heart Association

How is factor V Leiden thrombophilia diagnosed?

Your doctor would suspect a diagnosis of thrombophilia if you have a history of venous thrombosis and/or a family history of venous thrombosis. The diagnosis is made using a screening test called a coagulation screening test or by genetic testing (DNA analysis) of the F5 gene.

How is factor V Leiden thrombophilia treated?

The management of individuals with factor V Leiden depends on the clinical circumstances. People with factor V Leiden who have had a DVT or PE are usually treated with blood thinners, or anticoagulants. Anticoagulants such as heparin are given for varying amounts of time depending on the person's situation. It is not usually recommended that people with factor V Leiden be treated lifelong with anticoagulants if they have had only one DVT or PE, unless there are additional risk factors present. Having had a DVT or PE in the past increases a person?s risk for developing another one in the future, but having factor V Leiden does not seem to add to the risk of having a second clot. In general, individuals who have factor V Leiden but have never had a blood clot are not routinely treated with an anticoagulant. Rather, these individuals are counseled about reducing or eliminating other factors that may add to one?s risk of developing a clot in the future. In addition, these individuals may require temporary treatment with an anticoagulant during periods of particularly high risk, such as major surgery.

Factor V Leiden increases the risk of developing a DVT during pregnancy by about seven-fold. Women with factor V Leiden who are planning pregnancy should discuss this with their obstetrician and/or hematologist. Most women with factor V Leiden have normal pregnancies and only require close follow-up during pregnancy. For those with a history of DVT or PE, treatment with an anticoagulant during a subsequent pregnancy can prevent recurrent problems.

Information courtesy of: The American Heart Association

What do we know about heredity and factor V Leiden thrombophilia?

Factor V Leiden is the most common inherited form of thrombophilia. The risk of developing a clot in a blood vessel depends on whether a person inherits one or two copies of the factor V Leiden mutation. Inheriting one copy of the mutation from a parent increases by fourfold to eightfold the chance of developing a clot. People who inherit two copies of the mutation, one from each parent, may have up to 80 times the usual risk of developing this type of blood clot. Considering that the risk of developing an abnormal blood clot averages about 1 in 1,000 per year in the general population, the presence of one copy of the factor V Leiden mutation increases that risk to 1 in 125 to 1 in 250. Having two copies of the mutation may raise the risk as high as 1 in 12.

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