Genetics in Special Education Series

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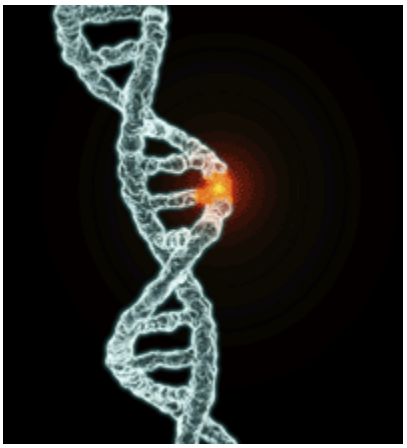

Genetic disorders presented in this issue:

Retinitis Pigmentosa

What is retinitis pigmentosa?

Retinitis pigmentosa (RP) is the name given to a group of inherited eye diseases that affect the retina (the light-sensitive part of the eye). RP causes the breakdown of photoreceptor cells (cells in the retina that detect light). Photoreceptor cells capture and process light helping us to see. As these cells breakdown and die, patients experience progressive vision loss.

The most common feature of all forms of RP is a gradual breakdown of rods (retinal cells that detect dim light) and cones (retinal cells that detect light and color). Most forms of RP first cause the breakdown of rod cells. These forms of RP, sometimes called rod-cone dystrophy, usually begin with night blindness. Night blindness is somewhat like the experience normally sighted individuals encounter when entering a dark movie theatre on a bright, sunny day. However, patients with RP cannot adjust well to dark and dimly lit environments.

What are the symptoms of retinitis pigmentosa?

As the disease progresses and more rod cells breakdown, patients lose their peripheral vision (tunnel vision). Individuals with RP often experience a ring of vision loss in their periphery, but retain clear central vision.

Others report the sensation of tunnel vision, as though they see the world through a straw. Many patients with retinitis pigmentosa retain a small degree of central vision throughout their life.

Other forms of RP, sometimes called cone-rod dystrophy, first affect central vision. Patients first experience a loss of central vision that cannot be corrected with glasses or contact lenses. With the loss of cone cells also comes disturbances in color perception. As the disease progresses, rod cells degenerate causing night blindness and peripheral vision.

Symptoms of RP are most often recognized in children, adolescents and young adults, with progression of the disease continuing throughout the individual's life. The pattern and degree of visual loss are variable.

What causes retinitis pigmentosa?

Retinitis pigmentosa is an inherited disorder, and therefore not caused by injury, infection or any other external or environmental factors. People suffering from RP are born with the disorder already programmed into their cells. Doctors can see the first signs of retinitis pigmentosa in affected children as early as age 10. Research suggests that several different types of gene mutations (changes in genes) can send faulty messages to the retinal cells which leads to their progressive degeneration. In most cases, the disorder is linked to a recessive gene, a gene that must be inherited from both parents in order to cause the disease. But dominant genes and genes on the X chromosome also have been linked to retinitis pigmentosa. In these cases, only one parent has passed the disease gene. In some cases, a new mutation causes the disease to occur in a person who does not have a family history of the disease. The disorder also can show up as part of other syndromes, such as Bassen-Kornzweig disease or Kearns-Sayre syndrome.

How is retinitis pigmentosa treated?

There is no known cure for retinitis pigmentosa. However, there are few treatment options such as light avoidance and/or the use of low-vision aids to slow down the progression of RP. Some practitioners also consider vitamin A as a possible treatment option to slow down the progression of RP. Research suggests taking high doses of vitamin A (15,000 IU/day) may slow progression a little in some people, but the results are not strong. Taking too much vitamin A can be toxic and the effects of vitamin A on the disease is relatively weak. More research must be conducted before this is a widely accepted form of therapy.

Research is also being conducted in areas such as gene therapy research, transplant research, and retinal prosthesis. Since RP is usually the result of a defective gene, gene therapy has become a widely explored area for future research. The goal of such research would be to discover ways healthy genes can be inserted into the retina. Attempts at transplanting healthy retinal cells into sick retinas are being made experimentally and have not yet been considered as clinically safe and successful. Retinal prosthesis is also an important area of exploration because the prosthesis, a man-made device intended to replace a damaged body part, can be designed to take over the function of the lost photoreceptors by electrically stimulating the remaining healthy cells of the retina. Through electrical stimulation, the activated ganglion cells can provide a visual signal to the brain. The visual scene captured by a camera is transmitted via electromagnetic radiation to a small decoder chip located on the retinal surface.

Data and power are then sent to a set of electrodes connected to the decoder. Electrical current passing from individual electrodes stimulate cells in the appropriate areas of the retina corresponding to the features in the visual scene.

What do we know about heredity and retinitis pigmentosa?

Since RP is an inherited disorder, it can potentially affect another member of the family. With retinal cells being among the most specialized cells in the human body, they depend on a number of unique genes to create vision. A disease-causing mutation in any one of these genes can lead to vision loss. Researchers have discovered over 100 genes that can contain mutations leading to retinitis pigmentosa. Approximately 50 percent of RP cases are isolated and have no previous family history. The cause of these cases cannot be explained. Other cases of RP, where family history has been determined, fall into three main categories: autosomal recessive, autosomal dominant, and X-linked recessive.

Autosomal recessive RP occurs when both parents are unaffected carriers of the same defective gene. The chances of a child being affected is one in four. This means the affected child must inherit the defective gene from each parent. The chances of a parent having an unaffected child who would be a carrier of the defective gene is one in two. The chance of parents having a child completely free of the RP gene is one in four.

In autosomal dominant RP, the disease is present in males or females only when a single copy of the gene is defective. Typically, one of the parents is affected by the disease. The chance is one in two of any given offspring being affected by the disease, if the affected parent has one normal and one defective gene.

X-linked recessive RP may occur in offspring in two ways. The fathers can be affected or mothers can be carriers of the defective gene. If the father is affected, all sons will be unaffected and all daughters will be carriers. If the mother is the carrier, 1 in 2 sons will be affected and 1 in 2 daughters will be carriers. In families with the X-linked type, only males are affected, while females carry the genetic trait but do not experience serious vision loss.

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Antiphospholipid Syndrome

What is antiphospholipid syndrome (APS)?

Antiphospholipid syndrome (APS), also known as antiphospholipid antibody syndrome and sometimes Hughes syndrome, is a disorder characterized by elevated levels of multiple different antibodies (proteins produced by the body to fight off foreign substances) that are associated with both arterial and venous thrombosis (clots in the arteries and veins).

There are two primary classes of antiphospholipid (aPL) antibodies, the antibodies associated with APS. These are called anticardiolipin antibodies and the lupus anticoagulant, and are directed against specific molecules. These aPL antibodies appear to be mainly directed against two particular molecules: beta-2-glycoprotein I (ß2GPI, a normal protein found in the blood whose function is unknown) and another molecule known as prothrombin (a normal blood protein that binds to phospholipids and plays a very important role in blood clotting).

These aPL antibodies were first noted in a group of people who had positive tests for syphilis without signs of infection. It was then noticed that some individuals who continued to have false-positive tests for syphilis went on to develop systemic lupus erythematosus (SLE) and other similar conditions. Later studies found a protein called the lupus anticoagulant in a number of individuals with SLE. A case report in 1956 described an individual with recurrent pregnancy loss, thrombophlebitis (inflammation of a vein related to a blood clot) and lupus anticoagulant. The work of Dr. Graham Hughes and his colleagues in the 1980s provided further understanding of APS, including the introduction of testing for anticardiolipin antibodies.

Up until the 1980s, it was thought that aPL antibodies were directed against a type of molecule known as anionoic phospholipids. However, in the early 1990s, several different groups discovered that this was not the case. Anticardiolipin antibodies were found to act against ß2GPI, while the lupus anticoagulant was first found to act against ß2GPI and, more recently, prothrombin.

There are two main classifications of APS. If the individual has no known underlying autoimmune disorder, the person is said to have primary APS. If the individual has SLE or another underlying autoimmune disorder, the person is said to have secondary APS. Although APS is divided into these two categories, research indicates that there is little essential difference between them.

What are some of the signs, complications and conditions associated with APS?

APS usually shows up for the first time as vascular thrombosis (a blood clot in an artery or vein) or embolism (the blockage of a blood vessel caused by a clot that has moved in the blood stream from the site where it formed to a different place in the body) or as recurrent pregnancy loss. Thrombocytopenia (a low platelet count), certain skin problems, neurological signs, heart valve disease and certain autoimmune diseases have also been noted in association with APS. Pulmonary hypertension (high blood pressure in the arteries that supply the lungs) and

sensorineural hearing loss (hearing loss caused by damage to the inner ear or to the nerve pathways from the inner ear) have been noted in some individuals with APS as well.

Conditions associated with APS include:

Systemic Vascular Thrombosis

While the deep veins of the legs are the most frequent sites of thrombosis, thromboembolism can involve virtually any vein or artery. Deep vein thrombosis tends to be the most common finding, occurring in half of affected individuals; other sites of venous thrombotic events include the veins of the lungs (due to pulmonary embolism, a clot that typically has dislodged from a vein below the pulmonary veins and lodged in a pulmonary vein), thoracic veins (veins in or above the chest that carry blood to the heart including the superior vena cava, subclavian vein, or jugular vein), and abdominal or pelvic veins.

A risk of recurrent thrombi is associated with APS as well. Most studies suggest that individuals who have a recurrent episode will have it in a similar blood vessel type. For example, individuals who have a stroke initially will most often have a stroke if they have a recurrence. Nonetheless, individuals are reported who have had different types of thrombotic events.

Pregnancy Loss and Other Complications

APS is associated with miscarriages as well as other complications of pregnancy. Most studies have estimated the prevalence of aPL antibodies among pregnant women at 5 percent or less; most of these women do not have any signs or symptoms of APS. Around 10-20 percent of women with multiple pregnancy losses are thought to have APS.

Women with APS often have a history of recurrent (usually defined as three or more) pregnancy losses. Pregnancies occurring in women with APS are at significantly increased risk of miscarriage, prematurity, slower than expected growth of the fetus, and preeclampsia (high blood pressure during pregnancy). Pregnant women with APS are also more prone to develop deep vein thrombosis during pregnancy or puerperium (the period between childbirth and the return of the uterus to its normal size).

Thrombocytopenia

An association with immune thrombocytopenia (low platelets) has also been established. This occurs to varying degrees in as many as 50 percent of individuals with APS. Because platelets help the blood to clot, thrombocytopenia can sometimes cause a bleeding disorder in an otherwise healthy person. However, in APS, thrombocytopenia is usually moderate and is rarely significant enough to cause bleeding complications or to affect anticoagulant (anti-clotting) therapy.

Skin Disorders

Certain skin conditions have also been observed in APS. These include livedo reticularis (mottled discoloration of the skin), ulcers (sores) on the skin, usually on the legs, and sometimes skin necrosis (a condition in which the skin tissue dies).

Stroke and Other Neurological Disorders

Stroke is associated with APS, as are some other neurological conditions. In addition to cerebrovascular thrombosis (a blood clot that forms in a blood vessel of the brain), embolic stroke (stroke caused by a blood clot that travels from a different location to a blood vessel in the brain) can also occur. Multiple strokes can sometimes lead to a condition called multi-infarct dementia.

Other neurological problems have been have been reported in people with aPL antibodies, although they are not as strongly associated with APS as stroke.

These include seizures, chorea (a movement disorder), migraines, Guillain-Barré syndrome, diabetic peripheral neuropathy, transverse myelitis (a disorder caused by inflammation across both sides of one level, or segment, of the spinal cord), and conditions similar to multiple sclerosis. Evidence for an association with cognitive dysfunction is growing.

Heart Valve Disease

A type of heart valve disease called Libman-Sacks endocarditis is sometimes seen in individuals with aPL antibodies. In this condition, growths on the heart valve can break off and travel through the blood stream, causing embolic events.

Lupus and Other Autoimmune Disorders

APS is classified within the category of autoimmune disorders (conditions caused by an immune response against the body's own tissues). Individuals with aPL antibodies sometimes have an additional autoimmune disorder, most commonly systemic lupus erythematosus (SLE). About 30-40 percent of individuals with SLE have elevated aPL antibodies. APS has also been associated with a number of other autoimmune disorders, including myasthenia gravis, Graves' disease, autoimmune hemolytic anemia, and Evan's syndrome.

How is APS diagnosed?

A diagnosis of APS is made based on both clinical and laboratory findings. APS is diagnosed if an individual experiences one or more episodes of thrombosis or pregnancy loss and if aPL antibodies are detected through laboratory testing of the individual's blood.

There are two main types of antiphospholipid antibody tests - immunological tests, like the anticardiolipin ELISA (enzyme-linked immunoassay), and coagulation-based tests for the lupus anticoagulant. ELISAs are immunologically-based tests, or immunoassays, in which an antigen-antibody reaction is used to detect the antibodies. In contrast, lupus anticoagulant tests detect antibodies based on their ability to slow down phospholipid-dependent clotting reactions. Most individuals with APS have antibodies that can be detected in both tests; however, a significant percentage of patients are positive in one test but not the other. Therefore, to diagnose APS, it is standard practice for both tests to be performed. The tests are then repeated six to eight weeks later to confirm the presence of aPL antibodies.For more about the tests used to diagnose APS, go to the APS Foundation of America, Inc. [apsfa.org]

Who gets APS?

There are no hard and fast statistics about the number of people with aPL antibodies or APS. What we know is based on estimates from different studies over time. Research suggests that aPL antibodies may be found in around 1 to 5 percent of the healthy general population. Primary APS accounts for over 50% of cases.

In individuals with SLE, approximately 30 percent have aPL antibodies, and around 30-50 percent of these individuals have symptoms and signs of APS. It is more difficult to measure the number of people with primary APS, but studies indicate that between 5-30 percent of individuals with thrombosis and no history of SLE have aPL antibodies. Additional studies suggest that aPL antibodies may play a role in approximately one-third of strokes in individuals under the age of 50.

A female predominance has been noted, especially for secondary APS. This parallels the association of APS with SLE and other connective-tissue diseases, which also have a female predominance.

If thrombosis occurs in an individual with APS, this usually happens between the ages of 35-45 years. After age 60, signs and symptoms of are APS rarely seen for the first time.

Is APS inherited?

Although APS has been reported to occur in multiple members of the same family, no clear inheritance pattern has been identified and no gene has been found to be the sole cause of this condition. One report in 1999 studied families with more than one affected member, examined possible modes of inheritance, and examined links with certain genes. In seven families, 30 out of 101 family members met diagnostic criteria for the syndrome. The data were fitted best by either a dominant (one copy of the altered gene inherited from one parent causes the condition) or codominant (features related to the condition from both parents are observed) model.

Is there an effective treatment for APS?

Treatment for APS must be individualized according to the person's current health status and the types of problems that person has experienced due to their APS. In general, for a person who has aPL antibodies and has had a thrombotic event, a short-term course of heparin (an anticoagulant, which is a type of medication used to prevent blood clots from forming or getting bigger) is followed by long-term - sometimes life-long - treatment with warfarin (another type of anticoagulant).

In women with moderate to high levels of aPL antibodies and a history of pregnancy loss who wish to get pregnant again, treatment is again individualized. After consulting with and obstetrician and rheumatologist and/or hematologist, women generally begin treatment with heparin and low-dose aspirin.

For those individuals who have been found to have aPL antibodies but have not had any signs or symptoms of APS, low-dose aspirin is generally recommended by their doctors.

If you or someone you know has been diagnosed with APS, we recommend talking with a health care provider to determine a personalized course of management.

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