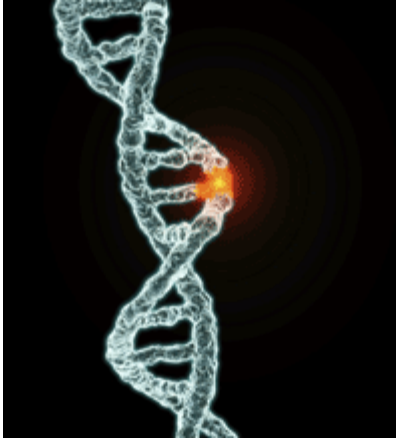


Genetics in Special Education Series

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Genetic disorders presented in this issue:

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Spinal Muscular Atrophy

What is spinal muscular atrophy?

Spinal muscular atrophy is a group of inherited disorders that cause progressive muscle degeneration and weakness. Spinal muscular atrophy (SMA) is the second leading cause of neuromuscular disease. It is usually inherited as an autosomal recessive trait (a person must get the defective gene from both parents to be affected).

There are several types of SMA called subtypes. Each of the subtypes is based on the severity of the disorder and the age at which symptoms begin. There are three types of SMA that affect children before the age of 1 year. There are two types of SMA, type IV and Finkel type, that occur in adulthood, usually after age 30. Symptoms of adult-onset spinal muscular atrophy are usually mild to moderate and include muscle weakness, tremor and twitching.

The prognosis for individuals with SMA varies depending on the type of SMA and the degree of respiratory function. The patient's condition tends to deteriorate over time, depending on the severity of the symptoms.

Spinal muscular atrophy affects 1 in 6,000 to 1 in 10,000 people.

What are the symptoms of spinal muscular atrophy?

Three types of SMA affect children before age one year. Type 0 is the most severe form of spinal muscular atrophy and begins before birth. Usually, the first symptom of type 0 is reduced movement of the fetus that is first seen between 30 and 36 weeks of the pregnancy. After birth, these newborns have little movement and have difficulties with swallowing and breathing.

Type I spinal muscular atrophy (called Werdnig-Hoffman disease) is another severe form of SMA. Symptoms of type 1 may be present at birth or within the first few months of life. These infants usually have difficulty breathing and swallowing, and they are unable to sit without support.

Children with type II SMA usually develop muscle weakness between ages 6 and 12 months. They cannot stand or walk without help.

Type III SMA (called Kugelberg-Welander disease or juvenile type) is a milder form of SMA than types 0, I or II. Symptoms appear between early childhood (older than age 1 year) and early adulthood. Individuals with type III SMA are able to stand and walk without help. They usually lose their ability to stand and walk later in life. There are two other types of spinal muscular atrophy, type IV and Finkel type that occur in adulthood, usually after age 30. Symptoms of adult-onset SMA are usually mild to moderate and include muscle weakness, tremor and twitching.

How is spinal muscular atrophy diagnosed?

To make a diagnosis of SMA, symptoms need to be present. When symptoms are present, diagnosis can be made by genetic testing. Gene alterations (mutations) in the SMN1 and VAPB genes cause SMA. Having extra copies of the SMN2 gene can modify the course of SMA.

Genetic testing on a blood or tissue sample is done to identify whether there is at least one copy of the SMN1 gene by looking for its special makeup. Mutations in the SMN1 gene cause types 0, I, II, III, and IV. Some people who have SMA type II, III, or IV have three or more copies of the SMN2 gene. Having these extra copies can modify the course of SMA. The more copies of SMN2 gene a person has, the less severe his or her symptoms.

Genetic testing for a mutation in the VAPB gene is done to diagnose the Finkel type SMA.

In some situations other tests such as an EMG electromyography (EMG) or muscle biopsy may be needed because it is not possible to conduct the SMN gene tests or no abnormality is identified.

What is the treatment for spinal muscular atrophy?

There is currently no specific cure for SMA. Infants who have a severe form of SMA frequently die of respiratory failure due to weakness of the muscles that help with breathing. Children who have milder forms of SMA will live much longer but they may need extensive medical support.

The current treatment for SMA involves prevention and management of the secondary effect of muscle weakness and loss.

Today, much can be done for SMA patients in terms of medical and in particular respiratory, nutritional and rehabilitation care. In addition, several drugs have been identified in laboratory experiments that may help patients. Some of the drugs that are currently being investigated include: Butyrates, valproic acid, hydroxyurea, and riluzole.

At present gene therapy - replacing the altered genes with a normal version ? is being tested in animals. Researchers believe that gene replacement for SMA will take many more years of research before it can be used in humans.

Is spinal muscular atrophy inherited?

SMA types 0, I, II, III, and IV are inherited in an autosomal recessive pattern in families. In autosomal recessive inheritance, a person who has SMA has inherited two altered (mutated) copies of the SMN1 gene from his or her parents. The parents of an individual with an autosomal recessive inherited disorder such as SMA are carriers of one copy of the altered gene. Since they carry a normal version of the gene they do not have signs or symptoms of the disorder.

Finkel type SMA is inherited in an autosomal dominant pattern. This means that the person has one copy of the altered gene in each cell that causes the disorder.

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Severe Combined Immunodeficiency (SCID)

What is Severe Combined Immunodeficiency (SCID)?

Severe Combined Immunodeficiency (SCID) may be best known from news stories and a movie in the 1980s about David, the Boy in the Bubble, who was born without a working immune system. Caused by defects in any of several possible genes, SCID makes those affected highly susceptible to life-threatening infections by viruses, bacteria and fungi. Because David's brother had died of the disease, doctors immediately placed him into a plastic isolation unit to protect him from infections. He lived in such isolators for nearly 13 years. David died in 1984 following an unsuccessful bone marrow transplant, an attempt to provide him with the capacity to fight infections on his own and thus free him from the bubble.

Although a rare disease, SCID has been extensively studied over the past several decades because of the insights it provides into the workings of the normal human immune system. In addition, one form of SCID became the first human illness treated by human gene therapy in 1990, a process in which a normal gene was transferred into the defective white blood cells of two young girls to compensate for the genetic mutation. These pioneering patients are still alive and continue to participate in on-going studies by physicians at the National Human Genome Research Institute.

What do we know about the immune system and SCID?

Lymphocytes, a type of white blood cell, are made from blood forming precursors, or "stem," cells in the bone marrow. Some lymphocyte precursors move to the thymus gland, where they become T cells. Others remain in the bone marrow where they mature into B cells and natural killer cells. Each specialized type of cell is responsible for a particular immune response.

Normally, T cells encourage other immune cells to respond to foreign substances as well as directly combat certain viral and fungal infections. B cells become antibody-producing cells. The antibodies attack foreign substances, or antigens, that mark invading viruses, bacteria and fungi.

Severe combined immunodeficiency, or SCID, is a term applied to a group of inherited disorders characterized by defects in both T and B cell responses, hence the term "combined." The most common type of SCID is called XSCID because the mutated gene, which normally produces a receptor for activation signals on immune cells, is located on the X chromosome. Another form of SCID is caused by a deficiency of the enzyme adenosine deaminase (ADA), normally produced by a gene on chromosome 20.

The classic symptoms of SCID include an increased susceptibility to a variety of infections, including ear infections (acute otitis media), pneumonia or bronchitis, oral thrush (a type of yeast that multiplies rapidly, creating white, sore areas in the mouth), and diarrhea. Because children with SCID experience multiple infections, they fail to grow and gain weight as expected (i.e., failure to thrive). Children with untreated SCID rarely live past the age of two.

How common is SCID?

There is no central record of how many babies are diagnosed with SCID in the United States each year, but the best estimate is somewhere around 40-100. So, SCID is a rare condition. On the other hand, researchers have no clear idea of how many babies are not diagnosed and die of SCID-related infections each year. The actual number of cases could be higher.

If a baby exhibits any of the following persistent symptoms within the first year of life, he or she should be evaluated for SCID or other types of immune deficiency syndromes:

- Eight or more ear infections
- Two or more cases of pneumonia
- Infections that do not resolve with antibiotic treatment for two or more months
- Failure to gain weight or grow normally
- Infections that require intravenous antibiotic treatment
- Deep-seated infections, such as pneumonia that affects an entire lung or an abscess in the liver
- Persistent thrush in the mouth or throat
- A family history of immune deficiency or infant deaths due to infections

What is XSCID?

X-linked severe combined immunodeficiency (XSCID) is caused by mutations in a gene on the X chromosome called IL2RG. This gene creates a key part of a receptor on the surface of a lymphocyte which, when activated by chemical messengers called cytokines, transmits information that directs lymphocytes to mature, proliferate and mobilize to fight infection. The

defective part of the lymphocyte receptor is called the "common" gamma chain (γ_c), because it is a common component of lymphocyte receptors for several types of cytokines, including the interleukin-2 (IL-2) receptor. Thus, it is a critical component for mobilizing the body's defenses against infection.

Because females have two X chromosomes, if they have a mutation that disrupts the IL2RG gene on one X chromosome, they still have a spare normal gene on the other X chromosome that can compensate for the mutation. Thus, they have normal immune systems. However, since males have only one X chromosome and one Y chromosome, they do not have a spare IL2RG gene. A male with a defect in his only IL2RG gene produces immune cells that are missing the γ_c part of their receptors. Because the receptors cannot respond to stimulation, immune dysfunction and SCID sets in. XSCID affects only males and is the most common type of SCID. Therefore, the overall incidence of SCID is higher in males than in females.

What is ADA deficiency SCID?

Adenosine deaminase deficiency SCID, commonly called ADA SCID, is a very rare genetic disorder. It is caused by a mutation in the gene that encodes a protein called adenosine deaminase (ADA). This ADA protein is an essential enzyme needed by all body cells to produce new DNA. This enzyme also breaks down toxic metabolites that otherwise accumulate to harmful levels that kill lymphocytes. People afflicted with this disease often have to take antibiotics and supplemental infusions of antibodies to protect themselves from serious infections. They can also receive adenosine deaminase injections given once or twice a week. ADA SCID is lethal without treatment.

How is SCID diagnosed?

Early diagnosis of SCID is rare because doctors do not routinely count each type of white blood cell in newborns. As a result, the average age at which babies are diagnosed with SCID is just over six months, usually because of recurrent infections (see below) and failure to thrive. Blood tests for SCID typically reveal significantly lower-than-normal levels of T cells and a lack of germ-fighting antibodies. Even if B cells are present in the blood of SCID patients, they do a poor job of producing antibodies. Low antibody levels and lack of specific antibodies after vaccination or a natural infection are characteristic features of SCID.

Can SCID be detected before birth (prenatally)?

If the mutation leading to SCID in a family is known, an at-risk pregnancy can be tested by sequencing DNA from the fetus. However, SCID is so rare that prenatal testing of a baby with no family history is probably not justified because the test is so expensive.

Is SCID diagnosis in the newborn period possible and beneficial?

Newborns with SCID generally appear healthy because they are protected for a few weeks by antibodies produced by the mother and then transferred into the baby's blood. In addition, newborns have not been exposed to infections. Diagnosis and treatment before the onset of infections and the complications they cause in immune-compromised babies reduces costly hospitalizations and leads to better outcomes. Testing immediately after birth can be done, either

by sequencing DNA if the family mutation is known or by counting the numbers of T and B cells and assessing their function. However, the current tests to confirm SCID must be applied to individual blood samples and take hours to prepare.

The high cost of current testing has prohibited newborn screening on a population-wide basis. To make screening for all newborns affordable, an automated screening method that could process hundreds of samples every day with minimal hands-on requirements would need to be developed. In addition, the results would have to be made quickly available to doctors for patient follow-up.

Is there effective treatment for SCID?

The most effective treatment for SCID is transplantation of blood-forming stem cells from the bone marrow of a healthy person. Bone marrow stem cells can live for a long time by renewing themselves as needed and also can produce a continuous supply of healthy immune cells. A bone marrow transplant from a tissue-matched sister or brother offers the greatest chance for curing SCID. However, most patients do not have a matched sibling donor, so transplants from a parent or unrelated matched donor are often performed. These latter types of transplant succeed less often than do transplants from a matched, related donor. All transplants done in the first three months of life have the highest success rate.

NHGRI Clinical Research on SCID

In 1990, National Institutes of Health (NIH) researchers performed the first successful human gene therapy on two girls with ADA SCID. The treatments consisted of removing some of the girls' own T cells, inserting a normal copy of the ADA gene into the cells, expanding the T cells in a culture system and returning them to the girls' bodies through a vein. Repeated treatments led to normalization of T cell numbers. Although the girls have continued to rely on ADA enzyme injections for their primary management, they have developed normal immunity.

Following this pioneering work, scientists at NHGRI and around the world have continued to conduct clinical research with ADA SCID and additional genetic forms of SCID. This work has led to breakthroughs for improving the efficiency of gene transfer as well as insights into the biology of XSCID and ADA SCID. NHGRI researchers are continuing to develop more effective gene therapy treatments, first in experimental animal models and then in very small numbers of humans. One particular discovery made by NHGRI investigators is the observation that in individuals in whom some cells naturally expressed normal levels of γ c or ADA, the expressing cells tend to grow better than the defective cells. This discovery showed that gene transfers could be accomplished with relatively few stem cells that would then outgrow the defective cells and give rise to a full complement of corrected T and B cells, restoring the immune system.

Gene therapy trials for SCID were halted worldwide for a number of years when it was reported that children who had been treated for XSCID in a French gene-therapy experiment had developed a type of leukemia. It was soon discovered that the mechanism used to insert the corrective gene had placed it in a region of a receiving cell's chromosome that switched on a cancer-causing gene (oncogene). Today, NHGRI researchers are evaluating insertion profiles of standard and novel gene delivery methods. A goal of this work is to find ways to achieve permanent correction of the DNA in blood-forming stem cells while avoiding the activation of oncogenes.

NHGRI investigators are also studying approaches to improve the effectiveness of bone marrow transplantation for these conditions. A major limitation to bone marrow transplantation is that blood-forming stem cells are not well understood. They are few in number and cannot be purified or expanded outside the body for very long. NHGRI researchers are investigating the roles of genes that control the reproduction and differentiation of blood-forming stem cells in order to significantly increase the supplies of these life-saving cells for clinical u

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