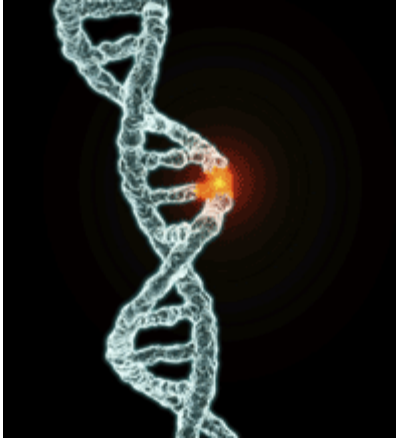


Genetics in Special Education Series

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Tuberous Sclerosis

What is Tuberous Sclerosis?

Tuberous sclerosis--also called tuberous sclerosis complex (TSC)¹--is a rare, multi-system genetic disease that causes benign tumors to grow in the brain and on other vital organs such as the kidneys, heart, eyes, lungs, and skin. It commonly affects the central nervous system and results in a combination of symptoms including seizures, developmental delay, behavioral problems, skin abnormalities, and kidney disease.

The disorder affects as many as 25,000 to 40,000 individuals in the United States and about 1 to 2 million individuals worldwide, with an estimated prevalence of one in 6,000 newborns. TSC occurs in all races and ethnic groups, and in both genders.

The name tuberous sclerosis comes from the characteristic tuber or potato-like nodules in the brain, which calcify with age and become hard or sclerotic. The disorder--once known as epiloia or Bourneville's disease--was first identified by a French physician more than 100 years ago.

Many TSC patients show evidence of the disorder in the first year of life. However, clinical features can be subtle initially, and many signs and symptoms take years to develop. As a result, TSC can be unrecognized or misdiagnosed for years.

What causes Tuberous Sclerosis?

TSC is caused by defects, or mutations, on two genes-TSC1 and TSC2. Only one of the genes needs to be affected for TSC to be present. The TSC1 gene, discovered in 1997, is on chromosome 9 and produces a protein called hamartin. The TSC2 gene, discovered in 1993, is on chromosome 16 and produces the protein tuberin. Scientists believe these proteins act in a complex as growth suppressors by inhibiting the activation of a master, evolutionarily conserved kinase called mTOR. Loss of regulation of mTOR occurs in cells lacking either hamartin or tuberin, and this leads to abnormal differentiation and development, and to the generation of enlarged cells, as are seen in TSC brain lesions.

Is TSC inherited?

Although some individuals inherit the disorder from a parent with TSC, most cases occur as sporadic cases due to new, spontaneous mutations in TSC1 or TSC2. In this situation, neither parent has the disorder or the faulty gene(s). Instead, a faulty gene first occurs in the affected individual.

In familial cases, TSC is an autosomal dominant disorder, which means that the disorder can be transmitted directly from parent to child. In those cases, only one parent needs to have the faulty gene in order to pass it on to a child. If a parent has TSC, each offspring has a 50 percent chance of developing the disorder. Children who inherit TSC may not have the same symptoms as their parent and they may have either a milder or a more severe form of the disorder.

Rarely, individuals acquire TSC through a process called gonadal mosaicism. These patients have parents with no apparent defects in the two genes that cause the disorder. Yet these parents can have a child with TSC because a portion of one of the parent's reproductive cells (sperm or eggs) can contain the genetic mutation without the other cells of the body being involved. In cases of gonadal mosaicism, genetic testing of a blood sample might not reveal the potential for passing the disease to offspring.

What are the signs and symptoms of TSC?

TSC can affect many different systems of the body, causing a variety of signs and symptoms. Signs of the disorder vary depending on which system and which organs are involved. The natural course of TSC varies from individual to individual, with symptoms ranging from very mild to quite severe. In addition to the benign tumors that frequently occur in TSC, other common symptoms include seizures, mental retardation, behavior problems, and skin abnormalities. Tumors can grow in nearly any organ, but they most commonly occur in the brain, kidneys, heart, lungs, and skin. Malignant tumors are rare in TSC. Those that do occur primarily affect the kidneys.

Kidney problems such as cysts and angiomyolipomas occur in an estimated 70 to 80 percent of individuals with TSC, usually occurring between ages 15 and 30. Cysts are usually small, appear

in limited numbers, and cause no serious problems. Approximately 2 percent of individuals with TSC develop large numbers of cysts in a pattern similar to polycystic kidney disease² during childhood. In these cases, kidney function is compromised and kidney failure occurs. In rare instances, the cysts may bleed, leading to blood loss and anemia.

Angiomyolipomas-benign growths consisting of fatty tissue and muscle cells-are the most common kidney lesions in TSC. These growths are seen in the majority of TSC patients, but are also found in about one of every 300 people without TSC. Angiomyolipomas caused by TSC are usually found in both kidneys and in most cases they produce no symptoms. However, they can sometimes grow so large that they cause pain or kidney failure. Bleeding from angiomyolipomas may also occur, causing both pain and weakness. If severe bleeding does not stop naturally, there may be severe blood loss, resulting in profound anemia and a life-threatening drop in blood pressure, warranting urgent medical attention.

Other rare kidney problems include renal cell carcinoma, developing from an angiomyolipoma, and oncocytomas, benign tumors unique to individuals with TSC.

Three types of brain tumors are associated with TSC: cortical tubers, for which the disease is named, generally form on the surface of the brain, but may also appear in the deep areas of the brain; subependymal nodules, which form in the walls of the ventricles-the fluid-filled cavities of the brain; and giant-cell tumors (astrocytomas), a type of tumor that can grow and block the flow of fluids within the brain, causing a buildup of fluid and pressure and leading to headaches and blurred vision.

Tumors called cardiac rhabdomyomas are often found in the hearts of infants and young children with TSC. If the tumors are large or there are multiple tumors, they can block circulation and cause death. However, if they do not cause problems at birth-when in most cases they are at their largest size-they usually become smaller with time and do not affect the individual in later life. Benign tumors called phakomas are sometimes found in the eyes of individuals with TSC, appearing as white patches on the retina. Generally they do not cause vision loss or other vision problems, but they can be used to help diagnose the disease.

Additional tumors and cysts may be found in other areas of the body, including the liver, lung, and pancreas. Bone cysts, rectal polyps, gum fibromas, and dental pits may also occur.

A wide variety of skin abnormalities may occur in individuals with TSC. Most cause no problems but are helpful in diagnosis. Some cases may cause disfigurement, necessitating treatment. The most common skin abnormalities include:

- Hypomelanotic macules ("ash leaf spots"), which are white or lighter patches of skin that may appear anywhere on the body and are caused by a lack of skin pigment or melanin-the substance that gives skin its color.
- Reddish spots or bumps called facial angiofibromas (also called adenoma sebaceum), which appear on the face (sometimes resembling acne) and consist of blood vessels and fibrous tissue.
- Raised, discolored areas on the forehead called forehead plaques, which are common and unique to TSC and may help doctors diagnose the disorder.
- Areas of thick leathery, pebbly skin called shagreen patches, usually found on the lower back or nape of the neck.

- Small fleshy tumors called ungual or subungual fibromas that grow around and under the toenails or fingernails and may need to be surgically removed if they enlarge or cause bleeding. These usually appear later in life, ages 20 - 50.
- Other skin features that are not unique to individuals with TSC, including molluscum fibrosum or skin tags, which typically occur across the back of the neck and shoulders, café au lait spots or flat brown marks, and poliosis, a tuft or patch of white hair that may appear on the scalp or eyelids.

TSC can cause seizures and varying degrees of mental disability. Seizures of all types may occur, including infantile spasms; tonic-clonic seizures (also known as grand mal seizures); or tonic, akinetic, atypical absence, myoclonic, complex partial, or generalized seizures.

Approximately one-half to two-thirds of individuals with TSC have mental disabilities ranging from mild learning disabilities to severe mental retardation. Behavior problems, including aggression, sudden rage, attention deficit hyperactivity disorder, acting out, obsessive-compulsive disorder, and repetitive, destructive, or self-harming behavior, often occur in children with TSC, and can be difficult to manage. Some individuals with TSC may also have a developmental disorder called autism.

How is TSC diagnosed?

In most cases the first clue to recognizing TSC is the presence of seizures or delayed development. In other cases, the first sign may be white patches on the skin (hypomelanotic macules).

Diagnosis of the disorder is based on a careful clinical exam in combination with computed tomography (CT) or magnetic resonance imaging (MRI) of the brain, which may show tubers in the brain, and an ultrasound of the heart, liver, and kidneys, which may show tumors in those organs. Doctors should carefully examine the skin for the wide variety of skin features, the fingernails and toenails for ungual fibromas, the teeth and gums for dental pits and/or gum fibromas, and the eyes for dilated pupils. A Wood's lamp or ultraviolet light may be used to locate the hypomelanotic macules which are sometimes hard to see on infants and individuals with pale or fair skin. Because of the wide variety of signs of TSC, it is best if a doctor experienced in the diagnosis of TSC evaluates a potential patient.

In infants TSC may be suspected if the child has cardiac rhabdomyomas or seizures (infantile spasms) at birth. With a careful examination of the skin and brain, it may be possible to diagnose TSC in a very young infant. However, many children are not diagnosed until later in life when their seizures begin and other symptoms such as facial angiofibromas appear.

How is TSC treated?

In October 2010 the U.S. Food and Drug Administration approved the use of everolimus to treat benign tumors called subependymal giant cell astrocytomas in individuals with TSC who require treatment but are not candidates for surgery. There is no cure for TSC, although treatment is available for a number of the symptoms. Antiepileptic drugs may be used to control seizures, and medications may be prescribed for behavior problems. Intervention programs including special schooling and occupational therapy may benefit individuals with special needs and developmental issues. Surgery including dermabrasion and laser treatment may be useful for

treatment of skin lesions. Because TSC is a lifelong condition, individuals need to be regularly monitored by a doctor to make sure they are receiving the best possible treatments. Due to the many varied symptoms of TSC, care by a clinician experienced with the disorder is recommended.

Recently much enthusiasm has arisen in regard to the use of rapamycin for treatment of TSC. Rapamycin is a drug that specifically blocks the activity of mTOR. In cell culture experiments and animal models of TSC, rapamycin appears to be very effective. Initial clinical experience with rapamycin and related drugs is also positive, but much additional study is required before these drugs become standard therapy.

What is the prognosis?

The prognosis for individuals with TSC depends on the severity of symptoms, which range from mild skin abnormalities to varying degrees of learning disabilities and epilepsy to severe mental retardation, uncontrollable seizures, and kidney failure. Those individuals with mild symptoms generally do well and live long productive lives, while individuals with the more severe form may have serious disabilities.

In rare cases, seizures, infections, or tumors in vital organs may cause complications in some organs such as the kidneys and brain that can lead to severe difficulties and even death. However, with appropriate medical care, most individuals with the disorder can look forward to normal life expectancy.

What research is being done?

Within the Federal Government, the leading supporter of research on TSC is the National Institute of Neurological Disorders and Stroke (NINDS). The NINDS, part of the National Institutes of Health (NIH), is responsible for supporting and conducting research on the brain and the central nervous system. NINDS conducts research in its laboratories at NIH and also supports studies through grants to major medical institutions across the country. The National Heart, Lung, and Blood Institute and the National Cancer Institute, also components of the NIH, support and conduct research on TSC.

Scientists who study TSC seek to increase our understanding of the disorder by learning more about the TSC1 and TSC2 genes that can cause the disorder and the function of the proteins-tuberin and hamartin-produced by these genes. Scientists hope knowledge gained from their current research will improve the genetic test for TSC and lead to new avenues of treatment, methods of prevention, and, ultimately, a cure for this disorder.

Research studies run the gamut from very basic scientific investigation to clinical translational research. For example, some investigators are trying to identify all the protein components that are in the same 'signaling pathway' in which the TSC1 and TSC2 protein products and the mTOR protein are involved. Other studies are focused on understanding in detail how the disease develops, both in animal models and in patients, to better define new ways of controlling or preventing the development of the disease. Finally, clinical trials of rapamycin are underway (with NINDS and NCI support) to rigorously test the potential benefit of this compound for some of the tumors that are problematic in TSC patients.

Marfan Syndrome

What is Marfan syndrome?

Marfan syndrome is one of the most common inherited disorders of connective tissue. It is an autosomal dominant condition occurring once in every 10,000 to 20,000 individuals. There is a wide variability in clinical symptoms in Marfan syndrome with the most notable occurring in eye, skeleton, connective tissue and cardiovascular systems.

Marfan syndrome is caused by mutations in the FBN1 gene. FBN1 mutations are associated with a broad continuum of physical features ranging from isolated features of Marfan syndrome to a severe and rapidly progressive form in newborns.

What are the symptoms of Marfan syndrome?

The most common symptom of Marfan syndrome is myopia (nearsightedness from the increased curve of the retina due to connective tissue changes in the globe of the eye). About 60 percent of individuals who have Marfan syndrome have lens displacement from the center of the pupil (ectopia lentis). Individuals who have Marfan syndrome also have an increased risk for retinal detachment, glaucoma and early cataract formation.

Other common symptoms of Marfan syndrome involve the skeleton and connective tissue systems. These include bone overgrowth and loose joints (joint laxity). Individuals who have Marfan syndrome have long thin arms and legs (dolichostenomelia). Overgrowth of the ribs can cause the chest bone (sternum) to bend inward (pectus excavatum or funnel chest) or push outward (pectus carinatum or pigeon breast). Curvature of the spine (scoliosis) is another common skeletal symptom that can be mild or severe and progressively worsen with age. Scoliosis shortens the trunk also contributes to the arms and legs appearing too long.

Cardiovascular malformations are the most life threatening symptom of Marfan syndrome. They include dilated aorta just as it leaves the heart (at the level of the sinuses of Valsalva), mitral valve prolapse, tricuspid valve prolapse, enlargement of the proximal pulmonary artery, and a high risk for aortic tear and rupture (aortic dissection).

How is Marfan syndrome diagnosed?

The diagnosis of Marfan syndrome is a clinical diagnosis that is based on family history and the presence of characteristic clinical findings in ocular, skeletal and cardiovascular systems. There are four major clinical diagnostic features:

1. Dilatation or dissection of the aorta at the level of the sinuses of Valsava.
2. Ectopia lentis (dislocated lens of the eye).
3. Lumbosacral dural ectasia determined by CT scan or magnetic resonance imaging (MRI).
4. Four of the eight typical skeletal features.

Major criteria for establishing the diagnosis in a family member also include having a parent, child, or sibling who meets major criteria independently, the presence of an FBN-1 mutation

known to cause the syndrome, or a haplotype around FBN-1 inherited by descent and identified in a familial Marfan patient(also known as genetic linkage to the gene).

The FBN1 gene is the gene associated with the true Marfan syndrome. Genetic testing of the FBN1 gene identifies 70 - 93 percent of the mutations and is available in clinical laboratories. However patients negative for the test for gene mutation should be considered for evaluation for other conditions that have similar features of Marfan syndrome such as Dietz syndrome, Ehlers Danlos syndrome, and homocystinuria. To unequivocally establish the diagnosis in the absence of a family history requires a major manifestation from two systems and involvement of a third system. If a mutation known to cause Marfan syndrome is identified, the diagnosis requires one major criterion and involvement of a second organ system.

To establish the diagnosis in a relative of a patient known to have Marfan Syndrome (index case) requires the presence of a major criterion in the family history and one major criterion in an organ system with involvement of a second organ system.

What is the treatment for Marfan syndrome?

Individuals who have Marfan syndrome are treated by a multidisciplinary medical team that includes a geneticist, cardiologist, ophthalmologist, orthopedist and cardiothoracic surgeon.

Eye problems are generally treated with eyeglasses. When lens dislocation interferes with vision or causes glaucoma, surgery can be performed and an artificial lens implanted.

Skeletal problems such as scoliosis and pectus excavatum may require surgery. For those individuals who have pes planus (flat feet) arch supports and orthotics can be used to decrease leg fatigue and muscle cramps.

Medication, such as beta blockers, is used to decrease the stress on the aorta at the time of diagnosis or when there is progressive aortic dilatation. Surgery to repair the aorta is done when the aortic diameter is greater than 5 mm in adults and older children, when the aortic diameter increases by 1.0 mm per year, or when there is progressive aortic regurgitation.

Cardiovascular surveillance includes yearly echocardiograms to monitor the status of the aorta. Currently the use of beta blocker medications has delayed but not prevented the need to eventually perform aortic surgery.

Recent work on Angiotensin II receptor blockers, another blood pressure medication like beta blockers, has shown additional promise to protect the aorta from dilatation. Clinical trials will be starting soon to see if this drug can prevent the need for surgery better than beta blockers have.

Individuals who have Marfan syndrome are advised to avoid contact and competitive sports and isometric exercise like weight lifting and other static forms of exercise. They can participate in aerobic exercises like swimming. They are also advised to avoid medications such as decongestants and foods that contain caffeine which can lead to chronic increases in blood pressure and stretch the connective tissue in the cardiovascular system.

Is Marfan syndrome inherited?

Marfan syndrome is inherited in families in an autosomal dominant manner. Approximately seventy-five percent of individuals who have Marfan syndrome have a parent who also has the condition (inherited). Approximately 25 percent of individuals who have Marfan syndrome, have the condition as a result of a new (de novo) mutation. When a parent has Marfan syndrome, each of his or her children has a 50% chance (1 chance in 2) to inherit the FBN1 gene. While Marfan syndrome is not always inherited, it is always heritable.

When a child with Marfan syndrome is born to parents who do not show features of the Marfan syndrome, it is likely the child has a new mutation. In this family situation, the chance for future siblings (brothers and sisters of the child with Marfan syndrome) to be born with Marfan syndrome is less than 50 percent. But the risk is still greater than the general population risk of 1 in 10,000. The risk is higher for siblings because there are rare families where a Marfan gene mutation is in some percentage of the germline cells of one of the parents (testes or ovaries).

Prenatal testing for Marfan syndrome is available when the gene mutation is known, and also using a technique called linkage analysis (tracking the gene for Marfan syndrome in a family using genetic markers).

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