Carpe Diem – Seize the Day Blog

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Tuberous Sclerosis Complex (TCS) is a rare genetic disorder that causes benign tumors and lesions to develop in multiple organ systems. TSC is the leading genetic cause of both epilepsy and autistic spectrum disorder. There is no cure for tuberous sclerosis complex yet, but advancements in treatment are giving people living with TSC more options for greater epilepsy control.

What Is Tuberous Sclerosis Complex?
Tuberous Sclerosis Complex is a neurocutaneous syndrome and a rare genetic disorder that affects 1 in 10,000 people across the globe. Neurocutaneous syndromes cause tumors to develop, as well as seizures, brain development problems, and intellectual disabilities. TSC causes noncancerous tumors or lesions, also known as hamartomatous lesions and tubers, on or in almost every organ system and part of the body.

An estimated 1 million people are living with TSC worldwide. The effects of TSC on different parts of the body vary greatly from person to person in severity and in symptoms. TSC usually presents in early infancy. Seizures known as infantile spasms usually present during the first year and can develop into other types of seizures over time.

Tuberous Sclerosis Complex is a lifelong, chronic condition that currently has no cure. However, TSC is manageable. With early diagnosis and intervention, specialized health care, and frequent monitoring, people with TSC often live high quality, productive lives and have a normal life expectancy.

What Causes TSC?
In most cases, TSC is caused by a gene mutation that occurs on the TSC1 or TSC2 genes. The TSC1 gene is thought to control a protein called hamartin that suppresses tumor growth. The TSC2 gene controls a protein called tuberin that moderates cell growth. Scientists believe the TSC genes control the growth and size of cells and tumors. The TSC gene mutation prevents the proteins from functioning properly, which leads to a proliferation of the benign — but potentially dangerous — tuberous growths that characterize TSC.

In about two-thirds of cases, neither parent had the gene mutations or TSC. This is called spontaneous or sporadic mutation. In approximately 30 percent of cases, the TSC mutation is inherited from a parent. TSC is an autosomal dominant disease, meaning only one parent needs to carry the gene mutation or have TSC to pass it on to their offspring. Someone with TSC (or one of the gene mutations) has a 50 percent chance of having a child born with TSC each pregnancy.

In very rare cases, the TSC mutation can be passed on to a child even though neither parent has tuberous sclerosis through a process known as germline or gonadal mosaicism. In instances where neither parent has TSC, the chances of having two children who both have TSC is about 1 percent to 2 percent.

How Is TSC Diagnosed?
Diagnosing tuberous sclerosis entails a thorough medical exam. The doctor will take a detailed medical history, conduct a TSC diagnostic assessment, and examine the skin — likely with a special UV light to help spot skin anomalies.

Diagnostic Criteria
Tuberous sclerosis' diagnostic criteria include 18 symptoms divided into 11 major features and seven minor features. A definite diagnosis of TSC must have two or more major features, or one major feature and two or more minor features of the disorder. A possible TSC diagnosis either has just one major feature or two or more minor features. In most cases, health care providers with experience diagnosing TSC are able to confirm a TSC diagnosis with the criteria alone.

Laboratory Tests
Genetic tests can identify a TSC1 or TSC2 mutation. The presence of a gene mutation confirms a TSC diagnosis. Between 75 percent and 90 percent of people with a confirmed TSC diagnosis who underwent genetic testing showed the gene mutations associated with tuberous sclerosis. The absence of a TSC mutation, however, does not rule out tuberous sclerosis. Around 15 percent of people with confirmed TSC do not show a genetic mutation of either TSC gene.

Imaging
Once a definite TSC diagnosis has been made, the doctor may order some of the following tests. These tests are necessary to set baseline measurements and assess organ function and health.

Computerized tomography (CT) uses rotating X-rays to determine the presence of tumors on the brain, lungs, and kidneys.

Magnetic resonance imaging (MRI) uses strong magnetic fields to detect tubers on the brain's surface and identify subependymal giant cell astrocytomas (SEGAs) before the tumors obstruct normal functioning.

An electroencephalogram (EEG) monitors brain waves for irregular activity through electrodes affixed to the scalp and can help diagnose seizures.

Echocardiography uses sound waves to study the heart's functionality and movement. It can be used to evaluate the heart for the presence of benign tumors known as rhabdomyomas.

Electrocardiograms (EKG or ECG) monitor and record the heart's electrical impulses and may reveal abnormal electrical patterns.

Renal ultrasonography uses sound waves and radio waves to take pictures of a person's internal organs to identify and measure renal cysts.

The United States is home to as many as 50,000 people diagnosed with TSC — and researchers say many more may be living with the condition. They believe TSC is underdiagnosed due to its relative obscurity and common misdiagnosis of the condition.

Tuberous Sclerosis Complex and Epilepsy

Epilepsy is the most common neurological symptom of TSC; around 80 percent of people living with TSC also have epilepsy. People with TSC can experience many different types of seizures including focal onset or partial seizures, tonic-clonic seizures, tonic seizures, atonic seizures, myoclonic seizures, and absence seizures. Over time, people living with TSC may become accustomed to antiepileptic drugs (AEDs), and their seizures may progress to refractory epilepsy.

Refractory seizures are those that do not respond to AEDs. Uncontrolled seizures can lead to status epilepticus, a life-threatening condition. Learn more about other types of epilepsy and other types of seizures.

While epilepsy is usually one of the first signs of TSC, these conditions can be diagnosed at any age and often change as a person grows older. Infantile spasms, also known as West syndrome, usually present in the first year of life and affect nearly 35 percent of babies born with TSC. West syndrome often leads to pediatric epilepsies, such as Lennox-Gastaut syndrome (LGS) and other AED-resistant epilepsies. West syndrome and LGS can cause major cognitive and developmental delays, as well as intellectual deficits. Stalling or regression of the baby's developmental progress may also result. Learn more about LGS symptoms, causes, and treatments.

TSC and the Brain

TSC causes different types of brain abnormalities, whose impact and severity vary depending on their location, size, and growth rate. Cortical tubers are lesions that develop and harden over time, usually on the brain’s surface. Subependymal giant cell astrocytomas (SEGAs) are benign tumors that can become large enough to restrict the flow of cerebrospinal fluid in the brain and spine. As SEGAs grow, they can cause headaches and blurred vision, and lead to fluid buildup around the brain (hydrocephalus).

TSC-associated neuropsychiatric disorders (TAND) are the cognitive, developmental, behavioral, intellectual, and psychosocial complications often associated with tuberous sclerosis. Between 25 percent and 50 percent of people living with TSC have autism spectrum disorder. At least 50 percent of children with TSC have learning disabilities, and 30 percent have severely impaired IQ. Children with TSC may be more likely to have emotional regulation or behavioral problems, which can make managing TSC even more challenging.

Major Organs

Almost half of all people with TSC experience a buildup of benign, fluid-filled cysts in their kidneys. In rare instances, these cysts can lead to kidney disease and kidney failure. Renal tumors called angiomyolipomas occur in up to 80 percent of people with tuberous sclerosis. These tumors usually present in late childhood or adolescence and can cause severe, sometimes life-threatening, complications. Approximately 50 percent of babies with TSC have cardiac

tumors called rhabdomyomas. Rhabdomyomas can grow smaller over time, but occasionally lead to problems like cardiac arrhythmias and congestive heart failure in older adults living with TSC.

How Are Seizures in Tuberous Sclerosis Treated?
TSC is a lifelong condition that requires specialized care from pediatricians, neurologists, dermatologists, and cardiologists with TSC expertise. Tuberous sclerosis symptoms manifest uniquely in each person. Individual TSC treatment plans need to meet those unique, often-changing needs aggressively and promptly.

Antiepileptic Drugs
Antiepileptic drugs are the primary treatment for recurrent seizures. AEDs successfully control epilepsy in about 70 percent of people prescribed them. TSC-related epilepsies are challenging to treat and even harder to treat long-term. Two out of every 5 cases of TSC-related epilepsy are or become intractable (resistant to AEDs). Only two medications are approved by the U.S. Food and Drug Administration (FDA) specifically to treat infantile spasms: Sabil (vigabatrin) and Corticotropin (adrenocorticotropic hormone). Both of these medications can have serious side effects. Although other medications can be prescribed off-label, there is a clear and growing need for faster drug development and better access to safer, more effective medications. Some promising treatments for TSC are in the pipeline.

Several efforts are focused on repurposing already approved drugs to treat tuberous sclerosis complex. Everolimus is FDA-approved to treat SEGAs, facial angiofibromas, and other tumors. Everolimus also shows off-label promise as an AED. While not yet FDA-approved, Rapamycin has shown efficacy in shrinking SEGAs, the brain tumor most commonly associated with TSC. Further studies exploring Rapamycin's effectiveness on other TSC-associated tumors are underway. In a trial involving more than 200 people with AED-resistant, TSC-related epilepsy, Epidiolex (Cannabidiol or CBD) reduced their seizure frequency by half. Epidiolex is already approved by the FDA to treat other refractory epilepsies like LGS and Dravet syndrome.

Devices and Surgery
Depending on the type and region of a person's seizure activity, epilepsy surgery may bring seizures under control. If the seizure focus can be targeted through precise brain imaging and an EEG, and if it is in a part of the brain that will not affect critical function or quality of life, surgery could reduce or eliminate epilepsy.

Vagus nerve stimulation (VNS) is a type of neuromodulation therapy approved by the FDA as an add-on treatment for refractory epilepsy in children 4 years old and older. VNS involves a small device, similar to a pacemaker, implanted in the chest. A magnet can also be incorporated into VNS, giving the person the ability to deliver extra stimulus between the device's regularly programmed pulses. In small studies among people living with TSC, VNS was shown to be effective in decreasing seizure frequency in some individuals. Responsive neurostimulation (RNS) is a similar type of neuromodulation therapy also used to treat epilepsy.

Dietary Therapy
Dietary therapy can be used in tandem with AEDs to control seizures. A ketogenic diet is a strict food regimen of high-fat and low-carbohydrate foods. It has proven effective in helping control

epilepsy in some individuals. The modified Atkins diet is similar to the ketogenic diet but includes more carbohydrates and greater flexibility.

What Is the Prognosis for Someone Living TSC?
The prognosis for people living with TSC is highly variable and depends on which organs are affected, as well as the severity of symptoms. Symptoms may change, and new symptoms can arise over time. Scientific research offers discoveries, treatment possibilities, and hope for a cure. With early diagnosis, lifelong monitoring of TSC symptoms, and working closely with a skilled treatment team, the prognosis for people living with tuberous sclerosis is excellent. Most people with TSC experience a high quality of life and can expect to live as long as their peers who do not have TSC. Some children diagnosed with TSC may require lifelong care, and parents must learn to advocate for their changing health needs.

Editor's Note: The Carpe Diem – Seize the Day Blog will be distributed and posted weekly.
Always remember – **CARPE DIEM – SEIZE THE DAY!**

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