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TSC Under the Microscope: Treatment & Diagnosis

Announcer:
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Your host is Dr. Charles Turck and will be joined by Dr. Elizabeth Thiele, who is not a representative of the company or any of those mentioned in the program. Here's Dr. Turck now.

Dr. Turck:
Because tuberous sclerosis complex can cause abnormalities in the brain, kidney, heart, and lungs, reaching a timely and accurate diagnosis may often be difficult, so to help us overcome this challenge, today we'll be reviewing what we know about this disease and even get a look ahead at what's on the horizon.

Welcome to *NeuroFrontiers* on ReachMD. I'm Dr. Charles Turck, and joining me in this discussion is neurologist and epileptologist Dr. Elizabeth Thiele. Dr. Thiele is a Professor of Neurology at Harvard Medical School, the Director of the Pediatric Epilepsy Program, and she also established the Carol and James Herscot Center for Tuberous Sclerosis Complex. Dr. Thiele, thanks for being here today.

Dr. Thiele:
Oh, thank you very much for having me.

Dr. Turck:
So, why don't we start at the beginning, Dr. Thiele. How does tuberous sclerosis complex usually present itself?

Dr. Thiele:
Well, that's a really good question cause it can present in different ways. Tuberous sclerosis complex is a very interesting disorder because it can involve almost every organ system. The brain and the skin are the two most frequently involved, and they're involved in about 90 percent of people with TSC. Oftentimes, TSC is diagnosed following the onset of seizures in early childhood. About 85 percent of people with tuberous sclerosis will have epilepsy, 70 percent with onset the first year of life, so it's often onset of seizures in a young infant that will lead to the diagnosis, but sometimes it's diagnosed other ways. The cardiac or heart manifestation of TSC is a cardiac rhabdomyoma, which is a benign tumor of the heart which is most common in late fetal or early infancy, so sometimes in the late gestation ultrasound, the question of possible TSC will be raised by the identification of several cardiac rhabdomyomas. We also have some of our patients that have been diagnosed by the skin findings or even the renal findings, so it can be diagnosed by five different organ system manifestations, but probably epilepsy is the most common symptom that leads to the diagnosis.

Dr. Turck:
And do we know what causes TSC and if there's a genetic component to it?

Dr. Thiele:
Yeah. We know that there's two genes that have been identified – the TSC1 gene on chromosome 9 and the TSC2 gene on chromosome 16, and we've been able to identify a disease-causing mutation in one of those two genes in about 85 percent of people who meet the clinical criteria for the diagnosis of TSC. We didn't know if there was a TSC3 or a TSC4, but in the past few years, I think the thoughts are now that many people in whom we cannot identify a disease-causing mutation in the blood are likely low-level mosaics, meaning they have TSC because of mutation in one of the two genes. Either it happened sometime during their development or does not affect enough cells in the body to identify it from the blood.

Dr. Turck:
And since TSC is a multisystem genetic disease with many different symptoms of varying severity, do you happen to have any best practices to share with respect to diagnosis?

Dr. Thiele:
I think that it really depends on what the presenting symptom is. I think that if a baby comes in with new onset seizures that have a focal onset or some focality to it, then neuroimaging is standard of care these days, and that would often lead to the diagnosis. If a dermatologist is seeing a adolescent for what they believe may be acne, and the dermatologist realize it's instead facial angiofibroma seen in TS, then the dermatologist in the office that day could make the definite diagnosis by looking at the rest of the skin and seeing if there are other skin manifestations. Since epilepsy is so common, I think that we're getting better and better at finding the etiology of epilepsy with gene panels in young children, and that would pick up a TSC1 or TSC2 mutation in some, and overall just an appreciation that this is a disorder that does not just affect the brain, does not just affect the skin, but can affect the heart, the kidneys, the lungs. It's also difficult because these different manifestations can occur at different times during the lifespan, so in babies, young children you look for the skin features, the brain features, and the heart rhabdomyoma. As people age, it's more likely to get renal involvement and pulmonary involvement, so it really depends at what point in time of a person's life that you're considering the diagnosis, how you go about securing the diagnosis. Even though we do have genetic testing available, the diagnosis continues to be made by clinical criteria, and the clinical criteria include major features and minor features, and the major features are things that are seen very commonly in TSC and not so much in the general population, like in the brain, the cortical tubers, which are areas of dysgenesis or subependymal nodules or subependymal giant cell tumors, and the skin, as we said, facial angiofibroma, the hypopigmented macule, shagreen patch, periungal fibroma. All of these things are major criteria, and any two of them would secure a definite diagnosis. Major criteria also involve the other organs, such as kidney, lung, and heart and eye with a hamartoma of the retina which typically do not affect vision, but can be very helpful in determining if a person has TSC or not.

Dr. Turck:
For those just tuning in, you're listening to *NeuroFrontiers* on ReachMD. I'm Dr. Charles Turck, and I'm speaking with Dr. Elizabeth Thiele about tuberous sclerosis complex. Dr. Thiele, we were just speaking about the available diagnostic tools, so now let's shift our focus and talk about treatment options. Would you give us a brief overview of the treatment landscape for TSC?

Dr. Thiele:
So, the treatment is largely treating the symptoms of TSC. So for managing the epilepsy, which, again, affects 85 percent of people with TSC, it really is very similar to managing other focal etiologies of seizures. Most of the anti-seizure medications could be effective. About two-thirds of individuals with TSC will develop refractory epilepsy, so refractory epilepsy is quite common in TSC, and dietary therapy can be effective. Epilepsy surgery can be very effective. With the identification of the TSC1 and TSC2 proteins being part of the mTOR pathway, or the mechanistic target of rapamycin pathway about 20 years ago led to really the identification that mTOR inhibitors, such as rapamycin or everolimus can be effective, and actually they've been FDA-approved for several of the symptoms of tuberous sclerosis complex, including renal angiomyolipoma, subependymal giant cell tumors, and pulmonary lymphangioleiomyomatosis. There's a lot of excitement kind of now with the evolving genetic therapies that hopefully in the future there will also be a genetic treatment of TSC, but we're just not there yet.

Dr. Turck:
You touched on it just a little bit just now, but what are some promising research areas? Are there any potential novel treatments on the horizon?

Dr. Thiele:
There's been a lot of enthusiasm over the past several years about the role of the mTOR inhibitors. Also cannabidiol was FDA-approved for the treatment of seizures associated with TSC, and there was a lot of enthusiasm about that. I think that people are now stepping back and saying, "Gee, we know the role of mTOR inhibitors," and if we start patients on mTOR inhibitors, we view that as long-term therapy. What happens with the mTOR inhibitor is the renal angiomyolipoma will shrink, the subependymal giant cell tumors will shrink, but if the treatment is stopped, there will be regrowth, so many people are thinking, could there be a more definitive treatment? And like I said, the concept of genetic treatments is very exciting, and in some disease spaces, including epilepsies, there are emerging genetic therapies. So, I think that there is a lot of hope and excitement that there will be that possibility in tuberous sclerosis complex as well.

Dr. Turck:
And finally, Dr. Thiele, as we've learned, TSC has far-reaching effects on not only our patients' lives but also on their loved ones, so what are some resources to which our audience might point family members as they embark on their caretaking journey?

Dr. Thiele:

Tuberous sclerosis complex is a very complicated disorder, and as we said, it can affect multiple organ systems and can affect different organ systems at different times during a person's life, so this disorder has significant impact not only on the patient, but on the family, and I've had families describe living with TSC as "walking in a minefield," not knowing when you're gonna step on the next landmine. Another family said, you know, "just waiting for the other shoe to drop," so the uncertainty of what course the disease will have as well as the different symptoms of the disorder, especially the epilepsy, cognitive impairment, autism, the other behavioral aspects, really have significant, significant impact, and I think it's important to acknowledge that when you're taking care of a person with TS, you're also taking care of that person's family, so I think that the TS Alliance, which is a patient advocacy group for people living with TSC in United States, and there's different TS similar organizations kind of worldwide, really, really important not only giving references for resources on education about the disorder, helping identify care providers in the area the patient lives that they would have experience with TSC, also just other types of support and a connection with other people living with the disorder, so I think the patient advocacy groups for TSC as well as other rare disorders are very important to people living with these disorders.

Dr. Turck:
That's great information you've shared with our audience and a wonderful way to round out our discussion on tuberous sclerosis complex. Dr. Thiele, it was great having you on the program.

Dr. Thiele:
Oh, thank you very much. Always happy to talk about tuberous sclerosis complex.

Announcer:
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