

Overcoming Treatment Challenges for Tuberous Sclerosis Complex: SEGA and the Future of Seizure Management

Moderator: Good day, everyone, and welcome. On behalf of AXIS Medical Education, I would like to welcome you to our educational event today entitled, *Overcoming Treatment Challenges for Tuberous Sclerosis Complex: SEGA and the Future of Seizure Management*.

AXIS would like to extend special thanks to our advocacy partner, the Tuberous Sclerosis Alliance, for their collaboration on this activity.

The next few very important slides review the disclosure and unlabeled use statements, as well as Dr. Krueger's disclosure statement of financial interests and relationships.

It is now my great honor to turn the controls over and to welcome Dr. Darcy Krueger. Dr. Krueger...

Darcy Krueger, MD: Thank you. And it's my pleasure to be with you today to review and also discuss some of the directions that we're going with regards to treatment and management of two important neurological aspects of tuberous sclerosis complex (TSC), which are SEGA (subependymal giant cell astrocytoma) as well as epilepsy.

We'll do some very quick walk-through to get us up to speed so that everybody understands where we are with how we have developed treatments for SEGA and also where we stand with the treatment of seizures with regards to conventional therapies, nonpharmacological therapies, and the role of mTOR inhibition as a potential treatment. We'll also at the very conclusion explore some of the most recent research as it pertains to the use of cannabidiol (CBD) oil as a potential treatment for epilepsy and TSC.

These are the learning objectives for our time and for the discussion today.

So I want to start with talking about tuberous sclerosis.

This is considered a rare disorder, but of the rare disorders, it's one of the more commonly encountered, particularly within neurology, with an instance of 1 in 6,000 live births. If you do the math out of the overall world population, this roughly equals between 1 and 2 million individuals worldwide who have tuberous sclerosis, whether they know it or not, and in the United States this probably is somewhere around between 40 and 70 thousand individuals when you go from infants all the way through adulthood.

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A decorative banner image showing a cross-section of a brain with a purple butterfly-like structure highlighted in a circular area, set against a blue and white background.

It's a disorder where we consider there's 100% penetrance, meaning that if you carry a pathological mutation in TSC and have the clinical features of TSC, you have the diagnosis, there is no carrier state where the disease is silent. Now some of those features may be fairly mild, and that's what we call variable expressivity, or variable penetrance, which means that although everyone is considered to have the disease, it does not look the same in every individual.

One-third of these cases are inherited from a mother or father affected with TSC, but in the majority of patients, roughly two-thirds of individuals, there is no inheritance that has been previously or able to be verified, meaning that mother and father, neither appear to have or have been excluded from having tuberous sclerosis, and the first case in that family lineage is in the child who has been born and diagnosed with tuberous sclerosis.

It is a disorder that affects every organ system in the body, whether it be the brain, the eyes, the lungs, the kidneys, the skin, and depending on where and when these features are manifest really has a lot to determine what that individual's experience with tuberous sclerosis might be.

Here are various examples of how these might look in different organ systems, and today we're going to focus particularly those aspects that affect the brain, which we'll go into more detail.

We make the diagnosis of tuberous sclerosis through clinical criteria. That means that we're able to examine the patient combined with various types of studies such as MRIs or ultrasounds that we can make a diagnosis based on the number of clinical manifestations that we know TSC can affect the body. This has had a long-standing development. It was first codified in 1998 as a set of diagnostic criteria of both major and minor features.

Oftentimes, I get asked about what's the difference between a major and a minor feature, and without getting overly technical it's real simple to think of major features as those aspects of TSC that can be present in other disorders, but most often if we see them present we should think about TSC as being the most likely cause.

Minor criteria are features that we see often in TSC, but they also appear with some regularity in many other disorders, as well, so, therefore, we can't automatically assume that they're caused by TSC even though in a patient with TSC they certainly are as the result of tuberous sclerosis.

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These were updated in 2012 when we convened an international consensus conference that involved international researchers and clinicians who have interest in caring and managing patients with tuberous sclerosis from across the world. And we made some modifications to the previous criteria in hopes of increasing the ability to confirm a diagnosis of tuberous sclerosis with less uncertainty and less ambiguity.

So to do that, you'll see that there were some additions or some clarifications regarding some of the skin manifestations. We took some related minor criteria and we pushed those into 1 single major criteria category, and then we also took some minor criteria that were really different manifestations in different organ systems and classified them together under a single heading as aspects of TSC that are not involved in the kidneys or have not already been named as manifestations in the major criterion category.

We also removed the diagnosis category of probable TSC and are able to move forward with either saying you definitely have tuberous sclerosis or that we're unable to diagnose it, but it still is under consideration, meaning it's a possible diagnosis of TSC, and this is determined by the combination of a number of major or minor disease manifestations that we can detect and confirm clinically.

The other addition from the 2012 consensus conference was that we now have the ability to diagnose tuberous sclerosis exclusively through genetic testing. And if we have a positive genetic test even if we cannot find other clinical manifestations, we still say that person has TSC, and this has manifestations for both surveillance as well whether it can be passed on to offspring.

Now, genetic testing often will result in a finding known as variation of unknown significance, and in those cases, genetic testing alone is not sufficient to make the diagnosis. The genetic mutation identified has to be definitely associated with dysfunction and disruption of the genes that are linked to tuberous sclerosis and not just a variation in the sequence of those genes.

We now diagnose tuberous sclerosis most commonly in children, and this is a study done by the TSC Research Group in the United Kingdom lead by Patrick Bolton that looked at the age at which patients first came to the clinic with symptoms that later were confirmed as due to tuberous sclerosis.

We even see that there's a significant amount of patients who we can diagnose prenatally through routine ultrasounds that are done on expectant mothers, that some of the TSC lesions

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and tumors particularly in the heart can be picked up during those routine testing. Other manifestations particularly in the first year of life are in the kidneys, or more prominently skin and neurological aspects of TSC.

However, as you'll see to the far right, there are people who are very mildly affected by tuberous sclerosis even though they've had it since birth—they don't develop clinical symptoms that reach the attention of the medical profession or specialists until later in life, and I've seen this happen mainly through 3 mechanisms. One is a diagnosis of facial lesions thought to be related to early-onset pubertal acne that turned out to be facial angiofibromas; I've seen this happen in later years when patients have new-onset kidney manifestations that can present in that timeframe, and then I've also seen it diagnosed in adults when they have a child with tuberous sclerosis and upon further examination we're able to identify mild features of tuberous sclerosis even in the parents or a genetic confirmation that the parents have it, as well.

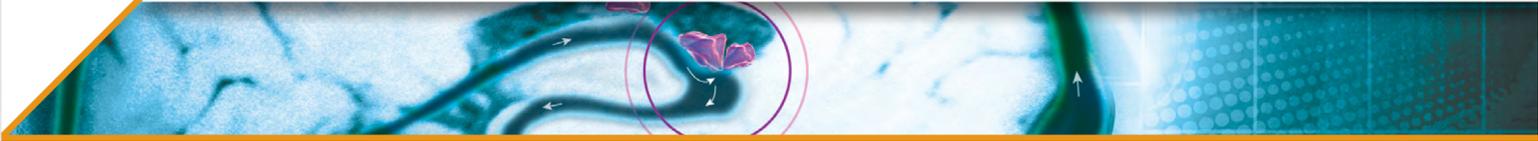
One of the things that makes TSC management sometimes challenging is the fact that not all aspects of tuberous sclerosis are present at each time point in a patient's lifetime. We'll see that cardiac manifestations can be present very early on in life, and although sometimes these can have ongoing ramifications with regard to things such as arrhythmias and influence drug treatment decisions, those often go away as a minor concern or a non-concern later in life.

Neurological manifestations may appear anytime during childhood particularly, and then as we know, TSC-associated neuropsychiatric disorders (TAN) is a lifelong manifestation of TSC that can have many different flavors throughout the course of a patient's lifetime.

Skin manifestations—some are present in the newborn nursery, others may show up during adolescence, and then finally others may be more of a problem during adulthood. Renal manifestations, depending on whether it's a cystic component or an angiomyolipoma component, likewise can have different timeframes of when they appear or when they cause potential medical complications.

And then, lastly, pulmonary manifestations are unique to women with TSC almost exclusively. There are some exceptions of men with TSC having lymphangioleiomyomatosis, but the vast majority are related to adult women who start to have regular hormonal cycles, as it seems to be that this is related closely to estrogen cycles, and, therefore, exclusively dominantly limited to adult women.

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As I mentioned, what we want to talk about today is specifically the neurological manifestations of TSC. We can see these on MRIs. Often, we see these if we get an MRI in the first week or first month of life in a patient who is suspected to have TSC, we can see cortical tubers—what you see here on the left—as these little white areas that are scattered throughout the brain. They often don't have very distinct borders particularly when the child is less than a year or two of age, and so they may not be always appreciated in that first scan if it's done very early in lifetime. However, later on when we do repeat the scans, we can see more of the tubers, and I have to remind parents that the child is not developing new tubers or getting worse tubers, these were always present, it's just that the MRIs get better at seeing them as the child gets older.

The other major manifestation we see are subependymal nodules which a subset, about 10% to 15% during childhood, can start to grow, and then that distinction of growth makes them become a SEGA.

Histologically, these appear highly identical to each other, have a lot of the same characteristics, and we're still working out the science on why a nodule will suddenly start growing because it doesn't happen to all nodules.

The nodules, if you're familiar with how the brain develops before a child is born, the brain develops from the center and adds layers on to the external aspects of the brain until you get the fully mature brain as it is when the child is born. These nodules represent cells that started to grow but they never actually achieved the ability to migrate and perform the functions that they were designed to do, and so they stay as these little nests of cells that failed to grow and failed to migrate within the brain before the child was born. And these, likewise, if they don't grow are something that are present from birth and are not thought to accumulate more as time goes on, even though our ability to see them may become improved as the child gets older.

Now what do these tubers and different lesions of TSC do? Well, the most dominant thing that they cause is epilepsy, which affects more than 85% to 90% of individuals with TSC. The vast majority who are going to have seizures, about two-thirds, will have it before their first birthday. Now we'll talk in a minute about how management of this is a challenge, but there are other aspects that also reflect on the brain being affected by tuberous sclerosis, which include autism spectrum disorder, intellectual disabilities, and attention deficit-hyperactivity disorder.

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Now we can have a lecture about those last three that would take an hour in and of itself, and so today we're going to focus on specifically the subependymal nodules and how they become SEGAs and how we manage those, and then we'll also focus on epilepsy.

However, before we do, we do need to review briefly on how the molecular aspects of TSC have guided a lot of our treatment decisions now available today.

There are 2 genes, *TSC1* and *TSC2*, that are responsible for tuberous sclerosis on 2 different chromosomes. The first encodes for a protein called hamartin and the second encodes a protein called tuberin, and these work together to control a very important molecular pathway within the body.

Now this is called the mechanistic target of rapamycin, or mTOR, and it's not just unique to TSC but there are a lot of different disorders as well as metabolic pathways that are dependent on mTOR to function. But the important aspect as it relates to TSC is that *TSC1* and *TSC2* act as kind of a brake system to prevent mTOR from behaving on its own, that it has to listen to what else is going on in the cell with regard to nutrients and growth factors and how much energy is available so that the cell can grow and divide and do what it's designed to do, but if these factors are not present, then *TSC1* and *TSC2* function to tell mTOR to stop.

Now what we find in TSC, and you see here on the left panel, is the normal state; *TSC1*, *TSC2* through a protein called RHEB, regulate mTOR so mTOR has to listen to these other signals that are going on around the body. In TSC where you don't have hamartin or tuberin functioning, then mTOR is allowed to just be active regardless of any other external signals, and this is what leads to all the different clinical manifestations as well as the tumor growth, which we call hamartomas that occur in kidneys and skin, and then also in the brain as tubers and subependymal nodules and SEGA.

Now what I'll show on the next slide is that we do have molecular treatments, medicines, that can partially repair or correct for when *TSC1* and *TSC2* aren't able to do the job because of the gene mutation, and these are able to prevent mTOR from doing that growth and that proliferation and those other things that it should not be doing in the absence of these other signals.

These drugs are called mTOR inhibitors, and we use predominantly 2 of these. There are actually a good half dozen of these that have been developed, and some of them are still being developed and used in other disorders beyond TSC. However, the 2 that we use predominantly

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in tuberous sclerosis are sirolimus, which has been around since the 1960s, and everolimus, which has been around since the late-1990s and started in clinical development in TSC in the first decade of the 2000s.

As you can see, they're both very, very similar. They do have slightly different properties with regard to how well they're absorbed, and how well they are moved through the body, and how fast the body breaks them down to get rid of them through metabolism, but by and large when they have access to the mTOR protein they inhibit mTOR fairly identically, such that we use both of them in clinical practice.

We now have FDA approval for sirolimus and everolimus to treat different manifestations of TSC. In the brain and in the United States, we can use everolimus for approved therapy of SEGA, we can use it for treatment of kidney angiomyolipomas, and then by extension it's also used for lymphangioleiomyomatosis, but in this case it's sirolimus rather than everolimus.

In the European Union, we also have everolimus approved for treatment of SEGA as well as renal angiomyolipoma, and we also have everolimus approval for epilepsy.

So for this next section, I want to focus exclusively on SEGA.

SEGAs are slow-growing tumors that occur predominantly near the foramen of Monro, which is the central area of the brain, which is critical to the flow of the spinal fluid that's manufactured and circulated around the brain. What happens is that the subependymal nodules that are located in this region for reasons, again, that we don't understand, suddenly start to grow, and if they grow to the point where they block the flow of this fluid, we can have significant clinical complications, including death.

Now these are generally slow growing, although there are exceptions where tumors can grow very rapidly in less than 6 to 12 months by 3, 4, or 5 times their original size, but the vast majority grow roughly about half a centimeter in volume per year if they have started to grow.

This is an example of one of our patients who was waiting to enroll in one of the clinical trials, in which case we've scanned him more often than normal or usual so that we could ensure that the patient was not developing complications that would require us to treat surgically before the introduction of mTOR inhibitors.

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It's important to know that in the vast majority, the average age when SEGA arises is around 7 to 10 years of age. They can arise any time before the age of 20, but there are cases more and more that have been reported in literature, and certainly we encountered in our clinic, where the patients are born with SEGA.

And this is an example of one of our patients who was having seizures on the first day of life and without any prior knowledge of tuberous sclerosis, and one of the things that we do as routine management, we get a head ultrasound to see if there's a reason to explain the seizures. In this case, what we see are 2 areas that are located right in the center that shouldn't be there.

A few days later, we were able to get an MRI of this same baby, and what you see here shown in the white areas are 2 large SEGAs that were present from birth in this patient. So these can be present even in newborn babies, which contributes to the reason why we want to get some imaging in these TSC babies from the get-go to make sure that they don't already have a SEGA that's developed before they were born.

This is why we care. These are 2 examples of patients that came to our center who had not been receiving previous MRIs to monitor for potential SEGA who developed clinical symptoms such as ataxia, decreased appetite, vomiting, and visual disturbances, and eventually mental status changes. So when you have obstruction of the cerebrospinal fluid, hydrocephalus develops that you can see here with these large areas that show up as black on these MRIs, which are basically just a backflow of fluid that can't escape the brain, and this can be eventually fatal if not identified and appropriately treated.

The mainstay of treatment for decades has been surgery, removal of the tumor through surgical processes, and there have been a variety of techniques developed. Here is the most recent strategy that would be preferred for removal of a SEGA, which is using endoscopes to go down the midline between the 2 cerebral hemispheres to the tumor itself and to remove that surgically through endoscopic procedures.

This is associated with the least amount of morbidity and least risk for long-term neurological deficits, but it also is limited in the size of the SEGA tumors as well as the location of the SEGA tumors that can make complete removal much more difficult.

The surgical success rate in published literature is roughly 80% to 85%, although I think that this is highly influenced by the surgical center's expertise and the individual neurosurgeon's

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technique and ability to remove the entire tumor. However, complications such as bleeding, infection, neurological injury, stroke, as well as delayed wound healing all have been reported, as well as if the tumor's not completely removed the ability for the remaining tumor tissue to regrow and cause SEGA complications all over again is extremely high if not universal.

As an alternative to surgical management, we started in 2005 to see if we could use the mTOR inhibitors, in this case sirolimus, to shrink the tumors and avoid surgery. And this is a paper done by my colleague, Dr. Franz, that was published in 2006 of the first 5 patients that he treated with sirolimus, and this is 1 example showing how much the tumor was reduced with just 3 months of treatment, and as I mentioned, avoiding surgical resection.

We followed up those 5 patients with the first open-label, prospective clinical trial with 28 patients who had been diagnosed with SEGA, and treated these patients for 6 months, and we evaluated side effects as well as other markers of TSC such as epilepsy and neurocognition in response to treatment with everolimus over that 6-month period.

This shows a case of one of these patients. You can see a large black area that represents a previous surgery to remove SEGA that had removed the tumor, but the tumor had regrown back from residual tissue that was not removed in the surgery. You see in the middle panel what it looked like after 3 months, and then you see in the far panel what it looked like after 6 months of treatment with everolimus.

The graph below this patient's case shows what all 28 patients did with a response to therapy over those 6 months, and the green line is those patients who showed a 30% reduction, which is considered a middle response, or better than a 50% reduction, which is considered a suitable or complete response. In addition, we see that roughly 30% of patients had a 50% reduction, and 75% of patients had a partial reduction.

This is that first patient I showed you early on that was waiting to enter the clinical trial, and this is how he responded after 6 months, and then his most recent follow-up at the close of the study was after treatment for 80 months. We see that he responded nicely at 6 months and that that response was maintained throughout the length of the study as he continued treatment.

This is another patient that enrolled into the study—this was the first patient who enrolled in the trial. You see her response after 6 months and then again after 80 months when she completed the study, and that response, again, was maintained throughout the whole time.

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Any open-label study says that a drug probably works and is probably safe, but really to get convincing proof as well as FDA approvals, you need to do what's called a phase 3 clinical trial. So this was done in follow-up to the 28 patients and is known as EXIST-1 and was sponsored as an international trial. It involved more than 100 patients who were randomized to receive everolimus or a placebo that was administered in blinded fashion.

Here are the results of that trial in a nutshell. What we see in the blue line here is the number of patients who received everolimus and had their SEGAs grow, which is 0, they all stayed at 100% as response. The red line is those who received placebo, and you see that a small number—6 out of the total 115 patients—showed progression of their SEGA, and those were the patients who had to be unblinded in the study and determined what group they were assigned to. All of them came from the placebo group, and then they started therapy as a result of their tumors continuing to grow. None of the tumors continued to grow in the treatment group.

And this is what we see here when it's done with numbers, how there's continued growth with those placebo, and the everolimus group showed reduction both at 3 months and at 6 months.

This is a girl from our center who participated in this trial. She had previous SEGA surgery, had a remnant left over. The SEGA grew back, and rather than undergo repeat surgery, she enrolled in the trial to be treated with everolimus.

You see here in the left panel what she looked like at baseline; at 6 months, there was a significant reduction in the tumor size when the main study ended, and then she continued treatment after the study for an additional 4 years, and you see that she continued to show an improved response with everolimus treatment.

Every medication has side effects. Just as I told you that surgery has certain risks associated with it in addition to its benefits, same thing here. I've shown you how everolimus can reduce the SEGA tumor size, but any medication therapy has its side effects.

The most common side effect we encounter that's definitely related to treatment with mTOR inhibitors, whether it be everolimus or sirolimus, are mouth sores or canker sores or aphthous ulcers. At a severe state, we call that stomatitis, but it's still the same process, and you see that this was much more likely to occur in the everolimus group compared to placebo.

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We also had increased numbers of patients reporting fatigue in the treatment group and for reasons we can't explain, but that was the only other aspect of adverse events that was increased and definitely related to drug.

What's important to note is we've seen this consistently through numerous trials, and notice it here because the SEGA trials preceded all the other development in tuberous sclerosis, is that side effects tend to decrease with time. Patients who experience side effects in the first 3 to 6 months report fewer in the second year, and even fewer in the third and fourth years, as you can see here on the right. So even though these side effects do occur and most of them are what we consider mild or moderate, meaning they don't lead to discontinuation of therapy or put the patient at undue risk, if we can get through that initial time period it certainly is worthwhile to know that most patients as time goes on get better and better at tolerating treatment.

We now have the final results of these SEGA trials published, both from the open-label 28-patient study that was published in 2015 by Dr. Franz, and then the final results of EXIST-1, which was the placebo-controlled trial that was published a year later, and basically see that treatment was continued to be observed throughout the length of the study, that we didn't lose efficacy as time went on, and we saw adverse events followed a very similar profile and got better as time went on.

One of the other things that we were able to do from the EXIST-1 study is ask, well, we're treating SEGAs, but what other aspects of TSC might be affected even though the reason we treated them was for the SEGA?

We saw that patients had better angiomyolipoma responses, and that skin lesions also improved in this patient population. And as I'll mention later, we also saw improvements in epilepsy in at least one of these trials. This just goes to show that mTOR inhibitors, the one advantage that they may hold over surgery particularly is that surgery can only treat the SEGA and it can't treat multiple aspects of TSC at the same time.

So what are the recommendations that come from the consensus conference in 2012? Well, all patients should have an MRI done when they get a new diagnosis of TSC no matter what their age is. We also assess their renal function and we treat renal manifestations alongside with that. In patients who are diagnosed with definite or possible TSC and they return for a follow-up, we need to keep monitoring for SEGA during the pediatric years until at least they're 20 to 25 years of age by repeating the MRI every 1, 2, or 3 years. The rate of that repetition, whether

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it's done annually, every 2 years, or every 3 years, really depends on the clinician's concern level for the ability for SEGA to start growing again, or to monitor a suspicious lesion that may or may not already have started growing.

It may be more necessary to do more often. As I mentioned in the previous trial, our patient, we started doing MRIs every 6 months while they waited to get in the trial, because we knew that that tumor was growing, and we didn't have a sense of whether or not it might start causing complications.

The recommendation for treatment, if a patient develops an acute SEGA, is to remove it surgically. This is based on data at the time that we lacked and whether or not a tumor could respond rapidly to an mTOR inhibitor so that the risk for complications would be reduced in a very short time once the patient already had symptoms.

In an asymptomatic SEGA, surgery is still an option, but also we can treat with an mTOR inhibitor such as everolimus in those patients where medical therapy is preferred or superior for a variety of reasons over surgery alone.

Still note that even patients who have their tumors removed surgically or treated with an mTOR inhibitor may ultimately require a shunt to treat hydrocephalus, although it seems to be that those patients who are identified with SEGA early on and appropriately managed particularly with mTOR inhibitors, that the rate of needing shunt diversion in patients with SEGA has gone down significantly.

Just thought that I'd throw this out here is a case that we published late in 2017. This is post-recommendations of that patient who was not returning for follow-up and not getting scans and presented acutely with neurological decline associated with hydrocephalus. Although this patient was worked up for surgery over the weekend, treatment with everolimus was initiated and within 24 to 48 hours showed clinical improvement of symptoms. So he stayed in the hospital for a couple weeks and was monitored with frequent imaging, as you see here at 12 days, and then 1 week after hospitalization at 20 days, where the tumor is significantly and steadily being reduced in size in response to treatment, and at the same time clinical ataxia and other symptoms of hydrocephalus resolved almost completely. Here is final imaging from 75 days out of this patient while he continued on therapy and did not undergo surgical resection. So there might be a possibility in the future of being able to treat even more acute cases under the right circumstances or if there are contraindications for surgical management.

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So now we'll jump ship and finish with the rest of the talk and talk specifically about seizures in tuberous sclerosis.

Very, very common, as I mentioned, these appear in the first year of life. We see all different seizure types, but the most common seizure types we'll see are infantile spasms and partial seizures or focal seizures.

We worry about this because it's very closely associated in babies and adults with their long-term cognitive outcome. This is a study that we published earlier this year that shows that this association with epilepsy that starts in the first year of life also is when we start to see the derailment of normal development in these patients, and so this has been the focus of much of our research here in Cincinnati, as well as with the Research Consortium of trying to tackle epilepsy and these general developmental disorders very early in life when they first appear.

We now have ways to predict whether a child's in trouble based on the age of their first seizure, and also the age of when they're being seen in the clinic, and that we can predict the probability of that patient having long-term cognitive deficits through modeling such as this.

Now treatment of epilepsy is not new in tuberous sclerosis; it's been a challenge from the get-go even before probably tuberous sclerosis had its name. This is a set of studies that Dr. Franz did several years ago just looking at various treatments that we use in the clinics today on how well they work in tuberous sclerosis. The long story short is in this series at least, one-third of patients, they did not respond to these treatments. Some other more widespread retrospective series from other centers have noted that this rate is probably higher—50%, 60%, maybe even 70%—and so this represents a very important aspect of TSC care that we really need to continue to work on to improve.

One of the treatments that we have used in the past 20 to 30 years for tuberous sclerosis is vigabatrin. As you can see at the top, it's chemical structure looks very similar to GABA, which is a normal transmitter that our bodies need for the brain to function correctly, and so vigabatrin mimics the effects of GABA to diminish seizure frequency.

It works particularly well for infantile spasm tuberous sclerosis, which has led to its recommendation as first-line therapy against infantile spasm tuberous sclerosis. And, in fact, attempts to use other medications such as phenobarbital, oxcarbazepine, levetiracetam to treat infantile spasms, even topiramate, are really doing a patient a disservice, and really there is no reason why a TSC patient should not be treated first with vigabatrin, or if there's reasons to not

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do vigabatrin, then the second-line therapy which is ACTH should be really the only 2 treatments for consideration in a patient with infantile spasms.

Of course, when medications aren't working, we have nonpharmacological treatments available, such as ketogenic or modified Atkins diet. We use vagus nerve stimulation, and we have epilepsy surgery in tuberous sclerosis as a highly effective treatment, particularly when medications against seizures are not working.

So every patient with newly diagnosed TSC should undergo EEG. We need to review seizures, what they look like, what they can do, and how to get a hold of us should seizures newly develop, particularly in any baby or infant during the newborn or toddler period.

It may be necessary to obtain prolonged EEGs. Sometimes we're not sure what's happening and whether it's a seizure or not, or whether there could be seizures going that don't have any outwardly manifestations but still are negatively impacting development.

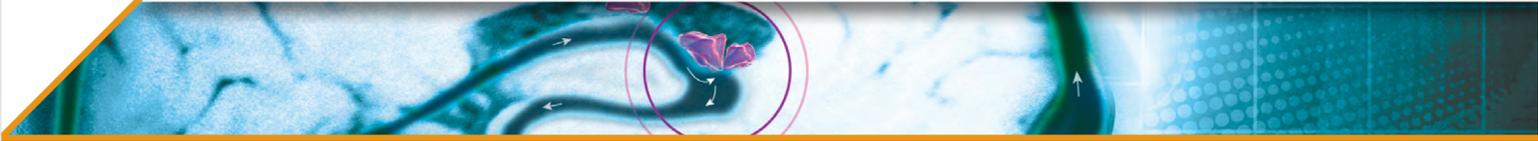
We should repeat these if we're unsure of how the next step to proceed both in treatment or diagnosis is, but we don't do them routinely with the exception of what I'll show here a little bit about screening. I already mentioned the treatments and how we should follow those in patients who are having repeated seizures, including infantile spasms.

I want to spend with the remaining time I have with you specifically about newer areas since the development of the consensus guidelines.

Many years ago, this is a series of 10 patients by Paulo Curatolo's group in Italy that noticed that the earlier you start treatment in TSC, the better off those patients do. And this was extended by a study published in 2011 by Dr. Sergio Jozwiaki in Poland that showed that even if you treat before the onset of seizures using the EEG as a marker of those patients who are going on to develop epilepsy, that we can both improve the ability to respond to treatment as well as their long-term neurodevelopmental and neurocognitive outcome, as you see on the right.

This has led to multiple studies, EPISTOP in Europe and also the PREVeNT trial here in the United States, as well as the epilepsy biomarker study that was led by the consortium where we looked at 42 patients and looked at those who went on to have seizures and asked whether or not the EEG was helpful and when it was helpful to tell us if the seizures were coming.

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A decorative banner image at the top of the slide. It features a blue-toned background with a brain scan (MRI) showing a cross-section of the brain. A purple butterfly is superimposed on the brain scan, and there are some white arrows and circular highlights indicating specific areas of interest. The banner is bordered by a blue diagonal line on the left side.

On the right, you see the actual results shown in graphical form, but the story really here is you see in the lower left, that the average time that a child with TSC has seizures is around 6 months, but there's a range. We see both infantile spasms and focal seizures in this timeframe, and that an EEG in asymptomatic patients was predictive of pending epilepsy in about three-fourths of cases, and there actually was a timeframe, on average, of about 2 to 3 months that we could notice the change in EEG before the child started having seizures. So this has led to a practice in many centers, including ours, to start to do serial EEGs every 4 to 6 weeks in infants diagnosed with TSC even if they've never had seizures just so that we can be in place to offer treatment should the seizures occur.

However, we also need to prove whether Dr. Jozwiaki's observation of early treatment truly is protective. This is important not just so that we can know this from a scientific perspective, but also from a regulatory perspective, that we're not going to get these treatments available to patients if we don't have the scientific proof that shows that it truly does help.

So the PREVENT trial is enrolling here in the United States currently at 7 centers across the United States, with additional centers becoming available in the coming 6 months, and it's funded by the National Institutes of Neurological Disorders and Stroke. So certainly reach out to me or to the TS Alliance, which is sponsoring this talk, for more information on how to identify a center and enroll any of your patients or children who are under the age of 6 years and have not had a seizure but are diagnosed with tuberous sclerosis.

We also have been developing everolimus as a treatment against epilepsy in TSC, and this is the first study that we published for 20 patients showing that it's highly effective for reducing seizures in patients whose other medicines aren't working, and we've shown that this is continued over time. We followed this up with a phase 3 study involving more than 300 patients across the world who were randomized to receive placebo or 1 of 2 doses of everolimus.

These are the results from that study. On the left, you see the change in seizure frequency, and on the right you see the number of days where a child goes without having any seizures, and with purple being the placebo treatments. You see that there is some improvement, but very minimal, and then as you see medium and especially high-dose treatment, you see that the amount of seizures decreases over time and simultaneously the number of days without having any seizures increases in response to dose.

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A decorative banner image showing a cross-section of a brain with a purple butterfly-like structure highlighted in a circular area, set against a blue and white background with a grid pattern on the right.

Also what this shows, and we've looked at this in long-term in patients who continue to receive treatment for more than 2 years, and we see that the response rate increases the longer the child's on treatment as much as 57%, showing a 50% reduction in seizures or better out as far as 2 years. So sometimes you may not see a difference in 3 months or even 6 months, and if a child's not having significant side effects and can continue to obtain the medication, it's worthwhile to consider treatment out to 12 months or 24 months before you determine that it absolutely is not of help to that patient in their management. We see that the percentage reduction in seizures overall also reduces over that same timeframe.

Side effects are the same as those in the previous studies; I don't have anything new to share here. However, what I do want to point out, that many people have worried about these medications making children sicker than usual. Whereas there probably are some individual cases where this is true because everybody's immune system is unique, overall these medications don't cause children to be sicker than usual compared to their peer groups.

And you see this when you compare the graph on the left, which is the mouth sores I talked about, and what you see in the placebo group in orange at the very bottom compared to those who were receiving medium and high dose on the top, you see a distinction very quickly between placebo versus those who get treatment.

Now what you see on the right is of the rate of infections, and you see that the rate of infections between the two groups is very parallel to each other, indicating that overall while there may be some subtle differences, it's not a major problem overall in the management of those patients who are treated with everolimus in this case for epilepsy.

Now I do want to mention briefly cannabinoids (CBDs), because that's a hot topic in how we might be treating epilepsy in TSC. This is a study that just looked at refractory epilepsy of all different kinds, with the 2 most common groups enrolled were Dravet syndrome or Lennox-Gastaut syndrome, which have very hard to treat epilepsy similar to that with tuberous sclerosis, but you see the number of TSC patients in this study was relatively mild.

However, what we saw in Dravet and Lennox-Gastaut, at least, that there was a significant reduction in seizure frequency over the time of getting treatment in 12 weeks with cannabinoid products.

These are the follow-up studies that were placebo-controlled. This was the first one that was done in Dravet syndrome, which showed convulsive seizures as well as total seizures, including

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those that may not be readily clinically apparent. Both showed a similar reduction with CBD oil, which you see in blue, compared to placebo, which you see in green. These are the results for Dravet syndrome.

These are the results for Lennox-Gastaut, which was a separate perspective clinical trial that was placebo-controlled. These results have been submitted to the FDA for potential approval of a CBD option for us that could be prescribed and paid for by insurance.

Now what does it do for tuberous sclerosis? Well, we don't have a controlled trial yet that's underway, but there was an opportunity to look at those patients who were treated with CBD oil for compassionate use between 2 large TSC centers in New York and Boston. What you see here, is that over time, particularly the longer the patient was on treatment, were fewer and fewer seizures per month in patients who received CBD treatment. You see it graphically on the left, but the table on the right shows they went roughly from about 15 seizures per period down to 8 seizures per monitoring period.

So this looks highly promising, and obviously we're looking forward to the results of that study. This is in process and hopefully we'll be able to get an FDA approval for CBD in these patients, as well, once these studies are completed.

So that completes the educational portion, but I want to just run through 2 cases that are relevant to SEGA management that might highlight many of these principles that we talked about in everyday scenarios.

So this was a girl with TSC, she had development delay, she's nonverbal, and she has epilepsy which is not fully controlled. The mother is noticing that she's starting to drop things and being a lot more clumsy than the mother's comfortable with, and certainly doesn't feel it's typical for this 10-year-old girl.

She took the daughter to the neurologist and the neurologist said, well, she's delayed. Let's just watch it and see what's happening. But she had not had any surveillance imaging of the brain for the previous 3 years, and the mother was very concerned about this. So she took her to the emergency room the following day, despite the neurologist saying we'll just watch her, and they got a CT and then a day later got an MRI.

This is what it looked like for her, that she had this large tumor that was unknown to the clinician that was managing her, and a large backflow of CSF, and with the clinical symptoms,

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meets the criteria for hydrocephalus. This is what we call an acute SEGA presentation, and certainly with surveillance I think this could have been avoided, but we don't know that for sure.

So she was urgently taken to surgery, and what you see on the left is what the surgeon started with. And what you see on the right is what the surgery resulted in which did not fully get the entire tumor out. As I mentioned earlier, if there are remains to the tumor left after the surgery, there's a very, very high likelihood it's going to start growing again.

Sure enough, this is what happened. She did fine immediately postoperatively, but a month later, mom brought her to the emergency room because she was having a hard time getting her daughter to wake up. An urgent CT and MRI were obtained. As you see here, she didn't have regrowth of SEGA, but she had a large fluid collection consistent with a large epidural hemorrhage that was contributing to her rapid decline, which is a known surgical risk associated with any type of craniotomy, not just SEGA but any type of brain surgery.

So that was evacuated surgically, but 3 months later, just a follow-up MRI at this time done for surveillance reasons, not because of new symptoms, showed that, indeed, that small area of SEGA had started to regrow.

At this point the mother, with all the drama and the complications that occurred with the original surgery, she came to our center to enroll into EXIST-1, the SEGA everolimus trial.

This is how she did. She responded in 3 months, and then you see in 6 months had a significant reduction to that tumor, and this answered one of the basic questions—and we've published information about this—is that whether or not leftover tissue is more aggressive than the original tissue. The answer is that it doesn't appear to be the case, that it responds just as equally well as the original tumors do. And then you see at 12 months, which was beyond the original start of this study.

This is what she looks like today in response to everolimus, and she's avoided any further brain surgery after those first 2 that I described.

So this highlights the case of the importance of surveillance, the importance of recognizing clinical symptoms of hydrocephalus, the importance of knowing the benefits as well as the potential risks of surgical intervention, and then lastly here, the benefits, and certainly as I

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highlighted earlier, the adverse risks associated with medical therapy and how they can be both effective if they're properly utilized in the care of TSC SEGA.

So my last case I want to talk about is the opposite case, so what to do in somebody who's very, very young. This is a baby who was born—and I showed you her ultrasounds earlier—that had an ultrasound that showed a large mass, and then when she was seizing on her first day of life prompted an ultrasound in the nursery, and that's when we saw bilateral SEGAs.

Unfortunately, seizures in this case were treated with phenobarbital which really, as I mentioned earlier, whether indications truly for infantile spasms but should be strongly considered for any seizure type in infants, would be vigabatrin.

Here you see large right-sided SEGA. This is actually a second congenital case that we treated here where you see it's largely on the right side and not bilateral, as I mentioned in the previous presentation. This is how she looked on day of life 2.

So everolimus was finally started. There were several delays on why it took a while to start, but it was started on day of life 29, so she was less than a month of age. At that time, we didn't have good information on how to dose this, so she was getting treated 3 times a week. And now we know that with the dispersed tablets we can actually just use smaller milliliter amounts and do daily dosing. She had a well-child follow-up with her PCP in 2 months and received all of her scheduled vaccinations. We do counsel against live vaccines, so she did not get rotavirus. And then for seizures, I mentioned we got her off of phenobarbital and put her on vigabatrin, and she had good seizure control and normalization of her EEG in that timeframe.

She did eventually still have some breakthrough seizures, but overall generally well controlled, and so at 1 year she's having about 1 seizure per month and that usually happens exclusively when she gets sick with a cold or otitis or something like that. She has started babbling and she was near crawling at that timeframe.

At 2 years, she still continued only to have seizures when she was ill and had had none in the previous 2 months. She is somewhat delayed, and she is having some behavioral difficulties and tantrums. She was delayed in her onset of walking, as well, but she is making consistent developmental progress.

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So this is her response imaging-wise. You see the baseline imaging there, and this is how she responded after 3 months.

This is the coronal images of the same.

This is what she's continued to do over time. So we see treatment now of 25 months of age and how it looks like coronally, and this is what it looks like now when we look at it through the axial images on MRI.

She does get sick a lot, so at some point the decision was mutually made between the parents and our team to go ahead and proceed to epilepsy surgery.

So she went ahead and had epilepsy surgery, and this is what she looks like following that procedure. There was complete resection, and she's discontinued any further treatment with everolimus.

However, it's interesting to note that she still continues to have frequent infections, and so I feel like this is her unique immune system rather than blaming everolimus for the cause. Nonetheless, that still was a reason why her therapy continued to get interrupted due to theoretic concerns and how we manage infections.

So that concludes our conversation today, and I want to certainly thank the Tuberous Sclerosis Alliance, which is a sponsor for this presentation, and will continue to be used and developed as an online resource material for both patients and clinicians who are managing tuberous sclerosis. For additional information on this and any other aspects of TSC, please visit the tsalliance.org website for such help and information.

Moderator: Thank you, Dr. Krueger, for that excellent session and your dedication to continuing medical education.

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