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Tackling TSC: A Neurologist's Perspective on Dermatologic Impacts

Dr. Greenberg:
Welcome to *DermConsult* on ReachMD. I'm Dr. Michael Greenberg, and joining me today to discuss the impacts of tuberous sclerosis is Dr. Peter Crino, who's the chair of the Department of Neurology at the University of Maryland School of Medicine. Hey Peter, thank you for being here today.

Dr. Crino:
Hey Michael, thanks very much for having me. It's really a pleasure to be on the show.

Dr. Greenberg:
Yeah, it's really an honor to have you. So, Peter, to start off with we all need a refresher, actually, from time to time on diseases we read about in medical school but have little contact with in our daily offices. So can you go over tuberous sclerosis complex for us, and the major organ systems that are involved?

Dr. Crino:
Sure. So tuberous sclerosis was originally designated as a rare disease but honestly, Michael, it's fairly common, happening in about one in six to eight thousand live births here in the United States. It affects men and women, just about equally, and it is a genetic disease, and when we say that, that means it can be passed along as a genetic disorder from parent to child, using an autosomal dominant pattern of inheritance. But it can also happen as a sporadic disease, which means that the mutations in the two genes, either TSC1 or TSC2, that cause tuberous sclerosis complex can just happen spontaneously during embryonic development. The disease is considered to be a multi-system disease, because it affects multiple organ systems across the body, obviously skin being a primary manifestation. But the main areas that we see clinical features of tuberous sclerosis complex include the brain, the eye, the skin, heart, lung, and kidneys. The term "tuberous sclerosis" in the past maybe decade, has been changed over to "tuberous sclerosis complex," to reflect the fact that this is indeed a multi-system disorder, and hence the term "TSC."

Dr. Greenberg:
So Peter, TSC has been referred to as a lynchpin disease. Can you tell us what that means?

Dr. Crino:
Sure. A lynchpin disease is a disorder that yields information about other diseases when you study the pathogenesis and the mechanisms and causes of that particular disease. So when we study tuberous sclerosis for example, understanding the molecular and cellular pathogenesis of TSC yields information about a number of disorders, some of which are actually quite distant from TSC. So maybe epilepsy, autism, which are part of the phenotype of TSC, but also things like obesity, diabetes, cancer. There's been some interesting developments recently that the tuberous sclerosis complex, which we usually think of as a neurodevelopmental or a developmental disorder, actually can yield insights into neurodegenerative diseases, like Alzheimer's disease. So a lynchpin disease really allows us to study one particular disease, but then use that learning to understand many other disorders, some related, but some quite distinct.

Dr. Greenberg:
Thanks. Now, I know for sure that there's people out there who have TSC, and they don't know it because as a clinical dermatologist I recall suggesting to a patient, a few years ago, that she might have the disease, and she did, and it was undetected until she was in her 50's. So, because this is *DermConsult*, how can our dermatologists listening get better at finding these people, including the symptomless, or the asymptomatic population?

Dr. Crino:
Yeah, that's a great question, Mike, and thanks for the clinical vignette there. In fact, this happens all the time. The scenario we see this the most is when a parent will bring in a child who has, for example, early onset epilepsy or autism, or skin findings compatible with TSC. And we go down the diagnostic pathway for tuberous sclerosis complex. We evaluate the child and say, "Yes, indeed. It seems that this child meets clinical criteria for TSC." And then, we ask the parent, "Hey, do you have any of the following things, any kind of skin features that we can talk a little bit about that? Have you ever had a seizure? Do you have any kidney disease or lung disease?" And sure enough, they'll say, "Oh yeah, I had that and I had that and I had that."

So there are really several cardinal manifestations of tuberous sclerosis that fall into the dermatologic sphere. They include the following: so-called hypomelanotic macules, which used to be referred to as ash leaf spots, because the actually often look a lot like the leaves of a European ash tree. Usually a couple centimeters of hypopigmented skin that can be seen, really anywhere on the trunk or on the extremities. You can have a couple of them, you can have a hundred of them on your body.

Facial angiofibromas, which are red, raised often fleshy lesions that appear in a relatively malar distribution across the face, sometimes in the fold of the chin usually not out on the cheeks and, a very characteristic look, often erythematous, red, they can be friable, they can actually tear and bleed quite significantly.

Third is lesions in and around the nail beds, which are called either ungual or subungual fibromas, and these are sort of wart-like, fleshy excrescences that stick up at the base of the nail bed or on the sides of the nail bed, oftentimes underneath the nail bed, leading to a condition of just deep nail groove. These can affect the fingers and they can affect the toes.

And then the final is a lesion that's known as the shagreen patch which is an area of skin usually seen in the lumbosacral flank region often has this so-called "peau d'orange" or orange peel-type consistency to it, sort of a roughened pitted looking appearance, usually about three to five centimeters in size, usually unilateral. But you can have multiple of these up the flank and the back, and frankly, they can appear on the front of the trunk as well.

There are a couple of other less common manifestations, so one of them is the cephalic forehead plaque or cephalic fibrous plaque, which is basically what looks like a large angiofibroma, often on the forehead and the temporal regions. You can see, hypomelanotic macules that are on the scalp, that lead to depigmentation of the hair, so you'll have a white patch of hair, and if you dig down deep in the scalp, you'll see that the skin is lacking in skin pigment. A number of skin tags in the axillary region, the neck region, they look a lot like molluscum fibrosum, but basically variable size skin tags. These are kind of the things that you look for, and challenging part is, often these will be seen in individuals that may not Have tuberous sclerosis, and so you do have to sort of look for a combination. I've seen a number of people over the years, with just simple vitiligo, represented as hypomelanotic macules. I actually have seen acne that's been misrepresented as facial angiofibroma. I'll tell you honestly the shagreen patch and the ungual fibroma, there's not too many other things that we see this in, so when I see that, I really do start thinking TSC. So all of those, Mike, are considered major diagnostic criteria of tuberous sclerosis complex, and if you have them, they would strongly support a clinical diagnosis.

Dr. Greenberg:
Wow, for a neurologist, you're speaking my language as a dermatologist.

So, for those of you just tuning in, you're listening to *DermConsult* on ReachMD. I'm Dr. Michael Greenberg, and today I'm speaking with Dr. Peter Crino about tuberous sclerosis complex. So, from everything you've said, Peter, I guess it's really important that family members be screened for this, because it's a genetic disease. What's a polite way to go about doing this as a dermatologist?

Dr. Crino:
If you have a patient in your office who you suspect or know has tuberous sclerosis complex, and you want to evaluate family members, obviously you do what your profession does best, which is a full dermatologic exam. So, all clothes off, gown on and you are looking for the aforementioned lesions, whether ungual fibromas or shagreen patch or hypomelanotic macules.

Of course, some of the other features of tuberous sclerosis that involve the brain, the lung, the kidney or the heart, for example, they're gonna required not just bedside examination, but they're gonna require diagnostic imaging. And so, if the skin exam is not supporting this diagnosis or it's inconclusive, it's absolutely reasonable to ask about getting an imaging study of the abdomen to look for renal disease in TSC, an scan of the brain to look for so-called "cortical tubers," or subependymal nodules, which are also a major diagnostic feature of TSC. And really it is incumbent upon the clinician seeing a TSC patient to do an evaluation to look for major diagnostic criteria that would support a diagnosis.

The final point, Michael, I will make is that in the last iteration, in 2012-2013, of the Clinical Diagnostic Criteria for TSC a consensus group got together and agreed that now, genetic testing is so efficient and so effective, that if you have a genetic test, which is available commercially from many different companies, that demonstrates a clearly pathogenic lesion, so a gene mutation in either TSC1 or

TSC2, that is interpreted as disease-causing, that also will serve as a major diagnostic criteria to make the diagnosis.

Dr. Greenberg:
Well, thanks. Let's shift a little bit here. The angiofibromas, for instance. What are some of the strategies that dermatologists should be aware of or treatments that we can use for these?

Dr. Crino:
So, the strategies now have changed dramatically with the advent of a class of medications that are called mTOR inhibitors. There are two that are on the market. The generic names are everolimus and sirolimus. These are medications that are taken by mouth. These work directly to counteract the effects of the TSC1 and TSC- gene mutations throughout the body, and one of the great benefits has been that it leads to a reduction in the size, erythema and kind of general facial spread of facial angiofibromas. So that has been something therapeutically that has been a great boon for patients, because really, when they go on an mTOR inhibitor, they often see significant improvement in their facial angiofibromas.

Some of the facial angiofibromas, especially those in the nose, in the ears, in and around the mouth, can be very troublesome for patients, especially men who are shaving. If they are cut, they often bleed because they are very vascular lesions, and indeed an engagement with a dermatologist, and sometime a plastic surgeon, is needed to remove surgically these larger lesions. Dermabrasion is considered basically an anathema approach to tuberous sclerosis, so no one would or should offer that to patients.

The final point that's the easiest one is that there's very solid data that the growth and progression of facial angiofibromas, believe it or not, is actually driven by UV sun exposure. And so, now we essentially counsel all TSC patients that when they go out into the sun, they should use high-level SPF to prevent against UV radiation absorption and the interesting prospective from the molecular side Mike, is that there are molecular ablations that happen in the TSC genes that look very similar to just standard UV irradiation causing mutations in DNA in certain types of skin cancer. So, clearly the use of high SPF sunblock can go a long way to prevent the growth and spread of facial angiofibromas.

Dr. Greenberg:
Now, there are special TSC clinics across the country. So, how can we help our patients go about finding them?

Dr. Crino:
Yeah, it's a really important question, and you know, a lot of community dermatologists, community neurologists, primary care physicians, take care of, TSC patients and do a fine job. The need to refer to a specialty clinic often happens when the level of care kind of escalates, but really particularly when the multi-system nature of TSC sort of combines in any one patient. And so, you have the effect of lung disease plus seizures, plus autism, plus kidney disease, it just gets a lot for a single specialist to handle.

The national advocacy organization, as you well know for TSC is the, TSC Alliance which is located here in the state of Maryland, and if you go to their website, TSAlliance.org, they have a fantastic listing of all the specialty clinics and indeed, some centers of excellence around the United States. I think we have clinics in just about all of the 50 United States and these are centers that have specific criteria for designation, in terms of what their bandwidth is physician coverage. Do they have individuals in all the subspecialties? Do they have imaging technologies, access to mTOR inhibitors? Do they have support services, etc. So, you know, I think if you're managing a single clinical feature of TSC, I think that's fine. If it really becomes multi-system management, then it's great to get patients to a specialty practice and these can be found easily online, on the TSAlliance website.

Dr. Greenberg:
Great, the last question for the day I'm gonna ask you is, Peter, what advances in TSC research can we see in the future? What can we expect?

Dr. Crino:
Yeah, it's very exciting with the advent of the class of medicines I mentioned, known as the mTOR inhibitors. We've made substantial strides in renal disease and pulmonary disease and TSC, with reduction in lesion size, reduction in lesion burden, improvement in patient outcomes, both short term and long term. The challenge remains though, is we really haven't cured TSC. These drugs seem to more mitigate or palliate the effects of TSC, but we haven't really cured this. There is a lot of work going on right now to look at agents that can further modify the mTOR signaling pathway, which is an important signaling pathway, modulating growth and metabolism, really ubiquitously throughout the body. So there's a lot of work using sort of high throughput drug screens to find new and more effective mTOR inhibitors. In addition, because this pathway plays such a critical role in metabolism across the body, there are other potential target signaling nodes to go after, so other kinases and other proteins in the pathway, that could be modulated as well. And again, there are several mouse models in which high throughput drug screens are being done to identify new compounds.

There are approaches that involve metabolomics and things like manipulations in the diet and the microbiome, that might augment or

foster quality of life, reduction in seizures, improvement in behaviors in autistic individuals with TSC.

There is, excitingly, I think, a little in the future, but potentially glimmering on the horizon, the consideration of using gene therapy in TSC, so a way to somehow replace either the mutated TSC1 or TSC2 genes with an intact copy of those genes, to somehow mitigate or rectify the genetic ablation that has caused TSC. That's a bit far in the future, but I think it is, in fact, glimmering on the horizon. So, very likely, there will be a new pharmacopeia of drugs coming in the next, I'd say, five years, targeting both mTOR itself as well as other proteins in the pathway, and maybe we'll actually come up with a gene therapy strategy.

Dr. Greenberg:
That's a great way to end our discussion on this disease that's really more common than some may think. And I want to thank my guest, Dr. Peter Crino, for joining me to talk about tuberous sclerosis complex. Peter, it was great speaking with you today.

Dr. Crino:
Mike, thanks so much for having me and giving me the opportunity to share this information with your audience.

Dr. Greenberg:
Thank you. For ReachMD, I'm Dr. Michael Greenberg. To access this episode, and others from *DermConsult*, visit ReachMD.com/Dermonsult where you can be part of the knowledge. We thank you for listening.