

Seizure Involvement in TSC

A brief review of its impact and underlying cause

Neurologic and neuropsychiatric disorders are the most frequent manifestations of tuberous sclerosis complex (TSC) and the cause of significant morbidity and mortality.¹⁻³ Of these TSC manifestations, seizures are the most common, occurring in approximately 85% of patients.^{3,4} Seizures are also reported to be the most common symptom that prompts patients with TSC (or their caregivers) to seek treatment.^{4,7}

The hallmark of TSC is the formation of hamartomas and lesions that can develop in virtually any organ system.⁵ In the brain, TSC lesions may include subependymal nodules (SENs), subependymal giant cell astrocytomas (SEGAs), and cortical dysplasia.^{2,5,8} In addition to seizures, TSC is associated with a high risk of neurodevelopmental disorders, such as autism and developmental delays, that are collectively known as tuberous sclerosis complex–associated neuropsychiatric disorders (TAND).^{4,9,10}

“Epilepsy is the most prevalent and clinically challenging manifestation of TSC...”

Curatolo et al⁴

While all of the neuropsychiatric disorders associated with TSC are serious, seizures are considered to be the most clinically challenging TSC manifestation.^{4,5,7} Patients with TSC can have almost any type of seizure.⁴ TSC-associated seizures often begin in infancy, are associated with developmental impairments, and have a high rate of recurrence.^{3,4,6} Among patients who have had a single TSC seizure, the probability of developing recurrent seizures is nearly 100%.³

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This newsletter is brought to you by the Tuberous Sclerosis Alliance and Novartis Pharmaceuticals Corporation.



A retrospective chart review of 291 patients with TSC seen at a TSC clinic between 2002 and 2008 demonstrates the high degree of risk.³ The study found that of the approximately 85% of patients who had a history of at least 1 seizure, more than 99% developed epilepsy and nearly 63% had seizures that could not be adequately controlled by medication.

In contrast, the authors point out, a study of patients who experienced seizures but did not have TSC found that 23% had seizures that could not be adequately controlled.^{3,11}

Patients with a history of infantile spasms were at an especially high risk of recurrent seizures: More than 75% developed refractory epilepsy compared with nearly 40% who had no history of infantile spasms ($P < .0001$).³

The youngest patients are at greatest risk

Studies have found that most patients with TSC begin having seizures within the first 2 or 3 years of life.^{3,4} In nearly 70% of patients, seizure onset occurs during their first year.⁹ The neurologic prognosis for patients with early seizure onset is generally poor: Infantile spasms and other seizures starting in infancy are associated with subsequent neurocognitive impairment.⁵⁻⁷ Compared with patients with TSC who have no history of seizure, patients with early seizure onset, particularly infantile spasms, have greater impairment in intellectual development.^{4,10} Refractory epilepsy, infantile seizures, and early seizure onset have been found to be strongly related to TAND.⁴

A recent prospective, longitudinal study investigating the relationship between seizures and early neurodevelopmental outcomes was conducted in 130 infants and toddlers with TSC by the TSC Autism Center of Excellence Network.¹² The occurrence of seizures was recorded continuously by parents/guardians in diaries, and assessments were performed at 3, 6, 12, 18, 24, and 36 months of age using standardized cognitive, adaptive, and autism-specific measures.



Not an actual patient. Cheesegirl/Shutterstock.com

Of the 130 patients evaluated, 73% developed epilepsy.¹² The most common type of seizure was infantile spasms and the average age at seizure onset was 5.6 months. A higher seizure frequency was associated with poorer outcomes at all time points but particularly at 12 months and beyond. The children who had higher seizure frequency during infancy continued to perform worse developmentally through 24 months. The study found that, although seizure type and frequency were important, the age of seizure onset was more predictive of developmental outcome and autism risk.

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Not actual patients. Mehmet Dilsiz/Shutterstock.com

It is important to bear in mind that for patients with TSC, **the risk of seizures is not limited to the young**. Adults with TSC who have never experienced a seizure are also at risk.³ A retrospective chart review of 291 patients with TSC found that more than 12% of adult patients who never had seizures as children subsequently experienced them.³

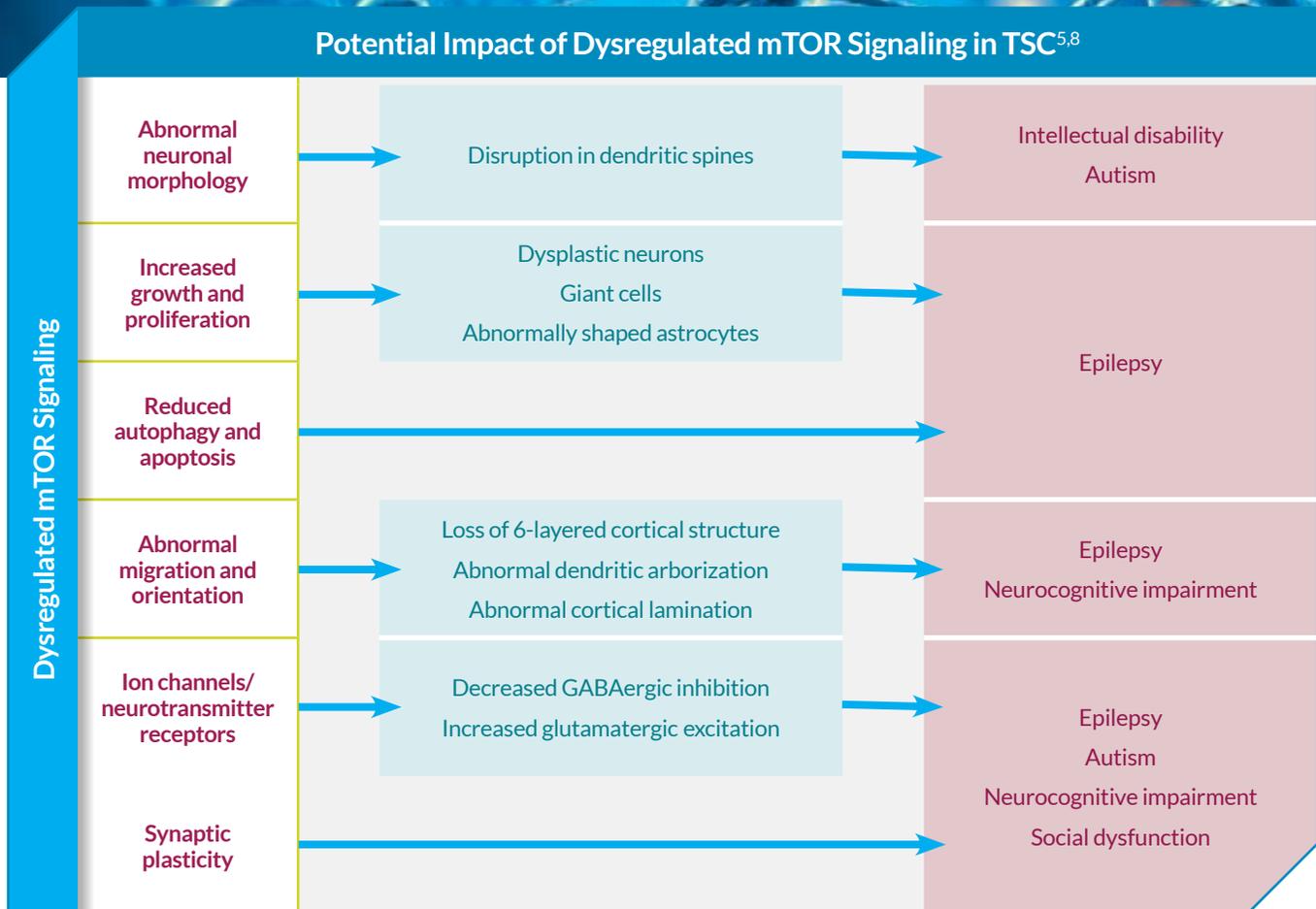
How mTOR hyperactivation is implicated

Insights into the pathophysiology of seizures in patients with TSC have progressed rapidly following the discovery of the 2 genes responsible for the disease and investigations into the role of mechanistic target of rapamycin (mTOR), also known as mammalian target of rapamycin.^{5,7} TSC was found to be the result of inactivating mutations in either the *TSC1* or *TSC2* genes, which lead to a loss of function of the TSC1/TSC2 hamartin/tuberin protein complex.^{8,13} In normal cells, 1 function of this complex is to inhibit mTOR, which is involved in the regulation of a number of processes integral to the development of a functional neural network and optimal neural communication.⁵ In most individuals with TSC, the loss of function of

the TSC1/TSC2 hamartin/tuberin protein complex leads to hyperactivation of the mTOR signaling pathway, resulting in uncontrolled cell growth, cell proliferation, metabolism, and angiogenesis.^{5,8}

Preclinical studies in TSC have also demonstrated that changes caused by mTOR dysregulation in the brain may influence neuronal excitability and precipitate epileptogenesis.^{5,8} In several different transgenic mouse models, for example, conditional knockout of the *TSC1* or *TSC2* genes was associated with elevated levels of mTOR signaling and spontaneous seizures.⁵

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GABA, gamma-aminobutyric acid.

mTOR hyperactivation has been found to impact both the structural and functional processes critical for normal brain development (see figure above).^{5,8} Because mTOR signaling plays such an intricate role in the development of normal neuronal structure and function, the hyperactivation of this pathway in TSC is believed to cause global disturbances in the architecture and connectivity in the brain.⁵ As outlined in the figure, mTOR dysregulation as a result of TSC can cause neuronal hyperexcitability, abnormalities in cortical structure and network function, and impaired synaptic plasticity, among other changes.⁵

Researchers propose that these disruptions in developmental processes caused by dysregulated mTOR signaling could lead to epilepsy, intellectual and neurocognitive impairment, and other neurologic disorders associated with TSC.⁵

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Consensus Panel



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Updated Recommendations on Managing TSC-Associated Seizures

Recently issued by a consensus panel of European experts

An update to the 2012 international tuberous sclerosis complex (TSC) guidelines, with a focus on management of TSC-associated seizures, has recently been published.¹

It reviews and revises the recommendations of the European Consensus Meeting on Management of Epilepsy Associated With Tuberous Sclerosis Complex.²

The 2012 guidelines were issued by an expert panel to address limitations in the medical community's understanding of this rare disease, discuss the potential for expanding treatment options, and propose outstanding questions to guide future research.² Given the advances in the past 5 years in preclinical and clinical investigations

of TSC-associated seizures, as well as recent expert opinion, a consensus meeting was convened in 2017 to revise and update the clinical recommendations.¹

The panel, which consisted of 15 experts from 11 European countries, reviewed recent literature to address specific questions on the clinical management of patients with TSC-associated epilepsy.¹ Five experts then presented the findings to the panel, and each issue was debated to arrive at a consensus for recommendations. Drafts of the recommendations were then circulated among the panelists and revised until agreement was reached on a final manuscript for publication.

Issues discussed included¹:

- » The evolution in our understanding of epileptogenesis in TSC and the underlying neurobiologic mechanisms
- » Research on biomarkers and electroencephalography (EEG) findings that could predict which patients with TSC are likely to develop seizures
- » Early diagnosis, presymptomatic assessment, and preventive treatment
- » Current treatment options for patients with TSC-associated seizures
- » New and outstanding questions and areas for future research

The update reports that the need for early diagnosis of TSC-associated seizures is well established and some European countries have adopted early EEG monitoring and a policy of educating parents to recognize seizures as soon as they appear.

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Imaging-Based Management of TSC-Associated Renal Angiomyolipoma

Recommendations of a multidisciplinary panel

Renal angiomyolipomas are the most common kidney manifestation of tuberous sclerosis complex (TSC) and are reported to affect up to 80% of patients with TSC.^{1,2} In fact, they are the main cause of morbidity and mortality in adults with TSC.²

TSC-associated renal angiomyolipomas are usually multiple and bilateral, and are asymptomatic until there is irreversible renal damage or bleeding.² They are also more prone to bleeding and growth than sporadic angiomyolipomas.² The presence of 2 or more angiomyolipomas (in the kidney or other organs) is a major diagnostic criterion for TSC.³ The diagnosis of TSC-associated renal angiomyolipomas and their follow-up are based mainly on imaging studies.²

In a 2017 article published in the *Clinical Kidney Journal*, a multidisciplinary expert panel provides recommendations for imaging-based management of patients with this manifestation of TSC. The panel's recommendations cover²:

- » Radiologic diagnosis and follow-up of the classic and atypical or fat-poor TSC-associated renal angiomyolipomas
- » Biopsy indications
- » Minimal requirements for radiologic requests and reports
- » Recommended technical features and protocols for computed tomography (CT) and magnetic resonance imaging (MRI)

Imaging-based diagnosis and monitoring of patients with TSC-associated renal angiomyolipomas are critical because of the risk of hemorrhage and the possibility of other types of tumors.² In those receiving treatment, imaging is also vital for monitoring the reduction in volume and stabilization of the angiomyolipomas.²

As outlined in the article, imaging studies in this patient population have 3 key objectives²:

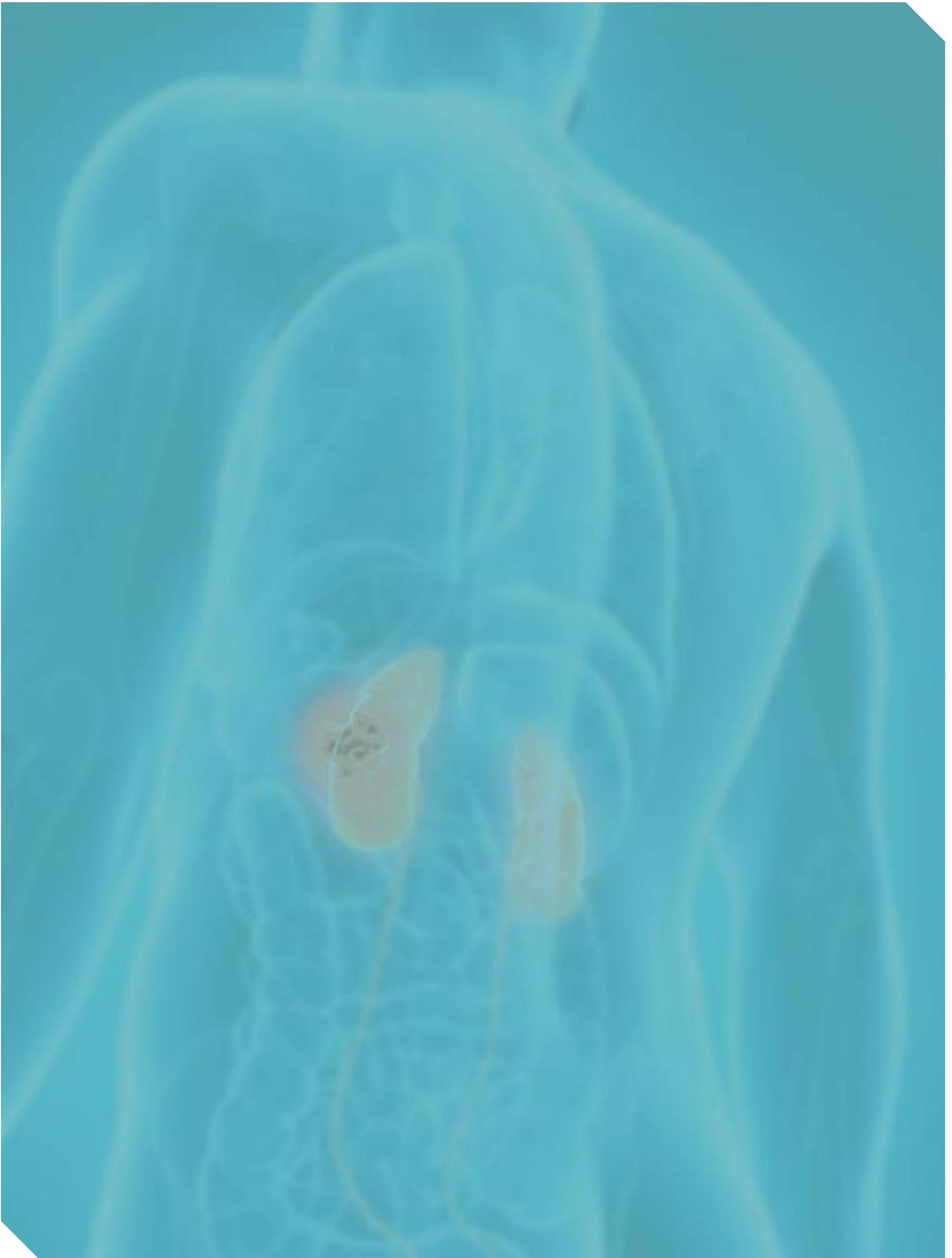
- » Detect and characterize tumors
- » Assess and detect the risk of complications, especially bleeding
- » Evaluate response to medical and surgical treatment

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Imaging enables identification of TSC-associated renal angiomyolipomas with a diameter >3 cm, which are prone to bleeding and carry a risk for potentially fatal hemorrhage.²



Not actual patients. Pangea8/Shutterstock.com, diyanski/Shutterstock.com, Garnet Photo/Shutterstock.com



The accompanying table highlights the panel’s recommendations for ongoing, imaging-based assessment. They are presented by the panel as a tool for specialists who care for patients with TSC-associated renal angiomyolipoma.² The article also provides an algorithm for the diagnosis of renal lesions in TSC.

Multidisciplinary Panel’s Recommendations for Use of Imaging in TSC-Associated Renal Angiomyolipoma²

USE OF IMAGING FOR DIAGNOSIS

- » Ultrasonography is useful as an initial approach to determine the presence of kidney lesions and whether these are solid or cystic
- » The finding of macroscopic fat tissue usually confirms the radiologic diagnosis of angiomyolipoma
- » Protocols for CT and MRI examinations are available
- » A hypointense renal mass on T2 that suppresses fat on the out-of-phase sequence is suggestive of isoattenuating fat-poor angiomyolipoma
- » If the diagnosis of angiomyolipoma is uncertain on CT or MRI, a percutaneous biopsy should be performed before surgery. If this biopsy is not performed or all tumors are thought to be angiomyolipomas, radiologic surveillance is essential

USE OF IMAGING FOR MONITORING

- » MRI does not radiate and is preferred to CT for the surveillance of patients with known angiomyolipomas
- » Regular radiologic monitoring is recommended to assess the risk of bleeding and the presence of tumors other than angiomyolipomas
- » In children, surveillance must be tailored to radiologic findings
- » In untreated adults, the frequency of follow-up examinations depends on tumor size

USE OF IMAGING IN THERAPY

- » Imaging-based assessment of renal angiomyolipomas is mandatory
- » CT is the test of choice for presurgical mapping or before embolization or resection
- » If an angiomyolipoma bleeds, urgent CT angiography is required and embolization may be needed
- » Radiologic interventional procedures with selective embolization should only be used in exceptional cases, such as acute bleeding

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Not an actual patient. Nadino/Shutterstock.com

47-Year-Old Man With Previously Undiagnosed TSC: A Case Report*

*Not an actual patient; for illustrative purposes only.

A 47-year-old man who otherwise reported good health consulted a dermatologist with concerns about “odd bumps” on his fingernails. On physical exam, 2 smooth, firm, flesh-colored lumps were found protruding from the nail folds on the second and fourth fingers of the left hand.

A complete skin exam revealed multiple hypomelanotic macules over his chest and abdomen and periungual fibromas. His blood pressure was 160/100 mm Hg.

The patient was referred to an internal medicine specialist for further evaluation. Laboratory studies showed blood urea nitrogen, serum creatinine, and electrolyte levels within reference ranges. Complete blood count and urinalysis were also within normal range. There were no symptoms of cardiovascular, endocrine, respiratory, immune, or musculoskeletal disorders.

Abdominal ultrasonography showed bilaterally enlarged kidneys with solid, heterogenic, and echogenic masses; the larger mass was in the left kidney and measured 5.4 cm. Other abdominal organs were reported as normal. An abdominal scan confirmed the diagnosis of renal angiomyolipoma.

The patient was referred to a nephrologist, who also suspected tuberous sclerosis complex (TSC) and explored the patient’s experience of seizures. The patient said he had not realized there could be a connection

between his history of periodic seizures and his original complaint about his nail. He said he “didn’t want to make a big deal” about having had seizures. He explained that he has been treated with antiepileptic drugs for the past 5 years and felt his seizures were “relatively under control.”

The co-occurrence of renal angiomyolipoma and skin lesions—in addition to the history of seizures—reinforced suspicion of TSC. Evaluation for other systemic manifestations of TSC was performed. An MRI of the brain (with and without gadolinium) was ordered, based on guideline recommendations that any patient suspected of having TSC should undergo such testing.¹ No abnormalities were observed. Chest radiograph was normal. An ophthalmologic exam found subretinal noncalcified hamartoma.

Based on the findings as a whole, a definite diagnosis of TSC was made. According to clinical guidelines, definite diagnosis of TSC is based on the presence of 2 major features or 1 major feature and 2 or more minor features of the disease.² The patient had at least 4 major features: angiomyolipoma, hypomelanotic macules, multiple retinal hamartomas, and unguinal fibromas.²

The patient now receives regular monitoring and specialists’ care. He has been referred to a TSC clinic as well as a patient support organization to help him deal with the broader impact of TSC, including the social and emotional effects on a newly diagnosed patient.

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MRI, magnetic resonance imaging.

Discussion:

Did it surprise you that the patient was asked about a history of seizures after being informed of his renal angiomyolipoma diagnosis?

TSC has affected multiple organ systems in this patient. How would you prioritize his care?

To what channels of support might newly diagnosed patients be referred?

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A Risk Model for Identifying Patients With TSC

Factors that may lead to earlier identification and care

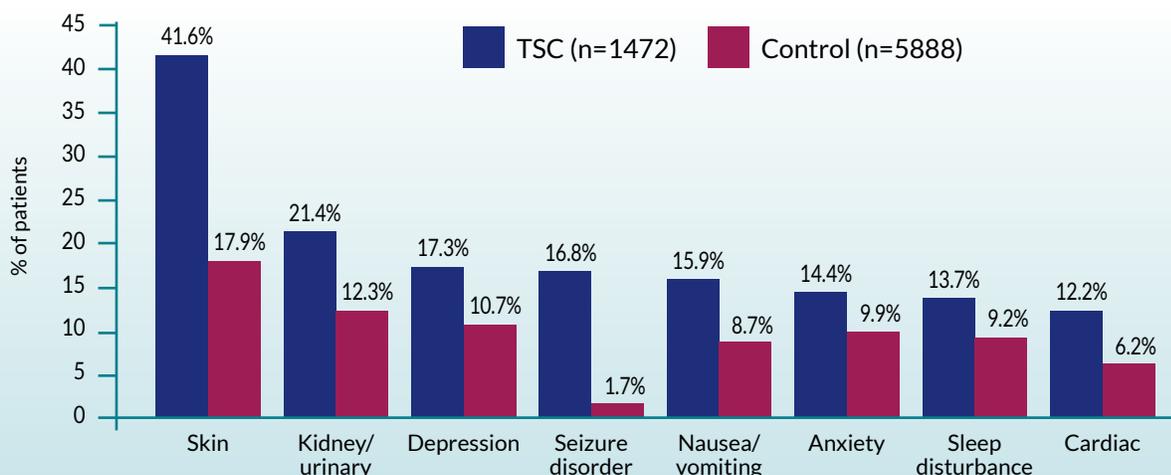
Early identification of patients with tuberous sclerosis complex (TSC) and appropriate intervention are critical for preventing further complications of this multisystem genetic disorder.^{1,2} With those needs in mind, researchers analyzed patient and treatment factors associated with a TSC diagnosis using medical and pharmacy claims in the United States.¹

The goal of their analysis was to develop a validated risk model that could potentially help health plans and accountable care organizations improve identification and quality of care for patients with TSC and reduce the economic burden associated with the disease.¹

The retrospective, case-controlled study identified 5525 patients with at least 1 medical claim of a TSC diagnosis occurring between January 1, 2000, and December 31, 2011, in 2 claims databases with records of 75 million patients.^{1*} A total of 7360 patients met inclusion criteria for use in risk-model development: 1472 patients with TSC and 5888 controls. The study analyzed 600 potential independent variables for use in the risk model.¹ Variables included demographics, comorbidity indexes, health care utilization and costs, diagnoses, procedures, and medications.¹

The most frequent diagnoses found among patients with TSC were skin disorders, kidney and urinary system disorders, depression, seizure disorders, nausea and vomiting, anxiety, sleep disturbances, and cardiac dysrhythmias and rhabdomyomas (see chart).¹

Top Diagnoses Among Patients With TSC Versus Controls^{1,a}



*Data are from analyses of the Optum Research database.

Adapted with permission from Johnson MP, et al. *Manag Care*. 2017;26(8):34-41.

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The diagnoses most strongly associated with patients who had TSC versus control patients were seizure disorders and renal angiomyolipomas.¹

The diagnoses found to be most strongly associated with patients with TSC versus controls were seizure disorders and renal angiomyolipomas, followed by skin disorders, renal failure, and cognitive disorders.¹

The authors advise that the risk model is not designed to have definitive predictive value.¹ Rather, it is intended to provide a measure that could alert providers to investigate TSC as a potential diagnosis in specific patients or target diagnosed patients for further management.¹ Based on the study results, the researchers conclude that a validated risk model could potentially serve as a quality-of-care tool, and that a data-driven approach such as the one outlined in the article could help improve patient outcomes and quality of life and reduce the economic burden of TSC.¹

*The Optum Research database and the Impact Benchmark database, which contain medical and pharmacy claims from US health plan members.

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Latest News & Events

From TS Alliance

2018 World TSC Conference

Empowering Nurse Care Coordination Through the Global TSC Community

Summary report from the Inaugural TSC Nurse Coordinator Conference

Ashley Pounders, MSN, FNP-C^a; Wynne Bird, BSN, RN, CPN^b; Jessica Krefting, BSN, RN^c; and Carol Hoskin, RN^d

Tuberous sclerosis complex (TSC) is a rare genetic disorder that causes lesions to grow in multiple organs. It can contribute to epilepsy, cardiac structural and electrical physiology abnormalities, developmental delay, psychiatric disorders, facial lesions, renal tumors, and pulmonary cystic changes.^{1,2} The clinical manifestations of TSC can vary widely and their complexity can be severe or life-threatening because any organ system may be involved.

The number of children born with TSC is an estimated 1 in 6000, and the disorder affects 1 million to 2 million individuals worldwide.³

Within the lifespan of a given patient, the navigation of care involves numerous subspecialists, diagnostic imaging, and a wide array of allied health resources. The number of TSC specialists and researchers around the globe is limited, making medical care challenging and further widening the gap in quality of care available to this underserved population. The profound barriers to care and disparities in access to care that many patients experience are remarkably similar around the globe.

Undoubtedly, the value and quality of the established coordination of care these patients receive directly influences their overall health care outcomes. Although there are published recommendations on the use of nurse coordinators in the surveillance and management of TSC, many health care professionals have not included high-quality nursing care coordination among multidisciplinary specialists.

Since the implementation of health care reform in 2010, the standard of care is measured by decreasing medical costs, individualizing patients' needs, increasing patient satisfaction, and improving patient outcomes. However, in a complex disease such as TSC, individuals and caregivers are often left on their own to navigate the complexity of coordinating their health care needs.

Currently, there is a growing body of evidence-based literature suggesting that coordination of care led by nurses is associated with decreased health care costs, increased patients' understanding of their condition and treatment, increased patient satisfaction, and improved overall outcomes of care.^{4,5} Yet, the nursing profession remains underrecognized as a leader in the TSC community and significantly underutilized as coordinators of patient care.

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The Tuberous Sclerosis Alliance is the only national organization dedicated to finding a cure for TSC while improving the lives of those affected. It works to improve quality of life for individuals and families affected by TSC by stimulating and sponsoring research; creating programs, support services, and resource information; and developing and implementing public and professional education programs designed to heighten awareness of TSC.

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A call to leadership and action

Two organizations—the Pediatric Epilepsy Research Foundation and Beureful—awarded a grant to Jo Anne Nakagawa, director of clinical projects and TSC clinical liaison of the TS Alliance, to recognize and empower the nursing profession to educate, advocate, and lead nurse care coordination through the global TSC community. This initiative led to the Inaugural TSC Nurse Coordinator Conference this past July. Participants included more than 40 nurse professionals from 31 TSC clinics across North America, representing nurse coordinators, advanced practice nurses, and nurse researchers. Nurse specialty areas consisted of neurology, nephrology, dermatology, developmental pediatrics, primary care, genetics, surgery, oncology, and behavioral health.

The conference generated profound positive feedback and requests for actionable educational opportunities, training courses, future conferences, and potential leadership roles within the TSC nursing professions to help narrow the medical inequalities faced by individuals with this complex disorder. Areas targeted for change via postconference feedback have included:

- » Optimizing multidisciplinary collaboration and involvement among TSC clinical team members
- » Implementing educational resource tools to improve coordination of care
- » Applying knowledge gained to improve education and advocacy for the patients and families we serve



Ashley Pounders presenting at the Inaugural TSC Nurse Coordinator Conference.

Enhancing leadership roles in the nursing profession can offer the TSC community higher quality of care and satisfaction by shifting the burden of coordination from the caregiver's shoulders to an orchestrated platform of multidisciplinary coordinated care that serves individual patients.

The overall success of nurse care coordination drastically depends on the nursing profession itself. Nurses must advocate for leadership roles as well as engagement, support, and commitment from TSC clinic directors, administrators, key organizations, and others who seek to establish lasting advances in the quality of care, research, and end goal of curing this devastating disease.

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TSC Support

There are several resources available to your patients who would like more information on tuberous sclerosis complex (TSC).

Tuberous Sclerosis Alliance

The Tuberous Sclerosis Alliance (TS Alliance) was formed in the 1970s by 4 mothers with a desire to provide fellowship, generate awareness, pursue knowledge about TSC, and provide hope to those with the condition. These goals still drive the organization today.

The alliance has a comprehensive website with information and educational materials for patients and their families about living with the disease (www.tsalliance.org). It also organizes frequent fund-raising activities for TSC patients, including the Step Forward to Cure Tuberous Sclerosis Complex[®] movement, the TS Alliance's largest national event, organized in more than 30 communities across the United States. This walk program offers the opportunity to make an impact on the lives of those living with TSC as well as fund research into cures for other diseases such as epilepsy, autism, and cancer.

The TS Alliance's **TSC Connect** is an organized partnership of people whose lives have been affected by TSC. It provides the latest medical information, education, and support to anyone seeking to understand TSC and offers them words of encouragement and empowerment.

Volunteers bring to the network a wealth of knowledge, awareness, and experience. They offer support and share their experiences with others who are facing the challenges of TSC. The program connects people by geographic area, manifestations, or age of the person with TSC and lets volunteers choose the issues with which they have personal experience and are willing to discuss with others. Patients can join TSC Connect by visiting www.tsalliance.org.

The TS Alliance Educator Mentor program

The TS Alliance also offers support to school systems that are educating a student with TSC and need support in understanding TSC or strategies to use in the classroom. The TS Alliance Educator Mentor program includes teachers, therapists, and administrators with experience in educating children with TSC. For more information, please contact Dena Hook, vice president of outreach, at dhook@tsalliance.org or 1-800-225-6872.



www.Inspire.com

Inspire.com provides an online patient support community for 750,000 patients and 3400 TSC board "peers." The organization partners with respected national patient advocacy groups to provide safe online health and wellness communities in which patients, families, friends, and caregivers connect with one another for support and information.

On the website, TSC patients can join groups about health topics that are important to them, make friends who share health interests, and control what they share with extensive privacy settings.



Not actual patients. Adapted from Pablo Rogat/Shutterstock.com with permission.

Patient resources and more on www.tuberous-sclerosis.com

Tuberous-sclerosis.com is a website sponsored by Novartis Pharmaceuticals Corporation that provides information and resources to patients and caregivers.

The website features sections in patient-friendly language on understanding TSC-associated conditions, the importance of monitoring, taking charge/staying informed, and free resources geared toward children and adults with TSC.

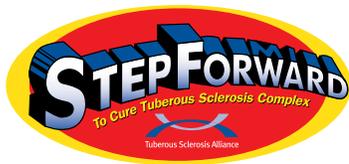
Upcoming TSC Events

TS Alliance Walks

Step Forward to Cure TSC is TS Alliance's largest national fund-raising event, organized in more than 30 communities across the country by local volunteers and families who are affected by TSC.

This successful grassroots fund-raising effort not only generates vital funds for TSC research but also raises awareness about TSC and the need for increased research funding to combat this complex disorder.

Register for a walk at www.tsalliance.org.



To obtain more information about TSC walks, please visit www.stepforwardtocurets.org

Regional TSC & LAM Conference Agenda

(As of October 1, 2018; subject to change)

April 13, 2019
> Boston, Massachusetts

June 15, 2019
> St. Louis, Missouri

September 7, 2019
> Chicago, Illinois

September 21, 2019
> Atlanta, Georgia

November 2, 2019
> Los Angeles, California

