Case Report

TUBEROUS SCLEROSIS CONFIRMED ON NEUROIMAGING: A CASE REPORT AND LITERATURE REVIEW

Idowu BM[1]*

[1]Department of Radiology, Union Diagnostics and Clinical Services, No 37 Tejuosho Street, Yaba, Lagos State, Nigeria.

***Correspondence:** Dr. Bukunmi Michael Idowu, ibmcontacts@gmail.com

Abstract

Background: Tuberous sclerosis (also known as Bourneville disease or Epiloia) is a neurocutaneous genetic syndrome secondary to autosomal dominant germline mutations (20 – 50% of cases) or spontaneous/sporadic gene mutations (50 – 80% of cases). The classical diagnostic triad, which is seen in only twenty-nine percent of patients, comprises of epilepsy, adenoma sebaceum, and mental retardation. Although the disease could be suspected clinically, cross-sectional neuroimaging with brain Computerized Tomography (CT) and/or brain Magnetic Resonance Imaging (MRI) is necessary for complete evaluation.

Case presentation: This is a case report of a 24 -year-old Nigerian male with tuberous sclerosis who presented with epilepsy, cutaneous lesions, and poor academic performance. The relatively unique feature of this case is the asymptomaticity of the disease from the age of 6 years until the age of 24 years (An 18-year interval).

Conclusion: TSC is diagnosed based on clinical and radiologic findings. Adequate control of seizures and prevention of organ failure are the cornerstone of management. Vigabatrin and rapamycin inhibitors are the current first-line pharmacologic agents for seizure control, while mTOR inhibitors like everolimus and sirolimus are the drug of choice for treating neurocognitive abnormalities.

Keywords: Epilepsy, Mental Retardation, Neurocutaneous syndrome, Imaging, Tuberous Sclerosis Complex

Cite this article: Idowu BM. Tuberous sclerosis confirmed on neuroimaging: A case report and literature review. Yen Med J. 2021;3(3):195–200.

INTRODUCTION

Tuberous sclerosis Complex (TSC) is a neurocutaneous syndrome with multisystemic manifestations characterized by neurological symptoms and hamartomatous lesions in several organs, including brain, skin, kidney, retina, heart, lungs & gastrointestinal tract.[1,2] It presents a spectrum of signs and symptoms over a patient's lifetime, including neurologic disorders, multisystem tumor growth, and dermatologic manifestations.[1] The classical diagnostic (Vogt's) triad of TSC is seizures, cutaneous angiofibroma (adenoma sebaceum), and mental retardation.[2] The disease burden varies from intense mental retardation and debilitating seizures to normal intelligence and absence of seizures.[1]

Tuberous sclerosis (also known as Bourneville disease or Epiploia) is a neurocutaneous disorder with a spectrum of phenotypic expressions.[3] It is caused by a single autosomal dominant germline mutation in tumor suppressor genes TSC1 and TSC2 in about 20 - 50% of cases, with an estimated prevalence of 1:50,000 – 300,000 live births.[3] Consequent to the mutation of the TSC1 or TSC2 tumor suppressor gene, the mammalian target of rapamycin (mTOR) signaling pathway becomes hyperactivated, leading to diverse derangement and abnormalities in many cell processes.[4] The mTOR signaling pathway regulates multiple cell functions.[5] TSC1 and TSC2 encode, respectively, for the proteins ha martin and tuberin, which serve as tumor growth suppres sors that control cell proliferation and differentiation.[1]

The remaining 50 - 80% of cases are due to spontaneous (sporadic) gene mutations, with a prevalence of 1:6,000 –

50,000 live births.[1,3,6] TSC affects both sexes and all ethno-racial groups.[6]

The multi-organ manfestations of TSC include cutaneous abnormalities (hypopigmented macules, facial angiofibromas, connective tissue nevi, periungual fibroma, gingival fibromas, dental enamel pits); renal abnormalities (angiomyolipomas, multiple renal cysts, renal cell carcinoma); pulmonary abnormalities (lymphangioleiomyomatosis, multifocal micronodular pneumocyte hyperplasia, clear cell tumour of the lung); cardiac abnormalities (rhabdomyoma); ophthalmic abnormalities (retinal hamartoma, retinal hypopigmented macule, retinal achromic patches); hepatic abnormalities (liver angiomyolipomas); epilepsy; and tuberous sclerosis-associated neuropsychiatric disorders (epilepsy, cognitive impairment, autism spectrum, mental retardation, mood disturbances, subependymal giant cell astrocytomas, aggressiveness, behavior changes, anxiety, sleep disorders, depressive mood, hyperactivity, learning difficulties, attention deficit) are seen in 90%, 2 - 80%, 40%, 80%, 30-50%, 10-25%, 70-90%, and 30-75% of patients, respectively.[7–9] Other tumors (thyroid papillary adenoma, PEComa of the uterus, hamartomatous colorectal polyps) and skeletal lesions (bone cyst, scoliosis, periosteal new bone formation, hyperostosis of the inner table of the calvarium, osteoporosis) have also been documented in patients with TSC. Neurological and renal complications are the primary cause of morbidity and mortality in TSC.[7–9]

The first inkling to the presence of TSC might be the detection of cardiac rhabdomyomas on obstetrics sonography or the presence of cognitive impairment, hypopigmented cutaneous macules, or seizures (especially infantile spasm) in a child.[7]

Since the traditional (Vogt's) triad of epileptic seizures, mental retardation, and facial angiofibroma (adenoma sebaceum) is present in only 29% of patients[3], the first comprehensive diagnostic criteria for tuberous sclerosis complex had to be formulated in 1998. In 2012, the revised diagnostic criteria were agreed upon at the second International Tuberous Sclerosis Complex Consensus Conference.

The new guidelines modify the previous diagnostic clinical criteria, incorporate genetic testing, and provide for a new category termed "probable diagnosis".[7] Identification of the pathogenic mutation (deletion, rearrangement, or inactivating mutation) in TSC1 or TSC2 gene on genetic testing is now an independent diagnostic criterion that can be used to diagnose TSC definitively. This is particularly useful in neonates in whom the usual clinical manifestations might still be latent.[7]

The modified clinical criteria are still the cornerstone of diagnosis in places where genetic testing is unavailable. The major clinical criteria are hypopigmented macules (≥ 3, with at least 5mm diameter), angiofibromas (≥ 3) or fibrous cephalic plaque, ungual fibromas (≥ 2), *shagreen* patch, multiple retinal hamartomas, cortical dysplasia, subependymal nodules, subependymal giant cell astrocytoma, cardiac rhabdomyoma, lymphangioleiomyomatosis, angiomyolipomas (≥ 2). The minor clinical criteria are: "confetti" lesion, enamel pits (> 3), intraoral fibroma (≥ 2), retinal hypopigmented macule, multiple renal cysts and nonrenal hamartomas. TSC is diagnosed when two major criteria or one major and two minor criteria are present in the patient. The detection of one major criterion or ≥ 2 minor criteria constitutes "probable diagnosis".[7]

CASE PRESENTATION

A 24-year-old male secondary school student presented with a history of fever, an episode of seizure, poor sleep, skin lesion on the forehead since birth, and irrational behaviour. Fever occurred mainly at night and was high-grade in nature. No associated chills or rigor. The seizure was said to have been generalized, tonic-clonic, and lasted about five minutes. There was no associated foaming from the mouth or urine incontinence. Seizure episode was reportedly aborted by pouring water on him. He had been unable to sleep soundly for the past three days before presentation and was said to have taken off his clothes in public on one occasion. No history of trauma to the head, persistent headache, effortless vomiting, or fainting spells.

He started to have seizures at the age of one. There were about four episodes per day, each lasting about 3 minutes. Non-itchy skin lesions in the right forehead were noticed at birth with a gradual increase in size over time. The pregnancy, labour, and delivery were uneventful. Skull radiograph, hematologic parameters, and blood chemistry assay were normal then. He was diagnosed with a seizure disorder (epilepsy) ? neurocutaneous syndrome and managed with phenobarbitone initially, which was later combined with phenytoin. He was regular in the pediatric out-patient clinic until he was six years old when he was lost to follow-up.

He re-presented with new episodes of seizure at the age of 24. He had been seizure-free throughout the intervening period on a daily intake of phenytoin. There was no history of flank/abdominal pain, early morning facial/ feet swelling, or bone pains. There was a history of poor academic performance (frequently repeating classes). No family history of seizure disorders.

On examination, he was conscious, kempt, and oriented in time, place, and person. The general examination was unremarkable. Chest, abdominal, and neurologic examinations were normal. Dermatological examination revealed multiple facial papules on the nose, cheeks, and jaws; left-sided sacral Shagreen's patches; epidermal nevus (linear) on the forehead; and ash leaf macules on the back. Musculoskeletal system examination was normal.

Hematological and clinical chemistry assays were within normal limits. A cranial Magnetic Resonance Imaging (MRI) showed a subcortical focus of increased signal intensity (cortical tuber) in the right frontal lobe **(Figure. 1)** and multiple subependymal hypointense foci (subependymal tubers) along the outer walls of the lateral ventricles **(Figure. 2)** on T2-weighted imaging. No evidence of cortical atrophy, ventricular dilatation, or a subependymal mass lesion.

Cranial CT revealed multiple hyperdense, calcific densities in the periventricular areas **(Figure. 3)**, and in the medial portion of the right frontal lobe **(Figure. 4).**

Abdominal and renal sonography was normal, with no evidence of angiomyolipoma.

Electroencephalography (EEG) showed a rhythmic ictal epileptiform activity. Intelligence Quotient testing and genetic testing could not be done due to the unavailability of the relevant equipment and expertise.

He was continued on phenytoin for the seizures and has been regular on out-patient follow-up, with adequate control of seizure.

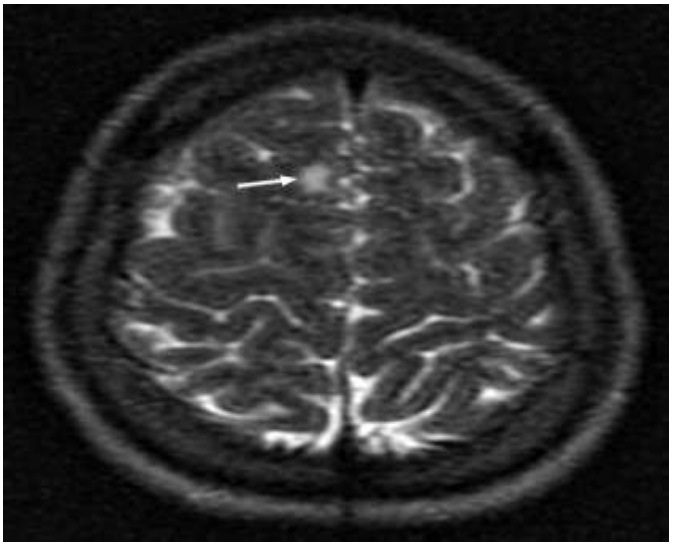

Figure 1: Axial T2-Weighted brain MRI showing a hyperintense focus (arrow) due to a cortical tuber in the right frontal lobe.

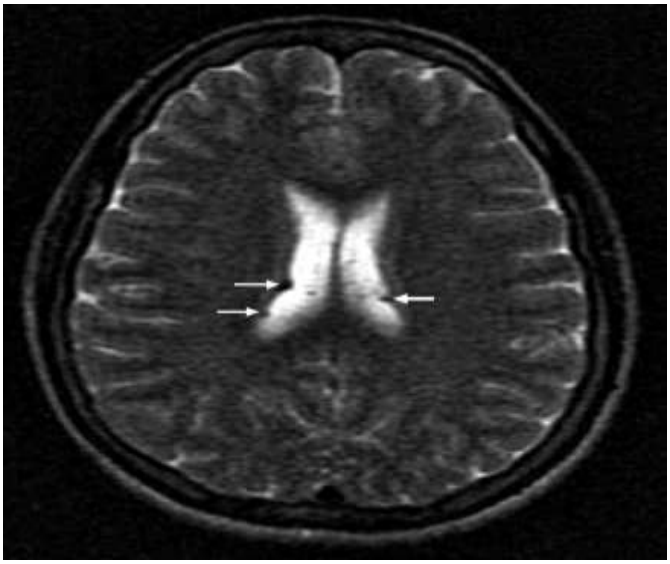

Figure 2: Axial T2-Weighted brain MRI showing multiple subependymal hypointense foci (arrows) due to subependymal tubers in the walls of the lateral ventricles.

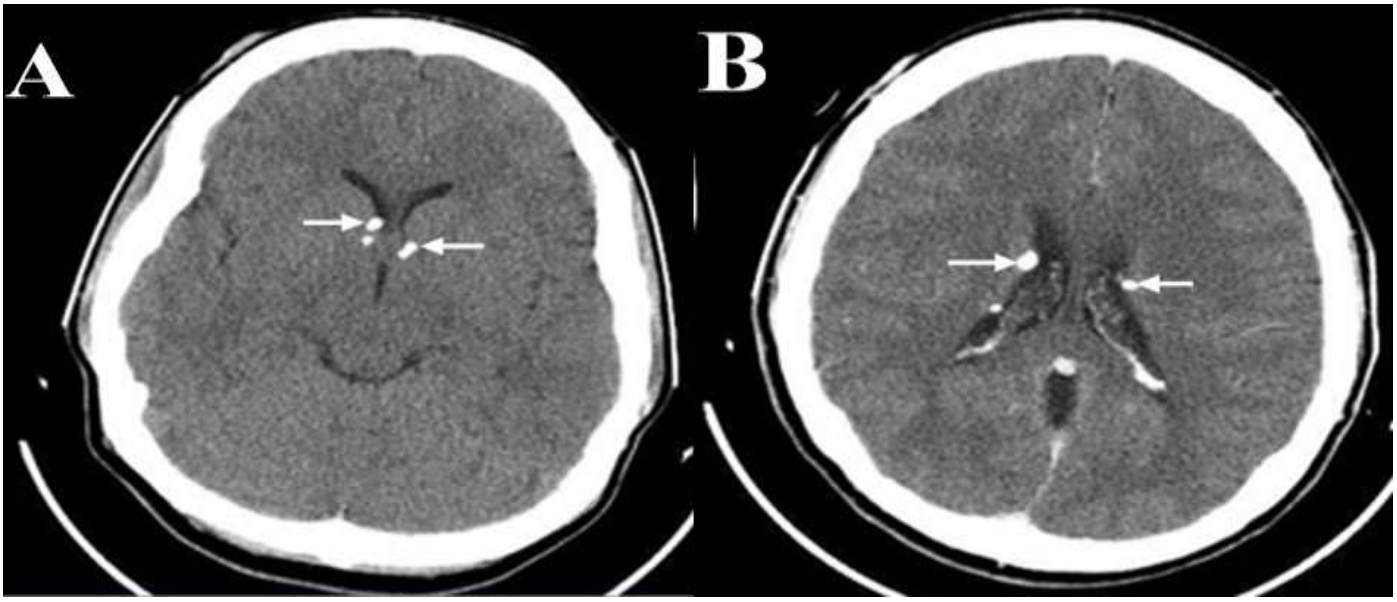

Figure 3: Axial CT at the level of the frontal horns (A) and bodies of the lateral ventricles (B) showing multiple calcified subependymal tubers (arrows).

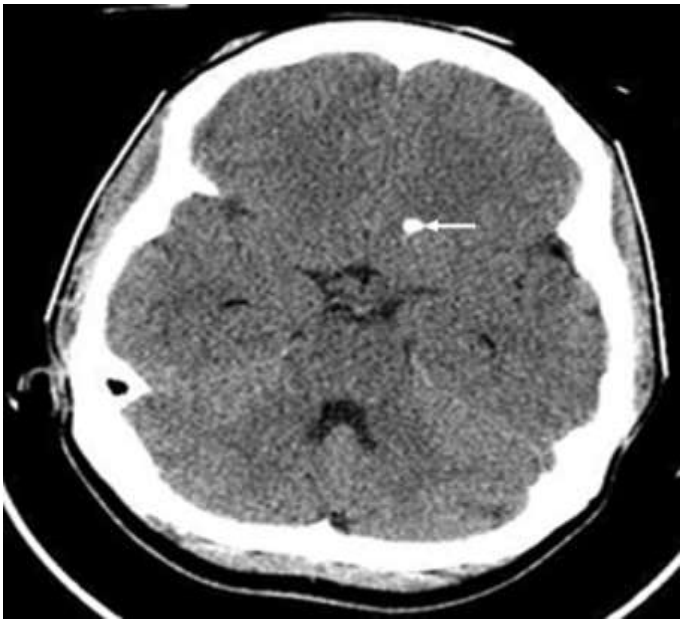

Figure 4: Axial CT at the level of the fourth ventricle showing a calcified cortical tuber in the left frontal lobe (arrow).

DISCUSSION

Five major features (cutaneous angiofibromas, Shagreen's patches, hypopigmented macules, cortical tubers, and subependymal tubers) were present in the index patient. There is a positive family history in 25 – 50% of TSC cases[3], but there was no family history in the index case.

Imaging plays a vital role in the diagnosis of tuberous sclerosis. MRI is the gold standard for evaluating the brain in suspected or diagnosed tuberous sclerosis, while CT is preferred for evaluating renal lesions.[10] The four common central nervous system (CNS) manifestations of TSC seen on cross-sectional neuroimaging are cortical tubers, subependymal nodules, subependymal giant cell astrocytomas (SEGCA), and white matter abnormalities.[6] Only cortical and subependymal tubers were seen in the index patient.

Cortical tubers correlate with the neurologic manifestations of TSC, including seizures, cognitive impairment, and neurobehavioral dysfunctions. Presence of diffuse cortical tubers tend to cause more cognitive impairment and more intractable seizures.[6] On CT, subependymal nodules are seen as multiple small foci with dense calcification along the lateral ventricles bilaterally.[6] MRI can demonstrate the presence of cortical hamartomas, white matter abnormalities, and subependymal nodules in the brain as early as six weeks of age.[1]

Subependymal nodules are hamartomatous change in the subependymal tissue of the lateral ventricles and usually occur as multiple nodules.[6] They are found anywhere along the surface of the ventricles but are most frequent at the caudothalamic groove.[11] Subependymal nodules are T1-hyperintense and T2-iso-/hypointense. Subependymal nodules have no impact on the clinical severity of the disease.[6]

Subependymal giant cell astrocytoma (SEGCA), which comprises of proliferative astrocytes and giant cells, is seen in 1.7 - 26% of patients with TSC. Classically, SEGCA is located at the foramen of Monro, leading to obstructive hydrocephalus. The peak age of occurrence is 8-18 years.[6] They appear inhomogeneous on MRI and enhance avidly with intravenous gadolinium contrast.[10] MR spectroscopy of SEGCA reveals a high Choline/Creatinine and low N-Acetyl Acetate/Creatinine ratios, which may help to distinguish them from subependymal nodules. SEGCA (>1 cm) is usually larger than subependymal nodules, and enhances more avidly.[6]

White matter abnormalities in TSC include cortical tubers-related superficial white matter abnormalities, cyst-like white matter lesions, and radial white matter bands.[6] They are seen as straight or curvilinear radial cerebral bands, wedge-like abnormalities, cerebellar radial bands, and non-specific conglomerate lesions.[10] On T1-weighted images, white matter lesions in older children and adults are usually iso-/hypointense to white matter; and on T2-weighted images, they are hyperintense to both gray matter and white matter. Very few white matter lesions enhance with contrast.[10]

The infrequent CNS findings include mild lateral ventricular dilatation due to atrophy/dysgenesis, brain infarction, cerebellar atrophy, intracranial aneurysm, corpus callosum dysgenesis, Chiari malformation, macrocephaly, microcephaly, arachnoid cyst, chordoma, and neurofibromatosis.[6]

Renal affectation of TSC includes angiomyolipoma (seen in 55-75% of patients), renal cell carcinoma, and renal cysts.[6,10] The index patient could not afford abdominal and chest CT; however, abdominal ultrasound was normal.

Brain Single-photon emission CT (SPECT) can help to detect hyperperfusion of an epileptogenic seizure focus during the ictal phase of seizures, which can be valuable for guiding selective resection of epileptogenic tubers.[10] PET-MRI imaging can localize tubers, which appear hypometabolic. A tuber with a significantly wider region of hypometabolism relative to its size on MR images is most definitely epileptogenic.[11] PET imaging using C-11 alpha-methyl tryptophan (C-11 AMT) can also help localize tubers acting as seizure foci.[10]

The prevalence of epileptic seizures in patients with tuberous sclerosis complex (TSC) is 62 – 93%.[12] Various types of seizures can occur and coexist in TSC patients. Focal seizures and infantile spasms (more prevalent in patients with TSC 2 mutation) are quite common.[12] Since the treatment of tuberous sclerosis is primarily geared towards the management of symptoms induced by hamartomas and avoidance organ failure[7], early identification and control of seizures is paramount.[13] Optimal seizure control is associated with reduced levels of intellectual disability.[14] The current first-line therapy for TSC is pharmacologic management (prophylactic or therapeutic) of seizures using Vigabatrin, adrenocorticotropic hormone, or rapamycin inhibitors.[14] Surgically suitable patients could also undergo resection of epileptogenic glioneuronal hamartomas. Palliative surgery (corpus callostomy or vagus nerve stimulation) is useful in patients with refractory seizure who are ineligible for hamartoma resection. Finally, ketogenic diet (because ketone bodies have anticonvulsant properties) is an ancillary tool for the management of intractable seizures.[14] Medical treatment of neurocognitive disorders in TSC involves the use of mTOR inhibitors (e.g., everolimus and sirolimus). Everolimus has shown promise for improving recall memory and executive function in TSC patients with such neurocognitive deficits.[15]

TSC is a lifelong condition. Life expectancy varies with the severity of disease manifestation.[2] Thirty percent of patients die by age five while 75% are dead by age 20.[3] (Patients with mild disease may survive until their 5th or 6th decades of life. The index patient is 24 years old and has been stable on anticonvulsant therapy. The relatively unique feature of this case is the seeming/apparent

asymptomaticity of the disease from the age of 6 years until the age of 24 years (An 18-year interval).

CONCLUSION

TSC is diagnosed based on clinical and radiologic findings. Imaging is necessary for comprehensive evaluation, determining the extent of disease, non-invasive localization of epileptogenic tubers for surgical resection, and overall follow-up/monitoring/surveillance for complications. Adequate control of seizures and prevention of organ failure are the cornerstone of management. Vigabatrin and rapamycin inhibitors are the current first-line pharmacologic agents for seizure control, while mTOR inhibitors like everolimus and sirolimus are the drug of choice for treating neurocognitive abnormalities. This case report underscores the importance of a high index of suspicion, as well as the place of a thorough physical examination in patients presenting with any of the components of Vogt's triad.

Conflict of interest

None

Ethical approval

Not applicable

REFERENCES

1. Mostafa K, Rasul C, Baruri N, Sultana R. Tuberous sclerosis misdiagnosed as epilepsy. *Bang Med J Khulna*. 2013;46:31–33.
2. Ishii M, Asano K, Kamiishi N, Hayashi Y, Arai D, Haraguchi M. Tuberous sclerosis diagnosed by incidental computed tomography findings of multifocal micronodular pneumocyte hyperplasia: A case report. *J Med Case Rep*. 2012;6:352.
3. Dahnert W. Tuberous sclerosis. In: Dahnert W, ed. Radiology review manual. 7th ed. Philadelphia: Lippincotts Williams & Wilkins; 2011:333–335.
4. Curatolo P, Moavero R. mTOR Inhibitors in Tuberous Sclerosis Complex. *Curr Neuropharmacol*. 2012;10(4):404–415.
5. Polchi A, Magini A, Meo DD, Tancini B, Emiliani C. mTOR Signaling and Neural Stem Cells: The Tuberous Sclerosis Complex Model. *Int J Mol Sci*. 2018;19(5):1474.
6. Umeoka S, Koyama T, Miki Y, Akai M, Tsutsui K, Togashi K. Pictorial Review of Tuberous Sclerosis in Various Organs. *Radiographics*. 2008;28(7):e32.
7. Portocarrero LKL, Quental KN, Samorano LP, de Oliveira ZNP, Rivitti-Machado MC da M. Tuberous sclerosis complex: review based on new diagnostic criteria. *An Bras Dermatol*. 2018;93(3):323–331.
8. Wataya-Kaneda M, Uemura M, Fujita K, Hirata H, Osuga K, Kagitani-Shimono K, et al. Tuberous sclerosis complex: Recent advances in manifestations and therapy. *Int J Urol*. 2017;24(9):681–691.
9. Radhakrishnan R, Verma S. Clinically Relevant Imaging in Tuberous Sclerosis. *J Clin Imaging Sci*. 2011;1(2):39.
10. Greenspan B, Jordan L, Glasier C, Coombs B, Krasny R, Smirniotopoulos J. Tuberous Sclerosis Imaging: Practice Essentials, Radiography, Computed Tomography. Available from: https://emedicine.medscape.com/article/385549-overview#showall. Accessed May 11, 2020.
11. Kalantari B, Salamon N. Neuroimaging of Tuberous Sclerosis: spectrum of pathologic findings and frontiers in Imaging. *Am J Roentgenol*. 2008;190(5):W304–W309.
12. Nabbout R, Belousova E, Benedik MP, Carter T, Cottin V, Curatolo P, et al. Epilepsy in tuberous sclerosis complex: Findings from the TOSCA Study. *Epilepsia Open*. 2018;4(1):73–84.
13. Słowińska M, Jóźwiak S, Peron A, Borkowska J, Chmielewski D, Sadowski K, et al. Early diagnosis of tuberous sclerosis complex: a race against time. How to make the diagnosis before seizures? *Orphanet J Rare Dis*. 2018;13(1):25.
14. Wang S, Fallah A. Optimal management of seizures associated with tuberous sclerosis complex: current and emerging options. *Neuropsychiatr Dis Treat*. 2014;10:2021–2030.
15. Randell E, McNamara R, Davies DM, Owen-Jones E, Kirby N, Angel L, et al. The use of everolimus in the treatment of neurocognitive problems in tuberous sclerosis (TRON): study protocol for a randomised controlled trial. *Trials*. 2016;17:398.