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Case Report

Case report on tuberous sclerosis: a rare cause of seizure

Kathir Nilavan Prahalathan[1]*, Sowmika Sureshkumar[1], Preethi Putti Reddy Subramani Reddy[1], Nawaf Abdulla[1], Divya Venkatesan[1], Balakrishnan Ramasamy[2]

[1]Department of Pharmacy Practice, PSG College of Pharmacy, Coimbatore, Tamil Nadu, India
[2]Department of Neurology, PSG College of Pharmacy, Coimbatore, Tamil Nadu, India

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***Correspondence:**
Dr. Kathir Nilavan Prahalathan,
E-mail: kathirnilavandev99@gmail.com

ABSTRACT

We report a case of tuberous sclerosis in a 19 years old teenage patient with generalized tonic-clonic seizure. MRI brain showed linear CSF filled structure with surrounding gliosis extending from the frontal horn of right lateral ventricle to the pial surface of right frontal lobe-postoperative change. Multiple small T2/ FLAIR hyper-intensities without diffusion restriction in bilateral frontal temporal parietal and left occipital lobes, predominantly involving the cortex and sub-cortical white matter and small focus of calcification in left parietal peri-ventricular white matter. He was treated with valproic acid, sodium valproate and levetiracetam and showed prompt improvement. Epilepsy in tuberous sclerosis complex is a group of genetic disorders manifesting in childhood. Secondary causes of tuberous sclerosis should be suspected when there is abrupt onset in adulthood. The case highlights an uncommon case of epilepsy in tuberous sclerosis in young adult patient.

Keywords: Tuberous sclerosis, Seizures, Adenoma sebaceum, Shagreen patches

INTRODUCTION

The tuberous sclerosis complex (TSC) is one of the hereditary causes of epilepsy. Epilepsy in TSC is characterized by early onset, a variety of seizure patterns, and intractability.[1] The progression of seizures in adults with TSC is poorly understood. In majority of the cases, the prevalent neurological symptom of TSC is seizures, which affect more than 80% of TSC patients.[2] They are most common in infancy and childhood, but they can also begin in adults. Seizures persist in a substantial number of patients after pharmacological and surgical treatment, making management difficult. This report summarizes the clinical recommendations for the management of TSC-associated epilepsy.

CASE REPORT

A 19-year-old male from a southern district in Tamil Nadu was presented with the history of generalized tonic-clonic seizure (GTCS) followed by loss of consciousness and presence of hyper pigmentation papules in bilateral face. He had 2 episodes of GTCS two days before hospital admission. There was no family history of epilepsy. In past, he had multiple hospital admissions for the same reason and was on antiepileptic drug since the age of seven years with poor adherence. In view of the history of GTCS and cutaneous findings, he underwent further evaluation to identify the aetiology. Patient interview was done which revealed the following details. At five years of age, he had head injury and treated with cold compression. At seven years of age, patient showed symptoms like sudden unresponsiveness and starring for

which he consulted government hospital at Bangalore and was diagnosed to have a clot in frontal horn of right ventricle. He underwent intracranial surgery to remove the clot (Figure 1). Post-operative status showed he was normal with no symptoms. At the age of seventeen, he gradually started showing symptoms like body stiffness, tiredness, unconsciousness, fainting and development of papules all over the face (under the nose, near the eyes and ears) and at posterior portion of the trunk. At present, he came with the complaints of GTCS followed by loss of consciousness and hyper pigmentation papules in Neurology Department in PSG Hospitals. He was diagnosed to have tuberous sclerosis complex (TSC). On investigation the patient's parameters, his hematological investigations were found to be satisfactory except for increased eosinophils is 14.5% (normal =1-6%). He underwent further evaluation of Thyroid function test, liver function test and renal function test which showed to have no abnormal findings.

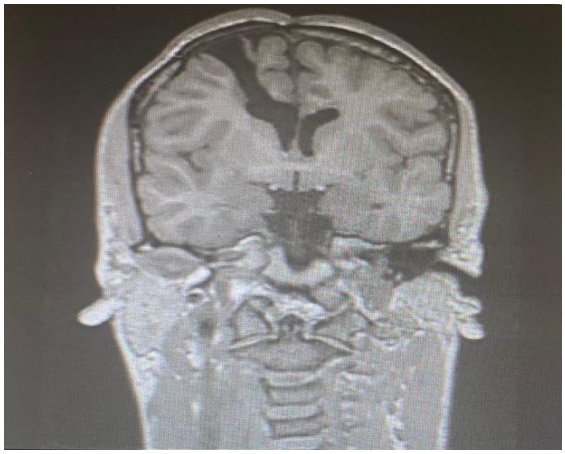

Figure 1: Post MRI report of patient underwent intracranial surgery.

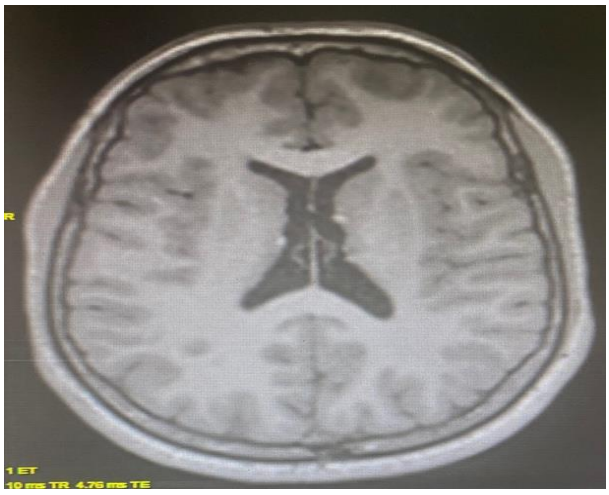

Figure 2: MRI scan of brain indicate bilateral cortical tubers.

MRI scan of the brain was done using T1, T2, Fluid attenuated inversion recovery (FLAIR) axial, T1 sagittal; T2 (transverse relaxation time) coronal diffusion, Apparent diffusion coefficient (ADC) and Susceptibility weighted imaging (SWI) axial sequences. The study reveals the following findings showing that Linear CSF filled structure with surrounding gliosis extending from the frontal horn of right lateral ventricle to the pial surface of right frontal lobe-Postoperative change, multiple small T2/FLAIR hyper-intensities without diffusion restriction in bilateral frontal temporal parietal and left occipital lobes, predominantly involving the cortex and sub-cortical white matter and small focus of calcification in left parietal peri-ventricular white matter (Figure 2). So finally suggesting that the features are likely to represent Tuberous sclerosis with possible cortical tubers and white matter changes. USG abdomen and ECHO showed no significant abnormalities.

Diagnostic criteria for TSC is as given in Table 1. Definite TSC can be made when two major or one major plus two minor features are demonstrated. Dermatologist opinion was sorted out and our patient was found to be having 3 major criteria-adenoma sebaceum which involves papules in a butterfly pattern across the bridge of the nose and cheeks (Figure 3B) and nasolabial folds and chin. Hypomelanotic macules along with Shagreen patches were seen over the posterior trunk of the body (Figure 3A). With the clinical features and imaging findings fulfilling the clinical diagnostic criteria for tuberous sclerosis, the final diagnosis was established.

Table 1: Updated diagnostic criteria for tuberous sclerosis complex 2012.

Major criteria	Minor criteria
Hypomelanotic macules (≥3, at least 5 mm diameter)	"Confetti" skin lesion
Angiofibromas (≥3) or fibrous cephalic plaque	Dental enamel pits (>3)
Ungual fibromas (≥2)	Intraoral fibromas (≥2)
Shagreen patch	Retinal achromic patc
Multiple retinal hamartomas	Multiple renal cysts
Cortical dysplasias	Nonrenal hamartomas
Subependymal nodules	
Subependymal giant cell astrocytom	
Cardiac rhabdomyoma	
Lymphangioleiomyomatosis	
Angiomyolipomas (≥2)	
Definite diagnosis: Two major features or one major feature with ≥ 2 minor features; Possible diagnosis: Either one major feature or ≥ 2 minor features; *Includes tubers and cerebral white matter radial migration lines; A combination of the two major clinical features (LAM and angiomyolipomas) without other features does not meet criteria for a definite diagnosis.	

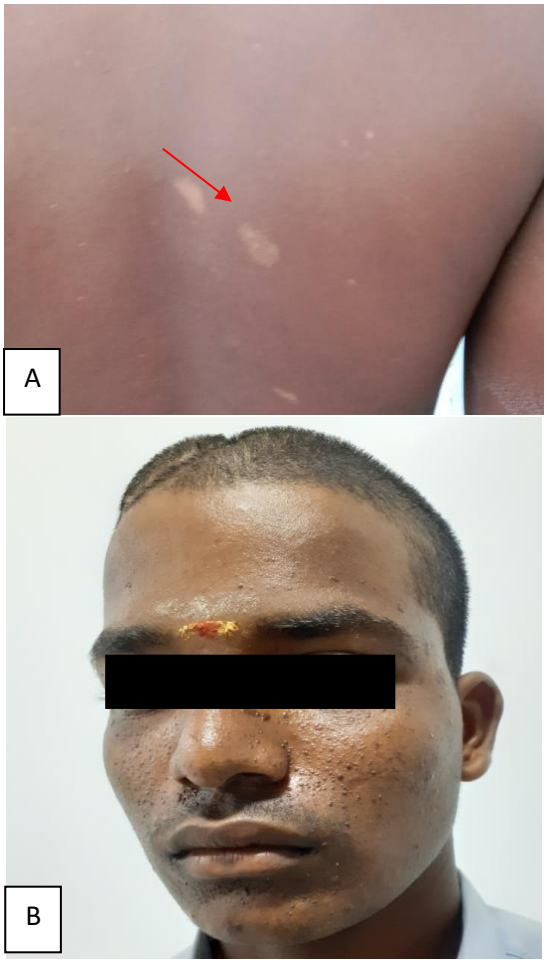

Figure 3: (A) Hypomelanotic Macules and (B) Adenoma Sebaceum (angiofibroma).

DISCUSSION

In children, the onset of Seizures usually has an identifiable aetiology like trauma, central nervous system (CNS) infections, space-occupying lesions, cerebro-vascular accidents (CVA), metabolic disorders, and drugs. In this case, patient had an etiological history of trauma in early childhood, due to which he developed Tuberous Sclerosis in his early adulthood life. Even though briefly many types of seizures were associated with TSC, like infantile spasm, tonic-clonic, focal, simple, complex, simple partial and epileptic spasms, and our patient has experienced generalized tonic clonic seizure and absence seizure. Treatment of seizures in tuberous sclerosis complex is similar to that of epilepsy from other causes, and anticonvulsant medications are the mainstay of treatment. Predominantly seizure management in TSC involves vigabatrin as the first choice of drug.[2] As a matter of fact, treatment of seizures in TSC is similar to that of epilepsy from other causes. Topiramate, lamotrigine, oxacarbazepine, and levetiracetam have all been found to be effective and well tolerated in small populations of individuals with TSC and epilepsy, but evidence supporting the use of other agents are comparatively negligible.[6]

In this case valproic acid was the drug of choice. The dose of antiepileptic drugs (levetiracetam, sodium valproate and valproic acid) was adjusted accordingly with the control of seizure. Injection Valproate 1 gram was started and dose was tapered to 500 mg during the patient's hospital stay. Combination of sodium valproate (200 mg) and valproic acid (87 mg) was added to the regimen. Injection levetiracetam 500 mg was given as a BD dose to control seizures.

Tuberous sclerosis complex (TSC) is an autosomal dominant disorder of cellular differentiation and proliferation with multiple system involvement.[8] The reported incidence is 1 case per 6,000 live births with no sexual or ethnic preponderance.[4] The underlying cause is the mutation in TSC1 (encoding hamartin) or TSC2 (encoding tuberin) which act as tumour growth suppressors regulating proliferation and differentiation. Diagnosis can be made by either the genetic or clinical criteria. TSC cannot be excluded by conventional genetic testing as it does not identify mutations in 10-25% cases of TSC. The index case was diagnosed as a definite case of tuberous sclerosis based on the clinical criteria.

Hake in the study on cutaneous manifestations of tuberous sclerosis observed that ash-leaf spots (hypopigmented macules) are the most common manifestation present in about 90% cases of TSC. Ungual fibroma, found in about 50% cases, is highly suggestive of TSC.

The cutaneous manifestations found in this case were ash leaf spots, facial angiofibromas, Shagreen patches, cortex and sub cortical tubers. Cases of TSC vary considerably in their manifestations and clinical findings.

The classical Vogt's triad of TSC i.e., skin lesions, mental retardation and seizures is present in about one-third of patients. Seizures present early and usually occur before 2 years of age. Zaroff et al, in their study noted a significant correlation between bilateral cortical tubers and age of onset of seizures with mental retardation.[5] The present case had bilateral cortical tubers but did not have any kind of mental retardation. Conventionally, TSC is accompanied by lower level of IQ (decreased cognition), however that is untrue in this case.

Radiological findings of Tuberous sclerosis include calcification seen on skull X-ray in about 50% of cases. Periventricular sub-ependymal nodules, parenchymal hamartomas or cortical tubers, ventriculomegaly are frequently noted in MRI and CT scans. Sub- ependymal giant cell astrocytomas can also be seen but are rare. The MRI Brain of this case had showed Linear CSF filled structure with surrounding gliosis extending from the frontal horn of right lateral ventricle to the pial surface of right frontal lobe-Postoperative change. Multiple small T2/ FLAIR hyper-intensities without diffusion restriction in bilateral frontal temporal parietal and left occipital lobes, predominantly involving the cortex and

sub-cortical white matter and small focus of calcification in left parietal peri-ventricular white matter. Tubers are the hallmark of TSC. They are present in 80-95% of children with TSC and can be either cortical or subcortical.[3,4]

Table-2: Supratentorial and infratentorial brain lesions.

Supratentorial	Infratentorial
Cortical/subcortical tubers Subependymal nodules Subependymal giant cell astrocytoma White matter (~ 30%): linear migration lines, "cystlike" lesions Corpus callosum agenesis/dysplasia Transmantle cortical dysplasia Association with: • Hemimegalencephaly • Schizencephaly • Intracranial arterial aneurysms (60%) • Intracranial moyamoya vasculopathy	Linear and gyriform cerebellar folia calcification Cerebellar nodular white-matter calcifications Cerebellar hemisphere/vermis agenesis and hypoplasia Cerebellar hemisphere enlargement Brain stem/fourth ventricle subependymal nodules and tubers
More than 95% of patients with tuberous sclerosis complex will demonstrate at least one of the lesions listed in Table 2.[5]	

Tuberous sclerosis may also have renal, cardiac and pulmonary involvement. Renal problems are very frequent in patients with TSC. The present case had no evidence of renal angiomyolipoma or renal symptoms. Pulmonary manifestations like spontaneous pneumothorax and haemoptysis are associated with poorer outcomes.

Regular fundoscopic examination is recommended as TSC is associated with visual impairment due to retinal detachment, vitreous haemorrhage and associated complications. A thorough evaluation did not reveal any such organ involvement in this case.

He had sleeping difficulty for which he was given with injection lorazepam 2 mg and retino-A cream 0.025% (local application on face) was given at night for angiofibroma. On discharge, 300 mg of oral valparin chrono and oral levetiracetam was given.

CONCLUSION

One of the most intriguing and challenging aspects of TSC is the occurrence of correlated epileptic seizures such that numerous attempts are now being made for better understanding as well as to enhance treatment. Managing seizures in TSC is important as it improves quality of life thus helps in living a hassle-free life. Epilepsy in TSC can be a lifelong disorder, but one-third of individuals become free from seizure by diagnosing at early adulthood. New research reveals that children with tuberous sclerosis who are extremely likely to become seizure-free can be identified non-invasively. Early control of seizures has a crucial role in preventing subsequent epileptic encephalopathy, and in reducing the cognitive/behavioural consequences of seizures, but does not guarantee for a normal mental outcome in children with TSC. Further investigation incorporating additional neuro-imaging factors, antiepileptic treatment effects, and genetic variables, is needed. Targeting seizure prevention or controlling it, is likely to provide the best opportunity for improving long-term developmental outcome in at-risk patients with TSC.

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