# TUBEROUS SCLEROSIS COMPLEX: A CASE OF RESISTANT SEIZURES

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## ABSTRACT

Tuberous sclerosis complex (TSC) is an autosomal dominant condition caused by genetic mutations at two loci i.e TSC1 on chromosome 9, and TSC2 on chromosome 16. Hamartomas in multiples systems is the hallmark of the disease. The three most striking features of the disease are learning disability, epilepsy, and skin lesions but there is a wide array of clinical manifestations in multiple systems apart from these. Skin changes include hypopigmented macules(ash leaf spots) in early childhood, yellowish pink papules in mid face known as adenoma sebaceum (AS) in adolescence, periungual and subungual fibromas, and connective tissue naevi(shagreen patch) on the lower back. Enamel pits, gingival hyperplasia, renal cysts, cerebral gliomas, calcified basal ganglia, lymphangioleiomyomatosis of lung, retinal phakomas and heart tumors are some of the other features. Here, we now present a case of 20 year old female with tuberous sclerosis having characteristic clinical and radiological features.

**Key Words:** Tuberous sclerosis complex (TSC), Adenoma sebaceum (AS), Hamartoma

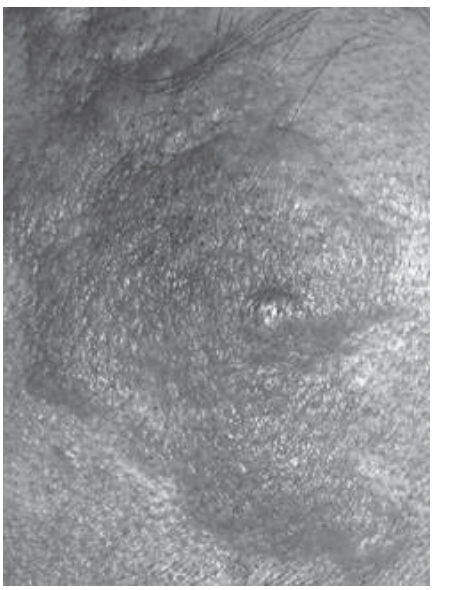
## INTRODUCTION

Tuberous sclerosis complex (TSC) is a rare autosomal dominant multisystem disease caused by inactivating mutation in either TSC1 gene on chromosome 9 encoding hamartin or TSC2 gene on chromosome 16 encoding tuberin.[1] Both the proteins are tumor suppressors. The prevalence of disease is round about 10/100000 in general population. Von Recklinghausen was the first to describe the disease in 1862.[2] The pathologic brain lesions were first described by Désiré-Magloire Bourneville in 1880 and termed "sclerose tubereuse"(tuberous sclerosis). Since the disease has various manifestations outside the brain, therefore the term "tuberous sclerosis complex" is preferred to describe the disease.[3]

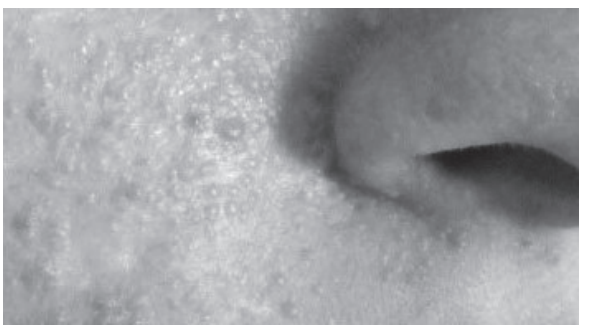
Disease is classified amongst the neurocutaneous syndromes. A case of 20 year old female with tuberous sclerosis is presented here with the consent of the patient and her parents.

## CASE REPORT

A 20 year old female patient presented to our ER on 15th January, 2018 with multiple episodes of generalized tonic seizures from the past 5 days. She was a diagnosed case of TSC from 2 years of age. She was on sodium valprote 250mg P/O BD right from childhood which had significantly controlled her fits. She used to have 4-5 episodes/day of myoclonic fits persistently over the years that were well tolerated. From past 5 days, her condition deteriorated significantly to the extent that the frequency of seizures increased to about 20-25 episodes/day and the nature of the fits changed



Forehead plaque



Adenoma Sebaceum

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from myoclonic to generalized tonic clonic seizure. She was admitted and sodium valproate dose was increased to 500mg PO BD. She was also put on Inf Ringer lactate 1L IV BD for her dehydration. She was closely observed and remained symptoms free for a period of about 10 hours.

During this period a detailed history was taken from her mother. According to her, the patient was quite lethargic and drowsy at birth. She wasn't as playful as other children of her age. At 2 years of age she began having eyesight problem. She couldn't reach a glass of water at about 2 feet distance. Two weeks later she started having seizures with a frequency of 3-4 times per day. Each episode lasted for about 1-2 minutes. With the onset of seizures her eyesight problem resolved according to the mother. She was taken to hospital where she got admitted for observation. Seizures were documented as of myoclonic type. All the necessary investigations were done and she was diagnosed as a case of TSC. She was started on Syp valproate 250mg/5ml 1.5TSF BD PO and Clonazepam 3 drops TDS. Her seizures frequency reduced to about 1 or 2 times per day and duration of each episode was from 30-45 seconds. Prognosis was explained to the parents and she was discharged on these medications with advice to stop Clonazepam after 3 months.

She was maintained on valproate life long with a slight change in formulation from syrup to tablets as her age increased until she presented to us with a significant increase in her seizures frequency and intensity. During all these years, she was quite a functional child helping her mother in home chores but her mental development didn't keep pace with her physical growth. She couldn't carry on her studies and was dropped out of school after just 1 year.

We also carried out a thorough examination and findings are presented now. She has pink papules bilaterally in the malar region suggestive of adenoma sebaceum (AS). She also has a large forehead plaque that has been removed twice but has recurred. Her mother reports her having had hypopigmented areas of skin in the past but currently no such lesions can be appreciated. She is having a large leathery lesion on her lower back which has orange peel appearance characteristic of shagreen patch. There are no peri or subungual fibromas. Oral examination was unremarkable. There were no other significant findings on systemic review.

All the baseline investigations were sent which came out to be normal. MRI brain with and without contrast was run which showed enhansing subependymal nodule in the frontal horn of the right lateral ventricle on post contrast T1-axial sequence. In addition bands of high T1 and T2/Flair signal were visualized bilaterally in the cortical and subcortical regions of the frontal lobes. Ultrasonogram abdomen was done which showed incidental gall bladder stones with biliary sludge. CXR was normal.

About ten hours after admission she suffered an intense episode of generalized tonic clonic seizure which was difficult to resolve. She was given sodium valproate 500mg in 100ml pladex IV stat, and diazepam 100mg in 500ml pladex at 40ml/hr IV stat. This resolved her seizure episode. After 2 hours, diazepam was discontinued. Her oral valproate dosage was replaced with intravenous sodium valproate 500mg TDS. In addition, levetiracetam 250mg P/O BD was also initiated. Her seizures resolved. She remained under observation for 3 days during which no seizure was documented. She was then discharged on oral valproate 500 mg TDS and levetiracetam 250mg BD.

## DISCUSSION

TSC is a complex disease having a wide range of clinical manifestations. Hamartomas in multiple organs is the hallmark of this disease. It usually manifests as a classic triad of epilepsy, learning problems and skin lesions but has a varied presentation in addition to this. [4] AS, an angiofibroma and not related to excess sebum, is the most prominent skin lesion. Other prominent lesions are:

- Shagreen patch( connective tissue nevus on trunk)
- Ungual or periungual fibromas
- Subependymal nodules and subependymal giant cell astrocytoma (commonest brain tumor) [5]
- Hypomelanotic macules at least 5mm in size
- Forehead plaque( fleshy indurated patch)
- All of the above lesions have been classified as major criteria for the diagnosis. Some of the minor criteria are as follows:
- Enamel pits at least 3
- Gingival hyperplasia( Fibromas)
- Multiple renal cysts

For diagnosis, at least 2 major criteria, or 1 major and 2 minor criteria should be met. Our patient meets 3 major criteria; Shagreen patch, subependymal nodule, AS and forehead plaque thus her level of diagnostic certainty is definite.

Management of TSC involves multiple modalities including pharmacotherapy, surgery and other interventions. Sirolimus can be used topically to treat facial angiofibromas since it has got better topical absorption than everolimus.[6] Vigabatrin and adrenocorticotropic hormone have been approved in 2009 and 2010 respectively to treat infantile spasms. Everolimus and Sirolimus can be used to treat subependymal giant cell astrocytomas and renal angiomyolipomas but everolimus has undergone more extensive study in treating SEGA.[7] Data on long term use of mTOR inhibitors has

so far been unable to reveal any additional adverse effects than short term therapy[8] thus its long term use can be incorporated in clinical practice in the years to come. Before pharmacotherapy, SEGAs were treated with surgical resection.[9] Angiomyolipomas with acute haemorrhage can be managed with embolization. Neurosurgical intervention may reduce the severity and frequency of seizures in TSC patients. For intractable epilepsies, a ketogenic diet may be of some benefit.

Prognosis of the disease depends on the severity of symptoms. Earlier age of seizures commencement has been associated with poor seizure control according to a study done in Egypt.[10] Higher tuber numbers and left hemispheric location is associated with poor outcome. Major causes of mortality in TSC are renal disease, brain tumors, lymphangioleiomyomatosis of the lung and status epilepticus. LMA is only a risk factor for females with angiomyolipomas.[11]

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