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**Case Report**

# An interesting case of tuberous sclerosis without cutaneous manifestations presenting with only neurological features

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## ABSTRACT

Tuberous Sclerosis Complex (TSC) is a neurocutaneous disorder characterised by hamartoma formation in multiple organs, particularly the skin, brain, eye, kidney and heart. It is rare for TSC to manifest as intractable seizures without cutaneous manifestations. Targeted history elicitation along with appropriate systemic examination backed by proper investigations in high index of suspicion is mandatory to diagnose a case of TSC in such scenario. We report such a case where a 27 year old male was diagnosed with TSC following admission with refractory seizures.

**Keywords:** Tuberous sclerosis complex, Refractory seizures

## INTRODUCTION

Tuberous sclerosis complex is a neurocutaneous disease characterised by diverse dermatological manifestations like angiofibromas, periungual fibromas (Koenen's tumour), shagreen patch and leaf macules, fibromatous plaque along with neurological features like as seizures, mental retardation and behavioural disorders. TSC can rarely present with isolated neurological features like seizures without cutaneous features. It is to be remembered that other features may develop later in life.

## CASE REPORT

A 27-year old male, born to nonconsanguineous parents, presented to the emergency with generalized tonic-clonic seizures for last 3 hours. He had no history of substance abuse or prior head trauma. He was managed as a case of status epilepticus in the ICU. Further history was revealed that he was suffering from convulsions for last 8 years. He was on 4 different medications but he required multiple hospital admissions. Similar complaints were reported to be found in his father and paternal grandmother. He also had a history of learning difficulty since childhood. He had developed 2 episodes of pneumothorax in the past although he was a non-smoker. A high suspicion of TSC was made. However, dermatological examination did not reveal any angiofibromas over face or shagreen patches over lumbosacral region or fibrous plaque over forehead or achrocordons over axilla. Woods lamp examination also did not show Ash-leaf macules over the back. Koenen's tumour (periungal fibroma) was not present. But fundus examination showed multiple retinal hemartomas although no radial lens opacities.

Routine laboratory investigations revealed normocytic, normochromic anemia (Hb - 10.1 g%). Liver function tests and renal function tests were normal. Urine routine examination was normal. Ultrasound examination did not reveal polycystic ovarian disease, renal angiomyolipomas, and renal cyst. CT brain showed calcified sub ependymal nodules around lateral ventricles. Chest X-Ray was normal but High Resolution CT (HRCT) showed Lymphangioleiomyomatosis (LAM). A final diagnosis of TSC without cutaneous features was made. Patient party was explained about the

disease course and nature and need for follow-up. Patient was discharged in stable condition after 12 days.

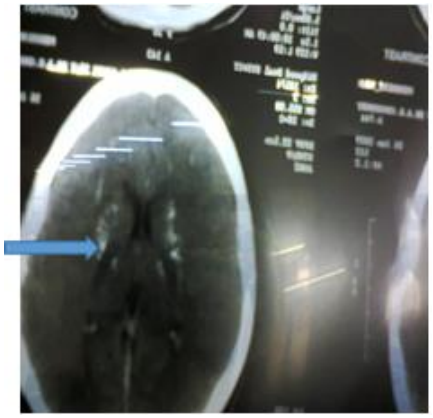

**Figure 1: Showing calcified sub ependymal nodules around lateral ventricles.**

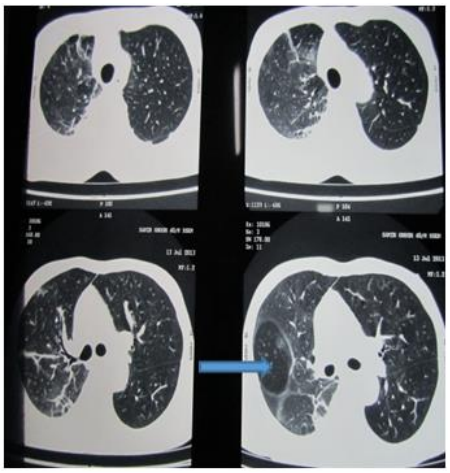

**Figure 2: Showing lymphangioleiomyomatosis (LAM) on HRCT.**

## DISCUSSION

Tuberous sclerosis was first recognised as a specific disease in the 19th century. In 1818, Bourneville, a French neurologist reported the case of a mentally retarded child with hemiplegia and epilepsy. Tuberous sclerosis complex (TSC) is an autosomal dominant disorder with high penetrance and extensive clinical variability; two-third of cases are caused by de novo mutations and are the effects of parentral mosaicism.[1] TSC is characterized by the hamartoma formation in many organs, particularly the skin, brain, eye, kidney and heart.[1] TSC is caused by mutations in TSC1 (9q34) and TSC2 (16p13) genes coding for hemartin and tuberin, respectively.[2] These proteins act as tumour growth suppressors, agents that regulate cell proliferation and differentiation.[3] The incidence is around 1 in 10,000 live births. In 1908 Vogt proposed a triad typical for TSC diagnosis, consisting of epilepsy, low intelligence and angiofibroma.[2] TSC is an autosomal dominant genetic disorder characterized by hamartomas in many organs. The pathognomic skin lesions include angiofibromas, periungual fibromas (Koenen's tumour), shagreen patch and leaf macules. Other cutaneous manifestations include fibromatous plaque on forehead and scalp, soft pediculated fibromas around the neck and axilla and poliosis.[3] Cerebral lesions may manifest as seizures, mental retardation and behavioural disorders. Cardiac rhabdomyomas are observed in about half of the patients with TSC.[3] Angiomyolipomas are observed in 75% of the patients over 10 years of age. Other renal manifestations include renal cyst, renal cell carcinoma and polycystic kidneys. Retinal astrocyte hamartomas are present in patients with TSC and hamartomatous colonic polyps may also been seen.

TSC has a wide clinical spectrum. Definitive TSC is diagnosed with either 2 major (out of total of 11) or one major and 2 minor features (out of total of 9).[4]

Major features:

1. Facial Angiofibromas of forehead plaque
2. Non -traumatic ungual or periungual fibroma
3. Hypomelanotic macules ( >3)
4. Shaqreen patch (Connective tissue nevus)
5. Multiple retinal nodular hemartomas
6. Cortical tuber
7. Subependymal nodule
8. Subependymal giant cell astrocytoma
9. Cardiac rhabdomyoma, single or multiple
10. Lymphangio leiomyomatosis
11. Renal angiomyolipomas

Minor features:

1. Multiple randomly distributed pits in dental enamel.
2. Hamartomatous rectal polyps
3. Bone cysts
4. Cerebral white matter radial migration lines
5. Gingival fibromas
6. Non renal hemartomas
7. Retinal achromic patch
8. Confetti skin lesions
9. Multiple renal cyst

Our patient presented with three major features (Subependymal nodules, lymphangio leiomyomatosis and multiple retinal nodular hemartomas) but no minor features but a definitive diagnosis of tuberous sclerosis was still made according to criteria.

Treatment is mainly symptomatic with electrocautery for angiofibromas and antiepileptics for seizures.[5,6] An exciting new therapeutic option in TSC is rapamycin and its analogues. Rapamycin is an inhibitor of mTOR pathway and can normalize this unregulated pathway in a TSC patient. Studies have shown that rapamycin treatment reduces TSC- related tumours, including brain, skin and kidney tumours. It has also led to the regression

of such hamartomas. Systemic rapamycin treatment has been found to be an effective antiepileptic medication in cases of epileptogenic cortical dysplasias and has reduced seizures and cognitive defects in mouse models. It can thus guide new insight in future therapy of TSC.

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