

## A rare case report on Tuberous Sclerosis



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### ABSTRACT

Tuberous sclerosis is a neurocutaneous syndrome with an autosomal dominant inheritance. Tuberous sclerosis has an approximate incidence of one in ten thousand to fifty thousand. Tuberous sclerosis complex Syndrome (TSCs) is a dominantly inherited disorder affecting multiple organs; caused by mutations of either the *TSC1* or *TSC2* gene encoding hamartin and tuber in respectively. It is characterized by the development of benign tumors affecting different body systems. The most common oral manifestations of TSC are fibromas (angiofibromas), gingival hyperplasia and enamel hypoplasia and the formation of hamartomas in multiple organ systems leading to morbidity and mortality. It is important to make an early diagnosis of TSC so that lifelong monitoring, early recognition of complications and proactive treatment can lower the morbidity and mortality rates. We report a case of 35 year old female in south India with the features of Tuberous sclerosis complex like seizures, weakness of the body, papules over the cheek, calcification noted in subependymal region in the brain and angiomyolipoma in both kidneys.

**Key words:** Tuberous sclerosis, Tuberous sclerosis complex Syndrome, seizures, hamartomas, subependymal, angiomyolipoma

### INTRODUCTION

Von Recklinghausen first described tuberous sclerosis in 1862. Desire- Magloire Bourneville (a French physician) coined the term sclerosetubereuse, from which the name of the disease has evolved. Sherlock coined the term EPILOIA encompassing the clinical trial of tuberous sclerosis (Epi: epilepsy, Loi: low intelligence, A: adenoma sebaceum). As the manifestations of the disease are variegated in nature, the term Tuberous Sclerosis Complex (TSC) is now widely used. It is an autosomal dominant neurocutaneous syndrome, characterized by the development of benign tumors such as neurofibromas and angiofibromas located anywhere in the body (skin, central nervous system, heart, kidneys etc). Patients with TSC present mutations of the *TSC1* and *TSC2* genes, which intervene in cell cycle regulation. This is a dominant autosomal hereditary disease, though 60- 70% of all cases are the result of spontaneous mutations.<sup>[1]</sup>

Tuberous sclerosis is a neurocutaneous syndrome with an autosomal dominant inheritance. Tuberous sclerosis has an approximate incidence of one in ten thousand to fifty thousand. The clinical trial of papular facial nerves, seizures and mental

retardation is found in less than half of the patient. Thus the radiological hallmarks of this neurocutaneous syndrome are universally accepted as sufficient for diagnosis.<sup>[2]</sup>

Tuberous Sclerosis or Tuberous Sclerosis Complex is a genetic disorder characterized by the growth of numerous benign tumours in many parts of the body; including the brain, heart, lungs, eyes, kidneys, skin and other organs, leading to significant health problems like seizures, intellectual disability, autism or developmental delay. TSC is caused by mutations on either of two genes, *TSC1* and *TSC2*, which encode for the proteins hamartin and tuberin respectively. These proteins act as tumour growth suppressors, agents that regulate cell proliferation and differentiation. The live-birth prevalence is estimated to be between 10 and 16 cases per 100,000. A 1998 study estimated total population prevalence between about 7 and 12 cases per 100 live births. TSC occurs in all races and ethnic groups, and in both genders. Tuberous sclerosis has no cure, but treatment as medicine, educational and occupational therapy can help relieve symptoms.<sup>[3]</sup>

Tuberous Sclerosis Complex manifests with variable signs and symptoms together with angiofibromas distributed in a characteristic “butterfly” pattern on the face and forehead. The most important neurological problems are mental retardation, seizures, autism and learning difficulties. The diagnostic criteria of TSC have been divided into major and minor features.<sup>[4]</sup>

### Diagnostic criteria of tuberous sclerosis complex (TSC)

#### Major features

- Facial angiofibromas or forehead plaque
- Nontraumatic ungual or periungual fibroma
- Hypomelanotic macules (>3)
- Shagreen patch (connective tissue naevus)
- Cortical tuber
- Subependymal nodule
- Subependymal giant cell astrocytoma
- Multiple retinal nodular hamartomas
- Cardiac rhabdomyoma, single or multiple
- Lymphangiomyomatosis
- Renal angiomyolipoma

#### Minor features

- Multiple randomly distributed pits in dental enamel
- Hamartomatous rectal polyps
- Bone cysts
- Cerebral white matter migration tracts
- Gingival fibromas
- Nonrenal hamartoma
- Retinal achromic patch
- Confetti skin lesions
- Multiple renal cysts

A molecular diagnosis is advised in patients at risk, in order to diagnose the disease before the actual symptoms appear. The most common oral manifestations of TSC are fibromas, gingival hyperplasia and enamel hypoplasia.<sup>[5]</sup> Other less frequent findings in the oral cavity are a high arched palate, bifid uvula, harelip and/or cleft palate, delayed dental eruption and the presence of diastemas.<sup>[6]</sup> Patients with TSC might have a delay in the diagnosis as some findings might be unrecognized during childhood by medical practitioners and some disease manifestations may not occur until adulthood. In the study of Seibert et

al, 56% of the patients were diagnosed in adulthood and two-thirds of these patients had symptoms in childhood.<sup>[7]</sup>

### CASE REPORT

A 35 years old female resident of Tirupati presented to the hospital through female general medicine department with the complaint of weakness of the body from 3 days and papules over the cheek from childhood. There was no preceding history of fever, cough, breathlessness, diarrhoea or fall. Not a known case of diabetes and hypertension.

Past history she was a known case of tuberous sclerosis and she was reported history of seizures 3 years back. She presented with one day history of generalized tonic-clonic seizures, each lasting for one minute, with a relaxation phase observed for 5-10 minutes. She did not regain consciousness in between. The seizures were associated with urinary incontinence, frothing, uprolling of eyeballs and tongue bite. She was on the treatment with the phenytoin sodium 300 mg per day in divided doses. On physical examination she was found to be conscious and coherent, vitals were stable. Physical signs include pallor present and there are no other physical signs like clubbing, pedal edema, lymphadenopathy.

Investigations showed normal study on Echo examination of the heart which means there is no abnormalities in the heart. CT examination in brain without contrast was done which showed calcification noted in subependymal region of bilateral ventricles, CT examination in abdomen was done which showed present of angiomyolipoma in both kidneys and CT examination in chest was showed normal study. No other laboratory examinations were done.

Summarizing her past history, extensive physical signs and investigations, the final diagnosis of Tuberous Sclerosis was made. She was taken treatment with phenytoin sodium tablets 300mg per day in divided doses, infusion fluids and vitamin supplements. On day 4 she had seizures generalized tonic-clonic type lasting for one minute, she was given with injection diazepam 10 mg in normal saline infusion along with phenytoin sodium. She remained seizures free for 6 days and was ultimately discharged on phenytoin sodium 300 mg per day in divided dose.

## DISCUSSION

Tuberous Sclerosis is an important genetic disorder that affects the patient and the family in various ways. Multiple research projects are being done around the world regarding further work up of the genes involved and treatment strategies.<sup>[8]</sup> Now, due to an understanding of its pathogenesis, multiple drug therapies are available for certain manifestations of the disease.<sup>[9]</sup> But the patient, along with symptomatic control of seizures, should also be offered special schooling, and occupational therapy. Surgery, including dermabrasion and laser treatment, may be useful for treatment of skin lesions. Multiple cases have been reported highlighting involvement of different organs in TSC.<sup>[10]</sup> In majority, there was probable diagnosis with one major plus and one minor positive feature. In our case, however, the interesting feature was the

presence of 8 major and 2 minor criteria, making it a very conspicuous presentation of TSC.<sup>[11]</sup>

## CONCLUSION

TSC is a lifelong condition, therefore individuals should be regularly monitored by an experienced clinician. It is not uncommon for patients with TSC to have symptoms or signs that do not lead to immediate diagnosis. In some cases, diagnosis is delayed for prolonged periods of time. Clinicians including child and adult neurologists, dermatologists, nephrologists and cardiologists should be aware of the myriad potential presenting symptoms and signs of TSC. Early diagnosis is very important for thorough clinical and radiological evaluation, continuous monitoring of symptoms, family planning, genetic counseling and reduction in morbidity and mortality rate.

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