

## Case Report

# Tuberous sclerosis complex: a case report

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### ABSTRACT

Tuberous Sclerosis Complex is an autosomal dominant phakomatosis. This neurocutaneous disorder usually presents with seizures, facial angiofibroma and mental retardation (Vogt's triad). Here we report a case where a 25 year old gentleman presented with recurrent seizures, and was diagnosed to have tuberous sclerosis complex.

**Keywords:** Tuberous Sclerosis, Facial angiofibroma, Ash-leaf macule, Periungual fibroma

### INTRODUCTION

Tuberous Sclerosis Complex (TSC) also known as Morbus Bourneville-Pringle disease is an autosomal dominant neurocutaneous disorder characterized by numerous hamartomas in multiple organs, particularly brain, skin, eyes, heart and kidney. They usually present with seizures, mental retardation and facial angiofibroma.

### CASE REPORT

A twenty five year old mentally challenged male, born out of non-consanguineous marriage, was brought to the Internal Medicine department by his mother, with history of recurrent seizures since childhood. Seizure was generalised tonic clonic type, and persisted despite the use of various antiepileptic drugs. Prenatal and perinatal history was unremarkable. Developmental milestones were delayed with poor scholastic performance. Family history was unremarkable. On examination, he had multiple papular lesions on face, hypopigmented macules on upper and lower limbs, and periungual fibromas on his toes. Systemic examination was unremarkable. Blood investigations including complete blood count, renal function tests, liver function tests, serum electrolytes and

urine analysis were normal. Chest radiograph was normal. Twelve lead electrocardiograms showed ventricular pre-excitation. Abdominal ultrasonography and transthoracic echocardiography were normal. A non-enhanced computed tomographic scan of the brain showed multiple calcified subependymal glial nodules in the wall of both lateral ventricles. EEG showed sharp wave discharges. After detailed examination and evaluation, he was diagnosed to have TSC, based on the standard criteria for diagnosis. He was treated with antiepileptic drugs and other supportive measures.



**Figure 1: Facial angiofibroma.**



**Figure 2: Ash leaf macule.**



**Figure 3: Periungual fibroma.**



**Figure 4: Subependymal calcified nodule.**

**DISCUSSION**

TSC was described by Desire-Magloire Bourneville in 1880<sup>1</sup>. Incidence of TSC is approximately 1 in 5000 to 10,000 live births.<sup>2-5</sup> TSC occurs in all races and ethnic groups and both genders. The disease is sporadic in two-third of the patients with no family history, and in remaining one-third it is inherited as an autosomal dominant trait. It has high penetrance and extensive clinical variability. TSC is caused by a mutation in either the TSC1 (Hamartin) gene on chromosome 9q34 or the TSC2 (Tuberin) gene on chromosome 16p13.3. Mutation of either Tuberin or Hamartin gene impairs the Hamartin-Tuberin complex. The Hamartin-Tuberin complex plays an important role in cell division & growth by inhibition of cellular signalling mediated by the mammalian target of rapamycin (mTOR).<sup>2,6</sup> The mTOR pathway is

important for regulating protein translation, cell cycle progression, and response to hypoxia.

TSC is characterized by pleomorphic clinical features in various combinations. Common dermatologic features include ash-leaf spots, angiofibromas, Shagreen patches, hypomelanotic macules, non-traumatic periungual & subungual fibromas. Characteristic central nervous system lesions include glioneuronal hamartomas, subependymal nodules & subependymal giant cell tumours, cognitive deficits, autism and behavioural problems. Cardiovascular manifestations commonly noted are cardiac rhabdomyomas, coarctation of aorta & rarely aortic aneurysms. Angiomyolipomas are the most frequent renal manifestation, less often manifestations being benign cysts, lymphangiomas & renal cell carcinoma. Pulmonary & ophthalmic manifestations are also seen in various combinations.

Although associated with benign hamartomatous tumours, patients with TSC are at risk for malignant tumours, primarily in the kidneys, brain and soft tissues.

In 1908, Vogt proposed a triad typical for diagnosis of tuberous sclerosis consisting of epilepsy, low intelligence and angiofibroma. However, the full triad occurs in only 29% of patients and 6% of them lack all three of them.<sup>7</sup>

**Table 1: Revised diagnostic criteria for TSC.**

| Major features                            | Minor features                                       |
|---|--|
| Facial angiofibroma or forehead plaque    | Multiple, randomly distributed pits in dental enamel |
| Nontraumatic ungual or periungual fibroma | Hamartomatous rectal polyps                          |
| Hypomelanotic macules (three or more)     | Bone cysts   |
| Shagreen patch (connective tissue nevus)  | Cerebral white matter radial migration lines         |
| Multiple retinal nodular hamartomas       | Gingival fibromas                                    |
| Glioneuronal hamartoma (cortical tuber)   | Nonrenal hamartoma                                   |
| Subependymal nodule                       | Retinal achromic patch                               |
| Subependymal giant cell astrocytoma       | "Confetti" skin lesions                              |
| Cardiac rhabdomyoma, single or multiple   | Multiple renal cysts                                 |
| Lymphangioleiomyomatosis                  |  |
| Renal angiomyolipoma                      |  |

According to these criteria, the diagnosis of TSC depends upon the number of major and minor features:

1. Definite TSC requires two major features (excluding women with only renal angiomyolipoma and pulmonary lymphangioleiomyomatosis) or one major and two minor features.

2. Probable TSC requires one major plus one minor feature.
3. Possible TSC requires one major feature only, or two or more minor features but no major features.

Our patient had 4 major features (facial angiofibroma, periungual fibroma, hypomelanotic macule and subependymal nodule).

The management of TSC is ideally done by a multidisciplinary team, and the focus is directed towards its neurologic and systemic manifestations, mainly seizures, cognitive and behavioural problems, brain tumours, skin lesions, renal disease and pulmonary disease. Treatment options in TSC are mainly symptomatic with antiepileptic drugs for seizures and electrocautery for angiofibromas.<sup>10,11</sup> Choice of anticonvulsant drug depends upon the type of seizure. For patients with medically intractable epilepsy, ketogenic diet or a vagus nerve stimulator can be considered.<sup>12</sup> Surgery is another treatment option for patients with TSC and drug-resistant epilepsy, especially when a glioneural hamartoma or tuber is identified as the primary epileptogenic focus. A remarkable new therapeutic option in TSC is Everolimus and its analogues. Everolimus is an inhibitor of mTOR pathway and can normalize this unregulated pathway in patients with TSC. The observation that various actions of the hamartin-tuberin complex are mediated by the mammalian target of rapamycin (mTOR) pathway led to the evaluation of targeted inhibitors of this pathway (viz. Everolimus) as a therapy for brain tumours in patients with TSC.<sup>13,14</sup>

Prognosis of TSC depends on the severity or multiplicity of organ involvement. Unless any vital function is affected, life expectancy is good.

## CONCLUSION

TSC is a neurocutaneous disorder with varied presentations. The classical presentation is the Vogt's triad with seizures, low intelligence and facial angiofibroma, although these may be absent in few patients. Standard criteria are used for diagnosis of TSC. Treatment is with antiepileptic drugs, supportive measures and symptomatic care. Prognosis depends on multiplicity and severity of organ involvement. In any case of intractable seizures, meticulous examination and evaluation should be done to rule out TSC complex. Awareness of the pleomorphic clinical manifestations of

TSC are necessary to establish the diagnosis and for optimal management.

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