

## Case Report

# Familial Tuberous Sclerosis: a case report

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### ABSTRACT

Tuberous sclerosis is a neurocutaneous syndrome with an autosomal dominant inheritance. Tuberous sclerosis complex Syndrome caused by mutations of either the TSC1 or TSC2 gene encoding hamartin and tuberin respectively. It is characterized by the development of benign tumors; 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. Familial tuberous sclerosis probably occurs more often than is indicated by the literature: many family members show signs of being carriers of gene for the disease when carefully examined. We report a case of 25 year old female with the features of Tuberous sclerosis complex like seizures, papules over the cheek, shagreen patch, hypomelanotic macule on arm, buttocks, pulmonary lymphangioleiomyomatosis, subependymal nodules and tubers in brain, angiomyolipoma in both kidneys and Cardiac rhabdomyoma. This article reports on a family with documented tuberous sclerosis in three generations.

**Keywords:** Tuberous sclerosis, TSC1 or TSC2 gene, Benign tumours

## INTRODUCTION

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.<sup>1</sup> 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 parental mosaicism and remaining cases caused by mutations in either the TSC1 gene, which maps to chromosome 9q34 and encodes a protein termed hamartin, or the TSC2 gene, which maps to chromosome 16p13.3 and encodes the protein tuberin.<sup>2</sup> Hamartin forms a complex with tuberin, which inhibits cellular signalling through the mTOR, and acts as a negative regulator of the cell cycle.<sup>3</sup>

In 1908 Vogt proposed a triad typical for TSC diagnosis, consisting of epilepsy, low intelligence and

angiofibromas.<sup>2</sup> Definitive TSC is diagnosed with either two major features (out of total of 11) or one major feature with two minor features (out of total of 9).<sup>4</sup> The most important neurological problems are mental retardation, seizures, autism and learning difficulties.

### *Tuberous Sclerosis Complex Consensus Conference: revised clinical diagnostic criteria 2012*

The definite diagnosis of TSC requires the presence of either 2 major features or 1 major and 2 or more minor features. Possible diagnosis requires either 1 major or >2 minor features.

#### A. Genetic diagnostic criteria

- The identification of either a TSC1 or a TSC2 pathogenic mutation in DNA from normal tissue is sufficient to make a definite diagnosis of TSC. A pathogenic mutation is defined as a mutation that clearly inactivates the function of the TSC1

or TSC2 proteins (e.g., out-of-frame indel or nonsense mutation), prevents protein synthesis (e.g., large genomic deletion), or is a missense mutation whose effect on protein function has been established by functional assessment.

- Other TSC1 or TSC2 variants whose effect on function is less certain do not meet these criteria, and are not sufficient to make a definite diagnosis of TSC. Note that 10% to 25% of TSC patients have no mutation identified by conventional genetic testing, and a normal result does not exclude TSC, or have any effect on the use of clinical diagnostic criteria to diagnose TSC.

## B. Clinical diagnostic criteria

- *Major features*
  - Angiofibromas (>3) or fibrous cephalic plaque
  - Ungual fibromas (>2)
  - Hypomelanotic macules (>3, at least 5 mm in diameter)
  - Shagreen patch (connective tissue nevus).
  - Cortical dysplasias.\*
  - Subependymal nodules.
  - Subependymal giant cell astrocytoma.
  - Multiple retinal hamartomas.
  - Cardiac rhabdomyoma.
  - Lymphangioleiomyomatosis (LAM)\*\*
  - Angiomyolipomas (>2).\*\*
- *Minor features*
  - Dental enamel pits (>3).
  - Intra-oral fibromas (>2).
  - Non-renal hamartomas.
  - Retinal achromic patch.
  - 'Confetti' skin lesions.
  - Multiple renal cysts.

\* Includes tubers and cerebral white matter migration tracts.

\*\* A combination of the 2 major clinical features (LAM and angiomyolipomas) without other features does not meet criteria for a definitive diagnosis.<sup>4</sup>

## CASE HISTORY

A 25-year-old nulliparous married woman was admitted to the hospital with complaints of multiple red, brown lesions over face, asymptomatic plaque over the lumbosacral area and single hypopigmented lesion over right arm 1.5 × 1.3 cm, right buttock 2.5 × 2 cm and left buttock 3 × 2 cm since birth. Headache, body ache, decreased vision since 6 months and abdominal pain, breathlessness on exertion since 2 months. She presented

with one day history of generalized tonic-clonic seizures, lasting for one minute, with a relaxation phase observed for 5-10 minutes. The seizures were associated with urinary incontinence, frothing, uprolling of eyeballs and similar episode of GTC 6 months and 2 years back. She had repetitive urinary tract infections, which resulted in progressive loss of renal function.

Dermatological examination revealed multiple angiofibromas over naso-labial folds, cheeks, chin, eyelids, forehead and neck. Two shagreen patches of size 3 × 2 cm and 4.5 × 2 cm are present over lumbosacral region. Koenen's tumour emerging from proximal nail folds present over right middle and index finger, left index finger and little finger. Her father had similar complaints and died at the age of 64 years and her niece had similar multiple angiofibromas, shagreen patches.

Laboratory evaluation revealed a red blood cell (RBC) count of  $2.81 \times 10^6/\text{mm}^3$ , hemoglobin level of 9.6 g/dL, hematocrit of 29 % and platelet count of  $230 \times 10^3/\text{mm}^3$ . Her WBC count was 6500/cmm. Serum creatinine was 4.1 mg/dL; urea 65 mg/dL; glucose 98 mg/dL; sodium 137 mEq/L; potassium 3.6 mEq/L; uric acid 4.5 mg/dL; albumin 2.8 g/dL; calcium 7.9 mg/dL



**Figure 1: Ungual fibromas.**



**Figure 2: Adenoma sebaceum.**



**Figure 3: Intraoral fibroma.**



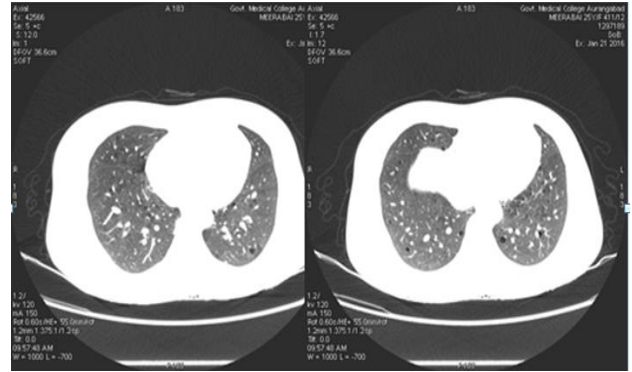
**Figure 4: Angiofibromas.**



**Figure 5: Hypomelanotic macules.**



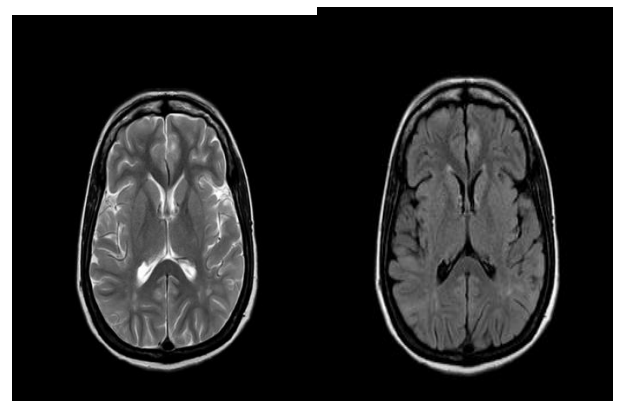
**Figure 6: Shagreen patch.**



**Figure 7: Chest computed tomography (CT) revealed cystic formations throughout the lungs, consistent with lymphangioleiomyomatosis**

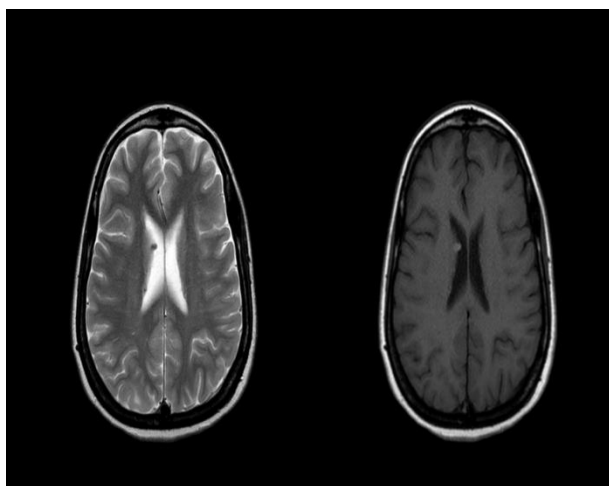


**Figure 8: An abdominal CECT scan demonstrated multiple well defined intensely enhancing soft tissue lesions arising from cortices of bilateral kidneys scattered throughout in upper, lower pole and interpolar region largest measuring  $3.7 \times 1.9 \times 3.1$  cm on right and  $3.3 \times 2.2 \times 4.4$  cm on left in interpolar region on both sides. These lesions show fat attenuation areas within corresponding to angiomyolipomas.**

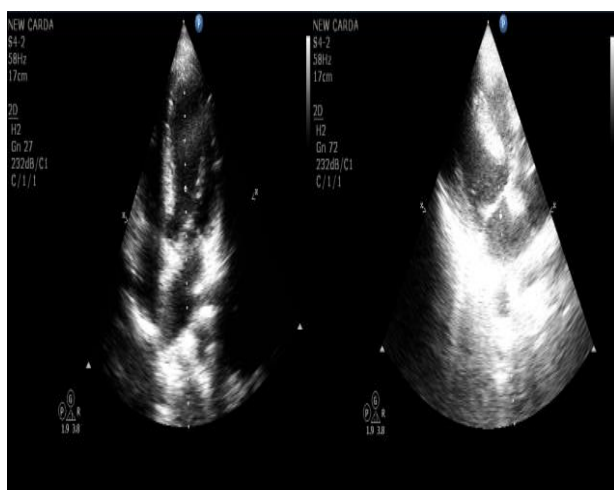


**Figure 9: MRI brain (plain and contrast) revealed multiple ill-defined t2 and flair hyperintensities are noted in bilateral cerebral cortex without restricted diffusion or blooming or contrast enhancement suggestive of cortical tubers.**





**Figure 10: MRI brain (plain and contrast) revealed multiple tiny subependymal nodules are seen in bilateral ventricles largest 6× 5 mm.**



**Figure 11: Cardiac rhabdomyomas were detected on echocardiography. Fundus examinations were within normal limit.**

## DISCUSSION

Tuberous sclerosis complex (TSC) is an autosomal-dominant disease, first described by Bourneville, characterized by hamartomatous lesions in various organs such as the skin, retina, kidney, central nervous system, heart, and lungs.<sup>5,6</sup> TS has a wide clinical spectrum. Patients with tuberous sclerosis may have seizures, mental retardation, adenoma sebaceum (facial angiofibromas), shagreen patch, hypomelanotic macules, periungual fibromas, renal angiomyolipomas, and cardiac rhabdomyomas. The diagnosis of definitive TS is based on specific clinical features and requires the presence of two major criteria, or one major and two minor.<sup>4</sup> Pulmonary lymphangioleiomyomatosis, renal angiomyolipoma and facial angiofibroma are some of the major clinical features.

The major pulmonary manifestations of TSC are lymphangioleiomyomatosis (LAM) and, to a lesser extent, multifocal micronodular pneumocyte hyperplasia (MMPH).<sup>7,8</sup> The most common kidney finding in TS is the presence of angiomyolipomas. These growths tend to be multiple and bilateral. Although they are usually benign, they may bleed. Surgical removal is often recommended as a prophylactic measure in people with angiomyolipomas larger than 4 cm in diameter. The cysts in TS are radiographically similar to those seen in ADPKD. In contrast to ADPKD, there is a clearly increased risk of renal cell carcinoma in TS patients. Regular periodic imaging is recommended in TS patients with kidney involvement to screen for the development of renal cell carcinoma. Although not common, TS may lead to significant chronic kidney disease (CKD) and progress to end-stage kidney failure. Patients with TS and CKD typically have unremarkable urine sediment and only minimal to mild amounts of proteinuria. These patients have an increased incidence of subependymal nodules, cortical tubers, and subependymal giant-cell astrocytomas (SEGA). Patients frequently require anticonvulsants for seizures.<sup>3</sup> Mental retardation and seizures are both neurologic manifestations of TSC and the overall incidence of mental retardation is 38 percent to 80 percent in TSC, while epilepsy is one of the most prevalent manifestations of TSC, occurring in more than 80 percent to 90 percent of patients with TSC.<sup>6,9,10</sup> These neurological manifestations are highly related to cortical tubers, which are detected in 80 percent of patients.<sup>6</sup>

SEGAs do not always require therapeutic intervention, but the most effective therapy is with the mTOR inhibitors sirolimus or everolimus, which often decrease seizures as well as SEGA size. Kidney cysts are a frequent feature of this condition, as are two other abnormalities of kidney growth, renal cell carcinoma and renal angiomyolipomas. The TSC2 gene is adjacent to PKD1 in the human genome. Some patients have deletions in their genomic DNA that inactivate these two genes. Such individuals may have manifestations of both ADPKD and TS. Mechanistically, the TSC1 and TSC2 gene products tuberlin and hamartin interact physically. This protein complex is localized to the base of the cilia and inhibits intracellular signalling processes mediated by mTOR, leading to abnormal growth in a number of tissues. Investigation of mTOR inhibitors as therapy for TS is on-going. Cardiac rhabdomyomas can be detected in up to 60% of children (<18 years) with tuberous sclerosis by echocardiography.<sup>3</sup> However, two-thirds of cases are caused by sporadic mutations, and this may also contribute to the under diagnosis of TSC cases without the classic triad.<sup>11</sup>

In tuberous sclerosis, the earliest cutaneous sign is macular hypomelanosis, referred to as an ash leaf spot. These lesions are often present at birth and are usually multiple; however, detection may require Wood's lamp examination, especially in fair-skinned individuals. The pigment within them is reduced, but not absent. The

average size is 1–3 cm, and the common shapes are polygonal and lance-ovate. Angiofibromas (adenoma sebaceum) are firm pink to skin-colored papules that measure from 3 mm to a few centimeters in diameter. When multiple lesions are located on the central cheeks (adenoma sebaceum), the patient has tuberous sclerosis or multiple endocrine neoplasia (MEN) syndrome, type 1. Additional cutaneous signs such as ungual and gingival fibromas, fibrous plaques of the forehead, and connective tissue nevi (shagreen patches) also seen. Ash leaf spot on the scalp will result in a circumscribed patch of lightly pigmented hair.<sup>3</sup> Our case satisfying eight major and one minor criteria. In our case three generations of family was affected so it's hereditary tuberous sclerosis.

## CONCLUSION

TSC is a lifelong condition. 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. Methodical Cutaneous and systemic examinations with appropriate investigations are mandatory to diagnose a case of TSC. Early diagnosis is very important for continuous monitoring of symptoms, family planning, genetic counseling and reduction in morbidity and mortality rate.

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