

*Case report-Olgu sunumu*

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# Tuberous sclerosis - A case report and review of literature

## *Tüberoz skleroz bir vaka ve literatürün gözden geçirilmesi*

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### **Abstract**

Tuberous sclerosis complex (TSC) is a neurocutaneous syndrome characterized by involvement of multiple system including central nervous system, kidney, skin, heart, lungs, and eye. It is frequently associated with skin lesions (96%); seizures (90%) and mental retardation (70%). Most common lesions associated with TSC are angiofibroma of face, ashleaf macules, shagreen patches, subependymal nodules, cortical tubers, mental retardation, and angiomyolipomas of kidney. The small benign tumours in the brain of affected individuals are the cause of neurological manifestations of the disorder. As prognosis depends on the involvement of brain, kidney and other vital organs; routine screening of a patient with tuberous sclerosis is required to determine the involvement of other organ systems. Combined skills of physician, radiologists and psychologist are required to manage a patient with TSC.

**Keywords:** Tuberous sclerosis, angiomyolipomas, shagreen patches, subependymal nodules, ashleaf macules, seizures

### **Özet**

Tüberoz skleroz kompleksi santral sinir sistemi, böbrek, deri, kalp, akciğerler ve göz gibi çoklu sistem tutulumlu nörokutanöz bir sendromdur. Deri lezyonları(%96), nöbetler(%90) ve mental retardasyonla (%70) ilişkilidir. En sık görülen lezyonlar yüzde anjiyofibrom, ash-leaf makülleri, shagreen lekeleri, subependimal nodüller, kortikal tüberler, mental retardasyon ve böbrekte anjiomyolipomlardır. Hastalığın nörolojik bulgularının nedeni beyindeki küçük benign tümörlerdir. Prognoz beyin, böbrek ve diğer hayati organların tutulumuna bağlı olduğu için diğer sistemik organ tutulumları da rutin taranmalıdır. Tüberoz sklerozlu hastanın tedavisinde hastayı izleyen hekimin; radyolog ve psikiyatristle de işbirliği içerisinde olması gerekmektedir.

**Anahtar sözcükler:** Tüberoz skleroz, anjiomyolipomlar, shagreen patchler, subependimal nodüller, ash-leaf maküller, nöbetler

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### **Introduction**

Tuberous sclerosis, also known as Bourneville's disease, is a neurocutaneous disorder characterized by cutaneous lesions, seizure and mental retardation. It is characterized by development of benign tumours, such as neurofibroma and angiofibroma located at multiple sites in the body (skin, central nervous system, kidney, heart etc.). It is an autosomal dominant hereditary disorder, though 60-70% of all cases are the result of spontaneous mutations [1, 2]. Patients with tuberous sclerosis have mutations in either

TSC-1 gene at chromosome 9q34 or the TSC-2 gene at chromosome 16p13. These genes encode hamartin and tuberin proteins respectively that modulate the GTPase activity of the other cellular signaling proteins [3]. The unpredictable distribution of the lesions results in a broad range of clinical phenotypes, with variable expression even in same family [4]. The disease affects 1/6000 to 1/10000 births, and diagnosis is established between 4-10 years of age or at puberty [5]. The cutaneous lesions include adenoma sebaceum (facial angiofibroma), ashleaf shaped hypopigmented macules (best seen under wood's lamp), shagreen patches, depigmented naevi, periungual fibromas (also known as Koenen's tumor), and forehead plaques. Central nervous system (CNS) involvement is variable, including learning difficulties, seizure disorders and tumors. Three brain tumors may be associated with Tuberous sclerosis complex (TSC): giant cell astrocytoma (grows and blocks the cerebrospinal fluid (CSF) flow leading to dilatation of ventricles causing headache and vomiting), cortical tubers and subependymal nodule (from wall of the ventricles). 60-80% of TSC patients have benign tumors of kidney called angiomyolipomas which frequently cause hematuria. Some patients may have autosomal dominant polycystic kidney disease. Patients may have rhabdomyoma of striated myocardial muscles. Eye lesions include astrocytichamartoma, coloboma, angiofibroma of eyelid, and papilloedema (related to hydrocephalus).

The most common oral manifestations of TSC are fibromas, gingival hyperplasia and enamel hypoplasia [6]. Other less frequent findings in oral cavity are high arched palate, bifid uvula, delayed dental eruption, cleft palate and the presence of diastemas [7].

### Case report

We hereby report a thirteen-year old young male who was admitted with history of generalized tonic clonic seizures since neonatal period. Patient was started on an antiepileptic drug (records not available) but seizures were not controlled, therefore patient was shifted to indigenous medications by parents, but got no relief. Patient presented in the emergency department with intractable seizures inspite of combination of antiepileptic medications. On examination, the patient had skin lesions over face especially concentrated around nose. The patient was hyperactive and had high arched palate, with depressed nasal bridge and frontal bossing. Dental hygiene was poor with generalized chronic gingivitis and gum inflammation. Skin examination showed adenoma sebaceum (angiofibromas) concentrated around nose, one fibrous plaque on forehead. Shagreen patches were present in preauricular region and hypomelanotic patches were present on trunk and face, most prominent in wood lamp examination (ashleaf macules) (Figure 1, 2 and 3).



**Figure 1. Photograph of patient showing shagreen patch.**

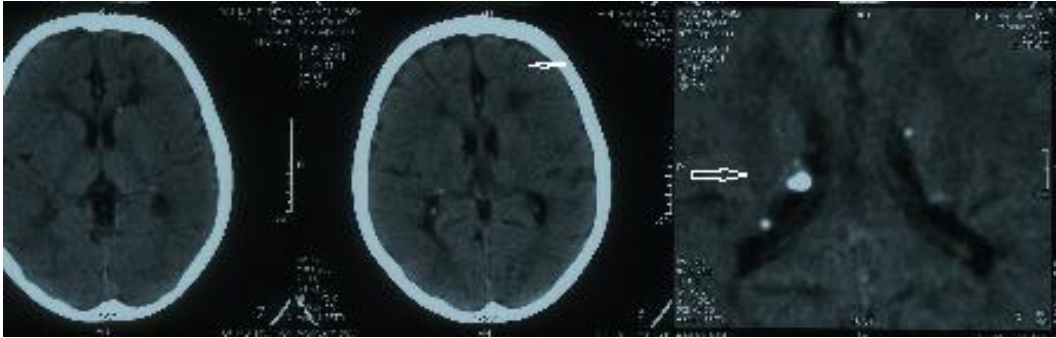


**Figure 2. Photograph of the patient showing adenoma sebaceum and gum hypertrophy.**



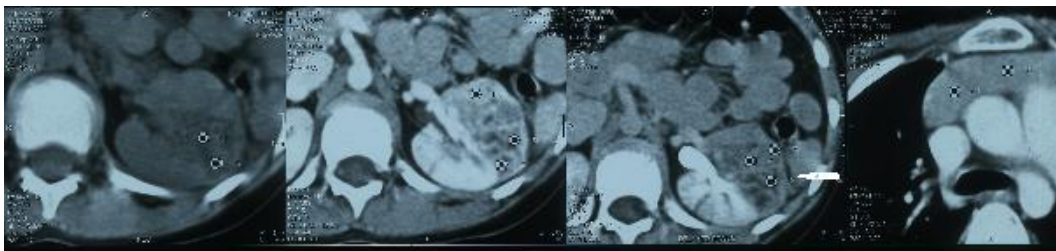
**Figure 3. Photograph of patient showing ashleaf macules.**

The intelligence quotient (IQ) of the patient was 30 indicating severe mental retardation with features suggestive of attention deficit and hyperactivity disorder (ADHD). Rest of systemic examination was normal. History of delayed gross motor, fine motor, language, perceptive cognitive, social and personal developmental milestones was present. There was no history of similar illness in any other sibling or family member. Subsequent investigations revealed normal hemogram including total leucocyte count, and platelet count, normal kidney and liver function tests, random blood sugar, serum electrolytes including calcium levels were within normal range. Urine complete examination shows no proteinuria, no hematuria. Chest radiography was normal. Ultrasonography of abdomen showed multiple echogenic lesions involving bilateral kidneys, the largest was 3.2 x 2.5 cms in size at midpole of left kidney suggestive of renal angiomyolipoma. Contrast enhanced computerized tomography (CECT) head shows calcified lesions in subependymal locations at bilateral lateral ventricles jetting into CSF, right cerebellar region and right occipital region suggestive of subependymal nodules, with non-enhancing, hypodense lesions seen scattered in the supratentorial brain parenchyma suggestive of cortical tubers (Figure 4).



**Figure 4. CECT brain showing subependymal nodule and cortical tubers.**

CECT of the abdomen showed a hypodense lesion with areas of fat density seen in the left kidney, lesions showing heterogenous contrast enhancement confirming angiomyolipoma (Figure 5). Echocardiography was normal. Twenty three channel electroencephalography recordings under sedation showed a poorly organized background activity of bursts of generalized spike and wave discharged admixed with low and high voltage slow waveforms. Photostimulation was non contributory. Patient was treated with valproic acid and vigabatrin and is now controlled for seizures.



**Figure 5. CECT abdomen showing angiomyolipoma.**

## Discussion

TSC is a neurocutaneous syndrome classically characterized by triad of skin lesions including facial angiofibromas (96%), seizures (90%) and mental retardation (70%). The disease is an autosomal dominant genetic disorder with variable penetrance. Around two third of TSC cases result from sporadic genetic mutation, not inheritance, but their offspring inherit it from them. TSC 1 encodes hamartin located on chromosome 9q34. TSC 2 is contiguous with PKD1, the gene involved in polycystic kidney disease (PKD) on chromosome 16P13, it encodes for tuberin protein.

TSC 1 and 2 are both tumor suppression genes that function according to Knudson's "two hit" hypothesis. That is, a second random mutation must occur before a tumor can develop. This explains why despite its 100% penetrance, TSC has wide expressivity (Table 1).

Physical manifestations of tuberous sclerosis are due to formation of hamartia (malformed tissue such as cortical tubers), hamartoma (benign growth such as facial angiofibroma and subependymal nodules) and very rarely, cancerous hamartoblastoma. The effect of these on the brain leads to neurological symptoms such as seizures, developmental delay and behavioural problems [8].

**Table 1. Diagnostic criteria for tsc.**

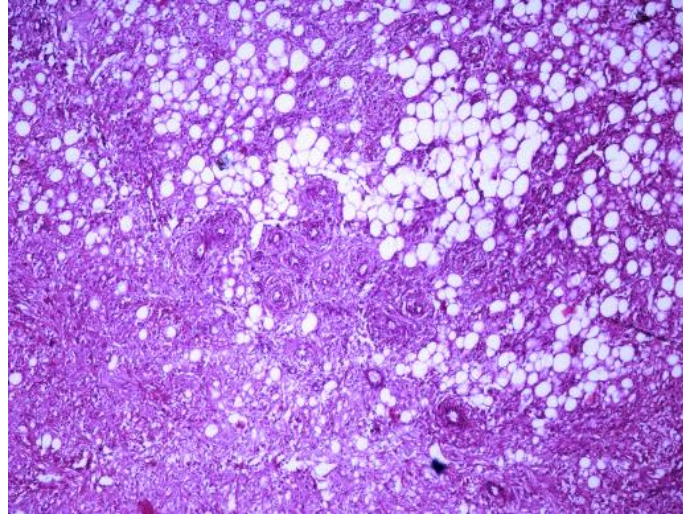
| <b>Major criteria</b>   | <b>Minor criteria</b>                |
|---|--------------------------------------|
| 1 Facial angiofibroma   | 1 Non calcified subependymal nodules |
| 2 Multiple ungula fibroma (Koenen tumours)                                    | 2 Hamartomatous, Rectal polyps       |
| 3 Cortical tuber  | 3 Gingival fibroma                   |
| 4 Subependymal nodules  | 4 Non renal hamartomas               |
| 5 Multiple astrocytomas   | 5 Multiple renal cysts               |
| 6 Renal angiomyolipomas   | 6 Retinal achromic patch             |
| 7 Lymphangioliomyomatosis   | 7 Enamel hypoplasia                  |
| 8 Hypomelanotic macules (3 or more)   | 8 Bone cysts                         |
| 9 Cardiorhabdomyoma   | 9 Confetti's skin lesion             |
| 10 Forehead plaque  |                                      |
| 11 Shagreen patches   |                                      |
| 12 Retinal macular hamartoma  |                                      |
| <b>Definitive diagnosis:</b> 2 major features or one major + 2 minor features |                                      |
| <b>Probable diagnosis:</b> 1 major + 1 minor features                         |                                      |
| <b>Suspected case:</b> Either 1 major or 2 minor features                     |                                      |

Angiofibromas are found in around 70% of patients of tuberous sclerosis, they appear on nose and cheeks in a butterfly distribution. They consist of blood vessels and fibrous tissue. Hypomelanotic macules (ashleaf spots) are white or lighter patches of skin that may appear anywhere on body due to lack of melanin. They are usually seen at birth but wood's lamp examination is necessary to see them in dark skinned person. Shagreen patches usually present on lower back or nape of neck. These are the areas of leathery skin that are dimpled like orange peel.

About 50% of the patients with TSC have learning difficulties, ranging from mild to significant [9]. Lower IQ is associated with more brain involvement. Classical intracranial manifestations of tuberous sclerosis include subependymal nodules and cortical tubers [10] Tubers are typically triangular in configuration with the apex pointed towards the ventricles, and are thought to represent foci of abnormal neuronal migration. The T2 signal abnormalities may subside in adulthood, but still visible on histopathological analysis. Subependymal nodules are composed of abnormal, swollen glial cells and bizarre multinucleated cells which are indeterminate for glial or neuronal origin, there is no interposed neural tissue. These nodules have a tendency to calcify as the patient ages. A nodule that markedly enhances and enlarges over time should be considered suspicious for transformation into a subependymal giant cell astrocytoma (SEGA). A SEGA typically develops in region of foramen monro and has risk of developing an obstructive hydrocephalus. Other less common CNS lesions include corpus callosum agenesis/dysgenesis, transmantle cortical dysplasia, and associations with hemimegalencephaly, schizencephaly, and intracranial arterial aneurysms (60%) [11].

About 60-80% of TSC patients have angiomyolipomas (AML) which frequently cause hematuria. Although our patient had angiomyolipomas, he did not have any episode of hematuria in past. These tumours are composed of vascular tissue, smooth muscle cells, and adipose tissue. Although benign, a patient with an AML larger than 4 cm is at risk of potentially catastrophic haemorrhage, either spontaneously or with minimal trauma. AML is found in 1 in 300 people without TSC. However, these are usually multiple and bilateral in TSC patient (Figure 6).

The respiratory system is rarely impaired with less than 1% of patients presenting with direct lung involvement due totuberous sclerosis [12]. Lung involvement by angiomyolipomas that produces generalized cystic or fibrous pulmonary changes can lead to spontaneous pneumothorax which may lead to tension pneumothorax while on positive pressure ventilation.



**Figure 6. Photomicrograph of angiomyolipoma of kidney revealing adipose tissue, smooth muscle and vessels (H & E 100X).**

Up to 50% of children with tuberous sclerosis will develop rhabdomyoma of heart, which may cause congestive heart failure, conduction abnormalities, refractory arrhythmias, and severe hemodynamic compromise [13]. Cardiac rhabdomyomas are normally observed before age of 25 years in 30-50% of all cases, and are also a cause for early death [14]. Our patient does not have any cardiac involvement. Drug therapy for some manifestations of TSC is currently in developmental stage [15]. Unless vital functions are affected, life expectancy is good. Majority of patients will require antiepileptics (Valproic acid, Vigabatrin, Topiramate) for control of seizure. Chiron et al. [16] and Aicardi et al. [17] reported efficacy of vigabatrin (VGB) in refractory infantile spasms and the best results in the patients of TSC. Of the patients affected by TSC 73 (95%) had complete cessation of infantile spasms, in contrast to 169 (54%) of patients without TSC. Topiramate is emerging as a more effective drug in partial seizures with or without secondary generalization and in Lennox-Gastaut syndrome [18]. Apart from state dependent blockade of sodium and calcium channels, the mechanism of action of Topiramate and inhibitory effect on carbonic anhydrase include enhanced GABA (Gamma aminobutyric acid) activity on GABAA receptors with elevated levels of cerebral GABA and antagonism of glutamate receptors. Everolimus was approved for treatment of SEGA in 2010. Behavioural therapy and educational strategies are required for mental retardation. Shunting for hydrocephalus may be required in some patients. Leading cause of death include renal disease, brain tumour, lymphangiomyomatosis of lung and status epilepticus or bronchopneumonia in those with severe mental retardation [19]. To conclude, patients of TSC can have variable presentations ranging from typical skin lesions, seizures and learning disabilities to atypical presentations like hematuria mimicking polycystic kidney disease, gum fibromas or rare CNS lesions. Hence, the diagnosis and management of patients with TSC require combined skills of a physician, radiologist and a psychologist. Seizure plays a major role in failure of mental development and deterioration of mental function, hence effective seizure control is needed. Though TSC is not a common diagnosis, it should be brought in mind when a young patient admits with complaints of resistant seizures with skin lesions and learning difficulties.

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