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**Case Report**

# A case of tuberous sclerosis - presenting as febrile seizures with status epilepticus

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## ABSTRACT

Tuberous sclerosis or Tuberous Sclerosis Complex (TSC) is an autosomal dominant disease which comes under a group of diseases known as Neurocutaneous syndromes or phakomas. Incidence of TCS is around 1 in 6000. It is characterized by the growth of numerous hamartomas in several organs including the brain, heart, skin, eyes, kidney, lung and liver. The affected genes are TSC1 and TSC2 encoding hamartin and tuberin respectively. Here, we are presenting a case of 2 year old male child born of a non-consanguineous marriage admitted in the pediatrics emergency ward with the history of fever since one day and continuous convulsions since past one hour GTCS type. Mother also gave history of recurrent attacks of convulsions since 9 months of age. On thorough clinical evaluation and radiological investigation, he was diagnosed as a case of tuberous sclerosis. This case report emphasizes the importance of complete evaluation of a case presenting with seizures and inclusion of TSC (Tuberous Sclerosis Complex) as a differential diagnosis in children presenting with seizures, developmental delay and autism.

**Keywords:** Tuberous sclerosis complex, Hamartin, Tuberin, Developmental delay

## INTRODUCTION

Tuberous sclerosis or Tuberous sclerosis complex (TSC), also known as epiloia or Bourneville–Pringle disease, is a autosomal dominant Neurocutaneous syndrome characterized by the growth of numerous benign tumors in many organs particularly the skin, brain, eye, kidney and heart. The characteristic skin lesions are angiofibromas, shagreen patches and ash leaf white macules classically although not invariably seen in association with epilepsy and mental retardation.[1] Multiple Von Recklinghausen first described tuberous sclerosis in 1862. Desire-magloire Bournville (a French physician) coined the term sclerose tubereuse, from which the name of disease Tuberous sclerosis has evolved.

Tuberous sclerosis (TSC) has an incidence of 1 in 6000 to 1 in 10000 live births with no ethnic clustering.[2] Thus, it is the second most common Neurocutaneous syndrome after neurofibromatosis. Genetic studies detected two loci e.g. TSC1, the abnormality is located on chromosome 9q34 and TSC2, the abnormality is located on chromosome 16p13. Approximately two thirds of cases are sporadic that is, affected individuals have no family history of the disease. TSC1 gene encodes tuberin and the TSC2 gene encodes hamartin. Hamartin and tuberin form a complex that is thought to negatively regulate the cell cycle. TSC results from mutations in the TSC1 (hamartin) and TSC2 (tuberin) genes.[4] The presence of either mutation produces uncontrolled proliferation and differentiation in numerous tissues including the skin, central nervous system (CNS), heart, eye and kidneys.

TSC is an extremely heterogeneous disease where affected members of the same family may be of normal intelligence, or they may be severely mentally retarded with seizures that are difficult to control.[5] The most frequently observed manifestations are those of the skin and of the central nervous system like seizures, mental retardation, followed by renal, cardiac and ocular manifestations. In addition to mental retardation, multiple behavioral problems including sleep disorder, hyperactivity, attention deficit, aggressiveness, and autism have been found in children with TSC.[6] Seizures are the most common neurologic symptom of TSC occurring in 92% of patients.[7] TSC has no cure but treatment with anticonvulsant medicines, educational and occupational therapy can help to relieve symptoms.

## CASE REPORT

A 2 years old male child born of a non-consanguineous marriage from a lower class family of a rural area in Karnataka presented to the emergency pediatrics ward of our hospital with history of fever and status epilepticus for past one hour before admission in to PICU.

Fever was moderate grade intermittent in nature. Convulsions were of GTCS type lasting for almost one hour involving both upper and lower limbs with up rolling of eyes and frothing from mouth. He had no fecal or urinary incontinence. Child was taken to local private hospital and was administered anticonvulsants. As convulsions were not controlled child was brought to our hospital. At admission child was febrile, convulsing continuously which was controlled with an initial one single bolus of Injection Phenytoin. Vitals were stable. Systemic examination was normal.

Past history was significant as mother gives history of recurrent episodes of convulsions since 9 months of age 3-4 episodes/day each episode lasting for 1-2 min. The child was developmentally lacking behind other children of the same age and sex .There was no other members of the family suffering from the disease.

Skin examination showed as following; (1) Multiple, soft dome shaped lesions around the nose and cheek (adenoma sebaceum); (2) Multiple hypo pigmented, lanceolate macules with serrated edges on back ( ash leaf macules); A thickened leathery area over lower back-shagreen patch.

Ophthalmic examination showed Retinal Astrocytoma of left eye.

As the child had stereotyped movements of the body parts and the limbs, eye to eye contact was not meaningful and also has delay in speech development; provisional clinical diagnosis of autism was made which was confirmed by Psychiatric assessment.

His laboratory investigations revealed normal blood counts and routine urinalysis, X-ray chest was normal. Renal function test and serum electrolytes were normal. Ultrasonography of kidneys showed left sided cortical renal cyst. Echocardiography of heart revealed a mass of 1.6 x 1cm mass attached to left ventricular apex suggestive rhabdomyoma and cardiac MRI was not done due to financial constraints. MRI brain showed multiple sub ependymal nodules/ hamartomas involving the bilateral lateral ventricles and in the left caudate nucleus. It also showed white matter degenerative changes with most of them cystic changes.

Seizures were controlled with intravenous phenytoin which was changed over to oral maintenance and also started on sodium valproate and phenytoin was slowly tapered off and stopped and was discharged after 2 weeks and was advised for regular follow up. Management of autism is deferred as per the psychiatrist's opinion.

This case is being reported because of its rarity in its presentation in childhood.

## DISCUSSION

Tuberous sclerosis is an autosomal dominant disorder which shows a wide variety of clinical expression. Some individuals are severely affected, while others have very few clinical features. Tuberous sclerosis is characterized by the development of unusual tumor growths like hamartoma in brain, skin, retina and other viscera.

The diagnostic criteria of TSC have been divided into major and minor features (Table 1).[8] Definite TSC is diagnosed when either 2 major features (out of total 11) or one major feature with 2 minor features (out of total 9) are present.[9]

Among cutaneous manifestations, hypomelanotic macules, facial angiofibromas, shagreen spots and fibrous plaques on the forehead are observed.[10] In our patient, we had multiple, soft dome shaped lesions around the nose and cheek (adenoma sebaceum) as shown in Figure 1A, fibrous plaque on forehead, multiple hypo pigmented lanceolate macules with serrated edges on back (ash leaf macules) and a thickened leathery area over lower back (shagreen patch Figure 1B).

Arguably the most important hamartomas are cerebral cortical tubers, which are regions of abnormal cortical architecture with distinctive large neuronal cells. Cortical tubers cause some of the most important clinical manifestations of tuberous sclerosis complex syndrome. Neurologic symptoms and complications due to the development of cortical tubers, sub ependymal nodules and sub ependymal giant cell astrocytoma's (SEGA) are common in patients with TSC.[11] Our patient had both cortical tubers ( Figure 2A) and sub ependymal nodules in bilateral ventricles (Figure 2B) and left caudate nucleus.

**Table 1 : Diagnostic criteria of tuberous sclerosis complex (TSC).**

| Major criteria | Minor criteria |
|---|---|
| • Facial angiofibromas or forehead plaques<br>• Hypomelanotic macules(>3)<br>• Shagreen patch (Connective tissue naevus)<br>• Cortical tuber<br>• Subependymal nodule<br>• Subependymal giant cell astrocytoma<br>• Multiple retinal nodular hamartomas<br>• Cardiac rhabdomyoma, single or multiple<br>• Lymphangiomyomatosis<br>• Renal angiomyolipoma | • Multiple randomly distributed pits in dental enamel<br>• Hamartomatous rectal polyps<br>• Bone cysts<br>• Cerebral white matter migration tracts<br>• Gingival fibromas<br>• Nonrenalhamartoma<br>• Retinal achromic patch<br>• Multiple renal cysts |

**Figure 1A: Showing adenoma sebaceum on the face.**

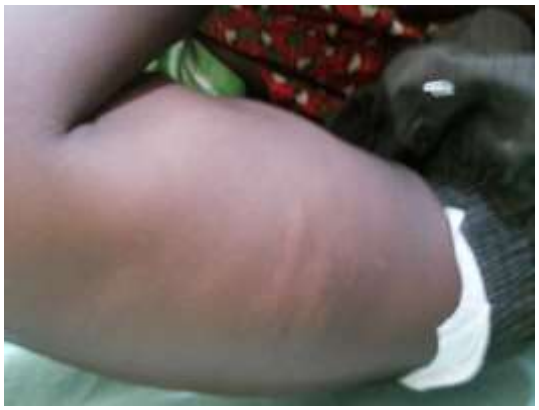

**Figure 1B: Showing shagreen patch on the back.**

**Figure 2A: MRI brain of patient showing cortical tubers.**

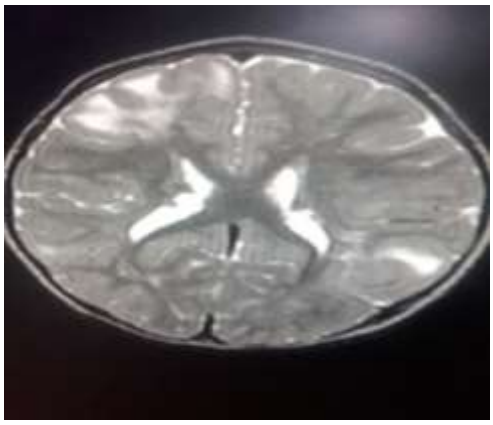

**Figure 2B: MRI brain of patient showing sub ependymal nodules.**

Systematic evaluation of neuropsychological attention skills in a population-derived sample of children and adolescents with TSC showed that, even when age, gender, IQ, and intra-familial clustering were controlled for, the TSC group had significantly lower scores than their unaffected siblings on a range of neuropsychological attentional tasks, and that they had significantly more neuropsychological attention deficits. The findings suggest that clinical neuropsychological evaluation of attentional skills should be performed in children and adolescents with TSC.[12] Psychometric analysis of our patient revealed poor eye to eye contacts, playing ability was poor, hyperactivity, impaired speech and language suggestive of autistic features.

Two types of renal lesions occur in patients with tuber sclerosis; (1) Angiomyolipomas and; (2) Renal cysts. They may be found independently or together: they may be unilateral, bilateral, single or multiple. Our case reported with single left cortical renal cyst.

In the heart, the most frequent and characteristic type of tumor is cardiac rhabdomyomas. Incidence of cardiac rhabdomyomas in children with tuberous sclerosis is higher than in adult patients with tuberous sclerosis. It

has been suggested that such lesions tend to regress in early infancy and adolescence and are normally observed before age 25 years in 30-50% of all cases, and are also a cause of early death.[11] Echocardiography of heart of our patient revealed a mass of 1.6 x 1cm attached to left ventricular apex suggestive of rhabdomyoma and cardiac MRI which was not done due to financial constraints.

Ophthalmic examination of our case also revealed Retinal Astrocytoma of left eye (Figure 3).

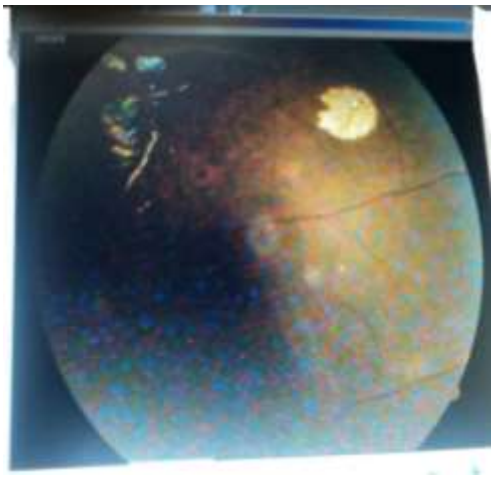

**Figure 3: Retinal astrocytoma of left eye.**

Treatment is symptomatic. Anticonvulsants for seizures, shunting for hydrocephalus, and behavioral and educational strategies for mental retardation are the mainstays of management. The mainstay of seizure control for patients with TS is medical therapy with anticonvulsant drugs and a ketogenic diet. Evidence is accumulating that vigabatrin, an inhibitor of γ aminobutyric acid transaminase, is the anticonvulsant medication of choice for patients with TSC.[13] In our case convulsions were controlled with phenytoin and sodium valproate and treatment for autism was deferred as per psychiatrist opinion and was advised for regular follow up.

Prognosis of the disease depends on the severity or multiplicity of organ involvement. About a quarter of severely affected infants are thought to die before age 10 years, and 75% die before age 25 years; however, the prognosis for the individual diagnosed late in life with few cutaneous signs depends on the associated internal tumors.

## CONCLUSION

The skin manifestations of tuberous sclerosis are the clinical hallmark and helpful in diagnosing this disorder. Unfortunately no specific prenatal laboratory test is available. Genetic counselling should be offered to families with affected members, even though accurate counselling remains difficult because of the variability of gene expression and mutation.

As there is no permanent cure for TSC early diagnosis is very important for continuous monitoring of clinical features and reduction in morbidity and mortality.

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