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# Unveiling Tuberous Sclerosis Complex: A Case Report of Seizure Disorder and Inherited Predisposition

**Keywords:** Tuberous sclerosis; Seizure; Adenoma; Sebacum

**Abstract**

Tuberous sclerosis complex (TSC) is an autosomal dominant genetic disorder with high penetrance and extensive clinical variability that affects multiple organ systems: the skin, brain, kidneys and heart. It is characterized by a variety of dermatological symptoms like angiofibromas, periungual fibromas, shagreen patch, and leaf macules, as well as neurological manifestations such as seizures, mental retardation and behavioral disorders. A typical clinical triad comprising epilepsy, intellectual disability, and adenoma sebaceum defines TSC.

We present a case report of an 18-year-old male with characteristic clinical and radiological features of tuberous sclerosis complex having a significant family history. The patient admitted to the hospital with features of status epilepticus revealed multiple hypo pigmented macules, adenoma sebaceum in a butterfly pattern, shagreen patch on the abdomen and a nodule in the fingertip, likely periungual fibroma thus fulfilling 5 major criteria of TSC. Patient also had a slightly impaired mental status. A tiny sub-enendymal nodule on brain MRI also supported the case. In general, only one-third of the disease is hereditary, while the rest are sporadic in nature. But significant family history is reported in our case where the 2 generations seem to be affected in sequence with variable manifestations. The severity has been noticed to be more in 2nd generations, mostly the younger siblings.

This case report intends to raise awareness of this illness among medical professionals and improve patient care. Further research on the genetic association of TSC and its severity as per generations needs to be evaluated to bring out more accurate statistical information. It is imperative to let the medical community know about the underlying condition, producing seizures to reduce the morbidity and mortality of this disease.

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## Introduction

Tuberous sclerosis complex is known as a neurocutaneous disease characterized by variety of dermatological symptoms like angiofibromas, periungual fibromas (Koenen'stumors), shagreen patch and leaf macules, fibromatous plaque as well as neurological manifestations including seizures, mental retardation and behavioral disorders.[1] It is an autosomal dominant genetic disease that affects multiple organ systems.[2] In 1862 Von Recklinghausen first described the disease.[3] Then Désiré-Magloire Bourneville first demonstrated the pathologic brain lesions in 1880 and termed "sclerosetubereuse"(tuberous sclerosis). Due to having various extra cranial manifestations, it is termed as "tuberous sclerosis". According to his name, it was also called "Bourneville's Disease".[4][2] A typical clinical triad comprising epilepsy (EPI), intellectual disability (LOI), and adenoma sebaceum (A), defines TS.[4] A recent study reported that about 80% of children with TS have epilepsy. The same study established that about 44% of the respondents had mental retardation, which was profound in two thirds of cases (IQo21). Patients without a history of seizures are extremely unlikely to have a significant learning problem.[5] People with TSC often acquire epilepsy within the first year of life, however people with TSC who have never had seizures continue to have a higher risk of developing epilepsy.[6]

Here we present a case report of a 18 years old male with characteristic clinical and radiological features of tuberous sclerosis complex having significant family history. It is imperative to let the medical community know about the underlying condition that produces seizures in order to reduce the morbidity and mortality of this disease. By disseminating this case report, we intend to raise awareness of this illness among medical professionals and improve patient care. This article was previously presented as a meeting abstract at the 2023 Bangladesh International Medical Students Scientific Congress (BIMSSCON) on 12 May, 2023.

## Case Presentation

An 18 yrs old male was admitted to The Department of Medicine, Mymensingh Medical College Hospital, Mymensingh, Bangladesh with presentation of status epilepticus. On query, he was on antiepileptic drugs for the last 8 years as recommended by primary health center but the control was very unsatisfactory. He used to have several episodes of generalized tonic clonic convulsion lasting for 7-8 minutes occuring at intervals of 3-4 min that relieved spontaneously. However due to their economic constraints it was not possible for his family to take further consultation. The status epilepticus was managed accordingly then further examination was done which imparted GCS= E1V1M3, pulse 80 bpm ,blood pressure 130/80, absence of bilateral Babinski sign, absence of meningeal irritation sign, decreased tone in both lower limbs, loss of deep tendon reflex.

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There were bumpy areas in the head, multiple hyperpigmented papular growth over the nasolabial region in a characteristic butterfly pattern consistent with adenoma sebaceum (Figure 1). We also noticed multiple (about 5) hypopigmented macules (ash leaf pattern) (Figure 2) with diameter greater than 5mm in body especially in trunk and abdomen along with a well defined roughened hypermelanotic patch region showing orange peel appearance indicative of Shagreen patch on his abdomen near left flank (Figure 3). A nodule was present in the finger tip with degenerative change of nail likely periungual fibroma (Figure 4). Other systems revealed no significant abnormality.

Further neurological examination was done to evaluate the mental status. Upon inquiry he was dropped out from school due to episodes of convulsion in his early childhood. Higher psychic function test revealed he is slightly unable to follow commands immediately, normal behavior, intact immediate, recent and remote memories. Visual memory was intact but verbal memory was disturbed. He couldn't perform calculations, mainly subtractions and slightly delayed abstract thinking. Constructional ability is impaired and has a depressed mood mostly worrying about his illness and was shy responding only to direct questions.

Investigation revealed a tiny subependymal nodule on MRI of Brain (Figure 5), fundoscopy was normal. Ultrasonography of the whole abdomen revealed a small focal lesion in the left kidney (Figure 6). Other tests like hemoglobin, complete blood count, renal function test and liver function test were within normal limits. Electrocardiogram, echocardiogram, chest Xray were also normal.

On the query about, he was born of consanguineous marriage and uneventful prenatal and postnatal birth history and there was significant family history. His father also has typical adenoma sebaceum on his nose (Figure 7A) (Figure 7B) but gave no history of having convulsion in his life and is found to be mentally sound. His mother is leading a normal life. The couple gave birth to 6 children out of which 3 died in early life due to various causes. Now they have an elder daughter of 21 years who also has skin manifestation (adenoma sebaceum) but no other features. The younger daughter is 11 years old and has skin manifestation (adenoma sebaceum) as well as neurological manifestation ( suffered from convulsions during 1st year of life and likely to be mentally retarted). As per her father, the youngest one being 11 years is unable to perform her daily routine on her own, needs help even for eating and using bathrooms, changing clothes. She is not able to communicate properly and becomes furious even with little things and in a new environment. Thus she is not even attending school. Further evaluation and diagnosis of siblings were not possible as they were not present in hospital.

Based on the findings of episodes of convulsion with status epilepticus in between, adenoma sebaceum, ash leaf patterns, shagreen patch, periungual fibroma, intellectual disability and subependymal nodules, which fulfilled most of the major criteria of TSC, the patient was diagnosed to be suffering from Tuberous Sclerosis Complex. Due to financial constraints and lack of facilities in Bangladesh genetic study could not be done.

## Discussion

Angiofibromas, periungual fibromas (Koenen'stumor), shagreen patch and leaf macules, fibromatous plaque, and certain other

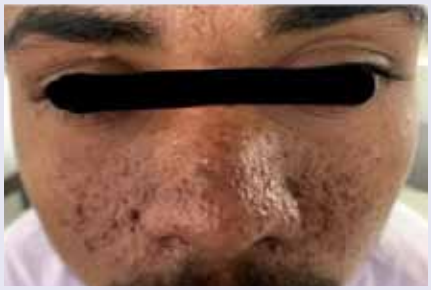

**Figure 1:** Showing adenoma Sebaceum

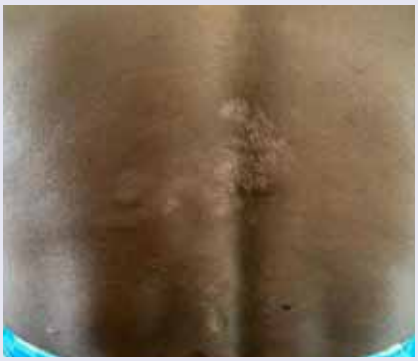

**Figure 2:** Showing Hypopigmented Macules in Ash Leaf Pattren

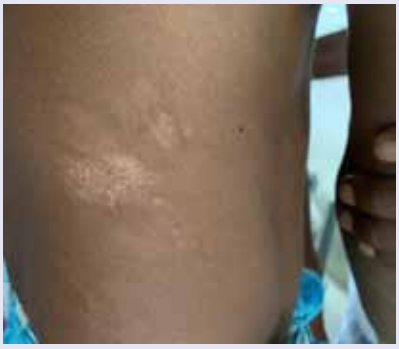

**Figure 3:** Showing Shagreen Patch Over left Abdominal Flank

**Figure 4:** Showing Subungal Fibroma

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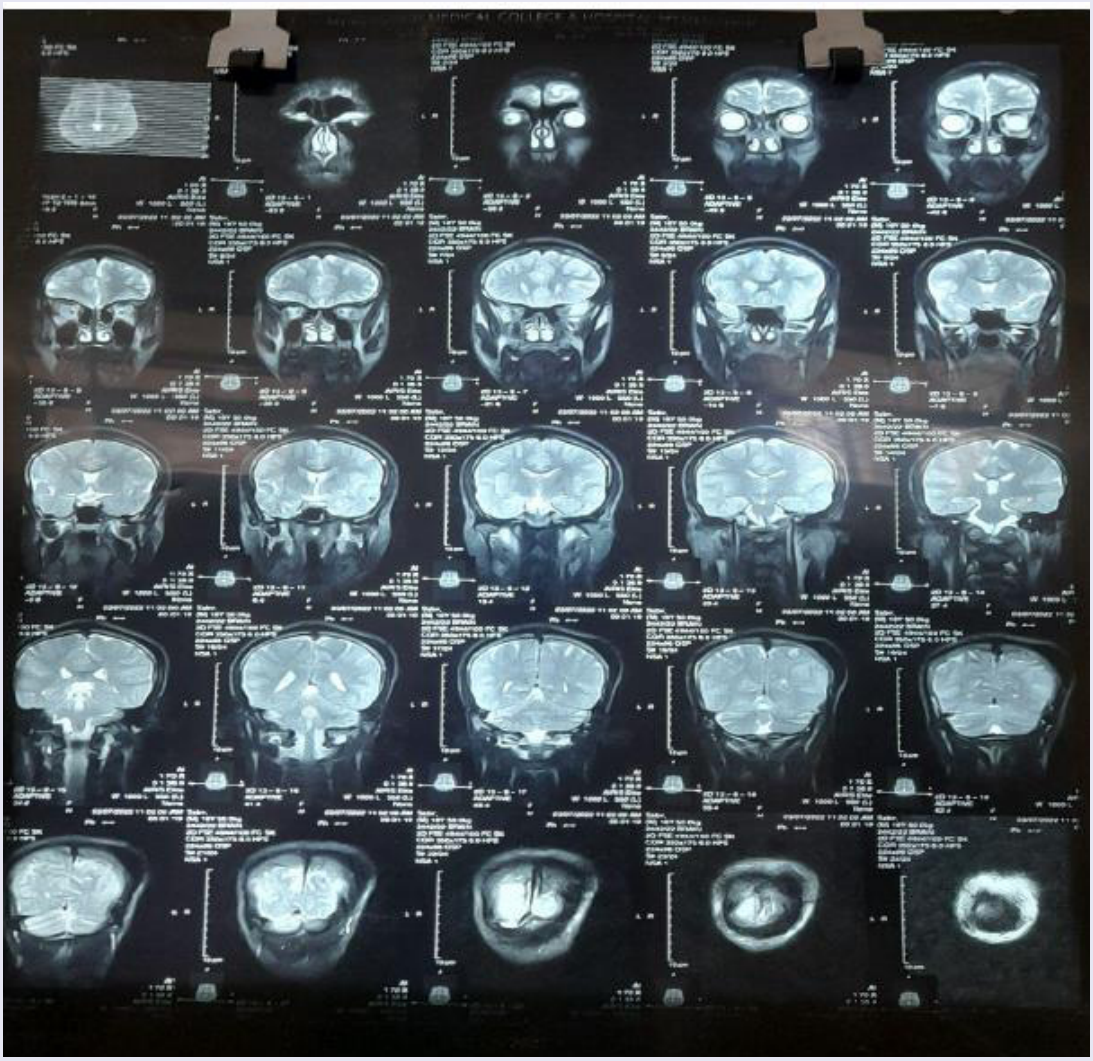

**Figure 5:** MRI Flim Showing Subependymal Nodule.

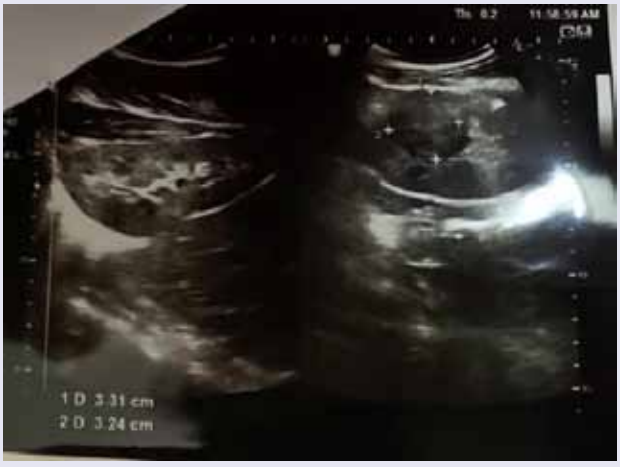


**Figure 6:** Showing a Small Focal Lesion in The Left Kidney

**Figure 7A:** Showing Adenoma Sebaceum of Father (Anterior View)

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**Figure 7B:** Showing Adenoma Sebaceum of Father (Lateral View)

dermatological manifestations, as well as neurological characteristics like seizures, mental retardation, and behavioral issues, are some of the different symptoms of the neurocutaneous disease, tuberous sclerosis complex.[1] Up to 90% of TSC patients have epilepsy, which is considered a significant contributor to intellectual disability.[7]

TSC has a specific set of clinical diagnostic criteria as per the Tuberous Sclerosis Consensus Conference of 1998 and are divided into major and minor features (Table 1). Presence of either 2 major features (out of total 11) or one major feature with 2 minor features (out of total 9) indicated definite TS.[8]

In our patient there are adenoma sebaceum, hypomelanotic macules, shagreen patch, periungual fibroma and subependymal nodules fulfilling 5 major criteria of tuberous sclerosis.

Though Tuberous sclerosis is characterized by the development of unusual tumor growths like hamartoma in brain, skin, retina and other viscera, Arguably the most important hamartomas are cerebral ones and these are responsible for the grave neurologic symptoms and complications. MRI of brain showing tiny subependymal nodule along with small focal lesion in left kidney in ultrasonography of abdomen are the positive imaging findings in our case.[8] The 18-year-old male in this case had neurological and skin manifestations with a normal chest radiograph and the unremarkable echocardiography finding. This is not surprising since the cardiac rhabdomyomas are usually seen in fetuses and neonates and disappear during infancy.[7]

Although tuberous sclerosis complex is a well-known genetic disorder of autosomal dominant category with high penetrance and extensive clinical variability.1 Only one-third of the disease is hereditary, while the rest is due to de novo mutations and are the effects of parental mosaicism, hence sporadic in nature.[1,2] But significant family history is reported in our case where the 2 generations seem to be affected in sequence with variable manifestations. The severity has been noticed to be more in 2nd generations, mostly the younger siblings. The father and 1st child had only dermatological manifestations but the younger children had both dermatological and neurological manifestations, where neurological manifestations were profound in the youngest child even leading to behavior problems like intellectual disability. So further research on the genetic association of TSC in

**Table 1:** Showing major and minor criteria of TSC

| Major criteria | Minor Criteria |
|---|---|
| Facial Angiofibromas or Forehead plaques | Multiple randomly distributed pits In dental enamel |
| Hypomelanotic macules(>3) | Hamartomatous Rectal polyps |
| Shagreen patch (Connective tissue nevus) | Bone Cysts |
| Cortical tuber | Cerebral white Matter migration Tracts |
| Subependymal nodule | Gingival fibromas |
| Subependymal Giant cell Astrocytoma | Nonrenal Hamartoma |
| Multiple Retinal Nodular hamartomas | Retinal achromic Patch |
| Cardiac Rhabdomyoma, Single Or multiple | Multiple renal cysts |
| Lymphangiomyomatosis | |
| Renal angiomyolipoma | |

Bangladesh and its severity as per generations needs to be evaluated to bring out more accurate statistical information.

While the case presented above is consistent with other published case reports on TSC, some differences are also noted. For example, the patient in this case had a family history of TSC, which is not always present in other cases. Additionally, the patient in this case had an unusually severe form of TSC, with intellectual disability and status epilepticus, which may not be present in all cases of TSC.

Prenatal diagnosis is not commonly practiced as no specific prenatal laboratory test is available but first trimester chorionic villus sampling and molecular genetic diagnosis is an option if the mutation in the index case is known.[4,5]

The severity or multiplicity of organ involvement determines the prognosis of TSC. About a quarter of severely affected infants is thought to die before the age of 10 years and 75% before 25 years. However, in the case of individuals diagnosed late in life with few cutaneous signs, prognosis depends on the associated internal tumors and cerebral calcifications.[8]

There is no absolute cure for TSC.[4] The management of these patients includes a multidisciplinary team approach including both medical and surgical methods. Seizures are treated with antiepileptic drugs and systemic complications are treated symptomatically. Surgery, including dermabrasion and laser treatment may be useful for treatment of skin lesions.

[2] Intervention programs including special schooling and occupational therapy may benefit individuals with special needs and developmental concerns. Drug therapy for some of the manifestations of TSC is currently in the developmental stage. Recent trials have shown the use of topical 0.1% rapamycin on facial angiofibromas. The use of inhibitors of mTOR like rapamycin in regression of various hamartomatous growths is a newer modality in the management[8] of TSC.[7]

Patients with TS have a 50% risk of passing on the condition to each of their offspring although the risk of a severely affected child is lower.[5,8] Hence genetic counseling should be offered to families with affected members, even though accurate counseling remains

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difficult because of the variability of gene expression.[8] All the patients diagnosed to have TSC should be evaluated for this by 2-D Echo, ECG, USG abdomen, cranial CT, and CT of the chest.[4]

TSC has no known cure, but treatment with anticonvulsant drugs, educational support, and occupational therapy can help with symptom relief, provide the best quality of life with the fewest complications from the underlying disease process, least harmful treatment effects, and require the fewest medications. [8,10]

TSC has a substantial negative impact on the quality of life (QoL) of patients, affecting psychosocial factors with negative consequences for education and career along with negative impacts on family, social and work-related dynamics.[9]Thus early analysis of a child will help us to control neurological manifestation mainly seizure at early phase thus reducing risk of neurological impairment, mental retardation, multiple behavioral problems including sleep disorder, attention deficit hyperactivity disorder and development of autism spectrum disorder and hence improving the quality of life of an individual.[8]

## Conclusion

As TSC is a lifelong condition, regular surveillance to look for symptoms and early treatment are associated with better health and quality of life outcomes for people with TSC. In our case, if the patient could be diagnosed in early childhood, the severity of Autism Spectrum Disorder, intensity of epilepsy could be minimized. The patient could live a near normal life. Moreover, minimal medication would have been sufficient in that case. Thus, this case report sheds light to the sheer importance of proper evaluation of a TSC patient during childhood. As skin manifestation is one of the most common presentations of this disease, any suspected skin pathology in a child must be evaluated with paramount concern. In addition, any risk factor such as positive family history needs to be excluded. From our findings, we can firmly say, despite the rare association of family history with TSC in various studies, it is indispensable to evaluate family history.

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**Consent**

Written consent was taken from the patient and his father

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