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CASE REPORT

TALE OF A TEENAGER: A CASE REPORT OF TUBEROUS SCLEROSIS

NAWSABAH NOOR[1], IFFAT ARA JURFA[2], HALIMA KHATUN[3], HOMAYRATAHSEEN[4], QUAZI TARIKUL ISLAM[5]

Abstract:

Tuberous sclerosis complex is an unusual neurocutaneous syndrome with autosomal-dominant inheritance. It is characterized by the development of benign tumors involving the brain, skin, retina, heart, kidneys, lungs, and liver. The classic triad of clinical features comprises learning disability, epilepsy and skin lesions but there is marked heterogeneity in clinical features. Here, we present a case report of a 17-old-year male with characteristic clinical and radiological features of tuberous sclerosis complex.

Key words: *Tuberous sclerosis, angiofibroma, shagreen patch, epilepsy.*

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Introduction:

Tuberous sclerosis complex (TSC) is a rare entity with variable incidence between 1/6,000 and 1/18,000 affected individuals[1]. Mutations of two genetic loci have been identified as the underlying pathogenic mechanism: *TSC-1* (chromosome 9) encoding hamartin, and *TSC-2* (chromosome 16) encoding tuberin are implicated via a loss of inhibition of the mammalian target of rapamycin (mTOR) pathway[2].

The predominant neurological and psychiatric manifestations of TSC include epilepsy, intellectual disability, autism, hyperactivity and mood disorders[3]. Epilepsy is present in up to 90% of TSC patients[4] which is proposed as a major factor contributing to intellectual disability[5]. Subependymal nodules, cortical tubers and giant cell astrocytomas are the characteristic brain lesions in TSC which result in the development neuropsychiatric menifestations[6]. Outside the brain, the main manifestations of TSC involving skin (hypomelanotic macules, Shagreen patch and angiofibromatomas), kidneys (renal angiomyolipomas), lungs (lymphangioleiomyomatosis), heart (cardiac rhabdomyomas), and eye (retinal hamartomas)[5]. Given the very high variability in the diverse manifestations of the disease[7], the diagnosis of TSC as well as the establishment of a severity prognosis remains a challenge.

Case Presentation:

A 17-year-old male with mental retardation presented to our institution complaining of vague dull abdominal pain for 2-3 months. Pain was mild to moderate in intensity according to the parent's statement. Due to difficulty in communication with the patient due to his intellectual impairment, we couldn't elicit the exact location, characteristics, aggravating or relieving factors of the pain. There was no history of fever, weight loss, altered bowel habits, jaundice, vomiting, burning micturition or haematuria.

The patient also has multiple growths in his face for the last 10-12 years. The patient's parents noticed

1. Registrar, Department of Medicine, Popular Medical College, Dhaka, Bangladesh.
2. Medical Officer, Sher-e-Bangla Medical College, Barishal
3. Assistant Registrar, Department of Medicine, Popular Medical College, Dhaka, Bangladesh.
4. Associate Professor, Department of Medicine, Popular Medical College, Dhaka, Bangladesh.
5. Professor, Department of Medicine, Popular Medical College, Dhaka, Bangladesh.

Correspondence: Dr. Nawsabah Noor, Registrar, Department of Medicine, Popular Medical College, Dhaka, Bangladesh. Email: nawsabah.noor@gmail.com

the lesions when he was 5 years old, which gradually increased in size to attain the present size. There was no history of pain, itchiness or blood/purulent discharge associated with the growth. On query Mother also mentioned that when her son was 2.5 years old, he started having multiple seizures which were generalized tonic-clonic in nature that lasted for a few minutes, about 3/4 times in a day and was treated at an outside hospital. With the antiepileptic medication, seizure came to control but didn't need to take any regular anticonvulsant. At the age of 10years, the patient developed status epilepticus and was admitted at Barishal Sadar Hospital and was managed accordingly. Since then he is taking anticonvulsant medication (Carbamazepine) regularly and the patient didn't have any further attack of seizure over the last 7years. The parents also mentioned about gradual impairment of the patient's speech since the age of 4/5years and now the patient cannot speak at all and has difficulty in understanding as well. There was no extended family history of this type of dermatological or seizure disorder. Pre-natal and post-natal periods were uneventful according to the mother and he had no delayed milestones. He is the second child of two siblings, the other one is healthy and doing well.

On general physical examination, multiple well-defined, reddish-brown nodular growths and shiny papular lesions were noted on the forehead, nose, and cheeks in a characteristic "butterfly pattern" consistent with adenoma sebaceum (Figure 1). Similar firm nodular growths were noted in the back of the head. We also noticed a well-defined roughened hypermelanotic patch region showing an orange peel appearance indicative of Shagreen patch (Figure 2) on his lower abdomen close to his left flank. Mother admitted to the application of topical agents which were unsuccessful in clearing the lesions. Vital signs were found to be within satisfactory limits. Other skin lesions of tuberous sclerosis such as periungal fibromas, ashleaf spots were not evident. On intraoral examination, marginal gingival enlargement was also observed and some dental anomalies were noted as well (Figure: 3). Based on the history and clinical findings, a provisional diagnosis of drug-induced

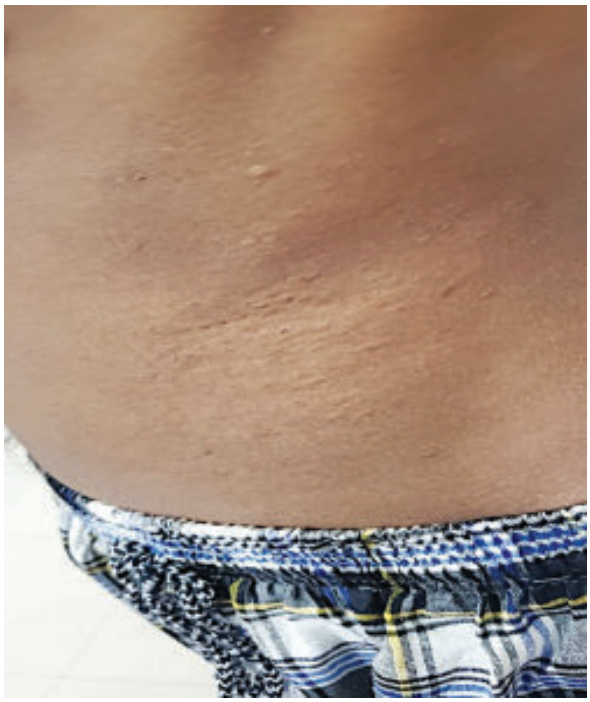

Fig.-2: *Shagreen Patch*

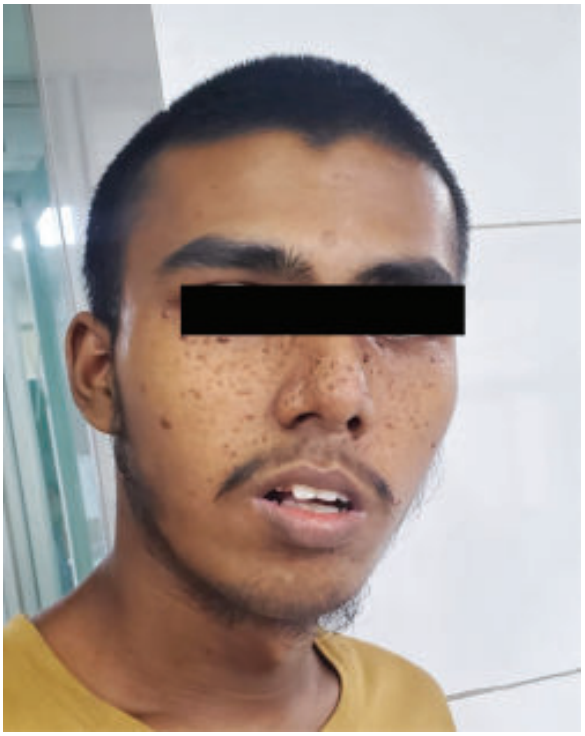

Fig.-1: *Adenoma Sebaceum*

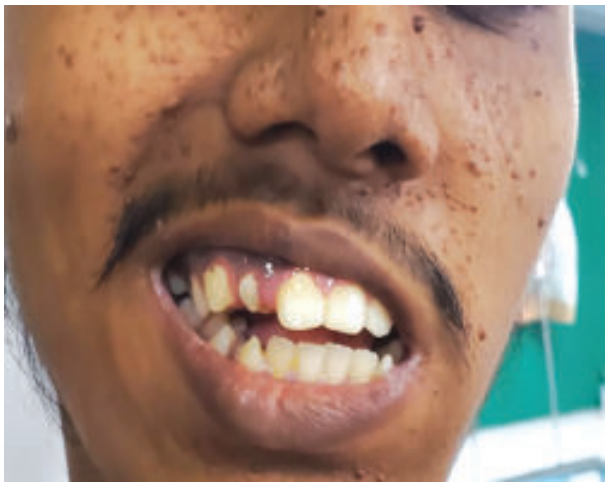

Fig.-3: *Dental anomaly, Gum hyperplasia*

gingival enlargement was considered. Differential diagnosis of gingival fibromas was also considered.

On investigations, his haemoglobin was 11.60g/dl (MCV: 80.7, MCH 27.3, MCHC 33.8). Rest of the blood investigations including serum creatinine, electrolytes, liver functions and urine routine examination were normal. Ultrasonography of the abdomen showed normal study but CT abdomen showed Hepatomegaly without any changes in echotexture (Figure:4).Color fundus photograph reveals circumscribed lipid deposition along the superior arcade of macular blood vessels on the right eye and left eye reveals no abnormality (Figure: 5).MRI brain with contrast showed encephalomalacic change in the left temporo occipital region. On FSE-T2 and T2 flair images of MRI brain showed discrete/ confluent hyperintense foci in sub-cortical & deep white matter of both cerebral hemisphere and few tiny subependymal nodules with signal void area which may suggest calcific nature of the lesion (Figure: 6). Following contrast augmentation these areas showed mild peripheral contrast enhancement. EEG showed occasional epileptiform discharge (spike and wave complexes) in the right temporo-occipital region.Chest X-Ray, ECG, color doppler Echocardiogram findings were normal.

Based on the findings of adenoma sebaceum, shagreens patch, learning disability, subependymal calcified tubers and evidence of old retinal haemorrhages, the patient was diagnosed as a case of TSC[8]. Due to financial constraints and lack of facilities genetic studies could not be done.

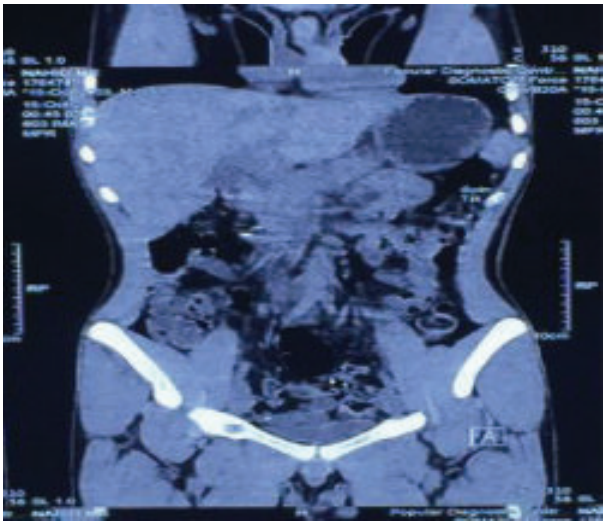

Fig.-4: *CT Abdomen*

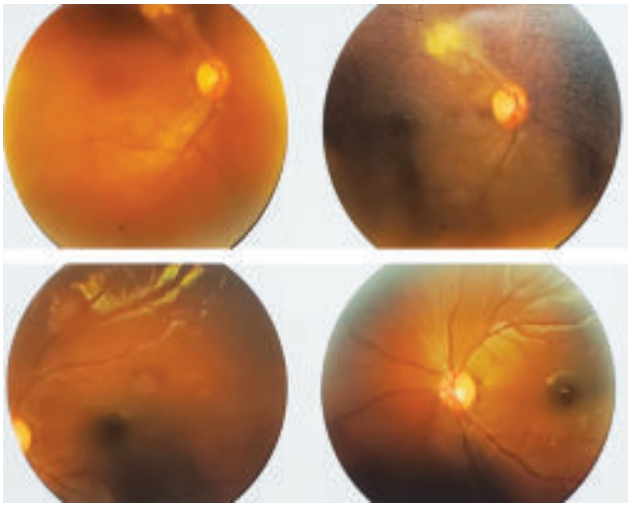

Fig.-5: *Color Fundus Photograph*

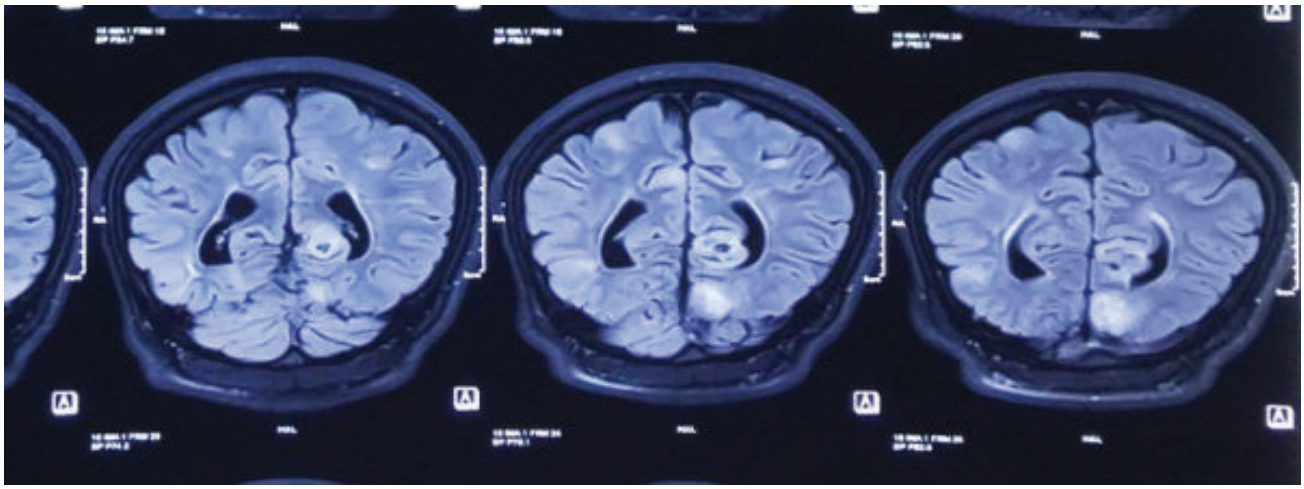

Fig.-6: *MRI Brain with Contrast*

Discussion:

Tuberous sclerosis (TS) is a rare autosomal dominant neurocutaneous syndrome that consists of numerous hamartomatous lesions. It has been seen that approximately two-thirds of the cases are sporadic[8]; this may explain why our patient has negative family history of TS. Sex and ethnic background don't affect the prevalence of this disease[9]. TS typically shows three clinical features, which consists of mental retardation, epilepsy, and facial angiofibroma; however, approximately half of TS patients have normal intelligence[8].

At the Tuberous Sclerosis Consensus Conference of 1998, the clinical diagnostic criteria of TSC were revised and a new classification system based on major and minor findings was established. The presence of two major features or one major and two minor features was considered sufficient for a definitive diagnosis. The major features include (a) Hypomelanotic macules (≥3, at least 5-mm diameter), (b) Angiofibromas (≥3) orfibrous cephalic plaque, (c) Ungual fibromas (≥2), (d) Shagreen patch, (e)Multiple retinal hamartomas, (f) Cortical dysplasias, (g) Subependymal nodules, (h)Subependymal giant cell astrocytoma, (i) Cardiac rhabdomyoma, (j) Lymphangioleiomyomatosis, and (k) Angiomyolipomas (≥2). The minor features include (a) "confetti" skin lesions, (b) dental enamel pits (≥3), (c) intraoralfibromas (≥2), (d) Retinal achromic patch, (e) Multiple renal cyst, and (f) Nonrenal hamartomas[10]. Our case presented with three major features – facial angiofibromas, Shagreen patch and subependymal nodules.

The 17-year-old boy in this case had seizure and facial angiofibroma with a normal chest radiograph and the echocardiography was unremarkable. This is not surprising since the cardiac rhabdomyomas are usually seen in fetuses and neonates and disappear during infancy[11]. Our patient had the brain findings on MRI which are discrete/confluenthyperintense foci in sub-cortical & deep white matter of both cerebral hemisphere and few tiny subependymal nodules with signal void area which may suggest calcific nature of the lesion along. As mentioned above, this finding is one of themajor clinical diagnostic criterias of tuberous sclerosis[12].

The management of these patients includes multidisciplinary team approach involving the neurosurgeon, neurologist, nephrologist, pulmonologist, cardiologist, ophthalmologist, and the genetic counselor. Surgery including dermabrasion and laser treatment may be useful for the treatment of skin lesions. Intervention programs including special schooling and occupational therapy may benefit individuals with special needs and developmental concern[13,14].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 in regression of various hamartomatous growths is a newer modality in the management of TSC[13].

For the proper management of our patient, we consulted with Nephrologist, Dermatologist and Ophthalmologist. For the control of seizure, the patient was on carbamazepine 40mg daily for last 7years. As seizure is in good control with above antiepileptic; we did not change the regimen. And patient is also advised to apply tacrolimus ointment (0.1%) over the facial adenoma sebacum with the expectation to reduce the hamaromatous growth on face. Nephrologist and Opthalmologist advised for regular follow up. Patient's parents were counselled regarding the prognosis of the disease and for regular follow up. They are also being sent for social support and rehabilitation.

The prognosis of TSC depends on the severity or multiplicity of organ involvement. About a quarter of severely affected infants is thought to die before the age of 10% 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[14].

Conclusion:

Despite the rarity of TS; it is crucial to diagnose as early as possible to prevent long term organ damage. Dermatological manifestations, learning impairment can give the clue and also imaging can help in diagnosis. As there is no cure, we should manage the patient through a multidisciplinary approach with symptomatic treatments. Support groups should be formed as well.

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Declaration of interest:

The authors report no conflict of interest.

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identifiable information provided in the article and has consented to this publication. The clinical tests were all done as part of clinical practice.

Abbreviations:

- TS: Tuberous Sclerosis

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