

Tuberous sclerosis complex: Case report and management by multidisciplinary approach

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Abstract

Tuberous Sclerosis Complex (TSC) is a syndrome characterized by cellular hyperplasia, tissue dysplasia and multiple organ hamartomas. It is a lifelong condition requiring periodic monitoring and evaluation to reduce morbidity and mortality. Our patient is a 32-year-old male who presented to us as an undiagnosed case since childhood with one-week history of abdominal pain. He was uneducated, as well as, suffering from bipolar disorder. On examination, he fulfilled five major clinical criteria required for diagnosis of TSC. The abdominal pain was due to renal complications of the disease, bilateral angiomyolipomas. The routine renal function tests were normal; however, confirmatory radioactive nuclear scan (DTPA) was done to evaluate detailed functional status of both kidneys. The results of DTPA indicated critically low split kidney function bilaterally, inhibiting us from any immediate surgical intervention. The patient was put up on monthly follow-up and treated for his bipolar disorder. Delay in diagnosis for more than 30 years lead to the complications of renal angiomyolipomas and bipolar disorder. Prompt diagnosis, periodic monitoring and evaluation based on individual TSC-associated neuropsychiatric disorders (TAND) profile will delay the complications and help patients becoming productive members of the society.

Key words

Tuberous sclerosis complex, bilateral renal angiomyolipomas, TAND profile, genetic disorders, diagnostic criteria.

Introduction

Tuberous sclerosis complex (TSC), also called Bourneville's (Bourneville- Pringle) disease, is a rare autosomal dominant neurocutaneous syndrome. It is characterized by cellular hyperplasia, tissue dysplasia and multiple organ hamartomas such as brain, skin and kidney due to which most patients present with epilepsy (96%) and skin lesions (> 90%).¹ Hence TSC is also remembered with the acronym EPILOA (epilepsy, low intelligence, adenoma sebaceum).

The disease is caused by mutation in either TSC 1 or TSC 2 gene leading to constitutive activation of mammalian target of rapamycin (mTOR) receptor, a regulator of cellular proliferation and differentiation.²

The presence of cutaneous stigmata of TSC such as ash leaf spots (hypomelanocytic macules) and facial angiofibromas should prompt a strong suspicion of the disease. The presence of ash leaf spots at birth or in later months along with seizures in early infancy, with or without family history, should be investigated for TSC. By the age of two years the presence of facial angiofibromas clues towards TSC.³ Prompt diagnosis at this age is of paramount importance for better follow-up of later expected complications of the disease process. We present

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case report of a 32-year-old undiagnosed male with classical signs who presented with known complications. We adopted a multidisciplinary approach to diagnose and treat the patient.

Case Report

A 32-year-old male, presented to emergency department of Shaikh Zayed Medical Complex, Lahore with one-week complaint of abdominal pain. It was mild and dull in nature, non-radiating and with no aggravating or relieving factors. For the last 1 year, he noticed an abdominal mass gradually increasing in size at the site of pain with generalized weight loss.

Since early childhood he had multiple small reddish papules in malar area of face and around the nasolabial folds. There was no history of bleeding, itching, pain or change in the size of these lesions. He had multiple episodes of seizures from 2 to 6 years of age. No antiepileptic was started. He was uneducated as he did not pursue school education due to learning difficulties. He had frequent mood swings, ranging from depression to rage and euphoria. There was no family history of seizures in his parents or siblings.

The patient was pale, unusually smiling and talkative. Upon examination he had a firm abdominal mass in the left lower quadrant, extending up to the umbilicus. His liver function tests, renal function tests, and complete blood count, were within normal limits except normocytic normochromic anemia having hemoglobin level of 10.1 g/dl (normal: 12-16 g/dl).

Ultrasonography of the abdomen identified the mass as moderately enlarged left kidney (14.0 x 5.3 cm) and mildly enlarged right kidney (12.0 x 5.2 cm). Hyperechoic areas around kidneys were most likely to be angiomyolipomas. Computed

tomography (CT scan) confirmed both kidneys to have angiomyolipomas.

Detailed evaluation of functional status of each kidney using nuclear radioactive tagged DTPA (diethylenetriaminepentacetate) scan from Institute of Nuclear Medicine Lahore (INMOL) revealed a split kidney function of 25% for left Kidney and 18% for right kidney.

We adopted a multidisciplinary approach to correlate the facial lesions, renal angiomyolipomas and mood swings. The facial findings over the malar area were angiofibromas (adenoma sebaceum) in a typical butterfly pattern (**Figure 1**), periungual fibroma (Koenen's tumor) on the left big toe (**Figure 2**) and hypomelanocytic macules around the neck (ash leaf spot) which is typical of tuberous sclerosis.⁴

Mini Mental State Exam (MMSE) for dementia was uneventful but the patient was evaluated to be suffering from bipolar disorder. MRI of brain (**Figure 3**) revealed cortical tubers with subependymal nodules (SEN), some of which were partially calcified. A retention cyst was also noted in maxillary antrum.

The patient had no eye symptoms and the retinal funduscopy was also within normal limits. He did not have any dental problems, oral fibromas, gingival hyperplasia or history of intake of any antipsychotic medications. His ECG and X-ray chest were unremarkable.

On a monthly follow-up basis the patient was prescribed tablet risperidone 1mg for bipolar disorder along with tablets folic acid 0.5 mg and ferrous sulphate 150 mg, both for anemia, all once daily. He was advised to report immediately if he had hematuria, abdominal swelling or severe pain.



Figure 1 Facial angiofibromas in malar area and nasolabial folds. Fibrous plaques are also visible on left temple and forehead.



Figure 2 Perinugal fibroma on right big toe.

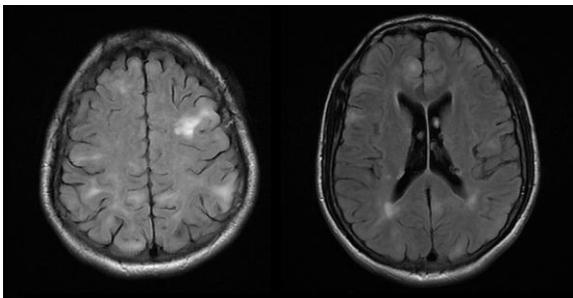


Figure 3 MRI axial view T2 flair showing cortical tubers.

Discussion

Our patient was a 32-year-old male, non-

hypertensive, non-diabetic, who fulfilled five major criteria (facial angiofibromas, periungual fibromas, ash leaf spots, cortical dysplasia, subependymal nodules (SEN), renal angiomyolipomas) of tuberous sclerosis complex (TSC) as per diagnostic criteria of the 2012 International Tuberous Sclerosis Complex Consensus Conference (**Box 1**).⁴

He had facial angiofibromas since the age of 2 year and untreated epilepsy throughout his early childhood. There was also history of psychiatric disorders including bipolar disorder, learning difficulties, abusive behavior and mood swings. However, a diagnosis of TSC was not made, even in presence of these classical clinical features, leading to patient presenting now at 32-year of age with known renal complications of bilateral renal angiomyolipoma, which was causing obstruction and pain as they enlarged.

A confirmatory radioactive nuclear scan (DTPA) to evaluate detailed functional status of both kidneys inhibited us from any immediate surgical intervention although routine RFTs were within normal limits.

Our patient had TSC most likely due to spontaneous genetic mutation which is seen in majority of patients, as there was no family history in his previous generation, although history of last three generations, as recommended, was not known to the patient.⁵ He had 3 children, aged 11-year, 7-year and 2-month from a non-consanguineous marriage. Up till now none of his children had skin lesions, seizures or any psychiatric disorder. All patients with family history or having one or more clinical diagnostic criteria, as mentioned in **Box 1**, must be suspected for TSC.

In our patient's future off springs, we plan to conduct antenatal screening as multiple imaging modalities can confirm *in utero* diagnosis of

Table 1 Clinical diagnostic criteria of tuberous sclerosis complex 2012 [4].

Major Features

1. Hypomelanotic macules (≥ 3 , at least 5-mm diameter)
2. Angiofibromas (≥ 3) or fibrous cephalic plaque
3. Ungual fibromas (≥ 2)
4. Shagreen patch
5. Multiple retinal hamartomas
6. Cortical dysplasias*
7. Subependymal nodules
8. Subependymal giant cell astrocytoma
9. Cardiac rhabdomyoma
10. Lymphangiomyomatosis (LAM)[†]
11. Angiomyolipomas (≥ 2)[†]

Minor features

1. "Confetti" skin lesions
2. Dental enamel pits (>3)
3. Intraoral fibromas (≥ 2)
4. Retinal achromic patch
5. Multiple renal cysts
6. Nonrenal hamartomas

Definite diagnosis: Two major features or one major feature with ≥ 2 minor features

Possible diagnosis: Either one major feature or ≥ 2 minor features

* Includes tubers and cerebral white matter radial migration lines.

[†] A combination of the two major clinical features (LAM and angiomyolipomas) without other features does not meet criteria for a definite diagnosis.

TCS.⁶ An anomaly scan done in 2nd trimester can identify major structural anomalies in about 60% cases, including fetal cardiac rhabdomyomas, polycystic kidney disease, or CNS lesions as seen in TSC.⁷ Genetic testing for TSC1 and TSC2 having more than 90% sensitivity is commercially available in developed countries of the world but rarely available and very costly in developing countries.

Our patient was uneducated as he never attended school due to behavioral and learning problems for which he never had any psychiatric evaluation. Children of school-going age suffering from TSC should be considered for an individual education plan (IEP) based on the individual TSC-associated neuropsychiatric disorders (TAND) profile so that they can be

enrolled in designated educational programs.⁸

TAND is new terminology proposed to describe the interrelated functional and clinical manifestations of brain dysfunction common in TSC. TAND checklist should be in routine practice for comprehensive neuropsychiatric evaluation of all patients with TSC and compared periodically for determining progression of disease.

The current research, for possible treatment modalities of TSC, is targeted towards use of negative regulators of mTOR signaling pathway, everolimus and sirolimus.⁹ Everolimus is approved by U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA) for use in adults with TSC-associated renal angiomyolipoma and subependymal giant cell astrocytoma (SEGA). However, due to financial constraints, everolimus was not used for renal angiomyolipomas in our patient.

Numerous clinical trials have shown sirolimus to be effective for facial angiofibromas. However, it is not approved by FDA or EMA and no commercial preparation is available as yet.

A multi-disciplinary management approach for TSC should be adopted due to its wide clinical spectrum as still the disease is incurable. It is a lifelong condition which should be diagnosed as early as possible so that patients can be periodically monitored, at least annually, throughout their lives, according to The 2012 International Tuberous Sclerosis Complex Consensus Recommendations. The recommendations emphasize on a multidisciplinary approach throughout the lifespan of the patient, for all organ systems.⁵

We also propose establishment of South Asian and Pakistan chapters of Tuberous Sclerosis Alliance for acting as a support group for

patients with TSC and creating awareness among general public about the disease.

Our patient has variable involvement of organs confined at present to brain, skin and kidney. Long-term follow-up is mandatory to ascertain the severity levels of organs involved and the possibility of other organs involvement and their management.

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