Tuberous Sclerosis Complex

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ABSTRACT

Tuberous Sclerosis Complex (TSC) is a rare, autosomal dominant, neurocutaneous disease characterized by the development of benign tumors that affect the brain, skin, retina, and other viscera. The clinical presentation is variable between and within families with respect to the number and severity of clinical manifestations. Nearly all patients have one or more dermatological manifestations, the most common being adenoma sebaceum, and most patients have epilepsy. The classic triad of facial adenoma sebaceum, epilepsy, and cognitive deficit (Vogt triad) is present only in one-third of the patients. Published cases of tuberous sclerosis had a maximum of four major clinical criteria. We report a 28-year-old lady with five major criteria for TSC who remained undiagnosed till she presented to the medical outpatient department for an unrelated complaint.

Keywords: Tuberous Sclerosis Complex, Genetic Disease, Case Reports.

INTRODUCTION

Tuberous sclerosis complex (TSC) is a genetic disorder that affects cellular proliferation and migration, resulting in hamartomatous lesions affecting different systems.[1] In 1862, von Recklinghausen described TSC as a rare autosomal dominant disorder, but it was not until the 1880's when the term "Sclerose Tubereuse" was first presented to the medical community diagnosed by Bourneville in subjects having epilepsy and mental retardation.[2] The first symptoms and signs of TSC can occur at birth but the majority of patients experience symptoms over time. Seizures and dermatological manifestations are the initial observed symptoms. Adenoma Sebaceum, which does not occur until late childhood or early adolescence, is the most common known skin manifestation of TSC.[3] Patients with TSC can have trouble learning.[4] The frequency of TSC in 10,000 live births is reported to be 1 and about a third as frequent as type 1 neurofibromatosis.[5]

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CASE PRESENTATION

A 28-year-old lady presented to the outpatient department of Hayatabad Medical Complex, Peshawar, Pakistan complaining of right flank pain for the last one week. This was associated with burning micturition and fever. Her history was remarkable for the use of anti-epileptic medication (Divalproex sodium 500mg BD) since the age of three months when she was diagnosed as having epilepsy based on clinically documented evidence of generalized tonic-clonic fits. Moreover, her mother reported she has cognitive and intellectual disabilities since childhood, due to which she could not have formal or informal education. She is the youngest child of non-consanguineously married parents, and her birth was by normal vaginal delivery with no significant perinatal morbidity. Her family history was unremarkable. Physical examination revealed facial angiofibromas (Adenoma sebaceum), Subungual fibroma on the right hand, and a Shagreen patch on her back (figure 1).

INVESTIGATIONS

Her baseline investigations were unremarkable except 10-12 red blood cells and 2 – 3 pus cells in her urine routine examination. She had normal-sized kidneys with slightly increase parenchymal echogenicity on ultrasound abdomen/pelvis. MRI brain was carried out which showed bilateral subependymal tubercles and subcortical tubercles in the frontal, parietal and occipital region (figure 2). She was taken for an ophthalmology review where choroid tubercles were found in both eyes.

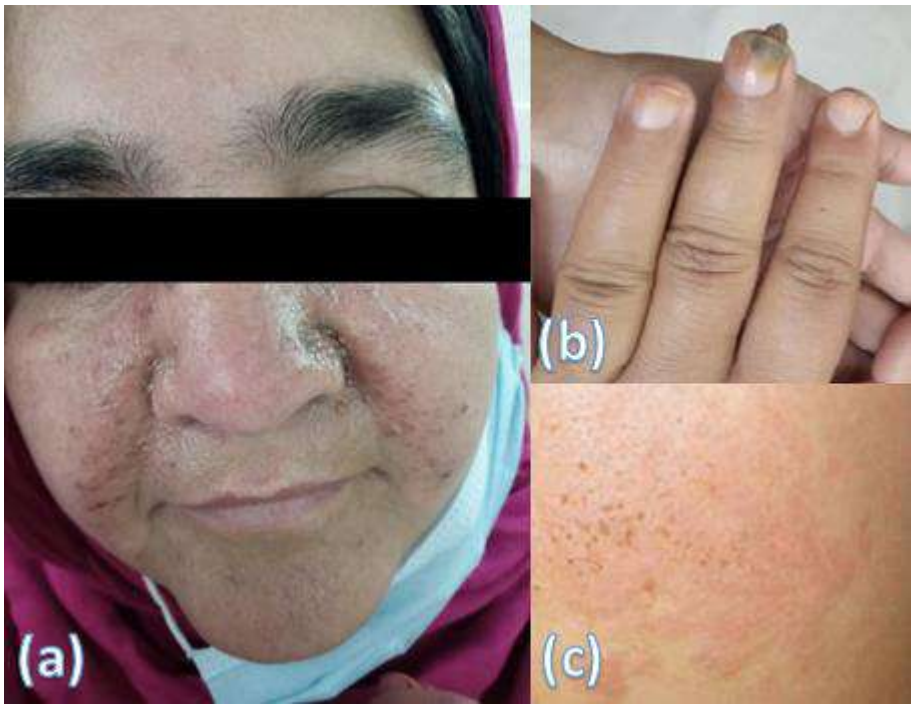

Figure 1: (a) Visible adenoma sebaceum on face; (b) Subungal Fibromata on patient's right hand; (c) Shagreen Patch on patient's left lumbar area.

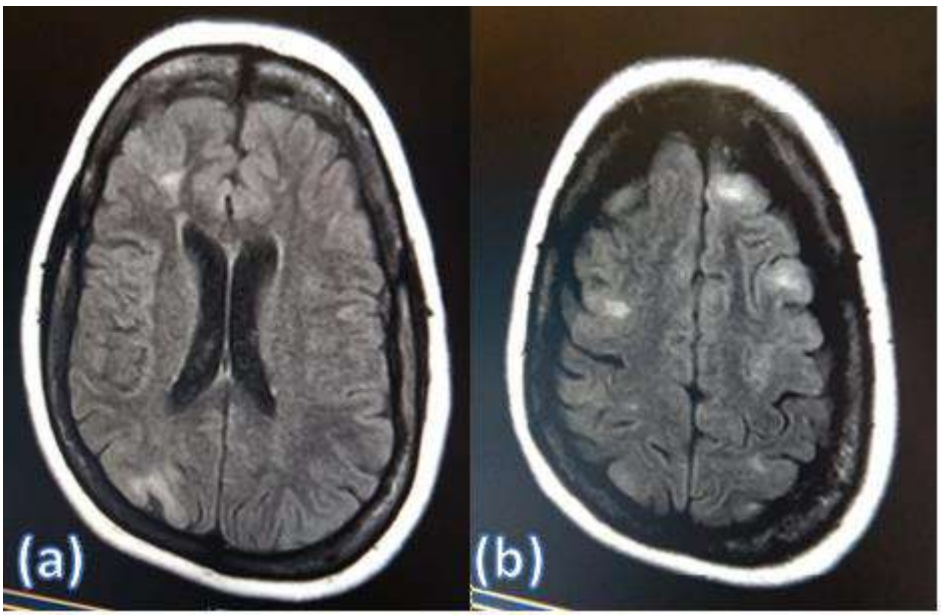

Figure 2: (a) T2 flair with Subependymal tubercles; (b) T2 flair with Subcortical tubercles in the frontal, parietal and occipital region.

DIAGNOSIS

The patient was diagnosed as a case of Tuberous Sclerosis Complex based on the fulfillment of 5 major criteria.

TREATMENT

During her stay in the hospital, she was conservatively managed, her regular antiepileptic medications were continued.

OUTCOME AND FOLLOW UP

She was advised for a follow-up visit in one month.

DISCUSSION

TSC is characterized by a variety of tumors, including brain tumors, skin tumors, retinal tumors, and visceral tumors. The "Tuberant Sclerosis" refers to multiple sclerosis masses spread throughout the brain. If these masses are in more than one organ, the TSC diagnosis is dependent upon the presence of hamartomas.

The diagnosis of definite TSC is made in a patient who fulfills any two of the major or one major and two minor criteria. A diagnosis of possible TSC is made if the patient has one major or two or more minor criteria. (Table 1)

Table 1: Diagnostic criteria for tuberous sclerosis complex.

Major Criteria	Minor Criteria
Cortical Tubercle	Multiple Dental Pits
Subependymal Nodule	Gingival Fibromas
Facial Angiofibroma Or Forehead Plaque	Retinal Achromatic Patch
Ungual Or Periungual Fibroma (Nontraumatic)	Confetti Skin Lesions
Hypomelanotic Macules (>3)	Nonrenal Hamartomas
Shagreen patch	Multiple Renal Cysts
Multiple Retinal Hamartomas	
Cardiac Rhabdomyoma	
Renal Angiomyolipoma	
Pulmonary Lymphangioleiomyomatosis	-
Sub Ependymal Gaint Cell Astrocytoma	-

In addition to clinical criteria, genetic testing to identify the causative gene is sufficient to make a diagnosis of definite TSC. Genetic testing is not needed for patients who meet the clinical criteria for definite TSC, but it is valuable for confirming the diagnosis in patients with possible TSC, for reproductive planning, and for identifying at-risk family members.

The patient being reported fulfilled five major criteria including the Vogt triad. A thorough search of reported cases revealed patients who have up to four major criteria manifestations at the time of diagnosis, and less than one-third of patients have the Vogt triad.[5–7]

The parents of the patient did not have any clinical manifestations of TSC. This may be explained by the phenomena of somatic mosaicism and variable penetrance. A parent with the somatic mosaicism for a mutation may have mild or no clinical features while an offspring who inherits the same mutated gene may develop severe clinical manifestations as compared to the parent.[8,9]

The treatment of such patients is often multi-disciplinary involving physicians, dermatologists, ophthalmologists, neurosurgeons, neurologists, and geneticists. Medical treatment in addition to supportive treatment like antiepileptic medications is currently in the developmental stage. The use of mTOR inhibitors for regression of various hamartomatous growths is a new approach6. Recent studies suggest that topical use of 0.1% rapamycin cream on facial angiofibromas is highly effective in such cases.[4,10] Surgery, like dermabrasion and laser surgery, is helpful in the treatment of skin lesions. Clinical intervention such as special educational programs and physical therapy are supportive of the special needs and developmental problems associated with TSC.[11,12]

LEARNING POINTS

Tuberous sclerosis complex presents as seizures in the majority of the patients. General practitioners and physicians shall have a high index of suspicion in patients of all ages presenting with seizures as these patients may have other clinical features of TSC at the initial presentation or may develop these features during follow-up. Moreover, a negative family history shall not preclude a diagnosis of TSC.

DECLARATIONS

Patients consent for use of data for publication:

The study certifies that its fulfillment of appropriate patient consent forms requirement. In the consent forms obtained the patient has

given her consent for her images and other clinical information to be reported in the journal. The patients share their understanding towards concealed identity and no name inclusion in the study, with efforts towards non-guaranteed anonymity.

Authors' contributions:

Ume Hani Naeem identified the case, all authors contributed to manuscript writing, and Mohammad Noor also did the overall supervision.

Conflicts of Interests:

The authors have no conflicts of interest to disclose.

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