Tuberous Sclerosis Complex – A Case Report

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Abstract

Tuberous sclerosis complex (TSC) is an autosomal dominant genetic disorder characterised by hamartoma formation in multiple organs, particularly the skin, brain, eye, kidney and heart. It is caused by mutation of two genes TSC1, and TSC2, which encode Hamartin and Tuberin, respectively. In this paper, a case of a 19-year-old female with TSC is reported as it is associated with angiomyolipomas of the kidneys, dentigenous cyst, polycystic ovarian disease, calcified subependymal nodules in the lateral ventricles of brain and multiple radial lens opacities in the eyes.

Methodical systemic examination with appropriate investigations is mandatory to diagnose a case of TSC.

Key-words: Tuberous sclerosis complex, angiomyolipomas, polycystic ovarian disease

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Introduction:

Tuberous sclerosis was first recognised as a specific disease in the 19th century. In 1818, Bourneville, a French Neurologist reported the case of a mentally retarded child with hemiplegia and epilepsy[1]. Tuberous sclerosis complex (TSC) is an autosomal dominant disorder with high penetrance and extensive clinical variability; two-third of cases are caused by de novo mutations and are the effects of parentral mosaicism.[2] TSC is characterized by the hamartoma formation in many organs, particularly the skin, brain, eye, kidney and heart.[1] TSC is caused by mutations in TSC_1,(9q34) and TSC_2 (16p13) genes coding for hemartin and tuberin,respectively.[2] These proteins act as tumour growth suppressors, agents that regulate cell proliferation and differentiation[3]. The incidence is as high as 1 in 10,000 live births[1]. In 1908 Vogt proposed a triad typical for Tsc diagnosis, consisting of epilepsy, low intelligence and angiofibroma[2]. Definitive TSC is diagnosed with either two major features (out of total of 11) or one major feature with two minor features (out of total of 9).[3]

The pathognomic skin lesions include angiofibromas, Periungual fibromas (Koenen's tumour), shagreen patch and ash-leaf macules. Other cutaneous manifestations include fibromatous plaque on forehead and scalp, soft pediculated fibromas around the neck and axilla and poliosis.[1,3,6]

In 1961, Nickel and Reed observed a fibromatous forehead plaque in a patient with advanced mental retardations. The presence of fibrotic plaque was a poor prognostic sign in tuberous sclerosis.[5]

Cerebral lesions may manifest as seizures, mental retardation and behavioural disorders. Cardiac rhabdomyomas are observed in about half of the patients with TSC.[1,3,6]

Angiomyolipomas are observed in 75 % of the patients over 10 years of age. Other renal manifestations include renal cyst, renal cell carcinoma and polycystic kidneys. Retinal astrocyte hamartomas are present in patients with TSC and hamartomatous colonic polyps may also been seen.[3]

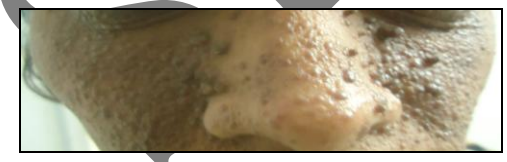
The clinical symptoms of Tuberous sclerosis may appear gradually during life.

CASE-REPORT

A 19-year-old female, born to consanguineous parents, presented to the outpatient unit of the department of skin with a history of multiple red-brown lesions over the face and swelling of the left jaw since 10 years, incidence H/o seizures since 2 years, a history of asymptomatic plaque over the forehead and lumbosacral area since the age of 5 years and a history of learning difficulty since childhood. Similar complaints were reported to be found in the paternal grandmother.

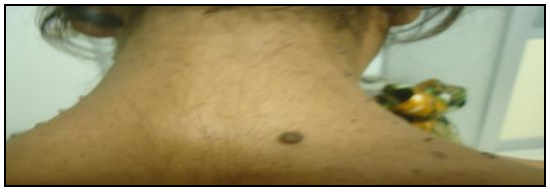
Dermatological examination revealed multiple angiofibromas over naso-labial folds, cheeks, chin, eyelids, forehead and neck. Two shagreen patches of size 3x2 cm and 18x4cm are present over lumbosacral region. Fibrous plaque of 1cm is present over forehead. Multiple giant achrocordons are present over axilla and supraclavicular region. Woods lamp examination showed Ash-leaf macules over the back ,smooth skin coloured nodules, Koenen's tumour emerging form proximal nail folds present over right and left index fingers (Figure 1).

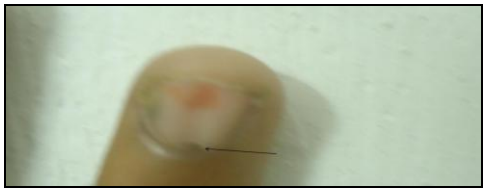
Figure 1: Dermatological manifestations



ANGIOFIBROMAS

SHAGREEN PATCH





GIANT ACHROCORDON KOENEN TUMORS

Oral cavity examination revealed dentiginous cyst of size 6x5cm present over left mandible, pigmentation of buccal mucosa and impaired dentition (Figure 2). Ophthalmic examination showed multiple radial lens opacities in the fundus (Figure 3).

Figure 2: Dentigenous Cyst

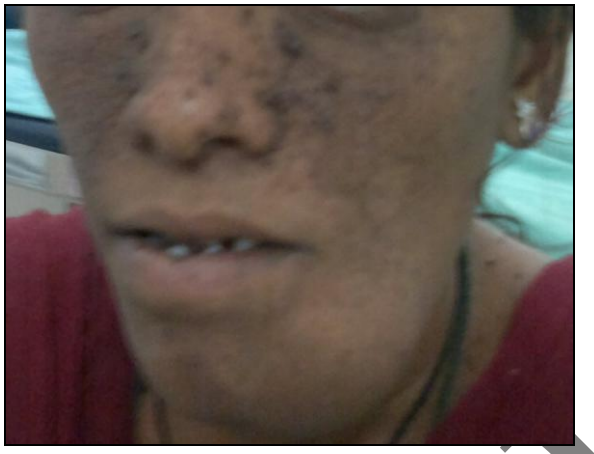


Figure 3: Radial Opacities in Eye

Investigations revealed Anemia (Hb 9.6g%). Liver function tests and renal function tests were normal. Urine routine examination was normal. X-Ray mandible and orthopantamogram showed dentiginous cyst (Figure 4 and 5). X-ray skull was normal. Ultrasound examination revealed bilateral polycystic ovarian disease, bilateral renal angiomyolipomas, and bilateral renal cyst .

CT scan confirmed angiolipomas and renal cyst (Figure 6). EEG examination showed frequent low voltage spikes and slow waves in both posterior frontal regions. Predominant low voltage alpha and increased activity were seen. CT brain showed calcified sub ependymal nodules in lateral ventricles. Chest X-Ray and skull X-ray ware normal. Fundus examination showed multiple radial lens opacities.

Figure4: DentiginousCyst

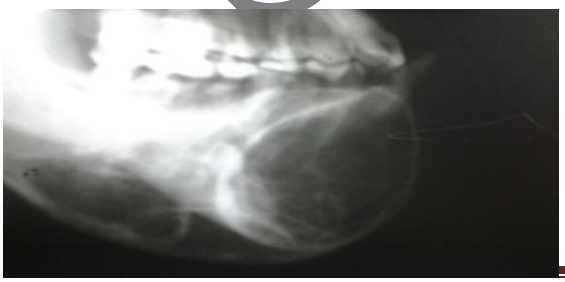


Figure 5: ORTHOPANTAMOGRAM

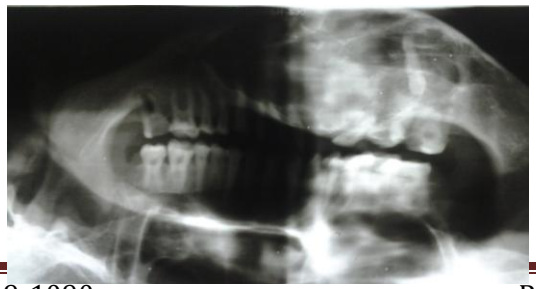
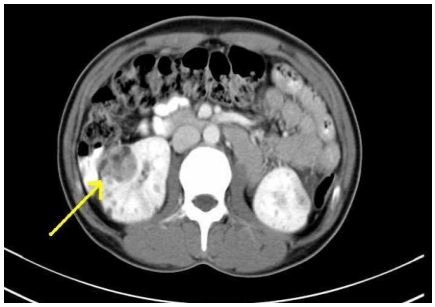
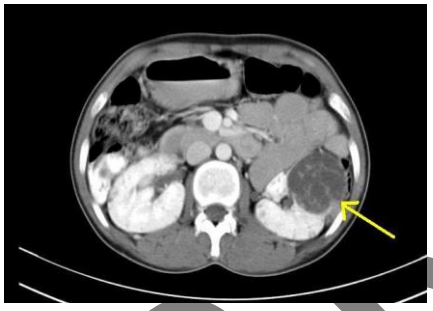


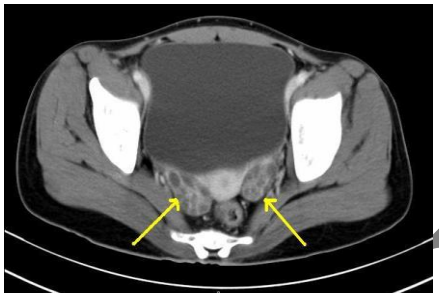
Figure 6: CT scan images of Tuberous Sclerosis Complex



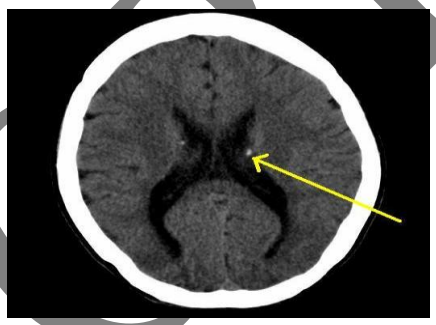
ANGIOMYOLIPOMA



HYPERNEPHROMA



BILATERAL OVARIAN CYSTS



SUBEPENDYMAL NODULES

Summarizing her history and clinical examination and investigations, final diagnosis of Tuberous sclerosis Complex was made.

Discussion

TSC is an autosomal dominant genetic disorder characterized by hamartomas in many organs. TSC has a wide clinical spectrum. Definitive TSC is diagnosed with either 2 major or one major and 2 minor features.[1] (Table 1)

Table 1: Major and minor features of Tuberous sclerosis Complex

Sr. No.	Major feature	Minor features
1	Facial Angiofibromas of forehead plaque	Multiple randomly distributed pits in dental enamel.
2	Non -traumatic ungual or periungual fibroma	Hamartomatous rectal polyps
3	Hypomelanotic macules (>3)	Bone cysts
4	Shagreen patch (Connective tissue nevus)	Cerebral white matter radial migration lines
5	Multiple retinal nodular hemartomas	Gingival fibromas
6	Cortical tuber	Non renal hemartomas
7	Subependymal nodule	Retinal achromic patch
8	Subependymal giant cell astrocytoma	Confetti skin lesions
9	Cardiac rhabdomyoma, single or multiple	multiple renal cyst
10	Lymphangio leiomyomatosis	
11	Renal angiomyolipomas	

In TSC patients, a wide spectrum of tumours can be observed. Careful evaluation and diagnosis of this disease is needed and summarised in table 2. Some of them are static but clinically important, such as cortical tubers; others cause clinical symptoms after a silent period of growth, such as subependymal astrocytomas or angiomyolipomas. Patients may present with astrocytomas or angiolipomas. Patients with TSC should remain under medical supervision and should be periodically examined, including radiological examination to asses TSC status and possible tumour regression.[2]

Table 2: Recommendations for diagnostic evaluation modified by Yates

Organ or Clinical sign	Proposed evaluation	When to carry out
Brain abnormalities	MRI or CT scans(preferably(MRI)	Confirmation of TSC diagnosis Evaluation of SEGA progression: every 1-3 years in children (at least every year if SEGA is >1 cm or if intellectual disability prevents the child from complaining
Epilepsy	EEG	In asymptomatic patients aged <2 years, control EEG recordings (every 6 weeks) should be used to indicate antiepileptic preventive treatment. Frequently of EEG depends on the course of epilepsy
Psychomotor Development	Psychomotor development evaluation with relation to child's age	During diagnosis before primary school
Skin	Careful physical examination with woods lamp	Confirmation of diagnosis
Eyes	Ophthalmologic examination of eye grounds	Confirmation of diagnosis
Heart	Ultrasonography , ECG	Confirmation of diagnosis especially in young children Clinical signs of heart tumour During diagnosis as a routine examination in arrhythmia during or before surgery
Lungs	CT scans of the chest Functional lung examination	Young asymptomatic women: single evaluation Women with clinical signs of LAM: every 6-12 months Women with clinical signs of LAM: every 6-12 months
Kidneys	Ultrasonography Renal efficiency examination	All patients during diagnosis Older children and adults every 1-3 Yrs Children with polycystic renal disease Adults with serious renal damage

An exciting new therapeutic option in TSC concerns rapamycin, also known as sirolimus, and its analogs. Rapamycin is an inhibitor of mTOR and can normalize this unregulated pathway in a TSC patient. Various preclinical models have shown that rapamycin treatment reduces TSC- related tumours, including brain skin and kidney tumours. In clinical studies oral rapamycin therapy has led to the regression of such hamartomas as SEGA's kidney AMLs and LAM in TSC patients additionally, systemic rapamycin treatment has been found to be an antiepileptic medication in cases of epileptogenic cortical dysplasias and has reduced seizures and cognitive defects in mouse models of TSC. Rapamycin also reduces skin lesions, especially facial angiofibroma, in TSC patients. Recently topical rapamycin treatment was shown to inhibit TSC-related tumours in a mouse model and facial angiofibromas in human[2]

Our patient presented with five major features and one minor features therefore a definitive diagnosis of tuberous sclerois was made. Angiofibromas were treated with electrocautery. She was treated for epilepsy. Patient was counselled for behavioural problems. The prognosis of angiomyolipomas was explained to the patient.

We are reporting this case because of the involvement of multiple organs

Conclusion: TSC is a lifelong condition. Methodical Cutaneous and systemic examinations with appropriate investigations are mandatory to diagnose a case of TSC. Intervention programmes, including special schooling and occupational therapy, may benefit the individuals with special needs and developmental issues.

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