Tuberous sclerosis complex: in mother and daughter

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Abstract
Tuberous sclerosis (TS) is an autosomal dominant multisystem disorder characterized by a triad of epilepsy, mental retardation and adenoma sebaceum with multisystem involvement including kidney, brain, skin, eyes, heart and lung. The most frequently affected organs in TSC are kidney and brain. We described TSC in mother and her daughter. We emphasized the importance of Dermatological and Radiological examination to find asymptomatic renal and Central Nervous System Lesion.

Keywords: Tuberous sclerosis, Hamartoma, Angiofibroma.

Introduction
Tuberous sclerosis also known as Bourneville’s disease; Pringle disease; EPILOIA (epilepsy, low intelligence, adenoma sebaceum). The name is derived from Latin tuber and the Greek skleros (hard). Tubers are potato-like nodules of glial proliferation and are characteristic central nervous system lesions of tuberous sclerosis complex.

Its Inheritance is autosomal dominant with variable expression and approximately 60-70% of tuberous sclerosis complex (TSC) is attributable to a new mutation.

There are two genes: TSC1 on chromosome 9q34, which encodes for the protein hamartin and TSC2 on chromosome 16, which encodes for the protein tuberin. These are tumor suppressor genes which when deficient can result in mammalian target of rapamycin (mTOR) disinhibition and abnormal proliferation of tissues, resulting in hamartomas.

The diagnosis of TSC is based on clinical criteria categorized as major or minor features.

Treatment is for cosmetic appearance and Neurosurgery should be considered when epilepsy is uncontrolled by drugs.

Case Reports
We are describing two cases of patients belonging to the same family, a mother (Case no.1), aged 40 years old and her daughter (Case no. 2), aged 18 years.

Case 1: A forty year old female presented to our OPD with facial angiofibroma which were firm, discrete, red brown, telangiectatic papules, 1-4 mm in diameter, symmetrically extending from the nasolabial furrows to the cheeks and chin with relative sparing of the upper lip and lateral face (Fig. 1). She developed such lesion from infancy. She also has shagreen patch which is irregularly thickened, slightly elevated, soft, skin-coloured plaque measuring 5cm x 3cm, in the lumbosacral region (Fig. 2). Physically and intellectually she was alright and her IQ test was normal.

On investigation Histopathology of facial and lumbosacral region were consistent with angiofibroma and shagreen patch respectively. Ultrasonography whole abdomen shows multiple renal angiomyolipoma (Fig. 3). Her CT KUB (Kidney, Ureter and Bladder) were consistent with angiomyolipoma (Fig. 4). MRI Brain showed presence of calcified tubers in foramen of monro, Non calcified subependymal nodule in bilateral peritrigonal area, cortical tuber was also found in left parietal lobe (Fig. 5). Ophthalmological examination, ECG, Echocardiography and X ray of Hands Were Normal.

Fig. 1: Pink to red small nodules 1-3mm symmetrically distributed in the nasolabial folds, cheeks and nose
Fig. 2: Shagreen patch in the lumbosacral region

Fig. 3: Renal Angiomyolipoma on USG

Fig. 4: Renal Angiomyolipoma on CT KUB

Fig. 5: MRI Brain showing non calcified Tubers

Case 2: An eighteen year old female presented to our OPD with facial angiofibroma (Fig. 6) which were firm, discrete, red brown, telangiectatic papules, 1-8 mm in diameter, extending from the nasolabial furrows to the cheeks and chin. Fibrous facial plaque on forehead show gradual development over years from infancy. It is an irregular, soft to firm, connective tissue nevus with hyperpigmentation (Fig. 6). She also had Gum Hypertrophy as irregularly thickened gums (Fig. 7) with randomly distributed multiple dental enamel pits (Fig. 7).

Besides, this she also had Koenen tumours (Periungual fibromas) smooth, firm, flesh-coloured excrescences emerging from the nail folds of 5-10 mm in length (Fig. 8) at fingers. Physically she was alright but on performing IQ test she had mild mental retardation.

On investigation Histopathology of facial lesion were consistent with angiofibroma. Ophthalmological examination shows achromic white patches in iris (Hetrochromia) on slit lamp examination and retina examination was normal (Fig. 9). Ultrasonography whole abdomen shows multiple renal angiomyolipoma and her CT KUB (Kidney, Ureter and Bladder) were consistent with angiomyolipoma (Fig. 10). CT Head showed presence of calcified tubers in foramen of monro, subependymal nodule and cortical tuber in parietal lobe (Fig. 11). ECG, Echocardiography and X ray of Hands Were Normal.

Fig. 6: Facial angiofibroma appearing as Pink to red and telangiectayic small nodules of 1–6 mm diameter, with glossy smooth surface symmetrically distributed in the nasolabial folds, cheeks and nose and Fibrous facial plaque on forehead

Fig. 7: Dental enamel pits and Gigival Hyperplasia
Tuberous sclerosis complex (TSC) is Autosomal dominant syndrome with variable expressivity. It is manifested by hamartomatous tumors in multiple organs, including brain (causing seizures), eyes, heart, kidneys, lungs, and skin. Skin lesions occur in nearly all individuals and are important for diagnosis. Skin lesions include hypomelanotic macules, “confetti” lesions, facial angiofibromas, fibrous facial plaque, shagreen patch, and ungual fibromas. Hypomelanotic macules appear at birth or shortly thereafter and are most useful in early diagnosis. Although the skin lesions are benign, they may require treatment due to symptoms or disfigurement.

The incidence of tuberous sclerosis complex (TSC) is as high as 1 in 6,000 live births.\(^7\) It occurs with equal frequency in males and females and in different races and ethnicities. Hereditary transmission is evident in approximately one-third of patients. Sporadic disease occurs in about two-thirds of patients, and this is attributed to de novo mutations.\(^8\)

TSC is caused by mutations in a tumor suppressor gene, either TSC1 or TSC2.\(^8\) Mutations in TSC2 are observed in about three-fourths of patients, and even more commonly in de novo cases. Patients with mutations in TSC2 tend to exhibit a more severe phenotype. TSC1 maps to chromosome band 9q34. The 8.6-kb full-length transcript encodes a protein called hamartin or TSC1. TSC2 maps to chromosome band 16p13.3. The 5.5-kb transcript encodes a protein called tuberin or TSC2.

**Dermatological presentation of TSC:**\(^9\)

A. **Ash leaf macule** - It is seen in 95% of the cases usually present at birth or appears in the neonatal period. Presence of three or more hypomelanotic macules at birth should raise the suspicion of tuberous sclerosis complex.

They are one to twenty, 0.5 to 3 cm diameter off-white macules. Some are oval at one end and taper to a point at the other and are hence called lanceolate or ash leaf macules. Confetti or polygonal macules with smooth or irregular margins can also occur. They fade or disappear in adulthood. New lesions can appear as
age increases. Histopathology shows normal number of melanocytes but absent melanosomes.

B. Facial angiofibromas – It is seen in 88-100% of cases and are present at 2-5 years. The lesions are heralded by excessive facial flushing in infancy. Later 1-3 mm, pink to red papules that have a smooth surface occur on the central face, and often concentrate around alar grooves, extending symmetrically over the nose, cheeks, nasal opening and chin with relative sparing of the upper lip and lateral face. During puberty, they may grow in size and number. In adulthood, they tend to be stable in size but redness may gradually diminish. Histopathologically plump, spindle-shaped or stellate fibroblasts are seen in the dermis among increased numbers of dilated blood vessels. Collagen fibers are oriented in onion skin pattern around follicles and blood vessels.

C. Fibrous facial plaque – It is seen in 2.5-55.5% cases. It may present at birth or appears shortly after birth.

These are Irregular, soft to firm, of normal skin colour, red or hyperpigmented in dark colored individuals. They are found on scalp, cheeks and elsewhere on the face. These do not spontaneously regress. These are connective tissue nevi of collagen type without vascular dilatation.

D. Shagreen patch – It is seen in 12.3-83% cases may present in infancy but can present later. These are skin coloured leathery plaque with prominent follicular openings resembling an orange peel, commonly seen over the lumbo-sacral area. Sclerotic bundles of collagen are found in the reticular dermis. Elastic fibers are typically reduced or absent. They do not spontaneously regress.

E. Ungual fibromas/Koenen's tumors – It is found in 6.2-66.6% of adults and usually appear after the first decade which may sometimes appear in middle age. They are 1 mm to 1 cm in diameter and arise from under the proximal nail fold or under the nail plate. They arise from the nail matrix and cause a longitudinal groove and sometimes a groove forms without a papule. Subungal fibromas can be seen through the nail plate as red or white oval lesions or red papules emerging from the distal nail plate causing distal subungal onycholysis. They do not spontaneously regress. Histology shows angiofibromas with prominent hyperkeratosis and a variable increase in vascularity.

F. Other dermatological features include

- Fibromas around the teeth and even on the tongue.
- Dental pits particularly affecting adult teeth.
- Skin tags called molluscum fibrosum pendulum especially around the neck.
- Café au lait macules.

Conclusion

The expectation of life for a very severely affected infant is poor: 3% die in the first year, 28% under 10 years and 75% before age 25 years. Death is usually due to epilepsy or intercurrent infection, but occasionally it is due to a tumour, cardiac failure or pulmonary fibrosis. The prognosis for the older child or young adult with cutaneous stigmata and epilepsy is unpredictable. Each case must be investigated in detail and individually assessed since we can identify treatable complication in early stage.

The idea of publishing this case is of rarity and presence of numerous clinical and radiological (ultrasonography, CT and MRI) classical findings in our patient.

Reference


International TSC Consensus Conference Revised Diagnostic criteria for tuberous sclerosis complex laid out in 2012

<table>
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<th>Diagnostic criteria for the tuberous sclerosis complex</th>
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<tr>
<td>Major features</td>
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<tr>
<td>1. Facial angiofibromas or forehead plaque</td>
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<td>2. Non-traumatic ungual or periungual fibroma</td>
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<td>3. Hypomelanotic macules (more than three)</td>
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<td>4. Shagreen patch (connective tissue naevus)</td>
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<td>5. Multiple retinal nodular hamartomas</td>
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<td>6. Cortical tuber</td>
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<td>7. Subependymal nodule</td>
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<td>8. Subependymal giant cell astrocytoma</td>
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<td>9. Cardiac rhabdomyoma, single or multiple</td>
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<td>10. Lymphangiomyomatosis</td>
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<td>11. Renal angiomyolipoma</td>
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<tr>
<td>Minor features</td>
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<tr>
<td>1. Multiple randomly distributed pits in dental enamel</td>
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<td>2. Hamartomatous rectal polyps</td>
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<td>3. Bone cysts</td>
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<td>4. Cerebral white matter migration lines</td>
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<td>5. Gingival fibromas</td>
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<tr>
<td>6. Non-renal hamartoma</td>
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<td>7. Retinal achromic patch</td>
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<td>8. ‘Confetti’ skin lesions</td>
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<td>9. Multiple renal cysts</td>
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<tr>
<td>Definite TSC: either two major features or one major feature with two minor features</td>
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<td>Probable TSC: one major feature and one minor feature</td>
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<td>Possible TSC: either one major feature or two or more minor features</td>
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