

## Tuberous Sclerosis – A Multi System Disease

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### ABSTRACT

Tuberous sclerosis is a genetic disease with autosomal dominant inheritance, associated with hamartomata in several organs and various skin findings. A case of a ten year old boy is presented here to highlight the multisystem involvement in tuberous sclerosis. The child had seizures, facial papular naevi and periungual fibromas. MRI revealed cortical tubers, white matter lesions and subependymal nodules. Orbital ultrasound showed retinal hamartoma on the left side. Ultrasound of the abdomen revealed a soft tissue mass at the upper pole of left kidney with a small cyst in right kidney. [Indian J Pediatr 2008; 75 (1) : 77-79] E-mail : dr\_vijinderarora@yahoo.co.in

**Key words :** Tuberous sclerosis; Hamartoma; MRI

Tuberous Sclerosis (TSC) was first described in the 1880's as "Bourneville's disease" named after the French physician Desire-Magloire Bourneville (1840-1909), tuberous sclerosis complex. It was an estimated prevalence of 3-10/100,000 worldwide.<sup>1</sup> It is a genetic disorder that affects multiple organs. Skin, brain, kidney, eyes and heart are some of the organs that may be involved. The term 'complex' emphasizes the multisystem involvement and variable expression of the disease.<sup>2</sup>

### CASE REPORT

A ten years old boy presented with history of seizures off and on for the last six months. He was mildly mentally retarded. There was no history of headache, chest pain, shortness of breath or any urinary or bowel complaints. He was the eldest of three siblings. The other two children were normal. There was no family history of any such skin lesion, fits or mental retardation. No such history was available in the first-degree relatives also.

On examination, the child was of lean built and was well oriented in time and space and afebrile. The vital signs were stable. There were multiple small skin coloured papules over the nose and both cheeks suggestive of a papular naevus (Fig. 1). A small reddish

projection was noted at the base of the nails in the left third finger (Fig 2) and right second finger indicative of an unguinal fibroma.

He was referred for MRI of the brain, which revealed multiple lesions in the cortex of both cerebral



Fig. 1. Photograph of the patient showing papular naevus



Fig. 2. Unguinal fibroma at the base of nail of left third finger

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hemispheres consistent with cortical tubers (Fig 3). Multiple subependymal nodules were detected jutting into both lateral ventricles (Fig 4).

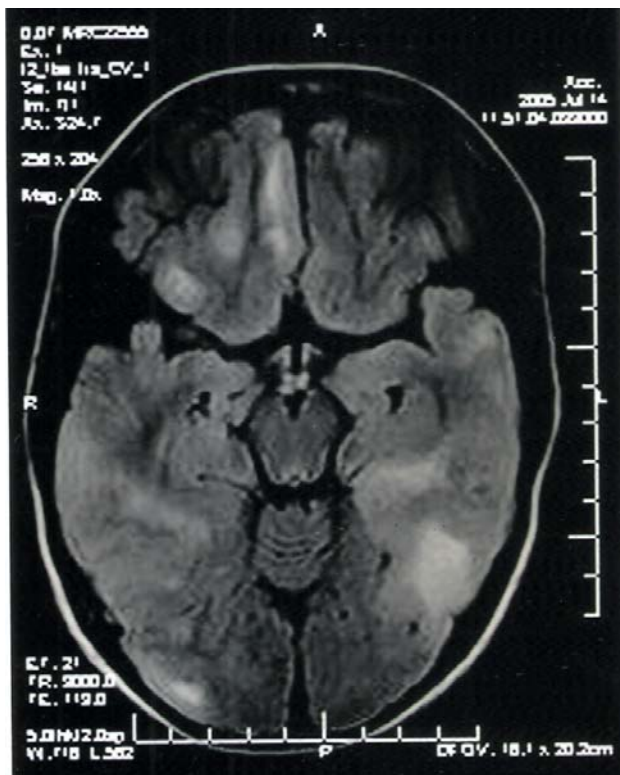


Fig. 3. FLAIR axial MR section depicting cortical tubers



Fig. 4. T1W axial MR section revealing subependymal nodules

Ultrasound of the abdomen demonstrated a small mass of intermediate echogenicity, measuring 1.5 x 1.2cm in size, at the upper pole of left kidney (Fig 5). A tiny cyst was seen in the interpolar region of right kidney. No lesion was observed in the liver or pancreas.

Ultrasound of the orbit showed a plaque like mass in the lateral quadrant of left eyeball suggestive of retinal hamartoma (Fig. 6).

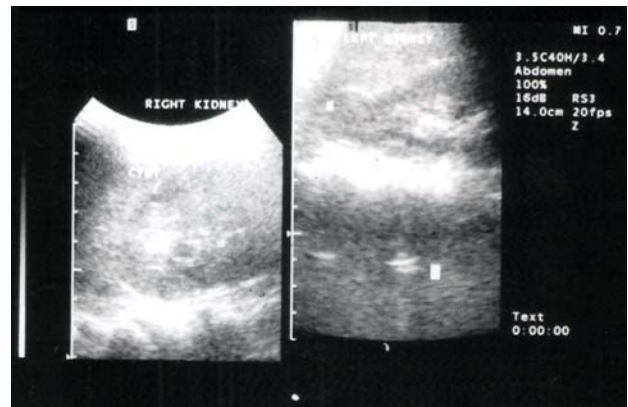


Fig. 5. Ultrasound abdomen showing left renal cyst



Fig. 6. Ultrasound of the orbit demonstrating plaque-like mass in the lateral quadrant of left eyeball

## DISCUSSION

Rayer gave the first complete description of tuberous sclerosis in 1835.<sup>3</sup> Sherlock<sup>4</sup> coined the name 'epiloia', which highlighted the previous diagnostic triad composed of epilepsy, low intelligence and adenoma sebaceum. However, the classic clinical triad is found in less than half the patients.

Onset before the age of 5 years with cutaneous changes or with epilepsy is usual, but the disease may remain latent until adolescence.<sup>5</sup> The disease shows variable expressivity even within the same family. It is now recognized that about half of the TSC families are linked to chromosome 9q34 (TSC1) and the other half to chromosome 16p13 (TSC2).<sup>6</sup> The inheritance is autosomal dominant.

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Histopathologically most of the lesions are hamartomas, and in many organs the cells resemble embryonic cells, suggesting that the defect occurs at an early stage of life. Most of the cutaneous lesions show excess of collagen. The angiofibromas consist of hyperplastic blood vessels and sebaceous glands of immature hair follicles, in addition to increased collagen synthesis.<sup>7</sup>

US National Tuberous Sclerosis Association has divided the clinical features into 3 groups: primary, secondary and tertiary.<sup>8</sup> Primary features include facial angiofibroma, multiple ungual fibroma, cortical tuber (histologically confirmed), subependymal nodules or giant cell astrocytomas, multiple calcified subependymal nodules and multiple retinal astrocytomas. Secondary features include an affected first degree relative, cardiac rhabdomyoma, retinal hamartoma, cerebral tubers (radiologically confirmed), non-calcified subependymal nodules, shagreen patch, forehead plaques, pulmonary lymphangiomyomatosis, renal angiomyolipomas and renal cysts (the last two features should be histologically confirmed). Tertiary features are hypomelanotic macules, renal cysts (radiologically confirmed), dental enamel pits, hamartomatous rectal polyps, bone cysts, pulmonary lymphangiomyomatosis (radiologically confirmed) and cerebral heterotopias, gingival fibromas, hamartomas of other organs and infantile spasm.

For the definitive diagnosis there should be either one primary and two secondary features or one secondary and two tertiary features. Our patient had at least three primary and three secondary features. All these features are found bilaterally. There were, however, a few case reports in which one of the features of the disease was found unilaterally.<sup>9</sup>

The skin lesions are found in 60-70% of cases. There are four characteristic skin lesions; angiofibromas, periungual fibroma (Koenen tumour), shagreen patch and ash-leaf macules. The angiofibromas are firm, discrete, red-brown, telangiectatic papules, 1-10 mm over nasolabial furrow, eyelids, cheek and chin. Periungual fibromas are smooth, firm, flesh-coloured excrescence emerging from nail folds. Shagreen patch is an irregular thickened, skin-coloured plaque, usually over lumbosacral region. Ash-leaf macules are ovoid, white macules, 1-3 cm in size, present over trunk or limbs.<sup>2</sup>

Mental deficiency is seen in 60-70% of cases and may progress. Epilepsy is seen in all mentally-retarded and

70% of individuals of average intelligence. Ocular signs occur in 50% of cases, but may be hard to detect. Other systemic abnormalities include cardiac rhabdomyomas, renal angioliipomas, spontaneous pneumothorax and hamartomatous colonic polyps.

The cosmetic appearance is improved by removing angiofibromas with pulse-dye vascular laser (wavelength 585nm) or by carbon dioxide laser. Surgical treatment may be required for relief of symptoms in other organs.<sup>2</sup>

The life expectancy of severely affected infants is poor. Three percent die in first year, 28% under 10 years and 75% before 25 years. The prognosis for older children or young adults with mild disease is unpredictable.<sup>2</sup>

Well conducted studies estimate that about 2/3 of cases are fresh mutations, and the remaining cases are familial in an autosomal dominant pattern of inheritance. For proper genetic counseling mutation studies should be carried out on the affected child. Both genes are studied in sequence. Children of an affected parent should be offered a skin examination for ash leaf spots, renal and liver ultrasound and cardiac ultrasound at the initial consultation.<sup>10</sup> Prenatal diagnosis is possible with DNA technology, provided mutation in the affected child is known.

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