

CASE REPORT

PHAKOMATOSIS: INTRESTING CASES OF TUBEROUS SCLEROSIS WITH RETINAL ASTROCYTOMA

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ABSTRACT: INTRODUCTION: Tuberous sclerosis complex (TSC) or Morbus Bourneville-Pringle disease is an autosomal dominant phakomatosis, first described by Desiree-Magloire Bourneville in 1880. Tuberous sclerosis is a genetic disorder characterized by the growth of numerous benign tumours in many parts of the body caused by mutations on either of two genes, TSC1 and TSC2. This rare genetic disorder is usually associated with a triad of seizures, mental retardation and cutaneous lesions. Approximately one half of all patients affected by TS develop at least one retinal astrocytoma in one eye. **PRESENTATION OF CASES:** In the department of ophthalmology, G.S.L Medical College, Rajahmundry, we came across 3 cases of tuberous sclerosis involving multi organ systems. Out of 3 cases, 2 cases were reported to be familial and 1case is sporadic, with a history of epilepsy with angiofibromatosis lesions over the face, multiple ash-leaf lesions over the abdomen, renal angiomyolipomas, multiple subependymal nodules in brain and retinal astrocytic hamartomas in the retina. **CONCLUSION:** It is important to be cognizant of the likely presence of systemic and ocular pathology in a child with mental retardation and skin lesions. Identification of retinal phakomatosis during ocular evaluation in any suspected case of Tuberous sclerosis can aid in the establishment of the diagnosis of the disease. **KEYWORDS:** Tuberous sclerosis, Astrocytoma, Hamartomas, Angiofibromas.

INTRODUCTION: Tuberous sclerosis complex (TSC) is an inherited neurocutaneous disorder characterized by the potential for the presence of hamartomas in almost every organ, most notably in the skin, brain, kidney, heart and eyes.^[1] The condition was described by von Recklinghausen in 1862.^[2] The term "tuberous sclerosis" refers specifically to the presence of multiple sclerotic masses scattered throughout the cerebrum. The diagnosis of TSC is based on the identification of hamartomas in more than one organ system. A hamartoma is a benign tumor composed of an overgrowth of mature cells and tissues that normally occur in the affected tissue, but often with one predominating element. The hamartoma formation is most notable in the skin, brain, kidneys, heart and eye. ^[1]

The kidney and brain are two of the most frequently affected organs in TSC.^[3]

The disease is an autosomal disorder with extensive clinical variability. The presence of hamartomas in two different organ systems is considered by some clinicians to be sufficient for the diagnosis.^[4]

MATERIALS AND METHODS: In the department of ophthalmology, we came across 3 cases of tuberous sclerosis involving multi organ systems.

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Out of 3 cases, 2 cases were reported to be familial and 1 case is sporadic, with a history of epilepsy with angiofibromatosis lesions over the face, multiple ash-leaf lesions over the abdomen, renal angiomyolipomas, multiple subependymal nodules in brain and retinal astrocytic hamartomas in the retina.

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CASE 1: 30 year old male presented with generalised tonic clonic seizures and a known epileptic since 18 years on regular medication. Was referred from the general medicine department for ocular evaluation. No history of similar complaints in the family. However, he had no ocular complaints and unaided visual acuity was 20/20 in each eye. On general physical examination. He was found to have multiple small nodular lesions over face more on cheeks (adenoma sebaceum). (Fig. 1), Hypomelanotic macules over left cheek, right thigh and leg, Shagreen patch in lower back region, Ash leaf spot over left forearm. (Fig. 2), Multiple pits in dental enamel. (Fig. 3). The slit-lamp examination of the anterior segment revealed normal findings and on dilatation, Fundus RE showed a circular elevated, white glistening mass measuring 2 DD and 2DD infero nasal to the optic disc surface is white mulberry fruit appearance, single mass seen. (Fig. 4) and neuro imaging CT brain showed few cortical/subcortical tubers and subependymal nodules. (Fig. 5).

CASE 2: 17 year old female presented with generalised tonic clonic seizures and known epileptic since the age of 3 years, on regular medication. Her mother had similar complaints in the family. On examination, She was having Multiple small nodular lesions over face more on cheeks and all over the face, neck and left ear pinna (adenoma sebaceum). (Fig. 6), Hypopigmented patch in right groin area (ashleaf spot), Shagreen patch is noted in lower back region. (Fig. 7), The slit-lamp examination of the anterior segment revealed normal findings. The slit-lamp examination of the anterior segment revealed normal findings and on dilatation Fundus LE showed perivasculitis seen, subhyaloid hemorrhage seen supratemporal to the disc. (Fig. 8). imaging showed U/S abdomen- right kidney angiomyolipoma and CT brain showed agenesis of corpus callosum, few cortical/subcortical tubers and subependymal nodules. (Fig. 9).

CASE 3: 45 years old female (Mother of case 2) has multiple hyperpigmented swelling present in malar region and had one episode of seizures during her pregnancy. She had no ocular complaints and unaided visual acuity was 20/20 in each eye. On examination, multiple hyperpigmented lesions seen on the malar area (Fig. 10) and right axilla, Hypopigmented patch seen on the Rt leg of 5x2cms. The slit-lamp examination of the anterior segment revealed normal findings and on dilatation Fundus BE is normal. Imaging, U/S abdomen- bilateral kidney angiomyolipoma and CT brain showed subcortical tubers and subependymal nodules seen. (Fig. 11).

RESULTS: In these 3 cases 1 case is sporadic and other 2 are familial. Every case with facial angiofibromas has to be evaluated clinically and systemically by MRI and CT to rule out multi systemic involvement and detail fundus examination for astrocytomas.

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DISCUSSION:

SYNONYMS:

BOURNEVILLE 'S DISEASE:

TUBEROUS SCLEROSIS COMPLEX: Tuberous sclerosis (TS) is an autosomal dominant inherited disease characterized by tumour-like lesions called hamartomas in the brain, skin, eyes, heart, lungs and kidneys.^[5]

The classical clinical triad of TSC symptoms are mental retardation, seizures, and cutaneous angiofibroma (formerly called adenoma sebaceum), reported by Vogt in.^[6]

Mental retardation and seizures are both neurologic manifestations of TSC.^[7]

One-third to one-half of patients with TSC have retinal or optic nerve hamartomas, and the hamartomas occurs bilaterally in half of the patients.

OPHTHALMIC MANIFESTATIONS: In the eyes, retinal astrocytic hamartomas are found in around half of affected individuals.^[8]

The classic raised multinodular 'mulberry' lesions are easily seen, but flat, semitransparent lesions are commoner and more difficult to identify. Retinal hamartomas seldom affect vision but are a useful diagnostic sign.

- Molecular and genetic basis of the disease: TS is caused by inactivating mutations in either the TSC1 gene at 9q34^[9] or the TSC2 gene at 16p13.^[10]
- Several studies have suggested that compared cases with TSC1 mutations, cases with TSC2 mutations tend to have a more severe phenotype with a higher frequency of mental retardation and seizures, more extensive renal involvement and more severe facial angiofibromas.^[11,12]

Somatic mutation often involves deletion of the chromosomal region spanning the gene, leading to loss of heterozygosity for markers in the deleted region.^[13] Separate lesions are presumed to result from independent somatic mutations but studies in patients who have both pulmonary LAM and renal AMLs have shown matching patterns of somatic mutation in the kidney and lung lesions, supporting the hypothesis that mutant cells in both locations have a common origin.^[14]

PROTEINS AND PATHWAYS: The products of the TSC1 and TSC2 genes, hamartin and tuberin, form a dimer,^[15] which mediates a key step in the phosphoinositide 3-kinase (PI3K) signalling pathway.

Mutations in TSC1 or TSC2 that impair the inhibitory function of the hamartin/tuberin complex lead to greatly increased activity of mTOR. As the name implies, mTOR is inhibited by the immunosuppressant drug rapamycin, which opens up exciting prospects for therapy. In TSC1 and TSC2 null cell lines, rapamycin restores phosphorylation downstream of mTOR to normal levels, and in rodent models of TS rapamycin and its analogues can inhibit the growth of hamartomas.^[16]

COURSE AND OUTCOME: Most retinal lesions remain stable and change little with time. Moderate progression of retinal hamartoma from a flat to a more elevated lesion without

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symptomatic changes may occur. But spontaneous symptomatic progression of these lesions has also been reported.^[17] The progressive growth of retinal astrocytic hamartomas may be associated with vitreous seeds, vitreous hemorrhage and exudative retinal detachment, which can simulate retinoblastoma or choroidal melanoma.^[18] Reports of marked enlargement of retinal astrocytic tumors eventually causing a total retinal detachment and neovascular glaucoma that required enucleation of the affected painful blind eye, are found in the literature.^[19] The life expectancy of individuals with TS is reduced substantially compared to normal population.

Diagnostic criteria for tuberous sclerosis (modified from Roach et al^[20]):

Definite diagnosis: Two major features or one major plus two minor features.

Probable diagnosis: One major and one minor feature.

Possible diagnosis: One major feature.

Major features:

- Facial angiofibromas or forehead plaque.
- Ungual fibroma, non-traumatic.
- Hypomelanotic macules, three or more.
- Shagreen patch.
- Multiple retinal nodular hamartomas.
- Cortical tubera.
- Subependymal nodule.
- Subependymal giant cell astrocytoma.
- Cardiac rhabdomyoma, single or multiple.
- Renal angiomyolipoma or pulmonary lymphangiomyomatosis.

Minor features

- Multiple randomly distributed pits in dental enamel
- Hamartomatous rectal polyps
- Bone cysts
- Cerebral white matter radial migration lines
- Gingival fibromas
- Non-renal hamartoma
- Retinal achromic patch
- 'Confetti' skin lesions
- Multiple renal cysts

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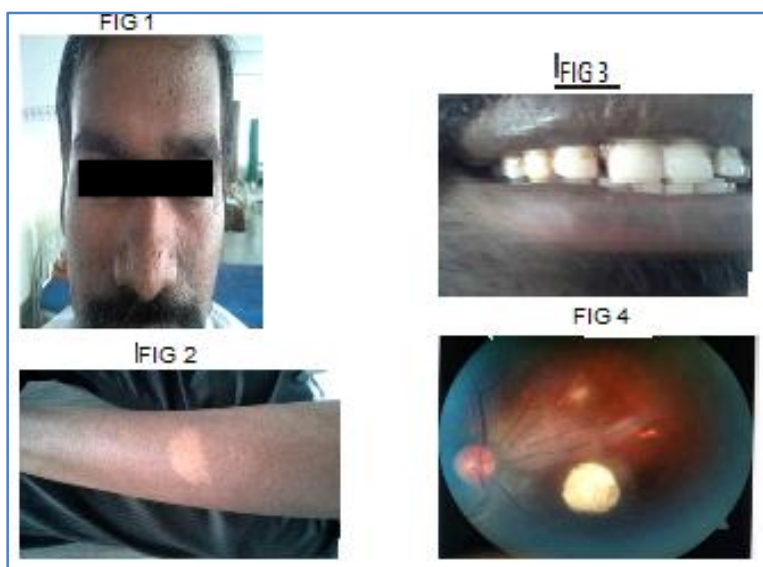
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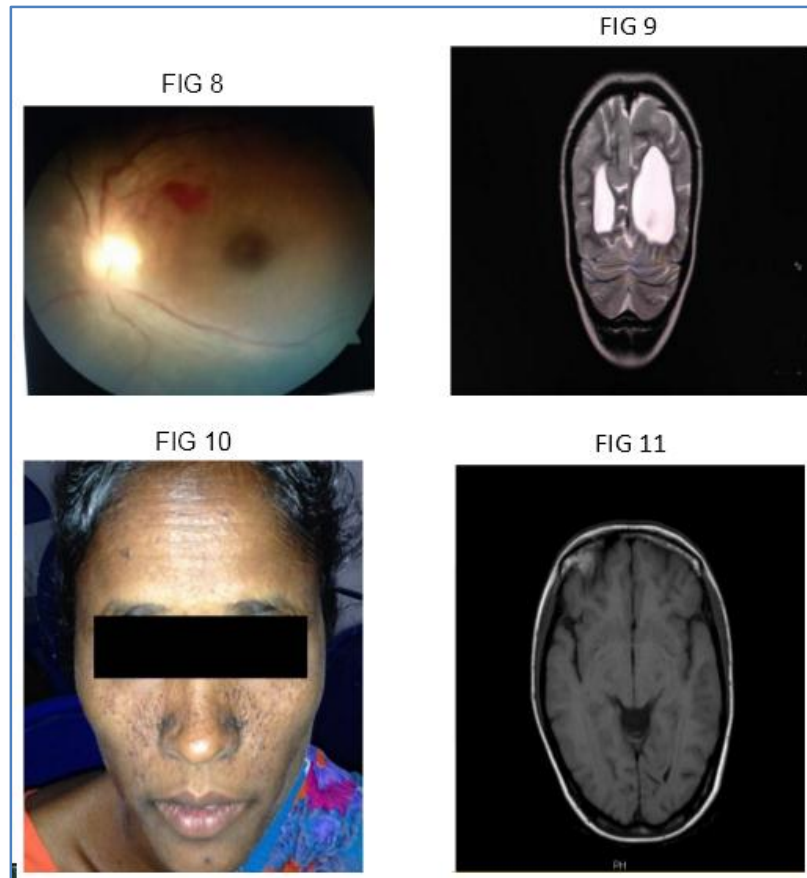
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