Retinal Hamartomas in a case of Tuberous Sclerosis

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Abstract :

A 21-year-old male patient suffering from epilepsy came for fundoscopic evaluation. Right eye showed a flat, smooth surfaced well circumscribed, non-calcified translucent lesion of 1 disc dioptre size, inferior to the optic disc, obscuring underlying vessels & an opaque, calcified, yellow white lesion having irregular surface & margins with mulberry appearance, elevated, supero-nasal to the disc, obscuring the underlying vessels. Adenoma sebaceum, periungual fibromas, Ash leaf macules were seen on general physical examination suggestive of tuberous sclerosis. MRI brain revealed subependymal nodules & subcortical tubers. OCT showed an optically hyper reflective mass with retinal disorganization and moth-eaten spaces. 2D echo showed mild Left Ventricular Hypertrophy, diastolic dysfunction, trivial mitral and tricuspid regurgitation. Ultrasonography of abdomen & pelvis showed fatty liver and renal angiomyolipoma. It was interesting to note cardiac & hepatic involvement in addition to the standard tuberous sclerosis complex (TSC) major & minor diagnostic criteria

Key-words: Retinal hamartomas, Neurocutaneous syndrome, Tuberous sclerosis complex

Introduction:

Tuberous Sclerosis (TS) or Bourneville disease is a rare, genetic, neuro-cutaneous disorder of autosomal dominant inheritance, which affects cellular differentiation, proliferation and migration early in development, leading to a variety of hamartomatous lesions that affect multiple organ systems in the body such as brain, kidney, heart, lungs, eyes and skin.

Estimates of prevalence of tuberous sclerosis range from as high as 1;6000 to 1;1,00,000 or lower.[1] Most frequent and characteristic ocular manifestation of TS is the retinal phakoma (hamartoma), which arises from the innermost layer of the retina and comprises nerve fibres and relatively undifferentiated cells that appear to be of glial origin.[2,3]

Case Report:

A 21-year-old male patient who was a diagnosed case of seizures presented to the outpatient department for ophthalmic examination. Birth history and family history were insignificant and there was no history of systemic comorbidities or retarded mental development.

On ophthalmic examination: The best corrected Snellen's visual acuity in the right and left eyes were 6/6 and 6/12, respectively. Examination of the anterior segment was normal in both eyes and so was the vitreous cavity.

·The optic disc and retinal examination in right eye were normal.

The following abnormalities were noted in the left eye:

I) A flat, smooth- surfaced well circumscribed, achromic, non-calcified and translucent lesion, 1 disc diameter in size, inferior to the disc, partially obscuring the underlying blood vessels was seen

ii) An opaque, calcified, glistening yellow-white lesion with an irregular surface and margins(mulberry-like appearance) which was slightly elevated and present superonasal to the optic disc, partially obscuring the underlying blood vessels was seen **(Figure 1).**

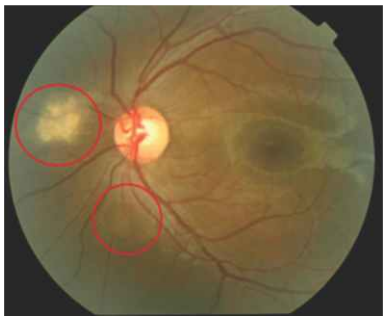

Figure 1

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·On general physical examination:

- General physical examination revealed multiple hyperpigmented macular lesions on the nose and cheeks in a characteristic "butterfly pattern", **suggestive of Adenoma sebaceum. (Figure 2a)**.
- Small nodules under the thumbs of both hands were seen, suggestive of **periungual fibromas (Figure 2b)** and multiple skin tags were present over the nape of the neck with hyperpigmentation.
- Irregular, hypopigmented patches were seen on the dorsum of left hand, and calves of both legs, suggestive of **ash leaf macule.(Figure 2c)**

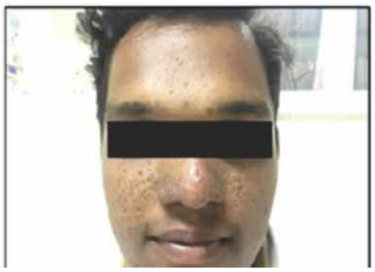

Fig. 2a: Adenoma sebaceum over the nose and cheeks

Fig. 2b: Showing periungual fibromas

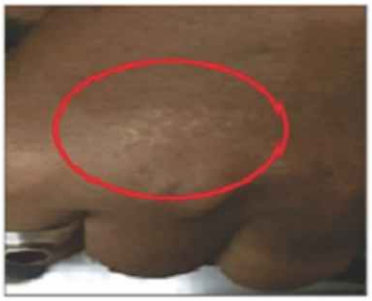

Fig. 2c: Showing ash leaf macule

Investigations:

- MRI brain: MRI brain revealed small focal calcified lesions in caudo-thalamic region along ependymal lining of left lateral ventricle were seen as T2 weighted, gradient echo hypointense focus, suggestive of sub-ependymal hamartoma **(Figure. 3a)** along with multiple tiny focal calcified lesions noted along sub ependymal linings of bilateral lateral ventricles **(Figure 3b)**.
- Abnormal T2 weighted and FLAIR (fluid attenuated inversion recovery) hyperintense focal ill- defined non-enhancing signals were noted in bilateral frontal, temporal, parietal and occipital lobes, suggestive of cortical- subcortical tubers. **(Figure 3c)**

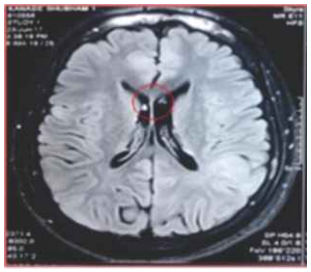

Fig. 3a

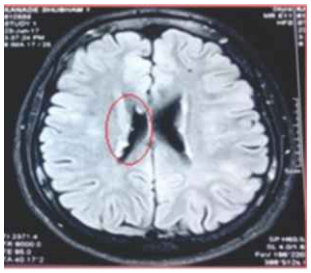

Fig. 3b

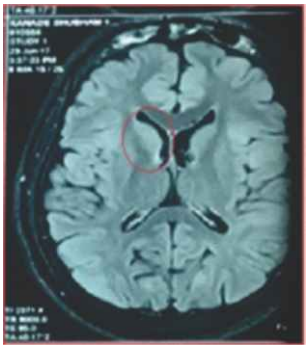

Fig. 3c

OCT showed an optically hyper-reflective mass with retinal disorganization and moth –eaten spaces **(Figure 4)** and B scan showed an elevated lesion within the inner retina, with high internal reflectivity. Cardiac evaluation was done, 2D echo showed mild LVH with grade II diastolic dysfunction, trivial mitral and tricuspid regurgitation. USG abdomen and pelvis showed the presence of a mass hyperechoic to renal parenchyma, suggestive of Renal angiomyolipoma of the left kidney and presence of fatty liver.

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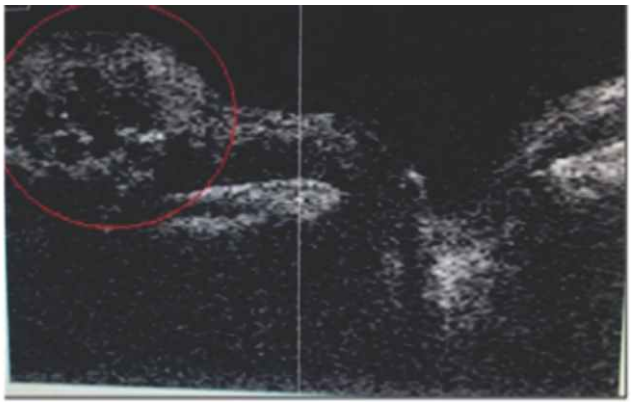

Fig. 4: OCT image showing moth-eaten spaces

Discussion:

TS was described for the first time by von Recklinghausen in 1862 and later elaborated by a French neurologist Desire-Magloire Bourneville in 1880, thus the condition is also known as Bourneville's disease.[2] In 1920 Van der Hoeve recognized retinal involvement in tuberous sclerosis.[3] It is an autosomal dominant disorder, caused by mutations of either the TSC1 gene on chromosome 9q34 encoding hamartin or the TSC2 gene on chromosome 16p13 encoding tuberin.[4] The mutation in these genes leads to mTOR activation and formation of various growths and hamartomas in various organs of the body.[4] The clinical features of tuberous sclerosis are highly variable, making the diagnosis of the disease very challenging.

The classic Vogt's triad which includes seizures, mental retardation, and cutaneous angiofibromas is known to occur only in 29% of cases.[5]

Ophthalmic Manifestations: About 50% of the total cases with Tuberous sclerosis have ocular involvement. The pathognomic retinal lesions of tuberous sclerosis are astrocytic hamartomas, which may be seen in about 53% of the patients.[6] Astrocytic hamartomas can be morphologically classified into two types:

(1) Large, whitish (calcified) nodular masses or

(2) Flat, translucent (noncalcified) smooth tumors.

An intermediate type of retinal hamartoma having features of both types has also been described.[7]

Rarely retinal hamartomas may be associated with complications such as vitreous hemorrhage, retinal vascular abnormalities (including telangiectasia, neovascularization, and exudation), and vitreous seeding. In presence of a single retinal (or optic nerve) hamartoma, only one additional major feature, or two or more minor features, are required to make the diagnosis of tuberous sclerosis complex. The diagnosis is based on the TSC diagnostic criteria (recently revised in 2012) laid down by the tuberous sclerosis complex consensus group1 (Table 1.1)

Table 1.1: Diagnostic criterion for tuberous sclerosis complex

Major Features	Minor features
Facial angiofibromas or forehead plaque	Multiple randomly distributed pits in dental enamel
Nontraumatic ungual/periungual fibromas	Hamartomatous rectal polyps
Hypomelanotic macules (three or more)	Bone cysts
Shagreen patch (connective tissue nevus)	Cerebral white matter radial migration lines
Multiple retinal nodular hamartomas	Gingival fibromas
Cortical tuber	Nonrenal hamartoma
Subependymal nodule	Retinal achromic patch
Cardiac rhabdomyoma, single or multiple	"Confetti" skin lesions
Lymphangioleiomyomatosis	Multiple renal cysts
Renal angiomyolipoma	

Definite diagnosis:

Two major features or one major feature with ≥ 2 minor features

Possible diagnosis:

Either one major feature or ≥ 2 minor features

* Includes tubers and cerebral white matter radial migration lines.

** A combination of the two major clinical features (LAM and angiomyolipomas) without other features does not meet criteria for a definite diagnosis.

Currently in addition to FDA approval for renal angiolipomas and subependymal astrocytomas that cannot be resected, mTORC inhibitors (like rapamycin or everolimus) are in clinical trials for TSC-related refractory epilepsy, neurocognitive manifestations, and facial angiofibromas.[8]

Conclusion:

Due to relative obscurity of the disease and the mild form of symptoms, many cases remain undiagnosed for years or decades.

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Early diagnosis and intervention can help overcome developmental delays & behavioural abnormalities.

Early seizure control in children can improve learning as compared to children without good seizure control.

Ophthalmologists play an important role in early diagnosis, as characteristic retinal hamartomas can often be detected within the first two years of life.

Although there is no specific treatment for tuberous sclerosis, early diagnosis & symptomatic management may improve the quality of life of such patients.

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