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Medicine

A RARE CASE REPORT OF TUBEROUS SCLEROSIS COMPLEX

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ABSTRACT Tuberous sclerosis complex is a rare genetic disorder inherited in autosomal dominant pattern. Tuberous sclerosis is a rare neurocutaneous syndrome exhibiting multiple hamartomatous proliferations that may involve multiple organ system such as brain, kidney, heart, lungs, eyes and skin. This is a case report of 22 yr old male patient who presented to emergency department with multiple episodes of seizures without prior diagnosis. Clinical examination revealed Butterfly like distribution of angiofibromas ,gum hyperplasia, ash leaf maculae and shagreen patch on back .CT Brain images showed multiple subependymal granulomas with calcification. This case report is a good example of complex nature of tuberous sclerosis.

KEYWORDS :

INTRODUCTION: Tuberous sclerosis complex (TSC)was first described by French physician Desire-Magloire Bourneville (1840-1909) was first described in 1880,hence also known as Bourneville's Disease . The name tuberous sclerosis is derived from the characteristic tuber like growth occurring in the brain which calcifies with age and become sclerotic. The prevalence of one in 6000 live birth, affecting both sexes and all ethnic groups[1]. TSC is caused by defects or mutations in two genes- TSC1 and TSC-2. Only one of the genes needs to be affected to produce the disease.[2-3]

CASE REPORT:

A 22 yr old male patient presented to emergency department with repeated episodes of convulsions in past 3 days .When brought to the hospital he was in postictal confusion, drowsy and disoriented state. While examining the patient he again had an episode of generalized tonic clonic like seizure . According to relatives this was his 5th episode since morning and the presentation was similar in previous episodes. History of seizures was given by relatives which started 3years back. He was started on phenytoin for the same .He had difficulty in learning and understanding since the age of 15.

Patient was shifted for emergency CT Brain plain after giving loading dose of Inj. Phenytoin and Inj.Lorazepam 2mg IV stat. He later was shifted to Medical ICU where he had another episode of seizure similar to prior episode. Patient was electively intubated and put on mechanical ventilation in view of airway protection.

Later On Clinical examination ,his vital parameters were : heart rate of 110/min,blood pressure 130/80mmhg, respiratory rate of 16/min and saturation of 100% on Fio2 of 100%.

Patient had multiple brown sessile nodular lesions over cheeks, forehead and nose ,suited the Butterfly pattern of distribution(Figure 2).Similar angiofibromas were present on back and trunk.On intraoral examination, similar well-defined, sessile, firm, and nodular growths were seen in the marginal and attached gingiva in the upper and lower anterior region of varying sizes(Figure 3). Multiple hypoplastic enamel pits were noted. Initially it was attributed to phenytoin therapy but phenytoin levels turned out to be normal.He had multiple hypopigmented macules on his back and trunk which depicted Ash Leaf macules(Figure 1). A well-defined roughened hypermelanotic patch was noted in the right lumbosacral region showing an appearance indicative of shagreen patch. Firm nodular growth was noted on toes of varying sizes, suggestive of early periungual fibromas or Köenen tumors.(Figure 4) . Fundus examination didn't show phekomas.

CT Scan brain revealed multiple calcified granulomas measuring 3mm in multiple subependymal areas.(Figure 5) USG Abdomen and pelvis did not show renal angiomyolipomas.2D Echocardiogram was normal. With seizures as presentation , malar distribution of brownish sessile nodules ,and gum hyperplasia ,ash leaf macules ,shagreen patch with history of difficulty in learning ,a diagnosis of tuberous sclerosis was kept in mind. After 24 hrs of mechanical ventilation ,the patient was successfully extubated.

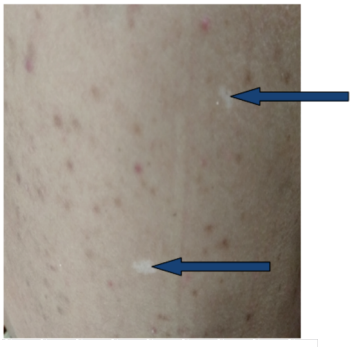

Figure 1 : Hypopigmented maculae on back and trunk- Ash leaf maculae

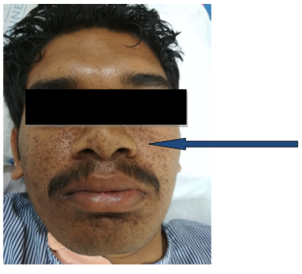

Figure 2: sessile nodular lesions over cheeks, forehead and nose-Angiofibrmas

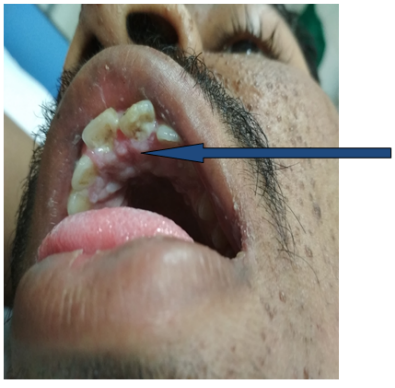

Figure 3: Multiple well-defined, sessile, firm, and nodular growths were seen in the marginal and attached gingiva .

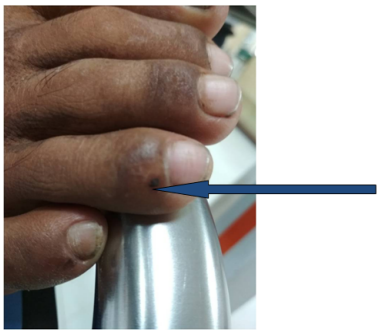

Figure 4: Early periungual fibromas or Köenen tumors.

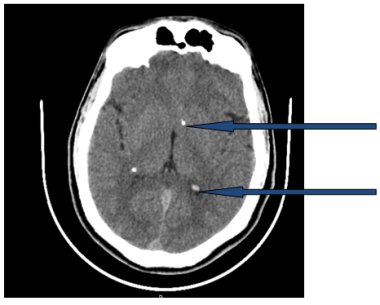

Figure 5: Multiple calcified granulomas in subependymal areas

DISCUSSION:

Tuberous sclerosis is a rare genetic disorder which is inherited in autosomal dominant pattern.

The inactivating mutation in one of the two genes, TSC1 encoding hamartin on chromosome 9, or TSC2 encoding tuberin on chromosome 16[45] is found to be responsible. It is a disorder of cellular differentiation and proliferation that can affect the brain, skin, kidneys, heart and other organs. The organs are affected with varying severity. Mental retardation, seizures, and cutaneous angiofibroma (formerly called adenoma sebaceum)[6] is the classical clinical triad of Tuberous sclerosis complex.

Abnormal neuronal migration plays a major additional role in neurological dysfunction.[7]

CNS Manifestations:

Cortical tubers, subependymal nodules, subependymal giant cell astrocytoma and benign white matter lesions are characteristic. By the age of ten, fifty percent of patients have calcified cortical tubers.[8]

Brain tumours associated with TSC include:

i. ***Giant cell astrocytoma*:** blocks the CSF flow leading to dilatation of ventricles.
ii. ***Cortical tubers***
iii. ***Sub-ependymal nodules*:** form in the walls of ventricles.[9]

Mental retardation and seizures are both neurologic manifestations of TSC . The overall incidence of mental retardation is 38 percent to 80 percent in TSC , while epilepsy is one of the most prevalent manifestations of TSC[10], occurring in more than 80 percent to 90 percent of patients with TSC.[11_12]

Skin Manifestations:

Most important characteristic finding on clinical examination[13]are Cutaneous lesions present in 96% of patients with tuberous sclerosis .The skin lesions commonly found are:

(i) ***Adenoma Sebaceum*** **:** Also called facial angiofibromas consists of blood vessels and fibrous tissue.
(ii) ***Ash-leaf spots*** **(hypomelanic macules):** One of the earliest signs of tuberous sclerosis.
(iii) ***Shagreen patches*:** Found usually on the back or nape of neck. These are areas of leathery and pebbly skin.

Renal Manifestations:

Angiomyolipomas and renal cysts are two types of renal lesions associated with tuberous sclerosis. They may be found independently altogether and may be unilateral, bilateral, single or multiple. [14_15]

Multiple bilateral angiomyolipomas, comprising abnormally organized blood vessels, smooth muscle cells, and adipose tissue, occur in approximately 80% of individuals with TSC1,2 and represent the leading cause of mortality in the TSC patient population secondary to spontaneous hemorrhage.[16]

Miscellaneous Lesions:

Cardiac rhabdomyomas occur in 30% of cases[17].Retinal hamartomas (phekomas) are found on funduscopic examination[18].Rarely ,invasive giant cell astrocytoma of the retina can be associated with tuberous sclerosis[19].Pulmonary involvement is rare and occur in form of cystic lymphangiomyomas, and chronic fibrosis.

DIAGNOSTIC CRITERIA FOR TUBEROUS SCLEROSIS:

Major Criteria	Minor Criteria
1. Cortical tuber	1. Cerebral white matter migration lines
2. Subependymal nodule	2. Multiple dental pits
3. Facial angiofibroma or forehead plaque	3. Gingival fibromas
4. Ungual or periungual fibroma (nontraumatic)	4. Bone cysts
5. Hypomelanotic macules (>3)	5. Retinal achromatic patch
6. Shagreen patch	6. Confetti skin lesions
7. Multiple rentinal hamartomas	7. Nonrenal hamartomas
8. rhabdomyoma	8. Multiple renal cysts
9. Renal angiomyolipoma	9. Hamaromatous rectal polyps
10. Pulmonary lymphangioleimyomatosis	

Definite TSC can be made when two major or one major plus two minor features are demonstrated.

Our patient had following definitive criteria for diagnosis of TSC :

A) MAJOR:

1) cortical tubers on CT Brain,
2) Facial angiofibroma
3) Ungual Fibromas
4) Hypomelanotic macules
5) Shagreen patch

B)MINOR:

1) Dental pits
2) Gingival fibrosis

Management:

Patients require anti-epileptics for the management of seizures[20], genetic counselingof the parents (if the family is not completed and to the patient himself) and supportive care for delayed neurocognitive development. Rapamycin (Sirolimus) is the drug developed for treatment of tuberous sclerosis[21]. Sirolimus is known to cause regression of angiofibromas and even astrocytomas[22].For our patient, we prepared 0.1% Sirolimus ointment, for topical application over angiofibromatous area on face, in collaboration with Department of Pharmacology(as commercial preparation of sirolimus is not available.)

CONCLUSION:

Increased awareness is required for early diagnosis of tuberous sclerosis cases and subsequent organ involvement associated with this disease. Appropriate symptomatic intervention should be thought of in such cases. Genetic counseling has an important role to play .Tuberous sclerosis complex must kept as a differential in children or young adults presenting with seizures, mental retardation and developmental delays.

REFERENCES:

1. Osborne JP, Fryer A. Epidemiology of Tuberous Sclerosis. NYAcad Sci 1991; 615: 125-7.
2. van Slegtenhorst M, et al. Identification of the tuberous sclerosis gene TSC1 on chromosome 9q34.Science 1997;277:805 808.
3. Kandt RS, et al. Linkage of an important gene locus for tuberous sclerosis to a chromosome 16 marker for polycystic kidney disease. Nat Genet 1992;2:37 41.
4. van Slegtenhorst M, et al. Interaction between hamartin and tuberin, the TSC1 and TSC2 gene products. Hum Mol Genet 1998;7:1053 1057
5. Jones AC, et al. Comprehensive mutation analysis of TSC1 and TSC2-and phenotypic correlations in 150 families with tuberous sclerosis. Am J Hum Genet 1999;64:1305 1315.
6. Roach ES, Gomez MR. Tuberous Sclerosis complex consensus conference. Revised clinical diagnostic criteria. J Child Neurosurgery 1998; 13: 624-8.
7. Crino PB, et al. The tuberous sclerosis complex. N Engl J Med 2006;355:1345 1356.
8. Tuberous Sclerosis with Unusual Presentation in an Adult Jitendra Ingole, AP Jain JIACM 2005; 6(1): 79-81

9. Goh S, et al. Subependymal giant cell tumors in tuberous sclerosis complex. Neurology 2004;63:1457 1461.
10. Holmes GL, Stafstrom CE. Tuberous sclerosis complex and epilepsy: recent developments and future challenges. Epilepsia 2007;48:617 630.
11. Prather P, de Vries PJ. Behavioral and cognitive aspects of tuberous sclerosis complex. J Child Neurol 2004;19:666 674.
12. Smalley SL. Autism and tuberous sclerosis. J Autism Dev Disord 1998;28:407 414.
13. Curatolo P, et al. Tuberous sclerosis. Lancet 2008;372:657 668.
14. Cook JA, et al. A cross sectional study of renal involvement in tuberous sclerosis. J Med Genet 1996;33:480 484.
15. Rakowski SK, et al. Renal manifestations of tuberous sclerosis complex: Incidence, prognosis, and predictive factors. Kidney Int 2006;70:1777 1782.
16. Shepherd CW, et al. Causes of death in patients with tuberous sclerosis. Mayo Clin Proc 1991;66:792 796.
17. Smythe JF, et al. Natural history of cardiac rhabdomyoma in infancy and childhood. Am J Cardiol 1990;66:1247 1249.
18. Mennel S, et al. Current treatment modalities for exudative retinal hamartomas secondary to tuberous sclerosis: review of the literature. Acta Ophthalmol Scand 2007;85:127 132.
19. Gunduz K, et al. Invasive giant cell astrocytoma of the retina in a patient with tuberous sclerosis.
20. Ophthalmology 1999;106:639 642.
21. Thiele EA. Managing epilepsy in tuberous sclerosis complex. J Child Neurol 2004;19:680 686.
22. Bissler JJ, et al. Sirolimus for angiomyolipoma in tuberous sclerosis complex or lymphangioleiomyomatosis. N Engl J Med 2008;358:140 151.
23. Franz DN, et al. Rapamycin causes regression of astrocytomas in tuberous sclerosis complex. Ann
24. `Neurol 2006;59:490 498.