

Case Report

# Everolimus: Paradigm Shift in the Management of Tuberous Sclerosis

Dr Sabarish Mahalingam<sup>1</sup>, Dr P. Z. Wadia<sup>2</sup>, Dr Priyanka Lad<sup>1</sup>,  
Dr Mithram Wadia<sup>3</sup>

<sup>1</sup>Resident Doctor, <sup>2</sup>Additional Professor,  
Department of Internal Medicine, Government Medical College, Surat  
<sup>3</sup>Intern Doctor, Government Medical College, Surat

Corresponding Author: Dr Sabarish Mahalingam

## ABSTRACT

Tuberous sclerosis, also known as Bourneville's disease, is a rare autosomal dominant genetic disorder classically characterized by the triad of mental retardation, seizures, and facial angiofibromas. We reported a case of 35 year old female with Tuberous sclerosis complex syndrome presented with facial angiofibromas, pulmonary cyst, pancreas hypoplasia, angiomyolipomas of the bilateral kidney and subependymal nodules.

**Keywords:** Tuberous sclerosis complex, facial angiofibromas, angiomyolipomas of the bilateral kidney, subependymal nodules.

## INTRODUCTION

The name, composed of the Latin *tuber* (swelling) and the Greek *skleros* (hard), refers to the pathological finding of thick, firm, and pale gyri, called "tubers", in the brains of patients post mortem. These tubers were first described by Desire-Magloire Bourneville in 1880. The cortical manifestations may sometimes still be known by the eponym Bourneville's disease. The full name of "tuberous sclerosis complex" is preferred among medical professionals and researchers today because the disease has manifestations outside of the brain. <sup>[1]</sup>

Tuberous sclerosis complex (TSC) is a rare multisystem genetic disease that causes benign tumors to grow in the brain and on other vital organs such as the kidneys, heart, liver, eyes, lungs, and skin. A combination of symptoms may include seizures, intellectual disability, developmental delay, behavioral problems, skin abnormalities, and lung and kidney

disease. TSC occurs in all races and ethnic groups, and in both genders. The live-birth prevalence is estimated to be between 10 and 16 cases per 100,000. TSC is caused by a mutation of either of two genes, *TSC1* and *TSC2*, which code for the proteins hamartin and tuberin, respectively. These proteins act as tumor growth suppressors, agents that regulate cell proliferation and differentiation. <sup>[2]</sup>

## CASE REPORT

A 30 years old female presented to emergency department with the history of first episode of generalised tonic clonic convulsion. Patient was born of non-consanguineous marriage. None of the family member was known to have similar complaints.

On examination, patient had multiple hyperpigmented papules over the nasolabial region Adenoma sebaceum (Figure 1), shagreen patch present over left shoulder and back (Figure 2) and periungual

fibroma (Figure 3). Systemic examination, slit lamp, fundus examination revealed no

abnormalities. Her Intelligence Quotient testing was done which was normal.



Figure 1: Adenoma sebaceum



Figure 2: Shagreen patch



Figure 3: Periungual fibroma



Figure 4: Echogenic lesions at the upper pole of right kidney

USG abdomen revealed, right kidney measuring (111\*47) mm<sup>2</sup> in size and left kidney measuring (99\*55)mm<sup>2</sup> in size. There is large ill defined exophytic echogenic lesion noted in relation to upper

mid of right kidney. Left kidney show altered echo textured and large ill defined echogenic lesion noted in relation to upper mid of left kidney. P/O Benign lesion Angiomyolipoma (Figure 4).

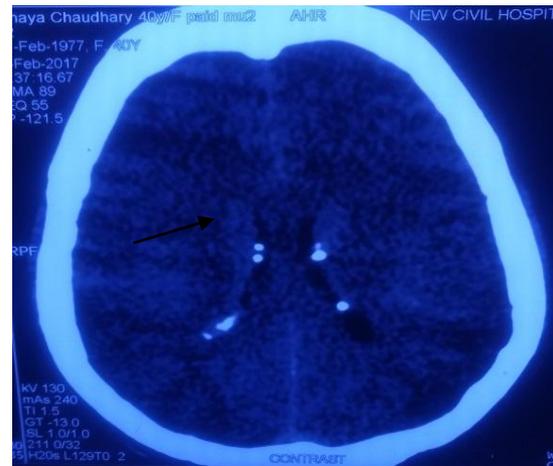


Figure 5: Subependymal nodules

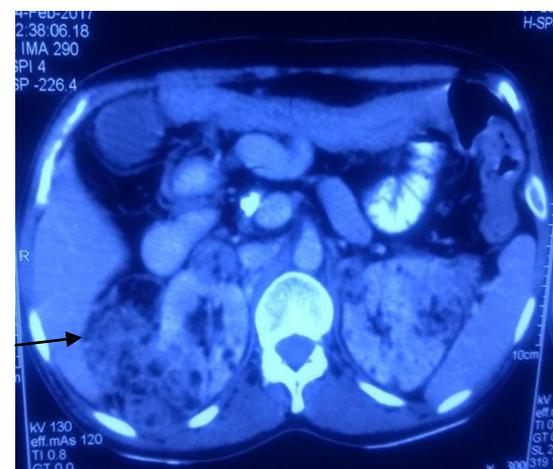


Figure 6: Renal angiomyolipoma

**Bilateral mammography-Normal**

CT scan of brain shows- Subependymal nodules involving ependymal surface of both lateral ventricle, Old infarct involving right temporal region, Cerebral oedema, Multiple sclerotic lesion involving skull vault (Figure 5).

CT scan of abdomen shows multiple bilateral renal angiomyolipomas, pancreas hypoplasia (Figure 6).

Finding of MRI brain were- (Figure 7)

1. Multiple recent ischemic areas involving right parieto-temporo-occipital and left parietal paramedian cortical-subcortical region.
2. Multiple small subcentimeter size altered signal lesions in the ependymal region along frontal horn, body and atrium of both the lateral ventricles, represents subependymal nodules
3. Subtle focal non-enhancing altered signal along the bilateral frontal cortical region, may represent cortical tubers/edema.

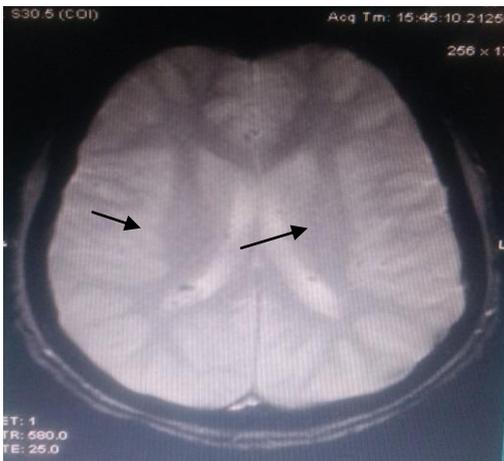


Figure 7: recent ischemic right parieto temporal occipital region and subependymal nodules in T2W1

**2D Echo - normal**

Patient was treated with antiepileptic drugs and Oncologist advised to start Tab. Everolimus.

**DISCUSSION**

Tuberous sclerosis complex (TSC) is a rare genetic disorder with heterogeneous presentation varying from severe mental retardation and incapacitating seizures to normal intelligence and an absence of seizure, often within the same family. It is due to inactivating mutation in one of the two genes, TSC1 encoding hamartin, or TSC2 encoding tuberin2.

The major neurological manifestations of tuberous sclerosis complex are seizures, autism, developmental delay and behavioral and psychiatric disorder. Seizure is present in about 80-90% of patient which begins during the first year of life; varies from subtle focal seizure, infantile spasm, to generalized seizure. [3-5]

Manifestations of tuberous sclerosis can become apparent in persons of any age, but most patients have clinical symptoms before they are aged 10 years. The disease develops as an abnormal growth of ectodermic cells producing tumors extending to areas of the head, heart, brain, eyes, skin and kidneys. [6] In 2012, the International Tuberous Sclerosis Complex Consensus Conference published new diagnostic criteria for diagnosis of tuberous sclerosis. (Table 1). [7]

TABLE 1: CLINICAL DIAGNOSTIC CRITERIA [7]

MAJOR FEATURES		MINOR FEATURES	
1	Hypomelanotic macules(3,at least 5-mm diameter)	1	“Confetti” skin lesions
2	Angiofibroma or fibrous cephalic plaque	2	Dental enamel pits(>3)
3	Ungual fibromas	3	Intraoral fibromas(2)
4	Shagreen patch	4	Retinal achromic patch
5	Multiple retinal hamartomas	5	Multiple renal cysts
6	Cortical dysplasia	6	Non renal hamartomas
7	Subependymal nodules		
8	Subependymal giant cell astrocytoma		
9	Cardiac rhabdomyoma		
10	Lymphangiioleiomyomatosis		
11	Angiomyolipomas		

Definite diagnosis: Two major features Possible diagnosis: Either one features or one major feature with 2 minor major feature or 2 minor features According

to the criteria the patient reported had more than 2 major criteria and was considered as TSC. There are many cutaneous stigmata of TSC and they are seen in almost all patients with the disorder. The most common and earliest skin finding in TSC is multiple hypopigmented macules (also called ashleaf spots). Adenoma sebaceum is a hamartoma composed of connective and vascular elements and is properly termed an angiofibroma they are pathognomonic of TSC. Angiofibromas form discrete pink papules on the malar region of the face in 70% of TSC patients. [8,9] Patients with tuberous sclerosis complex (TSC) can develop a number of renal lesions, the most common being angiomyolipomas and cysts. [10] Renal cysts are rarely symptomatic in patients with TSC, unless the patient exhibits the polycystic kidney variety of TSC. It has been reported that up to 80% of adult patients with TSC will develop angiomyolipoma and that these lesions tend to increase in size over time.

The intracranial features of TSC are cortical or subcortical tubers, subependymal nodules, subependymal giant cell astrocytomas, and white matter radial migration lines. [11] Tubers are most commonly found in the cerebrum, 90% being present in the frontal lobes. On NECT in early stages tubers appear as low density subcortical masses. In late stages they appear isodense to brain. 50% calcify by the age of 10 years. On T2-weighted and FLAIR MR images, tubers typically appear as areas of increased signal intensity in the cortical and subcortical regions. Tubers exhibit contrast enhancement in approximately 3–4% of cases. Ninety-five percent of tubers are multiple, but in rare instances solitary cortical tubers are seen. Less commonly tubers are present in the cerebellum.

Subependymal nodules (SEN) are found on the walls of the lateral ventricles and are either discrete or roughly confluent areas of rounded hypertrophic tissue. Typically benign, subependymal nodules can degenerate into subependymal giant cell astrocytomas in 5–10% of cases. On

NECT the nodules occur anywhere along the ventricular surface but are most commonly found at the caudothalamic groove in the region of the foramen of Monro. 50% calcify. Enhancing SEN may be suspicious for subependymal giant cell astrocytoma. Microcephaly may be found in patients with TSC. The cerebral gray and white matter volumes are lower than those of age-matched controls [12]

Pulmonary lymphangiomyomatosis probably affects 1–3% of patients with tuberous sclerosis.

A cardiac rhabdomyoma can be discovered using echocardiography in approximately 50% of TSC patients. However, the incidence in the newborn may be as high as 90% and in adults as low as 20%. Rhabdomyomas have been diagnosed by two-dimensional echocardiography in the fetus. [13] Ophthalmic features associated with TSC can be divided into retinal and non-retinal. The retinal lesions are known as astrocytic hamartomas. [14] Non-retinal lesions include coloboma, angiofibroma of the eyelid and papilledema (related to hydrocephalus).

Multiple bony changes have been described in TSC of which sclerotic lesions are the most common. Hyperostosis of inner table of skull, periosteal new bone formation, scoliosis, and bone cysts have also been described. [15] Patients with Tuberous sclerosis complex (TSC) range from intellectually normal to severely mentally retarded. TSC is often associated with mental retardation (in 70% of cases) and epilepsy (90%). Seizures are the most common neurologic symptom of TSC occurring in 92% of patients. [16] Prognosis of the disease depends on the severity or multiplicity of organ involvement.

## ROLE OF EVEROLIMUS IN TUBEROUS SCLEROSIS

Since the discovery of rapamycin in the 1960s, [17] mTOR inhibitors, particularly everolimus, have been used to prevent solid organ transplant rejection, augment anticancer treatment regimens, and prevent

neovascularization of artificial cardiac stents. [18] Following the identification of the genes involved in TSC in the 1990s, [19] evidence revealed mutations or deletions that allowed mTOR activity to go unchecked (Figure 8). [20-22] Subsequent clinical trials in patients with TSC led to the approval of the mTOR inhibitor everolimus

for TSC-associated subependymal giant cell astrocytoma (SEGA) by US Food and Drug Administration (FDA) in 2010; [23] it became the first-ever approved therapy for patients with TSC. Everolimus was also approved by the FDA in 2012 to treat renal angiomyolipomas in patients with TSC. [23]



Figure 8 : Action of Everolimus

Note: Adapted by permission from Macmillan Publishers Ltd: Nature Neuroscience. Costa-Mattioli M, Monteggia LM. mTOR complexes in neurodevelopmental and neuropsychiatric disorders. Nat Neurosci. 16(11):1537–1543. Copyright © 2013.9

Abbreviations: NMDA, N-methyl-d-aspartate; BDNF, brain-derived neurotrophic factor; NGF, nerve growth factor; TrkB, tyrosine receptor kinase B; IGF-1, insulin growth factor 1; IRS-1, insulin receptor substrate 1; PI3K, phosphatidylinositol 3-kinase; PIP<sub>2</sub>, phosphatidylinositol-4,5-bisphosphate; PIP<sub>3</sub>, phosphatidylinositol-3,4,5-trisphosphate; NF1, neurofibromin 1; PTEN, phosphatase and tensin homolog; PDK1, phosphatidylinositol-dependent kinase 1; TSC, tuberous sclerosis complex; Rheb, Ras homolog enriched in brain; mTORC1, mammalian target of rapamycin complex 1; S6K, S6 kinase; E-BP, eIF4E-binding protein; eEF2K, eukaryotic elongation factor-2 kinase; eIF4B, eukaryotic initiation factor 4B.

## CONCLUSION

The chance of progression to malignancy is more. Early Diagnosis and treatment with Everolimus is very important. Because this drug have the potential to not only treat other manifestations of TSC, such as angiofibromas, cardiac rhabdomyomas, LAM, and epilepsy, but they may also have

a role in modifying disease progression at a very young age.

## REFERENCES

1. “Google Ngram Viewer”. books.google.com. Retrieved 2017-02-03.
2. “Tuberous Sclerosis Fact Sheet”. NINDS. 1 April 2006. Retrieved 9 January 2007.

3. Curatolo P, Maria BL. Tuberous sclerosis. In: Dulac O, Lasonade M, Sarnat HB, editors. Pediatric Neurology part I. Elsevier B.V; 2013. P.323-31. (Handbooks of Clinical Neurology; volume 111).
4. Leung AKC, Robson LM. Tuberous Sclerosis Complex: A Review. J Pediatr Health Care. 2007; 21:108-114.
5. Finkelstein R. Advances in Tuberous Sclerosis Complex Research: The October 1, 2003, Child Neurology Society Workshop. J Child Neurol. 2004; 19:734.
6. Gupta S, Bhowate R, Degwekar SS. Clinical and Radiological Findings Related to Tuberous sclerosis Complex: A case report. JContemp dent Prac. 2008;(9)4:085-091
7. Northrup, Hope, Darcy A. Krueger, and on behalf of the International Tuberous Sclerosis Complex Consensus Group. "Tuberous Sclerosis Complex Diagnostic Criteria Update: Recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference." Pediatric neurology 49.4(2013):243-254.
8. Harper JJ, Trembath RC., Genetics and Genodermatosisin: breathnach, Neil Cox, Christopher Griffiths. Rook's Textbook of Dermatology, 7th edition, volume-1Blackwell, Australia. 2004; 1233-1237.
9. Henry J, Baskin Jr. The pathogenesis and imaging of the tuberous sclerosis complex. Pediatr Radiol. 2008; 38: 936-952.
10. Keith A, Casper MS, Lane FD, BinChen, John JB. Tuberous Sclerosis Complex: Renal Imaging Findings. Radiology. 2002; 225.
11. Babak NK and Noriko S. Neuroimaging of Tuberous Sclerosis: spectrum of Pathologic Findings and Frontiers in Imaging. American Journal of Roentgenology. 2008; 190(5): 304-309.
12. Flavia GV, Edson M, Glaucia Z. et al. tuberous sclerosis with pulmonary lymphangioliomatosis and renal angiomyolipomas. Computed tomographic findings: a case report. Cases Journal. 2009;2:9124.
13. Maryum M, Mohammad D, Mahmood M. Prenatal Diagnosis of Tuberous Sclerosis by Fetal Echocardiography with an Unusual Clinical course After Birth. archcardiovasc Image. 2013; 1(2):83-85.
14. Rowley SA, O'Callaghan FJ, Osborne JP. Ophthalmic manifestations of tuberous sclerosis: a population based study. Br jOphthalmol. 2001; 85: 420-423.
15. Rupa R, Sadhna V. Clinically relevant Imaging in tuberous Sclerosis. Journal of Clinical imaging Science. 2011; 1: 39.
16. Shobha B., Ashwini R, Veerendra SP, Sunil B. Tuberous Sclerosis Complex Syndrome A Rare Case Report. Journal of Medical Education & Research. 3(1):57-63.
17. Vézina C, Kudelski A, Sehgal SN. Rapamycin (AY-22,989), a new anti-fungal antibiotic. I. Taxonomy of the producing streptomycete and isolation of the active principle. JAntibiot (Tokyo) 1975;28(10):721-726.
18. Gabardi S, Baroletti SA. Everolimus: a proliferation signal inhibitor with clinical applications in organ transplantation, oncology, and cardiology. Pharmacotherapy. 2010; 30(10):1044-1056.
19. Povey S, Burley MW, Attwood J, et al. Two loci for tuberous sclerosis: one on 9q34 and one on 16p13. Ann Hum Genet. 1994;58(pt 2):107-127.
20. Dabora SL, Jozwiak S, Franz DN, et al. Mutational analysis in a cohort of 224 tuberous sclerosis patients indicates increased severity of TSC2, compared with TSC1, disease in multiple organs. Am J Hum Genet. 2001;68(1):64-80. [PMC free article]
21. Sancak O, Nellig M, Goedbloed M, et al. Mutational analysis of the TSC1 and TSC2 genes in a diagnostic setting: genotype – phenotype correlations and comparison of diagnostic DNA techniques in tuberous sclerosis complex. Eur J Hum Genet. 2005;13(6): 731-741.
22. Costa-Mattioli M, Monteggia LM. mTOR complexes in neurodevelopmental and

- neuropsychiatric disorders. *Nat Neurosci.* 2013;16(11):1537–1543.
23. Novartis Pharma, Stein AG. Prescribing Information, Afinitor (Everolimus) Tablets for Oral Administration.

[Accessed March 8, 2016]. Available from:  
<http://www.pharma.us.novartis.com/product/pi/pdf/afinitor.pdf>.

How to cite this article: Mahalingam S, Wadia PZ, Lad P et al. Everolimus: paradigm shift in the management of tuberous sclerosis. *Int J Health Sci Res.* 2017; 7(7):381-387.

\*\*\*\*\*