

Tuberous sclerosis–A Neurocutaneous Disorder

R J Akhter¹, B H N Yasmeen², N Begum³, AFM A Imran⁴

Tuberous Sclerosis or Tuberous Sclerosis Complex (TSC) is a genetic disorder characterized by the growth of numerous benign tumors (hamartomas) in many parts of the body including the brain, heart, lungs, eyes, kidneys, skin and other organs, leading to seizures, intellectual disability, autism or developmental delay.^{1,3}

TSC is an autosomal dominant disorder with an incidence of approximately 1 in 5000 to 10,000 live births.³⁻⁵ It presents with variable clinical manifestations together with angiofibromas distributed in a characteristic "butterfly" pattern on the face and forehead. TSC occurs in all races and ethnic groups, and in both genders.

Case Summary

An 11 month old completely immunized boy of a nonconsanguineous parents hailing from Shariatpur was admitted at Dhaka Shishu Hospital on 23 January 2017 with the complaints of abnormal jerky movement of both limbs and head for 2 months and Excessive cry for the same duration.

The movement was initially irregular with short duration (few seconds to minutes) and used to resolve spontaneously. But gradually it increases in duration and intensity. For the last fifteen days it became more frequent and nearly uncontrolled.

The Baby was delivered by LUCS at term at hospital without any complication. He was exclusively breastfed upto 6 months then complimentary feeding was started with khichuri and milk suzi. Developmentally he was age appropriate. There was no history of unconsciousness, hematuria or respiratory

distress or any family history of such type of illness.

With these complaints he was treated with some homeopathic medication but as the condition did not improve then he was admitted in to Dhaka Shishu Hospital.

On Examination the baby was irritable without any active convulsion. His vital signs were normal and anthropometrically he was age appropriate.

Skin survey revealed BCG mark was present. There were multiple hypopigmented areas over trunk and extremities, the largest one located on the back measuring about 2x1cm in diameter. Regarding systemic examination we found that his Nervous, Respiratory, Cardiac and Renal system reveals normal. Provisionally we thought of Neurocutaneous syndrome, Tuberous Sclerosis with Infantile spasm.



¹ Dr. Rowshan Jahan Akhter
Resident Medical Officer
Dept. of Neonatology
Dhaka Shishu (children) Hospital

² Prof. Dr. B H Nazma Yasmeen
Professor & Head
Dept. of Pediatrics
Northern International Medical
College, Dhaka

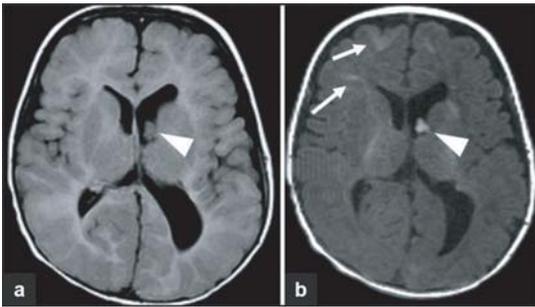
³ Dr. Nasreen Begum
Assistant Professor
Dept. of Community Medicine
Northern International Medical
College, Dhaka

⁴ Dr. AFM Ashik Imran
Lecturer
Dept. of Biochemistry
Ad-din Women's Medical College
Dhaka

Correspondence
Dr. Rowshan Jahan Akhter
Resident Medical Officer
Dept. of Neonatology
Dhaka Shishu (children) Hospital
email: rowshanfairuz22@gmail.com

On admission we treat the baby with Normal diet and Syrup Phenobarbitone. CBC, Serum Electrolyte, Serum Calcium, Random Blood Sugar, Chest X-ray findings were within normal limit.

But his USG brain revealed-Prominent of frontal horn, Ventricular index was 30% (Normal), Thickened Sulci. EEG showed abnormality with background activity with epileptiform discharges. and advised to correlate clinically with West syndrome. MRI Showed that Presence of cortical tuber with Candle dripping appearance.



Therefore, finally we diagnose the patient as a Neurocutaneous Syndrome-Tuberous Sclerosis. After final diagnosis patient was discharged on request with syrup Phenobarbiton as with this drug symptom were subsided. We asked the parents to come with the baby for follow-up after one month.

Discussion

The baby was presented with abnormal jerky movement of both limbs and head for 2 months since his 7 months of age and excessive cry for the same duration. He had typical multiple hypopigmented area of skin (Ash leaf spots) specially over the trunk, which was clinically consistent with Tuberous Sclerosis. MRI report was also consistent with Tuberous sclerosis.

Therefore, with the history of recurrent seizure, hypomelanotic macules (Ash leaf spots) and supportive evidences from imaging suggests the diagnosis of Tuberous Sclerosis. In addition he had clinical evidence of epilepsy, which was confirmed by EEG.

Tuberous sclerosis (TS) is also known as Bourneville disease, named after the French physician who described a series of patients with this illness in 1880.⁶ TS is thought to be result from sporadic mutation in the majority (Two-thirds) of patients, since most patients have no family history of the disease.² But

their offspring may inherit it from them. It is caused by a mutation in either the TSC1 gene or the TSC2 gene. TSC1 and TSC2 which code for the protein hamartin and tuberin respectively. These proteins act as tumor growth suppressor agents that regulate cell proliferation and differentiation.

The triad of symptoms of TS, as described by Vogt,⁷ consists of seizure, adenoma sebaceum (facial angiofibroma) and mental retardation. Not all patients have this classic triad, however, and half of all patients are of normal intellect and a quarter do not have seizures.⁸ Although facial angiofibromas are commonly described as the hamartomatous lesions of TS, hamartomas may involve virtually any organ.

The diagnostic criteria of TSC have been divided into major and minor features.^{9,10}

Major Criteria

Angiofibromas (3 or more) or forehead plaque, Hypomelanotic macules (3 or more), Ungual fibromas (2 or more), Shagreen patch or multiple collagenomas, Multiple retinal hamartomas, Cortical dysplasia's (More than 3). This includes tubers and cerebral white matter radial migration lines. Subependymal nodule(s), Subependymal giant cell astrocytoma (s), Cardiac rhabdomyoma, Lymphangiioleiomyomatosis (LAM), Angiomyolipomas (2 or more).

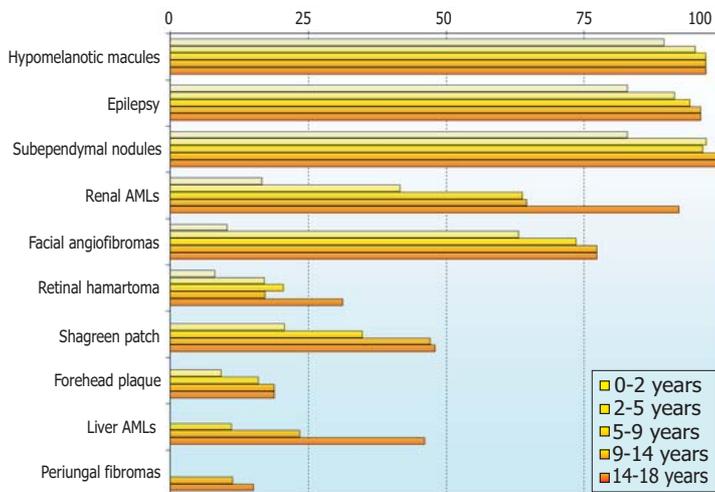
Minor Criteria

Multiple randomly distributed pits in dental enamel, Hamartomatous Rectal Polyps, Bone cysts, Cerebral white matter migration tracts, Gingival fibromas, Non-renal hamartomas, Retinal achromic patches, Confettis.

No pathognomic clinical signs for TSC complex are seen. In order to meet diagnostic criteria for TSC complex, an individual must either have: 1) Two or more major criteria. Or 2) One major criterion along with two or more minor criteria.¹⁰

Signs and symptoms of tuberous sclerosis may be noticed at birth or the first signs and symptoms of tuberous sclerosis may become evident during childhood or even years later in adulthood. Mildly affected individuals are now being diagnosed, including many older adults who do not have seizures or intellectual disabilities.

The frequency of signs in children with TSC, grouped by age⁹



Individuals with TSC may experience none or all of the clinical signs discussed above. The above table shows the prevalence of some of the clinical signs in individuals diagnosed with TSC. The typical findings of Hamartomas are the hallmark of TS. Patients with TS come to medical attention for a variety of reasons, including seizure, renal failure from cystic disease, and mental retardation.

There is no specific treatment and there's no cure for tuberous sclerosis. Because the disease can differ from person to person and treatment is based on the symptoms. The course or severity of the disease can't be predicted, but with appropriate care, many people who have TSC lead full, productive lives.

A multidisciplinary team approach is needed for diagnosis and medical care of tuberous sclerosis complex in order to treat many organ systems that are affected. Treatment of seizures and genetic counseling, learning skills and education should be advocated in these patients. Drug therapy, surgery, and other interventions can be effective in managing some of the manifestations and symptoms of TSC.

In the United States, the Food and Drug Administration has approved several drugs for managing some of the major manifestations of TSC. The antiepileptic medication Vigabatrin was approved in 2009 for treatment of infantile spasms and was recommended as first-line therapy for infantile spasms in children with TSC by the 2012 International TSC Consensus Conference.¹¹ Everolimus also showed evidence of effectiveness at treating epilepsy in some people with TSC.¹² In 2017, the

European Commission approved Everolimus for treatment of refractory partial-onset seizures associated with TSC.²⁷

In some cases Neurosurgical intervention may reduce the severity and frequency of seizures in TSC patients.

The prognosis for individuals with TSC depends on the severity of symptoms, which range from mild skin abnormalities to varying degrees of learning disabilities and epilepsy and kidney failure. Those individuals with mild symptoms generally do well and live long, productive lives, while individuals with the more severe form may have serious disabilities.

References

1. Crino PB, Nathanson KL, Henske EP. The tuberous sclerosis complex. *N Engl J Med* 2006; 355:1345.
2. Schwartz RA, Fernández G, Kotulska K, Jówiak S. Tuberous sclerosis complex: advances in diagnosis, genetics, and management. *J Am Acad Dermatol* 2007; 57:189.
3. Curatolo P, Bombardieri R, Jozwiak S. Tuberous scl
4. Hallett L, Foster T, Liu Z, et al. Burden of disease and unmet needs in tuberous sclerosis complex with neurological manifestations: systematic review. *Curr Med Res Opin* 2011; 27:1571.
5. Hong CH, Tu HP, Lin JR, Lee CH. An estimation of the incidence of tuberous sclerosis complex in a nationwide retrospective cohort study (1997-2010). *Br J Dermatol* 2016; 174:1282.
6. Bourneville DM. Sclerose tubereuse des circonvolutions cerebrales: idiotie et epilepsie hemiplegique. *Arch Neurol* .1880; 1:81-91.2. Winship IM, Connor JM, Beighton PH. Genetic heterogeneity in tuberous sclerosis: phenotypic correlations. *J Med Genet*. 1990; 27:418-421.
7. Vogt H. Zur pathologie und pathologischen anatomie der verschiedenen idiotieformer. *Monatsschr Psychiatr Neurol*. 1908; 24: 106-150.
8. O'Callaghan FJ, Osborne JP. Advances in the understanding of tuberous sclerosis. *Arch Dis Child*. 2000; 83:140-142.
9. Gomez MR. Diagnostic criteria. In: Gomez MR, ed. *Tuberous sclerosis*. 2nd ed. New York, NY: Raven.1985; 9-20.
10. Northrup H, Krueger DA, International Tuberous Sclerosis Complex Consensus Group (2013). "Tuberous sclerosis complex diagnostic criteria update: recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference". *Pediatr Neurol*. 49 (4): 243-54. doi:10.1016/j.pediatrneurol.2013.08.001.
11. Krueger, Darcy A.; Northrup, Hope; International Tuberous Sclerosis Complex Consensus Group (2013-10-01). "Tuberous sclerosis complex surveillance and management: recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference". *Pediatric Neurology*. 49 (4): 255-265. doi:10.1016/j.pediatrneurol.2013.08.002.
12. French, Jacqueline A; Lawson, John A; Yapici, Zuhai; Ikeda, Hiroko; Polster, Tilman; Nabbout, Rima; Curatolo, Paolo; Vries, Petrus J de; Dlugos, Dennis J. "Adjunctive everolimus therapy for treatment-resistant focal-onset seizures associated with tuberous sclerosis (EXIST-3): a phase 3, randomised, double-blind, placebo-controlled study". *The Lancet*. 388 (10056): 2153-2163. doi:10.1016/s0140-6736(16)31419-2.
13. AG, Novartis International. "Novartis drug Votubia® receives EU approval to treat refractory partial-onset seizures in patients with TSC". Retrieved 2017-02-08.