Case Reports

Familial Tuberous Sclerosis Complex: Tuberous Sclerosis Complex an a Patient Presenting in Status Epilepticus

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Abstract

Tuberous sclerosis complex is a rare multi-systemic disorder that could be complicated by disabling neurological manifestations including intractable epilepsy. It is an autosomal dominant disorder with variable penetrance. Familial tuberous sclerosis probably occurs more often than is reported in the literature. This article reports on a Nigerian man with tuberous sclerosis complex who presented in status epilepticus with documentation of tuberous sclerosis in his family and discussed the manifestations, diagnostic criteria, clinical evaluation, investigation and management of patients with tuberous sclerosis complex.

Keywords: *tuberous sclerosis complex, status epilepticus, epilepsy*

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Introduction

Tuberous sclerosis also called tuberous sclerosis complex (TSC) is a rare, multi-system autosomal dominant disorder of cellular differentiation and proliferation characterized by hamartomas in most organ systems including the brain and other vital organs such as the kidneys, heart, eyes, lungs, and skin[1,2]. It usually affects the central nervous system and results in a combination of symptoms including seizures, developmental delay, behavioral problems, skin abnormalities, and renal disease. Patients with TSC are frequently diagnosed with co-morbid neurological disorders including epilepsy, intellectual disability, behavioral abnormalities, sleep disorders, and autism spectrum disorders (ASD)[2,3]. The name tuberous sclerosis comes from the characteristic tuber or nodules in the brain, which calcify with age and become hard or sclerotic. The disorder, once known as epiloia or Bourneville's disease was first identified by Désiré-Magloire Bourneville, a French neurologist over 100 years ago[1,3].

The disorder affects as many as 25,000 to 40,000 individuals in the United States and about 1 to 2 million individuals worldwide, with an estimated prevalence of one in 6,000 to 9,000[1,2,3]. TSC occurs in all ages, races and ethnic groups, and in both genders.

TSC is caused by defects or mutations, on two genes-TSC1 and TSC2. The transmission of

TSC is by autosomal dominant trait with variable penetrance. Although some individuals inherit the disorder from a parent with TSC, most cases occur sporadically. Many TSC patients show evidence of the disorder in the first year of life. However, clinical features can be subtle initially and many signs and symptoms take years to develop. As a result, TSC may be unrecognized or misdiagnosed for years.

Case Presentation

An eighteen year old Urhobo man from Oghara was rushed into our emergency department by the father with complaints of repeated seizures and loss of consciousness. He had a fever three days prior to presentation. No history of use of any medication or trauma to the head. He has been having recurrent seizures since the age of eight. Review of systems was negative except for poor educational performance and occasional aggressive behavior. He was in primary six at the time of presentation. No history of birth asphyxia, neonatal or childhood major illness. He was fully immunized for age. He is the third child among five in a monogamous home. Three of his siblings have epilepsy. At the emergency room he was found to be having repeated generalized tonic-clonic seizures with Glasgow Coma Score (GCS) of 10 in between attacks, warm to touch with temperature of 37.5°C. He had facial angiofibroma – adenoma sebaceum on the face (figure 1) {this lesion appeared first on his face at age of 5 and has remained till date} and shagreen patches on the lumbar region (figure 2). Fundoscopic examination was normal. No signs of meningeal irritation or focal neurological deficit. He had intravenous diazepam 10mg and 5mg at five minutes apart and phenytoin infusions to abort the seizures. The motor seizures were aborted within two hours; however, his GCS remained 13 for twenty-four hours before full recovery. His working diagnosis was then status epilepticus precipitated by malaria in a patient with tuberous sclerosis. Malaria parasite test was positive (1+) for Plasmodium falciparum and he was treated with arthemeter-lumefantrine combination. The electrolytes,

Figure 1. *Facial angiofibroma (Adenoma sebaceum) in the patient, with lacerations on the lip and tongue following a seizure*

Figure 2. *Shagreen patches on the lumbar region of the patient*

Figure 3*. Patient's father with facial angiofibroma*

Figure 4*: CT brain of the patient showing Calcified Sub-ependymal nodules*

urea,creatinine, liver function tests and complete blood count results were normal.

On the third day of admission he had another seizure which started with an abnormal behavioral changes characterized by a strange expression of aggression on his face followed by slapping of a nearby patient and a nurse , screaming and generalized tonic-clonic seizures lasting for four minutes associated with foaming saliva, upward rolling of the eyes, urinary incontinence and post-ictal sleep. The patient had positive history of occasional aggressive behavior without accompanying motor seizures.

His brain computerized tomographic scan revealed calcified subependymal nodules (figure 4) and calcified occipital cortical tuber (figure 5).Renal ultrasound scan revealed no abnormality.

His father (figure 3) and one of his siblings have facial angiofibroma. His late paternal grandfather was said to also have facial angiofibroma. His father and siblings were examined and had no retina lesion or any other skin lesions. He was discharged after five days on admission on phenytoin and seen in the out-patient clinic a week after discharge. Further imaging evaluation planned for the family members could not be carried out as we lost the patient and his relatives to follow up.

Figure 5*: CT brain showing calcified left occipital Cortical Tuber*

Discussion

The case presented is that of a familial tuberous sclerosis complex. In familial cases, TSC is an autosomal dominant disorder, and can be transmitted directly from one parent with the

faulty gene to a child. An offspring of a patient with TSC has a 50 percent chance of developing the disorder. The offspring of a TSC patient has variable clinical expression and severity ranging from not manifesting the same symptoms to having milder or more severe form of the disorder. The patient reported in this article presented with a severe form of the disorder among the family members with a combination of epilepsy, mental retardation, abnormal behaviors, facial angiofibroma (adenoma sebaceum), shagreen patches, ash leaf and calcified subependymal nodules and occipital cortical tuber. The father of the index patient has an apparent mild disease. At the age of 56 years he has never experience any other manifestation except the skin lesion (facial angiofibroma).One of his siblings was reported to have the facial angiofibroma and epilepsy, while two other siblings have epilepsy with good educational records without skin manifestations. The presentation of the disorder in this family support the clinical variability in manifestations of the TSC as reported in literatures[1,2,3].

The transmission of the disorder is by an autosomal dominant trait with variable penetrance. Two genes are responsible for TSC, TSC1 and TSC2. The TSC1 gene, discovered in 1997, is on chromosome 9 and produces a protein called *hamartin*. The TSC2 gene, discovered in 1993, is on chromosome 16 and produces the protein *tuberin*[4]. These proteins regulate the enzyme complex, a kinase, mTORC1, which constitute a key cellular pathway important for protein synthesis and cell size regulation. Hamartin and tuberin act in a complex mechanism as growth suppressors by inhibiting the activation of the kinase, mTORC1. Loss of regulation of mTOR occurs in cells lacking either hamartin or tuberin, and this leads to the activation of the kinase, mTORC , abnormal differentiation and development, and the generation of enlarged cells as seen in TSC lesions.[4,5]

Most cases occur sporadically due to new, spontaneous mutations in TSC1 or TSC2. The frequency of mutations reported in *TSC2* is consistently higher than in *TSC1* in familial tuberous sclerosis complex as *TSC1* mutations account for only 10 to 30% of the families identified with TSC[6]. In sporadic cases of TSC, there is an even greater excess of mutations in *TSC2*. However, identification of *TSC1* mutations appears to be twice as likely in familial cases as in sporadic cases.

Three types of brain lesions are seen in TSC: cortical tubers, subependymal nodules (SEN) and subependymal giant-call astrocytomas (SEGA). The cortical tubers, for which the disease is named, generally form on the surface of the brain, but may appear deep in the brain parenchyma. The neurologic manifestations of TSC include epilepsy[7,8] cognitive disability, and neurobehavioral abnormalities, such as autism.[9,10] Seizures occur in about 90% of the patients[1,2]. Seizures of all types may occur, including infantile spasms; tonic-clonic seizures; or tonic, akinetic, atypical absence, myoclonic, complex partial or generalized seizures. The manifestations are closely related to the number of cerebral cortical tubers that are present in over 80% of patients[11,12]. Patients with numerous lesions on neuroimaging tend to have difficult seizure control[13]. Brain magnetic resonance imaging (MRI) or computerized tomographic (CT) scan usually

demonstrates the cortical tubers, subependymal nodules and subependymal gaint cell astrocytomas[14]. The CT best demonstrates the calcified subependymal nodules that characterize TSC[2,14] as shown in the case presented. Subependymal giant cell astrocytoma occur in 10% of the patients. About 50% to 60% of individuals with TSC have developmental delays ranging from mild learning disabilities to severe mental retardation. Behavioral problems, such as aggression, sudden rage, attention deficit hyperactivity disorder and obsessive-compulsive disorder occur in children with TSC and can be difficult to manage. About one-third of children with TSC meet criteria for autism spectrum disorder[1,10].

A wide variety of cutaneous lesions may be seen in patients with TSC. The most common skin lesions include: hypomelanotic macules (ash leaf spots), found in about 80% to 90% of the patients, may be seen anywhere on the body at birth; facial angiofibromas (adenoma sebaceum), which are reddish spots or acneiform eruptions[15] on the malar region of the face that become apparent around the age of five years are made up of vascular and connective tissue elements; shagreen patch; ungual and subungual fibromas and other pigmentary lesions such as confetti lesions, poliosis and café au lait spots. Shagreen patches, usually found on the lower back or nape of the neck are irregularly shaped, slightly raised, leathery textured skin lesions and appear after the age of five. The patient, his father and one of his siblings have facial angiofibromas, but he alone has shagreen patches. His facial angiofibroma and shagreen patches were noticed as from age 5.

Renal angiomyolipomas, which are seen in about 55 to 80% of the patients are benign tumors composed of abnormal vessels, immature smooth-muscle cells, and fat cells, with multiple tumors in each kidney[16,17]. They are the most common kidney lesions in TSC. These growths are also found in about one of every 300 people without TSC[1]. Angiomyolipomas caused by TSC are usually found in both kidneys and in most cases they produce no symptoms. However, they can sometimes grow so large that they cause pain or kidney failure. In addition to angiomyolipomas, epithelial renal lesions that include epithelial cysts, polycystic kidney disease, and renal-cell carcinomas may develop in patients with TSC. Epithelial cysts are generally asymptomatic and are more often associated with hypertension and renal failure than are angiomyolipomas.[18,19] Other rare kidney problems include renal cell carcinoma, developing from an angiomyolipoma, and oncocytomas, benign tumors unique to individuals with TSC.

Lung lesions are present in about one-third of adult women with TSC and are much less commonly seen in men. Lymphangiomyomatosis, also called lymphangioleiomyomatosis, affects women almost exclusively and is characterized by widespread pulmonary proliferation of abnormal smooth-muscle cells and cystic changes within the lung parenchyma[20]. Lymphangiomyomatosis is usually diagnosed during early adulthood and is initially manifested by dyspnea or pneumothorax. Multinodular, multifocal pneumocyte hyperplasia (MPH) is another lung lesion with a more benign tumor that occurs in men and women equally.

Tumors called cardiac rhabdomyomas are

found in 50% to 70% of hearts of infants and young children with TSC, and they are often seen on prenatal fetal ultrasonography. Rhabdomyoma may be associated with cardiac failure, dysrhythmias, including atrial tachycardia, ventricular tachycardia, complete heart block, and the Wolff–Parkinson–White syndrome[21]. Unlike other lesions seen in TSC, cardiac rhabdomyomas if they do not cause problems at birth-when in most cases they are at their largest size, they often regress spontaneously in later life[22].

Benign tumors called phakomas are sometimes found in the eyes of individuals with TSC, appearing as white patches on the retina. Pancreatic cysts, bone cysts, rectal polyps, gum fibromas, and dental pits may also be seen in individuals with TSC.

The diagnosis of TSC is based upon clinical criteria. The diagnostic criteria for TSC consist of a set of major and minor diagnostic features[23]. Currently the results of molecular genetic testing of the *TSC1* or *TSC2* loci are viewed as corroborative. No single feature is diagnostic thus, a detailed evaluation of all the clinical features is necessary to make the diagnosis. The clinical manifestations of TSC appear at distinct developmental points[23]. For initial diagnostic evaluation, careful dermatologic examination of the skin, funduscopic examination to identify retinal hamartomas, MRI or CT of the brain to identify tubers and subependymal giant-cell tumors and ultrasonography with or without CT, or MRI of the kidneys to identify angiomyolipomas are necessary. In women with TSC, CT of the lungs is indicated to look for subclinical lymphangiomyomatosis. In infants, echocardiography may reveal rhabdomyomas.

Based on the diagnostic criteria the clinical diagnosis could be classified as definite, probable or possible. Two major features or one major feature plus two minor features are required for a definite clinical diagnosis of TSC; one major and one minor feature are required for a probable diagnosis of TSC; one major or two or more minor features are needed for a possible diagnosis of TSC[23]. The major features are facial angiofibroma, ungual fibroma, shagreen patch, hypomelanotic macule, cortical tuber, subependymal nodule, subependymal giant-cell tumor, retinal harmatoma, cardiac rhabdomyoma, renal angiomyolipoma and lymphagiomyomatosis. The minor features are multiple pits in dental enamel, hamartomatous rectal polyps, bone cysts, cerebral white-matter radial migration lines, gingival fibromas, retinal achromic patch, multiple renal cysts and 'confetti' skin lesions[23].

The patient reported in this article has definite tuberous sclerosis complex with three major features namely facial angiofibroma (figure 1), shagreen patches (figure 2), subependymal calcified nodules (figure 4) and a calcified cortical tuber (figure 5). The presence of possible TSC in the father (figure 3), one of his siblings and in his grandfather (with the history of facial angiofibroma) strongly support the diagnosis of the rare presentation of familial tuberous sclerosis complex in this three generations.

There is no cure for TSC, although treatment is available for a number of the symptoms. Antiepileptic drugs may be used to control seizures. Vigabatrin, an inhibitor of Γ-aminobutyric

acid transaminase, is particularly useful for treatment of infantile spasms in TSC. Specific medications may be prescribed for behavioral problems. Interventional programs including special schooling and occupational therapy may benefit individuals with special needs and developmental issues. Surgery may be needed in case of complications connected to cortical tubers, SEN or SEGA, as well as in risk of hemorrhage from kidney tumors. Respiratory insufficiency due to LAM can be treated with supplemental oxygen therapy or lung transplantation if severe.

Everolimus, an mTOR inhibitor, was approved by the United States food and drug administration agency in 2010 to treat sub-ependymal giant cell astrocytomas in individuals with TSC who require treatment but are not candidates for surgery[1]. Rapamycin has been shown to be effective in treating SEGA, and it is still undergoing clinical trials.[24]

Another important issue in the management of TSC is long-term follow-up, including the monitoring of lesion growth. No conclusive guidelines for surveillance have been established for this disease, but most centers periodically image the brain and abdomen to monitor the growth of lesions in the brain and kidney.[25] It is a standard practice to perform brain and abdominal imaging at least every 3 years, and more often in patients with brain or renal lesions that have progressive growth. Annual MRI of the brain is suggested in patients until they are at least 21 years of age, and then MRI should be done every 2 to 3 years both to diagnose and to monitor subependymal giant-cell tumors. In patients with multiple angiomyolipomas or a single lesion that is progressive, yearly ultrasonography, MRI, or CT is indicated. In patients with lymphangiomyomatosis, annual pulmonary-function testing may be useful to monitor lung function, and some patients may require more frequent assessments. Although electroencephalography is not part of the diagnostic workup for TSC, it remains an important tool in patients with TSC and epilepsy to define background cerebral activity, characterize patterns such as hypsarrhythmia in infantile spasms, and identify seizure foci. Periodic dermatologic evaluation is useful, since facial angiofibromas can cause cosmetic challenges that may require laser therapy or surgical removal. In general, lifetime surveillance for lesion growth in patients with TSC permits early recognition of potentially life threatening complications.

Genetic counseling should be offered to patients to aid with family planning bearing in mind that as an autosomal dominant disorder, affected persons carries approximately 50% risk of having an affected child.

Conclusion

TSC is a rare multisytemic disorder that occurs worldwide. This report has documented the occurrence of this rare disorder among Nigerians. There is need for physicians to carefully evaluate patients with suspected TSC including screening of the family members for the occurrence of familial TSC.

References

1. "Tuberous Sclerosis Fact Sheet," NINDS. NIH Publication No. 07-1846 .http://www.ninds.nih.gov .
2. Walter GB,Robert BD,Gerald MF , Joseph J. Neurocutaneous syndromes. In: Pocket

Companion to Neurology in Clinical Practice. Walter GB,Robert BD,Gerald MF & Joseph J (eds). 4th edition .Elsevier Inc Philadelphia 2004. 455-458

3. Crino PB, Nathanson KL , Henske EP. The Tuberous sclerosis complex : N Engl J Med 2006;355:1345-56.
4. European Chromosome 16 Tuberous Sclerosis Consortium. Identification and characterization of the tuberous sclerosis gene on chromosome 16. Cell 1993;75:1305-15.
5. Huang J, Manning BD. The TSC1–TSC2 complex: a molecular switchboard controlling cell growth. Biochem J 2008; 412:179–190.
6. Jones AC, Shyamsundar MM, Thomas MW, et al. Comprehensive mutation analysis of TSC1 and TSC2 and phenotypic correlations in 150 families with tuberous sclerosis. Am J Hum Genet 1999;64:1305-15.
7. Curatolo P, Seri S, Verdecchia M, Bombardieri R. Infantile spasms in tuberous sclerosis complex. Brain Dev 2001;23: 502-7.
8. Prather P, de Vries PJ. Behavioral and cognitive aspects of tuberous sclerosis complex. J Child Neurol 2004;19:666-74.
9. Joinson C, O'Callaghan FJ, Osborne JP, Martyn C, Harris T, Bolton PF. Learning disability and epilepsy in an epidemiological sample of individuals with tuberous sclerosis complex. Psychol Med 2003;33:335-44.
10. Jansen FE, Vincken KL, Algra A, et al. Cognitive impairment in tuberous sclerosis complex is a multifactorial condition. Neurology 2008; 70:916–923.
11. Goodman M, Lamm SH, Engel A, et al. Cortical tuber count: a biomarker indicating neurologic severity of tuberous sclerosis complex. J Child Neurol 1997; 12:85–90.
12. Jambaque I, Cusmai R, Curatolo P, et al. Neuropsychological aspects of tuberous sclerosis in relation to epilepsy and MRI findings. Dev Med Child Neurol 1991; 33:698–705.
13. Thiele EA. Managing epilepsy in tuberous sclerosis complex. J Child Neurol 2004;19:680-6.
14. Luat AF, Makki M, Chugani HT. Neuroimaging in tuberous sclerosis complex. Curr Opin Neurol 2007; 20:142–150.
15. Olumide Y.M . Acne Vulgaris (Pimples). In: A Pictorial Self-instructional Manual on Common Skin Diseases (where there is no Dermatologist). Olumide Y.M. 1st edition Heinemann Educational Books (Nigeria) Plc Ibadan. 1993. 78-84.
16. Ewalt DH, Sheffield E, Sparagana SP, Delgado MR, Roach ES. Renal lesion growth in children with tuberous sclerosis complex. J Urol 1998;160:141-5.
17. Ewalt DH, Diamond N, Rees C, et al. Long-term outcome of transcatheter embolization of renal angiomyolipomas due to tuberous sclerosis complex. J Urol 2005; 174:1764-6.
18. Kothary N, Soulen MC, Clark TW, et al. Renal angiomyolipoma: long-term results after arterial embolization. J Vasc Interv Radiol 2005;16:45-50.
19. O'Callaghan FJ, Noakes MJ, Martyn CN, Osborne JP. An epidemiological study of renal pathology in tuberous sclerosis

complex. BJU Int 2004;94:853-7.

20. Ryu JH, Moss J, Beck GJ, et al. The NHLBI lymphangioleiomyomatosis registry: characteristics of 230 patients at enrollment.Am J Respir Crit Care Med 2006;173:105-11.
21. Bader RS, Chitayat D, Kelly E, et al. Fetal rhabdomyoma: prenatal diagnosis, clinical outcome, and incidence of associated tuberous sclerosis complex. J Pediatr 2003;143:620-4.
22. Smythe JF, Dyck JD Smallhorn JF, Freedom RM. Natural history of cardiac rhabdomyoma in infancy and childhood. Am J Cardiol 1990;66:1247-9.
23. Roach ES, Gomez MR, Northrup H. Tuberous sclerosis complex consensus conference: revised clinical diagnostic criteria. J Child Neurol 1998;13:624-8.
24. Franz DN, Leonard J, Tudor C, et al. Rapamycin causes regression of astrocytomas in tuberous sclerosis complex. Ann Neurol 2006;59:490-8.
25. Hyman MH, Whittemore VH. National Institutes of Health consensus conference: tuberous sclerosis complex. Arch Neurol 2000;57:662-5.