ABSTRACT

Tuberous Sclerosis Complex (TSC) is a rare autosomal dominant neurocutaneous syndrome. Patients with TSC may develop refractory epilepsy, and about one-fourth patients experienced seizure relapse after anticonvulsant discontinuation.

A 9 year old boy presented with focal seizure, which relapse after 6 years anticonvulsant discontinuation. He was diagnosed with refractory epilepsy. There are appearances of facial adenoma sebaceum, shagreen patch in neck, ash leaves macules in trunk. The laboratory, funduscopy, and echocardiography examination were normal. There are focal epileptiform waves from electroencephalography, subependymal nodul in paraventricular region of lateral lobe from head CT and multiple renal cysts from kidney USG. Tuberous sclerosis complex was diagnosed according to diagnostic criteria of the International Tuberous Sclerosis Complex Consensus Conference which fulfilled four major criteria and one minor criteria.

Tuberous sclerosis case has been reported on a 9 years old boy with history of refractory epilepsy, he experience recurrent seizure and have risk to develop another refractory epilepsy episode.

Keywords: tuberous sclerosis complex, children, refractory epilepsy, shagreen patch

INTRODUCTION

Tuberous sclerosis complex (TSC) is an unusual autosomal dominant neurocutaneous syndrome characterized by the development of benign tumors affecting different body systems. While TSC was recognized to be a genetic disease, the underlying molecular etiology was not clear until the discovery of the two causative genes, TSC1 and TSC2.

Tuberosclerosis was first described in 1862 by von Recklinghausen, and later was more completely elucidated by Bourneville, Pringle, and Vogt. In 1880, Bourneville described the pathologic features of the sclerotic tubers found post mortem in patients with epilepsy and mental retardation and coined the term "sclerose tubereuse".

The incidence of TSC is estimated to be between 1/6000 and 1/10,000 live births and the population prevalence is estimated to be 1/20,000. Worldwide, TSC is thought to affect 1 to 2 million individuals. The TSC has an autosomal dominant mode of inheritance with almost complete penetrance but variable expressivity. Approximately 65% of cases are caused by a spontaneous mutation.

The TSC is caused by mutations of two genes, TSC1 and TSC2, which encode for the proteins hamartin and tuberin...
respectively. These proteins act as tumour growth suppressors, agents that regulate cell proliferation and differentiation.

The clinical presentation of TSC is highly variable between individuals and typically varies throughout the lifetime of a single patient, both factors making for a highly heterogeneous presentation of the disease. The central nervous system (CNS), dermatological, renal, respiratory and circulatory organ systems are most commonly affected, although few of these manifestations are specific to TSC.

Seizures are extremely common in TSC, affecting up to 90% of patients. In 63% of TSC patients with epilepsy, the seizures appear in the first year of life; 80% of seizures begin before 3 years of age and 70% eventually become refractory to drugs. The seizures may be focal, multifocal, infantile spasms, or a combination of these or other seizure types.

CASE REPORT

A 9-year-old boy presented with history of focal tonic convulsions, head turned and eyes glanced to the right side. He looked daydream before seizure. He alerted after 5 minutes seizure without any medication. There was no prior history of fever, infection or any trauma. The patient was diagnosed with refractory epilepsy since 1-year-old and under anticonvulsants until 3 and a half years. The seizures re-occurred after 6 years without any medications. The patient also had multiple brown lesions over his face. There was no history of bleeding, itching, pain or change in the size of the lesions. None of his family members suffer from any similar condition.

On physical examination, the vital signs were stable, well-nourished according to CDC 2000 growth chart. Examination of eyes, ears, nose, throat and neck were unremarkable. There were facial adenoma sebaceum present over his center face (figure 1). The chest and abdomen examination were unremarkable. The extremities felt warm, with capillary refill time less than 2 seconds. On the skin, there were shagreen patch (resembling shark skin) on the left neck (figure 2a), and hypomelanotic macules or “ash leaves spots” in face and trunk (figure 2b). From neurological examination the power, tonus, and reflex of the extremities were unremarkable. The physiologic reflexes were positive, and no pathologic reflexes found.

The laboratory investigation showed complete blood count, liver function test, electrolytes, and kidney function tests were within normal limit. Head computed tomography (CT) scan revealed multiple calcifications on subependymal nodules in paraventricular region of lateral lobe (figure 4). Ultrasonography of the kidneys showed various sizes of calcifications and multiple renal simple cysts on both kidneys. The electroencephalography
was abnormal, it showed focal epileptic-form wave. Fundoscopic examination and echocardiography were unremarkable.

Based on clinical manifestation, past history, physical examination, and investigations, the patient assessed with tuberous sclerosis, treated with Oxcarbamazepine 5 mg/body weight/dose twice a day (per oral), and advised for routine follow up.

DISCUSSION

Tuberous sclerosis is a rare genetic disease associated with the development of non-malignant tumors throughout the body. Mutations in the TSC1 and TSC2 genes, which encode the proteins hamartin and tuberin.4,5,6 Manifestations of TSC can appear 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 ectodermal cells producing tumors extending to areas of the head, heart, brain, eyes, skin, and kidneys. The prognosis for patients with TSC depends on the severity of their symptoms. Individuals with mild forms of TSC generally do well and have a normal life expectancy.8

Comprehensive and reliable screens for TSC1 and TSC2 mutations are well-established, and many pathogenic mutations have been identified. The recommendation of the Genetics Panel was to make identification of a pathogenic mutation in TSC1 or TSC2 an independent diagnostic criterion, sufficient for the diagnosis or prediction of TSC regardless of the clinical findings. This will facilitate the diagnosis of TSC, particularly in young individuals, allowing earlier implementation of surveillance and treatment with potential for better clinical outcomes.7 The TSC1 and TSC2 genetic variants whose functional effect is less certain are not definitely pathogenic and would not be considered a major diagnostic criterion. Some patients (10-25%) with TSC have no mutation identified by conventional genetic testing. Therefore, a normal conventional genetic testing result does not exclude TSC. But if the mutation in an affected relative is known, genetic testing has very high predictive value for family members. Consensus Conference agreed with the recommendation that identification of a pathogenic mutation in TSC1 or TSC2 is an independent diagnostic criterion for TSC.2

The most common dermatologic manifestations of TSC are hypomelanotic macules, found in more than 90% of patients. The macules are usually present at birth and almost all lesions are evident within the first 2 years of life. Hypomelanotic macules usually become more apparent with age.8 Facial angiofibroma also occurs in about 75% of TSC patients with onset typically between ages 2 and 5 years. The lesions typically appear during preschool years in the malar area as small pink to red dome-shaped papules in a “butterfly distribution.” The lesions gradually enlarge and become more numerous with age. In our case, patient had multiple hyperpigmented papules over the nasolabial region (adenoma sebaceum). He also had multiple hypopigmented macules (ash leaf) over the face and trunk, along with a Shagreen patch on the left neck.

The major neurological manifestations of TSC 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,8 and in more than 80% of cases epilepsy begins in the first 3 years of life.8 Seizures are mostly refractory to pharmacological treatment and require polytherapy; this is believed to be a result of increased expression of multidrug resistance gene-1 P-glycoprotein (MDR1) and multidrug resistance-associated protein 1 (MRP1) in cortical tubers.10 The International League Against Epilepsy (ILAE) who suggests drug-resistant epilepsy term be used instead of the term ‘refractory epilepsy’ has proposed the definition as a failure of adequate trials of two tolerated, appropriately chosen and used antiepileptic drug schedules (whether as monotherapies or in combination) to achieve

Figure 4  Axial section of head computed tomography scan showed subependymal nodules in paraventricular region of lateral lobe.
sustained seizure freedom. Refractory epilepsy and status epilepticus are known to be associated with increased mortality and morbidity such as learning difficulties, behavioral problems and sleep alteration. Intratable or refractory epilepsy develops in two-thirds of individuals with TSC, which is twice as often as in the general epilepsy population. In our case, patient had seizures that were confirmed with appearance focal epileptic-form wave from electroencephalography, which need adjustment of antiepileptic drug. He was diagnosed with refractory epilepsy and under anticonvulsants until 3 and a half years. The seizures re-occurred after 6 years without any medications.

A magnetic resonance image (MRI) or a computed tomogram (CT) should be performed to look for confirmatory evidence of TSC such as tubers, subependymal nodules, and subependymal giant cell astrocytomas. Subependymal nodules are hamartomatous lesions that appear on the ependymal surface of the lateral ventricles. Subependymal nodules which often detectable prenatally, arise along the wall of the lateral and third ventricle, occur in about 80% of individuals with TSC. Subependymal nodules can be asymptomatic, but can grow, degenerate, or calcify. In our case, from head CT revealed multiple calcifications on subependymal nodules in paraventricular region of the lateral lobe.

Ophthalmic features associated with TSC can be divided into retinal and non-retinal. Retinal hamartoma is one of the major diagnostic criteria for TSC. There are three basic morphological types: A flat smooth, noncalcified, translucent lesion; an elevated, multinodular, calcified, opaque, lesion resembling mulberries; and a lesion with the features of both. In our case, the patient's fundoscopic was unremarkable.

At least 50% of children with TSC have rhabdomyomas, which usually asymptomatic. However, these lesions can cause outflow obstruction, valvular dysfunction, arrhythmias, especially Wolff-Parkinson-White syndrome, and cerebral thromboembolism. Cardiac rhabdomyomas can be detected prenatally or postnatally. In prenatal life, ultrasound detection of multiple cardiac tumors is often the first sign of TSC. Echocardiography is the imaging modality of choice for assessing cardiac involvement in TSC. Typically, cardiac rhabdomyomas are visible as multiple, echogenic, nodular masses embedded in the ventricular myocardium, sometimes protruding into the involved chamber. They are homogeneous and hypechoic compared with normal myocardium. In our case, the patient never felt palpitate, and from the echocardiography showed no masses on the myocardium.

Renal complications are the common cause of mortality. There are three different types of lesions can be found: angiomyolipoma (AML), cysts and clear cell carcinoma. A combination of renal cysts and angiomyolipomas is characteristic of TSC. Angiomyolipomas are benign tumors composed of blood vessels with thickened walls, immature smooth muscle cells, and adipose tissue. The lesions are often multiple and bilateral and increase in size and number with age, giving an enlarged appearance to the kidneys. Multiple cysts occur in 18-53% of patients with TSC and usually occur in younger children. They are usually asymptomatic unless they occur as a contiguous mutation in TSC2 and PKD1 on chromosome 16 in which case the cysts have an early onset of development and cause hypertension or renal failure in early adulthood. An abdominal MRI is recommended every 1-3 years, and renal function and blood pressure should be monitored annually. In this case, the patient has no history of hematuria or flank pain. Renal function test and urine analysis were unremarkable. The kidney USG showed multiple renal cysts and calcification spot on both kidneys.

The diagnosis of TSC is basically clinical following the classification of the findings. In 2012, the International Tuberous Sclerosis Complex Consensus Conference published new diagnostic criteria for diagnosis of tuberous sclerosis. The clinical diagnostic criteria divide into two features, major and minor. Major features are hypomelanotic macules (≥3, at least 5mm diameter); angiofibromas (≥3) or fibrous cephalic plaque; ungual fibromas (≥2); shagreen patch; multiple retinal hamartomas; cortical dysplasias; subependymal nodules; subependymal giant cell astrocytoma; cardiac rhabdomyoma; lymphangioleiomyomatosis (LAM); and angiomyolipomas (≥2). Minor features are “Confetti” skin lesions; dental enamel pits (>3); intraoral fibromas (≥2); retinal achromic patch; multiple renal cysts; and non-renal hamartomas. Definite diagnosis of TSC can be made when two major features or one major feature with 2 or more minor features are demonstrated. Additional diagnostic category is possible TSC, when either one major feature or 2 or more minor features are present.

In this case, the patient fulfilled four major criteria (subependymal nodules in head CT, facial angiofibroma, hypomelanotic macules (>3), Shagreen patch) and one minor criteria (multiple renal cysts) of diagnostic criteria. Therefore, the patient diagnosed with TSC.
CONCLUSION

We present a 9-year-old boy with focal seizure, facial adenoma sebaceum, shagreen patch on the left neck, and ash leaves macules in trunk and abdomen. He has history of refractory epilepsy, which re-occurred after 6 years without any medications. There was focal epileptic-form wave from electroencephalographic examination. No abnormality from laboratory investigation, funduscopie of the eyes and echocardiography. Tuberous sclerosis complex was diagnosed according to diagnostic criteria of the International Tuberous Sclerosis Complex Consensus Conference which fulfilled four major criteria and one minor criteria. He was on therapy with oxcarbamazepine to control the seizure.

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