

## Tuberous sclerosis complex in a child: diagnosis and management

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**T**uberous sclerosis complex (TSC) is a multisystem, autosomal dominant disorder affecting children and adults, resulted from mutations in one of two genes, *TSC1* (encoding hamartin) or *TSC2* (encoding tuberin) genes located on chromosomes 9 and 16 respectively.<sup>1,2</sup> Synonyms of TSC are Bourneville Pringle syndrome, epiloia, or tuberous sclerosis. This disorder is characterized by seizures, mental disability, and small noncancerous tumors on the skin and other body tissues, such as brain, eye, lung, and kidney. The classic triad are seizures, mental retardation, and cutaneous angiofibromas.<sup>3</sup>

The incidence of TSC has been reported to be between 1 in 5800 and 1 in 10,000; however, the exact incidence is not known because of a number of undiagnosed cases consisting mostly of mildly affected or asymptomatic individual.<sup>3</sup> In China, the incidence of TSC is 1 in 170,000 population.<sup>4</sup> It occurs with equal frequency in males and females in different races and ethnicities. This disorder is transmitted as an autosomal dominant, but only about one-third of cases is familial. The nonfamilial cases can represent either spontaneous mutations or mosaicism, in which only some cells in the affected parent express the mutant gene.<sup>5</sup>

The diagnostic criteria for TSC, as developed by a consensus conference in 1998, are based upon specific clinical features.<sup>5</sup> Definite diagnosis of TSC is

established when at least two major or one major plus two minor features are present.<sup>6</sup> Early recognition of TSC is vital, because prompt implementation of the recommended diagnostic criteria may prevent serious clinical consequences. Neurologic manifestations of TSC represent the leading cause of associated morbidity and mortality.<sup>3</sup> We report a case of TSC in a child focusing on diagnostic approach and management.

### The Case

A 7-year-old girl was admitted to the Dermato-venereology Department Soetomo Hospital on April 17<sup>th</sup> 2008 for asymptomatic reddish papules on her face. They were symmetrically and bilaterally distributed over centrofacial areas, especially on the nasolabial folds, appeared over the previous 3 years. The initial papules arose on cheek and then they became numerous and scattered on nose and chin.

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There were also whitish patches on her trunk, chest, abdominal, and lower extremities since her birth and some new whitish patches appeared few years after birth. But there were no new patches appeared after 5 years of age.

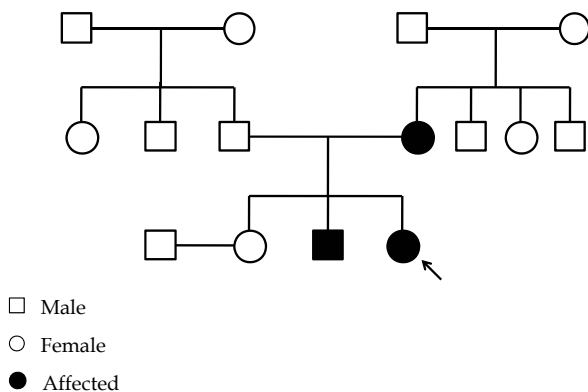
She had history of recurrent seizures since 4 years old and recently became more frequent and severe. When the seizure occurred, all of her body went rigid. She looked like sleep after the seizure. She was diagnosed as a case of epilepsy by Neuropediatric Division with abnormal ECG since 3 years before admission. The patient was already on multiple anticonvulsant therapy but she did not routinely take the medicine. There was no history of trauma, fever, ear discharge, or loose of motion. She did not have any symptoms pertaining to heart, kidney, eyes and lungs. There was no family history of seizures.

She was spontaneously delivered with birth weight of 3100 g. Antenatal and perinatal history was uneventful. She was breastfed until the age of 24 months and her immunization schedules was up to date. She was able to sit without support at the age of 7 months, pulled to standing position at 10 months, and walked at 11 months. There was delay in mental development; the child only spoke simple sentences (she had difficulty to speak more than two words simultaneously) and could not read or count, but she could obey simple commands. On formal testing, the IQ score was 94 (under average score).

She is the youngest among 3 siblings from non-consanguineous marriage. Her mother and older

brother also had the similar facial redness papules. Her mother has more sparse brown-reddish pimples on cheek and nose. There were also pits on the mother's teeth, and the ultrasonography (USG) examination showed bilateral renal cysts, but without any white patch or history of seizures. Her brother also had whitish patch on his back and brownish plaque on his right forehead (Figure 1), but he had no history of seizure. He was 14 years old and there was no problem in his education.

On admission she looked alert and hyperactive. The body weight was 17.5 kg and body height was 111.5 cm, categorized as mild malnutrition. Her blood pressure was 90/60 mmHg, pulse rate was 92 per minute, respiration 24 per minute, temperature was 36.7°C. Dental enamel pits were noted. There was no motoric weakness or sensoric deficit. Bilateral physiological reflexes were equivocal and pathologic reflexes were negative. On nasal, right and left maxillae and mental regions there were discrete, multiple, round, brown-reddish papules 1-2 mm in size, with smooth surfaces and firm consistency (angiofibromas), concentrated near the nasolabial folds, with relative sparing of the upper lip and lateral face. On anterior and posterior thorax region, abdomen and both inferior extremities there were round and oval shaped hypopigmented macules, 2-3 cm sized, known as ash-leaf hypomelanotic macules. No Shagreen patch and no confetti macules were found. Other physical findings were not remarkable.



**Figure 1.** Pedigree of patient family in three generation



**Figure 2.** Renal Abdomen USG showed bilateral renal cysts

Laboratory results disclosed hemoglobin 10.4 g/dl, hematocrit 32.1%, platelet count 781.000/ $\mu$ L and leukocyte count 18.600 / $\mu$ L. Serum creatinine level was 0.4 mg/dl, blood urea nitrogen 8.4 mg/dl, aspartate aminotransferase level 57 IU/L and alanine aminotrasferase level was 29 IU/L. Potassium level was 4.2 mEq/L, sodium level 136 mEq/L and chloride was 103 mEq/L. Urinalysis examination revealed: leukocyte 0-1/hpf, erythrocyte 0-1/hpf, epithelia (-), crystals (-), bacteria (-), and protein (-).

Based on the history, clinical manifestation, and laboratory findings the patient was diagnosed as suspected tuberous sclerosis complex. The patient was planned to undergo histopathologic examination of skin lesions, EEG, ECG, echocardiography, chest X-ray, USG, brain computed tomography (CT) scan and brain magnetic resonance imaging (MRI). The initial treatment was trichloroacetic acid (TCA) 35% solution. However the patient's parents refused the TCA therapy because they were afraid that she would scratch the treated area, so they decided to wait until she understood and grown up.

On the second day of hospitalization the child was consulted to a neuropsychiatrist who assessed the patient as epilepsy, and suspicions of mental retardation and advised to give oral phenytoin 80 mg 3 times daily, oral piracetam 100 mg 3 times daily, and sodium valproate 250 mg 3 times daily. Five days later the patient had recurrent seizures about 11 times per day and she was transferred to Department of Child Health for further treatment. The dose of sodium valproate was increased to 400 mg 3 times daily.

The child underwent a thorough investigation to establish the diagnosis of tuberous sclerosis. Histological examination of the papules on right maxilla region revealed epidermal atrophy and hypopigmented, fibrosis in dermis with perivascular lymphocyte infiltration. Skin biopsy from right femoralis region revealed epidermal atrophy, hypopigmentation and dermal fibrosis with many hair follicles. The conclusion of the histopathology finding was fibroma, which might occur in early stage of tuberous sclerosis. The result of chest X-ray, CT scan, and MRI were within normal limits. Abdominal USG examination showed bilateral renal cysts (Figure 2). There were no specific treatment. However, further monitoring was planned to observe the possibility of potential problems related to these cysts.

The result of EEG was abnormal, indicated general epileptogenic potency with diffuse mild degree encephalopathy. The patient was also consulted to Psychiatric Department, Dental Department and Ophthalmologic Department. Psychiatric Department assessed her as organic mental disorder due to epilepsy and they could not evaluate mental retardation because the patient was not cooperative during the examination. Dental Department only assessed her dental pits; they could not evaluate other dental abnormalities because the patient was not cooperative. They suggested an examination and workup under general anesthesia. The result of consultation to Ophthalmologic Department concluded that there were no abnormalities on right and left ocular fundi, and there was no "mulberry" lesion on retina as a specific sign of TSC.

Based on clinical findings, abdominal USG and EEG, the child was diagnosed as a case of TSC. She was prescribed sodium valproate 400 mg 3 times daily and oral phenytoin 80 mg 3 times daily. The seizures were diminished. After two weeks without any seizures, the child was discharged and advised for follow-up visit.

## Discussion

In most patients with TSC, the first management issue is making the appropriate diagnosis by identifying major and minor diagnostic features. The second important issue in the management of TSC is long-term follow-up, including monitoring of lesion growth. Treatment for TSC is mostly supportive and symptomatic because no specific therapy has been found yet. Finally, genetic counseling should be offered to aid family planning.<sup>1</sup>

TSC persists throughout life. The patients need to be checked up regularly in order to prevent episode of seizures and its effects. The prognosis depends on illness severity, from mild to severe organ/tissue lesion, from epilepsy to severe mental retardation, uncontrolled seizures and vital organs failure.<sup>3</sup> Poor prognostic signs include multiple seizure types, seizure onset before one year of age, and multifocal electroencephalography (EEG).<sup>7</sup>

Tuberous sclerosis complex is an autosomal dominant neurocutaneous syndrome characterized by

a wide variation of phenotype and the development of multiple hamartomas distributed at various sites throughout the body, especially the brain, skin, retina, kidney, heart, and lung.<sup>3</sup> The clinical presentation of TSC depends on the age of the patient, the organ involved, and the severity of the involvement.<sup>7</sup> The skin is affected in virtually 100% of individuals with TSC. Skin lesions include hypomelanotic macules (87-100%), facial angiofibroma (47-90%), Shagreen patches (20-80%), fibrous facial plaques and ungula fibromata (17-87%). Facial angiofibromas cause the most disfigurement. None of the skin lesions results in serious medical problems.<sup>8</sup>

The patient was admitted to the hospital with the main complaint of asymptomatic reddish papules on face. The skin lesions in this patient consisted of angiofibromas, ashleaf hypomelanotic macules without any Shagreen patches on lumbosacral area. Meanwhile, the patient's older brother and her mother had the same skin lesions plus forehead plaque on his head. The result of histopathology examination was fibroma that could be found in early stage of TSC. These skin lesions confirmed the diagnosis of TSC.

Neurologic manifestations of TSC include epilepsy, cognitive disability, and neurobehavioral abnormalities. Epilepsy is maybe the most challenging clinical manifestation of TSC. Epilepsy occurs in more than 70 to 80% of patients with TSC and virtually all subtypes of seizure (simple partial, partial complex and generalized tonic clonic seizures) have been reported. They can occur at any age after birth, but most begin in the first year of life. TSC seizures are often refractory to treatment, even with combined antiepileptic therapy.<sup>1,7</sup> In this case, according to her mother, the child had been suffering from seizures since the age of 3 years. The history of infantile spasms was denied. The seizures were more frequent after she was 5 years old although she received medication. The types of seizures were generalized including tonic, clonic, and recently akinetic episodes. She was diagnosed as a case of epilepsy by Neuropediatric Division since 3 years before admission with the abnormalities of EEG (indicated general epileptogenic potency with diffuse mild degree of encephalopathy).

Jozwiak S et al stated that poorly controlled seizures as well as certain types of seizures.<sup>9</sup> At least 50% of individuals with TSC have developmental delay or mental retardation. The leading cause of

premature death (32.5%) among individual with TSC is complication of severe mental retardation, e.g., status epilepticus and bronchopneumonia. Individuals with TSC also have a great risk of neurodevelopmental and behavioral impairment. The common behavioral and psychiatric disorders in TSC include pervasive developmental disorder and autism.<sup>8</sup>

Central nervous system tumor is the leading cause of morbidity and mortality in TSC. The brain lesions of TSC, include subependymal glial nodules (90%), cortical or subcortical tubers (70%), and subependymal giant cell astrocytoma (6-14%).<sup>8</sup> Cortical tubers represent the hallmark of TSC and are pathognomonic of cerebral TSC. Tubers consist of abnormal cells with both neural and glial marker protein, suggesting that they arise early in development. The number and localization of cortical tubers may account for the variability of the neurological phenotype observed in patients with TSC.<sup>7</sup>

Neuroimaging is one of the most important tools in the diagnosis of TSC. MRI appears to be more sensitive than CT scan in detecting parenchymal tubers, which are more likely to cause seizures. The size and configuration of the signal abnormalities on cranial MRI have been found to correlate exactly with the pathological findings seen macroscopically and microscopically. Recommended factor for performance of MRI in TSC is 1.5 Tesla in field strength.<sup>10</sup> In one study, the existence of probable microstructural changes in white matter and deep gray matter, that were evaluated as normal TS with conventional MRI, were investigated with diffusion weighted MRI.<sup>11</sup> CT scan and MRI were performed to identify the lesions in this patient. Even though there was a point-shaped of radio-contrast near the left ventricle, the radiologist concluded that there was no abnormality and advised to undergo MRI. The result of MRI stated that there was no characteristic sign of TSC, which maybe due to Soetomo Hospital' MRI field strength (0.5 Tesla) wasn't strong enough to identify TSC brain lesions.

Renal disease is the second leading cause of early death (27.5%) in individual with TSC.<sup>12-13</sup> Cysts that are more than 4 cm in diameter are more likely to cause symptoms such as flank pain, a palpable tender mass, and gross hematuria that require treatment.<sup>14-16</sup>

Cardiac rhabdomyosarcomas (CRs) are present in 47-67% of individual with TSC.<sup>8</sup> Most TSC patients with CRs do not exhibit any clinical manifestation. Cardiac symptoms depend on tumor size and location within the heart. Congestive heart failure develops in 2% to 4% of children with CRs. Echocardiography is perhaps the most useful single diagnostic test for TSC in this group.<sup>18</sup> Cardiac symptoms in this patient were not found, ECG was in normal limits, and echocardiography was normal without any intracardiac masses.

Pulmonary involvement in TSC has been reported to occur in less than 1% of patients. The histological appearance of pulmonary involvement is identical to pulmonary lymphangiomyomatosis (LAM).<sup>19</sup> Retinal lesions of TSC are hamartomas (elevated mulberry lesions or plaque-like lesions) and achromic patches (similar to the hypopigmented skin lesions). One or more of these lesions may be present in up to 75% of cases. These lesions are usually asymptomatic. The eye examination of this child showed no abnormalities on right and left ocular fundi and no "mulberry" lesions were found.<sup>8</sup>

The diagnosis of the TSC continues to be based primarily on clinical grounds. In 1998, a consensus conference held in Annapolis, Maryland, assembled by the Tuberous Sclerosis Alliance for the purpose of re-evaluating and updating the clinical diagnostic criteria. The revised criteria were simplified into two main categories, major and minor, based on the diagnostic importance and degree of specificity for TSC of each clinical and radiographic feature.<sup>3</sup> Definite diagnosis of TSC is established when at least two major or one minor plus two minor features are present.<sup>6</sup>

Management of TSC consists of seizure control, baseline and monitoring studies (includes abdominal USG, echocardiography, chest X-ray, brain CT scan and MRI) to make appropriate diagnosis and long-term follow-up by identifying major and minor diagnostic features. No conclusive guidelines for surveillance have been established for this disease, but most centers periodically perform brain and abdomen radioimaging to monitor the growth of lesions in the brain and kidney.<sup>1,6</sup>

Refractory seizures and developmental delay in children are associated with TSC. These seizure are often resistant to antiepileptic drug treatment, may

be severe, and usually have a negative impact on the child's neurological and cognitive development.<sup>21</sup> In this patient, the seizures were controlled by multiple antiepileptic medications (phenytoin 80 mg three times daily and valproate acid 400 mg three times daily).

The prognosis depends on illness severity; from mild to severe organ/tissue lesion, from epilepsy to severe mental retardation and uncontrolled seizures and vital organs failure.<sup>3</sup> Poor prognostic signs include multiple seizure types, onset of seizure before one year of age, and multifocal EEG. Based on the history of seizures, this patient had multiple seizures type, so she had a poor prognosis. Patients with TSC have the worst theoretical prognosis for successful epilepsy surgery because of several factors. The epileptogenic tubers are often extratemporal, multifocal, bilateral, and may overlap with eloquent cortex. Intracranial electrode monitoring also is limited by the presence of secondary epileptogenic foci that may be resection of the primary focus, and by the fact that the margins of the primary epileptogenic zone may overlap with functional cortex.<sup>22</sup>

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