

## Long-term follow up of a tuberous sclerosis patient: evaluation of anti-epileptic drugs and self-management support therapy

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**T**uberous sclerosis (TSC) (OMIM 191100) is an inherited, autosomal dominant disorder affecting multiple organ systems.<sup>1</sup> A genetic mutation in one of the tumor suppressor gene (TSG) alleles causes tumor growth in various organ systems. Tuberous sclerosis can be found in people of all races, and does not differ in men and women, with an incidence 1 in 6,000 births and prevalence of 1 in 20,000.<sup>1-3</sup> Although the prevalence is quite high, diagnosing this disorder is often difficult and delayed due to diverse disease manifestations and varied age at onset.

Tuberous sclerosis (TSC) is associated with significant disease burden and has a considerable impact on quality of life.<sup>4</sup> Individuals with tuberous sclerosis need multidisciplinary treatment by experts because of the various clinic spectrums. To date, no single therapy can cure tuberous sclerosis. Management of tuberous sclerosis is done with the aims of helping patients achieve better quality of life, minimizing complications, and avoiding side effects of drugs.<sup>3-6</sup> With early detection, aggressive monitoring, and handling emerging symptoms, individuals with tuberous sclerosis may have longer life expectancy and learn independent survival skills.<sup>3,6-8</sup> Here we present an 18-month follow-up case report on a patient with tuberous sclerosis and intractable epilepsy, focusing on medical aspects and quality of life. [Paediatr In-

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### The Case

A 13-year-old boy was diagnosed with epilepsy at the age of 8 years, and received regular valproic acid therapy from that time. Despite receiving anti-epileptic monotherapy, seizures continued to recur every 1-2 weeks and the frequency of seizures increased. At the age of 10 years, seizures occurred almost everyday, so carbamazepine was added to the valproic acid treatment. An electroencephalography

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**Table 1.** Clinical findings in the patient

Major criteria	The patient	Minor criteria	The patient
Hypomelanotic macules > 3, minimum diameter 5mm	Macules > 5, diameter 1-3cm	Confetti skin lesion	Multiple, 1-3mm
Angiofibroma or fibrous cephalic plaque	Facial angiofibroma (+)	Dental enamel pits >3	Not checked yet
Ungual fibroma > 2	Found	Intraoral fibroma	Not found
Shagreen patch	Multiple, in back and knees	Retinal achromic patch	Not found
Multiple retinal hamartomas	Not found	Multiple renal cyst	Not found
Cortical dysplasia	(+)	Non renal hamartoma	Not found
Subependymal nodules	Not found		
Subependymal giant cell astrocytoma	Not found		
Cardiac rhabdomyoma	Not checked yet		
Lymphangioliomyomatosis of the lung	Not checked yet		
Renal angiomyolipoma	Not found		

\*Definitive diagnoses: fulfilling 2 major criteria OR 1 major with >2 minor criteria. Possible diagnosis: fulfilling 1 major criteria OR >2 minor criteria.

(EEG) examination performed when he was 8 years of age in September 2014, revealed an epileptiform wave in all leads, and an MRI scan of the head revealed the presence of calcification in the temporal lobes of the left caudatus and ventriculomegaly with cavum septum pelusidum. Head MRI revealed some tubers in brain parenchyme and sub-ependymal nodule at the wall of the lateral ventricle (**Figure 1**).

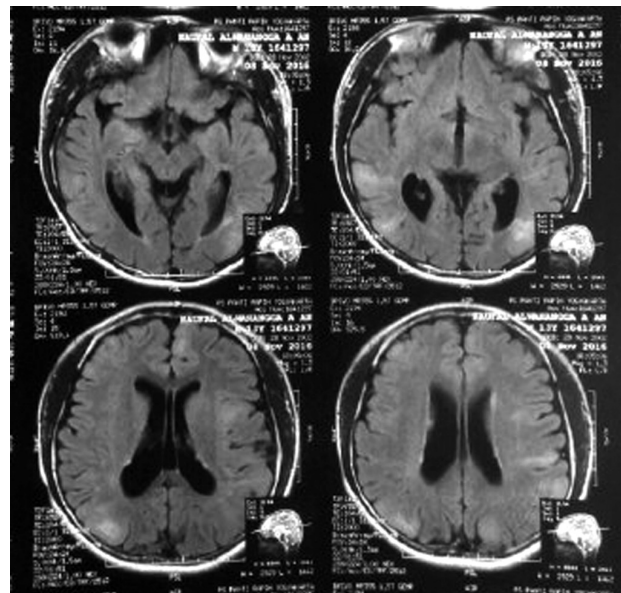
The child had a facial skin lesion recognized by his parents at the age of 9 years, one year after a seizure (**Figure 2**). There were some white patches on the the body and back (**Figure 3a**). The initial tracking of involvement of other organ systems was done when he was 10-year-old, with no evidence of retinal hamartoma, dental pit, gingival fibroma, or abnormalities in the kidneys and intraabdominal organs in abdominal CT scan.

No family members had similar disease. The child had delayed gross motor and speech skills (walking at the age of 17 months and speaking fluently at the age of 3 years). He dropped out of school in grade 5 due to daily seizures. In mid-2014, the patient was diagnosed with tuberous sclerosis (fulfilled  $\geq 2$  major diagnostic criteria according to the 2012 consensus) and intractable epilepsy. Anti-epileptic drugs given were carbamazepine 5mg/kg body weight (BW)/12 hours, clonazepam 0.05mg/kg BW/12 hours, and valproic acid 20mg/kg BW/day.

Observations were conducted prospectively for 18 months (July 2016-January 2018). The dependent variables observed were epilepsy, clinical

manifestations in organ systems, and patient quality of life (see **Appendix**). Independent variables observed were anti-epileptic drug doses and self-management support for the patient.

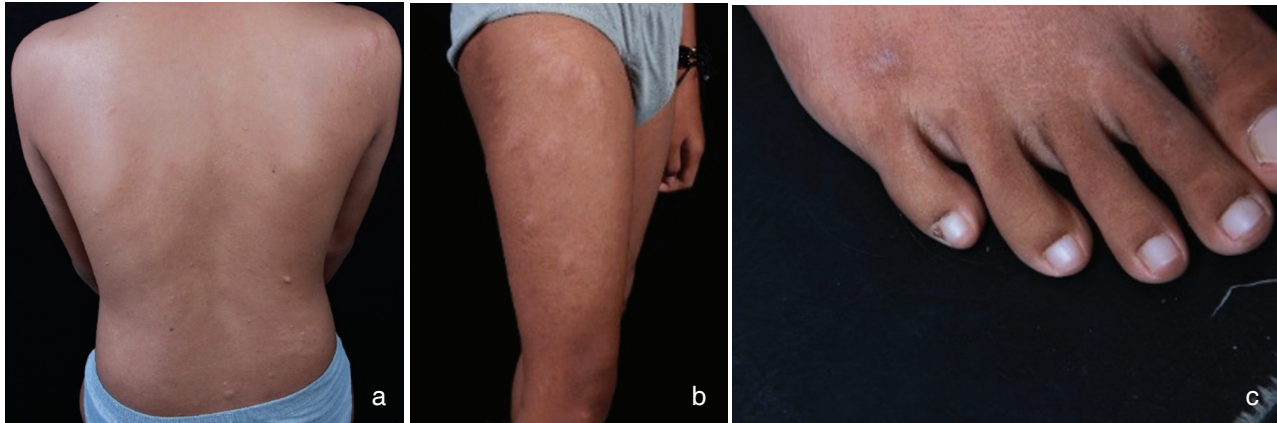
The patient had clinical manifestations of tuberous sclerosis complex (TSC) in the form of distinctive skin lesions including ash leaf macules, facial angiofibroma, and shagreen patch that was recognized at the age of 9 years. During our 18-month



**Figure 1.** MRI showed some tubers in brain parenchyme (white circles) and sub-ependymal nodule at the wall of the lateral ventricle (red circle)



**Figure 2.** Skin lesions found in our patient: angiofibroma and fibrous cephalic plaque



**Figure 3.** Multiple shagreen patches and ashleaf macules on the (a) back and (b) leg; (c) unguinal fibroma on nails

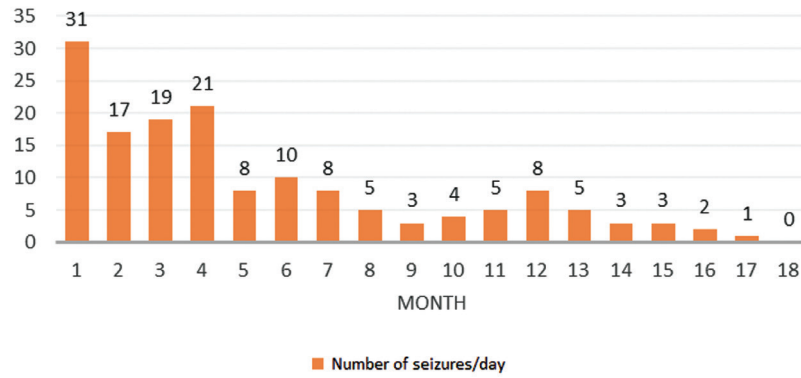
observation, the shagreen patch enlarged and the facial angiofibroma increased in number (**Figure 2** and **Figure 3**).

Seizures began at age 8, with focal and secondary generalized types. During the observation, seizures were still present even with three anti-epileptic drugs (carbamazepine, clonazepam, and valproic acid), thus the patient was considered to have intractable epilepsy. At the beginning of the observation, our patient experienced seizures almost everyday. Topiramate was added to his daily regimen at an adjusted dose. During the observation, our patient showed improvement in clinical symptoms with an increased topiramate dose of 3mg/kg BW/day. The seizures resolved with valproic acid 60mg/kg BW/day, carbamazepine 18 mg/kg BW/day, and topiramate 3 mg/kg BW/day (**Figure 4** and **Figure 5**). The last EEG monitoring in October 16, 2017 showed an improvement from the previous one, although diffuse epileptiform waves were still found (**Figure 6**).

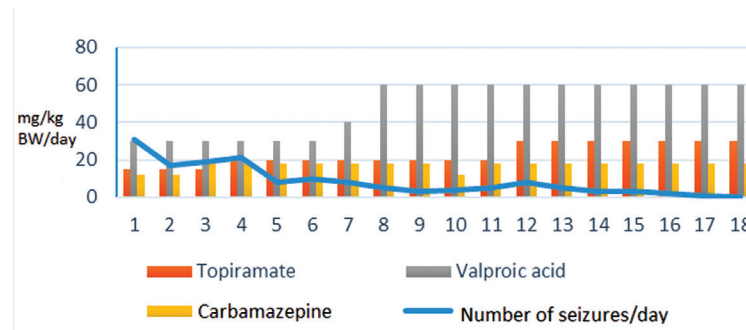
## Discussion

Epilepsy is found in 85% of TSC patients. Most epilepsy in TSC is refractory to anti-epileptic drugs.<sup>9</sup> Multi-organ abnormalities in TSC occur at specific ages. We observed the patient from 13 to 15 years of age. At this age, abnormalities that can arise include gum fibroma and dental pits, unguinal fibroma, and the development of pre-existing subependymal nodule (SEN) to subependymal giant cell astrocytoma (SEGA). As stated in a previous study, TSC skin lesions can appear as early as the neonatal stage, yet they are difficult to detect even with Wood's lamp examination. A hypomelanotic macula is clearly visible at age of 5 years, while angiofibroma may be found starting at the age of 5-10 years.<sup>9</sup>

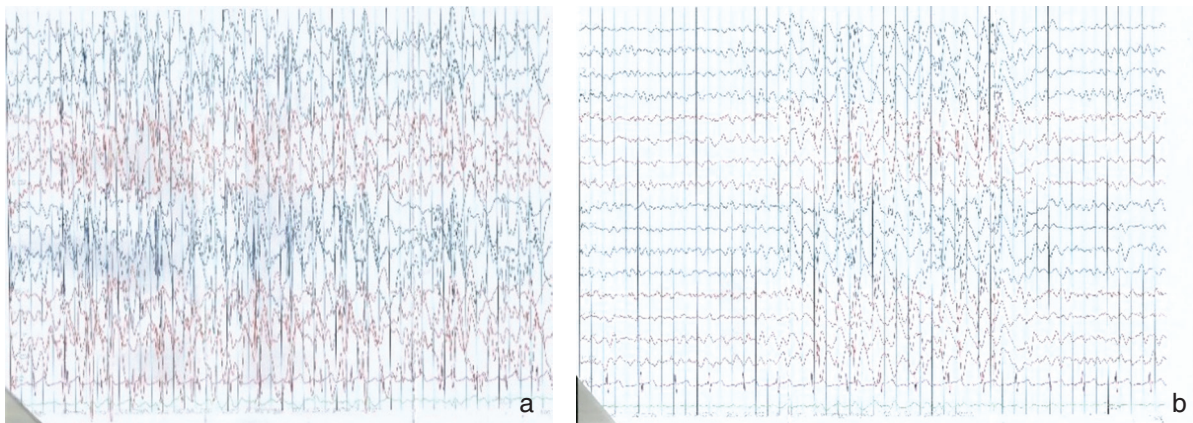
Renal manifestations such as polycystic kidney disease and renal angiomyolipoma can be found in 85% of adult TSC patients. Pulmonary lymphangiomyomatosis is present in 40-80% of adult female TSC patients, but in a smaller percentage of men. Cardiac abnormalities could appear from as early as 20 weeks of gestation, persist in neonatal period (80%),



**Figure 4.** Frequency of seizures/month during the 18-month study



**Figure 5.** Decreasing frequency of seizures related to increasing doses of anti-epileptic drugs during the 18-month observation. Seizures resolved with valproic acid 60mg/kg BW/day, carbamazepine 18 mg/kg BW/day and topiramate 3 mg/kg BW/day



**Figure 6.** (a) Earlier EEG showed diffuse abnormal (hypsarrhythmia-like) epileptiform waves. (b) The EEG at the end of the study showed improvement of the epileptiform waves

then decrease over time.<sup>10</sup> In adolescence, heart abnormalities may be found, especially disturbances in heart rhythm. We found no dental pit or gum fibroma, over a series of physical examinations. However, when our patient was 14 years of age, we found periungual fibromas. There were multiple tubers in the cortex and subependymal nodule (SEN) in the last MRI examination. Chest x-ray, electrocardiography, and abdominal CT examination revealed no abnormalities in the lungs, heart rhythm, or kidneys.

Topiramate is a new drug effective for treating focal seizures with or without secondary generalization in tuberous sclerosis patients.<sup>2,3</sup> Topiramate's mechanisms of action are to inhibit voltage-dependent sodium channels, increase GABA activity in GABA(A) receptors, and act as a NMDA-glutamate receptor antagonist. Topiramate is currently used as an add-on therapy in focal and secondary generalized epilepsy at a dose of 2.5 - 4.5 mg/kg BW/day, divided into two doses, with a maximum dose of 200mg/12 hours.<sup>4</sup>

Self-management support should be provided by the government through a community health system for individuals and families dealing with chronic diseases to improve health outcomes and reduce utilization, cost, and caregiver burden.<sup>11</sup> The system involves collaboration of patients, families, and health care providers.<sup>12</sup> In adult populations, self-management support was shown to improve health outcomes and patient independence.<sup>13,14</sup> Self-management support is one of the pillars in the primary care services provided to patients with chronic disease.<sup>13</sup> Although considered to be a best practice in the care of adults with chronic conditions, comprehensive self-management support (SMS) programs are not typically available in pediatric practices. Self management support has not been widely developed for children and adolescents and has not been formally integrated in our health services.

Our patient was seizure-free at the end of our study. As his physical, emotional, and social functions improved, the child returned to school. The quality of life of tuberous sclerosis patients is significantly reduced compared to the normal population, with the psychosocial aspect most affected.<sup>15</sup> Neuropsychological intervention is needed to improve patient quality of life,<sup>16</sup> as the quality of life in such patients is mainly influenced by neurological

and neuropsychiatric manifestations. Epilepsy is the main factor affecting the patient quality of life. If the epilepsy can be controlled, it can improve the patient's quality of life. As the main outcome of this study, we used PedsQL inventory to evaluate the quality of life of our patient. After intervention, his Peds QL score showed improvement. As such, with good medication compliance and appropriate anti-epileptic drugs doses, we could control the epilepsy symptoms so that he achieved a better quality of life at the end of the observation.<sup>4,7,8,17,18</sup>

## Conflict of interest

None declared.

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**Appendix: Summaries of evaluation and monitoring during study**

No.	Variables	Basic data	Intervention	Results
1	Manifestations of the nervous system	Head CT scan: calcification in temporal lobes and caudate nucleus sinistra, ventriculomegaly with cavum septum pellucidum	1. Physical examination 2. Head MRI every 1-2 years	Head MRI results: No visible nodular hypointense lesion on T1W1, hyperintense on T2W1 nor hypointense on FLAIR Impression: no / not yet seen tuberous sclerosis cyst. Cavum septum pellucidum
2	Skin manifestations	Multiple facial angiofibroma Multiple shagreen patches on the right thigh and waist Ashleaf macule on right leg	Observation and monitoring	The amount and the size of facial angiofibromas increased Shagreen patch size enlarged Found unguual fibroma on the right and left foot toenails Laser treatment for facial angiofibroma was planned to patient
3	Cardiac manifestations	No complaints of chest pain. On physical examination, there was no interruption of heart rhythm and heart sound was within normal limits. ECG and echocardiography have not yet been done	1. Physical examination 2. ECG 3. Echocardiography	No impaired arrhythmia, heart sound within normal limits. ECG: normal sinus rhythm; no conduction disorder or arrhythmia.
4	Pulmonary manifestations	No complaints of shortness of breath. Thoracic X-ray and CT scan had not yet been done	1. Physical examination 2. Thoracic X-ray examination	No complaints of breathlessness and thoracic X-ray examination was normal

**Appendix: Summaries of evaluation and monitoring during study (continued)**

No.	Variables	Basic data	Intervention	Results
5	Self-management support for chronic disease	<ol style="list-style-type: none"> <li>1. Patients and families did not understand the disease</li> <li>2. Parents did not have daily diaries of drugs taken by children</li> <li>3. The parents objected to follow-up visits to the Pediatric Polyclinic, RSUP Dr. Sardjito, due to the tiered referral process and the long queue</li> <li>4. There was no daily record of the child's major complaints or other complaints</li> <li>5. The child had not attended school since the age of 10 because he was embarrassed by his seizures</li> <li>6. The child tended to be alone at home, found it difficult to socialize, and had no peers</li> </ol>	<ol style="list-style-type: none"> <li>1. Overarching care processes</li> <li>2. Informational support</li> <li>3. Peer support</li> <li>4. Coaching support</li> <li>5. Informational and technological support</li> <li>6. Family daily management support</li> </ol>	<ol style="list-style-type: none"> <li>1. Patients and families were able to understand the illnesses with regards to etiology, disease process, complications and prognosis</li> <li>2. The child had a diary to record prescribed medications and medication schedule</li> <li>3. Parents routinely brought the patient to the neurology clinic every month and to the child psychologist every 3 months</li> <li>4. The child had a diary to record the frequency and type of seizures</li> <li>5. The child had returned to school with the goal of achieving national equivalency education (package A)</li> <li>6. The child was more extroverted and able to communicate with peers and people outside the family. He felt more confident. From the last examination by a psychologist, the child no longer experienced anxiety disorders or depression</li> <li>7. Parents and children communicated with the doctor at any time if needed and can easily accessed information related to the child's health</li> </ol>
6	Quality of life	<ol style="list-style-type: none"> <li>1. Child General QoL: 65.21</li> <li>2. Mother General QoL: 56.45</li> </ol> <p>Impression: poor quality of life</p>	<ol style="list-style-type: none"> <li>1. Pharmacological therapy with anti-epilepsy drugs</li> <li>2. Self-management support</li> <li>3. Behavioral therapy</li> <li>4. PedsQL score re-evaluation</li> </ol>	<ol style="list-style-type: none"> <li>1. Child General QoL: 71.4</li> <li>2. Mother General QoL: 63.75</li> </ol> <p>Impression: the quality of life according to the perception of the child and mother was quite good, and better than at the initial examination</p>