CASE REPORT

Seizure and Mild Cognitive Impairment in Tuberous Sclerosis Complex

Iswandi Erwin,[1*] Aida Fithrie,[2] Alfansuri Kadri[2]

[1]Departement of Neurology, National Brain Centre Hospital, Jakarta, Indonesia
[2]Departement of Neurology, Faculty of Medicine,Universitas Sumatera Utara,
Medan, Indonesia

*Coressponding author: wandierwin@yahoo.com
Received 11 March 2018; Accepted 3 December 2019
DOI: 10.23886/ejki.7.9212.

Abstract

Tuberous sclerosis complex (TSC) is syndrome characterized by hamartomal growth on multiple organ systemcaused by genetic disturbance especially on TSC1 gene producing hamartin and TSC2 gene producing tuberin, most clinical syndrome are facial angiofibroma, renal angiomyolipoma(AML), pulmonary lymphangiomatosis(LAM) and several other clinical feature of multiorgan distubance while neurological manifestation of TSC usually seizure caused by either intracranial tubers, subependymal nodules (SEN) and subependymal giant cell astrocytoma (SEGA). We report a case ofa girl, 18th years old with main complaint of seizure since 5 years ago. Electroencephalography (EEG) show abnormal epileptiform activity of 4 Hz-spike-wave complex predominantly on left temporal region while head CT scan showed multiple calcification. Neurobehavior assessment revealed mild cognitive impairment on memory, language and visuospatial domain. Chromosom analysis showed no major structural disorders. Seizure is now controlled with valproic acid.
***Keywords**: Tuberous sclerosis complex, epilepsy, neurogenetics.*

Bangkitan dan Gangguan Kognitif Ringan pada *Tuberous Sclerosis Complex*

Abstrak

Tuberous sclerosis complex (TSC) merupakan sindrom dengan karakteristik pertumbuhan hamartoma di berbagai organ dan disebabkan oleh gangguan genetik terutama pada gen TSC1 yang memproduksi hamartin dan gen TSC2 yang memproduksi tuberin. Gejala klinis TSC adalah facial angiofibroma, renal angiomyolipoma (AML), pulmonary lymphangiomatosis (LAM) dan gangguan multiorgan lainnya. Manifestasi neurologis TSC umumnya berupa bangkitan yang disebabkan oleh tuber intrakranial, subependymal nodules (SEN) and subependymal giant cell astrocytoma (SEGA). Kami melaporkan kasus perempuan berusia 18 tahun dengan keluhan utama bangkitan yang dialami sejak 5 tahun sebelum masuk rumah sakit. Elektroensefalografi (EEG) menunjukkan aktivitas epileptiform abnormal berupa kompleks paku-ombak 4 spd predominan di regio temporal kiri dan CT-scan kepala menunjukkan kalsifikasi intrakranial multipel. Penjajakan neurobehavior menunjukkan gangguan kognitif ringan pada domain memori, bahasa dan visuospasial. Pada analisis kromosom tidak ada gangguan struktural mayor. Bangkitan kini terkontrol dengan asam valproat.
***Kata kunci:** Tuberous sclerosis complex, epilepsi, neurogenetika.*

Introduction

First described by Bourneville, Pringle and Von Recklinghaussen on 19th century, tuberous sclerosis complex (TSC) is manifestation syndrome caused by genetic alteration on TSC1 genes on chromosome 9q34 coding hamartin protein and/or TSC2 genes on chromosome 16p13.3 coding tuberin protein. Extracranial clinical appearance of TSC include facial angiofibroma, renal angiomyolipoma (AML) and pulmonary lymphangiomyomatosis (LAM), while intracranial involvement manifest as intracranial tubers, subependymal nodules (SEN) and subependymal giant cell astrocytoma (SEGA) as consequences of these protein function disturbances on cellular growth. Cortical tubers that occurred mostly on 90% TSC cases could be classified as focal cortical dysplasias which is disruption of laminar organization of cerebral cortex in between grey and white matter junction, along with SEN and SEGA are considered as foci of epileptogenesis, autism and learning difficulties in TSC patients. The lesions are considered benign, although in some cases it can grow on ependymal cell of the ventricular system causing hydrocephalus.[1-4]

Epidemiology of this entity in general population is 1 in 6000 including almost all race and ethnicity. However, occurence in asian population estimated much preceed caucasian people (1:95 vs 1:10,000-25,000) with only 15% of case have family history of the spectrum, proving that this disease was not only inherited as autosomal dominant but also could occur in sporadic manners.[1,2]

TSC1 and TSC2 genes act as tumor suppressor genes, while alleles inactivation on both would lead into tumorigenesis process, germinal mutation and also second-hit mutation.[4,5] Tuberin and hamartin protein, coexpressed on multiple organs such as kidney, brain, lungs and pancreas, specifically on apparatus golgi for TSC2 and centrosome for TSC1.[6] Both normally will form intracellular heterodimer protein complex of TSC1/TSC2 that will interact with many others protein. Those complex will converse brain-guanosine triphosphate (brain GTP)-enriched Ras homologues which will inactivate mammalian target of rapamycin (mTOR), a serine-treonine kinase that regulate cellular metabolism, differentiation and proliferation.[7,8]

Case Report

A case of 18 years old girlcame to neurology clinics of Adam Malik General Hospital, Medan consulted from dermatovenerology clinics and came with main complaint of seizure 1 day before hospital admission. She was conscious and complained feeling unwell, nauseaous, and chilling response before ictal state. On ictal, she was suddenly unconscious, while her mouth excreted frothy saliva. Involuntary jerks happened first on the right arm and propagated onto whole body becoming tonic-clonic seizure. Post ictal, she fell asleep for about 1 hour, urinating and did not remember the incident. Seizure has occurred since 5 years ago, approximately 2 times a day with duration of 5 minutes. Inadequate antenatal care, childbirth abnormality, history of developmental delay andor failure to thrive was denied.

General physical examination revealed hyperpigmentation macules accompanied with multiple papules on fronto-facial and posterior colli region, left shoulder and on the left lower back (shagreen patch) accompanied with enamel and periungual pits. Neurology examination showed vital signs, consciousness, cranial nerve function, funduscopy, sensibility and propioseptive, motoric strength, tones and all reflex are within normal limit. Cognitive function examination using several neurobehavioral tools as constituted on Table 1.

Table 1. Neurobehavioural Score Results

Neurobehaviour Tools	Score
Mini mental state examination(MMSE)	28
Clock drawing test (CDT)	3*
Word list memory task	25
Word list recall	5*
Word list recognition	9.5*
Forward digit span	4
Backward digit span	2
Verbal fluency	23
Constructional praxis	10
Recall of Constructional Praxis	5
Boston naming test	11*
Trail making test (TMT) A	60 sec
Trail making test (TMT) B	65 sec

*indicating norm deviation

General laboratory test such as complete blood count (hemoglobin, erythrocyte, leucocyte, platelet counts, erythrocyte sedimentation rate), haemostatic test (prothrombin time/PT, thrombin time/TT, activated partial thromboplastin time/aPTT, international normalized ratio/INR), random blood sugar level, electrolytes (sodium, potassium, chloride), renal

function test (ureum, creatinin) and liver function test (alanine and aspartate aminotransferase/ALT and AST) are within normal limit.

We also checked level of luteinizing hormone (LH), follicle stimulating hormone (FSH), estradiol, progesterone and β-human chorionic gonadotropine (β-HCG) which are also within normal limit. On the same day, EEG was done with photic stimulation and hyperventilation on conscious state and eye closed without premedication as long as 30 minutes resulting after 3 minutes hyperventilation test. We found abnormal epileptiform activity of 4 Hz-spike-wave complex (SWC) predominantly on montage T3 (left temporal region) as seen on Figure 1.

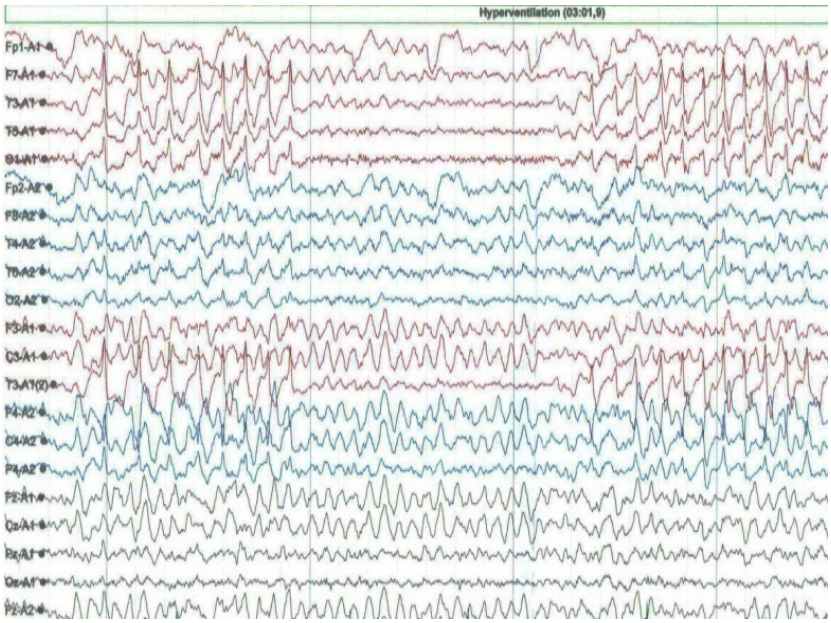

Figure 1. SWC on T3 Montage of EEG

Plain thorax radiology show that there is no abnormalities of cor and pulmo, while functional spirometric examination shows mild restrictive function (forced expiratory volume (FEV_1)/forced vital capacity (FVC) = 93,6%; FEV_1 = 76%, FVC: 71%, forced expiratory flow (FEF) 25%-75%=69%).

Multisliced axial head CT scan without IV contrast resulting on multiple hyperdense lesions on subependymal projections, corona radiata, basal ganglia and subcortical of left parietal region while bulbus oculi, sulcus, gyrus, sylvian fissure, white-grey matter differentiation, infratentorial region (cerebelli, cerebello-pontine angle and pons area), cysternal and ventricles were decently visualized and within normal limit, suggesting multiple calcifications imaging of tuberous sclerosis (Figure 2).

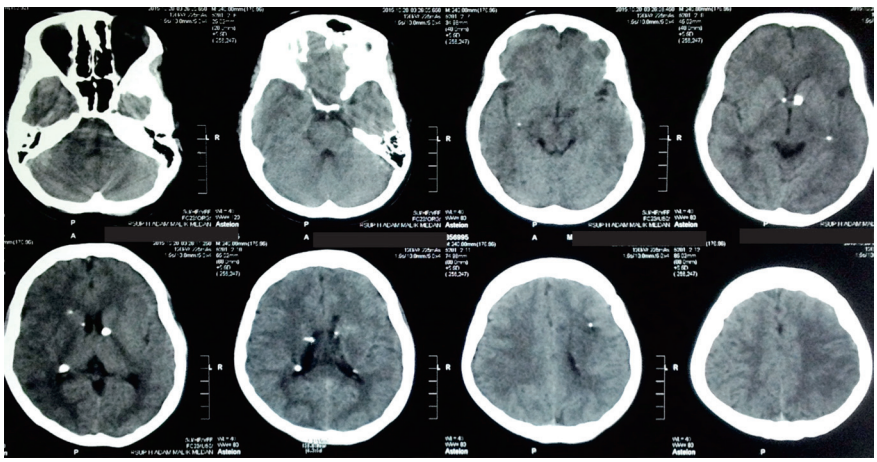

Figure 2. Multiple Calcification on Non-contrast Head CT

Genetics examination of chromosomal analysis (karyotyping) was done using peripheral blood-heparin samples. Using G-banding methods, the sample chromosom was studied resulting in complete 46,XX without no major mutation and chromosom structural disturbance (Figure 3).

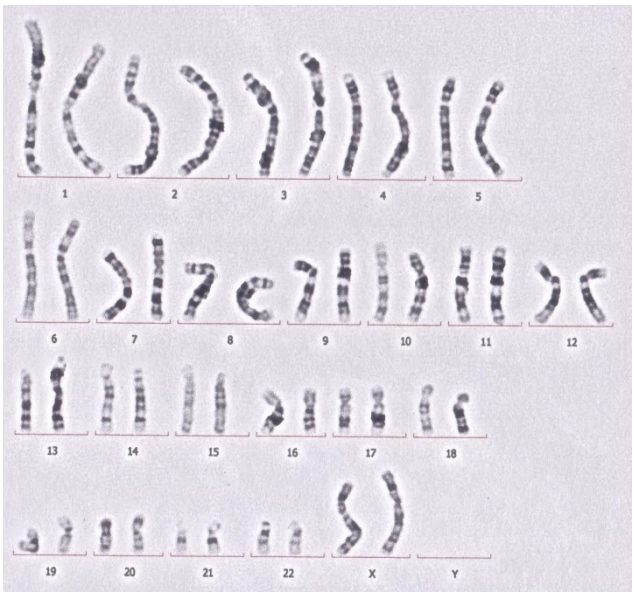

Figure 3. Result of the Patient Chromosom Analysis

We diagnosed the patient with clinical diagnosis of secondary symptomatic generalized epilepsy and mild cognitive impairment due to etiological diagnosis of tuberous sclerosis complex and topical diagnosis of cortical-subcortical cerebri. Differential diagnosis were fahr's disease and neurocysticercosis. We gave oral sodium divalproate 250 mg bid and folic acid 400 µg qd. Patient was performed electrodesiccation procedure followed by lesions excision by dermatovenerologist resulting in pathologically 1x0.6 cm sized irregular thickness, spongy grey colored, hyperkeratotic, fibrous subepithelial and collagenous tissue with vascular component; no sign of malignancy. Impression of fibroma.

We were also planning on giving everolimus as mTOR inhibitory drugs, but it was unapproved due to its restriction on Indonesian national drugs formularium due to its only indication on patients with renal impairment condition, specifically on chronic allograft nephropathy.[9]

Discussions

This patient's seizure started 5 years ago, which is quite unusual for seizure in TSC usually begin as infantile spasm (69%) although diverse type of seizure could be observed in TSC patients such as partial seizure to secondary generalized seizure, atypical absence, myoclonic jerks andor general tonic-clonic seizure. Based on diagnostic criteria of International TSC Consensus Group-Revision 2012, we found at least 3 major and 1 minor feature on this patients (major: facial angiofibromas, shagreen patch, SEN; minor: dental enamel pits), so that definite TSC diagnosis could be established.[7,10,17]

We also checked several hormones level (FSH,LH, β-HCG, progesteron and estradiol) of these patient, for its importance of female TSC patients could undergo hormones-mediated cellular transference (also known as pseudo-metastasis from primary AML lesions to the pulmonary LAM). We could not established such findings based on CT nor USG standard findings, based on normal renal function test and thorax radiography although there was some inconclusive result of mild restrictive function of the lungs.[6]

On cognitive function examination using several tools, we found some several norm deviation accounted for mild cognitive impairment, which are on CDT, Word List Recall, Word list Recognition and Boston Naming Test. Addressing on these disturbance on memory, language and visuospatial domain was in parallel with study conducted by Ridler et al,[12] which show intracranial lesions of TSC could affect structural-functional tract relationship especially on thalamus, nucleus caudate, cingulate cortex and diminishing spatial parenchyma of the brain based of volumetric basal ganglia measurement would directly affect subdomain of long term memory and also verbal-spatial working memory.[11]

G-banding is one of the most used methods for identification of abnormalities of chromosome numbers such translocation, deletion, inversion, amplification andor other mutations on some gene-associated disease, for example philadelphia chromosome for chronic myelogenous leukemia.[13] In association with TSC, we were trying to elaborate if there were any alteration on chromosome 9 (TSC1) andor chromosome 16 (TSC2). As much as 50-80% TSC patient suffered a sporadic mutation. In a study of 325 TSC patients, 17% mutation was found on TSC1 genes, 50% was found on TSC2 genes, 4% categorized onto unclassified variants while 29% remaining into group of "no mutation identified"(NMI) or even germline mosaicism.[2,14]

Likewise this patient's chromosom analysis result, sporadical TSC could be occurred without

disease history in family and even could reach 67% of all patients. On several cases, identification of mutation could help clinician on emphasize the diagnosis. However, positive result would confirm the diagnosis meanwhile negative result does not rule out diagnosis of TSC. This is because TSC genes naturally also have high rates of polymorphism, so it is even better to compare genetical alteration, if any existed, with widely available mutational and single nucleotide polymorphism (SNP) database.[1,7,14]

Due to secondary generalized epilepsy diagnosis, the patient seizure now has been controlled with initial dosage of sodium divalproic 250 mg bid, titrated on the second week to 500 mg bid. There is also opinion that other than antiepileptic drugs (AED), ketogenic diet and vagal nerve stimulation also tuber resection in intractable seizure and hydrocephalus caused by obstructive intracranial nodules could also improve quality of life in TSC. However due to lack of surgical indication, such intervention was not planned. On the era of genomics, best pharmacotherapy for TSC today other than symptomatic management of the clinical events such seizure include use of mTOR inhibitor drugs such as everolimuswhich will inhibit mTOR activation, whereas this process will stop phosporylation of 2 effector molecules which is S6Kinase1 (S6K1) and 4EBinding Protein-1 (4E-BP1), both initially act as protein synthesis stimulants that wil increase cell growth, proliferation also angiogenesis.

This drug is recommended by Food and Drugs Administration (FDA) on 2010 that for TSC patient who did not undergo any surgical intervention, as showed also by clinical trial phase II on mTOR inhibitor that could reduce size of SEGA up to 35-50% from its baseline size. This point of view also supported by phase III clinical trial, Examining Everolimus in a Study of TSC (EXIST) I and II trial recruiting 99 samples other than SEGA volume and also accounted for dermatological lesions, cognitive functions, seizure recurrency and pulmonary function.[15,16]

Conclusions

TSC is a clinical syndrome assumed happened as consequences on alteration of hamartin on chromosome 9 (TSC1) and tuberin on chromosome 16 (TSC2) characterized by multiorgan hamartomal formation, such renal AML, pulmonary LAM, cortical tubers, SEN and SEGA. Most common neurology manifestation of TSC is epileptic seizure and must be controlled with AED. While treatment should be coped on symptomatic complaint, clinician should also consider using mTOR inhibitor such everolimus as proper genomic management. Multidiscipline assessment, serial physical examination, complete diagnostic test surveillance and proper treatment as indicated also side effect of pharmacotherapy monitoring are encouraged to control progressivity of the disease and to achieve patient's optimal quality of life.

Acknowledgements

We thank Department of Clinical Pathology-Adam Malik General Hospital and Genneka Genetic Clinic-Eijkman Institute of Molecular Biology for laboratory and genetical assessment of this patient.

References

1. Budde K, Gaedeke J. Tuberous sclerosis complex–associated angiomyolipomas: focus on mTOR Inhibition. Am J Kidney Dis.2012;59(2):276-83.
2. Cheng TS. Tuberous sclerosis complex: an update. Hongkong J. Dermatol Venereol.2012;20:61-7.
3. Curatolo P, Verdecchia M, Bombardieri R. Tuberous sclerosis complex: a review of neurological aspects. Euro J of Ped Neurol. 2002;6:15-23.
4. De Waele L, Lagae L, Mekahli D. Tuberous sclerosis complex: the past and the future. Pediatr Nephrol. 2015;30:1771-80.
5. Knudson AG. Two genetic hits (more or less) to cancer. Nat Rev Cancer. 2001;1:157-61.
6. Crino PB, Nathanson KL, Henske EP. The tuberous sclerosis complex. N Engl J Med.2006; 355:1345-56.
7. Roach ES, Whittemore VH. Diagnosis, screening and clinical care of individuals with tuberous sclerosis complex. Novartis Oncol. 2011;1:1-38.
8. Turnpenny PD,Ellard S. Mapping and identifying genes for monogenic disorders. Emery's Element of Medical Genetics 13th ed.Edinburgh-New York: Churchill-Livingstone-Elsevier;.2007.
9. Kemenkes RI. Keputusan Menteri Kesehatan Republik Indonesia Nomor HK.02.02/Menkes/137/2016 tentang Perubahan atas Keputusan Menteri Kesehatan Nomor HK. 02.02/Menkes/523/2015 tentang Formularium Nasional. Jakarta: Kementerian Kesehatan Republik Indonesia; Jakarta.2015.
10. Northrup H, Krueger DA. Tuberous sclerosis complex diagnostic criteria update: recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference. Pediatr Neurol. 2013; 49(4):243-54.
11. Ellingson BM, Hirata Y, Yogi A, Karavaeva E, Leu K, Woodsworth DC, et al. Topographical distribution of epileptogenic tubers in patients with tuberous sclerosis complex. J Child Neurol. 2015;31(5):1-12.
12. Ridler K, Suckling J, Higgins NJ, De Vries PJ, Stephenson CME, Bolton PF, et al. Neuroanatomical correlates of memory deficits in tuberous sclerosis complex. Cerebral Cortex. 2007;17:261-71.

13. Bickmore WA. Karyotype analysis and chromosome banding. Nature eLS.2001;1-7.
14. Yates JRW. Tuberous sclerosis: practical genetics. Eu J Hum Genet.2006;14:1065-73.
15. Bissler JJ, Kingswood JC, Radzikowska E, Zonnenberg BA, Frost M, Belousova E, et al. Everolimus for Angiomyolipoma Associated with Tuberous Sclerosis Complex or Sporadic Lymphangioleiomyomatosis (EXIST-2): a multicenter, randomised, double-blind, placebo-controlled trial. Lancet. 2013;381:817-24.
16. Franz DN, Capal JK. mTOR inhibitors in the pharmacologic management of tuberous sclerosis complex and their potential role in other rare neurodevelopmental disease. Orphanet J Rare Dis. 2017;12(51):1-9.
17. Curatolo P, Seri S, Verdecchia M, Bombardieri R. Infantile spasm in tuberous sclerosis complex. Brain Dev. 2001;173: 502-7.