CLINICAL EXPERIENCE

WILEY

Independent temporal lobe epilepsy in patients with tuberous sclerosis complex

Tinghong Liu[1*] | Jing Ding[2*] | Shaohui Zhang[3] | Yangshuo Wang[1] | Jinshan Xu[1] | Liu Yuan[1] | Feng Zhai[1] | Guojun Zhang[1] | Shuli Liang[1]

[1]Department of Functional Neurosurgery, Key Laboratory of Major Disease in Children, Ministry of Education, Beijing Children's Hospital, Capital Medical University, National Center for Children's Health, Beijing, China
[2]Department of Neurology, Zhongshan Hospital, Fudan University, Shanghai, China
[3]Department of Neurosurgery, Fourth Medical Center, PLA General Hospital, Beijing, China

Correspondence
Guojun Zhang and Shuli Liang, Department of Functional Neurosurgery, Key Laboratory of Major Disease in Children, Ministry of Education, Beijing Children's Hospital, Capital Medical University, National Center for Children's Health, Beijing 100045, China.
Email: zgj62051@163.com and 301_1sjwk@sina.cn

*These authors contributed equally to this study.

Funding source
Beijing Natural Science Foundation of China, Grant/Award Number: 7202045; National Nature Science Foundation of China, Grant/Award Number: 82071488

Received: 26 November 2021
Accepted: 14 February 2022

ABSTRACT

Tuberous sclerosis complex (TSC) is a rare disease that involves multiple organs, including the brain; approximately 80%–90% of TSC patients exhibit TSC-associated epilepsy. Independent temporal lobe epilepsy (TLE), TSC-unrelated epilepsy, is particularly rare in patients with TSC. Here, we describe three patients with TSC with independent TLEs that were confirmed by stereo-electroencephalography (EEG), postoperative pathological findings, and seizure outcome at follow-up. The patients were retrospectively enrolled at two centers; their ictal epileptiform discharge onsets were determined using electrode contacts in the hippocampus during stereo-EEG. The three patients underwent anterior temporal lobectomies and remained seizure-free at 1–5 years after surgery. Postoperative pathological examinations confirmed hippocampal sclerosis in all three patients. Furthermore, postoperative intelligence quotient improvement was evident in one patient, while the quality of life was improved in two patients at 12 months after surgery.

KEYWORDS

Anterior temporal lobectomy, Hippocampal sclerosis, Temporal lobe epilepsy, Tuberous sclerosis complex

INTRODUCTION

Temporal lobe epilepsy (TLE) is one of the most common intractable focal epilepsies; hippocampal sclerosis (HS) is the most frequent postoperative pathological finding after epilepsy surgery, with incidences of 45% in adults and 15% in children.[1] The T2-fluid-attenuated inversion recovery (FLAIR) sequence in high-resolution magnetic resonance imaging (MRI) can detect most instances of HS, and quantitative MRI indices can assess HS severity in TLE.[2] Seizure

DOI: 10.1002/ped4.12315

outcomes are classified as Engel I in 71%–84% of patients with TLE who undergo anterior temporal lobectomy.[3–5]

Tuberous sclerosis complex (TSC) is an autosomal dominant neurocutaneous syndrome with *TSC-1/TSC-2* gene mutations; more than 60% of patients with TSC exhibit intractable epilepsy.[6] Resective surgery is the most effective treatment for patients with TSC-related intractable epilepsy; the rates of postoperative seizure freedom are 71% and 51% at 1 and 10 years after surgery, respectively.[7] The most recent meta-analysis revealed seizure freedom in 64.4% of patients who underwent tuberectomy, 68.9% of patients who underwent lobectomy, and 65.1% of patients who underwent multilobar resection.[8]

It is reported that patients with TSC coexisted in other brain lesions, such as cavernous angioma, corpus callosum agenesis, hemimegalencephaly, schizencephaly, and intracranial arterial aneurysms.[9] However, there are few reports that patients are free from TSC-related intractable epilepsy when TSC and other brain lesions are concomitant. Sakakura et al.[10] reported a 33 years old man diagnosed with TSC since he exhibited weekly impaired awareness seizures when he was 7 years old. He reached seizure-free for 10 years after the removal of the cavernous angioma. HS can also occur in patients with TSC.[11,12] Gama et al.[11] reported the presence of typical HS in four patients (13%) with TSC. The relationship between TSC and HS is unknown, but frequent seizures may contribute to the development of HS.[12] In 2016, Lang and Prayson[13] reported a unique pathologically confirmed case of HS and TSC-related epilepsy in a 6-month-old boy; that patient underwent right frontoparietal lobectomy, which revealed that both cortical tubers and sclerosis hippocampus were epileptogenic zones.[13] However, it has remained unclear whether independent TLE is present in patients with TSC. Here, we describe independent TLE in three patients with TSC.

RESULTS

Case 1

A right-handed boy exhibited unprovoked seizures that involved impaired awareness with oropharyngeal and hand automatisms for 1–2 min; these symptoms had occurred at intervals of 7–10 days since he was 7 years old. He had no notable family history of seizures. Computed tomography (CT) revealed bilateral subependymal calcification nodes, while MRI revealed three cortical tubers in the right frontal and occipital lobes, as well as right HS (Figure 1A–D). Interictal scalp electroencephalography (EEG) showed sharp-slow complex discharges in the right temporal region. The patient was diagnosed with epilepsy, focal seizure with impaired consciousness, and TSC.[12] Hence, oxcarbazepine (600 mg/day) was administered; valproate (750 mg/day) was added after poor seizure control for 3 months. However, the patient continued to exhibit seizures. The preoperative evaluation was performed at the age of 8 years. Kidney and cardiac ultrasound findings were normal, as were chest CT findings. The patient exhibited hypomelanotic macules on the skin of his left arm and right side of the back. He did not have any low back shagreen patch, facial angiofibroma or forehead plaque, or ungual/periungual fibroma. The genetic assessment showed a *de novo TSC1* c.2356C>T (p.Arg786*) pathogenic mutation. Positron emission tomography (PET) revealed multiple hypometabolic zones in the right frontal, occipital, and temporal lobes (Figure 1E). Scalp EEG showed epileptic discharges in the right temporal region (F8, T4, and T6) during the interictal period and ictal epileptic discharge onset in the right anterior temporal region (F8 and T4) (Figure 1F,G). The patient's full intelligence quotient (IQ) score using the Wechsler Intelligence Scale for Children IV (Chinese Revision) was 83; his total quality of life (QOL) score was 70, according to the QOL in children with epilepsy (i.e., QOLCE). Our preoperative evaluation indicated that the patient fulfilled the criteria for diagnosis of TLE with HS and TSC; however, stereo-EEG was necessary to confirm the relationship between seizures and cortical tubers. Therefore, four stereo-EEG electrodes were implanted; they covered three cortical tubers and the sclerosis hippocampus (Figure 1H). Interictal stereo-EEG showed frequent high-amplitude spike or spike-slow-wave in the right hippocampus; sclerosis hippocampus-onset ictal epileptic discharges were observed in all three seizures that occurred during the 7-day stereo-EEG monitoring period (Figure 1I–K). Anterior temporal lobectomy was performed (Figure 1L,M). Postoperative pathology examination confirmed HS without dimorphic neurons and balloon cells in the temporal neocortex. The scores of full IQ and total QOL were improved by 11 and 7, respectively, at the 12-month follow-up. The patient has been seizure-free for more than 62 months with oxcarbazepine 600 mg/day; his postoperative scalp EEG findings have remained normal (Figure 1N).

Case 2

A right-handed boy exhibited recurrent transient seizures with impaired awareness, bilateral asymmetric limb tonic seizures, and leftward head and eye deviations for 1–3 min; these symptoms had occurred at intervals of 3–7 days since he was 3 years old, along with an occasional palpitation aura. The seizures sometimes involved behavior arrest, impaired awareness, and both oropharyngeal and hand automatisms for 2–3 min at intervals of 1–2 months. Furthermore, he experienced an epileptic status for 3–10 h at an interval of 2 years, which required emergency medical treatment for stabilization. Kidney and cardiac ultrasound findings were normal, as were chest CT findings. The patient exhibited facial angiofibroma

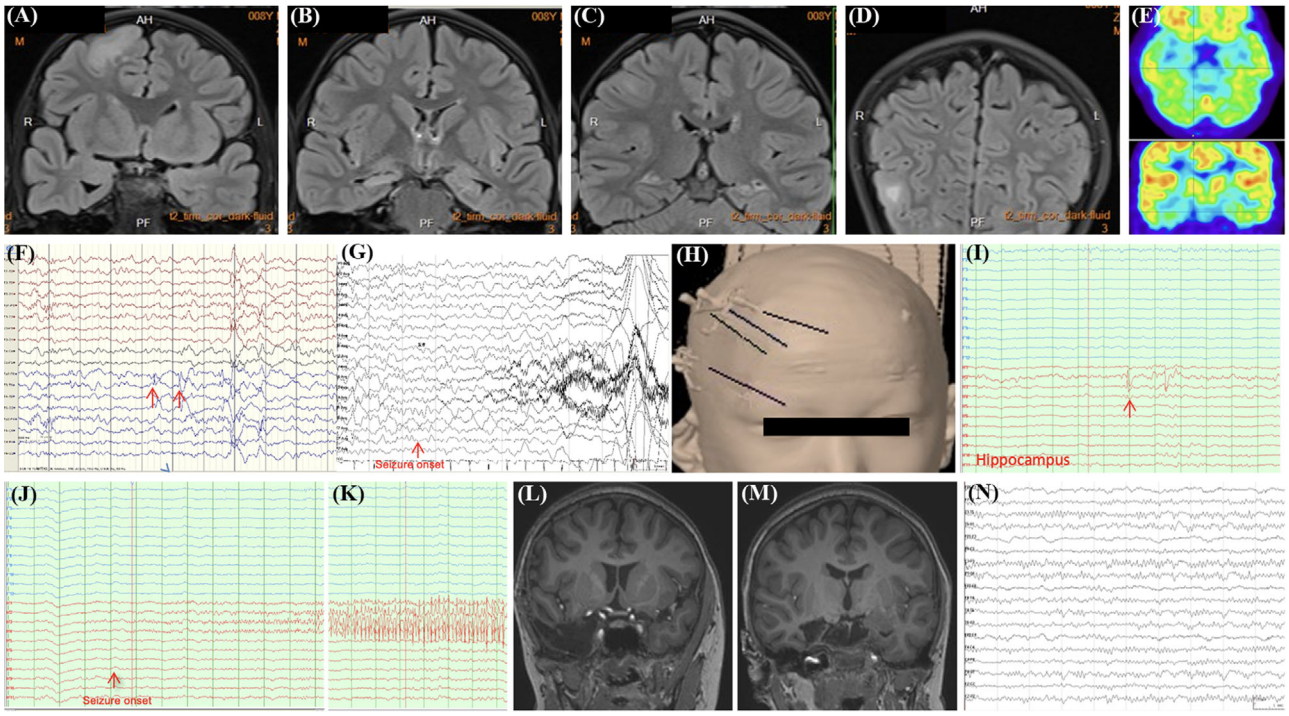

FIGURE 1 Pre- and postoperative MRI and EEG findings, along with preoperative PET findings, in patient 1. Two cortical tubers in the right frontal lobe (A–C) and one tuber in the right occipital lobe (D). (B) Coronal T2-FLAIR showed right hippocampal sclerosis with high signal and low volume. PET revealed hypometabolic zones in the mesial temporal lobe (E). Scalp EEG showed sharp-slow complex discharges (red arrows) in the right temporal region during the interictal period (F), as well as right temporal region-onset ictal (red arrow) discharge (G). Four stereo-EEG electrodes were implanted (H). Stereo-EEG showed interictal frequent high-amplitude spike or spike-slow-wave in the right hippocampus (I), along with sclerosis hippocampus-onset (red arrow) ictal epileptic discharges (J, K). Postoperative T1 images showed resected right anterior temporal lobe (L) and body of the hippocampus (M). Scalp EEG findings were normal at 2 years after surgery (N). EEG, electroencephalography; MRI, magnetic resonance imaging; FLAIR, fluid-attenuated inversion recovery; PET, positron emission tomography.

and hypomelanotic macules on the skin of the arms, back, and abdomen (Figure 2A,B). Brain CT showed a left subependymal calcification node (Figure 2C), along with five obvious cortical tubers in the left parahippocampal gyrus, neocortex of the left temporal lobe, right frontal lobe, parietal lobe, and parietooccipital junctional region; it also showed right HS (Figure 2D–G). Interictal scalp EEG showed medium–high-amplitude spike-slow complex discharges in the right frontotemporal region (FP2, F8, and M2 [sphenoid electrode]) and the temporal region (M2 and F8). The patient was diagnosed with epilepsy, focal seizure with impaired consciousness with or without a secondary generalized tonic-clonic seizure, and TSC. Carbamazepine (400 mg/day), topiramate (100 mg/day), and valproate (1000 mg/day) were administered, but the seizures could not be controlled. Scalp EEG showed epileptic discharges in right temporal regions during the interictal period (Figure 2H), as well as right temporal area-onset epileptic discharge during the ictal period (Figure 2I,J). The patient's full IQ score was 100, while his total QOL score was 60. The genetic assessment showed a *de novo TSC1* c.1525C>T (p.Arg509*) pathogenic mutation. The patient fulfilled the criteria for diagnosis of intractable epilepsy, HS, and TSC. Stereo-EEG was used to confirm the epileptogenic zone when the patient was 11 years old. Six stereo-EEG electrodes were implanted; they covered all five cortical tubers and the right sclerosis hippocampus (Figure 2K). Interictal stereo-EEG showed frequent high-amplitude spike or spike-slow-wave in the right hippocampus (Figure 2L); sclerosis hippocampus-onset ictal epileptic discharges were observed in all four seizures that occurred during the 5-day stereo-EEG monitoring period (Figure 2M). Anterior temporal lobectomy was performed (Figure 2N,O), and postoperative pathology examination confirmed HS. The scores of full IQ and total QOL were improved by 3 and 13, respectively, at the 12-month follow-up. The patient has been seizure-free for more than 53 months with oxcarbazepine 600 mg/day and valproate 750 mg/day; his postoperative scalp EEG findings have remained normal.

Case 3

A right-handed man exhibited recurrent seizures with impaired awareness, left-hand waving, and shouting for up to 20 s. These symptoms were followed by head and body

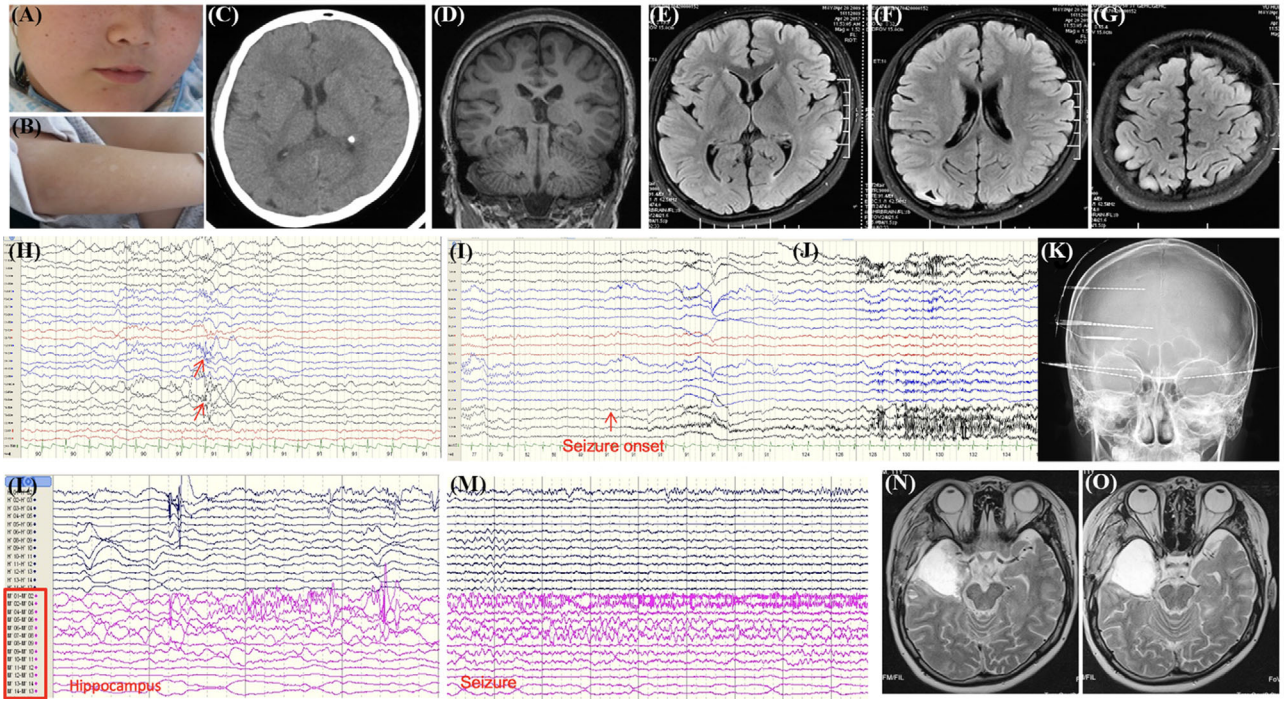

FIGURE 2 Pre- and postoperative MRI and EEG findings, along with a photo of the face and skin of the arm, and X-ray of the skull with stereo-EEG electrodes of patient 2. Facial angiofibroma was present (A), as were hypomelanotic macules on the arms (B). CT showed a left subependymal calcification node (C). Coronal images showed right hippocampal sclerosis with a small volume (D) and cortical tubers in lateral regions of the temporal lobe (E), right occipital lobe (F), and parietal and frontal lobes (G). Scalp EEG showed interictal sharp-slow complex discharges in the right temporal region (red arrows) (H) and onset (red arrow) ictal epileptic discharges from the right temporal region (I, J). Six stereo-EEG electrodes were implanted (K). Stereo-EEG showed interictal frequent high-amplitude spike or spike-slow-wave in the right hippocampus (red frame) (L), and sclerosis hippocampus-onset ictal epileptic discharges (M). Postoperative T2 images showed resected right anterior temporal lobe (N) and body of the hippocampus (O). CT, computed tomography; EEG, electroencephalography; MRI, magnetic resonance imaging; PET, positron emission tomography.

twisting to the left, leftward deviations in both eyes, convulsions in the left corner of the mouth and facial muscles, and left upper limb clonic seizures; finally, the seizures progressed into secondary generalized tonic-clonic attacks. These symptoms had occurred 4–5 times per month since the patient had been 11 years old. The patient also exhibited paroxysmal loss of consciousness with chewing and groping movements for 2–4 min each week; this type of seizure had occurred since he was 13 years old. After the use of lamotrigine and valproic acid, his total seizure frequency had decreased to 1–3 seizures per month. When the patient was 16 years old, he was diagnosed with TSC; genetic assessment showed a *TSC2* c.1789C>T (p.His597Tyr) pathogenic mutation. He exhibited renal angiomyolipoma, facial angiofibroma, and hypomelanotic macules on the skin of the back. Cardiac ultrasound and chest X-ray findings were normal (Figure 3). He was administered lamotrigine 200 mg/day, perampanel 6 mg/day, and sirolimus 100 mg/day; however, he continued to experience weekly seizures. Brain CT showed bilateral subependymal calcification nodes. MRI revealed nine cortical tubers, including two in the right frontal lobe, two in the right temporal lobe, two in the right insular operculum, two in the bilateral occipital lobe, and one in the left frontal lobe; it also showed mild right HS. Interictal scalp EEG showed scatter or short-term rhythmic sharp wave discharges in the right temporal area (FP2, T10 [sphenoid electrode], and T8 [sphenoid electrode]), which could involve the ipsilateral frontal area; they become more frequent during sleeping. Ictal scalp EEG showed right frontotemporal region (FP2, F4, F8, and T10) epileptiform discharge onset with artificial electromyography. The patient was diagnosed with epilepsy, focal seizure with impaired consciousness with or without a secondary generalized tonic-clonic seizure, and TSC. His full IQ score was 91, while his total QOL score was 64. Eight stereo-EEG electrodes were implanted to cover the six cortical tubers in the right inferior and superior temporal gyrus, right insular operculum, right frontal lobe, and the amygdala and hippocampus when the patient was 19 years old. Interictal stereo-EEG showed frequent high-amplitude spike or spike-slow-wave in the right hippocampus and amygdala; right hippocampus-onset ictal epileptic discharges were observed in all three seizures that occurred during the 6-day stereo-EEG monitoring period. Anterior temporal lobectomy was performed, and postoperative pathology examination confirmed HS. The QOL score

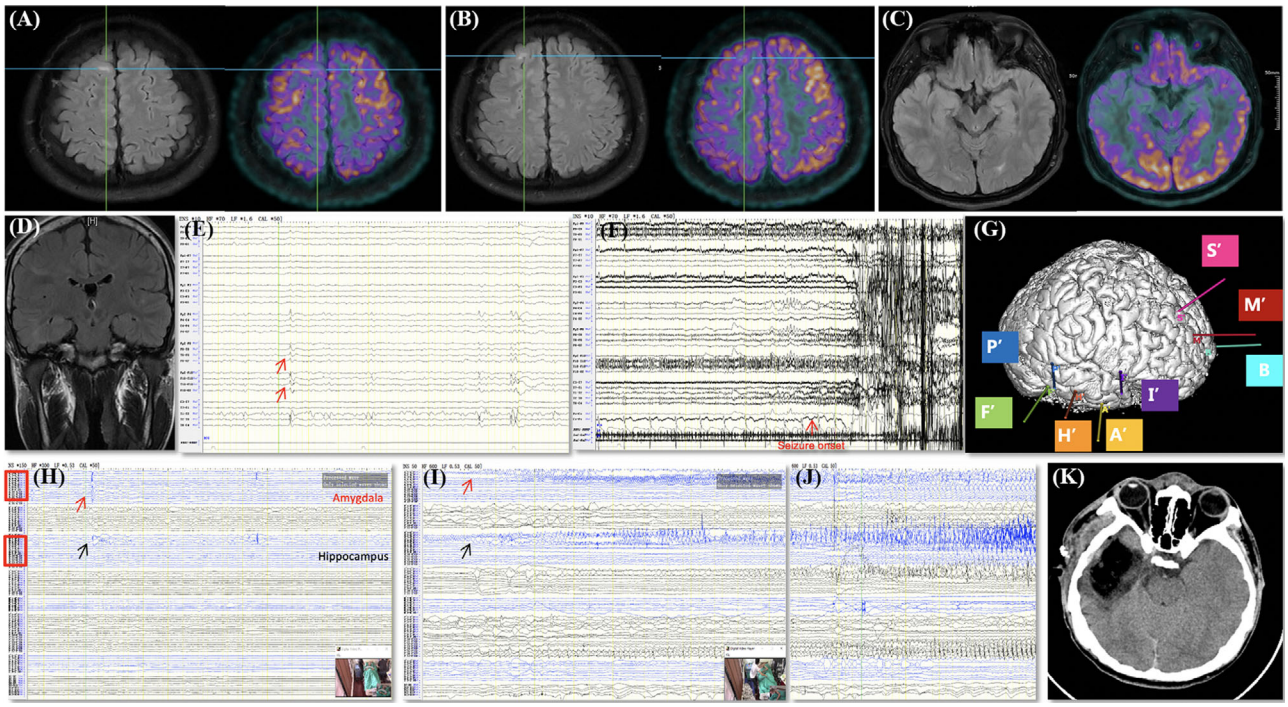

FIGURE 3 Pre- and postoperative EEG findings, preoperative MRI and postoperative CT, along with preoperative PET findings, and stereo-EEG electrodes implanting plan of patient 3. Multiple high signals on MRI-FLAIR and low hypometabolic zones on PET in bilateral hemispheres (A–C). A coronal image showed that the right hippocampus was slightly smaller than the left hippocampus (D). Interictal scalp EEG showed short-term rhythmic sharp wave discharges in the right temporal area (red arrows) (E) and ictal scalp EEG showed right frontotemporal region epileptiform discharge onset (red arrow) with large artificial electromyography (F). Eight stereo-EEG electrodes were implanted (G). Interictal stereo-EEG showed frequent high-amplitude spike or spike-slow-wave in the right hippocampus (red arrow) and amygdala (black arrow) (H); the right hippocampus was the onset zone of ictal epileptic discharges (I, J). Postoperative CT showed that the right anterior temporal lobe, including the head and anterior body of the hippocampus was removed, along with the exterior amygdala (K). CT, computed tomography; EEG, electroencephalography; MRI, magnetic resonance imaging; FLAIR, fluid-attenuated inversion recovery; PET, positron emission tomography.

increased by 10 and the IQ score decreased by 1 at the 12-month follow-up. The patient has been seizure-free for more than 13 months with lamotrigine 600 mg/day and perampanel 6 mg/day.

DISCUSSION

The prevalence of TLE with HS is reportedly 5.1–6.6/10 000 people, while the prevalence of TSC is approximately 0.5/10 000.[7,14] Furthermore, 80%–90% of patients with TSC exhibit TSC-associated seizures. These data suggest that the prevalence of independent TLE in patients with TSC is very low or is not generally recognized. In this report, all three patients were diagnosed with TSC with a specific *TSC1/TSC2* mutation; however, the seizure onset zone was localized in the unilateral hippocampus, rather than a cortical tuber. Furthermore, all patients have exhibited more than 1 year of seizure freedom after anterior temporal lobectomy; postoperative pathology examinations confirmed changes in HS and the absence of dysmorphic neurons and balloon cells in the excised temporal neocortex.

Epilepsy is the most common neurological symptom in patients with TSC; it is associated with gene mutations and cortical tubers.[15] All three of our patients achieved seizure freedom without epileptiform discharge on scalp EEG. However, they continue to receive anti-seizure medications to prevent seizure recurrence. Therefore, we cannot determine whether epilepsy was completely resolved in these patients; confirmation of seizure resolution requires seizure freedom for 10 years without the use of anti-seizure medicines for the second half of that period (i.e., 5 years).[16] Furthermore, more than 4% of patients with TSC exhibit seizures after 12 years of age[7]; at least 20% of patients with TLE and HS experience seizure relapse after anterior temporal lobectomy.[4]

In conclusion, independent TLEs can be co-existed in patients with TSC. Comprehensive preoperative evaluations with an interdisciplinary team are necessary for detecting the real epilepsy focus when patients with TSC present with epilepsy, atypical clinical symptoms or EEG finding, and other lesions on MRI.

CONSENT FOR PUBLICATION

Consent were obtained from the patients' parents and/or patients.

CONFLICT OF INTEREST

All authors declare no conflict of interest.

REFERENCES

1. Blumcke I, Spreafico R, Haaker G, Coras R, Kobow K, Bien CG, et al. Histopathological findings in brain tissue obtained during epilepsy surgery. *N Engl J Med*. 2017;377:1648-1656. DOI: 10.1056/NEJMoa1703784
2. Dou W, Zhao L, Su C, Lu Q, Liu Q, Guo J, et al. A quantitative MRI index for assessing the severity of hippocampal sclerosis in temporal lobe epilepsy. *BMC Med Imaging*. 2020;20:42. DOI: 10.1186/s12880-020-00440-z
3. Mathon B, Bielle F, Samson S, Plaisant O, Dupont S, Bertrand A, et al. Predictive factors of long-term outcomes of surgery for mesial temporal lobe epilepsy associated with hippocampal sclerosis. *Epilepsia*. 2017;58:1473-1485. DOI: 10.1111/epi.13831
4. Liang S, Wang S, Zhang J, Ding C, Zhang Z, Fu X, et al. Long-term outcomes of epilepsy surgery in school-aged children with partial epilepsy. *Pediatr Neurol*. 2012;47:284-290. DOI: 10.1016/j.pediatrneurol.2012.06.014
5. Mehvari Habibabadi J, Badihian S, Tabrizi N, Manouchehri N, Zare M, Basiratnia R, et al. Evaluation of dual pathology among drug-resistant epileptic patients with hippocampal sclerosis. *Neurol Sci*. 2019;40:495-502. DOI: 10.1007/s10072-018-3677-7
6. Yu X, Ding P, Yuan L, Zhang J, Liang S, Zhang S, et al. Cortico-cortical evoked potentials in children with tuberous sclerosis complex using stereo-electroencephalography. *Front Neurol*. 2019;10:1093. DOI: 10.3389/fneur.2019.01093
7. Liu S, Yu T, Guan Y, Zhang K, Ding P, Chen L, et al. Resective epilepsy surgery in tuberous sclerosis complex: a nationwide multicentre retrospective study from China. *Brain*. 2020;143:570-581. DOI: 10.1093/brain/awz411
8. Specchio N, Pepi C, de Palma L, Moavero R, De Benedictis A, Marras CE, et al. Surgery for drug-resistant tuberous sclerosis complex-associated epilepsy: who, when, and what. *Epileptic Disord*. 2021;23:53-73. DOI: 10.1684/epd.2021.1253
9. Tatli Mehmet, Guzel Aslan. Bilateral temporal arachnoid cysts associated with tuberous sclerosis complex. *J Child Neurol*. 2007;22:775-779. DOI: 10.1177/0883073807304014
10. Sakakura K, Fujimoto A, Ichikawa N, Baba Shimpei, Enoki Hideo, et al. Removal of a temporal lobe cavernous angioma to control epileptic seizures in a patient with tuberous sclerosis complex. *Heliyon*. 2020;6:e04229. DOI: 10.1016/j.heliyon.2020.e04229
11. Gama HP, da Rocha AJ, Valério RM, da Silva CJ, Garcia LA. Hippocampal abnormalities in an MR imaging series of patients with tuberous sclerosis. *AJNR Am J Neuroradiol*. 2010;31:1059-1062. DOI: 10.3174/ajnr.A1972
12. Helbok R, Kuchukhidze G, Unterberger I, Koppelstaetter F, Dobesberger J, Donnemiller E, et al. Tuberous sclerosis complex with unilateral perisylvian polymicrogyria and contralateral hippocampal sclerosis—a case report. *Seizure*. 2009;18:303-305. DOI: 10.1016/j.seizure.2008.11.005
13. Lang M, Prayson RA. Tuberous sclerosis complex coexistent with hippocampal sclerosis. *J Clin Neurosci*. 2016;24:28-29. DOI: 10.1016/j.jocn.2015.05.048
14. Fisher RS, Acevedo C, Arzimanoglou A, Bogacz A, Cross JH, Elger CE, et al. ILAE official report: a practical clinical definition of epilepsy. *Epilepsia*. 2014;55:475-482. DOI: 10.1111/epi.12550
15. Northrup H, Krueger DA. Tuberous sclerosis complex diagnostic criteria update: recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference. *Pediatr Neurol*. 2013;49:243-254. DOI: 10.1016/j.pediatrneurol.2013.08.001
16. Asadi-Pooya AA, Stewart GR, Abrams DJ, Sharan A. Prevalence and incidence of drug-resistant mesial temporal lobe epilepsy in the United States. *World Neurosurg*. 2017;99:662-666. DOI: 10.1016/j.wneu.2016.12.074

How to cite this article: Liu T, Ding J, Zhang S, Wang Y, Xu J, Yuan L, et al. Independent temporal lobe epilepsy in patients with tuberous sclerosis complex. *Pediatr Investig*. 2022;6:23–28. https://doi.org/10.1002/ped4.12315