Acta Med. Okayama, 2022
Vol. 76, No. 3, pp. 323–328

Acta Medica Okayama
http://escholarship.lib.okayama-u.ac.jp/amo/

Case Report

A Case of a Solitary Cortical Tuber with No Other Manifestations of Tuberous Sclerosis Complex Mimicking Focal Cortical Dysplasia Type II with Calcification

Kakeru Hosomoto[a], Tatsuya Sasaki[a]*, Koji Kawai[a], Yosuke Okazaki[a], Yuki Hyodo[b], Takashi Shibata[b], Susumu Sasada[a], Takao Yasuhara[a], Katsuhiro Kobayashi[b], Hiroyuki Yanai[c], and Isao Date[a]

Departments of [a]Neurological Surgery, [b]Child Neurology, [c]Diagnostic Pathology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama 700-8558, Japan

Cortical tubers are one of the typical intracranial manifestations of tuberous sclerosis complex (TSC). Multiple cortical tubers are easy to diagnose as TSC; however, a solitary cortical tuber without any other cutaneous or visceral organ manifestations can be confused with other conditions, particularly focal cortical dysplasia. We report a surgical case of refractory epilepsy caused by a solitary cortical tuber mimicking focal cortical dysplasia type II, and describe the radiological, electrophysiological, and histopathological findings of our case.

Key words: cortical tuber, epilepsy, focal cortical dysplasia, transmantle sign, tuberous sclerosis complex

Tuberous sclerosis complex (TSC) is an autosomal dominant multisystem disorder that affects children and adults and often causes epilepsy or other neurological disorders [1]. Cortical tubers, most of which (95%) appear in complexes of multiple tubers [2], are one of the major clinical diagnostic criteria of TSC. The diagnosis of TSC is relatively easy in patients with multiple tubers and other typical cutaneous or visceral manifestations of the disease. However, when a solitary cortical tuber appears in a patient without the other typical manifestations of TSC, it can be difficult to distinguish TSC from other disorders [3]. In particular, focal cortical dysplasia (FCD) type II, which is a subset of malformations of cortical development and a common cause of refractory epilepsy in the pediatric population, can be confused with a solitary cortical tuber, because FCD usually involves a single lesion [4-7]. In addition, FCD type II has some resemblance to cortical tubers in terms of its clinical signs, radiological findings, and histopathology [8-14]. On the other hand, some features that can distinguish between a cortical tuber and FCD type II have been reported. In particular, the transmantle sign, which is defined as a change in subcortical white matter signal intensity tapering toward the ventricle, is a typical finding in FCD type II [15,16]. Distinguishing between a cortical tuber and FCD is important for disease management as well as genetic counseling. In this article, we discuss a surgically treated case of a solitary cortical tuber without any of the other typical manifestations of TSC and which mimicked FCD type II with a transmantle sign.

Case Report

The patient was a 22-year-old man. He was born at 33 weeks of gestation weighing 1,644 g without fetal asphyxia. All developmental milestones were regularly

Received October 27, 2021; accepted December 16, 2021.
*Corresponding author. Phone: +81-86-235-7336; Fax: +81-86-227-0191
E-mail: tsasaki1219@okayama-u.ac.jp (T. Sasaki)

Conflict of Interest Disclosures: No potential conflict of interest relevant to this article was reported.

achieved. He had neither cutaneous nor visceral disease, and he had no family history of epilepsy or other central nervous system disorders. He developed seizures with motion arrest, right conjugate deviation, head version to the right, and occasionally automatism at the age of 7 years (focal impaired awareness seizures). Scalp electroencephalography (EEG) revealed interictal spikes in the right frontotemporal area (Fig. 1). Brain magnetic resonance imaging (MRI) showed a calcification with surrounding T2 hyperintensity at the bottom of the sulcus in the right frontal lobe near the anterior horn of the right ventricle. (The brain images taken at age 7 are not shown here.) He was diagnosed with focal epilepsy (frontal lobe epilepsy), and the calcified lesion was presumed to be a cavernous malformation. Although various antiepileptic drugs were tried, including carbamazepine, lacosamide, and perampanel, his seizure remained intractable.

At the age of 20, he underwent presurgical evaluations. Ictal scalp EEG revealed 5-6 Hz theta activity in the bilateral frontopolar region (Fig. 2D). Computed tomography (CT) and MRI showed a calcification in the right frontal lobe (Figs. 2A-C) that had remained unchanged from the first imaging. In addition, high-resolution (3 tesla) and thin-slice MRI revealed a subcortical T2-high signal tapering towards the ventricle, which was considered to be the transmantle sign [16], subjacent to the calcification (arrows in Figs. 2B, C). Based on these findings, the epileptogenic condition was assumed to be FCD. 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) showed hypometabolism in the right frontal lobe and interictal 99mTc ethyl cysteinate dimer single photon emission computed tomography (SPECT) showed hypoperfusion in the same region (FDG-PET and SPECT images are not shown here). Ictal SPECT could not be performed. Iomazenil SPECT and magnetoencephalogram did not show any specific findings.

When the patient was 22 years of age, chronic subdural electrodes were placed on the lateral surface of the right frontal lobe by means of a right frontal craniotomy. In addition, three depth electrodes were placed around the calcified lesion through the cortical T2 hyperintensity lesion (Figs. 3A-D). During an intracranial EEG study, the habitual seizure did not occur, while nocturnal seizures with staring and oral automatism were observed twice and subclinical seizures were observed twice.

Ictal electrocorticography (ECoG) indicated that ictal 30 Hz fast activities began at the contact point of the depth electrode that was placed in the cortical T2 hyperintensity lesion (electrode number 9 in Figs. 3D, E), and this electrode was 1 cm (two contacts) away from the calcified lesion. Then, the ictal change spread to the other depth electrodes (electrodes 8, 15, 16, 1, and 22 in Figs. 3D, E). Twenty sec after the beginning of the ictal discharges, the clinical manifestations appeared (staring, oral automatism). Interictal

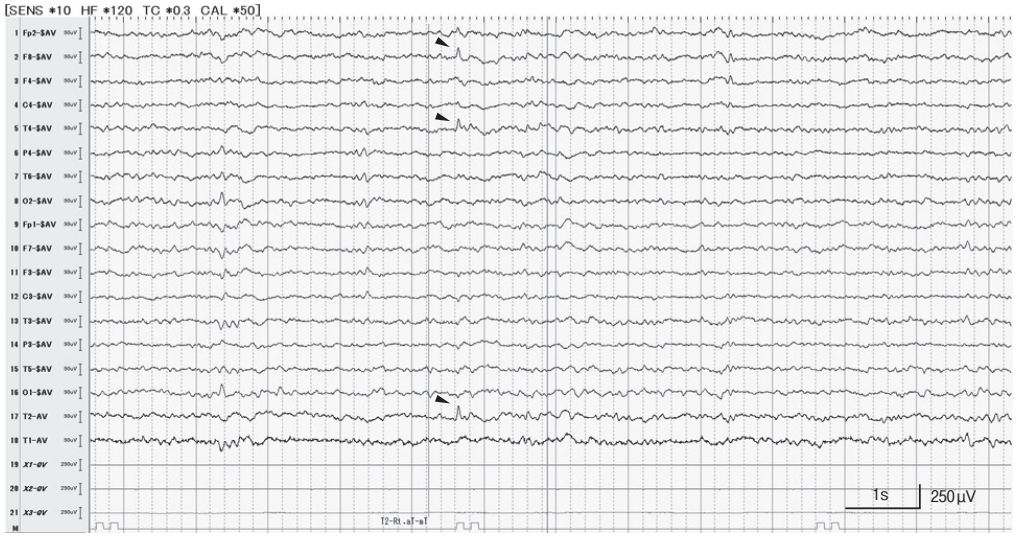

Fig. 1 Interictal scalp electroencephalography. Epileptic discharges (arrowheads) are visible in the right frontotemporal area.

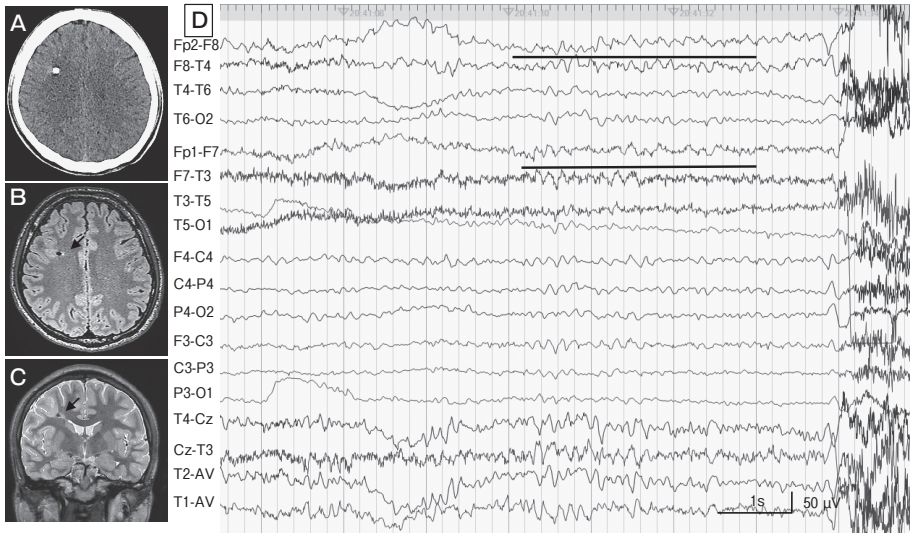

Fig. 2 Presurgical evaluation. (**A**) Presurgical CT scans showed a small calcified lesion in the subcortical white matter of the right frontal lobe. (**B**) An MRI fluid-attenuated inversion recovery image and (**C**) a T2-weighted image showed a transmantle sign (arrows in [B, C]) subjacent to a calcification. (**D**) An ictal scalp electroencephalogram showed bifrontal theta rhythmic waves (underlines).

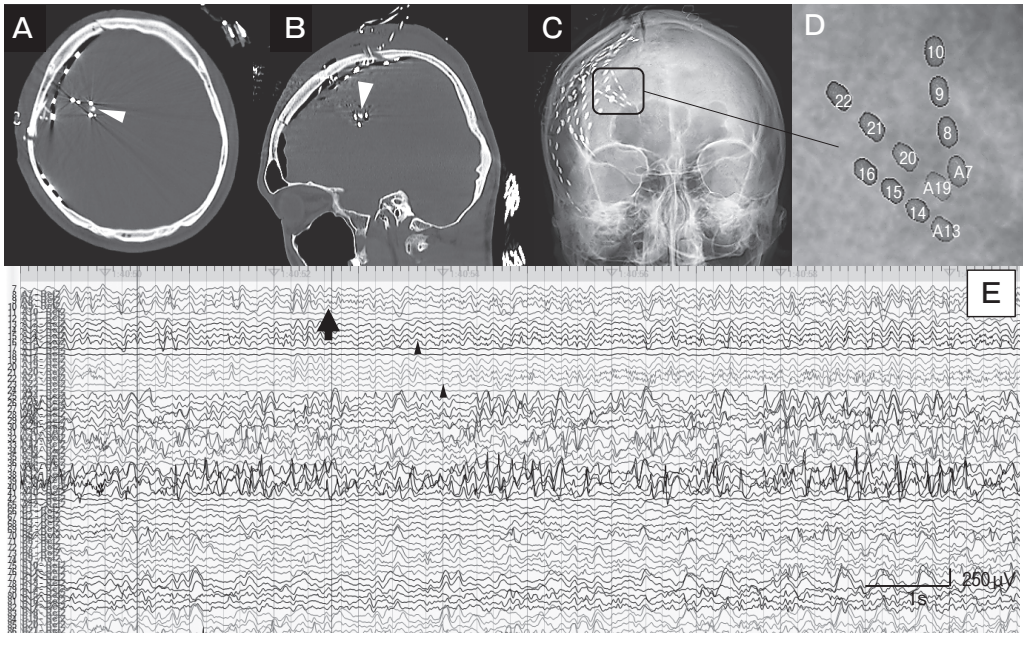

Fig. 3 Intracranial electroencephalogram study. (**A**, **B**) CT scans obtained after the implantation of intracranial electrodes. Arrowheads indicate a calcification, and the surrounding high densities indicate the depth electrodes. (**C**) Subdural and depth electrodes were implanted in the right frontal area. (**D**) Higher magnification of the black box in (**C**) shows a 3D image of the depth electrodes. (**E**) Ictal electrocorticography indicates that the ictal 30 Hz activities (arrow) began at the depth electrode placed near but two contacts away from a calcification (electrode number 9 in [D]), and then the ictal discharges (arrowheads) propagated to the surrounding electrodes (electrode numbers 8, 15, 16, 21, and 22).

high-frequency oscillations and ictal direct-current shifts [17] were also detected at the depth electrodes (figure not shown). The cortical and subcortical lesions and the subjacent calcification were resected (Figs. 4G, H). In the brain functional mapping, stimulation at the gyrus just above the calcification did not induce any reaction. However, stimulation at the gyrus adjacent to the posterior region was positive; that is, twitching of the face and hand was recognized. Thus, the cortex just above the calcification was resected, but not that at the posterior region. At one year after surgery, seizure recurrence was observed twice; thus, the seizure outcome was Engel class IIa [18]. The postoperative seizures were milder than the preoperative ones. An interictal scalp EEG at 6 months after surgery showed spikes or spikes and waves at the right frontal area, a finding that was almost the same as those of the preoperative interictal scalp EEG.

Histological examination of the resected specimen revealed cortical neuronal dyslamination, particularly in layers II and III (Fig. 4A; immunohistochemistry for NeuN). Neurons in the cortex were immunoreactive for MAP2 (figures not shown), and the pyramidal cells in layer III were larger than those in layer V, which appeared to be characteristic of hypertrophic neurons. The specimens of solid gray matter showed calcification (Fig. 4B), balloon/giant cells (Fig. 4C), and a relatively small number of dysmorphic neurons (Fig. 4D) with dense fibrillary gliosis, which is not usual in cases of FCD type IIb. In addition, several other features that differed from the typical features of FCD type IIb were observed: (1) many of the balloon/giant cells had clear boundaries and halo-like artifacts around the cell body (Fig. 4C), which suggested the features of giant cells in cortical tubers rather than balloon cells in FCD type IIb; (2) marked calcification was seen (Fig. 4B); (3) the astrocytes had large nuclei that were brighter than usual; (4) the expression of CD34 class II was seen in some balloon/giant cells and glial cells (Fig. 4E); and the nuclei of vascular endothelial cells appeared to be larger than usual. In our case, dysmorphic neurons were immunoreactive or variably immunoreactive for NeuN (Fig. 4F), immunoreactive for synaptophysin, and strongly immunoreactive for non-phosphorylated neurofilament (figures not shown). Balloon/giant cells were immunoreactive for vimentin, and faint or negative for glial fibrillary acidic protein (figures not shown). There were few olig2-positive nuclei in the lesion (figures not shown), and they seemed to be slightly enlarged atypical nuclei rather than healthy oligodendrocytes. Abnormal cells such as dysmorphic neurons and balloon/giant cells were immunoreactive for p-S6-Ser235/236 (figures not shown), suggesting the constant activation of the mammalian target of rapamycin

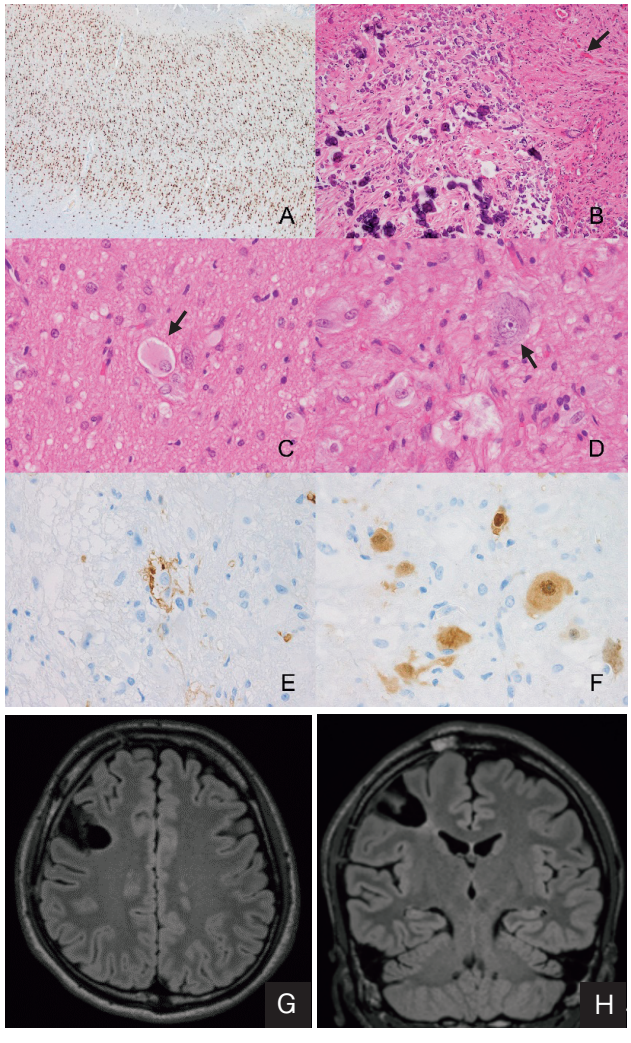

Fig. 4 Microscopic findings of the resected specimen and postoperative magnetic resonance imaging. (**A**) Cortical dyslamination, particularly in layers II and III. (**B**) Calcification and fibrillary gliosis in the deep layer. The arrow indicates a Rosenthal fiber. (**C**) Balloon/giant cells (arrow) showing clear boundaries and halo-like artifacts around their cell bodies. (**D**) Dysmorphic neuron (arrow). (**E**) Expression of CD34 class II is seen in some balloon/giant cells. (**F**) Dysmorphic neurons immunoreactive for NeuN. (**G**, **H**) Lesionectomy including the calcification was performed. Hematoxylin-eosin staining (B-D), immunohistochemistry for NeuN (A, F), and CD34 class II (E).

(mTOR) signal. The specimens of the calcified lesion showed marked calcification and fibrous gliosis accompanied by a small number of Rosenthal fibers (Fig. 4B).

The overall histopathological findings were suggestive of a cortical tuber of TSC rather than FCD type IIb, and a low possibility of ganglioglioma. Informed consent and genetic testing for TSC1 and TSC2 are planned for the future follow-up periods.

Discussion

In this article, we report the case of an isolated cortical/subcortical lesion that led to refractory epilepsy. Before surgery, it was believed to be FCD with calcification. However, histopathology revealed it to be a cortical tuber of TSC. In this case, the single calcified lesion in the frontal lobe without any other cortical abnormalities suggested a cortical tuber, and there was also a subcortical signal change that seemed to be a transmantle sign. As previous reports have described, it can be difficult to distinguish a solitary cortical tuber from FCD type II preoperatively [3,6,12]. The typical finding of a cortical tuber on a brain MRI is a triangular-shaped cortical or subcortical lesion with the apex pointing toward the ventricle; the lesion is typically hypointense on T1-weighted images and hyperintense on T2-weighted images (T2WIs) [8,9]. Most cortical tubers appear in the form of multiple tubers (95%), and about half of them are accompanied by calcification [2]. On the other hand, FCD type II can present as increased cortical thickness or thinning, areas of local brain atrophy, blurring of the gray-white junction, or an increased signal in the subcortex on T2WI [10,19]. FCD is rarely accompanied by calcification; only a few such cases have been reported [20-22]. In addition, the transmantle sign is an MRI feature of FCD that is almost exclusively observed in FCD type II [16,23]. The transmantle sign is indeed helpful for diagnosing FCD type II; however, radial migration lines or the radial bands sign, which are occasionally observed in relation to cortical tubers, are sometimes similar to the transmantle sign, and it may be difficult to distinguish among them [24,25]. In our case, it is possible that a radial migration line appeared as the transmantle sign.

In epilepsy surgeries for TSC, the clinical question arises whether seizures start within the tubers themselves or in the adjacent perilesional area, and there is no firm consensus on this issue [13,26,27]. The surgeon is faced with the question of whether a lesionectomy will be sufficient to achieve freedom from seizures or whether the perilesional margin should be included in the resection. Previous studies have reported that a lesionectomy resulted in a 60~75% seizure-free rate in TSC [13]; however, this result suggests that the epileptogenic zone was not contained entirely within the lesion in the subjects who did not achieve freedom from seizures. Wong *et al.* found that cortical tubers are the primary site of epileptogenesis, but that seizures can potentially arise from the non-tuber region as well [13]. On the other hand, Major *et al.* reported that the tuber was electrographically silent, whereas the surrounding cortical tissue showed epileptiform activity as measured by intracranial ECoG in three pediatric patients with TSC [26]. In the present case, the seizures originated from the cortical T2 hyperintensity lesion, not from the calcified lesion, and the peri-tuber cortex, which appeared normal on MRI, did not show seizure onset activity.

Histopathological findings show that the dysmorphic neurons and balloon cells in FCD type IIb are morphologically similar to the dysmorphic neurons and giant cells of cortical tubers. Thus, making a differential diagnosis can be difficult. Miyata *et al.* described the points of distinction between cortical tubers and FCD type IIb as follows: (1) the matrix reaction is fibrillar and strand-like in cortical tubers, but diffuse and granular in FCD type IIb; (2) the astrocytes have larger nuclei with an uncondensed chromatin structure in cortical tubers, but smaller nuclei with more condensed chromatin in FCD type IIb; and (3) the balloon/giant cells are accompanied by a halo-like artifact around the giant cells in cortical tubers, but there is no halo-like artifact around the balloon cells in FCD type IIb [14]. These pathological features of cortical tubers were also observed in our present case.

A diagnosis of TSC is either based on clinical diagnostic criteria or genetic diagnostic criteria [28]. The clinical diagnostic criteria consist of 11 major and 6 minor features, and cortical tubers are one of the major features. However, a patient with only one major feature is classified as possible TSC, not definite TSC. Among the genetic diagnosis criteria, a TSC1 or TSC2 pathogenic mutation in DNA obtained from normal tissue is sufficient to make a definite diagnosis of TSC. Our present case was classified as possible TSC. Thus, in order to make a definitive diagnosis, genetic testing

should be performed. We are planning to obtain informed consent and perform a genetic test at a future follow-up.

In this article, we presented the case of a solitary cortical tuber mimicking FCD with a transmantle sign and discussed the issues surrounding making a differential diagnosis between the two conditions.

Acknowledgments. The authors acknowledge Dr. Hajime Miyata (Akita Cerebrospinal and Cardiovascular Center) and Dr. Soichiro Fushimi (Himeji Red Cross Hospital) for performing the histological analysis and diagnosis.

References

1. Crino PB, Nathanson KL and Henske EP: The tuberous sclerosis complex. N Engl J Med (2006) 355: 1345–1356.
2. Houser OW and Gomez MR: CT and MR imaging of intracranial tuberous sclerosis. J Dermatol (1992) 19: 904–908.
3. Yagishita A and Arai N: Cortical tubers without other stigmata of tuberous sclerosis: imaging and pathological findings. Neuroradiology (1999) 41: 428–432.
4. Taylor DC, Falconer MA, Bruton CJ and Corsellis JA: Focal dysplasia of the cerebral cortex in epilepsy. J Neurol Neurosurg Psychiatry (1971) 34: 369–387.
5. Siedlecka M, Grajkowska W, Galus R, Dembowska-Bagińska B and Jóźwiak J: Focal cortical dysplasia: Molecular disturbances and clinicopathological classification (Review). Int J Mol Med (2016) 38: 1327–1337.
6. Hirfanoglu T and Gupta A: Tuberous sclerosis complex with a single brain lesion on MRI mimicking focal cortical dysplasia. Pediatr Neurol (2010) 42: 343–347.
7. DiPaolo D and Zimmerman RA: Solitary cortical tubers. AJNR Am J Neuroradiol (1995) 16: 1360–1364.
8. Kalantari BN and Salamon N: Neuroimaging of tuberous sclerosis: spectrum of pathologic findings and frontiers in imaging. AJR Am J Roentgenol (2008) 190: W304–309.
9. Manoukian SB and Kowal DJ: Comprehensive imaging manifestations of tuberous sclerosis. AJR Am J Roentgenol (2015) 204: 933–943.
10. Crino PB: Focal Cortical Dysplasia. Semin Neurol (2015) 35: 201–208.
11. Jansen FE, van Huffelen AC, Algra A and van Nieuwenhuizen O: Epilepsy surgery in tuberous sclerosis: a systematic review. Epilepsia (2007) 48: 1477–1484.
12. Mackay MT, Becker LE, Chuang SH, Otsubo H, Chuang NA, Rutka J, Ben-Zeev B, Snead III OC and Weiss SK: Malformations of cortical development with balloon cells: clinical and radiologic correlates. Neurology (2003) 60: 580–587.
13. Wong M: Mechanisms of epileptogenesis in tuberous sclerosis complex and related malformations of cortical development with abnormal glioneuronal proliferation. Epilepsia (2008) 49: 8–21.
14. Miyata H, Fushimi S, Ota Y, Vinters HV, Adachi K, Nanba E and Akiyama T: Isolated cortical tuber in an infant with genetically confirmed tuberous sclerosis complex 1 presenting with symptomatic West syndrome. Neuropathology (2021) 41: 58–64.
15. Mellerio C, Labeyrie MA, Chassoux F, Roca P, Alami O, Plat M, Naggara O, Devaux B, Meder JF and Oppenheim C: 3T MRI improves the detection of transmantle sign in type 2 focal cortical dysplasia. Epilepsia (2014) 55: 117–122.
16. Colombo N, Tassi L, Deleo F, Citterio A, Bramerio M, Mai R, Sartori I, Cardinale F, Russo GL and Spreafico R: Focal cortical dysplasia type IIa and IIb: MRI aspects in 118 cases proven by histopathology. Neuroradiology (2012) 54: 1065–1077.
17. Lee S, Issa NP, Rose S, Tao JX, Warnke PC, Towle VL, van Drongelen W and Wu S: DC shifts, high frequency oscillations, ripples and fast ripples in relation to the seizure onset zone. Seizure (2020) 77: 52–58.
18. Engel J Jr: Surgical treatment of the epilepsies. 2nd Ed, Raven Press, New York (1993) p 786.
19. Tahta A and Turgut M: Focal cortical dysplasia: etiology, epileptogenesis, classification, clinical presentation, imaging, and management. Childs Nerv Syst (2020) 36: 2939–2947.
20. Samura K, Morioka T, Yoshida F, Hashiguchi K, Miyagi Y, Mizoguchi M, Shono T, Nagata S, Suzuki SO and Sasaki T: Focal cortical dysplasia with calcification: a case report. Childs Nerv Syst (2008) 24: 619–622.
21. Maehara T, Arai N, Shimizu H, Yagishita A and Oda M: Cortical dysplasia with ossification. Epilepsia (2000) 41: 1489–1493.
22. You SJ, Lee JK and Ko TS: Epilepsy surgery in a patient with Lennox-Gastaut syndrome and cortical dysplasia. Brain Dev (2007) 29: 167–170.
23. Colombo N, Tassi L, Galli C, Citterio A, Lo Russo G, Scialfa G and Spreafico R: Focal cortical dysplasias: MR imaging, histopathologic, and clinical correlations in surgically treated patients with epilepsy. AJNR Am J Neuroradiol (2003) 24: 724–733.
24. Bernauer TA: The radial bands sign. Radiology (1999) 212: 761–762.
25. van Eeghen AM, Terán LO, Johnson J, Pulsifer MB, Thiele EA and Caruso P: The neuroanatomical phenotype of tuberous sclerosis complex: focus on radial migration lines. Neuroradiology (2013) 55: 1007–1014.
26. Major P, Rakowski S, Simon MV, Cheng ML, Eskandar E, Baron J, Leeman BA, Frosch MP and Thiele EA: Are cortical tubers epileptogenic? Evidence from electrocorticography. Epilepsia (2009) 50: 147–154.
27. Schwartzkroin PA and Wenzel HJ: Are developmental dysplastic lesions epileptogenic? Epilepsia (2012) 53: 35–44.
28. Northrup H, Krueger DA and International Tuberous Sclerosis Complex Consensus Group: Tuberous sclerosis complex diagnostic criteria update: recommendations of the 2012 Iinternational Tuberous Sclerosis Complex Consensus Conference. Pediatr Neurol (2013) 49: 243–254.