Child's Nervous System (2019) 35:2405–2409
https://doi.org/10.1007/s00381-019-04382-y

CASE REPORT

Non-convulsive status epilepticus in two patients with tuberous sclerosis

Yuksel Erdal[1] · Alper Alnak[2] · Ozgur Oztop[3] · Pınar Tekturk[4] · Zuhal Yapici[4]

Received: 2 July 2019 / Accepted: 20 September 2019 / Published online: 29 October 2019

Abstract

Tuberous sclerosis (TSC) is an autosomal dominantly inherited genetic disorder that chiefly affects the central nervous system, along with the other multiple systems. While phenomenology and symptom severity may vary greatly from one individual to another, the most common neurological presentation is epilepsy, which may be refractory in a considerable number of patients. Convulsive SE is seen frequently in TSC patients due to the high ratio of refractory seizures in well-studied cohorts. Status epilepticus (SE) is a life-threating condition and requires urgent medical care. Non-convulsive status epilepticus (NCSE) is an epileptic state with no convulsive seizures but impaired consciousness and corresponding electrophysiological findings. Due to its heterogeneity of clinical features, it is generally hard to recognize, and thus difficult to treat promptly. The relationship between TSC and NCSE is a relatively less emphasized issue in the literature. Here, we present two cases of TSC with NCSE with a view to increasing clinicians' awareness of the association between refractory epilepsy and NCSE.

Keywords Tuberous sclerosis · Status epilepticus · Non-convulsive status epilepticus · mTOR inhibitors

Introduction

Tuberous sclerosis (TSC) is an autosomal dominant genetic disorder that chiefly affects the central nervous system [6]. Epilepsy is the most common neurological presentation of TSC and affects 72–85% of the patients afflicted by this disease [13]. While early-onset epilepsy usually presents with focal seizures or infantile spasms, all seizure types can be seen clinically, especially in the later periods of the disease and seizures may remain refractory in up to 60% of the patients with TSC. Risk of neurodevelopmental disorders, such as autism spectrum disorder and intellectual disability, seems to be increased in the presence of early-onset epilepsy [8].

✉ Yuksel Erdal
erdalyuksel_355@hotmail.com

[1] Department of Neurology, Health Science University, Istanbul Training and Research Hospital, Istanbul, Turkey

[2] Department of Child and Adolescent Psychiatry, Istanbul Faculty of Medicine, Istanbul University, Istanbul, Turkey

[3] Department of Neurology, Faculty of Medicine, Koc University, Istanbul, Turkey

[4] Division of Child Neurology, Department of Neurology, Istanbul Faculty of Medicine, Istanbul University, Istanbul, Turkey

Drug-resistant epilepsy and, in particular, status epilepticus (SE) are considered as life-threatening neurological conditions. To the best of the authors' knowledge, there are only a few studies and case reports in the literature on SE in TSC patients, and even fewer when it comes to non-convulsive status epilepticus (NCSE) [15]. Here, we present two TSC patients with refractory epilepsy who later developed NSCE and aim to increase clinicians' awareness and draw their attention to this emergency condition.

Case 1

A 9-year-old male patient was brought to the emergency unit with complaints of drowsiness and decreased appetite for days. He had focal motor seizures in his left arm at the 10th day after birth, which was followed by generalized seizures with impaired consciousness, and he was diagnosed with TSC at the age of 1 according to the criteria of this disorder. While his focal motor seizures showed good improvement after sirolimus was added to his medical regimen at the age of 3, he started to have atonic seizures, presenting as head or whole-body drop at the age of 6. Various antiepileptic drugs were used in order to treat his refractory epilepsy during his admissions to emergency units after that age. He was on sirolimus 5 mg/day, sodium valproate 27 mg/kg/

day (bid), clobazam 1 mg/kg/day (bid), topiramate 6 mg/kg/day (bid), and carbamazepine 28 mg/kg/day. Still, he had been suffering from seizures with head dropping concurrent with tonic flexion in his arms twice a day since the previous month. In his neurological examination in the emergency unit, he was in the stupor and unable to communicate verbally with a grimacing response to the painful stimulus. His plantar reflex response was dorsiflexion on the right and flexion on the left. After the initial clinical and laboratory results were obtained, a diagnosis of pneumonia was made, and an antibiotic therapy was started immediately. His skin examination was remarkable for multiple hypopigmented macules over his extremities and trunk and a left-sided forehead fibrous plaque. Multiple tubers showing confluence and bilateral subependymal nodules were identified on his cranial MRI. When compared with the cranial neuroimaging taken 3 years before, the new MRI revealed that his subependymal giant cell astrocytoma (SEGA) volume was significantly reduced after treatment with sirolimus. Electroencephalography (EEG), performed when the patient was in an unconscious state, revealed slow background activity and very frequent groups of tonic bursts and generalizations, which are compatible with NCSE (Fig. 1a). After several consecutive unsuccessful trials of intravenous midazolam, intravenous corticosteroid treatment was started, as it is one of the acute management interventions in epileptic encephalopathy. Over the next 5 days, 25 mg/kg of methylprednisolone was administered daily, and the patient gradually regained consciousness. Apart from focal motor seizures with unimpaired consciousness lasting for 5 s and occurring a few times a day, no other types of seizures were observed during his hospitalization period. EEG performed approximately 1 week after treatment showed almost complete improvement in SE findings (Fig. 1b).

Case 2

An 8-year-old male patient presented with complaints of an increased number of epileptic seizures and impaired consciousness. After an uneventful birth, he started to suffer from focal seizures with either starring or eye deviation at the age of 2 and later had generalized tonic seizures. He was diagnosed with TSC and has been under regular follow-up at the

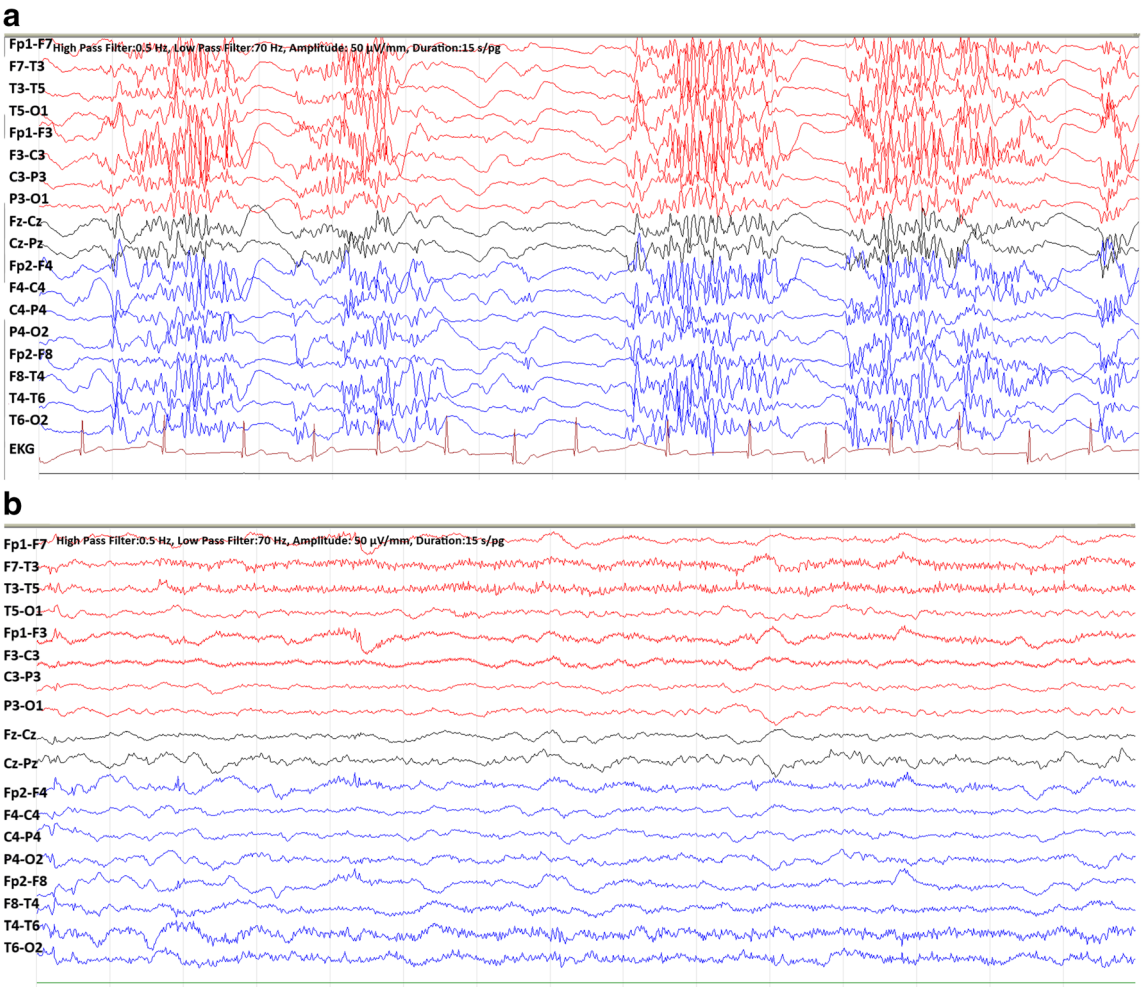

Fig. 1 (Case 1): On EEG, groups of tonic bursts (a) were seen, the epileptic discharges disappeared, and generalized slowing was detected after treatment (b)

Tuberous Sclerosis Unit for the past 4 years. He has been treated with sodium valproate 24 mg/kg/day (bid), levetiracetam 30 mg/kg/day (bid), and oxcarbazepine 30 mg/kg/day (bid), including everolimus 8 mg/day for the last 2 years. He still had seizures with head drop together with flexor spasms of the extremities lasting up to 2–3 min and occurring more than several times a day during the previous month. His vital signs and blood test results were within normal limits, and no triggering factor, such as an infection or non-compliance with medication, was identified. His skin examination was unremarkable other than adenoma sebaceum. In his neurological examination, he was confused, non-cooperative, and unable to respond verbally. Spontaneous movements of arms and limbs were observed. Plasma valproate level, complete blood count, liver function, and renal function test results as well as plasma electrolyte levels were within normal ranges. His cranial MRI revealed multiple tubers in bilateral frontoparietal lobes, subependymal nodules at the level of lateral ventricles, and 15 × 5.5 mm lesion at the level of left caudate compatible with SEGA. The awake and sleep EEG showed multiple epileptogenic foci together with severe widespread disorganization and almost continuous generalized epileptiform anomaly, which was compatible with NCSE (Fig. 2a). Because there was no response to intravenous midazolam therapy, 16 mg/kg/day intravenous methylprednisolone treatment was started. Over two consecutive days following this intervention, the patient gradually regained full consciousness. Apart from two seizures with starring lasting for 10 s, no other seizures were observed during his 2-week hospitalization. EEG performed in the first week after the treatment made it certain that there was an almost complete improvement in electrophysiological findings (Fig. 2b).

Discussion

Tuberous sclerosis is an autosomal dominantly inherited, multi-system disease, typically caused by mutations in TSC1

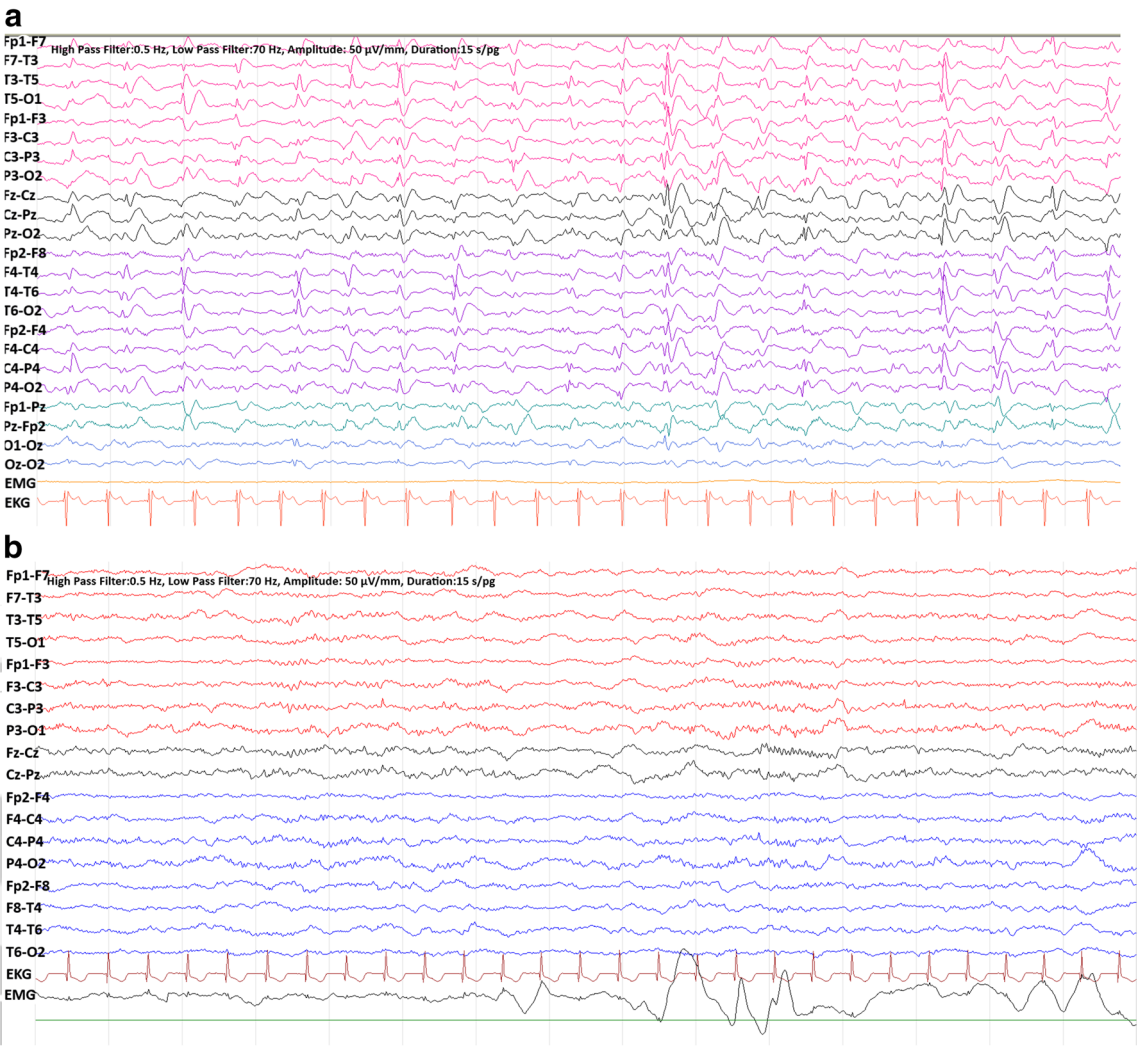

Fig. 2 (Case 2): Generalized epileptiform discharges together with multifocal activity are seen on EEG (**a**) and resolution of generalized sharp-wave activity after treatment (**b**)

or TSC2 genes [14]. The disease most commonly affects the central nervous system (CNS) of the vast majority of the patients (presumably more than 90%). It is thought that epilepsy and some other neuropsychiatric conditions are associated with various CNS lesions, namely cortical or subcortical tubers, subependymal nodules, SEGA, and white matter migration lines [6]. Both of our patients meet the major criteria of TSC, for they have multiple tubers, subependymal nodules, and SEGA, as well as skin findings. SEGA identified in case 1 at the lateral side of foramen Monroe on the cranial MRI taken 3 years ago disappeared after treatment with sirolimus. As far as psychiatric comorbidity is concerned, case 1 was previously diagnosed with autism spectrum disorder and moderate-level intellectual disability, while case 2 was found to have attention deficit hyperactivity disorder and mild-level intellectual disability.

Epilepsy is the most common neurological symptom in TSC with a prevalence of up to 85% of patients. Two-thirds of the seizures start at the first year of life in the form of focal seizures or infantile spasms [3]. More than 60% of the seizures remain refractory to various treatments, including antiepileptic medications, epilepsy surgery, ketogenic diet, and vagal nerve stimulation [8]. Both cases 1 and 2 presented with focal seizures. Over time, however, the former case developed atonic and tonic seizures and the latter developed tonic seizures with impaired consciousness. Since seizures remain uncontrolled despite multiple medical treatments, the condition is considered as refractory epilepsy.

SE is a clinical condition that requires urgent medical care in children since it is associated with a considerable amount of cognitive, neurological, and behavioral morbidities and mortalities [9]. The most common risk factors for epileptic seizures to progress into SE include, but are not limited to, nonadherence to treatment, sleep deprivation, fatigue, and infections. Some other individual factors, such as intellectual disability and having symptomatic epilepsy rather than idiopathic, may further increase the risk of SE in general [16]. When all these factors are taken into consideration, the risk of SE in our TSC patients seems to have already increased. NCSE is a clinical condition in which impairment of consciousness may vary from confusion to coma without convulsive phenomenon and in which electrophysiological characteristics are consistent with an epileptic state. Recognition and diagnosis of NCSE may be difficult since the contributing factors in its etiology and EEG characteristics may vary greatly [11]. Studies have demonstrated that 20% of all adult SE cases have NCSE. However, there are not enough studies to show its frequency in pediatric population. Frequency of NCSE following an epileptic state is reported to be 16–27% [1], and metabolic disorders, infections, drugs, toxins, acute brain lesions, and presence of previous epilepsy are considered as the main etiological factors of NCSE [11]. Of the relatively few studies on NCSE in patients with TSC, one reports that 7 (21.9%) of the 32 SE episodes were NCSE [15]. In another study conducted by Kuki et al., five patients with SEGA treated with everolimus were followed over 12 months, and febrile epileptic status was observed in 3 [10].

TSC 1 and TSC 2 play a regulatory role in the mTOR pathway, which is crucial in tumoral cell proliferation and energy metabolism, as well as cortical development and growth control [5]. Pathogenic role of dysregulations of mTOR pathway signaling has been associated with numerous neurological and neuropsychiatric disorders, such as epilepsy, autism spectrum disorder, intellectual disability, neurodegenerative disorders, and even some epileptic syndromes [4]. Sirolimus (rapamycin) and everolimus are mTOR inhibitors, which inhibit mTOR signaling by reducing the phosphorylation of mTOR effectors [7]. Findings of EXIST-3 (Examining Everolimus in a Study of Tuberous Sclerosis Complex) have indicated that therapeutic effect of everolimus on refractory focal seizures associated with TSC in children above 2 years old is very promising [8]. Seizures in case 1 improved significantly for a period of more than 3 years; however, their frequency increased thereafter with a changing phenomenology. Here, pneumonia was identified as a triggering factor for the development of NCSE. In case 2, however, everolimus treatment over 2 years did not produce any considerable effect on tonic and atonic seizures, and no identifiable triggering factor was found for NCSE. Though the effect of everolimus on focal seizures has been proven, there is still a need for further studies that will investigate whether treatment with this medicine is worthwhile as far as tonic, atonic, and other secondary generalized polymorphic seizures are concerned. Refractory epilepsy and intellectual disability are expected to be more common among patients carrying mutations in TSC 2 than among those with mutations in TSC 1. Nevertheless, we lack the necessary genetic information related to our patients that may authorize us to comment on or discuss this issue. We would like to stress that, to the best of the authors' knowledge, there are few, if any, studies that have examined how different mutations within the same gene effect clinical manifestation individually. Such studies may shed light on different subtypes of mTOR signaling pathway in epileptogenesis.

Pulse steroid therapy may be a useful and well-tolerated option when antiepileptic drugs fail in intractable epilepsy [2, 12]. Steroids, in particular adrenocorticotropic hormone (ACTH), have been frequently used in children especially with infantile spasm**.** Furthermore, although there is no data on optimal usage, the efficacy of high-dose steroid therapy has been demonstrated in epileptic encephalopathies [12]. Both of our patients were using multiple antiepileptic drugs together with mTOR inhibitor, and they were in therapeutic range**.** Clinical and electrophysiological improvement was clearly observed in both patients after pulse methylprednisolone treatment.

In conclusion, NCSE is an underdiagnosed condition, especially when seen in conjunction with other systemic diseases. It is important to recognize NCSE, for it impairs consciousness and causes electrophysiological dysfunction but responds to appropriate treatments. Of note, the frequency of NCSE may be higher than expected in patients with refractory epilepsy associated with TSC. Thus, NCSE should be kept in mind whenever a TSC patient with impaired consciousness is encountered for the first time or during the treatment process, and electrophysiological evaluation should be considered as a standard of care.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Akman CI (2010) Nonconvulsive status epilepticus and continuous spike and slow wave of sleep in children. Semin Pediatr Neurol 17(3):155–162
2. Almaabdi KH, Alshehri RO, Althubiti AA et al (2014) Intravenous methylprednisolone for intractable childhood epilepsy. Pediatr Neurol 50:334–336
3. Chu-shore CJ, Major P, Camposano S, Muzykewicz D, Thiele EA (2011) The natural history of epilepsy in tuberous sclerosis complex. Epilepsia 51(7):1236–1241
4. Crino PB (2016) The mTOR signalling cascade: paving new roads to cure neurological disease. Nat Rev Neurol 12(7):379–392
5. Curatolo P, Jóźwiak S, Nabbout R (2012) Management of epilepsy associated with tuberous sclerosis complex (TSC): clinical recommendations. Eur J Paediatr Neurol 16(6):582–586
6. Curatolo P, Moavero R, De Vries PJ (2015) Neurological and neuropsychiatric aspects of tuberous. Lancet Neurol 14(7):733–745
7. Curatolo P, Nabbout R, Lagae L et al (2018) Management of epilepsy associated with tuberous sclerosis complex: updated clinical recommendations. Eur J Paediatr Neurol 22(5):738–748
8. French JA, Lawson JA, Yapici Z et al (2016) Adjunctive everolimus therapy for treatment-resistant focal-onset seizures associated with tuberous sclerosis (EXIST-3): a phase 3, randomised , double-blind , placebo-controlled study. Lancet 6736(16):1–11
9. Jafarpour S, Stredny CM, Piantino J, Chapman KE (2018) Baseline and outcome assessment in pediatric status epilepticus. Seizure 68: 52–61
10. Kuki I, Kawawaki H, Okazaki S, Ehara E, Yoshida Y, Kunihiro N, Matsusaka Y (2018) Efficacy and safety of everolimus in patients younger than 12 months with congenital subependymal giant cell astrocytoma. Brain and Development 40(5):415–420
11. Maganti R, Gerber P, Drees C, Chung S (2008) Nonconvulsive status epilepticus. Epilepsy Behav 12:572–586
12. Pera MC, Randazzo G, Masnada S et al (2015) Intravenous methylprednisolone pulse therapy for children with epileptic encephalopathy. Funct Neurol 30(3):173–179
13. Savini MN, Mingarelli A, Vignoli A et al (2018) Ictal signs in tuberous sclerosis complex : Clinical and video-EEG features in a large series of recorded seizures. Epilepsy Behav 85:14–20
14. Schubert-bast S, Rosenow F, Martin K, Reif PS, Kieslich M, Strzelczyk A (2018) The role of mTOR inhibitors in preventing epileptogenesis in patients with TSC: current evidence and future perspectives. Epilepsy Behav 91:94–98
15. Shehata HS, Abdel Ghaffar HM, Nasreldin M, Elmazny A, Abdelalim A, Sabbah A, Shalaby NM (2017) Clinical patterns and outcomes of status epilepticus in patients with tuberous sclerosis complex. Ther Clin Risk Manag 13:779–785
16. Trinka E, Cock H, Hesdorffer D et al (2015) A definition and classification of status epilepticus–report of the ILAE Task Force on Classification of Status Epilepticus. Epilepsia 56(10):1515–1523