CASE REPORT

A Case of Tuberous Sclerosis Presenting with Gelastic Seizures

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Received on: 06 April 2023; *Accepted on*: 10 June 2023; *Published on*: 21 December 2023

Abstract

Gelastic seizures (GS), an uncommon epileptic seizure type, have been described as the hallmark of seizures arising from the hypothalamus, with hypothalamic hamartoma (HH) being the frequent underlying pathology. These are mostly seen in children as intractable seizures with sudden outbursts of unprovoked stereotyped laughter as the main ictal manifestation, commonly in association with precocious puberty, behavioral disturbances, and cognitive impairment. Gelastic seizures are also seen with complex partial seizures of the frontal or temporal lobe as well as the cingulate gyrus with or without radiologically evident structural lesions.

Herein, we present a child with tuberous sclerosis complex (TSC) who presented with GS not associated with HH.

Keywords: Case report, Cortical tubers, Gelastic seizure, Tuberous sclerosis complex.

Bengal Physician Journal (2023): 10.5005/jp-journals-10070-8011

Case Description

A 13-year-old girl, born out of nonconsanguineous marriage with normal birth and development without antecedents, presented with recurrent seizures since 7 years of age. Seizure semiology is characterized by behavioral arrest, screaming with fidgetiness and giggling followed by uncontrolled laughter, leading to generalized tonic–clonic seizures associated with uprolling of eyeballs and frothing from the mouth (Supplementary Video 1). The frequency was 6–7 episodes per day and each episode lasting for 5–10 minutes. There are no behavioral or cognitive disturbances. No family history of seizures. She had facial adenoma sebaceum (Fig. 1). Electroencephalography (EEG) showed interictal epileptiform abnormalities in bilateral frontotemporal regions (Fig. 2). Magnetic resonance imaging (MRI) brain showed nonenhancing foci of T2 hyperintensities in the right frontal lobe in the parasagittal location and left precentral gyrus suggestive of cortical tubers (Fig. 3), and on CT correlation, subependymal calcified tubers were noted (Fig. 4).[1,2]

Discussion

Tuberous sclerosis complex (TSC), also known as Bourneville–Pringle disease, was characterized by classic clinical triad of adenoma sebaceum, seizure, and mental retardation. It is an autosomal-dominant, multiorgan disease with the presence of dysgenic and hamartomatous lesions in multiple organs with highly variable phenotypic expressions. Mutations were found in one of the two genes, the *TSC1* gene located on chromosome 9p34 encoding *hamartin* and the *TSC2* gene located on chromosome 16p13 encoding *tuberin* protein. Both proteins are inhibitors of the mammalian target of rapamycin (mTOR) signaling cascade. Loss of this function lead to disorganized arrangement of neurons in the cerebral cortex with cortical defects and tubers along with subependymal nodules and also hamartomas such as facial angiofibromas (adenoma sebaceum), shagreen patches, cardiac rhabdomyoma, renal angiomyolipomas, and pulmonary lymphangioleiomyomatosis.

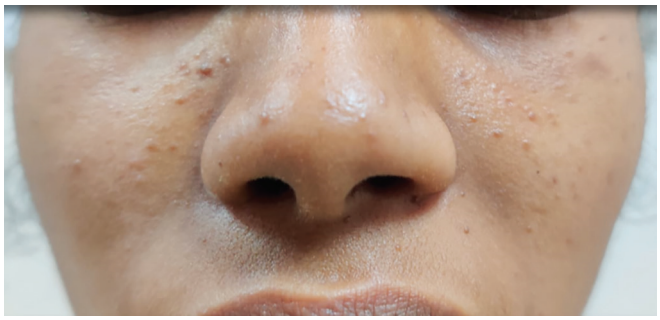

Fig. 1: Adenoma sebaceum

Brain is frequently affected in TSC with epilepsy being the most common symptom affecting 80–90% of patients with infantile spasms or simple or complex partial seizures and one-fourth of the patients may present with Lennox–Gastaut syndrome. *Electroencephalography* abnormalities were seen in 75% of patients. The literature on TSC with GS is very limited. A case report of Cook

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How to cite this article: Srinivas NPS, Jeyaraj M, Velayudham S, *et al*. A Case of Tuberous Sclerosis Presenting with Gelastic Seizures. Bengal Physician Journal 2023;10(3):99–101.

Source of support: Nil

Conflict of interest: None

Patient consent statement: The author(s) have obtained written informed consent from the patient's parents/legal guardians for publication of the case report details and related images.

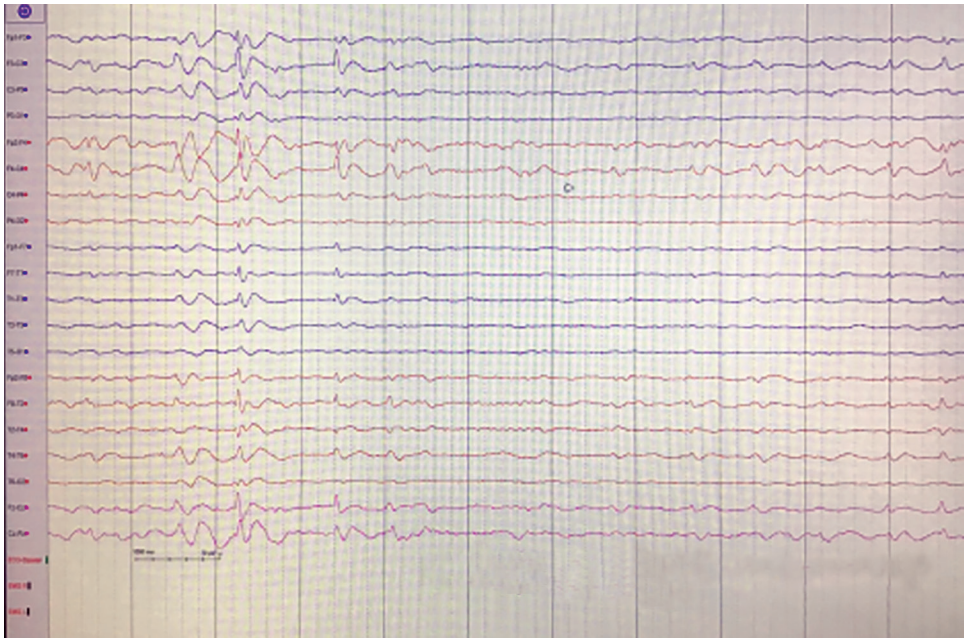
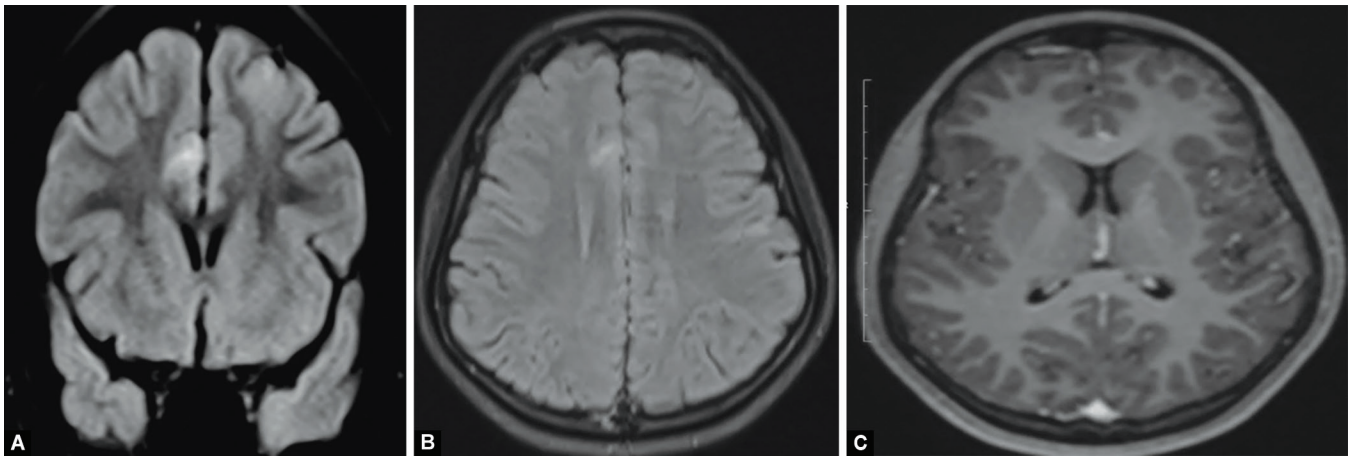
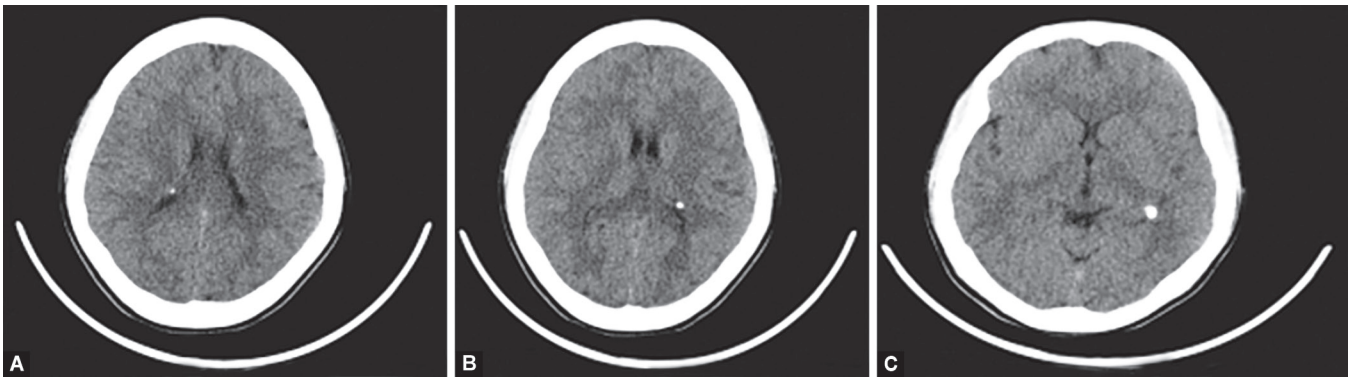


Fig. 2: Interictal EEG showing B/L Frontotemporal spikes



Figs 3A to C: (A) MRI brain axial section showing T2/FLAIR hyperintensity in right frontal lobe in the parasagittal location; (B) MRI brain coronal section showing T2/FLAIR hyper intensity in right frontal lobe in the parasagittal location and left precentral gyrus s/o cortical tubers; and (C) CE MRI brain showing no enhancement of the lesions



Figs 4A to C: CT brain showing subependymal calcified tubers in the lateral ventricles

and Joshi stated that only two cases of TSC with GS have been reported before.[3]

Gelastic seizures are brief, usually 5–20 seconds in duration and frequent, typically multiple episodes in a day, characterized by unprovoked spells of smile or laughter (with or without a mirth), sometimes associated with crying episodes (dacrystic seizures with or without sobbing), and it may progress to have generalized tonic–clonic seizures. Gelastic seizures may be associated with pathology elsewhere in the brain that may or may not be visible in MRI (lesional or nonlesional GS), but are most commonly associated with hypothalamic hamartoma (HH). Recent reports have indicated that there is extrahypothalamic epileptogenesis in cases of HH, which is facilitated by the plethora of connections between the hypothalamus and other brain areas.[4]

The division of the anatomical separation of emotionally driven mirth (localized to the temporal lobe, amygdala, thalamus, and hypothalamus), from the motor act of laughter (localized to the frontal lobe, cingulated gyrus, and brain stem), was first postulated by *Gascon* and *Lombroso*.[5] However, a clear anatomic pathway for laughter still remains unclear.

Gelastic seizures due to HH are often brief, without loss of consciousness, preceded by an aura, and not associated with multiple seizure types. Patients of HH were often present with pharmacoresistant epilepsy with an associated history of precocious puberty. Whereas GS of the fronto-temporal origin are usually longer in duration and associated with multiple seizure types. In our case, the patient had no aura, and GS were associated with secondary generalized tonic–clonic seizures.

Epilepsy is often refractory in two-thirds of the TSC patients. However, nearly one-third of the patients show improvement through medical management, surgical intervention, or through the natural course of the disease. A study done by Giulia Iapadre et al. showed that patients with nonlesional GS have a more favorable outcome with better drug response, less need for polytherapy, and good long-term prognosis.[6] The existence of an independent, secondary epileptogenic area with persistent seizures after resection of the presumably primary lesion in cases of HH could be related to either an extrahypothalamic structural lesion (visible on MRI or on neuropathology) or to a functional alteration with enhanced epileptogenic properties where the patient needs two-step surgery for better results.[4] In our case, GS are of extrahypothalamic origin and are well-controlled with the regimen of lamotrigine, levetiracetam, and clobazam.

Conclusion

Majority of GS are of hypothalamic origin, however, extrahypothalamic GS and cryptogenic GS have also been reported. A secondary extrahypothalamic epileptogenesis resulting in independent secondary epileptogenic foci in patients of HH has also been described in the literature. There is a lack of clear knowledge about the anatomical pathways of laughter; however, the emotional aspect of laughter is localized to the basal–temporal lobe and the motor act of laughter to the frontal lobe. The seizures in TSC are often diverse with multiple types of seizure semiologies, but presentation with GS is a rare phenomenon. Our patient was diagnosed to have TSC with multiple cortical tubers and presented with GS and they are not associated with HH. There is a greater tendency to develop drug-resistant epilepsy in TSC patients. Planning for surgery in TSC is challenging due to the presence of multiple tubers and difficulty in identifying the exact epileptogenic area that may include an altered cortex around the tuber. Hence, the trial of combination of multiple antiepileptic medications and/or mTOR inhibitors, keto diet, or neuromodulation therapy is prudent in most of the cases of TSC.

Supplementary Material

Supplementary Video 1 showing gelastic seizures is available online on the website of www.apibpj.com.

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