Received: 5 January 2026 | Accepted: 11 March 2026

DOI: 10.1002/epd2.70229

Epileptic Disorders

CLINICAL VIGNETTE

Epileptic encephalopathy with spike-and-wave activation in sleep associated with Tatton–Brown–Rahman syndrome responsive to highly purified cannabidiol

Anita N. Datta

Division of Neurology, Department of Pediatrics, BC Children's Hospital, Faculty of Medicine, University of British Columbia, Vancouver, British Columbia, Canada

Correspondence
Anita N. Datta, Department of Pediatrics, BC Children's Hospital, University of British Columbia, 4480 Oak Street, Vancouver V6H 3N1, BC, Canada.
Email: anita.datta@cw.bc.ca

Tatton-Brown–Rahman syndrome (TBRS) is a congenital overgrowth disorder caused by *DNMT3A* mutations, marked by overgrowth and intellectual disability, with variable features including facial dysmorphism, hypotonia, autism, psychiatric comorbidities, orthopedic, and cardiac abnormalities.[1] Approximately 20% of affected individuals have epilepsy; however, as TBRS was first described in 2014, seizure-related data remain limited.[2] Here, we describe a 10-year-old patient with TBRS, confirmed by whole-exome sequencing, and developmental and epileptic encephalopathy with spike-and-wave activation in sleep (DEE-SWAS), who demonstrated an electroclinical response to cannabidiol (Epidiolex).

The patient was born at term after an uncomplicated pregnancy and later showed developmental delay, walking at 15 months with ongoing coordination and fine motor difficulties. Early language milestones were appropriate, with 50 words and two-word phrases by 24 months and sentence speech by 3 years. Growth parameters were consistently greater than the 90th percentiles. Examination revealed hypotonia, joint hypermobility, and facial features consistent with TBRS.

At 2.5 years, she developed focal impaired consciousness seizures associated with throat clearing and left facial and arm clonic movements, sometimes progressing to bilateral tonic–clonic seizures. EEG showed occasional bilateral central-parietal epileptiform discharges in awake and sleep states (EEGs are depicted in Figure 1). Brain MRI demonstrated incomplete right hippocampal inversion (Figure 2).

By 3.5 years, seizures increased to monthly frequency, and sleep EEG showed >80% bilateral centrotemporal–parietal spike-and-wave activity consistent with DEE-SWAS. Neuropsychological testing revealed mild intellectual disability. Multiple antiseizure medications (clobazam, sulthiame, ethosuximide) were ineffective or poorly tolerated, accompanied by marked developmental regression, including loss of sphincter control, fine motor and gait skills, and language decline from sentences to single words, with overall functioning approximating a 2-year level.

Clinical seizure freedom was achieved by age 6 years with divalproex sodium and lamotrigine; however, DEE-SWAS persisted and developmental progress remained limited. By ages 7–8 years, she functioned at a 4-year-old level despite ongoing supports.

At 9.5 years, cannabidiol (10 mg/kg/day) was initiated. Within 5 months, marked cognitive and language improvements were noted, including increased alertness, situational awareness, and use of short phrases rather than single words. Ambulatory EEG showed complete DEE-SWAS resolution at 5 and 17 months. Neuropsychological testing, 10 months after DEE-SWAS resolution, demonstrated moderate intellectual disability, suggesting

This work has not been presented at a meeting or conference.

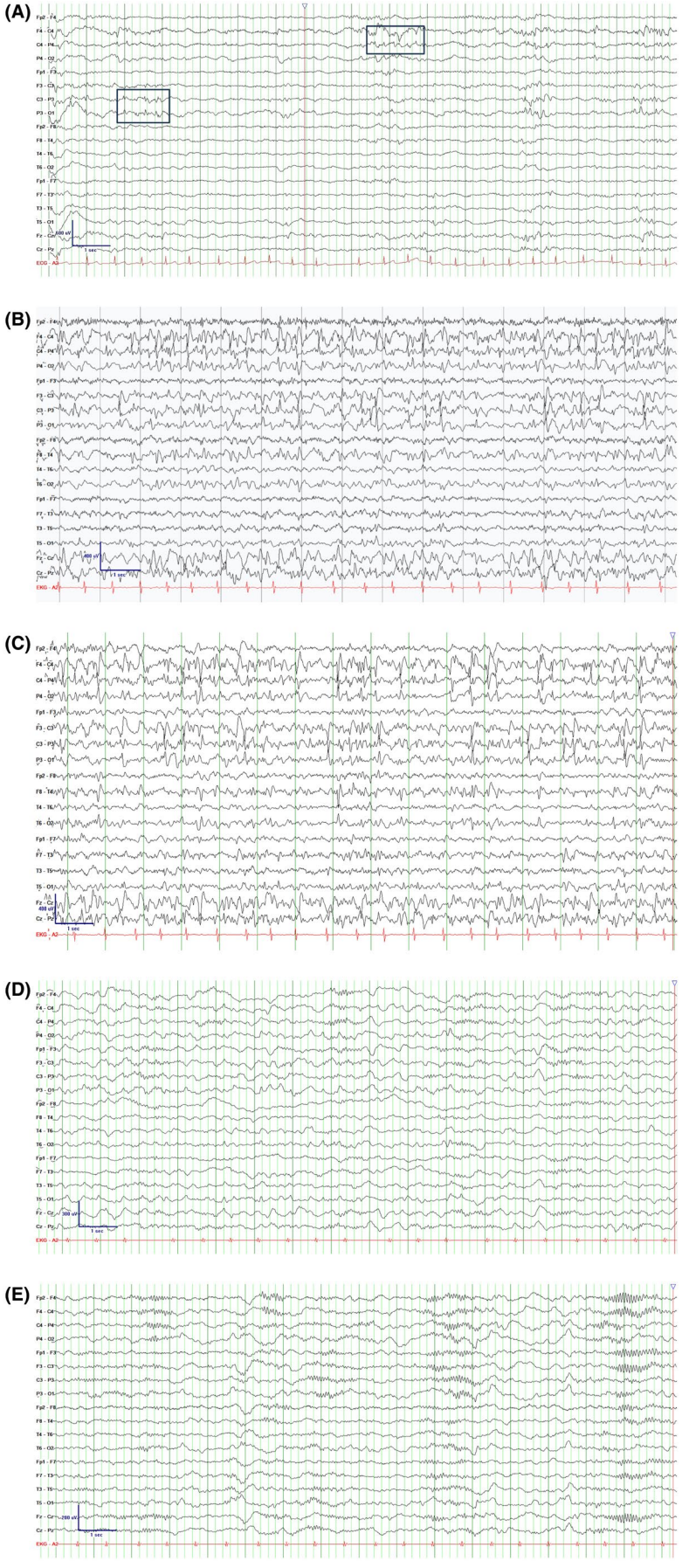
(A)
(B)
(C)
(D)
(E)

FIGURE 1 Evolution of sleep (N1/N2) EEG patterns over time in DEE-SWAS. For all EEG tracings: Low frequency filter = .5 Hz and High frequency filter = 70 Hz. (A) Age 2.5 years: New-onset focal seizures. Occasional spikes and sharp waves in the bilateral centroparietal regions during sleep (e.g., highlighted in boxes). Routine EEG; Longitudinal bipolar montage; paper speed 30 mm/s. Medications: None. (B) Age 3.5 years: Nearly continuous 1.5–2 Hz bilateral centrotemporal–parietal spike-and-wave complexes in non-rapid eye movement sleep, associated with developmental regression. Ambulatory EEG; Longitudinal bipolar montage; paper speed 30 mm/s. Medications: Clobazam (1 mg/kg) and sulthiame (20 mg/kg). (C) Age 9 years: Persistent, nearly continuous 1.5–2 Hz bilateral centrotemporal–parietal spike-and-wave complexes in non-rapid eye movement sleep, associated with minimal developmental gains. Ambulatory EEG; Longitudinal bipolar montage; paper speed 30 mm/s. Medications: Valproic acid (25 mg/kg) and lamotrigine (3 mg/kg). (D) Age 9.5 years: Cannabidiol initiated. No epileptiform discharges during sleep, with re-emergence of sleep spindles. Findings indicate resolution of DEE-SWAS, accompanied by parent reported developmental improvement. Ambulatory EEG; longitudinal bipolar montage; paper speed 30 mm/s. Medications: Cannabidiol (10 mg/kg), valproic acid (25 mg/kg), and lamotrigine (3 mg/kg). (E) Age 10.5 years: Continued therapy with cannabidiol, valproic acid, and lamotrigine. No epileptiform discharges during sleep, with preserved sleep spindles and vertex waves. Sustained resolution of DEE-SWAS with ongoing developmental improvement reported by parents. Ambulatory EEG; Longitudinal bipolar montage; paper speed 30 mm/s. Medications: Cannabidiol (10 mg/kg), valproic acid (22 mg/kg), and lamotrigine (2 mg/kg).

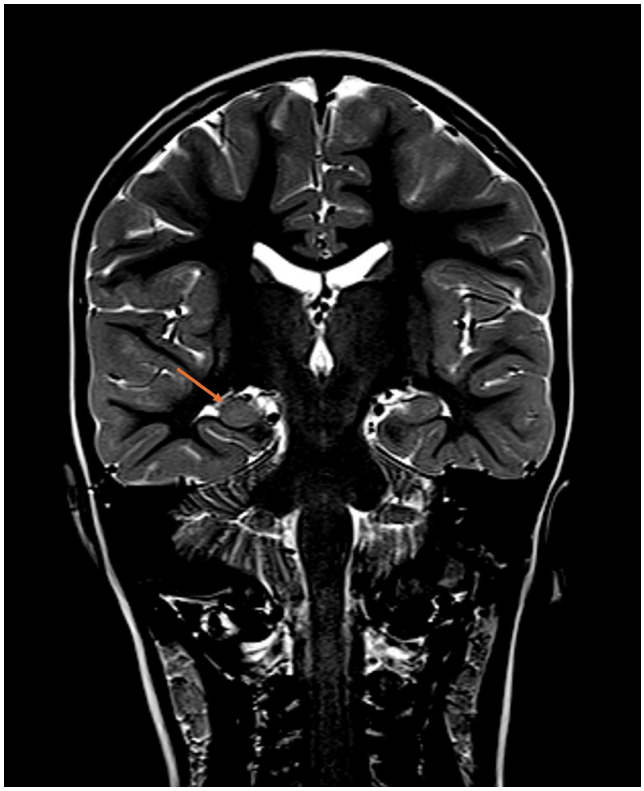

FIGURE 2 MRI brain. Coronal T2-weighted brain MRI demonstrating a rounded configuration of the right hippocampus (depicted by arrow) compared with the left, consistent with incomplete hippocampal inversion.

cumulative neurodevelopmental impact of prolonged DEE-SWAS. She continues to have gross and fine motor difficulties but now participates in therapeutic horseback riding and attends full school days with support.

This case demonstrates cannabidiol response in TBRS-associated DEE-SWAS, underscoring the epileptic burden in overgrowth–intellectual disability syndromes and potential for mechanism-based therapies. Resolution of DEE-SWAS suggests cannabidiol effects beyond seizure suppression alone. Given TBRS is newly recognized, seizure prevalence and characteristics may be underestimated.[1] The Overgrowth Syndromes Alliance (2023) identified seizures as a high-priority shared challenge, with diagnostic delays often attributable to limited phenotype characterization.[2] In TBRS, patients typically demonstrate relatively preserved verbal abilities compared with nonverbal reasoning.[3] Therefore, our patient's language decline was atypical and attributable to DEE-SWAS.

TBRS is caused by pathogenic variants in *DNMT3A*, encoding DNA methyltransferase 3A, a key regulator of DNA methylation during neurodevelopment. Haploinsufficiency likely results in global hypomethylation and dysregulated gene expression. Epigenetic regulatory genes have increasingly been implicated in epilepsy, with DNA methylation changes contributing to epileptogenesis, neuroinflammation, ion channel dysfunction, and altered synaptic plasticity.[4]

To our knowledge, there are no prior reports of cannabidiol efficacy in *DNMT3A*-related epilepsy or TBRS-associated DEE-SWAS. However, cannabidiol has benefited a small number of patients with DEE-SWAS.[5–7] Cannabidiol may act through reduced hyperexcitability (via GPR55 inhibition, TRPV1 desensitization, and adenosine reuptake blockade) and anti-inflammatory effects mediated by CB2 receptor interactions that lower TNF-α and IL-6.[6] Given that DEE-SWAS often responds to corticosteroids and is associated with elevated inflammatory cytokines (TNF-α, IL-6, IL-1α), an immune-mediated component is likely.[8] Notably, cannabidiol induces epigenomic changes, as one study demonstrated thousands of differentially methylated loci identified in the mouse hippocampus after short-term exposure, affecting genes involved in synaptic function and neurodevelopment.[9] These effects raise the possibility that cannabidiol may partially counteract methylation dysregulation due to *DNMT3A* haploinsufficiency. Notably, valproic acid, a

histone deacetylase inhibitor, helped control clinical seizures.[10]

This report broadens the TBRS seizure phenotype and supports further investigation of cannabidiol for DEE-SWAS, including its potential as a mechanism-informed therapy in TBRS and other disorders of chromatin remodeling and DNA methylation.

FUNDING INFORMATION

The author has nothing to report.

CONFLICT OF INTEREST STATEMENT

The author has received speaker honoraria from Jazz Pharmaceuticals. She has served on an advisory board for Knight and Acadia Pharmaceuticals. The author declares no other conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

PATIENT CONSENT

The patient provided consent to publish the case.

ORCID

Anita N. Datta https://orcid.org/0000-0001-7620-4868

REFERENCES

1. Tatton-Brown K, Zachariou A, Loveday C, Renwick A, Mahamdallie S, Aksglaede L, et al. The Tatton-Brown-Rahman syndrome: a clinical study of 55 individuals with de novo constitutive DNMT3A variants. Wellcome Open Res. 2018;3:46.
2. Grens K, Church KM, Diehl E, Hunter SE, Tatton-Brown K, Kiernan J, et al. Epilepsy and overgrowth-intellectual disability syndromes: a patient organization perspective on collaborating to accelerate pathways to treatment. Ther Adv Rare Dis. 2024;5:4123.
3. Lane C, Tatton-Brown K, Freeth M. Tatton-Brown-Rahman syndrome: cognitive and behavioural phenotypes. Dev Med Child Neurol. 2020;62:993–8.
4. Forero DA. Functional genomics of Epileptogenesis in animal models and humans. Cell Mol Neurobiol. 2021;41:1579–87.
5. Ferrera G, Ricci E, Peron A, Parrini E, Vignoli A, Canevini MP. Continuous spike-wave of slow sleep in a patient with KCNB1-related epilepsy responsive to highly purified cannabidiol: a case report and comparison with literature. Neurocase. 2024;30:68–72.
6. Szaflarski JP, Hernando K, Bebin EM, Gaston TE, Grayson LE, Ampah SB, et al. Higher cannabidiol plasma levels are associated with better seizure response following treatment with a pharmaceutical grade cannabidiol. Epilepsy Behav. 2019;95:131–6.
7. Caraballo R, Reyes G, Demirdjian G, Huaman M, Gutierrez R. Long-term use of cannabidiol-enriched medical cannabis in a prospective cohort of children with drug-resistant developmental and epileptic encephalopathy. Seizure. 2022;95:56–63.
8. van den Munckhof B, de Vries EE, Braun KP, Boss HM, Willemsen MA, van Royen-Kerkhof A, et al. Serum inflammatory mediators correlate with disease activity in electrical status epilepticus in sleep (ESES) syndrome. Epilepsia. 2016;57:e45–e50.
9. Wanner NM, Colwell M, Drown C, Faulk C. Subacute cannabidiol alters genome-wide DNA methylation in adult mouse hippocampus. Environ Mol Mutagen. 2020;61:890–900.
10. Romoli M, Mazzocchetti P, D'Alonzo R, Siliquini S, Rinaldi VE, Verrotti A, et al. Valproic acid and epilepsy: from molecular mechanisms to clinical evidences. Curr Neuropharmacol. 2019;17:926–46.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Datta AN. Epileptic encephalopathy with spike-and-wave activation in sleep associated with Tatton–Brown–Rahman syndrome responsive to highly purified cannabidiol. Epileptic Disord. 2026;28:1285–1289. https://doi.org/10.1002/epd2.70229

Test yourself

1. Cannabadiol has an antiseizure effects via all of the following mechanisms, except:
   A. GPR55 inhibition
   B. TRPV1 desensitization
   C. Adenosine reuptake inhibition
   D. Voltage-gated sodium channel inhibition
2. Which of the following statements regarding TBRS-related epilepsy are FALSE?
   A. As TBRS is a recently recognized disorder, further characterization of seizure phenotypes is needed.
   B. Patients may experience multiple and variable seizure types.
   C. Seizures occur in approximately 20% of individuals with TBRS.
   D. DEE-SWAS is commonly reported in patients with TBRS.
3. Which of the following statements regarding cannabidiol and epilepsy is CORRECT?
   A. Cannabidiol has not previously been shown to be effective in patients with DEE-SWAS.
   B. Published data demonstrate the efficacy of cannabidiol only in Lennox–Gastaut syndrome, tuberous sclerosis complex, and Dravet syndrome.
   C. Randomized controlled trials exist evaluating cannabidiol across multiple forms of developmental and epileptic encephalopathies.
   D. Based on its mechanism of action, cannabidiol may reduce a broad range of seizure types.

Answers may be found in the supporting information.