Vigabatrin-associated Reversible MRI Abnormalities in an Infant with Tuberous Sclerosis

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ABSTRACT

Vigabatrin therapy is commonly used in infants diagnosed with tuberous sclerosis complex, particularly in the setting of epilepsy. Utilization of vigabatrin can result in bilateral and symmetric abnormal sequence changes within the deep brain matter and brainstem on magnetic resonance imaging. These abnormalities occur predominantly in infancy, are reversible, and can be asymptomatic or result in symptomatic clinical manifestations. We present a case with classic neuroimaging findings. Familiarity with these findings can prevent unnecessary follow up tests or studies and the cost of continuing or discontinuing vigabatrin therapy should be weighed heavily against the potential manifestation of extrapyramidal symptoms.

CASE REPORT

CASE REPORT

During a previously unremarkable pregnancy, a 34-week-old male fetus was discovered to have cardiac rhabdomyomas on prenatal ultrasound. After an uneventful full-term delivery, postnatal ultrasound revealed a cyst in the right kidney. A subsequent Magnetic Resonance Image (MRI) of the brain demonstrated multiple subependymal nodules and several scattered cortical tubers, diagnostic of Tuberous Sclerosis Complex (TSC).

The patient displayed unremarkable psychomotor development until the fourth month of life, when he exhibited several documented episodes of right arm extension, head tilting to the right, and short arrest of motor activity lasting about one minute at a time—compatible with complex partial seizures. Due to the refractory nature of these complex partial seizures to conventional antiepileptic treatment, the patient was enrolled in a randomized, double-blind seizure prevention clinical trial for infants with TSC. At the time, vigabatrin (VGB) treatment was initiated with progressive doses reaching 150mg/kg/day.

The patient did not experience any additional generalized seizures upon the initiation of VGB until ten months of age, whereupon a routine electroencephalogram (EEG) recorded seizures with breakthrough events, for which the patient was admitted to the hospital for continuous video EEG to determine seizure frequency. A follow-up MRI near discharge revealed a symmetric pattern of diffusion restriction involving the bilateral thalami, subthalamic nuclei, central tegmental tracts and dentate nuclei (Figure 1).

In light of these classic findings, vigabatrin-associated brain abnormalities on MRI were suspected. Despite achieving a low-normal serum value of VGB at the time of discharge of 24.5 ug/mL, (normal 20-160 ug/mL), the decision was made by the clinical team to reduce the patient's dose to

100mg/kg/day. The patient did not experience any additional seizures over the course of nine months, when a follow-up MRI of the brain showed resolution of the previously seen lesions involving the aforementioned regions (Figure 2).

DISCUSSION

Vigabatrin

TSC is characterized by hamartomatous lesions involving multiple organ systems. Some patients with TSC experience infantile spasms or other forms of epilepsy. Vigabatrin is considered first-line therapy in infants with TSC and infantile spasms as well as in pediatric patients aged 10 to 16 years with treatment-refractory complex partial seizures [1,2]. Other patients receive it for compassionate use or Institutional-board approved protocols, as is seen in this case. Other diagnoses that receive VGB therapy include cortical dysplasia, metabolic encephalopathy, and mesial temporal sclerosis [1].

Vigabatrin is a γ-aminobutyric acid (GABA) analog that irreversibly inhibits γ-aminobutyric acid transaminase, serving to increase the concentration of GABA in order to depress epileptogenic circuits. VGB is a first-line therapy based on its remarkable effectiveness in reducing seizures, (>95% reduction), and good tolerability [2]. Initially, there was only one well-known, demonstrated side effect—retinotoxicity—resulting in permanent visual field constriction in approximately 30% of patients after 1 year and termed "vigabatrin-associated visual field loss" (VAVFL) [3,4].

At the time, VAVFL was the limiting factor to the use of VGB, but in more recent years the safety of VGB has been challenged by the emergence and recognition of vigabatrin-associated brain abnormalities on MRI (VABAM) [5].

Etiology & Demographics:

VABAM only affects a small subset of the pediatric population. Review of current available literature indicates that vigabatrin associated changes predominantly affect children younger than 2 years, with a mean age of 19.1 ± 25.6 months, and affects an estimated 22-32% of patients with TSC and infantile spasms undergoing treatment with vigabatrin[5]. There is little to no evidence of VABAM affecting individuals over the age of two.

The pathophysiology of VABAM is not well understood. Several animal studies have implicated a demyelination process with associated intramyelinic edema, intracellular cytotoxic edema, and microvacuolation of the deep brain structures [4]. The occurrence of these findings largely in the infancy period has led to the suggestion that brain maturation may play an important role, with vulnerability of immature myelin to the toxicity of vigabatrin a consideration. Other considerations include an indirect infant effect related to elevated GABA levels, or that pathologic neuronal epileptogenic circuitry may make infants susceptible [5,6]. Additionally, the distribution of these changes within the deep brain matter may reflect a specific glial or neuronal vulnerability to this medication [4].

Clinical & Imaging Findings:

VABAM encompasses a spectrum of changes that represent new-onset vigabatrin-related bilateral and symmetric T2 hyperintensities with varying degrees of diffusion restriction involving any or all of the following structures: the globi pallidi (most commonly affected), thalami, midbrain, dentate nuclei, brainstem, corpus callosum, tectal plate, or medial longitudinal fasciculus [1,2,3,4].

There have been several rare reports in the literature describing neurological symptoms in the setting of VABAM, termed "symptomatic VABAM" [7]. In these cases, the affected areas on MRI studies correlated with patient symptomatology: Extrapyramidal involvement was seen in an infant with dystonia, athetoid movements, and tremor; midbrain/brainstem involvement was seen in an infant with hypotonia and bradycardia; hypervigilance was seen in infant with thalamic involvement. Supplemental associations with headache, drowsiness, fatigue, and dizziness are non-descript, but were also reported. These events are not isolated, and extrapyramidal involvement with related clinical symptomatology has been confirmed in several follow-up studies, including in a retrospective study population of 124 children detailed by Fong et al., whereupon 8 cases of symptomatic VABAM were identified [8]. Fortunately, in all cases VABAM resolved after cessation/reduction of vigabatrin treatment, as was demonstrated in our patient.

Lastly, no statistically significant association of symptomatic VABAM with vigabatrin dosage, (peak or cumulative), was uncovered. However, Hussain et al did suggest a possible association between symptomatic VABAM and concomitant hormonal, (read: "steroidal"), therapy, as is often additionally used in the treatment regimen of epileptic individuals [3]. Thus, assuming symptomatic VABAM is a worse or more severe case of asymptomatic VABAM is too simplified, and one does not necessarily precipitate the other.

Treatment & Prognosis:

Little attention has been shifted towards researching vigabatrin-associated brain abnormalities on MRI since their appearance in the literature approximately 15 years ago. In 2017, Hussain et al. set out to identify predictors of these so-called "asymptomatic VBAM," which are seen in approximately 22-32% of infants taking vigabatrin [3]. Through their retrospective cohort review, tracking 507 brain MRI studies of 257 patients with infantile spasms taking vigabatrin, (10 of whom demonstrated VABAM), Hussain et al. suggested an association that the appearance of asymptomatic VABAM was dose-dependent, linked to peak—but not cumulative—vigabatrin dosage. Meanwhile, an additional retrospective cohort review by Dracopoulos et al. detailing follow-up MRI studies in 25 pediatric patients with asymptomatic VABAM demonstrates the statistically significant, reversible nature of these findings after treatment cessation/reduction [5].

Differential Diagnoses:

Given that VABAM is a recently identified phenomenon, this abnormal state can easily be confused with other entities that cause deep brain MRI signal changes. This can be

complicated because there are no necessarily distinguishing neuroimaging findings for several of the following afflictions, including: VABAM, posterior reversible encephalopathy syndrome, West syndrome, or phenytoin toxicity. In fact, several of the aforementioned abnormalities occur in the same patient population as VABAM, and thus will best be differentiated by respective clinical scenarios, i.e. clinical vigabatrin utilization, phenytoin utilization, or clinical history of infantile spasms, pathognomonic EEG pattern, and developmental regression—the triad of findings in West Syndrome. Neuroimaging findings in respect to the above differential are summarized in ***Table 2*** and presented below.

Posterior Reversible Encephalopathy Syndrome

Common patterns manifest with T_2-weighted hyperintensities within the occipital and parietal regions relating to the posterior cerebral artery supply, but non-posterior distribution variants can manifest in watershed areas within the frontal, cerebellar, and brainstem regions.

Other antiepileptic Drug Toxicity (I.e. Phenytoin toxicity)

Demyelination of the splenium of the corpus callosum.

West Syndrome

Transient DWI abnormalities involving the globi pallidi and the dorsal part of the brainstem.

Conclusion

We present a classic case where T_2-hyperintentisies on brain MRI have been associated with the use of vigabatrin in the setting of TSC complicated by a form of epilepsy. VABAM can either manifest as symptomatic or asymptomatic. Familiarity with these neuroimaging findings can prevent unnecessary follow up tests and studies. The cost of precipitating, albeit reversible, extrapyramidal symptoms should be weighed heavily in the practitioner's utilization of vigabatrin therapy.

TEACHING POINT

Predominantly within infancy, vigabatrin utilization can lead to asymptomatic or symptomatic manifestations of symmetric and bilateral MRI signal hyperintensities with varying degrees of restricted diffusion involving the globi pallidi, brainstem, thalami, anterior commissure, tectum, and dentate nuclei. Asymptomatic VABAM have been demonstrated to be dose-dependent and reversible. Symptomatic VABAM is seemingly dose-independent, and potentially associated with concomitant hormonal therapy.

REFERENCES

1. Sullivan M. MRI is a Must in Children on Vigabatrin Therapy. Pediatric Neurology 2007;10.1016:13.Available at: https://www.mdedge.com/clinicalneurologynews/article/4766 pediatrics/mri-must-children-vigabatrin-therapy. Accessed February 15, 2020.

2. Hsieh D, Thiele E. Vigabatrin-Related Magnetic Resonance Imaging Abnormalities in an Infant with Tuberous Sclerosis Complex and Infantile Spasms. J Pediatr 2013; 162-215. PMID: 22979977.

3. Hussain S, Tsao J, Li M, et al. Risk of Vigabatrin-associated brain abnormalities on MRI in the treatment of infantile spasms is dose-dependent. Epilepsia 2017; 58(4): 674-682. PMID: 28230253.

4. Pearl P, Vezina L, Saneto R, et al. Cerebral MRI abnormalities associated with vigabatrin therapy. Epilepsia 2009; 50(2): 184-194. PMID 18783433.

5. Dracopoulos A, Widjaja E, Raybaud C, Westall CA, Snead OC 3rd. Vigabatrin-associated reversible MRI signal changes in patients with infantile spasms. Epilepsia 2010; 51(7): 1297-1304. PMID: 20384718.

6. Schonstedt V, Stecher X, Venegas V, Silva C. Vigabatrin-induced MRI changes associated with extrapyramidal symptoms in a child with infantile spasms. Neuroradiol J 2015; 28(5): 515-518. PMID: 26306928.

7. Dill P, Datta A, Weber P. Are vigabatrin induced T2 hyperintensities in cranial MRI associated with acute encephalopathy and extrapyramidal symptoms? Eur J Paediatr Neurol 2013; 17: 311-315. PMID: 23199677.

8. Fong C, Osborne J, Edwards S, et al. An investigation into the relationship between vigabatrin, movement disorders, and brain magnetic resonance imaging abnormalities in children with infantile spasms. Dev Med Child Neurol 2013; 55: 862-867. PMID: 23789722.

FIGURES

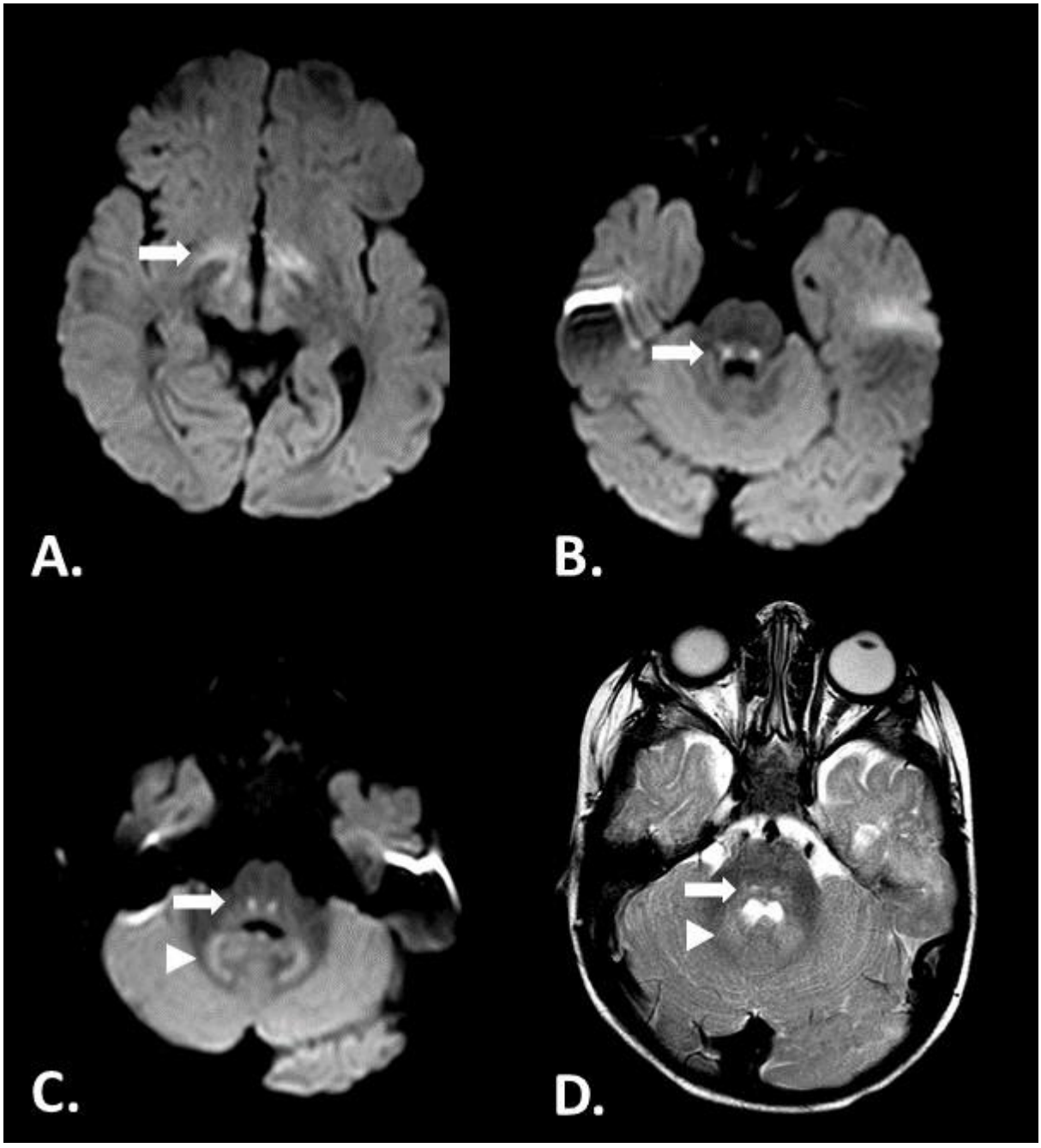

Figure 1: 10-month-old male with tuberous sclerosis and complex partial seizures, treated with vigabatrin at a dosage of 150mg/kg/day and subsequent Vigabatrin-associated brain abnormalities.

FINDINGS: Axial Diffusion Weighted Images (1A, 1B, and 1C) and T2 Spin Echo image (1D) depict abnormal T2-weighted signal hyperintensities and restricted diffusion at the level of the bilateral subthalamic nuclei (A, arrow), central tegmental tracts (B,C, and D, arrows), and bilateral dentate nuclei (1C and 1D, arrowheads).

TECHNIQUE: 3 tesla MRI (Philips Intera). Images 1A, 1B, and 1C: axial DWI, b1000, isotropic. Slice thickness: 4mm. Images 1D: axial T2 SE, Tr/TE: 2000/80. Flip angle: 90. Slice thickness: 4mm.

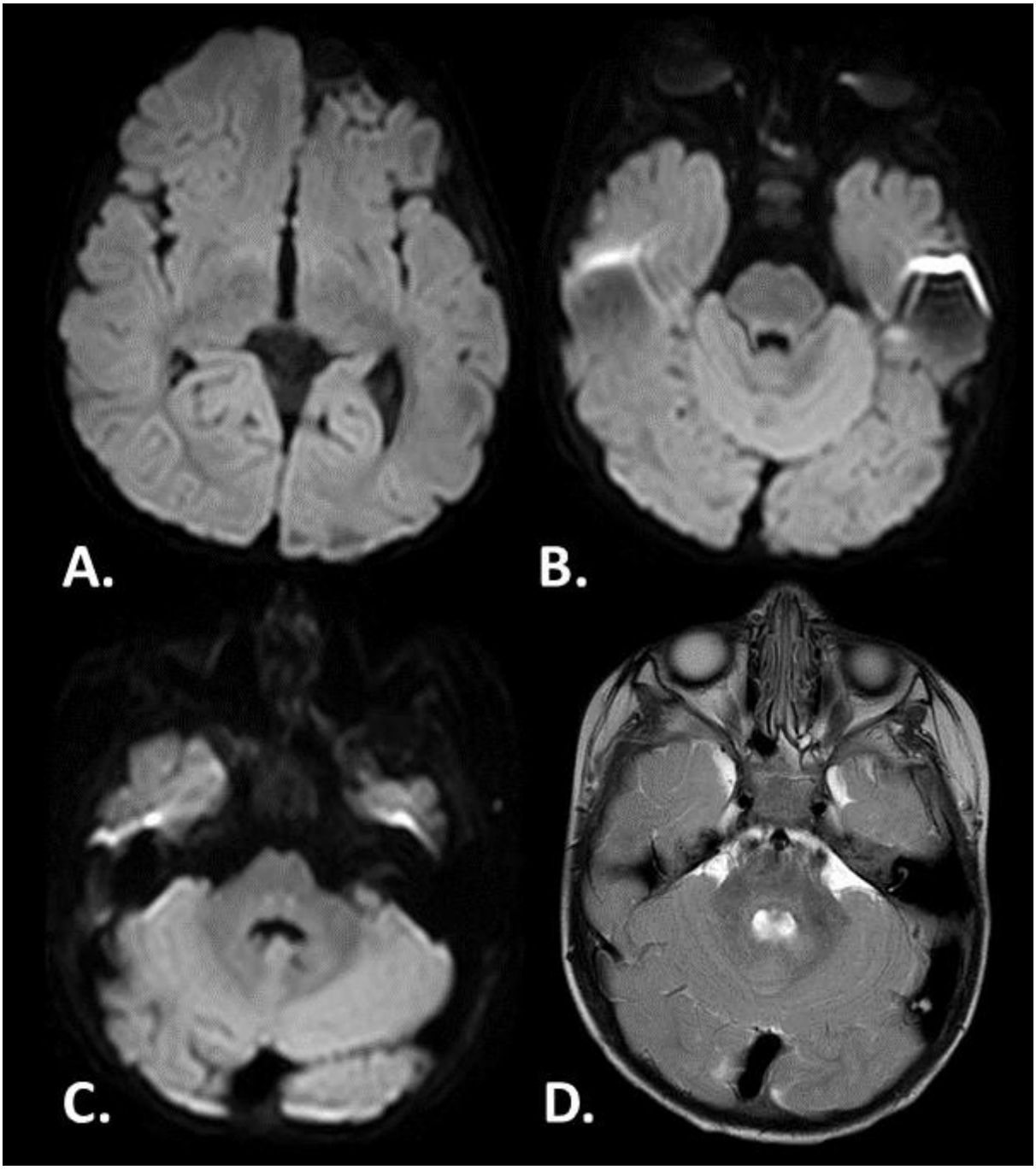

Figure 2: 19-month-old male with tuberous sclerosis and complex partial seizures, treated with vigabatrin at a reduced dosage of 100mg/kg/day.

FINDINGS: Axial Diffusion Weighted Images (1A, 1B, and 1C) and T2 Spin Echo image (1D) demonstrate resolution of the abnormal T2-weighted signal hyperintensities and restricted diffusion involving the subthalamic nuclei (A), central tegmental tracts (B,C, and D), and bilateral dentate nuclei (1C and 1D).

TECHNIQUE: 3 tesla MRI (Philips Intera). Images 1A, 1B, and 1C: axial DWI, b1000, isotropic. Slice thickness: 4mm. Images 1D: axial T2 SE, Tr/TE: 2000/80. Flip angle: 90. Slice thickness: 4mm.

Etiology	Undefined etiology; most popular leading theory suggests VGB alters immature myelin formation, resulting in intramyelinic edema, intracellular cytotoxic edema, and microvacuolation of the deep brain structures
Incidence	22-32% of patients with infants with TSC and infantile spasms undergoing treatment with VGB.
Gender Ratio	No gender predilection
Age Predilection	Mean age of 19.1 ± 25.6 months
Risk Factors	<2 years of age, TSC with infantile spasm, undergoing treatment with VGB, high dosage of VGB
Treatment	Cessation/reduction of VGB therapy
Prognosis	Quite favorable, although there is limited data as it not usually standard medical practice to obtain posttreatment MRI. Only a rare set of cases in the literature result in symptomatic VABAM.
Findings on Imaging	Bilateral and symmetric T_2-weighted signal hyperintensities and restricted diffusion in thalami, globi pallidi, dentate nuclei, brainstem, tectum, corpus callosum.

Table 1: Summary table of Vigabatrin-associated MRI abnormalities.

Diagnosis:	**MRI Neuroimaging findings:**
VGB-associated MRI brain abnormalities on MRI (VABAM)	New-onset and reversible bilateral and symmetric T_2-weighted signal hyperintensities and restricted diffusion in thalami, globi pallidi, dentate nuclei, brainstem, tectum, corpus callosum.
Posterior Reversible Encephalopathy Syndrome	Common patterns manifest with T_2-weighted hyperintensities within the occipital and parietal regions relating to the posterior cerebral artery supply, but non-posterior distribution variants can manifest in watershed areas within the frontal, cerebellar, and brainstem regions.
Other antiepileptic Drug Toxicity (i.e. Phenytoin toxicity)	Demyelination of the splenium of the corpus callosum.
West Syndrome	Transient DWI abnormalities involving the globi pallidi and the dorsal part of the brainstem.

Table 2: Differential diagnosis table for pathologic processes resulting in similar neuroimaging findings to Vigabatrin-associated MRI abnormalities (VABAM).

ABBREVIATIONS

EEG = Electroencephalogram/ Electroencephalography
GABA = Gamma-aminobutyric Acid
MRI = Magnetic Resonance Imaging
TSC = Tuberous Sclerosis Complex
VABAM = VGB-associated brain abnormalities on MRI
VAVFL = VGB-associated visual field loss
VGB = Vigabatrin

KEYWORDS

Vigabatrin; Vigabatrin Toxicity; VABAM; Vigabatrin-associated brain abnormalities; Tuberous Sclerosis Complex; Pediatric Neuroimaging; MRI

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