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RESEARCH ARTICLE

Vigabatrin-associated brain magnetic resonance imaging abnormalities and clinical symptoms in infants with tuberous sclerosis complex

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Abstract

Objective: Previous retrospective studies have reported vigabatrin-associated brain abnormalities on magnetic resonance imaging (VABAM), although clinical impact is unknown. We evaluated the association between vigabatrin and predefined brain magnetic resonance imaging (MRI) changes in a large homogenous tuberous sclerosis complex (TSC) cohort and assessed to what extent VABAM-related symptoms were reported in TSC infants.

Methods: The Dutch TSC Registry and the EPISTOP cohort provided retrospective and prospective data from 80 TSC patients treated with vigabatrin (VGB) before the age of 2 years and 23 TSC patients without VGB. Twenty-nine age-matched non-TSC epilepsy patients not receiving VGB were included as controls. VABAM, specified as T2/fluid-attenuated inversion recovery hyperintensity or diffusion restriction in predefined brain areas, were examined on brain MRI before, during, and after VGB, and once in the controls (at approximately age

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2 years). Additionally, the presence of VABAM accompanying symptoms was evaluated.

Results: Prevalence of VABAM in VGB-treated TSC patients was 35.5%. VABAM-like abnormalities were observed in 13.5% of all patients without VGB. VGB was significantly associated with VABAM (risk ratio [RR] = 3.57, 95% confidence interval [CI] = 1.43–6.39), whereas TSC and refractory epilepsy were not. In all 13 VGB-treated patients with VABAM for whom posttreatment MRIs were available, VABAM entirely resolved after VGB discontinuation. The prevalence of symptoms was 11.7% in patients with VABAM or VABAM-like MRI abnormalities and 4.3% in those without, implicating no significant association (RR = 2.76, 95% CI = .68–8.77).

Significance: VABAM are common in VGB-treated TSC infants; however, VABAM-like abnormalities also occurred in children without either VGB or TSC. The cause of these MRI changes is unknown. Possible contributing factors are abnormal myelination, underlying etiology, recurrent seizures, and other antiseizure medication. Furthermore, the presence of VABAM (or VABAM-like abnormalities) did not appear to be associated with clinical symptoms. This study confirms that the well-known antiseizure effects of VGB outweigh the risk of VABAM and related symptoms.

KEYWORDS

brain MRI, epilepsy, tuberous sclerosis complex, vigabatrin

1 | INTRODUCTION

Tuberous sclerosis complex (TSC) is a multisystem autosomal dominant genetic disorder that causes malformations and tumors in multiple organs, including the brain, skin, lungs, and kidneys.[1] The central nervous system (CNS) is affected in >90% of patients.[2] Structural CNS lesions include malformations of cortical development, referred to as tubers, and are associated with neurological symptoms such as epilepsy, intellectual disability, and neuropsychiatric disorders.[1] Epilepsy occurs in 80% of children with TSC by the age of 2 years.[3,4] Early and refractory seizures, including infantile epileptic spasms syndrome (IESS), are linked to poorer neurodevelopmental outcome.[5–7] Early treatment improves neurodevelopmental outcomes and reduces the rate of refractory epilepsy.[8–10] Vigabatrin (VGB) is currently the preferred treatment for focal seizures or epileptic spasms in TSC with onset in the first 2 years of life.[11–14] VGB is thought to exert its antiepileptic effect by irreversibly inhibiting γ-aminobutyric acid (GABA) transaminase, resulting in increased brain GABA levels, and in inhibition of the mTOR pathway, which has a critical role in epileptogenesis in TSC.[15,16] The recent EPISTOP trial has suggested that presymptomatic treatment with VGB in TSC infants delays the onset and reduces the severity of epilepsy.[17] However, neurodevelopmental outcome at the age of 2 years was not significantly different between patients treated presymptomatically and those who received treatment only after the occurrence of seizures as demonstrated in the PREVeNT trial.[18] The PREVeNT trial also demonstrated that preventive VGB was associated with later time of onset and lower incidence of infantile spasms.[18] Current clinical recommendations therefore propose early presymptomatic treatment in infants

Key points

- VGB is associated with characteristic brain abnormalities on MRI in infants with TSC, but these MRI lesions disappear over time.
- T2/FLAIR hyperintensities in predefined areas are not exclusive for VGB or TSC, and the cause of these MRI abnormalities is unknown.
- The presence of VABAM did not appear to be associated with predefined clinical symptoms.
- The antiseizure effects of VGB outweigh the risk of VABAM.

with TSC to delay epilepsy onset and reduce the risk of epileptic spasms.[19] This will likely increase the proportion of children with TSC treated with VGB. The most feared adverse effect of VGB treatment is retinal toxicity and related visual field defects, although prevalence is highly variable in the literature.[20] Less is known about the frequency and clinical significance of presumed VGB-associated brain abnormalities on magnetic resonance imaging (VABAM), which have previously been reported to occur in 15%–47% of children.[16,21–28]

Rodent and dog studies investigating VGB adverse effects revealed microvacuoles in the outer layers of myelin (known as intramyelinic edema), reactive astrocytosis, and microglial activation in several brain areas, such as the cerebellum, optic tract, fornix, and basal ganglia during VGB treatment.[29–37] These histopathological lesions correlated with changes on magnetic resonance imaging (MRI),[38] were dose-dependent, and were completely reversible after cessation of VGB treatment.[29–37] Previous small retrospective studies in children who were treated with VGB for epileptic spasms of any etiology described T2 hyperintensities or diffusion restriction in basal ganglia, thalamus, brain stem, corpus callosum, cerebellum, and hippocampus.[16,21–28] These abnormalities, labeled VABAM, were observed more often in younger infants[22,25,26] and were peak dose-dependent.[1–4]

This study aimed to (1) correlate the occurrence of presumed VABAM with VGB use in TSC infants and (2) evaluate to what extent VABAM were accompanied by clinical symptoms. Because TSC itself and refractory epilepsy are predisposing factors for changes in white matter integrity,[39–41] we hypothesized that TSC patients or patients with refractory epilepsy not related to TSC might be more susceptible to VABAM or to VABAM-like MRI abnormalities even in the absence of VGB use. Additionally, we aimed to identify potential associated variables of VABAM and accompanying clinical symptoms.

2 | MATERIALS AND METHODS

2.1 | Study population

This study consecutively enrolled children (1) with a confirmed genetic and/or clinical diagnosis of TSC,[2] (2) who had VGB treatment initiation before the age of 24 months, and (3) who had MRI before and during VGB use (and preferably but not necessarily also after VGB discontinuation). Patients were enrolled from the prospective EPISTOP study and trial database ($n = 97$) or the retrospective Dutch TSC Registry ($n = 142$). Patient inclusion took place from 2014 onward, and data were extracted in 2023.

In addition, we constructed (1) a control group that included children with TSC who did not use VGB (TSC+VGB−), recruited from the same two databases; and (2) a control group of age-matched children with epilepsy but without TSC and without VGB treatment (TSC−VGB−), who were recruited from the Wilhelmina Children's hospital outpatient clinic ($n = 298$). Children with etiologies that could lead to MRI changes in the regions of interest for this study—such as those with suspected mitochondrial disease—were excluded. Patients were also excluded in the case of perinatal asphyxia, defined as APGAR score < 7 after 5 min, or other etiological diagnoses associated with extrapyramidal symptoms, ataxia, autonomic dysregulation, or acute encephalopathy.

The Dutch Medical Research Involving Human Subjects Act did not apply, as confirmed by the ethical committee of the University Medical Center in Utrecht. All TSC patients who were included previously consented to study participation via the Dutch TSC Registry and EPISTOP prospective study and trial. For the non-TSC epilepsy patients without VGB, additional informed consent was not necessary according to the Dutch Medical Research Involving Human Subjects Act. Patients who actively objected to any research participation in the past were excluded from study participation.

2.2 | Brain MRI evaluation

Brain MRIs (three-dimensional MRI at 1.5 or 3.0 T) were independently reviewed by two researchers (M.L. and C.S.) blinded for VGB status. In the case of disagreement, a third investigator (F.J.) was consulted. We assessed hyperintensity on T2-weighted and fluid-attenuated inversion recovery (FLAIR) images, as well as diffusion restriction on diffusion-weighted imaging and apparent diffusion coefficient maps in the regions of interest (ROIs). The ROIs were defined based on previous publications[16,21–28] and included basal ganglia, thalamus, brain stem, corpus callosum, fornix, cerebellum, and hippocampus. The ROIs were atlas-selected and manually positioned without using software. They covered the entire studied anatomical structure, but for the basal ganglia, dorsal midbrain, and cerebellum, we specifically described the anatomical region the abnormalities were observed in. We scored whether an ROI was affected and assessed the localization and severity of these abnormalities in the ROIs. To define the severity of the abnormality, we developed a scoring system adapted from the scoring system used by Milh and colleagues,[24] presented in Figure 1. We evaluated MRIs per patient chronologically to observe the course of VABAM over time.

score	definition
0	no abnormalities in a region of interest on FLAIR, T2WI or DWI
1	subtle hyperintensity on FLAIR and/or T2WI in a region of interest, no diffusion restriction
2	evident hyperintensity on FLAIR and/or T2WI in a region of interest, no diffusion restriction
3	severe hyperintensity on FLAIR and/or T2WI in a region of interest, and also diffusion restriction classified as hyperintense signal on DWI and hypointense signal on ADC

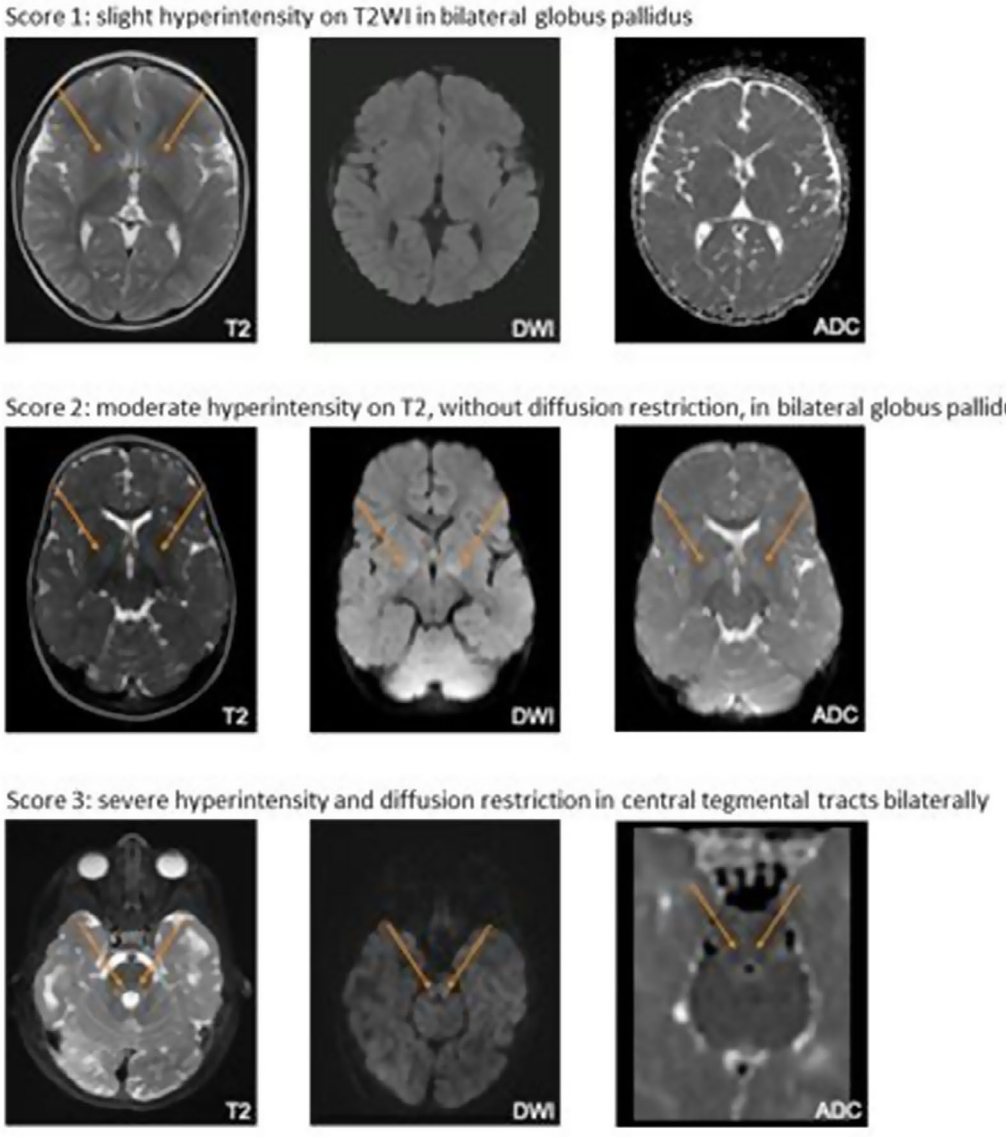

FIGURE 1 Severity of vigabatrin-associated brain abnormalities on magnetic resonance imaging: examples and scoring system. ADC, apparent diffusion coefficient; DWI, diffusion-weighted imaging; FLAIR, fluid-attenuated inversion recovery; T2, T2-weighted imaging. Arrows point toward the brain abnormalities of interest.

2.3 | VGB exposure quantification

VGB dosage, patient weight, and treatment duration were extracted from patients' medical records. Peak dosage, cumulative dosage, and weighted mean dosage, all corrected for weight, were calculated from treatment initiation until brain imaging.

2.4 | Clinical symptoms of interest

The presence of VABAM-related clinical symptoms during VGB treatment was determined based on available clinical data in patients' records (patients from the Dutch TSC Registry) and EPISTOP electronic case record forms (eCRFs). Symptoms considered were movement disorders, ataxia, respiratory distress, bradycardia, and acute encephalopathy.[16] The presence and prevalence of symptoms and their course over time after VGB treatment discontinuation were evaluated. If information about visual field deficits, regardless of type, severity, and reversibility, was mentioned in the eCRF and medical files, this was registered, as well as other VGB-related adverse effects.

2.5 | Study endpoints and analysis

The primary study endpoints concerned (1) the presence of VABAM or VABAM-like abnormalities in patients not using VGB and (2) the presence of VABAM accompanying clinical symptoms during study follow-up. Study objectives are presented in Figure 2. The prevalence of VABAM or VABAM-like MRI abnormalities for patients with and those without VGB, respectively, was calculated using descriptive statistics. If VABAM were seen in children who would later be treated with VGB but were not using VGB yet at the time of MRI acquisition, and these MRI abnormalities were still detected during VGB treatment, this patient was excluded from further analysis. If VABAM were seen in children—in either the VGB-treated or VGB-naïve study group—on MRI in the first year of life (before VGB initiation) or on MRI at the age of approximately 4 years (after VGB discontinuation), but not on MRI during VGB use, these MRI changes were noted. However, solely the presence of VABAM on MRI at the age of approximately 2 years (during VGB treatment) was taken into account to determine the prevalence of VABAM and associated variables in statistical analysis. Differences in highest severity score, number of ROIs affected, and individual ROIs affected between VABAM-affected patients with VGB and those with VABAM-like MRI abnormalities but without VGB were calculated using Student *t*-test for normally distributed continuous variables, Mann–Whitney *U*-test for nonnormally distributed continuous variables, and chi-squared test with continuity correction for categorical variables. Interrater reliability for MRI evaluation was calculated using Cohen kappa (κ).[42] The association between VGB use and VABAM (objective 1) was evaluated using multivariable logistic regression, including VGB use, TSC diagnosis, and refractory epilepsy at the time of MRI as dichotomous determinants, and presence or absence of VABAM as outcome variable. Possible VGB exposure-related determinants of VABAM were evaluated using univariable logistic regression, including age at VGB initiation, VGB treatment duration, peak VGB dosage until MRI, cumulative VGB dosage until MRI, and weighted mean VGB dosage until MRI as continuous predictors and concomitant hormonal or steroid therapy as a categorical predictor.

The prevalence of predefined clinical symptoms for patients with and without VABAM/VABAM-like MRI abnormalities was calculated using descriptive statistics. The prevalence of each symptom of interest and the number of symptoms per patient were compared between patients with and without VABAM, using Student *t*-test for normally distributed continuous variables, Mann–Whitney *U*-test for nonnormally distributed continuous variables, and

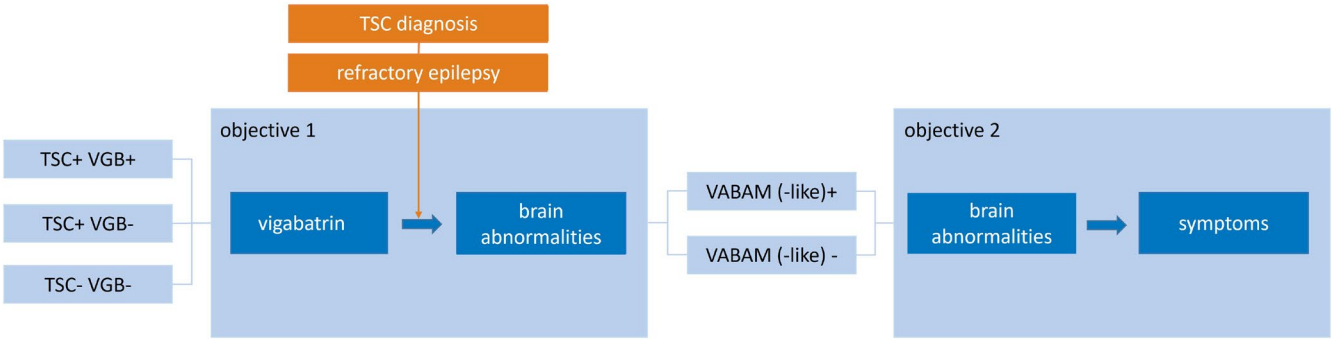

FIGURE 2 Study objectives. TSC, tuberous sclerosis complex; VABAM, VGB-associated brain abnormalities on magnetic resonance imaging; VABAM (-like), VABAM or VABAM-like changes; VGB, vigabatrin.

chi-squared test with continuity correction for categorical variables. The association between VABAM and accompanying clinical symptoms was determined with univariable logistic regression analysis, with VABAM as the determinant and clinical symptoms as the dichotomous outcome variable. VGB treatment during MRI and concomitant hormonal and steroid therapy were evaluated as categorical determinants of VABAM accompanying clinical symptoms using univariable logistic regression.

Baseline data consisted of general patient and epilepsy characteristics, developmental quotient, and information about other antiseizure medications, ketogenic diet, and concomitant hormonal or corticosteroid therapy around the time of included MRIs and were evaluated using descriptive statistics. All statistical analyses were performed using R statistical software version 4.3.2. Odds ratios were converted to risk ratios (RRs).[43] For all analyses, $p < .05$ was considered statistically significant.

3 | RESULTS

3.1 | Baseline characteristics

We included 80 TSC infants with VGB treatment during MRI (TSC+VGB+), 23 TSC infants without VGB treatment during the entire study period (TSC+VGB−), and 29 epilepsy patients without TSC and VGB treatment (TSC−VGB−). In the VGB-treated TSC cohort, 52.2% had refractory epilepsy at the time of the second MRI (at the age of approximately 2 years), in comparison to 21.7% and 37.9% in the comparative groups of TSC patients without VGB use and non-TSC epilepsy patients, respectively. The median age at start of VGB treatment was 3.5 months (interquartile range [IQR] = 1.6–6.2), the mean treatment duration until MRI was 19.2 (±5.7) months, and the median age at which VGB treatment ceased was 42.6 months (IQR = 27.3–69.0). In 39 of 80 VGB-treated TSC patients (48.8%), VGB treatment was continued during the study period. Baseline characteristics are presented in Table 1. All VGB-treated patients had MRIs within the first year of life and at the age of approximately 2 years. Interrater reliability for evaluating the presence of VABAM or VABAM-like MRI abnormalities in patients not using VGB was high ($\kappa = .71$, $p < .001$).

3.2 | Association between VGB and VABAM

The flow of patients with evolution and resolution of VABAM during study follow-up is presented in Figure 3. In 31 of 80 VGB-treated patients (38.8%), VABAM was seen on MRI during VGB treatment. In four of these 31 patients, these MRI abnormalities were already present on the first MRI before VGB initiation, and therefore, these four patients were excluded from further analysis. In six of the VGB-treated patients, VABAM-like abnormalities were seen only before VGB initiation and were absent on the MRI during VGB use. In one other patient, they appeared only after VGB discontinuation. We included the findings on MRI during VGB treatment, or at the age of approximately 2 years for the control groups, for logistic regression analyses. The six VGB-treated patients with VABAM-like abnormalities before VGB initiation, and the one patient with VABAM-like abnormalities after VGB discontinuation, were therefore considered to be VABAM-negative during VGB treatment for logistic regression analyses.

3.2.1 | VABAM possibly VGB-related

Prevalence of "VABAM possibly VGB-related" was solely based on the presence of VABAM at the MRI during VGB treatment and concerned 35.5% of patients (27/76 patients, after excluding the four patients with VABAM-like abnormalities before and during VGB treatment). In all 13 VGB-treated patients with "VABAM possibly VGB-related" for whom posttreatment MRIs were available, VABAM entirely resolved after VGB discontinuation with a median time of 10.8 months (IQR = 5.9–22.6) between cessation of VGB and posttreatment MRI. In only two of the 27 "VABAM possibly VGB-related" patients (7.4%), T2/FLAIR-hyperintensity and diffusion restriction (severity score = 3) were present. None of the patients had ROI abnormalities characterized by diffusion restriction without T2/FLAIR signal changes. The median highest severity score reported in one of the ROIs was 2.0 (IQR = 1.0–2.0), and the median number of ROIs affected was 1.0 (IQR = 1.0–2.0), as presented in Table S1. Brain stem (restricted to the central tegmental tracts) and basal ganglia (restricted to the globus pallidus) were most frequently affected, in 22 of 27 patients (81.5%) and 11 of 27 patients (40.7%), respectively; the prevalence of VABAM in the other ROIs affected is presented in Table S1. Cerebellar abnormalities were primarily observed in the dentate nucleus. Other regions that were not identified in previous studies were the subthalamic tracts and anterior commissure, each in two patients. In all cases, VABAM were bilateral.

3.2.2 | VABAM-like MRI abnormalities not VGB-related

In two of 23 TSC patients without VGB treatment and in five of 29 epilepsy patients without TSC and VGB treatment,

TABLE 1 Baseline table.

Characteristic	TSC+VGB+, $n=80$	TSC+VGB−, $n=23$	TSC−VGB−, $n=29$
Female gender	38 (48.8)	10 (43.5)	12 (41.4)
TSC mutation type			
TSC1 [pathogenic]	17 (21.3)	12 (52.5)	
TSC2 [pathogenic]	62 (77.5)	9 (39.1)	
Unknown/not identified	1 (1.3)	2 (8.7)	
Epilepsy characteristics			
Clinical or electrographic seizures	65 (81.3)	12 (52.2)	29 (100)
Age at epilepsy onset, months	4.6 (2.4–9.3)	12.7 (6.0–20.8)	14.1 (5.9–18.4)
Refractory epilepsy at time of second MRI[a]	42 (52.5)	5 (21.7)	11 (37.9)
Epileptic spasms during study follow-up	19 (23.8)	4 (17.4)	3 (10.3)
VGB characteristics			
Age at the start of VGB treatment, months	3.5 (1.6–6.2)		
Treatment onset age ≤ 12 months	74 (92.5)		
VGB treatment duration, months[b]	19.2 (±5.7)		
Age at stopping VGB treatment, months	42.6 (27.3–69.0)		
VGB treatment continuation during study period	39 (48.8)		
Peak VGB dosage, mg/kg/day[b]	141.9 (±25.6)		
Weighted mean dosage, mg/kg/day[b]	126.5 (102.8–136.2)		
Cumulative VGB dosage, mg/kg/lifetime[b]	78 683.5 (48 569.9–91 416.4)		
Developmental quotient[c,d]	70.0 (58.0–87.0)	90.0 (76.0–102.5)	72.0 (60.0–104.3)
Autism spectrum disorder diagnosis or suspicion[c]	24 (26.3)	2 (8.7)	1 (3.4)
Concomitant therapies during VGB treatment			
Other antiseizure medications, n[c]	1 (0–3)	0 (0–2)	1 (1–2)
Ketogenic diet[c]	4 (5.0)	0 (0)	0 (0)
Hormonal or corticosteroid therapy[c]	8 (10.0)	0 (0)	0 (0)
Brain surgery during follow-up			
Epilepsy surgery	11 (13.8)	4 (17.4)	7 (24.1)
Other type of surgery[e]	3 (3.8)	1 (4.3)	0 (0)

Note: Continuous variables are depicted as mean (±SD), or median (25th percentile–75th percentile) if not normally distributed, and count variables as n (%).

Abbreviations: MRI, magnetic resonance imaging; n, number of patients; NPA, neuropsychological assessment; TSC, tuberous sclerosis complex; VGB, vigabatrin.

[a]Refractory epilepsy was defined as failure of adequate trails of two tolerated and appropriately chosen antiseizure medication schedules (whether as monotherapies or in combination) to achieve seizure freedom, with a timespan of a maximum of 1 month before MRI.

[b]Until MRI during VGB.

[c]Ascertained on MRI at age of approximately 2 years (during VGB).

[d]Composed of the developmental quotient, total intelligence quotient, and cognition index, depending on the type of NPA used, and solely for the patients with NPA available.

[e]Subependymal giant cell astrocytoma resection or ventriculoperitoneal shunt.

VABAM-like MRI abnormalities were seen on MRI at approximately 2 years of age. Prevalence of "VABAM-like MRI abnormalities not VGB-related" was, therefore, 13.5% (7/52 patients). In all of these patients, "VABAM-like MRI abnormalities not VGB-related" were completely resolved on follow-up MRI. Central tegmental tracts (6/7 patients, 85.7%) and globus pallidus (1/7 patients, 14.3%) were bilateral; again, the most prevalent locations for "VABAM-like MRI abnormalities not VGB-related" and "other regions" included subthalamic tracts in two patients. In two of seven "VABAM-like MRI abnormalities not VGB-related" patients (28.6%), T2/FLAIR-hyperintensity and diffusion restriction (severity score = 3) were present. There were no significant differences in the ROIs affected, median highest

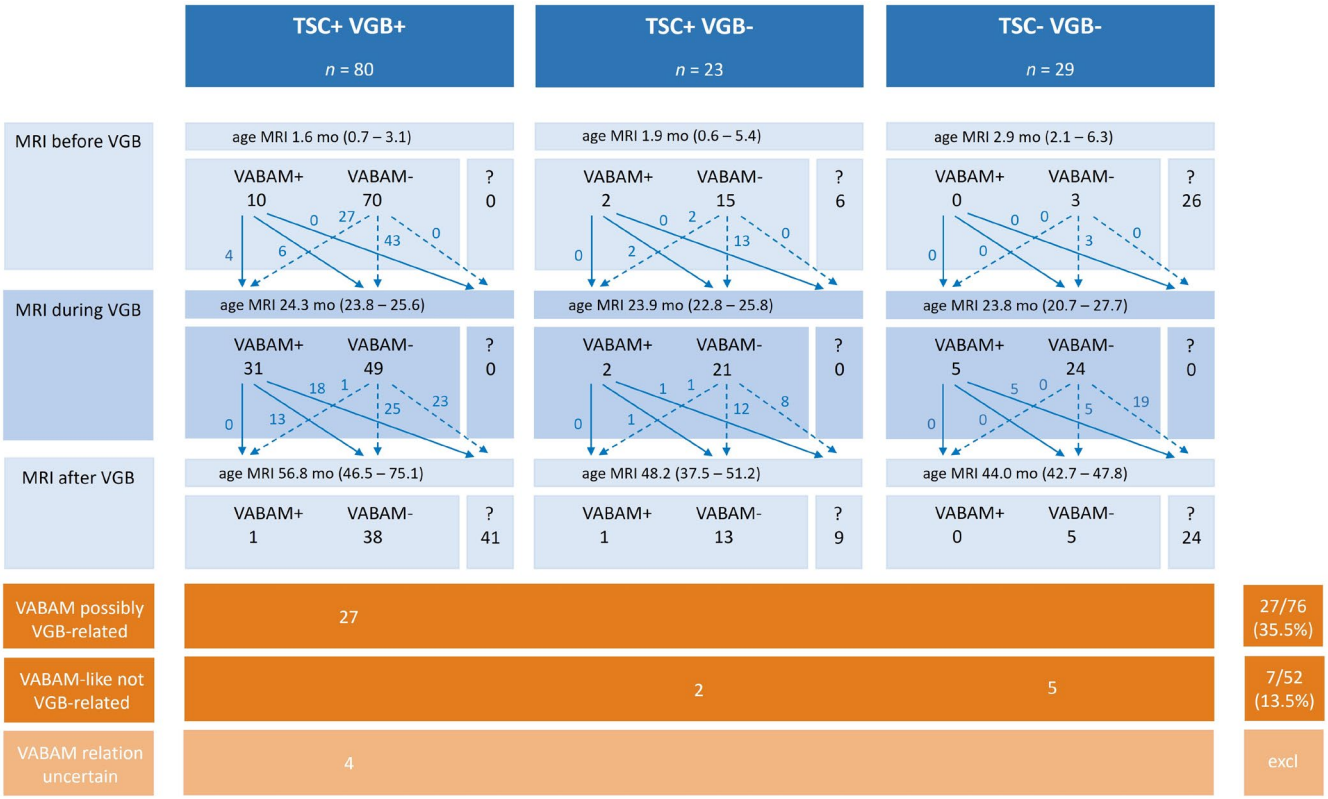

FIGURE 3 Flow of study participants. ?, missing MRI data; age MRI, median age (interquartile range) at MRI of study subgroup; excl, excluded; mo, months; MRI, magnetic resonance imaging; *n*, number of participants; TSC, tuberous sclerosis complex; VABAM, VGB-associated brain abnormalities on magnetic resonance imaging; VGB, vigabatrin.

severity score, or number of ROIs affected between patients with VGB and those without (Table S1).

3.2.3 | Association analyses

VGB was significantly and independently associated with the detection of VABAM (RR = 3.57, 95% confidence interval [CI] = 1.43–6.39), whereas refractory epilepsy (RR = .92, 95% CI = .43–1.81) and TSC (RR = .49, 95% CI = .07–1.99) were not. We did not identify significant VGB exposure-related determinants of the occurrence of VABAM. The results of regression analyses are presented in Table 2.

3.3 | Association between VABAM and predefined clinical symptoms

The prevalence of accompanying clinical symptoms was 11.7% (four patients) in the pooled group of 34 patients with VABAM/VABAM-like MRI abnormalities (with or without VGB treatment) at the 2-year MRI time point. The median number of symptoms per patient was 1.0 (IQR = 1.0–1.2). Two patients had a movement disorder, one had ataxia, and one had respiratory distress. In the three patients with VABAM who used VGB, symptoms completely resolved after dose reduction or withdrawal of VGB. In the other patient with VABAM-like brain abnormalities, the symptoms resolved spontaneously after days.

The prevalence of predefined clinical symptoms was 4.3% (four patients) in the 94 patients without VABAM (or VABAM-like abnormalities) at the time of MRI. The median number of symptoms per patient was 1.0 (IQR = 1.0–1.5). Of the four VABAM-negative patients with clinical symptoms, two had a movement disorder, one had respiratory distress, and one had bradycardia. There were no significant differences in the number of symptoms per patient or prevalence of each symptom of interest between patients with and without VABAM (or VABAM-like MRI abnormalities), as presented in Table S2.

The presence of VABAM (or VABAM-like MRI abnormalities) was not significantly associated with predefined clinical symptoms (RR = 2.76, 95% CI = .68–8.77). VGB treatment during MRI was also not significantly associated with clinical symptoms (RR = 4.79, 95% CI = .88–34.24). Concomitant hormonal or steroid therapy appeared to be a significant predictor of predefined clinical symptoms, associated with a nine times higher risk for these symptoms compared to patients without hormonal or steroid

treatment (RR = 9.00, 95% CI = 2.21–18.43), although there were only eight patients treated with hormonal or steroid therapy. Although these patients had more clinical symptoms, they did not have higher VABAM severity scores ($p = .06$, Cohen $d = 1.37$) or higher numbers of ROIs affected in comparison to patients without hormonal or steroid therapy ($p = .77$, Cohen $d = -.14$). The results of regression analyses are presented in Table 3.

In addition to the symptoms of interest in this study, we noted the prevalence of visual field deficit in patient subgroups. A visual field deficit was reported in five of 69 VGB-treated patients (7.3%) compared to none in the non-VGB patients, although this difference was not significant ($p = .10$). There were also no significant differences in the prevalence of visual field deficits between patients with and without VABAM ($p = .45$) nor between patients with and without predefined clinical symptoms ($p = .26$).

TABLE 2 Association between VGB and VABAM and predictors.

	RR (95% CI)	*p*
VABAM/VABAM-like changes[a]		
VGB treatment during MRI	3.57 (1.43–6.39)	**.02**
Refractory epilepsy at the time of MRI	.92 (.43–1.81)	.82
TSC diagnosis	.49 (.07–1.99)	.37
VGB exposure-related predictors of VABAM/VABAM-like changes[b]		
VGB initiation age[c]	1.04 (.96–1.12)	.33
VGB treatment duration[c]	.98 (.95–1.00)	.08
Peak VGB dosage[c]	1.00 (.99–1.01)	.49
Cumulative VGB dosage[c]	1.00 (1.00–1.00)	.58
Weighted mean VGB dosage[c]	1.00 (.99–1.01)	.47
Concomitant hormonal/steroid therapy	.94 (.17–2.27)	.92

Note: $p < .05$ was considered statistically significant and marked bold.

Abbreviations: CI, confidence interval; MRI, magnetic resonance imaging; RR, risk ratio; TSC, tuberous sclerosis complex; VABAM, VGB-associated brain abnormalities on MRI; VGB, vigabatrin.

[a]Multivariable analyses including VGB, refractory epilepsy at the time of MRI, and TSC diagnosis as predictors.

[b]Univariable analyses, as none of the predictors was statistically significantly associated with the specific brain MRI changes.

[c]Continuous independent variables.

4 | DISCUSSION

In this study, including a large and homogenous cohort of TSC patients with and without VGB treatment and age-matched non-TSC epilepsy patients as controls, we demonstrated that treatment with VGB is associated with characteristic brain MRI changes in patients with TSC, with basal ganglia and central tegmental tracts being the most frequently affected regions. Discontinuation of VGB led to complete resolution of VABAM. However, these T2/FLAIR hyperintensities in the predefined areas were not specific, neither for VGB treatment nor for TSC. In addition, we demonstrated that the presence of VABAM-like MRI abnormalities was not necessarily associated with clinical symptoms, but concomitant hormonal or steroid therapy increased the risk of these predefined clinical symptoms.

The prevalence of VABAM in 35.5% of our TSC cohort treated with VGB corresponds with the prevalence of 15%–47% reported in previous studies with varying sample sizes of VGB-treated children with IESS and various etiologies.[16,21–28] Two of these studies also included children with IESS without VGB treatment as controls, demonstrating a significant difference in the prevalence of VABAM in VGB-treated children with IESS compared to non-VGB-treated IESS children, in line with the results of the present study.[25,26] None of the previous studies included control groups of epilepsy patients without TSC and VGB treatment. Little is known about the etiology of these brain abnormalities in patients without VGB treatment. It could be hypothesized that the observed brain MRI changes are attributed to abnormal myelination, recurrent seizures, other antiseizure medications

TABLE 3 Association between VABAM/VABAM-like changes and predefined clinical symptoms, and determinants.

	RR (95% CI)	*p*
Clinical symptoms[a]		
VABAM/VABAM-like changes	2.76 (.68–8.77)	.14
Determinants of clinical symptoms[a]		
VGB treatment during MRI	4.79 (.88–34.24)	.13
Concomitant hormonal/steroid therapy	9.00 (2.21–18.43)	**.002**

Note: $p < .05$ was considered statistically significant and marked bold.

Abbreviations: CI, confidence interval; MRI, magnetic resonance imaging; RR, risk ratio; VABAM, VGB-associated brain abnormalities on MRI; VGB, vigabatrin.

[a]Univariable logistic regression analysis.

or different underlying etiology. Young age at VGB initiation (particularly <12 months) appeared to be a risk factor for VABAM in earlier studies.[22,25,26] Our study was not able to evaluate age as a dichotomous predictor, because 92.5% of our patients started with VGB treatment before the age of 12 months. Age was a continuous variable; however, it was not predictive of VABAM. In previous studies, high VGB peak doses were associated with increased VABAM risk, including IESS patients of any etiology.[16,25–28] Although the average peak dosage in the present study was comparable to earlier studies (141.9 mg/kg/day compared to 110–170 mg/kg/day),[1–4] we did not find an association between high peak dosage and the prevalence of VABAM. One possible explanation is that TSC patients might be less susceptible to higher VGB (peak) dosage, because TSC infants seem to be less prone to VABAM compared to IESS patients due to other pathophysiological mechanisms related to underlying etiology.[44]

Clinical symptoms of VABAM were previously studied in two cohorts.[16,28] Reyes Valenzuela et al.[28] reported a prevalence of clinical symptoms in 25 of 44 VGB-treated VABAM cases (56.8%), manifesting as a movement disorder in 22.6%. However, it remains unclear whether all clinical symptoms of interest could be attributed to either VABAM, VGB treatment itself, or the underlying etiology, because symptoms were already reported before VGB initiation in some patients and/or did not improve after treatment withdrawal or dose reduction in that study. Hussain and colleagues documented VABAM-associated symptoms in four of 10 patients with VABAM (40%), compared to 2.9% in those without visible VABAM.[16] This prevalence was also higher than that found in our study, namely, 11.7% in VABAM and VABAM-like MRI abnormalities patients. This might be explained by the larger sample size in our study and potential selection bias, as MRIs were performed only in cases of "VABAM-related symptoms" in the study of Hussain et al. Surprisingly, we did not find an association between VABAM or VGB and predefined symptoms. This might be due to the low prevalence of these symptoms in our cohort, potentially explained by the low incidence of severe VABAM and the young age of our patients, which may have complicated the assessment of movement disorders, among other symptoms. Although we did not find a statistically significant association, the symptoms of interest resolved in all cases after VGB dose reduction or treatment discontinuation, and so did VABAM, suggesting some co-occurrence. However, this does not exclude spontaneous resolution as well. Finally, our study revealed that concomitant hormonal or steroid therapy was independently associated with the occurrence of the specific clinical symptoms, which was still under debate in previous studies due to contradicting results.[16,28]

This is the first study evaluating VABAM and VABAM-like MRI abnormalities in a large homogenous cohort of children with TSC with and without VGB treatment with MRIs performed at approximately the same age. Moreover, it is the first study to include age-matched non-TSC patients with epilepsy without VGB treatment as controls. Investigators evaluating brain MRIs were blinded, reducing the risk of bias. All VGB-treated TSC patients had imaging before treatment initiation, which made it possible to evaluate a potential causal relation between VGB and VABAM. Finally, the risk of selection bias was limited, as all TSC patients had regular brain MRIs at least every 2 years, which implies that MRIs were not performed in response to clinical symptoms.

There are, however, some limitations to consider. First, we were not able to include a group of non-TSC epilepsy patients with VGB treatment, which would have improved the study design and enabled investigation of the influence of TSC compared with other etiologies and refractory epilepsy on VABAM evolution. Second, due to the retrospective nature of the study, data collection regarding VGB dosage and treatment duration may not have been entirely accurate during the MRI. However, we generally advise patients to keep a stable dose. Moreover, we focused on conventional MRI in the current study, although spectroscopy or diffusion tensor imaging could be of interest to evaluate as well, to further characterize the microstructural and metabolic changes associated with these lesions. Additionally, although this is one of the largest cohort studies, the sample size was still limited, hampering association analyses between VABAM and clinical symptoms due to the low prevalence of the latter. Moreover, event rates were low, and therefore advanced models could have fit the data better. However, we chose standard regression, as we expected the effects to be small. Finally, we included a selected cohort of infants with TSC, with treatment initiation before the age of 2 years. Although young age has previously been suggested to confer a higher risk of VABAM, the risk of VABAM to older TSC patients on VGB is uncertain.

5 | CONCLUSIONS

Brain MRI changes are common in VGB-treated patients with TSC, but VABAM-like MRI abnormalities are exclusive neither for VGB nor for TSC. Therefore, one may argue that the term VABAM is incorrect, because these typical MRI abnormalities are also seen in young children with epilepsy who are not treated with VGB, here labeled

VABAM-like MRI changes. The origin of these brain MRI changes is unknown, although factors such as abnormal myelination, etiology of epilepsy, recurrent seizures, or certain antiseizure medications may have contributed to its occurrence. VABAM disappeared after VGB discontinuation, and the presence of VABAM/VABAM-like MRI abnormalities was not associated with clinical symptoms, suggesting that the clinical impact of VABAM is minimal. Current clinical recommendations[19] that propose early, even presymptomatic, VGB treatment in infants with TSC are justified, as this study confirms the notion that the well-known beneficial antiseizure effects of VGB outweigh the risk of irreversible clinical consequences of VABAM.

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CONFLICT OF INTEREST STATEMENT

The authors have no financial relationships and no conflicts of interest relevant to this article to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

DATA AVAILABILITY STATEMENT

Anonymized data generated and analyzed during the current study are available from the corresponding author on reasonable request. Statistical code will be shared with any qualified investigator by emailing the corresponding author.

CONSENT TO PARTICIPATE

All TSC patients who were included previously consented to study publication via the Dutch TSC Registry and EPISTOP prospective study and trial. For the non-TSC epilepsy patients without VGB, additional informed consent was not necessary according to the Dutch Medical Research Involving Human Subjects Act. Patients who actively objected to any research participation in the past were excluded from study participation.

PREVIOUS PUBLICATION OF STUDY RESULTS

Preliminary results of this study were presented by poster at the European Pediatric Neurology Society Congress in 2023 and European Congress of Epileptology in 2024.

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SUPPORTING INFORMATION

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

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