UCLA

UCLA Previously Published Works

Title

Risk of vigabatrin-associated brain abnormalities on MRI in the treatment of infantile spasms is dose-dependent.

Permalink

<https://escholarship.org/uc/item/0s78r2g7>

Journal

Epilepsia, 58(4)

ISSN

0013-9580

Authors

Hussain, Shaun A
Tsao, Jackie
Li, Menglu
et al.

Publication Date

2017-04-01

DOI

10.1111/epi.13712

Peer reviewed

Risk of vigabatrin-associated brain abnormalities on MRI in the treatment of infantile spasms is dose-dependent

*Shaun A. Hussain, *Jackie Tsao, †Menglu Li, ‡Madeline D. Schwarz, *Raymond Zhou, *Joyce Y. Wu, §Noriko Salamon, and *¶Raman Sankar

Epilepsia, 58(4):674–682, 2017

doi: 10.1111/epi.13712

SUMMARY

Objective: Although the link between vigabatrin (VGB) and retinotoxicity is well known, little attention has been focused on the risk of VGB-associated brain abnormalities on magnetic resonance imaging (MRI) (VABAM), namely reversible—and largely asymptomatic—signal changes in the thalami, basal ganglia, brainstem tegmentum, and cerebellar nuclei. Using a large infantile spasms cohort, we set out to identify predictors of these phenomena.

Methods: Children with infantile spasms were retrospectively identified. Brain MRI reports were serially reviewed without knowledge of VGB exposure. Upon VABAM discovery, records were systematically reviewed to ascertain presence of symptoms attributable to VGB. Separately, progress notes were sequentially reviewed to identify and quantify VGB exposure.

Results: We identified 507 brain MRI studies among 257 patients with infantile spasms. VGB treatment was documented in 143 children, with detailed exposure data available for 104, of whom 45 had at least one MRI study during VGB treatment. Among the limited subset of asymptomatic children who underwent MRI ($n = 40$), 6 exhibited VABAM. Risk of asymptomatic VABAM was dose-dependent, as peak (but not cumulative) VGB dosage was strongly associated with asymptomatic VABAM ($p = 0.0028$). In an exploratory analysis, we encountered 4 children with symptomatic VABAM among 104 patients with detailed VGB exposure data. Risk of symptomatic VABAM was seemingly dose-independent, and potentially associated with concomitant hormonal therapy (i.e., prednisolone and adrenocorticotrophic hormone [ACTH]) ($p = 0.039$).

Significance: We have demonstrated dose-dependent risk of asymptomatic VABAM and uncovered a possible association between symptomatic VABAM and concomitant hormonal therapy. Caution should be exercised in the use of high VGB dosage (i.e., >175 mg/kg/day), and further study is warranted to confirm the potential impact of hormonal therapy.

KEY WORDS: West syndrome, Epileptic spasms, Toxicity, Neuroimaging.

Dr. Hussain is the Director of the UCLA Infantile Spasms Program, David Geffen School of Medicine and Mattel Children's Hospital UCLA, Los Angeles, California.

Accepted January 25, 2017; Early View publication February 23, 2017.

*Division of Pediatric Neurology, David Geffen School of Medicine and Mattel Children's Hospital UCLA, Los Angeles, California, U.S.A.; †School of Medicine and Health Sciences, George Washington University, Washington, District of Columbia, U.S.A.; ‡School of Medicine, University of California, San Francisco, San Francisco, California, U.S.A.; §Departments of §Radiology, and ¶Neurology, David Geffen School of Medicine and Mattel Children's Hospital UCLA, Los Angeles, California, U.S.A.

Address correspondence to Shaun A. Hussain, UCLA Pediatric Neurology, 10833 Le Conte Ave, Room 22-474, Los Angeles, CA 90095-1752, U.S.A. E-mail: shussain@mednet.ucla.edu

Wiley Periodicals, Inc.

© 2017 International League Against Epilepsy

Infantile spasms (also known as epileptic spasms in the most recently proposed International League Against Epilepsy (ILAE) classification scheme¹) is an often devastating form of epilepsy with onset in the first year of life; is frequently attributed to one of many structural, genetic, or metabolic disorders; and is usually accompanied by neurodevelopmental arrest or regression.² Infantile spasms is characterized by clusters of brief seizures termed spasms and a spectrum of severe electroencephalographic abnormalities including hypsarrhythmia.³ A lack of prompt and successful treatment is associated with adverse long-term

KEY POINTS

- Asymptomatic vigabatrin-associated brain abnormalities on MRI (VABAM) are common and associated with peak—but not cumulative—dosage
- Although relatively uncommon, symptomatic VABAM is a significant risk and does not appear to be dose-dependent
- Symptomatic VABAM might be associated with concomitant hormonal therapy (corticosteroids and ACTH)

developmental outcomes.⁴ As such, practitioners regularly utilize high-risk treatments, including natural⁵ and synthetic⁶ adrenocorticotrophic hormone (ACTH), prednisolone,⁷ and vigabatrin (VGB).⁸ Despite recognized efficacy,^{9,10} the use of VGB has been limited foremost by reports of retinopathy resulting in permanent peripheral visual field defects termed VGB-associated visual field loss (VAVFL).^{11,12} Estimates of VAVFL risk vary substantially, though the risk appears to be lower among children,¹³ and especially low among infants with treatment duration <12 months.¹⁴ Similarly, in a recent large-scale study using electroretinography (ERG)—defined retinotoxicity as a surrogate marker for VAVFL, retinotoxicity was least frequent among children treated for <6 months.¹⁵ However, the actual impact of VAVFL on patient functioning and quality of life—especially among children—may be quite modest and, in our own experience, the risk of clinically apparent vision loss approaches zero.¹⁶

VAVFL is certainly not the only potential side effect of VGB.¹⁷ Of perhaps greater concern in the treatment of infantile spasms is the emergence of VGB-associated brain abnormalities on magnetic resonance imaging (MRI) (VABAM), namely reversible high T2 signal and restricted diffusion in the thalami, basal ganglia, brainstem tegmentum, and cerebellar dentate nuclei. Whereas VABAM does not seem to occur in older children and adults, the risk of asymptomatic VABAM in infancy is approximately 22–32%.^{18–20} Furthermore, VABAM appears to be associated with high dosage,^{18,19} younger age,^{18,20,21} and “cryptogenic” etiology.²⁰ The reversibility and largely asymptomatic character of this imaging phenomenon may provide some consolation, but VABAM have been linked in rare reports to hyperkinetic movement disorders,^{22,23} including choreoathetosis, myoclonus, and tremor, as well as life-threatening acute encephalopathy.^{22,24} An example of MRI findings in a case of symptomatic VABAM is presented in Figure 1. Still, the pathophysiologic mechanism is unknown—although both intramyelinic edema²⁵ and axonal phenomena²⁶ are suspected culprits—and a causal relationship linking VGB to movement disorders and severe encephalopathy has not been established. In the study of Fong and colleagues,²³ the attribution of movement disorders to VGB exposure was

specifically challenged, as they encountered several cases in which movement disorders (1) occurred in the absence of VGB exposure, (2) occurred in the absence of VABAM, (3) resolved despite continuation of VGB, or (4) continued despite withdrawal of VGB.²³

Given the high prevalence of asymptomatic VABAM among infants and the potentially life-threatening (albeit rare) consequences of symptomatic VABAM, we set out to identify predictors of both symptomatic and asymptomatic VABAM using a large infantile spasms cohort with meticulously quantified VGB exposure.

METHODS

Standard protocol approvals

The use of human subjects and the analyses presented herein were approved by the UCLA Institutional Review Board.

Patients

All patients with video electroencephalography (EEG)—confirmed infantile spasms evaluated at UCLA between February 2007 and February 2014 were identified retrospectively by searching a clinical EEG database that includes all patients who underwent video-EEG at our center. There were no exclusion criteria.

Ascertainment of characterization of VABAM

Ascertainment of VABAM was accomplished in a three-stage process. First, all MRI reports were screened in chronological order by a reviewer who was specifically blinded to VGB exposure. For each MRI report, we sought to identify “potential” VABAM by noting any mention of restricted diffusion and/or hyperintense signal on T2 or fluid-attenuated inversion recovery (FLAIR) sequences, if localized to the thalami, basal ganglia, brainstem, or cerebellar nuclei. Second, for each case of potential VABAM, the actual MRI images were reviewed to confirm VABAM and to distinguish it from other potential entities (e.g., posterior reversible encephalopathy syndrome). Third, the final identification of VABAM required documentation of VGB exposure. We verified that all MRI studies with VABAM took place during VGB exposure (separately abstracted from the medical record; see below). In contrast, the ascertainment of symptomatic VABAM was not blinded. When VABAM was identified on review of MRI, progress notes in the medical record were serially reviewed in the search for symptoms consistent with VABAM (i.e., movement disorders, encephalopathy, bradycardia, and respiratory distress/arrest).

Quantification of VGB exposure

The quantification of VGB exposure was accomplished independent of VABAM ascertainment. For each patient, neurology progress notes were reviewed sequentially, with notation for each encounter of (1) date, (2) VGB dosage

Figure 1.
Example of symptomatic VABAM.
Example of VABAM (patient 2,
Table 1) during symptomatic phase
(A and B), and several months later
after clinical resolution (C and D).
Epilepsia © ILAE

(mg/day), (3) patient weight (kg), and (4) VGB titration/taper schedule. This allowed calculation of (1) duration of VGB treatment, (2) peak weight-based dosage, (3) weighted-average weight-based dosage, and (4) cumulative total dosage (grams).

Statistical methods

Continuous summary data were presented as mean and standard deviation, or median and interquartile range based on nonparametric distributions where appropriate. Comparisons of percentages, means, and medians were accomplished with the Fisher's exact test, heteroscedastic independent samples *t*-test, and Wilcoxon rank-sum test, respectively. We did not adjust for multiple comparisons. Univariate and multivariate logistic regression was used to evaluate potential predictors of VABAM. Whereas *p*-values < 0.10 were explicitly reported, only *p*-values < 0.05 were considered statistically significant. Statistical calculations were facilitated with STATA software (version 11; Statacorp, College Station, TX, U.S.A.).

RESULTS

Subjects

Clinical and demographic characteristics of the study population have been described previously,¹⁶ and are

summarized in Table S1. We identified 257 patients with infantile spasms, who underwent a total of 507 brain MRI studies. One hundred forty-three (55.6%) were treated with VGB, with detailed dates of exposure available for 104 (72.7%). Inadequate exposure data (especially dates of exposure) was explained in most cases by patients having received (or at least started) VGB at other centers. Those patients with (*n* = 104) and without (*n* = 39) detailed VGB exposure data did not differ on the basis of sex, age of onset of infantile spasms, or etiology (Table S1). Of these 104, 45 (43.3%) underwent at least one MRI brain study during VGB treatment. For five children, MRI was specifically obtained to evaluate for symptoms suspicious for VGB toxicity (i.e., hyperkinetic movements, severe encephalopathy). In the remaining 40 cases, MRI was obtained for other reasons (i.e., etiologic or surgical evaluation).

Vigabatrin-associated brain abnormalities on MRI

The pattern of VABAM ascertainment is illustrated in Figure 2 and clinical characteristics of the patients with VABAM are summarized in Table 1. Five children underwent MRI specifically to evaluate for VGB toxicity, having presented with unexplained hyperkinetic movements, marked encephalopathy, respiratory arrest, and/or bradycardia in the midst of VGB treatment. VABAM was identified among four (80.0%). Of note, although respiratory arrest

Figure 2.

Ascertainment of vigabatrin-associated brain abnormalities on MRI (VABAM). “VABAM symptoms” included hyperkinetic movements, severe encephalopathy, and respiratory compromise. *Epilepsia* © ILAE

has not been reported previously as a specific manifestation of VABAM, the two cases we present here (Table 1, patients 2 and 3) are compelling given the distribution of pontine and medullary MRI changes, as well as associated encephalopathy. Symptoms resolved in all four patients within days to weeks of VGB discontinuation. Follow-up MRI was obtained in three patients and demonstrated complete resolution of MRI changes. One patient (Table 2, patient 3) did not undergo MRI during UCLA follow-up. Another patient with infantile spasms of unknown cause and suspected VABAM (acute encephalopathy, respiratory distress, and apnea) did not exhibit any MRI changes. In this case, VGB was immediately discontinued, symptoms promptly resolved, and no other explanation for symptoms was identified.

Among the 40 children who underwent MRI for other reasons, we encountered asymptomatic VABAM in 6 (15.0%). VGB was promptly discontinued among five patients, and follow-up MRI demonstrated resolution of VABAM in these five cases. In the sixth case (Table 1, patient 9), the medical record does not indicate that the significance of

VABAM was recognized, although the findings are clearly stated in the radiology report and evident on re-review of the actual MRI images, VGB was not discontinued during UCLA follow-up, and no subsequent MRI was obtained.

Vigabatrin exposure

Among the 104 patients with detailed VGB exposure data, the median peak dosage was 141.5 mg/kg/day (104.8–166.0), median weighted-average dosage was 115.0 mg/kg/day (88.4–144.0), and median cumulative dosage was 314.0 g (140.8–645.7). A dose-dependent risk of asymptomatic VABAM was identified in an analysis that considered only the 40 children who underwent MRI for reasons other than VABAM ascertainment (Table 2). Median peak VGB dosage among children with asymptomatic VABAM (198.4 mg/kg/day) was significantly higher than peak dosage among children without VABAM (132.0 mg/kg/day), $p = 0.0028$. The same effect was observed in evaluating median weighted-average VGB dosage, as patients with asymptomatic VABAM exhibited higher weighted-average dosage (145.9 mg/kg/day) in comparison to patients without VABAM (103.3 mg/kg/day), with $p = 0.031$. Conversely, in comparing children with peak VGB dosage above and below the median (140.2 mg/kg/day), we observed all six cases of asymptomatic VABAM among the children with higher than median peak dosage ($p = 0.020$). Although we hypothesized that VABAM risk might increase with higher cumulative VGB dosage or longer treatment duration, no such effect was observed; a potential cumulative exposure effect was likely confounded by early VGB discontinuation upon the discovery of VABAM. These associations were not modified when we included patients with symptomatic VABAM, such that the 10 patients with any VABAM (symptomatic or asymptomatic) exhibited higher peak and weighted-average VGB dosage than the 34 patients with confirmed absence of VABAM, with $p = 0.016$ and $p = 0.033$, respectively. However, in considering the specific risk of symptomatic VABAM across peak-dosage quartiles ($n = 26$, each), there was no trend, as we observed one case of symptomatic VABAM in each quartile. The occurrence of VABAM is displayed as a function of peak and cumulative VGB dosage in Figure 3. Foremost, 9 of 10 VABAM cases occurred with peak VGB dosage >125 mg/kg/day, and 6 occurred with dosage >175 mg/kg/day. On the other hand, one case (Table 1, patient 3) exhibited symptomatic VABAM with a peak dosage of just 26.5 mg/kg/day and cumulative dose of only 30 g. Similarly, many patients without VABAM, or with possible asymptomatic VABAM, tolerated high peak VGB dosage (>150 mg/kg/day) and high cumulative VGB dosage (>1 kg).

In reviewing the four cases with symptomatic VABAM, we noticed that three children were simultaneously treated with VGB and hormonal therapy (prednisolone and/or ACTH). Similarly, three of six patients with asymptomatic

Table 1. Characteristics of subjects with VABAM

Patients	Age at IS onset (mo) / sex	Etiology	Age at VGB start (mo)	Peak VGB dosage (mg/kg/day)	Cumulative VGB dosage (g)	Duration of VGB (mo)	Other treatments during VGB exposure	Distribution of VABAM	VABAM resolution	VABAM symptoms	Latency to symptoms (mo)	Symptom resolution
1	3.0/M	Unknown	36.5	159.7	2,241.5	42.6	CLB, TPM, CLN, KD	T, BS, CBL	Yes	MM	37.5	Yes
2	4.7/M	DEND	5.8	220.6	74.3	2.4	PRED, ACTH, ZNS, LEV	T, GP, P, CBL, CP	Yes	E, RA, BC	2.0	Yes
3	3.0/F	HME	4.3	26.5	30.0	3.9	ACTH	BS, CBL	Unknown	E, RA, BC	3.8	Yes
4	5.8/F	Lissencephaly	11.7	127.6	272.5	12.1	PRED, ACTH, CLN, CLB, PHB, ZNS	T, BS	Yes	CA	12.0	Yes
5	6.1/F	Hemorrhage	7.8	182.9	229.5	5.0	None	BS, GP	Yes	None	—	—
6	3.0/M	TSC	3.4	141.5	586.5	12.8	CLB, LEV, ZNS, LAC, tuber resection	T, BS	Yes	None	—	—
7	6.7/M	PMG	8.9	202.0	239.5	5.0	LEV, TPM, LTG, CLN, ZNS	T, BS	Yes	None	—	—
8	7.0/F	Hemorrhage	14.7	204.1	718.5	22.4	ACTH, TPM, VPA, LEV, KD, DZP	T, GP, BS, CBL	Yes	None	—	—
9	4.0/M	Unknown	7.1	238.1	54.6	2.1	ACTH, B6, TPM	BS	Unknown	None	—	—
10	2.6/M	Unknown	4.0	194.8	327.8	9.4	ACTH, VPA, ZNS	T, GP, BS	Yes	None	—	—

ACTH, adrenocorticotropic hormone; B6, pyridoxine; BC, bradycardia; BS, brainstem tegmentum; CA, choreoathetosis; CBL, deep cerebellar nuclei; CLB, clobazam; CLN, clonazepam; CP, cerebral peduncle; DEND, developmental delay, epilepsy, and neonatal diabetes; DZP, diazepam; E, encephalopathy; GP, globus pallidus; HME, hemimegalencephaly; KD, ketogenic diet; LAC, lacosamide; LEV, levetiracetam; LTG, lamotrigine; MM, multifocal myoclonus; P, putamen; PMG, polymicrogyria; PRED, prednisolone; RA, respiratory arrest; T, thalamus; TPM, topiramate; TSC, tuberous sclerosis complex; VABAM, vigabatrin-associated brain abnormalities on MRI; ZNS, zonisamide.

VABAM exhibited dual therapy. This contrasted with dual therapy observed in just 7 (20.6%) of 34 cases with confirmed absence of VABAM (Table 2). Although the difference was statistically significant ($p = 0.043$) when contrasting the 10 patients with any VABAM compared to the 34 patients without VABAM, this was not a planned comparison and should be interpreted with caution.

In an exploratory analysis, we performed multiple logistic regression to evaluate the independent effect of dosage measures—and more importantly—to search for potential confounding among candidate predictor variables (Table 3). Because VABAM does not appear to occur in older children and adults, our *a priori* hypothesis was that—in addition to higher dosage—lower age at VGB treatment and possibly lower age at infantile spasms onset increase risk of VABAM. Although we suspected specific etiologic classifications or coadministration of hormonal therapy (prednisolone and/or ACTH) might impact risk, there was no specific pre-test rationale as to the direction or magnitude of effect. Furthermore, there was no prior suspicion that risk factors would differ for symptomatic and asymptomatic VABAM. In the evaluation of asymptomatic VABAM, the previously identified risk associated with peak or weighted-average VGB dosage was again observed, and was not confounded by any other candidate predictors. Conversely, in the evaluation of symptomatic VABAM we identified neither a dose–response effect nor any confounding of dose–response by other candidate predictors. However, we did observe significant risk associated with concomitant hormonal therapy. Of note, because there were only four cases of symptomatic VABAM, the risk estimate (odds ratio) exhibited an exceptionally large confidence interval (odds ratio [OR] 18.1, 95% confidence interval 1.15–282.6).

DISCUSSION

This study is significant in that we have determined that risk of asymptomatic VABAM is linked to high peak VGB dosage, but not associated with high cumulative VGB exposure. Secondly, in an exploratory analysis, our results suggest that symptomatic VABAM may be associated with concomitant hormonal therapy. However, this study has several significant limitations. Foremost, this is a retrospective report, lacking randomization of treatment allocation, dosage, or duration of treatment. Secondly, despite our efforts to mitigate bias in the ascertainment of VABAM, this was imperfect. This is especially true in the case of symptomatic VABAM, as our search for symptoms of VGB toxicity was specifically guided by imaging findings. Moreover, even though MRI reports were reviewed without knowledge of parameters of VGB exposure, a few reports included information indicating that patients were receiving VGB or that the reason for obtaining the MRI was to specifically search for symptomatic VGB toxicity. As a result, our identification of VABAM was biased to some extent. It is

Table 2. Comparison of patients without VABAM, with asymptomatic VABAM, or with any VABAM

	VABAM absent (n = 34)	Asymptomatic VABAM present (n = 6)	Sig. ^a	Asymptomatic or symptomatic VABAM present (n = 10)	Sig. ^b
Demographics					
Age of onset of infantile spasms, mo ^c	5.2 (2.4–7.6)	5.0 (3.0–6.7)	NS	4.4 (2.0–6.1)	NS
Female sex, n (%)	17 (50.0%)	2 (33.3%)	NS	4 (40.0%)	NS
Etiology					
Known etiology	31 (91.2%)	4 (66.7%)	NS	7 (70.0%)	NS
Tuberous sclerosis complex	11 (32.3%)	1 (16.7%)	NS	1 (10.0%)	NS
Treatment characteristics					
Age at VGB treatment, mo ^c	9.9 (5.5–22.0)	7.4 (4.0–8.9)	NS	7.4 (4.3–11.7)	NS
Concomitant hormonal therapy, n (%)	7 (20.6%)	3 (50.0%)	NS	6 (60%)	0.043
VGB exposure					
Peak dosage, mg/kg/day ^c	132.0 (106.4–156.3)	198.4 (182.9–204.1)	0.0028	188.9 (141.5–204.1)	0.016
Weighted-average dosage, mg/kg/day ^c	103.3 (83.3–121.0)	145.9 (103.2–160.2)	0.031	132.1 (103.2–160.2)	0.033
Cumulative dosage, g ^c	565.0 (199.7–812.5)	283.7 (229.5–586.5)	NS	256.0 (74.3–586.5)	NS
Treatment duration, mo ^c	13.3 (6.8–21.2)	7.2 (5.0–12.8)	NS	7.2 (3.9–12.8)	NS

^ap-Value for comparison of patients without VABAM to patients with asymptomatic VABAM.^bp-Value for comparison of patients without VABAM to patients with any (asymptomatic or symptomatic) VABAM.^cData presented as median (interquartile range). **Figure 3.**

VABAM as a function of peak and cumulative VGB dosage. All but one patient with asymptomatic VABAM had a peak VGB dose >175 mg/kg/day, and only one patient with VABAM exhibited a high cumulative VGB exposure. Sixty patients (open circles) did not undergo MRI and could only be classified as not exhibiting symptomatic VABAM, but nevertheless could have had asymptomatic VABAM.

Epilepsia © ILAE

evaluation. Similarly, we have likely failed to identify patients with symptomatic VABAM who did not undergo MRI during VGB treatment (i.e., when clinicians did not recognize or document “mild” symptoms, or—perhaps most likely—simply failed to recognize that that symptoms were potentially related to VGB exposure). There was unfortunately no systematic effort to ascertain potential symptoms of VABAM, especially as some of the patients in this series were treated before VABAM was first described. Furthermore, our search for VABAM was critically dependent on the original clinical interpretations of the MRI studies. We reviewed only the MRI reports, not the actual images of all studies. Accordingly, our identification of VABAM is vulnerable to the biases of the radiologists who performed the initial clinical interpretations. We suspect there were cases in which VABAM—especially asymptomatic VABAM—was simply missed in the setting of subtle signal changes or in the presence of other distracting imaging abnormalities. Indeed, we encountered one case in which VABAM was identified on an index MRI study and then retrospectively identified on a prior study in which VABAM had been missed. Even more broadly, clinical-radiologic correlation might be poor. There may certainly be cases of symptomatic VGB toxicity without conspicuous MRI abnormalities, as suggested by the patient we have reported with clinically suspected VGB toxicity, absent MRI findings, and prompt clinical recovery following VGB withdrawal. On this basis, we may have failed to identify cases with symptomatic VABAM. An ideal study would implement independent and blinded review of de-identified MRI images on a prospective basis by multiple neuroradiologists so as to eliminate bias and establish measures of interrater reliability. Similarly, an ideal study to quantify symptomatic VABAM risk would employ unbiased measures of clinical

notable that we have assumed that the 40 asymptomatic patients who underwent MRI are representative of all asymptomatic patients. A variety of factors (e.g., seizure burden, refractoriness, etc.) might have impacted the decision to obtain neuroimaging, especially as part of a surgical

Table 3. Logistic regression analyses

	OR	95% CI	Sig.
Symptomatic VABAM (n = 104)			
Sequential univariate models			
Age of onset of infantile spasms (mo)	0.84	0.62–1.16	NS
Female	1.22	0.17–9.0	NS
Etiology unknown (vs. known)	1.25	0.12–12.7	NS
Age at VGB treatment (mo)	0.99	0.92–1.07	NS
Concomitant hormonal therapy	11.3	1.12–114.1	0.040
Peak VGB dosage (mg/kg/day)	1.00	0.98–1.02	NS
Weighted-average VGB dosage (mg/kg/day)	1.00	0.97–1.03	NS
Cumulative VGB dosage (kg)	1.31	0.35–4.78	NS
VGB treatment duration (mo)	1.01	0.95–1.07	NS
Multivariate model			
Age at VGB treatment (mo)	0.82	0.57–1.19	NS
Concomitant hormonal therapy	18.1	1.15–282.6	0.039
Peak VGB dosage (mg/kg/day)	0.99	0.97–1.01	NS
Cumulative VGB dosage (kg)	2.08	0.47–9.13	NS
Asymptomatic VABAM (n = 40)			
Sequential univariate models			
Age of onset of infantile spasms (mo)	0.93	0.75–1.17	NS
Female	0.50	0.08–3.10	NS
Etiology unknown (vs. known)	5.17	0.65–41.0	NS
TSC (vs. other)	0.42	0.04–4.0	NS
Age at VGB treatment (mo)	0.92	0.79–1.06	NS
Concomitant hormonal therapy	1.93	0.29–12.8	NS
Peak VGB dosage (mg/kg/day)	1.05	1.01–1.10	0.008
Weighted-average VGB dosage (mg/kg/day)	1.05	1.008–1.09	0.017
Cumulative VGB dosage (kg)	0.28	0.02–3.30	NS
VGB treatment duration (mo)	0.94	0.83–1.05	NS
Multivariate model			
Age at VGB treatment (mo)	0.96	0.80–1.15	NS
Concomitant hormonal therapy	1.38	0.12–15.9	NS
Peak VGB dosage (mg/kg/day)	1.05	1.003–1.10	0.034
Cumulative VGB dosage (kg)	0.97	0.10–9.04	NS

severity with raters specifically blinded to both VGB exposure and MRI findings.

This report of substantial dose-dependent risk of asymptomatic VABAM with uniform resolution after VGB discontinuation suggests that VGB plays a causal role in the development of VABAM, and that VGB is not merely *associated* with VABAM, as implied by our acronym. Nevertheless, this study does not prove cause and effect. This is particularly true of symptomatic VABAM given our lack of observed dose–response, and especially in light of the observation of Fong and colleagues that movement disorders reported during the International Collaborative Infantile Spasms Study (ICISS) were not strongly linked to MRI changes or VGB exposure.²³ Moreover, there are reports of other pathologic entities that can mimic VABAM such as posterior reversible encephalopathy syndrome (PRES) with atypical distributions of reversible MRI signal changes, including the thalami, cerebellum, brainstem, and basal ganglia.²⁷ Similarly, reversible signal changes have been reported in association with other

antiepileptic drugs, including phenytoin.²⁸ It is important to acknowledge that 9 of the 10 patients with VABAM in this series received other antiseizure drugs during VGB exposure, and six specifically received hormonal therapy (prednisolone and/or ACTH).

Although concomitant hormonal therapy (prednisolone and/or ACTH) was not associated with the presence of asymptomatic VABAM, we detected a significant association with symptomatic VABAM, as three of four patients with symptomatic VABAM were exposed to hormonal therapy during VGB treatment. However, this conclusion is based on a very small number of symptomatic cases and should be regarded as a potential association that requires replication in a separate cohort. Nevertheless, although the index case described by Pearl et al.¹⁸ with suspected symptomatic VABAM manifesting in opisthotonus was not simultaneously treated with hormonal therapy, it is noteworthy that hormonal therapy was coadministered with VGB in both cases of symptomatic VABAM in the series reported by Dill et al.,²² as well as each case independently reported by Hernández et al.²⁴ and Schonstedt et al.²⁹ Similarly, the only patient reported by Fong et al.²³ with “possible” VGB-induced choreoathetosis and typical MRI changes was also treated with simultaneous VGB and prednisolone. In addition, just as we found no association between symptomatic VABAM and peak VGB dosage in our series, VGB dosage in each of the aforementioned case reports was not exceptionally high and did not exceed 150 mg/kg/day. This potential association is of concern given recent findings from the ICISS,³⁰ indicating that combined hormonal therapy (high dose prednisolone or tetracosactide depot) and VGB is more efficacious than hormonal therapy alone. However, the possibility that simultaneous hormonal therapy may increase the risk of symptomatic VABAM may deter practitioners from adopting combination therapy protocols. Indeed, although the addition of VGB yielded substantially higher efficacy in the ICISS study (NNT = 7), the prevalence of reported movement disorders was higher among those patients treated with VGB (7.5%) in comparison to patients treated with hormonal therapy alone (1.0%, $p = 0.002$).³⁰

Our understanding of VABAM is incomplete. Although this study adds to a growing body of circumstantial data implicating VGB as the proximate cause of VABAM, identified risk factors have varied somewhat across studies, and none are especially robust predictors of VABAM. It is perplexing that risk factors for asymptomatic VABAM are seemingly distinct from predictors of symptomatic VABAM. The conceptualization of symptomatic VABAM as a “severe” case of VABAM is likely an oversimplification, and although logical, there are no data demonstrating that asymptomatic VABAM is a harbinger of symptomatic VABAM. We suspect that there are other genetic, metabolic, and environmental (treatment) modifiers of VABAM risk.

Further study is of course warranted. With the perspective that infantile spasms pose a significant neurodevelopmental threat, we view VGB as a relatively safe drug with low risk of meaningful vision loss,¹⁶ and with substantial—and perhaps modifiable—risk of VABAM. It is notable that our data suggest that the risk of asymptomatic VABAM may be mitigated by avoidance of exceptionally high dosage (e.g., peak dosage >175 mg/kg/day). The risk of symptomatic VABAM may be reduced by deferring simultaneous hormonal therapy, although the latter suggestion is predicated on very limited exploratory data, and the avoidance of hormonal therapy may jeopardize response rates. Above all, the risks and costs of ongoing infantile spasms and hypsarrhythmia must weigh heavily the practitioner's decision to withhold or delay VGB.

ACKNOWLEDGMENTS

This study was accomplished with funding from the Epilepsy Therapy Project, Milken Family Foundation, Hughes Family Foundation, the Elsie and Isaac Fogelman Endowment, and the UCLA Children's Discovery and Innovation Institute.

DISCLOSURE OF CONFLICT OF INTEREST

Dr. Hussain has received research support from the Epilepsy Therapy Project, the Milken Family Foundation, the Hughes Family Foundation, the Elsie and Isaac Fogelman Endowment, Eisai, Lundbeck, Insys Therapeutics, GW Pharmaceuticals, and the National Institutes of Health (NIH; R34MH089299), and has served on the scientific advisory boards of Questcor Pharmaceuticals, Mallinckrodt Pharmaceuticals, and Upsher-Smith Laboratories, and as a consultant to Eisai. Dr. Wu serves on the professional advisory board for the Tuberous Sclerosis Alliance; has received honoraria from and serves on the scientific advisory board and the speakers' bureau for Novartis Pharmaceuticals Inc. and Lundbeck; and has received research support from the Tuberous Sclerosis Alliance, Novartis Pharmaceuticals Inc., Today and Tomorrow Children's Fund, Department of Defense/Congressionally Directed Medical Research Program, and the NIH (P20NS080199, U01NS082320, R01NS082649, U54NS092090, and R01 NS092595). Dr. Sankar serves on scientific advisory boards for and has received honoraria and funding for travel from Eisai, UCB Pharma, Sunovion, Supernus, Upsher-Smith, Acorda, and Lundbeck Pharma; receives royalties from the publication of *Pediatric Neurology*, 3rd ed. (Demos Publishing, 2008) and *Epilepsy: Mechanisms, Models, and Translational Perspectives* (CRC Press, 2011); and serves on speakers' bureaus for and has received speaker honoraria from Eisai, UCB, GlaxoSmithKline, Cyberonics, Supernus, and Lundbeck. The remaining authors have no conflicts of interest. 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.

REFERENCES

- Berg AT, Berkovic SF, Brodie MJ, et al. Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005–2009. *Epilepsia* 2010;51:676–685.
- Shields WD. Infantile spasms: little seizures. BIG consequences. *Epilepsy Curr* 2006;6:63–69.
- Hrachovy RA, Frost JD, Kellaway P. Hypsarrhythmia: variations on the theme. *Epilepsia* 1984;25:317–325.
- O'Callaghan FJK, Lux AL, Darke K, et al. The effect of lead time to treatment and of age of onset on developmental outcome at 4 years in infantile spasms: evidence from the United Kingdom Infantile Spasms Study. *Epilepsia* 2011;52:1359–1364.
- Baram TZ, Mitchell WG, Tournay A, et al. High-dose corticotropin (ACTH) versus prednisone for infantile spasms: a prospective, randomized, blinded study. *Pediatrics* 1996;97:375–379.
- Lux AL, Edwards SW, Hancock E, et al. The United Kingdom Infantile Spasms Study comparing vigabatrin with prednisolone or tetracosactide at 14 days: a multicentre, randomised controlled trial. *Lancet* 2004;364:1773–1778.
- Hussain SA, Shinnar S, Kwong G, et al. Treatment of infantile spasms with very high dose prednisolone before high dose adrenocorticotrophic hormone. *Epilepsia* 2014;55:103–107.
- Elterman RD, Shields WD, Bittman RM, et al. Vigabatrin for the treatment of infantile spasms: final report of a randomized trial. *J Child Neurol* 2010;25:1340–1347.
- Appleton RE, Peters AC, Mumford JP, et al. Randomised, placebo-controlled study of vigabatrin as first-line treatment of infantile spasms. *Epilepsia* 1999;40:1627–1633.
- Elterman RD, Shields WD, Mansfield KA, et al. Randomized trial of vigabatrin in patients with infantile spasms. *Neurology* 2001;57:1416–1421.
- Eke T, Talbot JF, Lawden MC. Severe persistent visual field constriction associated with vigabatrin. *BMJ* 1997;314:180–181.
- Vanhatalo S, Noursiainen I, Eriksson K, et al. Visual field constriction in 91 Finnish children treated with vigabatrin. *Epilepsia* 2002;43:748–756.
- Maguire MJ, Hemming K, Wild JM, et al. Prevalence of visual field loss following exposure to vigabatrin therapy: a systematic review. *Epilepsia* 2010;51:2423–2431.
- Riikonen R, Renner-Primec Z, Carmant L, et al. Does vigabatrin treatment for infantile spasms cause visual field defects? An international multicentre study. *Dev Med Child Neurol* 2015;57:60–67.
- Westall CA, Wright T, Cortese F, et al. Vigabatrin retinal toxicity in children with infantile spasms: an observational cohort study. *Neurology* 2014;83:2262–2268.
- Schwarz MD, Li M, Tsao J, et al. A lack of clinically apparent vision loss among patients treated with vigabatrin with infantile spasms: the UCLA experience. *Epilepsy Behav* 2016;(Part A)57:29–33.
- Walker SD, Kälviäinen R. Non-vision adverse events with vigabatrin therapy. *Acta Neurol Scand Suppl* 2011;192:72–82.
- Pearl PL, Vezina LG, Saneto RP, et al. Cerebral MRI abnormalities associated with vigabatrin therapy. *Epilepsia* 2009;50:184–194.
- Wheless JW, Carmant L, Bebin M, et al. Magnetic resonance imaging abnormalities associated with vigabatrin in patients with epilepsy. *Epilepsia* 2009;50:195–205.
- Dracopoulos A, Widjaja E, Raybaud C, et al. Vigabatrin-associated reversible MRI signal changes in patients with infantile spasms. *Epilepsia* 2010;51:1297–1304.
- Wheless JW. Nonpharmacologic treatment of the catastrophic epilepsies of childhood. *Epilepsia* 2004;45(Suppl. 5):17–22.
- Dill P, Datta AN, Weber P, et al. Are vigabatrin induced T2 hyperintensities in cranial MRI associated with acute encephalopathy and extrapyramidal symptoms? *Eur J Paediatr Neurol* 2013;17:311–315.
- Fong CY, Osborne JP, Edwards SW, 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.
- Hernández Vega Y, Kaliakatos M, U-King-Im J, et al. Reversible vigabatrin-induced life-threatening encephalopathy. *JAMA Neurol* 2014;71:108–109.
- Cohen JA, Fisher RS, Brigell MG, et al. The potential for vigabatrin-induced intramyelinated edema in humans. *Epilepsia* 2000;41:148–157.
- Simao GN, Zarei Mahmoodabadi S, Snead OC, et al. Abnormal axial diffusivity in the deep gray nuclei and dorsal brain stem in infantile spasm treated with vigabatrin. *AJNR Am J Neuroradiol* 2011;32:199–203.
- McKinney AM, Short J, Truwit CL, et al. Posterior reversible encephalopathy syndrome: incidence of atypical regions of involvement and imaging findings. *AJR Am J Roentgenol* 2007;189:904–912.

28. Kim SS, Chang KH, Kim ST, et al. Focal lesion in the splenium of the corpus callosum in epileptic patients: antiepileptic drug toxicity? *AJNR Am J Neuroradiol* 1999;20:125–129.
29. Schonstedt V, Stecher X, Venegas V, et al. Vigabatrin-induced MRI changes associated with extrapyramidal symptoms in a child with infantile spasms. *Neuroradiol J* 2015;28:515–518.
30. O'Callaghan FJK, Edwards SW, Alber FD, et al. Safety and effectiveness of hormonal treatment versus hormonal treatment with vigabatrin for infantile spasms (ICISS): a randomised, multicentre, open-label trial. *Lancet Neurol* 2017;16:33–42.

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Table S1. Characteristics of the study population (n = 143).