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Publication Date

2024-11-21

DOI

10.1002/epi4.13099

Peer reviewed

Received: 30 April 2024 | Revised: 26 September 2024 | Accepted: 31 October 2024

DOI: 10.1002/epi4.13099

Epilepsia Open® Open Access

SHORT RESEARCH ARTICLE

Symptomatic vigabatrin-associated MRI toxicity is associated with simultaneous hormonal therapy among patients with infantile spasms

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Funding information
John Hench Foundation

Abstract

Vigabatrin-associated brain abnormalities on MRI (VABAM) are observed in approximately 20% of children who receive vigabatrin for treatment of infantile epileptic spasms syndrome. Although usually reversible and asymptomatic, VABAM is occasionally symptomatic. Whereas asymptomatic VABAM appears to be dose-dependent, symptomatic VABAM is possibly associated with co-administration of vigabatrin and hormonal therapy (i.e., corticosteroids or adrenocorticotropic hormone). With retrospective study of a cohort of vigabatrin-treated children, we evaluated candidate risk factors for VABAM. Among 108 children with detailed vigabatrin exposure data, we identified VABAM in 17 children (11 symptomatic). Symptomatic VABAM was strongly associated with simultaneous exposure to hormonal therapy ($p = 0.001$). Neither symptomatic nor asymptomatic VABAM were associated with peak vigabatrin dose. Although these data support the hypothesis that symptomatic VABAM risk is higher with coadministration of vigabatrin and hormonal therapy, this study does not establish a causal link. Further study is warranted to better understand the pathogenesis of VABAM and devise strategies to mitigate risk. Clinicians should carefully weigh the potential risk of symptomatic vigabatrin toxicity against the known benefit of vigabatrin and hormonal therapy coadministration.

Plain Language Summary: Several case reports suggest that the combination of vigabatrin and hormonal therapy for treatment of infantile spasms may provoke an adverse reaction known as symptomatic vigabatrin MRI toxicity (sVABAM, which includes characteristic changes on MRI images and associated symptoms). In response to these reports, we studied a large single-center cohort of children with infantile spasms and determined that combination therapy is indeed statistically associated with sVABAM. However, we have not proven that combination therapy actually causes sVABAM. Further study is needed to clarify the nature of sVABAM and risk factors thereof.

KEYWORDS
adrenocorticotropic hormone, prednisolone, corticosteroids, vigabatrin, west syndrome

1 | INTRODUCTION

Vigabatrin is an efficacious treatment for infantile epileptic spasms syndrome (IESS), both alone[1,2] and in combination with hormonal therapy (i.e., corticosteroids or ACTH).[3] However, safety is a major concern given risks of (1) irreversible vigabatrin-associated visual field loss (VAVFL)[4] and (2) vigabatrin-associated brain abnormalities on MRI (VABAM).[5–7] VABAM, which may represent white matter spongiosis and intramyelinic edema,[8] are observed in approximately 20% of infants with IESS who receive vigabatrin.[9] Based on MRI (hyperintensity on T2 or diffusion-weighted imaging), VABAM are localized to the basal ganglia, thalami, brainstem tegmentum, deep cerebellar nuclei,[5–7] as well as the hippocampus in a single case series.[10] When symptomatic, VABAM typically manifests as severe encephalopathy, a movement disorder (chorea or multifocal myoclonus), hypotonia, dysautonomia (chiefly bradycardia or respiratory suppression), or a combination thereof. Nevertheless, VABAM is usually asymptomatic and thought to be reversible in the vast majority of cases.[9] In a prior study from our group, asymptomatic VABAM (aVABAM) was associated with higher vigabatrin dosage, but symptomatic VABAM (sVABAM) appeared to be independent of vigabatrin dosage and potentially linked to simultaneous treatment with vigabatrin and hormonal therapy (VGB-HT).[11] Although several fulminant cases of sVABAM have been reported in the setting of VGB-HT,[11–13] no other large-scale studies have evaluated this potential association. Given these data suggesting a link between VGH-HT and sVABAM, and our adoption of a protocol that encourages VGB-HT as first line treatment,[14] we reexamined risk factors for VABAM by evaluating a contemporary cohort with IESS.

Key points

- Symptomatic VABAM is strongly associated with coadministration of hormonal therapy with vigabatrin.
- Contrary to prior research, asymptomatic VABAM was not associated with vigabatrin dosage in this study.
- Further study is warranted to determine if the association between concomitant hormonal therapy and VABAM is causal.

2 | METHODS

2.1 | Institutional approvals

This study was approved by the institutional review board at the University of California, Los Angeles.

2.2 | Hypotheses

We hypothesized that (1) sVABAM is associated with concomitant hormonal therapy and (2) aVABAM is associated with higher vigabatrin dosage.

2.3 | Subjects and data acquisition

All data were abstracted from the electronic medical record. Using a clinical EEG database, we identified all patients who have been evaluated for IESS at UCLA Mattel Children's Hospital between March 2014 and March 2021. For each subject, exposure data for vigabatrin and hormonal therapy were ascertained by review of all neurology consultation notes in chronological order, without knowledge of MRI evidence of VABAM, to minimize potential bias. Conversely, VABAM was ascertained by chronological review of MRI reports, without explicit knowledge of vigabatrin exposure. However, VABAM identification was not completely free of exposure bias because, in some cases, the reason for MRI was VABAM ascertainment. This was known to both the radiologist who interpreted MRI on a clinical basis as well as the data abstractor using the MRI report for data gathering. VABAM was then confirmed with unblinded review of digital MRI images by a pediatric neurologist familiar with VABAM (SAH), and with review of neurology progress notes before and after MRI to query possible alternative toxic/metabolic causes of the imaging abnormalities. Thereafter, sVABAM was ascertained by review of progress notes from any healthcare provider within 1 month of the MRI demonstrating VABAM. sVABAM was classified as present if progress notes mention treatment-emergent side-effects consistent with sVABAM, including encephalopathy, chorea, multifocal myoclonus, respiratory depression, or bradycardia. All cases of VABAM that were not classified as symptomatic in this fashion were deemed asymptomatic.

2.4 | Statistical methods

Continuous summary data were presented as median and interquartile range. Comparisons of continuous and dichotomous variables were accomplished with the Wilcoxon rank-sum test and the Fisher exact test, respectively. Exploratory multivariable analyses were conducted with multivariable logistic regression. All comparisons were two-sided and only *p*-values less than 0.05 were considered statistically significant. Statistical calculations were facilitated with Stata software (Statacorp, version 14, College Station, Texas, USA).

3 | RESULTS

3.1 | Subjects

Characteristics of the study population are summarized in Table 1. We identified 198 patients with IESS, among whom 114 (58%) were treated with vigabatrin. There was no overlap with our previously reported vigabatrin cohort.[11] In 6 cases, detailed exposure data (i.e., peak dosage and dates of treatment) were unavailable because vigabatrin treatment commenced at another center and records were unavailable for review. The remaining 108 subjects comprise the study population for the analyses that follow. We reviewed 263 total brain MRI reports and identified 56 patients who had at least one MRI conducted during vigabatrin treatment. Overall, we identified 17 children with VABAM, of which 11 were symptomatic (sVABAM) and 6 were asymptomatic (aVABAM). There were no cases in which the impression of the clinical radiologist was in conflict with the impression of the research team, and no cases in which an alternative toxic/metabolic cause of the imaging abnormality was identified. Accordingly, 39 subjects underwent MRI without discovery of VABAM, including 3 children for whom sVABAM was clinically suspected but deemed absent on MRI. Among the 11 subjects with sVABAM, specific symptoms included "significant" encephalopathy ($n=7$), movement disorder ($n=5$, choreoathetosis and/or multifocal myoclonus), and respiratory depression ($n=2$). With respect to cases with movement disorders, we believe symptoms are not better explained by the etiology of affected patients, including trisomy 21 ($n=1$), tuberous sclerosis complex ($n=1$), focal cortical dysplasia ($n=1$), CDKL5 deficiency disorder ($n=1$), and unknown ($n=1$). In the two patients with CDKL5 and unknown etiology, the timing of symptom onset and offset was closely related to VGB-HT exposure.

TABLE 1 Characteristics of the study population.

	No identified VABAM ($n=91$)	Any VABAM ($n=17$)	Sig[a]	Asymptomatic VABAM ($n=6$)	Sig[b]	Symptomatic VABAM ($n=11$)	Sig[c]
Demographics							
Female, *n* (%)	34 (37%)	11 (65%)	0.06	5 (83%)	0.04	6 (55%)	0.33
Age of IESS onset, months[d]	6.3 (3.9, 12.8)	5.2 (3.4, 8.3)	0.28	5.1 (2.0, 6.9)	0.17	5.5 (3.4, 12.0)	0.69
Development							
Normal development at onset, *n* (%)	48 (53%)	7 (41%)	0.44	1 (17%)	0.11	6 (55%)	1.00
Etiology							
Known etiology	61 (67%)	10 (59%)	0.58	3 (50%)	0.41	7 (64%)	1.00
Tuberous sclerosis complex, *n* (%)	14 (15%)	2 (12%)	1.00	0 (0%)	0.59	2 (18%)	0.68
Structural[e], *n* (%)	42 (46%)	4 (24%)	0.11	1 (17%)	0.22	3 (27%)	0.34
Genetic[e], *n* (%)	32 (35%)	8 (47%)	0.42	2 (33%)	1.00	6 (55%)	0.32
Treatment							
Vigabatrin treatment attributes							
Peak dose, mg/kg/day[d]	146 (116, 172)	152 (132, 167)	0.33	156 (132, 172)	0.49	152 (132, 166)	0.45
Duration of treatment, months[d]	9.4 (4.0, 20.1)	5.0 (1.9, 14.4)	0.12	10.0 (2.8, 39.4)	0.98	4.4 (1.8, 10.5)	0.04
Simultaneous hormonal therapy and vigabatrin, *n* (%)	40 (44%)	15 (88%)	0.001	4 (67%)	0.41	11 (100%)	0.001

[a]*p*-value for comparison of 'any VABAM' group ($n=17$) with 'no identified VABAM' group ($n=91$).

[b]*p*-value for comparison of 'Asymptomatic VABAM' group ($n=6$) with 'no identified VABAM' group ($n=91$).

[c]*p*-value for comparison of 'Symptomatic VABAM' group ($n=11$) with 'no identified VABAM' group ($n=91$).

[d]Median (interquartile range).

[e]Structural etiology was coded as present regardless of any genetic etiology. As such, tuberous sclerosis was coded as both genetic and structural, and therefore the sum of identified etiologies is greater than the sum of patients with known etiology.

3.2 | Concomitant hormonal therapy

Consistent with our hypothesis, and as illustrated in Table 1 and Figure 1A, concomitant hormonal therapy (VGB-HT) was associated with sVABAM. All 11 children with sVABAM were treated with VBG-HT, in comparison to 40 of 91 children without identified VABAM ($p = 0.001$). Among the 11 children with sVABAM, one received ACTH only, four received prednisolone only, and 6 received prednisolone followed by ACTH. Whereas, our center adopted a protocol in 2017 for initial treatment that mandates combination therapy from the outset (prednisolone 8 mg/kg/day [max 60 mg/day] and vigabatrin 100–150 mg/kg/day), the vast majority of subjects did not follow this protocol as they had most often initiated treatment at another center. Nevertheless, 65 (60%) of subjects were treated with concomitant hormonal therapy at some point during their vigabatrin exposure interval.

Of note, sVABAM did not uniformly occur with simultaneous initiation of both vigabatrin and hormonal therapy. In a majority of cases, vigabatrin treatment was already well established without symptoms (for more than 1 year in two cases) and sVABAM then emerged within weeks of subsequent hormonal therapy initiation, having been prompted by epileptic spasms exacerbation or relapse. In addition, hormonal therapy initiation often occurred in close temporal proximity to vigabatrin titration. After identification of sVABAM, all subjects exhibited dose reduction or discontinuation of vigabatrin. However, follow-up progress notes inconsistently described symptom resolution. Whereas some subsequent notes explicitly indicate rapid clinical improvement (including both cases of respiratory symptoms), some notes simply cease to mention symptoms, and in two cases notes were conflicting.

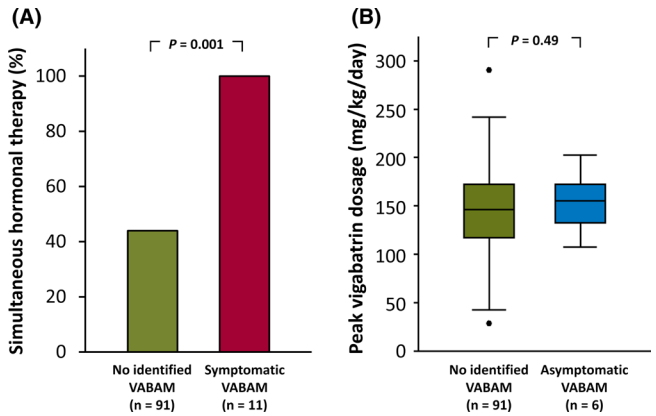

FIGURE 1 Association of VABAM with hormonal therapy but not vigabatrin dosage. In comparison to subjects without identified hormonal therapy, subjects with symptomatic VABAM were more likely to have been treated with simultaneous vigabatrin and hormonal therapy (Panel A). Peak vigabatrin dosage was similar among subjects with and without asymptomatic VABAM (Panel B).

For example, in one note the interval history mentions resolution of encephalopathy but the physical exam indicates severe encephalopathy (without any edit/revision from note prior to MRI). Importantly, there were no cases in which follow-up notes indicate that an impression of sVABAM was incorrect or that symptoms explicitly failed to improve upon vigabatrin dose adjustment.

To evaluate a potential association between aVABAM and concomitant hormonal therapy, we first compared the 6 children with MRI-proven aVABAM to 39 children with MRI-proven absence of VABAM. In this well-controlled but underpowered comparison, concomitant hormonal therapy was observed in 4 (67%) children with aVABAM and 17 (44%) children without VABAM, with $p = 0.40$. Next, in a still underpowered comparison of 6 children with aVABAM to the 91 children without *identified* VABAM (including 52 children without MRI during vigabatrin, of which we estimate eight harbored undetected aVABAM), we again found no difference in exposure to concomitant hormonal therapy ($p = 0.41$).

3.3 | Vigabatrin dosage and duration

Contrary to our hypothesis, peak vigabatrin dosage was not associated with aVABAM, sVABAM, or any VABAM (all $p >> 0.05$, Table 1 and Figure 1B). Although duration of vigabatrin exposure was not associated with aVABAM, median duration of treatment among the 11 subjects with sVABAM was shorter than the remaining subjects with or without aVABAM ($p = 0.04$).

3.4 | Exploratory analyses

On an exploratory basis, we screened for associations between VABAM and sex, age, etiology, and developmental status. In this manner, as illustrated in Table 1, we observed an association between female sex and aVABAM. No other associations were observed. We then conducted a series of multivariable logistic regression analyses, with inclusion of both main effects (concomitant hormonal therapy and peak vigabatrin dosage) as well as candidate demographic/etiologic variables. We did not detect interaction between hormonal therapy and vigabatrin dosage, and female sex did not remain a significant predictor of aVABAM after inclusion of concomitant hormonal therapy in the regression model.

4 | DISCUSSION

This study is significant in that we have identified an association—without proving causality—between sVABAM

and concomitant hormonal therapy. This is of particular concern given the demonstration in the International Collaborative Infantile Spasms Study (ICISS) that VGB-HT is more efficacious than hormonal therapy alone, at least with respect to short-term electroclinical outcomes.[3] Based on the present study, centers that adopt protocols that mandate first-line VGB-HT may be expected to observe higher rates of sVABAM and may need to consider treatment protocol modifications to address this risk. One option is to simply employ sequential treatment, in which vigabatrin is reserved for patients who are refractory to hormonal therapy, or vice versa, to minimize the number of children who receive VBG-HT.[15,16] Even though such a modification might be expected to yield inferior long-term developmental outcomes, it does not appear to be the case thus far; in comparison to hormonal monotherapy, VBG-HT was not associated with superior developmental outcomes at 18 months in ICISS.[17]

Our lack of observed association between aVABAM and peak vigabatrin dosage was surprising in that a prior study from our group[11] identified a seemingly robust association. Both the prior study and the current study were conducted at the same center and examined IESS cohorts with similar demographic characteristics and similar overall burden of aVABAM (6/40 patients in our prior study and 6/39 patients in the present study). Furthermore, both cohorts were managed by the same clinicians who utilized similar vigabatrin dosages. One possibility is that the lack of association in the present study is spurious, as there were only 6 subjects with aVABAM in each study. However, it is also notable that VGB-HT was utilized far more frequently in the contemporary study (~50% versus ~20%), and clinician awareness of VABAM—and especially sVABAM—has grown steadily over the course of these two studies. We speculate that patients at risk for VABAM (due to possible genetic or other unknown risk factors) in the setting of our prior study tended to develop aVABAM because clinicians preferentially titrated vigbatrin to high doses in the effort to achieve clinical response. In contrast, in the contemporary cohort, we suspect that patients at risk for VABAM may have tended to develop sVABAM because of greater use of concomitant hormonal therapy, instead of—or before—significant vigabatrin titration. Indeed, although not statistically distinct ($p = 0.07$), the prevalence of sVABAM in the current study (11/108; 10.2%) was almost triple the prevalence observed in our prior study (4/104; 3.8%). Alternatively, perhaps VABAM risk is chiefly related to disease severity. We would expect higher disease burden—and treatment refractoriness—to be associated with more aggressive therapy, i.e., higher vigabatrin dosage and concomitant hormonal therapy. Accordingly, it is possible that our identified associations of VABAM with vigabatrin dosage (prior study) or concomitant hormonal therapy (prior and current study) are proxies for a link between VABAM and disease burden. As such, it is paramount to recognize that we have not established causation in these analyses, and that further study is warranted to better understand the pathobiology of VABAM.

In addition to the association between sVABAM and VGB-HT, we observed that sVABAM was associated with shorter duration of vigabatrin treatment, and that aVABAM was associated with female sex. The link between sVABAM and treatment duration is not surprising in that discovery of sVABAM often prompts clinicians to reduce vigabatrin dosage or discontinue it entirely. In contrast, the association between aVABAM and female sex is not easily explained. We suspect this is a type-1 error, as this association was not based on a planned statistical comparison, we did not statistically adjust for multiple comparisons, and the association did not remain statistically significant in exploratory multivariable analysis.

More broadly, our symptomatic vs. asymptomatic dichotomization of VABAM may be misleading to some extent. Given that the mechanisms underlying aVABAM and sVABAM are likely overlapping, it is surprising that risk factors would vary as a function of symptomatic characterization. However, it may be that VABAM risk is generally dose-dependent and that sVABAM is more idiosyncratic. We suspect that some patients with aVABAM in our cohort study may have exhibited relatively mild symptoms (especially encephalopathy) that were insufficiently severe to be documented in the medical record, and thus escaped identification in this study. Similarly, as illustrated in Table 1, it is noteworthy that when the aVABAM and sVABAM subgroups are combined, the association of VABAM with VGB-HT (as well as the lack of association with VGB dosage) is preserved.

Beyond limitations in the interpretation of our findings, it is also important to note that this study is methodologically limited in several respects. Foremost, the study was retrospective, MRI assessments were not uniform (repeat MRI most often conducted for surgical evaluation rather than VABAM assessment), and all aspects of treatment (i.e., utilization and dosage of vigabatrin and hormonal therapy) were non-random. Furthermore, although we took steps to minimize bias in the identification and characterization of VABAM, there is nevertheless some risk of confounding. Radiologist's clinical impressions, on which our identification of VABAM was based, were not blinded to vigabatrin exposure. In addition to patients with clinically mild sVABAM symptoms who might not undergo MRI at all, there may also be radiologically mild aVABAM cases with subtle MRI findings that were missed by clinical radiologists and thus not identified in our workflow. Furthermore, our definition of sVABAM is imperfect. In particular, given that both aVABAM and sedation (i.e., cortically mediated

encephalopathy in the absence of VABAM) are common side effects of vigabatrin, it is possible that some of our sVABAM cases may represent coincident aVABAM and cortically mediated sedation rather than sVABAM per se (i.e., encephalopathy that is specifically thought to be mediated by thalamic or brainstem dysfunction). Conversely, we may have missed sVABAM cases. On a clinical basis, outside of the conduct of this study, we have encountered several patients with severe treatment-emergent encephalopathy for whom practitioners simply reduced vigabatrin dosage, observed rapid clinical improvement, and never obtained MRI. Such cases might represent sVABAM but are coded as VABAM-absent in our analysis. In sum, there are multiple mechanisms by which we may have over- or underestimated the prevalence of VABAM.

Despite the limitations of this study, and the absence of an identified mechanism of harm, our results lend support to—but do not prove—the notion that hormonal therapy exacerbates VABAM. In weighing the risks and benefits of VGB-HT versus vigabatrin or hormonal monotherapy, clinicians should specifically consider the risk of sVABAM and possible exacerbation of this risk with VGB-HT. However, it is the opinion of the authors that the risk and consequences of VABAM are small relative to the risk of continued epileptic spasms, and that clinicians should not necessarily be dissuaded from use of aggressive treatment protocols (e.g., vigabatrin dose >100 mg/kg/day and/or VGB-HT combination therapy).

In view of the severity of potential sVABAM, and the lack of causal inference in this report and all prior descriptions of sVABAM, we believe further study is clearly warranted to better understand the mechanisms underlying VABAM and its suspected exacerbation by hormonal therapy. A potential next step is a large prospective observational study with standardized longitudinal symptom screening and surveillance MRI obtained in all vigabatrin recipients upon conclusion of vigabatrin dose titration, or upon the addition of concomitant hormonal therapy where applicable.

AUTHOR CONTRIBUTIONS

RS, HN, RRR, and SAH contributed to conceptualization. RS, GS, AT, DT, and SAH contributed to data collection and curation. RS and SAH contributed to data analysis and drafting of the manuscript. All authors participated in data interpretation and revision of the manuscript.

ACKNOWLEDGMENTS

This study was accomplished with generous support from the John C. Hench Foundation.

CONFLICT OF INTEREST STATEMENT

Dr. Rajaraman has received research support from Marinus and the International CDKL5 Research Foundation. Dr. Nariai is supported by the National Institute of Neurological Disorders and Stroke (NINDS) K23NS128318, the Sudha Neelakantan & Venky Harinarayan Charitable Fund, the Elsie and Isaac Fogelman Endowment, and the UCLA Children's Discovery and Innovation Institute (CDI) Junior Faculty Career Development Grant (#CDI-TTCF-07012021). Dr. Hussain has received research support from the John C. Hench Foundation, the CJDA Foundation, the Mohammed F. Alibrahim Endowment, the Elsie and Isaac Fogelman Endowment, the Epilepsy Therapy Project, the Milken Family Foundation, Paul Hughes Family Foundation, the Pediatric Epilepsy Research Foundation, Bio-Pharm, Eisai, GW Pharmaceuticals, Insys, Lundbeck, Marinus, Takeda, UCB Biopharma, Zogenix, and the NIH. He has received compensation for service as a consultant to Amzell, Aquestive Therapeutics, Biohaven, Eisai, Equilibre Biopharmaceuticals, Insys, Jazz, GW Pharmaceuticals, Mallinckrodt, Marinus, MGC Pharmaceuticals, Radius, Shennox, Takeda, UCB Biopharma, Upsher-Smith Laboratories, West Therapeutic Development, and Zogenix. The remaining authors report 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.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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How to cite this article: Sathe R, Shrestha G, Terango A, Tabibzadeh D, Rajaraman RR, Nariai H, et al. Symptomatic vigabatrin-associated MRI toxicity is associated with simultaneous hormonal therapy among patients with infantile spasms. Epilepsia Open. 2025;10:314–320. https://doi.org/10.1002/epi4.13099