Received: 17 March 2023 | Revised: 14 October 2023 | Accepted: 19 October 2023

DOI: 10.1111/epi.17808

Epilepsia®

RESEARCH ARTICLE

Fifteen years of real-world data on the use of vigabatrin in individuals with infantile epileptic spasms syndrome

Mathieu Kuchenbuch[1,2,3] | **Tommaso Lo Barco**[1] | **Nicole Chemaly**[1,2] | **Catherine Chiron**[1] | **Rima Nabbout**[1,2,4]

[1]Department of Pediatric Neurology, Reference Center for Rare Epilepsies, Hôpital Necker-Enfants Malades, member of ERN EpiCARE, Paris, France

[2]Laboratory of Translational Research for Neurological Disorders, INSERM MR1163, Imagine Institute, Paris, France

[3]Service de Pédiatrie, Reference Center for Rare Epilepsies, member of ERN EpiCARE, Université de Lorraine, CHRU-Nancy, Nancy, France

[4]Université de Paris Cité, Paris, France

Correspondence
Rima Nabbout, Department of Pediatric Neurology, Reference Center for Rare Epilepsies, Necker Enfants Malades Hospital, 149 rue de Sèvres, 75015 Paris, France.
Email: rima.nabbout@aphp.fr

Abstract

Objective: This study was undertaken to evaluate our treatment algorithm for infantile epileptic spasms syndrome (IESS) used between 2000 and 2018. We initiated vigabatrin (VGB), and steroids were added if the electroclinical response (spasms and electroencephalogram [EEG]) to VGB was not obtained or incomplete.

Methods: Individuals with IESS treated with VGB were recruited from our hospital clinical data warehouse based on electronic health records (EHRs) generated since 2009 and containing relevant keywords. We confirmed the diagnosis of IESS. Clinical, EEG, imaging, and biological data were extracted from the EHRs. We analyzed factors associated with short-term response, time to response, relapse, time to relapse of spasms, and the presence of spasms at last follow-up.

Results: We collected data from 198 individuals (female: 46.5%, IESS onset: 6 [4.5–10.3] months, follow-up: 4.6 [2.5–7.6] years, median [Q1–Q3]) including 129 (65.2%) with identifiable etiology. VGB was started 17 (5–57.5) days after IESS diagnosis. A total of 113 individuals were responders (57.1% of the cohort), 64 with VGB alone and 38 with VGB further combined with steroids (56.6% and 33.6% of responders, respectively). Among responders, 33 (29%) experienced relapses of spasms, mostly those with later onset of spasms ($p = .002$) and those who received VGB for <24 months after spasms cessation compared to a longer duration on VGB (45% vs. 12.8%, $p = .003$). At follow-up, 92 individuals were seizure-free (46.5% of the whole cohort), including 26 free of therapy (13.1%). One hundred twelve individuals (56.6%) were still receiving VGB, with a duration of 3.2 (1.75–5.7) years.

Significance: Our sequential protocol introducing VGB then adding steroids is an effective alternative to a combined VGB–steroids approach in IESS. It avoids steroid-related adverse events, as well as those from VGB–steroid combination. According to our data, a period of 7 days seems sufficient to assess VGB response and enables the addition of steroids rapidly if needed. Continuing VGB for 2 years may balance the risk of relapse and treatment-induced adverse events.

KEYWORDS

infantile spasms relapse, long-term outcome, steroids, West syndrome

1 | INTRODUCTION

Infantile epileptic spasms, developmental plateauing or regression, and interictal hypsarrhythmia electroencephalographic (EEG) pattern compose the triad of West syndrome.[1] However, all individuals with infantile spasms might not fulfill all the triad criteria, and the term infantile epileptic spasms syndrome (IESS) is used to encompass individuals with West syndrome and those with infantile spasms who do not fulfill the triad, as both groups are candidates for the same therapy algorithm.[2] IESS is a rare age-related developmental and epileptic encephalopathy. Its incidence is estimated at 30/100 000 liveborn infants. Epileptic spasms, the key seizure type of this syndrome, appear between 1 and 24 months and might be preceded by focal seizures.[2] The developmental outcome of individuals with IESS is often poor.[3] The key determinants of favorable prognosis identified in the literature are etiology, normal initial development, and short time to treatment.[4]

Since the 1950s, adrenocorticotropic hormone (ACTH) and corticosteroids (referred to here as steroids) have been identified as treatments with specific efficacy in IESS.[5,6] We added vigabatrin (VGB) to the therapeutic arsenal in the 1990s.[7] VGB is now prescribed worldwide in addition to steroids as one of the first-line therapies for individuals with IESS.[8,9] However, the optimal use of VGB in IESS remains a matter of debate, especially for two decisive phases of the treatment: whether we should initiate with VGB monotherapy and when to stop VGB. VGB is recommended as first monotherapy for individuals with IESS due to tuberous sclerosis complex (TSC) based on randomized clinical trials (RCTs).[10] In other IESS etiologies, ICISS trials showed that using VGB combined to steroids as first-line therapy for IESS was more effective than steroids alone in the short term, but they did not show any difference on cognitive or epilepsy outcomes.[4,11] Another challenge is the optimal duration of IESS treatment. On one hand, VGB and steroids present adverse events (AEs), and there is a gap of knowledge on the minimal duration of therapy with the lowest cumulative AEs. AEs reported with steroids are mainly increased risk of infection, arterial hypertension, arrhythmia, irritability, hypokalemia, and exogenous Cushing syndrome, and those reported with VGB encompass visual field loss (VFL) or abnormal magnetic resonance imaging (MRI) hypersignals.[12,13] On the other hand, there is a high risk of relapse of spasms (20%–53%) after stopping these medications,[14–16] and the probability of recontrolling spasms afterward is low.[17]

Key Points

- VGB was started at a median of 17 days after spasms onset, and steroids were added at 3 weeks if spasms and/or hypsarrhythmia persisted
- Of 198 individuals, 113 showed a short-term response, with 64 being treated solely with VGB, thus allowing 56.6% of the short-term responders to avoid exposure to steroids
- Thirty percent of responders showed spasm relapses, with a higher rate of relapse when VGB treatment lasted <2 years
- This argues for a preventive role of VGB against relapse provided treatment is maintained for at least 2 years

To address these questions, we report our experience with the use of VGB in IESS in a tertiary center cohort over the past 15 years, with a focus on short-term efficacy, AEs, and long-term relapses.

2 | MATERIALS AND METHODS

2.1 | Materials

Dr Warehouse (DrWH) is a document-based open-source clinical data warehouse oriented toward free text, which allowed exploration of more than 4.5 million free text clinical documents produced for more than 465 000 individuals followed in more than 20 departments in Necker Enfants-Malades Hospital.[18] We used DrWH to identify individuals with IESS and who received VGB as first treatment at our center. We selected individuals whose medical records contained the words “spasms” or “West syndrome” and “vigabatrin” or “Sabril”. Then, all identified medical records were individually read by a child neurologist (T.L.B.) to select individuals who met the inclusion criteria for this study, that is, a confirmed history of IESS treated with VGB as first-line therapy for epileptic spasms for at least 7 days, a clearly documented clinical history since the onset of epilepsy, and a minimum follow-up of 6 months from VGB initiation.

Clinical epilepsy data were collected at spasms' onset, at 2 months on VGB, at relapse (if any), and at last follow-up. Epilepsy etiologies were classified in six categories according to International League Against Epilepsy classification (genetic, structural, infectious, metabolic, immune, unknown), with a special highlight for cases with TSC. We defined responders as individuals achieving spasm cessation for at least 2 months, clinically and on video-EEG, and without hypsarrhythmia pattern, whether or not it was present at the time of syndrome identification. Spasm relapse was defined by the reappearance of spasms after this 2-month period, clinically witnessed or recorded on video-EEG. The AEs of steroids and VGB were identified through a search of the following terms in various medical reports from the cohort: "adverse events", "side effects", "brain MRI report", "visual field", "visual evoked potential", "electroretinogram", "supplementation", "septic shock", "arterial blood hypertension", "weight gain", "hyperexcitability", "cardiac hypertrophy", "proton-pump inhibitor", and "adrenal insufficiency". Similarly, the evolution toward Lennox–Gastaut syndrome was analyzed using the term "Lennox–Gastaut" or "LGS" in the medical reports. The selected documents were thoroughly reviewed to extract the final data. All individual's data were deidentified. The ethics committee of our institution approved the study protocol. In accordance with French legislation on the use of deidentified retrospective data, the nonopposition of the individuals' legal representatives to use these data was obtained.

2.2 | Sequential management of IESS in our center

We use VGB as first-line therapy as soon as the diagnosis of IESS is confirmed, using an initial dose of 100 mg/kg/day in two doses (60 mg/kg/day in individuals aged >1 year) with a 24–48 h titration. At day 7–10, we perform a first evaluation based on the family diary and an awake and sleep video-EEG (using electromyographic recordings of the deltoids and recording at least 15 min after awakening). VGB is increased to 150 mg/kg/day in two doses (100 mg/kg/day in individuals aged >1 year) in the case of no response or an incomplete response, that is, spasms are clinically reported and/or spasms or hypsarrhythmia are recorded on video-EEG. We repeat the same clinical and video-EEG evaluation at day 20–25, and if the response is not complete (hypsarrhythmia or clinical or electrical spasms persisting), hydrocortisone is added to VGB (15 mg/kg/day in individuals aged <1 year and 10 mg/kg/day for those >1 year) for 15 days followed by a progressive withdrawal over 15 days. At day 35–40, hydrocortisone is replaced by ACTH if hypsarrhythmia or spasms persist (0.5 mg/kg/day for 15 days, followed by hydrocortisone 10 mg/kg/day with gradual withdrawal over 6 months). After 15 days, if there is no response, the steroids are stopped, and second-line treatments are tried (Figure 1). This protocol may occasionally be adapted, for example if the individual was referred with a preexisting treatment, or more rapid sequential management, especially in cases of long-lasting spasms before referral or preexisting demonstrated psychomotor delay. In the case of using other antiseizure medications (ASM) therapies, such as valproate or topiramate, for instance, we rapidly titrated the therapy to the high-range recommended dose within 2 weeks. We empirically considered that the response could be assessed after 1 month of reaching the targeted dose. For ketogenic diet (KD) treatment, the response was assessed at month 1, month 2, and month 3, following the recommendation of the RCT protocol.[19] If KD showed no improvement after 3 months, it was stopped for inefficacy.

To monitor the AEs of VGB, we tailored the ophthalmological and brain MRI follow-up based on the children's age and phenotypes. For infants and individuals with severe intellectual disability, we used electroretinogram and visual evoked potential. In some individuals with severe and profound intellectual disability (ID) and no eye contact before VGB administration, the ophthalmological follow-up was difficult to establish. As the functional impact of a visual field restriction was a minor issue in the balance benefit-risk, we agreed with the families not to perform this additional examination. For individuals older than 6 years with moderate or slight ID, we conducted visual field studies. Similarly, brain MRI scans were adjusted according to individual characteristics, with an increased frequency in cases of identification of abnormal MRI hypersignals with clinical manifestation. Serial MRIs were difficult to achieve because of the need for general anesthesia in many individuals in this population.

2.3 | Statistical analyses

Descriptive statistics are reported as n (%) and median [25th–75th percentile]. Descriptive analyses provide details of age, gender, seizures, etiology, presence of hypsarrhythmia, and treatment. As steroids are not sensu stricto ASMs, we designated as "therapies" the combination of ASM and steroids. We compared the characteristics of individuals whose epilepsy started with spasms to those who started with other types of seizures before spasms in terms of gender, age at onset, and etiological categories using logistic regressions.

Then, we studied short-term response to therapies. To determine the factors positively or negatively influencing

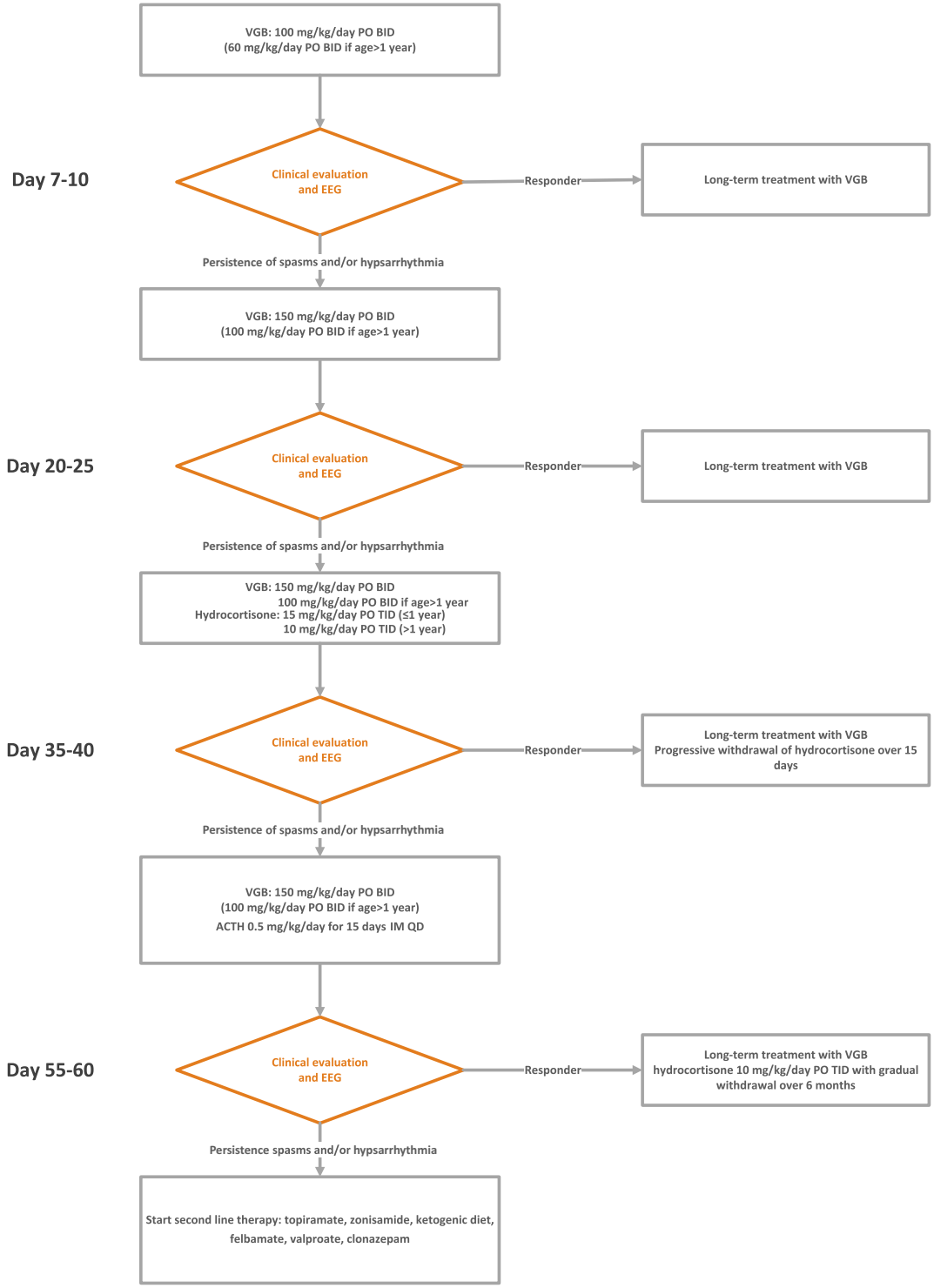

FIGURE 1 Proposed protocol for treatment of infantile spasms at our institution between 2000 and 2018. ACTH, adrenocorticotropic hormone; BID, twice daily administration; EEG, electroencephalogram; IM, intramuscular; PO, per os; QD, every day; TID, thrice daily administration; VGB, vigabatrin.

response, we used multivariate logistic regression with the following factors: gender, age at onset, etiological categories (grouped as follows: dysplasia, clastic, tuberous sclerosis, genetic, and unknown), delay between spasms onset and administration of VGB, the presence of ASM before VGB introduction, and the initial presence of hypsarrhythmia. After describing the subpopulation of individuals who responded only to VGB and those who required a combination of VGB and other therapies, we studied the factors associated with the number of therapies required to achieve

short-term response using analysis of variance with the factors sex, age at spasms onset, delay between spasms onset and onset of VGB, the presence of ASM before VGB introduction, and the etiological categories. A similar approach was applied to determine the factors associated with the delay to achieve spasm freedom. We added the number of therapies required to achieve the short-term response to the factors mentioned above.

Finally, we described spasms' relapse rate in short-term responders with a focus on VGB status (ongoing or withdrawn). To identify the potential predictors of spasm relapse in this subpopulation, we used Kaplan–Meier survival associated with Cox regression analyses with the following factors: sex, age at onset of spasms, delay between spasms onset and initiation of VGB, the presence of ASM before VGB introduction, and etiological categories. We used chi-squared tests or Fisher exact tests to study the impact of VGB withdrawal, between 4 and 24 months and after 24 months, on the risk of relapse by comparing with the relapse rate of individuals with ongoing VGB therapy during the same periods. Finally, to assess the impact of VGB treatment duration (<24 months or >24 months) as a factor of spasm relapse previously identified, we conducted a Kaplan–Meier analysis combined with Cox regression analyses.

A p-value of <.05 was considered statistically significant and $p < .1$ as a tendency. Statistical analyses were performed using R software.[20]

3 | RESULTS

3.1 | Individual characteristics and VGB initiation

Among the 399 individuals followed at our epilepsy center from 2000 to 2018 for IESS, 198 fulfilled the inclusion criteria (Table 1). The others were mostly excluded because of incomplete clinical or EEG recordings data ($n = 125$), insufficient follow-up ($n = 47$), or VGB initiation preventively in patients with antenatal or early postnatal TSC diagnosis before clinical spasms' onset ($n = 17$).

One hundred sixty-two individuals started IESS during the first year of life (81.8%). In 20.7% of individuals (41/198), other types of seizures preceded the spasms' onset, by 1.1 [0–6.3] days, in particular focal seizures ($n = 28/41$, 68.3%). There was no significant difference between individuals starting with seizures other than epileptic spasms and those starting directly with epileptic spasms in terms of sex, age at onset of spasms, or etiology. Epileptic spasms were identified at a median age of 6 months, with hypsarrhythmia in approximately half of cases at diagnosis. In 70.7% of individuals, VGB was started as first-line medication

TABLE 1 Demographic data of individuals with infantile epileptic spasms syndrome included in this study.

Characteristic	*n* (%) or median [25th–75th percentile]
Gender, M/F	106/92
Current age, years	9.3 [6.7–11.9]
Starting with other types of seizures	41 (20.7%)
Other ASM before VGB	58 (29.3%)
Age at epilepsy onset, months	5.8 [3.7–9]
Age at spasm onset, months	6 [4.5–10.3]
Hypsarrhythmia on EEG	76/153 (49.7%)
Delay between spasms and VGB introduction, days	17 [5–57.5]
Delay between VGB introduction and spasms' stop, days	15 [7–40]
Follow-up duration since spasms onset, years	8.2 [5.8–10.8]
Etiologies	
Unknown	69 (34.8%)
Structural	58 (29.3%)
Clastic lesion	25
Neonatal hypoxic–ischemic encephalopathy	7
Perinatal stroke	6
Postnatal hypoxic–ischemic encephalopathy	2
Perinatal brain hemorrhage	2
Subdural hematoma	1
Periventricular leukomalacia	4
Porencephaly	3
Focal cortical dysplasia	13
Sublobar dysplasia	7
Polymicrogyria	6
Lissencephaly	4
Pachygyria	2
Megalencephaly	1
Genetic	35 (17.7%)
Partial or total polysomies (15,13,18)	7
Rett syndrome	6
Aicardi–Goutières syndrome	5
Down syndrome	2
STXBP1-DEE	2
del 1p36	2
GRIN-related DEE	2
CREBBP	1
GNAO1	1

TABLE 1 (Continued)

Characteristic	*n* (%) or median [25th–75th percentile]
IQSEC2	1
KIF1A	1
NF1	1
del 11p11.2	1
SCN8A	1
WWOX	1
TCF4	1
Tuberous sclerosis	24 (12.1%)
Infectious	7 (3.5%)
HSV encephalitis	4
Congenital CMV	2
Neonatal meningitis	1
Metabolic	5 (2.5%)
Neonatal hypoglycemia	2
Maple syrup urine disease	1
Methionine synthase deficiency	1
X-linked congenital disorder of glycosylation (*ALG13*-CDG)	1

Abbreviations: ASM, antiseizure medications; CDG, congenital disorder of glycosylation; CMV, cytomegalovirus; DEE, developmental and epileptic encephalopathy; EEG, electroencephalogram; F, female; GRIN, glutamate receptor ionotropic N-methyl-D-aspartate, HSV, herpes simplex virus; M, male; VGB, vigabatrin.

($n=140$). VGB was used as adjunctive therapy in the remaining 29.3% as added to other ASMs (58 individuals already had 1 [1–2] ASM, mainly valproate, $n=40$; levetiracetam, $n=15$; and benzodiazepines, $n=12$). VGB was started 17 [5–57.5] days after the onset of epileptic spasms identified by caregivers. This delay was not impacted significantly by the presence of ASM before the initiation of VGB (15 [5–65.75] days for VGB as monotherapy vs. 53.5 [10.25–65.75] as add-on to another ASM, $p=.11$). An etiology was identified in two thirds of cases, mostly structural (41%) or genetic (33%), with both groups including 24 individuals with TSC. The details of etiologies are shown in Table 1.

3.2 | Short-term response

Remission was obtained after VGB introduction in 64 individuals (32.3% of the whole cohort, 56.6% of the responders), including 17 individuals with TSC. The dosage of VGB was 100 [100–110] mg/kg/day, with six individuals receiving >100 mg/kg/day. In 49 individuals, remission was obtained using a combination including VGB (24.7% of the whole cohort, 43.4% of the responders), including five individuals with TSC. The main dual therapy to stop spasms was VGB + hydrocortisone ($n=25$; 12.6% of the whole cohort, 22.1% of the responders), and the main triple therapy was VGB + hydrocortisone + ACTH ($n=9$, 4.6% of the whole cohort and 8% of the responders). The number of required therapies to achieve remission was statistically impacted by the age at spasms onset ($F_{1,107}=12.6$, $p=.001$) and etiology ($F_{4,107}=2488$, $p=.048$); fewer drugs were needed in the older individuals (VGB alone: 6.5 [5.4–12.1] months, VGB + 1: 5.6 [3.4–7] months, VGB + 2: 5 [4–6.3] months, and VGB + 3: [5.7] months) and in individuals with TSC compared to genetic etiology (1 [1–1] vs. 2 [1–2], $p=.038$).

By taking the whole cohort, more than half of individuals (57.1%, 113/198) were responders in the short term (Figure 2), 92 from the proposed therapeutic algorithm initiating with VGB (92/140, 65.7%) and 21 already having ASM before initiating this algorithm (21/58, 36.2%). In the nonresponders, our protocol for IESS decreased the frequency of spasms in 39 (19.7%) and was ineffective in 46 (23.2%). Multivariate analysis identified TSC as a predictor of good response (odds ratio [OR] = 10.3 [2–52.9] vs. clastic etiology, $p=.005$). By contrast, the presence of ASM before VGB was a risk factor of resistance (OR = .35 [.19–.71], $p=.004$). Age at spasm onset ($p=.052$ in univariate analysis and .41 in multivariate) and delay before VGB initiation ($p=.19$ in univariate analysis) had no significant impact on short-term response. The duration to achieve epileptic spasms cessation was 15 [7–40.3] days.

3.3 | Relapse of spasms

Among the 113 individuals achieving spasms remission, 30% relapsed ($n=34$), 10 after VGB withdrawal (29.4%) and 24 on VGB (70.5%). Relapses occurred at a time lag of 7.7 [3.7–18.2] months after spasms had stopped, the earliest at 2.5 months, the latest at 86 months (Figure 3).

Spasm relapse occurred with VGB therapy in 24 individuals (21.2% of the responders cohort), between 2.5 and 58 months from spasm response (6.6 [3.2–12] months). Twenty individuals were on VGB for <24 months, including 10 who relapsed early, that is, between 2 and 4 months after starting VGB, and four on VGB for >24 months. Age at spasms onset was the only factor significantly impacting the survival distribution function, with more relapses in older individuals (hazard ratio = 1.036 [1.013–1.06], $p=.002$). There was no impact from the delay between spasms and VGB initiation, the delay between VGB and spasms cessation, the etiology, or the presence of hypsarrhythmia.

VGB was withdrawn in 50 individuals (44.2% of those with short-term remission), at a median of 28 [15–53] months after spasms cessation. The reason was, in decreasing order, the disappearance of spasms ($n=40$), the

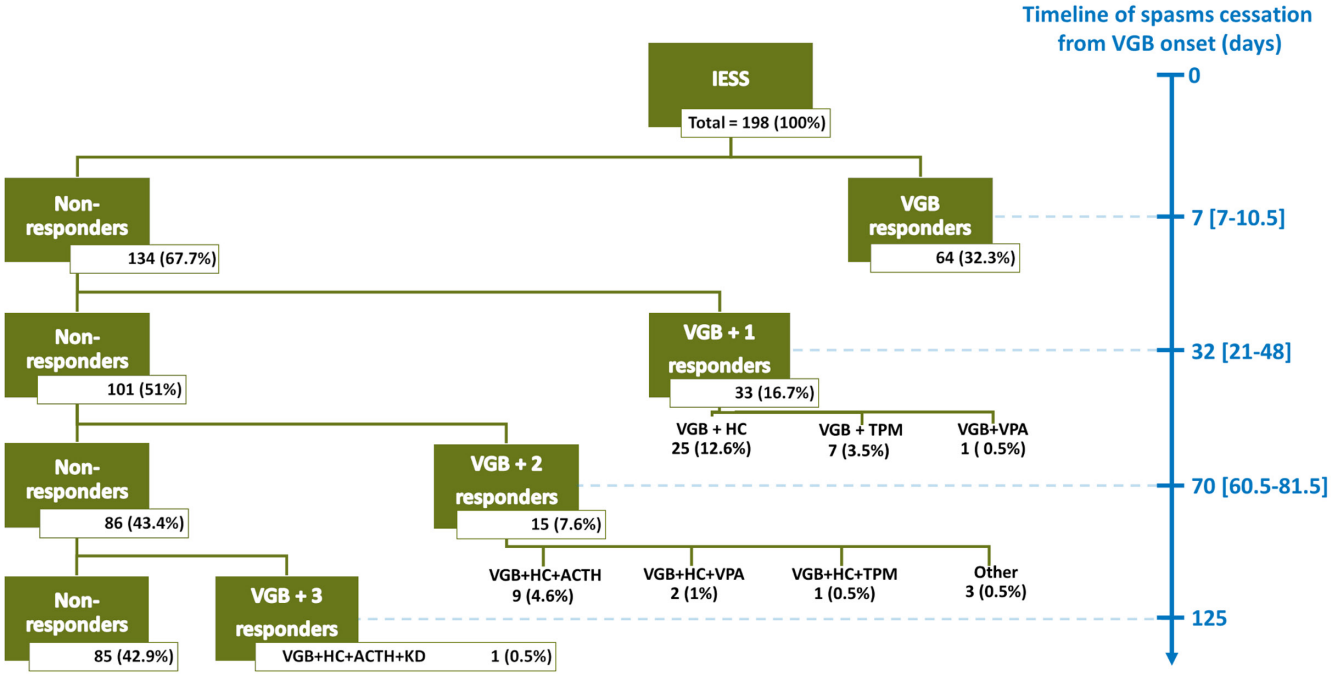

FIGURE 2 Flowchart of the response to antiseizure medicines in our cohort and time to response. Responders are defined as an individual achieving spasms cessation for at least 2 months, clinically and on video-electroencephalography. The "Other" group comprised three individuals with different medication combinations: one with VGB + HC + CLO, another with VGB + CLO + VPA, and the third with VGB + VPA + CNZ. ACTH, adrenocorticotropic hormone; CLO, clobazam; CNZ, clonazepam; HC, hydrocortisone; IESS, infantile epileptic spasms syndrome; KD, ketogenic diet; TPM, topiramate; VGB, vigabatrin; VPA, valproate.

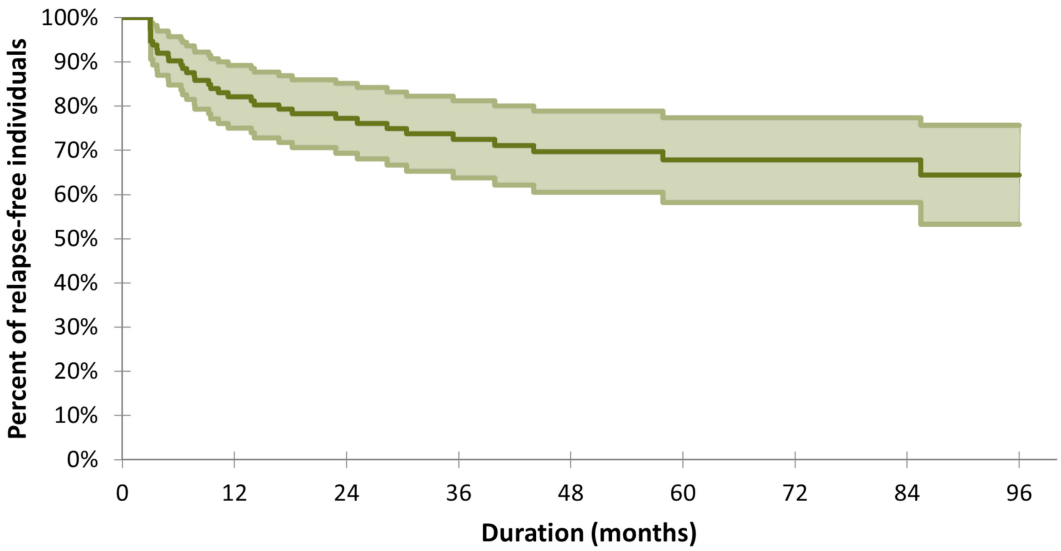

FIGURE 3 Spasm relapse-free survival curve of the 113 short-term responders.

shift to another ASM due to the occurrence of a new seizure type ($n = 7$), or the families' decision ($n = 3$). A relapse occurred after the withdrawal of VGB in 10 of 50 individuals, distributed as follows: seven of the 40 individuals who stopped after spasms cessation, two of the three who stopped on the families' initiative, and one of the seven shifting to another ASM due to a new seizure type. In individuals who stopped VGB <24 months after spasm remission, 40% (8/20) relapsed. The relapse occurred after 4 months of cessation of spasms (Figure 4A). In contrast, in those who were on VGB after 24 months of their spasms' cessation, 19.2% (16/83) relapsed ($p = .074$). The comparison of the survival curves of the individuals who stopped VGB corrected for age at spasms onset showed a tendency to a better outcome in individuals who received VGB for >24 months (OR = .44 [.18–1.04], $p = .062$; Figure 4B).

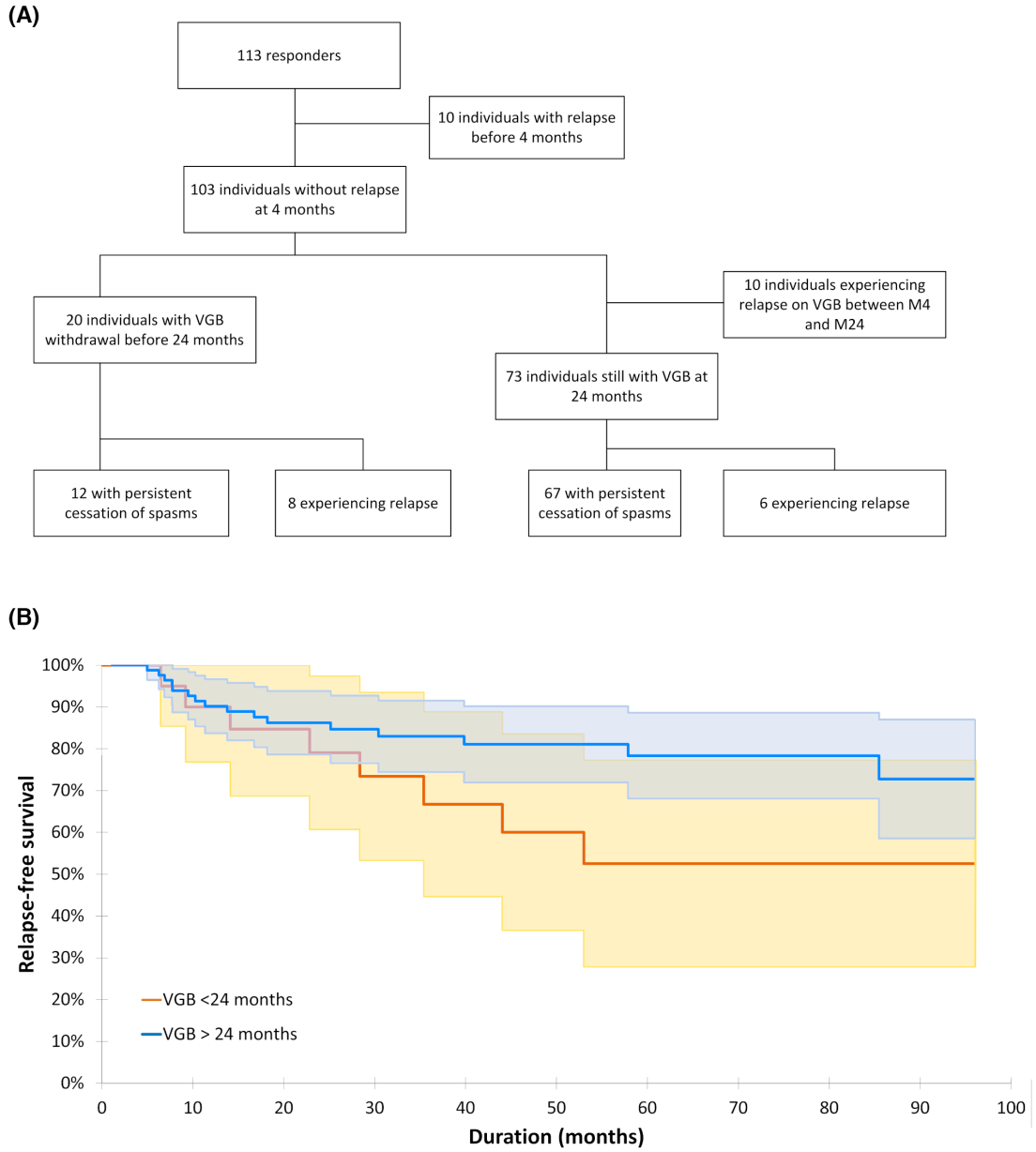

FIGURE 4 Flowchart (A) and survival curves (B) illustrating the spasm relapse-free survival curves of individuals in relation to the duration of vigabatrin (VGB). M, month.

In eight individuals, a reintroduction of VGB was proposed following the relapse. It was effective in controlling the spasms in five (62.5%).

3.4 | AEs of the treatments

In our cohort, a median of 1 [1–2] brain MRI per individual was conducted on 100 individuals during VBG treatment a median of 16.1 [5.2–30.4] months after VGB initiation. Twenty percent (20 individuals) showed VGB-associated brain abnormalities on MRI (VABAM) on brain MRI scans, two of them receiving steroids in addition to VGB. VABAM occurred on average 6.5 [2.6–15.7] months after starting VGB. However, no associated clinical symptoms were observed. Of these cases, nine individuals demonstrated a disappearance of VABAM in the subsequent MRI scan, whereas 10 individuals did not undergo a follow-up MRI, and one individual still had persistent VABAM 33 months after starting VGB. None presented related symptoms such as additional motor or cognitive regression.

For ophthalmological evaluation, 85 individuals (42.9%) underwent sequential evaluations (last evaluation after an average of 4 [1–6.8] years from the initiation of VGB). Among them, 47 individuals (23.7% of the

cohort) received visual field testing, whereas 38 individuals (19.2%) had electroretinogram or visual evoked potentials. Only one individual with Aicardi–Goutières syndrome exhibited discrete visual field damage 1 year after VGB initiation at a maximum dosage of 150 mg/kg/day. Subsequently, the treatment was reduced to 100 mg/kg/day. This condition remained stable during follow-up tests until the discontinuation of VGB. This child had no visual contact, and the clinical impact of visual field deficit was challenging to establish. However, caregivers did not report any significant change in her behavior. The reduction in VGB dosage resulted in an increase in the frequency of spasms after an initial partial response.

Regarding the 150 individuals who received steroids, medical reports indicated AEs in 73 individuals (48.6%), categorized in descending order as follows: hypertension requiring treatment ($n = 29$, 19.3%), with one third of them requiring two or more antihypertensive drugs; potassium supplementation ($n = 26$, 17.3%); proton-pump inhibitor for gastritis ($n = 19$, 12.6%); significant weight gain (with a weight above the 90th–99th percentile on the French growth chart, $n = 17$, 11.3%); agitation and hyperexcitability behavior disorder ($n = 15$, 10%); postcorticosteroid adrenal insufficiency necessitating steroid supplementation for >3 months ($n = 10$, 6.6%); septic shock ($n = 3$, 2%); and cortisone-induced cardiac hypertrophy ($n = 1$, .6%).

3.5 | Long-term follow-up

Seventeen individuals developed secondary Lennox–Gastaut syndrome, 4 [2–7.3] years after the onset of epileptic spasms (8.6% of cohort). At last follow-up, at 5 [3–7.7] years old, 92 individuals were seizure-free (46.5% of the whole cohort) including 26 without any ASM (13%). In the remaining 106 individuals (53.5%) with active epilepsy, 29.8% ($n = 59$) had epileptic spasms, including 36 (18%) associating epileptic spasms and focal seizures, and 47 had focal seizures only (24%). The only factor statistically associated with spasms at last follow-up was the presence of ASM before VGB initiation (OR = 2.36 [1.24–4.5], $p = .009$). The median number of ASMs at last follow-up was 2 [1–3] per individual, a number significantly dependent on the type of persistent seizures ($F_{3\ 194} = 33$, $p < 10^{-4}$), from 1 [0–2] if no seizures to 2 [2–3] if spasms or other seizure type, and 3 [2–3] if both. At last follow-up, 57% individuals ($n = 112$) had received VGB for a total duration of 3.2 [1.8–5.7] years and a dosage of 60 [33–87] mg/kg/day. In this cohort, there were no reports of clinical manifestations consistent with VGB-associated VFL or brain abnormalities on MRI.

4 | DISCUSSION

This study is a retrospective evaluation of the sequential treatment of IESS, based on clinical and video-EEG monitoring, which was in use for >15 years at our tertiary center for rare epilepsies. There are several points to emphasize regarding these real-world data from a large number of individuals. First, 32.3% of our cohort (27% if individuals with TSC are excluded) were responders with VGB as first-line specific therapy, thus avoiding the AEs of steroids. Second, our sequential approach adding steroids after VGB failure yielded a response in 57.1% of the whole cohort. Finally, our data suggest that long-term VGB treatment is reasonably safe and may significantly reduce the risk of epileptic spasms relapse.

This study does not question the superiority of the combination of steroids and VGB in the management of individuals with IESS, but it raises some concerns. One of the main principles is to "use a single antiseizure medication (monotherapy) to treat epilepsy whenever possible."[21] Our protocol aims to limit the risks of overtreatment leading to AEs, which are sometimes serious, without reducing the effectiveness of treatment. However, finding a balance between achieving a rapid therapeutic response and minimizing exposure to AEs is a challenge in the treatment of infants with IESS. We believe that such an approach is key when advocating personalized medicine to avoid exposing a population to possibly avoidable AEs.[22]

Comparisons with previous studies are difficult due to the variability of study designs.[3] For instance, the ICISS study comparing VGB/steroids combination to steroids alone excluded TSC individuals (known to be good responders to VGB) and defined response as spasms cessation maintained at day 42 without reporting EEG data.[11] We did not exclude TSC individuals, because this diagnosis is sometimes made after spasms onset (1.3% in the ICISS study), but we used more stringent response criteria (spasms cessation for 2 months and hypsarrhythmia disappearance when present). Our study added to the evidence that members of the TSC-related IESS subpopulation are specific candidates for VGB, possibly due to an inhibitory action of VGB on the mammalian target of rapamycin pathway.[23]

Despite the evidence that the combination of VGB and steroids was more effective on spasms than steroids alone in the short term in the ICISS study, the 18-month extension study did not find any significant difference in terms of epilepsy or developmental outcome (measured using the Vineland Adaptive Behavior Scales [VABS]).[11] This might also emphasize the key role of VGB. In this study, lead time to treatment was found to be a significant predictor of both VABS score and epilepsy outcome. This delay refers to "the time from onset of spasms to the

initiation of treatment" presumed effective for epileptic spasms. As child neurologists and epileptologists, our aim is to minimize diagnostic wandering in individuals with IESS and to weigh the risk–benefit balance as accurately as possible. In this syndrome, diagnosis can take several weeks or months, and this will have a major impact on long-term outcomes. However, there is no evidence that a 7-day delay between VGB and corticosteroids, or the combined use of corticosteroids and VGB from the outset, makes a difference in outcome in terms of epilepsy or development. In the ICISS study, the combination of VGB and steroids resulted in a response a few days faster than steroids alone. Unfortunately, this difference does not have a significant impact on outcome at 14 months, either for epilepsy or on developmental outcome.[11] Despite the lack of a lead time to treatment as a predictor of epilepsy outcome, possibly due to a small population and a lower percentage of participants with a lead time surpassing 1 month (29% compared to the ICISS study's 50%), we consider it a crucial factor in the management of these individuals. It was previously reported that parents of children with epileptic spasms often consult a first care practitioner in <1 week, feeling that "something was wrong," whereas it took nearly 1 month to identify the epileptic spasms and IESS.[24] These findings stress the absolute necessity of educating the families of infants at risk for epileptic spasms, such as those with tuberous sclerosis, as well as health care providers.

As far as first-line monotherapy is concerned, our short-term results are in line with the previous observational or randomized data: 32% of responders with VGB alone compared to 35%–43% in the literature.[16,25–28] The response to VGB was obtained at day 7 with a median dosage of 100 mg/kg/day, and few individuals achieved better response after increasing VGB up to 150 mg/kg/day. By sequentially adding oral steroids to VGB, we increased the responder rate to 45% and then by replacing oral steroids with ACTH to 49.5%. Although comparable to the 42%–55% and 39%–44.5% at 3–4 months of ACTH and hydrocortisone, respectively,[3,25] our responder rates are below the 72% when using a combination of VGB and steroids or ACTH from the start.[29] Note that this ICISS study rate may be overestimate due to the evaluation criteria used (clinical response at day 42 without reporting the EEG aspects). Nevertheless, we decided to modify our protocol to implement the combination of hydrocortisone and VGB earlier (Figure 5). All individuals were given an initial dose of 100 mg/kg/day of VGB, according to pharmacological simulations recommending a minimum dose of 80 mg/kg/day.[30] In the revised protocol, we shortened the time to evaluate VGB to 7 days instead of 20–25 days. We eliminated the additional time to titrate till 150 mg/kg/day due to the low response benefit (increase of 5% of responders) and the increased risk of persisting spasms affecting cognitive outcome.[11] Contrarily to previous studies,[25,31–33] the switch from hydrocortisone to ACTH followed by hydrocortisone over 6 months presently allowed recovery in 9% of nonresponders. As the clinical cessation of spasms on hydrocortisone occurred <1 week in the literature,[26,32,33] we proposed an assessment 15 days after the initiation of hydrocortisone with a switch from hydrocortisone to ACTH in the case of poor response. All these changes should allow accelerated implementation of hydrocortisone in addition to VGB in individuals lacking positive response to VGB (day 7 vs. day 20–25 in the old protocol) and ACTH (day 21 vs. day 35–40). We also strengthened the possible role of surgery in the management of IESS and the need for an early presurgical work-up to identify patients that are candidate for this therapy. We believe that this revised protocol will better address the challenge of IESS therapy limiting the use of unnecessary steroid therapy and resulting AEs in 30% of individuals on one hand, and a quick evaluation of VGB efficacy after 1 week on the other hand allowing rapid adjunction of steroids without any loss of chance for the non reponders.

The side effects observed in our cohort associated with the use of steroids (48.6%) were consistent with the literature, although their identification may have been limited to clinically significant ones due to the retrospective study design. High doses of steroids have been linked to numerous AEs in 50%–95% of individuals with IESS, such as hypertonia (85%), weight gain (12%–23%), infection (8%–29%), adrenal insufficiency (75%), hypertension, cardiac hypertrophy (33%), and even death in a few cases.[19,27,29,32,34,35] Concerning VGB, primary safety concerns are VFL and VABAM. VFL have been identified since 1997 in individuals on VGB.[12] The main factors of VFL related to VGB described in the literature are the cumulative dose and the duration of VGB exposure.[36,37] The prevalence of VFL ranged from 10% to 90% of VGB-treated individuals.[38] However, a phase 4 VGB vision study in adults showed that vision abnormality concerned 66% of individuals at baseline, including abnormal central 30° visual field measurements in 20% and thin retinal nerve fiber layer in 32%.[39] No individuals with symptomatic visual loss were identified either in this phase 4 study[39] or in the drug registry.[38] In our cohort, we identified only one individual with VFL. This finding aligns with a recent study on this topic, where it was reported that .7% of the 284 children in the VGB cohort experienced definite VGB-related ocular toxicity, and 1.4% exhibited optic atrophy with an unclear relation to VGB, categorized as possible toxicity.[40] Considering the challenges associated with conducting electroretinograms, such as the requirement for a specialized and trained team, and sometimes the need for

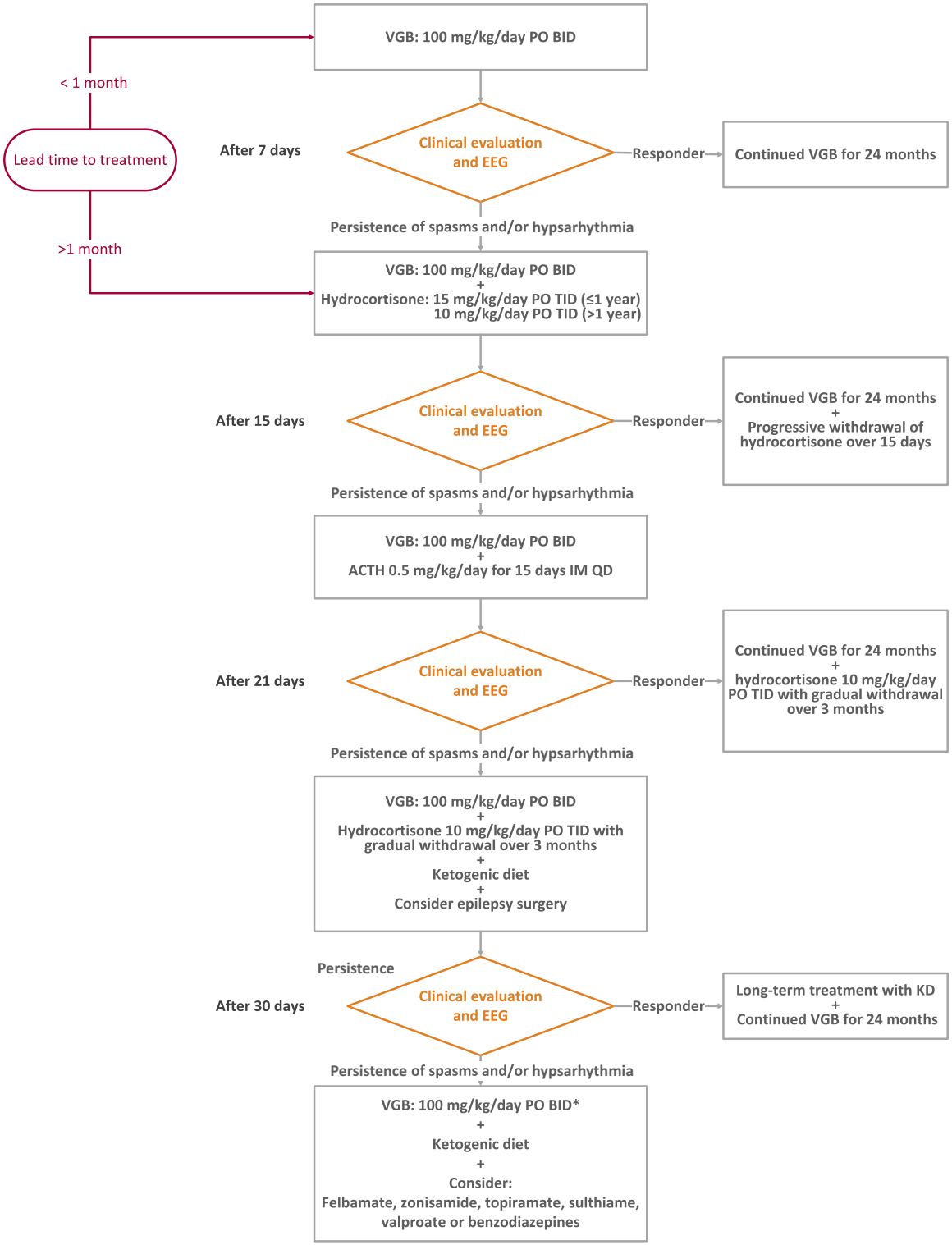

FIGURE 5 Proposition of algorithm for treatment of individuals with infantile epileptic spasms syndrome based on our results and on the literature review. *In the case of partial efficacy on epileptic spasms or resurgence of spasms during vigabatrin (VGB) tapering phase before discontinuation. ACTH, adrenocorticotropic hormone; BID, twice daily administration; EEG, electroencephalogram; IM, intramuscular; KD, ketogenic diet; PO, per os; QD, every day; TID, thrice daily administration.

sedation or anesthesia, their use remains a subject of controversy. Moreover, it has been noted that abnormal results from electroretinograms may lead to minimal changes in clinical decision-making.[41] VABAM are seen on high T2-weighted imaging and/or restricted diffusion-weighted imaging in the deep basal ganglia and brainstem. VABAM are identified in 20%–30% of individuals on VGB and are usually asymptomatic.[42–44] There were

17 individuals reported in the literature with symptomatic VABAM (abnormal movements, dysautonomia, and acute encephalopathy)[13,45–50]; it is noteworthy that 85% had taken a combination of VGB and steroids at the time of presentation, suggesting that symptomatic VABAM may have been due to the combination therapy rather than VGB alone.[50] This raises the possibility that polytherapy may increase the severity of AEs. However, these data are difficult to trace in a retrospective study and in young individuals with intellectual disability. Finally, by starting with relatively low-dose VGB monotherapy (100 mg/kg/day), our protocol allowed preservation of >50% of the responders (56.6%, 51.6% if individuals with TSC are excluded) from AEs associated with the addition of steroids (48.6% of the individuals exposed to steroids in our cohort).

Our study confirms the high rate of spasm relapse in IESS: 29% in our whole cohort, within the range of the 15%–58% reported in the literature.[14,15,51–53] We also confirm that relapse can occur many years after an initial good response to VGB, alone or combined with steroids,[15,53] and that relapse can be "intractable."[17] There are few therapeutic options to prevent spasms relapse. Obviously, steroids cannot be sustained due to safety risk linked to prolonged exposure. Zonisamide and topiramate failed to prevent spasm relapse,[15] so they cannot be recommended as third-line therapy. In our study, 40% of individuals with VGB withdrawal before 24-month duration experienced relapse versus 12.8% of those still on VGB after 24 months. In an RCT comparing ACTH and KD for IESS, spasm relapse rate at 18 months was 43% on ACTH (28 days of total treatment duration) versus 16% on KD.[19] It is noteworthy in this study that the subpopulation with prior VGB treatment had a relapse rate of 0% compared to 26% in the population on KD alone. We therefore suggest that extending VGB treatment to 24 months may be a good balance between reducing the risk of relapse and maintaining safety. Interestingly, the same 24-month duration was recommended in the EPISTOP trial for preventing VGB treatment in TSC, and none of the individuals in that trial experienced epileptic spasms during this period.[54] Moreover, EEG was able to predict the relapse in 83% of cases in a retrospective study.[51] Using EEG monitoring as a personalized biomarker of IESS relapse risk could allow the identification of the subpopulation of individuals with a high risk of relapse who should continue VGB, thus avoiding long-term VGB exposure for the others.

Some limitations should be highlighted in this study. It is a monocentric retrospective study of a single pediatric tertiary epilepsy center. However, our center has been a pioneer and has long experience in the use of VGB in IESS,[7,55,56] and the long-term outcome reports of individuals who received VGB are scarce.[57,58] Moreover, "real-world data (RWD) and real-world evidence (RWE) are playing an increasing role in health care decisions."[59] The US Food and Drug Administration has recognized their value and now accepts them as key players to support clinical trial. In this context, it is essential that we take a rigorous approach to use or reuse clinical data collected over many years, as in this study, to reevaluate our practices and gain new knowledge.[60] This disparity can lead to some individuals not receiving appropriate care.[61] The retrospective nature of our study introduces a potential selection bias due to individuals with insufficient data, representing approximately one third of the initial cohort. A large number of patients were referred and had a single outpatient or in-hospital visit for diagnosis, workup, and establishment of the therapy. They were followed later on by their local pediatric neurologist. Likewise, the study revealed few deviations from the initial protocol, highlighting the possible deviation in real word between clinical practice and protocols and guidelines. Further prospective studies are needed to assess the impact of such a sequential proactive protocol in terms of efficacy and safety and allow comparison with previous studies. Although KD seems to show interesting results in terms of efficacy, safety, and risk of relapse, this therapy is implemented after the second line in our proposed treatment algorithm due to the limited randomized trials on this topic.[19]

In conclusion, proactive sequential treatment with VGB alone followed within 7 days in the case of nonresponse to VGB-steroids combination seems a viable alternative to the initiation of the combined approach for IESS treatment. The response to VGB is evaluated at day 7, avoiding a delay of >1 week from diagnosis for the VGB-steroids combination. Along the same lines, we propose that the combination should be used in individuals with delayed diagnosis for >1 month. This approach should limit steroid-related AEs when VGB alone is sufficient and potentiation of VGB-related AEs when combined with steroids. Maintaining VGB treatment for a period of 24 months seems to be a good compromise to limit the risk of relapse with a balanced risk of treatment-induced AEs. Multicentric randomized studies or real-world prospective data are needed to validate these proposals.

AUTHOR CONTRIBUTIONS

RN conceptualized and designed the study. TLB, NC, CC supervised data extraction and collection. MK and TLB did the statistical analysis, designed the figures. MK and RN wrote the manuscript. All authors critically revised the manuscript and approved the final version submitted.

ACKNOWLEDGMENTS

We thank the patient and her family for supporting this publication. R.N. was supported by state funding

from the Agence Nationale de la Recherche under the Investissements d'avenir program (ANR-10-IAHU-01) and the Fondation Bettencourt Schueller.

CONFLICT OF INTEREST STATEMENT

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

CONTRIBUTION TO THE FIELD STATEMENT

IESS is a rare developmental and epileptic encephalopathy characterized by epileptic spasms, disorganized interictal patterns called hypsarrhythmia, and psychomotor regression. Commonly, this syndrome is associated with drug resistance and poor neurodevelopmental outcome. Factors identified that improve prognosis are the underlying etiology, preexisting normal development, and early introduction of syndrome-specific antiseizure medicine, namely VGB and/or steroids. However, there is much discussion about the use of steroids or VGB as first-line monotherapy or in combination. We used a rapid sequential approach starting with VGB monotherapy rapidly combined with corticosteroids in the case of nonresponse. To evaluate the impact of such an approach, we reviewed the data from the last 20 years at our tertiary epilepsy center. This approach appears to have similar efficacy to other approaches in the medium term but avoids corticosteroids AEs in >50% of individuals. Our study is the first to identify the value of maintaining treatment with VGB for at least 2 years after the cessation of spasms to limit the risk of spasm relapse. The long-term outcome of our cohort was consistent with the literature, with 46.5% seizure-free, of whom 26% were ASM-free.

ORCID

Mathieu Kuchenbuch https://orcid.org/0000-0002-5944-2204
Tommaso Lo Barco https://orcid.org/0000-0002-3103-230X
Nicole Chemaly https://orcid.org/0000-0002-2333-9408
Catherine Chiron https://orcid.org/0000-0002-9096-1694
Rima Nabbout https://orcid.org/0000-0001-5877-4074

REFERENCES

1. Fukuyama Y. History of clinical identification of West syndrome—in quest after the classic. Brain Dev. 2001;23:779–87.
2. Specchio N, Wirrell EC, Scheffer IE, Nabbout R, Riney K, Samia P, et al. International League Against Epilepsy classification and definition of epilepsy syndromes with onset in childhood: position paper by the ILAE Task Force on Nosology and Definitions. Epilepsia. 2022;63:1398–442.
3. Riikonen R. Infantile spasms: outcome in clinical studies. Pediatr Neurol. 2020;108:54–64.
4. Darke K, Edwards SW, Hancock E, Johnson AL, Kennedy CR, Lux AL, et al. Developmental and epilepsy outcomes at age 4 years in the UKISS trial comparing hormonal treatments to vigabatrin for infantile spasms: a multi-centre randomised trial. Arch Dis Child. 2010;95:382–6.
5. Low NL. Infantile spasms with mental retardation. II. Treatment with cortisone and adrenocorticotropin. Pediatrics. 1958;22:1165–9.
6. Sorel L, Dusaucy-Bauloye A. A propos de 21 cas d'hypsarhythmia de Gibbs; son traitement spectaculaire par l'ACTH. Acta Neurol Psychiatr Belg. 1958;58:130–41.
7. Chiron C, Dulac O, Luna D, Palacios L, Mondragon S, Beaumont D, et al. Vigabatrin in infantile spasms. Lancet. 1990;335:363–4.
8. Hussain SA. Treatment of infantile spasms. Epilepsia Open. 2018;3:143–54.
9. Song JM, Hahn J, Kim SH, Chang MJ. Efficacy of treatments for infantile spasms: a systematic review. Clin Neuropharmacol. 2017;40:63–84.
10. Chiron C, Dumas C, Jambaqué I, Mumford J, Dulac O. Randomized trial comparing vigabatrin and hydrocortisone in infantile spasms due to tuberous sclerosis. Epilepsy Res. 1997;26:389–95.
11. O'Callaghan FJK, Edwards SW, Alber FD, Cortina Borja M, Hancock E, Johnson AL, et al. Vigabatrin with hormonal treatment versus hormonal treatment alone (ICISS) for infantile spasms: 18-month outcomes of an open-label, randomised controlled trial. Lancet Child Adolesc Health. 2018;2:715–25.
12. Eke T, Talbot JF, Lawden MC. Severe persistent visual field constriction associated with vigabatrin. Br Med J. 1997;314:180–1.
13. Hussain SA, Tsao J, Li M, Schwarz MD, Zhou R, Wu JY, et al. Risk of vigabatrin-associated brain abnormalities on MRI in the treatment of infantile spasms is dose-dependent. Epilepsia. 2017;58:674–82.
14. Hayashi Y, Yoshinaga H, Akiyama T, Endoh F, Ohtsuka Y, Kobayashi K. Predictive factors for relapse of epileptic spasms after adrenocorticotropic hormone therapy in West syndrome. Brain Dev. 2016;38:32–9.
15. Rajaraman RR, Lay J, Alayari A, Anderson K, Sankar R, Hussain SA. Prevention of infantile spasms relapse: Zonisamide and topiramate provide no benefit. Epilepsia. 2016;57:1280–7.
16. Kalra V, Gulati S, Pandey RM, Menon S. West syndrome and other infantile epileptic encephalopathies—Indian hospital experience. Brain Dev. 2002;24:130–9.
17. Camfield P, Camfield C, Lortie A, Darwish H. Infantile spasms in remission may reemerge as intractable epileptic spasms. Epilepsia. 2003;44:1592–5.
18. Garcelon N, Neuraz A, Salomon R, Faour H, Benoit V, Delapalme A, et al. A clinician friendly data warehouse oriented toward narrative reports: Dr. Warehouse. Journal of Biomedical Informatics. 2018;80:52–63.
19. Dressler A, Benninger F, Trimmel-Schwahofer P, Gröppel G, Porsche B, Abraham K, et al. Efficacy and tolerability of the ketogenic diet versus high-dose adrenocorticotropic hormone for infantile spasms: a single-center parallel-cohort randomized controlled trial. Epilepsia. 2019;60:441–51.

20. R Core Team. R: A language and environment for statistical computing (v. 4.0. 2). Vienna: R Foundation for Statistical Computing; 2020.
21. Epilepsies in children, young people and adults NICE guideline [Internet]. 2022. Available from: www.nice.org.uk/guidance/ng217
22. Nabbout R, Kuchenbuch M. Impact of predictive, preventive and precision medicine strategies in epilepsy. Nat Rev Neurol. 2020;16:674–88.
23. Zhang B, McDaniel SS, Rensing NR, Wong M. Vigabatrin inhibits seizures and mTOR pathway activation in a mouse model of tuberous sclerosis complex. PLoS One. 2013;8:e57445.
24. Hussain SA, Lay J, Cheng E, Weng J, Sankar R, Baca CB. Recognition of infantile spasms is often delayed: the ASSIST study. J Pediatr. 2017;190:215–221.e1.
25. Grinspan ZM, Knupp KG, Patel AD, Yozawitz EG, Wusthoff CJ, Wirrell EC, et al. Comparative effectiveness of initial treatment for infantile spasms in a contemporary US cohort. Neurology. 2021;97:e1217–28.
26. Hahn J, Park G, Kang HC, Lee JS, Kim HD, Kim SH, et al. Optimized treatment for infantile spasms: vigabatrin versus prednisolone versus combination therapy. J Clin Med. 2019;8:1591.
27. Knupp KG, Coryell J, Nickels KC, Ryan N, Leister E, Loddenkemper T, et al. Response to treatment in a prospective national infantile spasms cohort. Ann Neurol. 2016;79:475–84.
28. Ko A, Youn SE, Chung HJ, Kim SH, Lee JS, Kim HD, et al. Vigabatrin and high-dose prednisolone therapy for patients with West syndrome. Epilepsy Res. 2018;145:127–33.
29. O'Callaghan FJK, Edwards SW, Alber FD, Hancock E, Johnson AL, Kennedy CR, 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.
30. Ounissi M, Rodrigues C, Bienayme H, Duhamel P, Pons G, Dulac O, et al. Proposition of a minimal effective dose of vigabatrin for the treatment of infantile spasms using pediatric and adult pharmacokinetic data. J Clin Pharmacol. 2019;59:177–88.
31. Li S, Zhong X, Hong S, Li T, Jiang L. Prednisolone/prednisone as adrenocorticotropic hormone alternative for infantile spasms: a meta-analysis of randomized controlled trials. Dev Med Child Neurol. 2020;62:575–80.
32. Wanigasinghe J, Arambepola C, Sri Ranganathan S, Sumanasena S, Attanapola G. Randomized, single-blind, parallel clinical trial on efficacy of oral prednisolone versus intramuscular corticotropin on immediate and continued spasm control in west syndrome. Pediatr Neurol. 2015;53:193–9.
33. Gowda VK, Narayanaswamy V, Shivappa SK, Benakappa N, Benakappa A. Corticotrophin-ACTH in comparison to prednisolone in west syndrome—a randomized study. Indian J Pediatr. 2019;86:165–70.
34. Lux AL, Edwards SW, Hancock E, Johnson AL, Kennedy CR, Newton RW, et al. The United Kingdom Infantile Spasms Study (UKISS) comparing hormone treatment with vigabatrin on developmental and epilepsy outcomes to age 14 months: a multicentre randomised trial. Lancet Neurol. 2005;4:712–7.
35. Doré-Brabant G, Laflamme G, Millette M, Osterman B, Chrestian N. Adrenal insufficiency among children treated with hormonal therapy for infantile spasms. Epilepsia. 2022;63:2350–8.
36. Maguire MJ, Hemming K, Wild JM, Hutton JL, Marson AG. Prevalence of visual field loss following exposure to vigabatrin therapy: a systematic review. Epilepsia. 2010;51:2423–31.
37. Wild JM, Martinez C, Reinshagen G, Harding GFA. Characteristics of a unique visual field defect attributed to vigabatrin. Epilepsia. 1999;40:1784–94.
38. Foroozan R. Vigabatrin: lessons learned from the United States experience. J Neuroophthalmol. 2018;38:442–50.
39. Sergott RC, Johnson CA, Laxer KD, Wechsler RT, Cherny K, Whittle JA, et al. Retinal structure and function in vigabatrin-treated adult patients with refractory complex partial seizures. Epilepsia. 2016;57:1634–42.
40. Schein Y, Miller KD, Han Y, Yu Y, de Alba Campomanes AG, Binenbaum G, et al. Ocular examinations, findings, and toxicity in children taking vigabatrin. J AAPOS. 2022;26:187.e1–187.e6.
41. Strong AD, Sturdy A, McCourt EA, Braverman RS, Singh JK, Enzenauer RW, et al. Clinical utility of electroretinograms for evaluating vigabatrin toxicity in children. J Pediatr Ophthalmol Strabismus. 2021;58:174–9.
42. Xu Y, Wan L, He W, Wang Y-Y, Wang Q-H, Luo X-M, et al. Risk of vigabatrin-associated brain abnormalities on MRI: a retrospective and controlled study. Epilepsia. 2021;63(1):120–9.
43. Dracopoulos A, Widjaja E, Raybaud C, Westall CA, Snead OC. Vigabatrin-associated reversible MRI signal changes in patients with infantile spasms. Epilepsia. 2010;51:1297–304.
44. Wheless JW, Carmant L, Bebin M, Conry JA, Chiron C, Elterman RD, et al. Magnetic resonance imaging abnormalities associated with vigabatrin in patients with epilepsy. Epilepsia. 2009;50:195–205.
45. Schonstedt V, Stecher X, Venegas V, Silva C. Vigabatrin-induced MRI changes associated with extrapyramidal symptoms in a child with infantile spasms. Neuroradiol J. 2015;28:515–8.
46. Vega YH, Kaliakatsos M, U-King-Im JM, Lascelles K, Lim M. Reversible vigabatrin-induced life-threatening encephalopathy. JAMA Neurol. 2014;71:108–9.
47. Fong CY, Osborne JP, Edwards SW, Hemingway C, Hancock E, Johnson AL, 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;55:862–7.
48. Dill P, Datta AN, Weber P, Schneider J. Are vigabatrin induced T2 hyperintensities in cranial MRI associated with acute encephalopathy and extrapyramidal symptoms? Eur J Paediatr Neurol. 2013;17:311–5.
49. Sun LR, Bosemani T, Smith-Hicks CL. Neuroimaging abnormalities in a child with infantile spasms on high-dose vigabatrin. Pediatr Neurol. 2017;67:109–10.
50. Bhalla S, Skjei K. Fulminant vigabatrin toxicity during combination therapy with adrenocorticotropic hormone for infantile spasms: three cases and review of the literature. Epilepsia. 2020;61:e159–64.
51. Wan L, Lei Y-Q, Liu X-T, Chen J, Yeh C-H, Zhang C-T, et al. Assessing risk for relapse among children with infantile spasms using the based score after ACTH treatment: a retrospective study. Neurol Ther. 2022;11:835–49.
52. Mytinger JR, Vidaurre J, Moore-Clingenpeel M, Stanek JR, Albert DVF. A reliable interictal EEG grading scale for children with infantile spasms—The 2021 based score. Epilepsy Res. 2021;173:106631.

53. Kröll-Seger J, Kaminska A, Moutard ML, de Saint-Martin A, Guët A, Dulac O, et al. Severe relapse of epilepsy after vigabatrin withdrawal: for how long should we treat symptomatic infantile spasms? Epilepsia. 2007;48:612–3.
54. Kotulska K, Kwiatkowski DJ, Curatolo P, Weschke B, Riney K, Jansen F, et al. Prevention of epilepsy in infants with tuberous sclerosis complex in the EPISTOP trial. Ann Neurol. 2021;89:304–14.
55. Chiron C, Dulac O, Beaumont D, Palacios L, Pajot N, Mumford J. Therapeutic trial of vigabatrin in refractory infantile spasms. J Child Neurol. 1991;6(2):S52–9.
56. Nabbout RC, Chiron C, Mumford J, Dumas C, Dulac O. Vigabatrin in partial seizures in children. J Child Neurol. 1997;12:172–7.
57. Djuric M, Kravljanac R, Tadic B, Mrlješ-Popovic N, Appleton RE. Long-term outcome in children with infantile spasms treated with vigabatrin: a cohort of 180 patients. Epilepsia. 2014;55:1918–25.
58. Cohen-Sadan S, Kramer U, Ben-Zeev B, Lahat E, Sahar E, Nevo Y, et al. Multicenter long-term follow-up of children with idiopathic west syndrome: ACTH versus vigabatrin. Eur J Neurol. 2009;16:482–7.
59. US Food and Drug Administration. Real-world evidence|FDA [Internet]. Science and Research Special Topics [cited 2023]. 2020. Available from: https://www.fda.gov/science-research/science-and-research-special-topics/real-world-evidence
60. Concato J, Corrigan-Curay J. Real-world evidence—where are we now? N Engl J Med. 2022;386:1680–2.
61. Ebben RHA, Vloet LCM, Verhofstad MHJ, Meijer S, de Groot JAM, van Achterberg T. Adherence to guidelines and protocols in the prehospital and emergency care setting: a systematic review. Scand J Trauma Resusc Emerg Med. 2013;21:9.

How to cite this article: Kuchenbuch M, Lo Barco T, Chemaly N, Chiron C, Nabbout R. Fifteen years of real-world data on the use of vigabatrin in individuals with infantile epileptic spasms syndrome. Epilepsia. 2024;65:430–444. https://doi.org/10.1111/epi.17808