Pediatric Neurology 46 (2012) 276–280

Contents lists available at ScienceDirect

Pediatric Neurology

journal homepage: www.elsevier.com/locate/pnu

Original Article

Outcomes of Epileptic Spasms in Patients Aged Less Than 3 Years: Single-Center United States Experience

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ARTICLE INFORMATION

Article history:
Received 17 November 2011
Accepted 22 February 2012

ABSTRACT

Retrospective review was performed of children aged <3 years with epileptic spasms at our center from 2004-2010. Short-term (<6 months) and long-term (≥6 months) outcomes were assessed. We included 173 children (104 boys; median age of onset, 6.8 months) with epileptic spasms of known (62%) and unknown (38%) etiology. Treatments included adrenocorticotropic hormone (n = 103), vigabatrin (n = 82), phenobarbital (n = 34), and other agents (n = 121). Short-term treatment with adrenocorticotropic hormone and vigabatrin provided better epileptic spasm control in groups with known and unknown etiology than other agents. At follow-up (6-27 months), 54% of children manifested seizures, and 83% manifested developmental delay. Known etiology was a predictor of poor developmental outcome ($P = 0.006$), whereas bilateral/diffuse brain lesions predicted both poor development and seizures ($P = 0.001$ and 0.005, respectively). Initial presentations of epileptic spasms with hypotonia or developmental delay most strongly predicted both seizures and neurodevelopmental outcomes ($P < 0.001$). In a child presenting with epileptic spasms with developmental delay or hypotonia, no specific treatment may offer superior benefit.

Introduction

Epileptic spasms are characterized by short and abrupt movements involving truncal flexion or extension, or mixed presentations, possibly associated with arm (and leg) abduction and extension, generally occurring in clusters [1]. They present during infancy and early childhood. Their peak onset occurs between 4 and 10 months of age, at an incidence of about 0.4/1000 live births [1,2]. Epileptic spasms are typically associated with psychomotor delay or developmental stagnation/regression, and a typical electroencephalographic pattern of hypsarrhythmia [2,3]. In the new classification, "infantile spasms," as they were called previously, have been grouped together with those occurring in patients aged >3 years, and are renamed "epileptic spasms" [4].

In more than half of children with epileptic spasms, an underlying neurologic etiology, such as hypoxic-ischemic injury, tuberous sclerosis, or genetic/metabolic syndromes, can be identified [2]. Epileptic spasms of no identifiable cause in infants with normal development before the onset of infantile spasms are classified as "of unknown etiology" (previous nomenclature included the terms "cryptogenic" and "idiopathic"), whereas those with an identifiable cause are classified as "of known etiology" (previous nomenclature included the term "symptomatic") [4].

Long-term prognoses are generally more favorable in cases of unknown etiology, although overall, epileptic spasms are associated with poor long-term prognoses for intellectual development, and with severe cognitive impairments and seizures later in life [5-7].

Current therapies for epileptic spasms consist of high doses of adrenocorticotropic hormone, oral prednisone, or the γ-aminobutyric acid transaminase inhibitor vigabatrin, although their efficacy remains unclear, and no consensus on first-line vs second-line treatment exists [8]. However, vigabatrin was demonstrated as more effective than adrenocorticotropic hormone in epileptic spasms secondary to tuberous sclerosis. Furthermore, the effectiveness of certain traditional anticonvulsants (such as valproic acid and phenobarbital) in the treatment of epileptic spasms has not been adequately assessed [6]. In addition, few data indicate which treatment may conclusively improve the long-term intellectual outcomes of infants with epileptic spasms [6].

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doi:10.1016/j.pediatrneurol.2012.02.022

This study aimed to describe the experience in evaluation, diagnosis, management, and outcomes of epileptic spasms in patients younger than age 3 years during a 7-year period (2004-2010) at a tertiary care center in the United States.

Study Design and Methods

After obtaining Institutional Review Board approval, we performed a retrospective electronic chart review of patients with epileptic spasms at Children's Hospital Boston. The inclusion criteria comprised:

(1) Age of less than 3 years at the onset of epileptic spasms;
(2) Assessment of patients between January 2004 and December 2010;
(3) Epileptic spasms consisting of abrupt movements, characterized by subtle (facial), flexor, extensor, or mixed movements occurring in clusters (more than two movements);
(4) Abnormal electroencephalogram findings; and
(5) A minimum follow-up of 6 months after the onset of spasms and treatment at Children's Hospital Boston.

A subset of patients with tuberous sclerosis complex was identified, using clinical diagnostic criteria and genetic testing. Patients were grouped according to the treatment they received:

(1) Adrenocorticotropic hormone;
(2) Vigabatrin;
(3) A combination of adrenocorticotropic hormone followed by vigabatrin, or vice versa; and
(4) Other drugs.

The primary (short-term) outcome involved the cessation of epileptic spasms, as defined by the West Delphi Group in 2004: "no clinical spasms witnessed from a time commencing within 14 days of treatment and for a period of >28 days from the time of last observed spasm," and our measurement was binary (cessation of epileptic spasms or treatment failure) [9]. Cessation of spasms was documented by video-electroencephalogram monitoring in a significant number of patients, and by clinical observation in the remaining patients.

Secondary (long-term) outcomes included:

(1) The appearance of other seizure types and electroclinical syndromes according to the criteria of the International League Against Epilepsy [4] after the cessation of spasms; and
(2) The presence of developmental delay at follow-up, as assessed by the Denver Developmental Scales [10,11] when available, and by the assessment of clinical milestones in the office.

Outcomes were analyzed according to:

(1) Etiology:
  (a) Known; or
  (b) Unknown;
(2) Age at onset of epileptic spasms:
  (a) Early (<4 months);
  (b) Classic (≥4 and <10 months); and
  (c) Late (≥10 months);
(3) Electroencephalogram patterns:
  (a) Hypsarrhythmia;
  (b) Variants of hypsarrhythmia, as described by Hrachovy and Frost [1] in 1984; and
  (c) Other abnormal electroencephalogram patterns, including slowing or interictal epileptiform discharges;
(4) Imaging findings from 1-1.5 T magnetic resolution scans, classified as:
  (a) Normal; or
  (b) Abnormal, including diffuse and bilateral abnormalities, and focal or midline lesions; and
(5) Developmental delay, i.e., a 3-month delay in the acquisition of age-appropriate milestones (classified as severe developmental delay), or a 1-month delay (classified as mild developmental delay).

Binary associations were analyzed using the χ^2 test or Fisher exact test. To determine the relationships between treatment groups and outcome measures, we used logistic regression. This procedure allowed us to calculate odds ratios and directly compare the effects of treatment on outcomes. If a likelihood ratio test for groups was significant at the 0.05 level, we compared groups by constructing Wald tests to compute the significance of the pairwise comparison. For example, to compare the adrenocorticotropic hormone group directly to the vigabatrin group, we tested whether the logistic regression coefficients were significantly different from each other. We expanded this analysis to adjust for confounders or effect modifiers. The covariates under consideration included the presence of a proven etiology, age, sex, type of epileptic spasms, and duration of epileptic spasms. Interactions with treatment groups were included in the model for effect modifications. Terms were dropped from the model if the likelihood ratio for their inclusion was not significant at the 0.05 level. The Akaike information criteria were used to compare non-nested models. The data were analyzed with Stata-11 (Stata Corporation, College Station, TX) and R (R Foundation for Statistical Computing, Vienna, Austria).

Results

The inclusion criteria were met by 173 children (104 boys), with a median age of 6.8 months (range, 0-108 months; mean, 9.8 months; standard deviation, 14 months) during their first visit at Children's Hospital Boston. An underlying etiology was identified in 62% (107/173) (Table 1). An electroencephalogram was performed in 168 patients at their time of diagnosis, and indicated hypsarrhythmia in 101 (60%) patients, whereas the study was interpreted as "abnormal," but hypsarrhythmia was not evident, in 67 patients (40%). Abnormal imaging findings were present in 116 of 173 patients (67%), consisting of bilateral/diffuse lesions in 72/173 (42%), and focal lesions in 44/173 (25%).

The median age at onset of epileptic spasms was 5.5 months (range, 0.13-21 months; mean, 5.9 months; standard deviation, 3.3 months). The median age at which patients presented at our institution was 6.8 months (range, 0-108 months; mean, 9.8 months; standard deviation, 14 months). Overall, the diagnosis of epileptic spasms was rendered by a neurologist in 149 cases, by the treating pediatrician in 10 cases, and by other physicians in four cases (and in 10 cases, this information was unavailable). Upon diagnosis, 52% (91/173) demonstrated developmental delay, which was severe in 27% (47/173) and mild to moderate in 25% (44/173). Seventy-seven (44%) patients presented with hypotonia, whereas in 54 (31%), tone was normal, and in 35 (20%), tone was increased. In 7 patients (4%), this information was missing.

Medications to treat epileptic spasms included adrenocorticotropic hormone (n = 103), vigabatrin (n = 82), phenobarbital (n = 34), and others (n = 121), including valproic acid (n = 7), topiramate (n = 35), lamotrigine (n = 1), zonisamide (n = 5), levetiracetam (n = 22), and rufinamide (n = 1). In 12 patients, adrenocorticotropic hormone was used as first-line treatment, followed by vigabatrin. Our retrospective analysis did not allow us to assess whether phenobarbital and other antiepileptic drugs were used before or after initiating treatment with adrenocorticotropic hormone or vigabatrin.

We did not observe any significant changes in practice patterns after the United States Food and Drug Administration approval of vigabatrin in August 2009. Before 2009, 145 patients were

Table 1. Underlying etiologies of epileptic spasms

Underlying Etiology	Number of Patients*
Unknown	66
Chromosomal disorders	44
Malformations of cortical development	25
Tuberous sclerosis	15
Perinatal stroke	13
Hypoxic-ischemic brain injury	7
Genetic/neurometabolic disorders	7
Postinfection brain injury	3
Neurofibromatosis	2
Trauma	1

* A single patient can manifest more than one underlying etiology.

Table 2. Response to therapy according to etiology

	Known Etiology (n = 107)			Unknown Etiology (n = 66)		
	Number (%)*	Responders	Relapses	Number (%)*	Responders	Relapses
ACTH	55 (51%)	37 (67%)	5	48 (72%)	24 (50%)	3
VGB	47 (44%)	28 (60%)	2	34 (52%)	19 (56%)	3
PB	23 (21%)	5 (22%)	0	11 (17%)	4 (27%)	0
Other AEDs	76 (71%)	22 (29%)	0	45 (68%)	13 (29%)	0

Abbreviations:
ACTH = Adrenocorticotropic hormone
AEDs = Antiepileptic drugs
PB = Phenobarbital
VGB = Vigabatrin
* A single patient can be included in more than one treatment category.

examined at our center, and 60 were treated with vigabatrin (41%). After 2009, 12 of 28 received vigabatrin (43%).

Response to therapy according to etiology of epileptic spasms

Responder rates and relapses after response to each treatment in children with known and unknown etiologies of epileptic spasms are presented in Table 2. Overall, response rates were similar in the group with known etiology, compared with the group with unknown etiology. In both groups, adrenocorticotropic hormone and vigabatrin provided better epileptic spasm control than phenobarbital and other agents, for 67% and 60% of responders, respectively, in the known etiology group, and for 50% and 56% of responders, respectively, in the unknown etiology group. Responder rates with phenobarbital and other agents were significantly lower, i.e., at 22% and 29% for the known etiology group, respectively, and at 27% and 29% for the unknown etiology group, respectively ($P < 0.05$). Of 34 children treated with phenobarbital, 24 did not exhibit changes in the frequency of their epileptic spasms, eight exhibited a reduction, and two demonstrated a worsening in frequency of their epileptic spasms.

Our series included 15 patients with tuberous sclerosis complex. Two children received adrenocorticotropic hormone and 13 received vigabatrin as first-line therapy. One of the two children on adrenocorticotropic hormone responded to therapy (50%), and 10 out of 13 children on vigabatrin responded to therapy, at a response rate of 76%.

Development of other seizures and developmental outcomes

All patients received a minimum follow-up of 6 months at our center. The median follow-up time was 27.2 months (range, 6-117 months; mean, 36 months; standard deviation, 27.6 months), and the median age of patients at follow-up was 36.8 months (range, 6-116 months; mean, 43.6 months; standard deviation, 28.1 months).

Of 173 patients, 93 (54%) manifested other seizure types during their most recent follow-up. Tonic seizures comprised the most common epileptic seizure type, in 30 cases (32%). Four patients with tonic seizures had developed Lennox-Gastaut syndrome. In addition, 21 patients were still experiencing epileptic spasms. Developmental delay was observed in 144 of the 173 patients (83%).

Predictors of long-term seizures and developmental outcomes are detailed in Tables 3 and 4. Etiology did not predict long-term seizure outcomes. Thirty-four of 66 patients with an unknown etiology and 63 of 107 patients with a known etiology manifested seizures as of their most recent follow-up ($P > 0.05$). However, known etiology was a predictor of poor developmental outcome. Twenty-three of 66 patients (35%) with an unknown etiology and 60 of 107 patients (56%) with a known etiology experienced developmental delay as of their most recent follow-up ($P = 0.006$).

Initial electroencephalogram findings (hypsarrhythmia vs normal/abnormal electroencephalogram) were not predictive of developmental or seizure outcomes. Patients with findings of bilateral/diffuse lesions on imaging presented more frequently with developmental delay and seizures ($P = 0.001$ and 0.005, respectively) during follow-up.

Initial presentations of epileptic spasms with hypotonia or developmental delay comprised the strongest predictors for both long-term seizures and neurodevelopmental outcomes. Furthermore, according to our subset analysis, no differences were evident among children with initial developmental delay or hypotonia in terms of epileptic spasm control between adrenocorticotropic hormone, vigabatrin, and other agents, independent of the etiology of epileptic spasms (Table 5).

Discussion

The major findings of this study indicate that:

(1) Bilateral lesions of known etiology, initial hypotonia, and developmental delay represent risk factors for poor developmental outcomes; and
(2) When hypotonia and developmental delay are present at the onset of epileptic spasms, the prognosis is poor, regardless of various treatment options.

Given the retrospective nature of this study, meaningful conclusions in terms of treatment efficacies cannot be drawn.

Table 3. Risk factors for persistent seizures

Variable	Present	Absent	χ^2 *P* Value	OR	95% CI
Known etiology	51%	58%	0.8	0.74	0.4-1.37
ACTH treatment	35.9%	25.5%	0.17	0.79	0.4-1.12
VGB treatment	30.4%	22%	0.84	0.91	0.5-1.55
PB treatment	23.5%	19.6%	0.88	0.85	0.36-2.0
Atypical age of spasm onset	56.7%	52.8%	0.6	1.17	0.63-2.17
EEG hypsarrhythmia	51.4%	58.1%	0.5	1.3	0.67-2.54
MRI with bilateral/diffuse lesions	66.6%	44%	0.005	2.5	1.35-4.77
Hypotonia at presentation	58.9%	51.1%	0.05	1.96	1.03-3.70
Developmental delay at presentation	61.9%	44.8%	0.02	2.0	1.08-3.6

Abbreviations:
ACTH = Adrenocorticotropic hormone
CI = Confidence interval
EEG = Electroencephalographic
MRI = Magnetic resonance imaging
OR = Odds ratio
PB = Phenobarbital
VGB = Vigabatrin

Table 4. Risk factors for developmental delay

Variable	Present	Absent	χ^2 *P* Value	OR	95% CI
Known etiology	56%	34%	0.006	1.86	1.10-1.79
ACTH treatment	42%	39.9%	0.5	0.5	0.3-0.85
VGB treatment	23.3%	21%	0.88	1.08	0.6-1.8
PB treatment	11.5%	15%	0.46	0.68	0.30-1.50
Atypical age of spasm onset	89%	77.5%	0.04	2.39	1.00-5.68
EEG hypsarrhythmia	86%	87%	0.84	1.08	0.47-2.46
MRI with bilateral/diffuse lesions	88.8%	64%	0.001	3.8	1.69-8.75
Hypotonia at presentation	96%	40.9%	<0.001	35.6	10.41-121.90
Developmental delay at presentation	96.7%	63.7%	<0.001	16.85	4.8-58.8

Abbreviations:
ACTH = Adrenocorticotropic hormone
CI = Confidence interval
EEG = Electroencephalographic
MRI = Magnetic resonance imaging
OR = Odds ratio
PB = Phenobarbital
VGB = Vigabatrin

Overall, treatments with adrenocorticotropic hormone and vigabatrin demonstrated similar response rates. The major limitation of this study involves selection bias. Adrenocorticotropic hormone therapy may have been chosen rather than vigabatrin in children with a potentially better outcome (e.g., patients with fewer brain lesions), who would perhaps demonstrate a better chance of positive outcome, regardless of therapy.

The overall response to vigabatrin in our series is comparable to that in other studies [12-16]. Vigabatrin was effective in controlling spasms in 76% of patients with tuberous sclerosis complex (10 out of 13 on vigabatrin). However, probably because of selection bias regarding choice of treatment, only two of the 15 children with tuberous sclerosis complex were treated with adrenocorticotropic hormone, and therefore meaningful comparisons between treatments are not feasible. A recent report from the United Kingdom presented similar findings [16], and randomized studies indicate better responses with vigabatrin in cases of tuberous sclerosis complex [13,17].

We were able to identify specific predictors of long-term outcome. In concordance with others [16,18-20], known etiology was associated with worse long-term seizure and developmental outcomes. Furthermore, diffuse imaging abnormalities were more likely associated with developmental delay and persistent seizures on follow-up. According to some authors, structural abnormalities such as severe brain malformations and postinfectious lesions may influence the prognosis of epileptic spasms [20].

Different treatments were not predictive of outcomes. This finding is concordant with results from follow-up data on United Kingdom Infantile Spasms Study subjects at age 4 years. For all 77 infants, developmental and epilepsy outcomes were not significantly different between the two treatment groups [21].

Initial presentations of epileptic spasms with hypotonia or developmental delay were the strongest predictors for both poor long-term seizure and neurodevelopmental outcomes. Furthermore, we observed that when a child presented with developmental delay or hypotonia, poor outcomes could be predicted, regardless of treatment. These findings are in agreement with the 6-year follow-up data on 363 infants with epileptic spasms reported by Lombroso [22], indicating worse outcomes in children with preceding neurologic impairment. Similar to our results, Lombroso also reported poor developmental outcomes in children with an early onset of spasms [22].

Another important observation in our study should be emphasized. In only 10 of 173 patients was the diagnosis of epileptic spasms rendered by a pediatrician. Thus, primary care physicians need to be aware of the presentations, electroencephalogram features, and diagnostic tools for the evaluation of children with epileptic spasms. Recent evidence from the United Kingdom Infantile Spasms Study supports the notion that prompt diagnosis and prompt treatment of epileptic spasms may help prevent subsequent development delay [23]. To this effect, previous evidence also indicates that duration of epilepsy and age at onset may constitute the best predictors of development during the first years of age in patients with epilepsy [24]. In addition, research on surgical interventions for epileptic spasms revealed that patients who were operated on at younger ages exhibited the largest increase in developmental quotients after surgery [25].

Our findings need to be interpreted in the context of data acquisition. Because of the selection biases outlined above and our retrospective design, meaningful conclusions regarding the efficacy of different treatments cannot be drawn. Selection bias may also explain why we observed better seizure control in patients with known etiology than in those with unknown etiology (although seizure control was not significantly different between groups). Furthermore, we have limited information on the medication doses, seizure frequencies and descriptions, changes in electroencephalogram features with treatment, and neuropsychologic assessments in this study. Moreover, we cannot exclude confounding by indication, and must assume that clinical assignment to either vigabatrin or adrenocorticotropic hormone treatment was informed by clinical presentation. Therefore, to compare outcomes after adrenocorticotropic hormone and vigabatrin treatment with

Table 5a. Response to therapy in children with developmental delay

Drugs	Severe Developmental Delay			Mild/Moderate Developmental Delay		
	ACTH	VGB	Others	ACTH	VGB	Others
Failure of spasm control	55.6% (10/18)	50% (11/22)	53% (8/15)	45.5% (15/33)	47.6% (10/21)	44.4% (8/18)

Abbreviations:
ACTH = Adrenocorticotropic hormone
VGB = Vigabatrin

Table 5b. Response to therapy in children with hypotonia

Drugs	Hypotonia		
	ACTH	VGB	Others
Failure of spasm control	48% (12/25)	42.3% (11/26)	44.4% (8/18)

Abbreviations:
ACTH = Adrenocorticotropic hormone
VGB = Vigabatrin

each other directly would be difficult, although overall outcome data after vigabatrin and after adrenocorticotropic hormone treatment in this selected tertiary care center patient population will likely be reproducible, and some confounders may have been controlled by regression modeling. An ultimate comparison between both drugs can only be achieved by a prospective, randomized, controlled trial. To the best of our knowledge, we provide the first large cohort of epileptic spasm treatments in the United States that may serve as the basis for such a study. This study may also provide even more detailed information on dose, titration schedule, and length of therapy of adrenocorticotropic hormone and vigabatrin. Kwan and Brodie reported that any first drug used had a 46% efficacy, any second another 24%, and any third an additional 4% [26]. Similar trends were observed in our series, with adrenocorticotropic hormone possibly constituting the first-line drug, hence demonstrating better efficacy, followed by vigabatrin.

Known etiology, bilateral lesions, initial hypotonia, and developmental delay represent risk factors for poor developmental outcomes, and when hypotonia and developmental delay are present at the onset of epileptic spasms, the prognosis is poor, regardless of various treatment options.

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