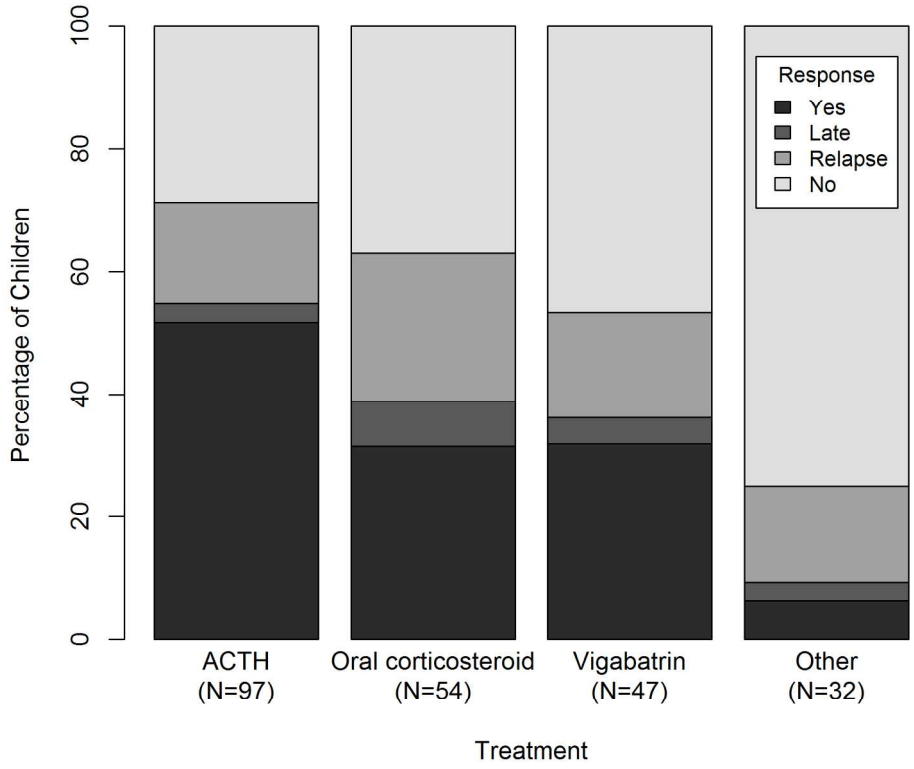

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Response to Treatment in Infantile Spasms

Title: **Response To Treatment In A Prospective National Infantile Spasms Cohort**

Running Head: **Response to treatment in Infantile Spasms**

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Response to Treatment in Infantile Spasms

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Abstract: 243
Introduction: 502
Discussion: 1234
Body of manuscript: 3480
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Response to Treatment in Infantile Spasms

Abstract

Objective: Infantile spasms are seizures associated with a severe epileptic encephalopathy presenting in the first 2 years of life, and optimal treatment continues to be debated. This study evaluates early and sustained response to initial treatments and addresses both clinical remission and electrographic resolution of hypsarhythmia. Secondarily, it assesses whether response to treatment differs by etiology or developmental status.

Methods: The National Infantile Spasms Consortium established a multi-center, prospective database enrolling infants with new diagnosis of infantile spasms. Children were considered responders if there was clinical remission and resolution of hypsarhythmia that was sustained at three months after first treatment initiation. Standard treatments of ACTH, oral corticosteroids, and vigabatrin were considered individually, and all other non-standard therapies were analyzed collectively. Developmental status and etiology were assessed. We compared response rates by treatment group using Chi-square tests and multivariable logistic regression models.

Results: Two hundred and thirty infants were enrolled from 22 centers. Overall, 46% of children receiving standard therapy responded compared to only 9% who responded to non-standard therapy ($p<0.001$). 55% of infants receiving ACTH as initial treatment responded, compared to 39% for oral corticosteroids, 36% for vigabatrin, and 9% for other ($p<0.001$). Neither etiology nor development significantly modified the response pattern by treatment group.

Interpretation: Response rate varies by treatment choice. Standard therapies should be considered as initial treatment for infantile spasms, including those with impaired development or known structural or genetic/metabolic etiology. ACTH appeared to be more effective than other standard therapies.

Response To Treatment In A Prospective National Infantile Spasms Cohort

Introduction

West syndrome is an infantile epileptic encephalopathy, typically occurring within the first two years of life with an incidence of 2-5 per 10,000 live births. [1-4] Infantile spasms, a subtype of epileptic spasms are the pathognomonic seizure type and are frequently associated with hypsarhythmia on electroencephalogram (EEG) and developmental plateau or regression. The literature on preferred treatment is inconsistent and at times conflicting, suggesting multiple treatment options and dosing regimens. The most accepted treatments are adrenocorticotropic hormone (ACTH), oral corticosteroids (OCS), and vigabatrin, although other therapies have been used.[5] Despite consensus statements, recent surveys of child neurologists showed little agreement regarding best initial therapy, preferred dose, route of administration, and adjunctive medications. [6, 7]

The effective use of ACTH and OCS was first reported in 1958. [8, 9] The Food and Drug Administration dosing guidelines for ACTH recommend initial high dose therapy (150 international units [IU]/m2/Day divided twice daily)[10]. Studies have reported response rates of 86-93% with high dose ACTH, [11, 12] while a randomized study indicated that high dose ACTH was not superior to low dose (20-30 IU/ day).[13] Some trials comparing ACTH and OCS utilized low doses (20-30 IU) of ACTH, and failed to observe significant

differences in response rates.[14, 15] The United Kingdom Infantile Spasms Study (UKISS) observed similar response rates between OCS and synthetic ACTH (tetracosactide) (70% and 76%), with both superior to vigabatrin (54%). [16] UKISS was not powered to compare hormone subgroups and electroencephalogram (EEG) data was not used in the assessment of the primary outcome measure. Higher dosing of prednisolone in UKISS (40-60 mg/day in three to four divided doses) than in previous clinical trials, may account for the higher response rate. Finally, case series utilizing "high dose" OCS (initial 40-45 mg/day, increased to max 60 mg/day)[17] and "very high dose" OCS (8 mg/kg/day, max 60 mg/day)[18] reported two week response rates of 67% and 63%. Trials of vigabatrin (100-148 mg/kg/day in two divided doses) reported a 36% remission rate. [19] The response rate to vigabatrin was higher in those with tuberous sclerosis compared to other conditions (52% and 16%)[19]. Additional trials comparing low dose ACTH to vigabatrin as first line therapy found better response to ACTH (74%) than vigabatrin (48%). [20]

Aside from those including children with tuberous sclerosis, few prospective studies have assessed etiology and development as predictors of outcome. The largest demonstrated higher IS resolution in cryptogenic cases with ACTH compared to OCS.[21] A retrospective study showed no difference in response between ACTH and vigabatrin (88% and 80%) among children with unknown etiology (normal early development and MRI brain). [22]

Multi-center collaboration has been recommended to increase understanding of effective treatments. [6] This study presents data from a large multi-center consortium evaluating early and sustained response to initial treatments and addresses both clinical remission and electrographic resolution of hypsarhythmia. The study aims were to observe response rates by primary treatment type, and to ascertain if children with varying etiologies or developmental status had differential responses to treatment in a prospective manner.

Methods

In 2012, The Pediatric Epilepsy Research Consortium (PERC) developed the National Infantile Spasms Consortium (NISC) database, which is a multi-center database enrolling children prospectively. Children with new onset infantile spasms between two months and two years of age were eligible for enrollment. Clinical information was collected at time of diagnosis and three months after diagnosis. Medication dosing recommendations for ACTH, oral corticosteroids and vigabatrin is provided to all NISC centers (see table 1 for dosing recommendations) to improve homogeneity for analysis, although compliance with these recommendations was not necessary for inclusion. Treatment decisions for individual children were made by the treating clinician.

The parents or guardians provided consent for all children according to center-specific IRB requirements. The study was approved by all participating site IRBs. Data collected from June 2012 to July 2014 were used for this study. Children with an early

infantile epileptic encephalopathy (Ohtahara syndrome/ Early Myoclonic Encephalopathy) and/or missing treatment or response data due to lack of follow up or incomplete data entry were excluded from the analysis.

Data collected for each child included age at onset of IS, gestational age at birth, sex, presence of seizures prior to spasms, etiology, height, weight, MRI, genetic and metabolic testing, developmental assessment, presence of hypsarhythmia at onset, IS medication, and dosage. Hypsarhythmia was assessed at individual institutions and defined as multifocal spikes, disorganization, and >200 microvolts [peak-to-peak] in any epoch on a bipolar longitudinal montage.[23] At three months, etiology, new MRI findings, new genetic and metabolic testing, developmental assessment, response to medication(s), and EEG findings were collected. Response to medications was recorded as response at 2 weeks from initiation of medication and response at 3 months from enrollment into study.

Standard therapy was defined as ACTH, oral corticosteroids or vigabatrin. All other medications were considered nonstandard therapy. Children initiated on simultaneous standard and non-standard therapy (e.g. ACTH and levetiracetam), had response attributed to the standard medication. Body surface area was calculated for each child using the Haycock formula.[24] Dosing for ACTH was considered high dose if greater than 140 IU/m^2/day was used at initiation of medication. All others were categorized as low/intermediate dose. For analysis, ACTH was combined with all doses due to small number of children receiving low/intermediate dose ACTH.

Response to initial medication was classified into one of four response categories based on clinical infantile spasm response rate and resolution of hypsarhythmia on EEG (when hypsarhythmia was present at onset): early responders, late responders, relapse and non-responders. Early responders had resolution of clinical spasms documented in the medical record by two weeks and ongoing remission three months after the start of treatment with an EEG to confirm remission of hypsarhythmia. Various EEGs were used including routine, video and prolonged EEG. Late responders had clinical remission starting after two weeks of treatment and had an EEG to confirm remission of hypsarhythmia. Relapse included children who initially met response criteria and then had return of either clinical spasms or hypsarhythmia. All others were considered non-responders. In our primary analyses, we defined two response categories as follows: responders included children who responded both early and late, and the non-responder group included non-responders and those who relapsed. In order to compare our results to other studies, in separate analyses, we defined 2 week responders as those who responded early and those who responded early but then relapsed.

Development was recorded as the clinician's perception of overall development, motor and cognitive status, with each defined as normal, mild or equivocal delay, or definite abnormality. These three domains were then used to create an overall assessment of development categorized as normal, mild, moderate and severe. Children with no domain marked as abnormal were classified as having normal development. If one domain was marked as mild, the child was included in the mild developmental delay group. The moderate developmental delay group consisted of children with two or more domains marked as mild or one domain marked as a definite

abnormality. Severe developmental delay included children with two or more domains were marked as definite abnormality.

Etiology was classified into five primary etiologic classifications: genetic/metabolic, malformation of cortical development, prior acquired injury, other structural, and unknown. Tuberous sclerosis was classified as other structural according to International League Against Epilepsy (ILAE) guidelines[25] and was not removed from analysis due to small numbers. For data analysis, those with unknown etiology were further categorized into normal and abnormal development. Unknown etiology with normal development was analyzed as a separate category, while genetic/metabolic was combined with unknown etiology and abnormal development. The latter group likely represents presumed genetic causes, but without a determined etiology in the 3 month follow-up period (either due to late diagnosis, decreased utilization of testing, or genetic influences that are non-Mendelian). Additionally, malformations of cortical development, prior injury, and other structural were categorized together as a structural cause of epilepsy.

Statistical analysis

We compared demographic and clinical characteristics by treatment group (ACTH, oral corticosteroid, VGB, or other) using Chi-square tests for categorical covariates and Kruskal-Wallis tests for continuous covariates. To understand the association of demographic and clinical covariates with treatment response, we used Chi-square tests to compare the proportions of responders in each group. Next, we fit multivariable

logistic regression models to estimate crude and adjusted relative risk of responding to treatment.[26] We also estimated the adjusted predicted probability of treatment response for each treatment and etiologic or developmental category of interest. Prior to selecting final models we explored the possibility of interaction between treatment and etiology or development. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

Results

Entrance criteria were met by two hundred eighty-two subjects. 52 were excluded due to: 33 lack of adequate data, eight lost to follow up, six deceased and five with early infantile epileptic encephalopathy (Ohtahara syndrome/ Early Myoclonic Encephalopathy). Two hundred thirty subjects had complete follow-up information including clinical and EEG response to individual treatments for a three month period. Twenty-two centers contributed data with 1-43 children enrolled per center. The median (Q1, Q3) age of infantile spasm onset was 6.5 months (4.5, 8.5), and the time from spasm infantile onset to initiation of treatment was 15 days (6, 37) (Table 2).

The first treatment choice for infantile spasms was ACTH in 42%, oral corticosteroids (OC) in 23%, vigabatrin in 20%, while 14% were prescribed non-standard therapies (levetiracetam, topiramate, clobazam, valproic acid, zonisamide, oxcarbazepine, phenobarbital, clonazepam and ketogenic diet). Clinicians followed NISC dosing recommendations in 80/96 (83%) of ACTH treated children, 34/50 (68%) of OC treated children and 32/41 (78%) of those treated with vigabatrin. We did not observe any

significant differences in the distribution of treatment choice based on sex, race, ethnicity, gestational age, age at infantile spasm onset, time to diagnosis, or time to treatment. However, we did observe differences in choice of treatment by other clinical characteristics. Children with a history of prior seizures or anti-seizure medication use were less likely to be treated with ACTH and more likely to be treated with a non-standard therapy. (Table 2) The etiology of infantile spasms was also associated treatment choice, with vigabatrin prescribed more frequently to those with a structural cause. There was prescribing variation based on development at the time of presentation; children prescribed ACTH had the highest percentage of mild or no developmental issues while children prescribed non-standard therapy were most likely to have severe development issues ($p<0.001$). (Table 2)

Ninety-one out of 198 (46%) children receiving standard therapy were responders with early or late clinical remission and resolution of hypsarhythmia by EEG, while only three out of 32 (9%) responded to non-standard therapy ($p<0.001$). Fifty-three out of 97 (55%) infants receiving ACTH as initial treatment responded, compared to 21/54 (39%) for oral corticosteroids, 17/47 (36%) for vigabatrin, and 3/32 (9%) for other (overall $p<0.001$). When we compared response rate between pairs of treatments, we observed significant differences (all $P< 0.01$ between each standard treatment and other, non-standard treatment. The response rate in the ACTH group was significantly higher than the vigabatrin group ($p=0.038$) and marginally higher than the oral corticosteroid group ($p=0.06$). We did not observe a significant difference in response rate between oral corticosteroids and vigabatrin. In 11 children with tuberous sclerosis, eight were

treated with VGB and five responded (62%); those treated with ACTH (1) and non-standard therapy (2) did not respond. Of the 80 children who received high dose ACTH, 46 (58%) responded, compared to 6 (38%) of the 16 who received low/intermediate dose ACTH (p=0.14).

Detailed two week and three month response by treatment is shown in Figure 1. We observed the greatest relapse rate in the oral corticosteroids group (24%) compared to the other three treatment groups (18% overall), but this difference was not significant (p=0.21). At two weeks 66/97 (68%) on ACTH and 30/54 (56%) on oral corticosteroids had responded (p=0.13). The response rate to ACTH at two weeks was dingificanlty higher that the rate in those on vigabatrin (23/47, 49%, p=0.027) or non-standard treatment (7/32, 22%, p<0.001).

Response rates were also significantly higher for those without a history of prior seizures or anti-seizure medication use. (Table 3) In unadjusted analysis, children with normal development or mild developmental delay had a higher response rate than children with moderate or severe delay (p=0.025). Children with unknown etiology and normal development had a higher response rate (20/34, 59%) than children with genetic (40/106, 38%) or structural (34/90, 38%) etiologies though this was not statistically significant. (p=0.07).

Our final multivariate logistic regression analyses consisted of two models, one including treatment and developmental status as covariates, the other including

treatment and etiology. Model ~~results are~~results are shown in Tables 4 and 5. Crude and adjusted relative risks of response between treatment groups and development and etiology categories are shown in Table 4. These analyses showed that after adjusting for development and etiology, choice of treatment was still as significant predictor of response. Children on standard treatments had more than three times greater probability of responding than those on non-standard treatments, with children on ACTH over five times as likely to respond. In models adjusting for treatment, the effects of etiology and development on response were weaker than the effects seen in the unadjusted models. The predicted probability of response to specific treatments is presented for each etiology and developmental status group (Table 5). We did not observe modification of the overall treatment effect by either etiology or development; the predicted treatment response patterns were similar across the etiologic and developmental sub-groups.

Discussion

The National Infantile Spasms Consortium (NISC) database provides a multicenter, prospective cohort of children with newly diagnosed infantile spasms. The large prospective nature of the study allows for assessment of selection bias of treatment for a number of factors including baseline development and etiology. The size of this multicenter study also enables greater power to distinguish outcomes. Assessing outcome at three months allows for more a clinically appropriate analysis of response to medication accounting for relapse rates.

The determination of efficacy by both immediate and sustained response at three months, in our study, allows for a more complete clinical picture regarding response to treatment. The majority of studies have assessed outcome at two weeks. [11, 12, 16-20, 27] Similar to other studies, we found that ACTH (all doses combined) was associated with higher early response rate than vigabatrin or oral corticosteroids, although this did not reach statistical significance for oral corticosteroids. [11, 16, 20, 22] At 3 months, after taking into account relapse rates, the sustained response rate in those treated with ACTH was still significantly higher compared to those treated with vigabatrin and marginally higher than those treated with oral corticosteroids. The difference in outcomes particularly between ACTH and oral corticosteroids may be due to the increased relapse rate that was present in the oral corticosteroid group. Previous studies with shorter follow up often did not account for relapse rates and the only long-term follow-up studies were smaller (24 and 97 subjects each) [14, 15] and used variable dosing of ACTH and oral corticosteroids. This may have led to an overestimation of response rate to oral corticosteroids. In the current study, relapses occurred with all treatments, but were more frequent with oral corticosteroids. Future study designs should account for relapse rates as it may vary by treatment. Our data also demonstrate higher response rate to ACTH in children with unknown etiology which differs from a previously published study demonstrating vigabatrin as equally effective to ACTH;[20] this may be due to the larger size of our study and its prospective design.

Children were more likely to respond to standard therapies than non-standard therapies. Our findings suggest the importance of using standard therapeutic agents for treatment

of infantile spasms. These differences were seen for early response, 3 month response, and relapse rates. The large cohort relative to other studies and observation nature of this study allows for evaluation of a sizeable group of children on non-standard therapy (therapies other than ACTH, oral corticosteroids, and vigabatrin). This was a heterogeneous group in regards to treatment. Currently available information regarding non-standard treatments for infantile spasms is limited to small retrospective cohorts and limited case studies. A recent study demonstrated improved rates of spasm remission after a standard treatment protocol was implemented (78.8% post-standardization compared to 30.6% pre-standardization). Treatment was standardized to ACTH, oral corticosteroids, or vigabatrin and other anti-seizure medications were no longer used, providing indirect evidence of poor outcomes with non- standard medications.[28] Our findings provide additional evidence of poor response to non-standard medications. The most recent guidelines on treatments of infantile spasms from AAN/CNS state there is insufficient evidence to determine whether other (non-standard) therapies, including valproic acid, pyridoxine, and ketogenic diet are effective treatments for spasms.

The etiology of spasms and the presence of moderate-severe delays at onset were not as strongly associated with treatment response as the choice of treatment itself. There were differences in prescriber choice of initial therapy based on patient development and etiology. Children with mild or no developmental issues were more often prescribed ACTH while those with severe impairments were more likely to be prescribed a non-standard treatment. This suggests some of the poor response to non-standard

treatments may have been due to selection bias and underlying etiology. However, adjusted models demonstrate that response was not significantly affected by etiology or development once adjusted for treatment, though we had limited power to detect response differences between etiology and development groups. Based on these findings, there is not good evidence to alter treatment choice due to existence of a structural abnormality or pre-existing developmental delay. However, there is still likely a role for treatment-specific therapies, such as vigabatrin for those with tuberous sclerosis.

This study showed a trend for higher response rates with high dose ACTH compared to low/intermediate dose ACTH. However, this study was not sufficiently powered to determine differences in outcome between high dose and low/intermediate dose ACTH response. Due to the NISC dosing guidelines, there were fewer subjects on low/intermediate-dose ACTH. The most effective dose of ACTH is variably reported in the literature and several reports suggest low/intermediate dose ACTH is as effective as high dose ACTH.[5, 13, 27, 29] The most recent evidence-based guidelines on the medical treatment of infantile spasms from the American Academy of Neurology and the Child Neurology Society suggests consideration for "low-dose" ACTH as an alternative to high dose ACTH,[5] although the majority of surveyed child neurologists use higher doses of ACTH.[6] While the efficacy of other therapies is often compared to the efficacy of ACTH, the dose, type and duration of treatment of ACTH is inconsistent among studies, making interpretation of the available literature challenging. This merits further study.

There were some limitations to this study. First, the therapies were not randomized and providers were allowed to choose the medications, including those that were not considered "standard." There is evidence of medication selection bias based on underlying etiology and developmental status, as well as variability in doses. However, in multivariable analysis we did not observe significant differences in overall treatment response patterns based on underlying etiology or development. Although this suggests that the lack of randomization did not contribute to the results of this study, we cannot exclude unknown confounders given the observational nature of study design. Developmental assessment was based on clinical exam and not on formal assessment tools, although recent studies suggest that tests such as the Bayley Scales of Infant Development (BSID) do not always correspond to long term cognitive outcome and are associated with reporting errors. [30, 31] The use of broad developmental classifications in this study to determine the effect of development at the onset of spasms on treatment bias and response rates, though crude, was likely sufficient to identify those with moderate to severe developmental delay. As improvement in developmental outcomes is the ultimate goal in the treatment of infantile spasms, further long term developmental assessments need to be performed. Finally, this study was not sufficiently powered to identify response to treatment based on each specific etiology and merging of etiological categories was necessary.

Using a multicenter prospective design, this study was able to incorporate larger numbers of children than previous studies, providing increasing insight about the most

effective initial treatment for infantile spasms. Extended follow-up of a large cohort provides the most extensive data regarding relapse rates, and how relapse varies by treatment choice providing a more complete clinical picture. The larger enrollment enabled assessment of response differences among developmental and etiologic subgroups. ACTH is likely more effective for children with infantile spasms regardless of development or etiology (perhaps with the exception of tuberous sclerosis). Our data do not support the use of non-standard medications as initial therapy for infantile spasms. Additional prospective treatment trials are needed to determine optimal dosing of ACTH, further explore the implications of etiology, provide expanded developmental assessments and long term outcome of development and epilepsy.

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Author Contributions

The named authors participated in the conception and design of the study, and in the data analysis and editing. ~~Please see table indicating additional author~~

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~~contributions.~~The members of the Pediatric Epilepsy Research Consortium contributed data and participated in editing the manuscript. They and their academic affiliations are included in Table ~~X~~6.

Potential Conflicts of Interest

Author SH received grant support from Lundbeck which owns rights to vigabatrin, and served on the scientific advisory board of Questcor/Mallinckrodt which owns rights to ACTH. No additional authors had conflicts of interest to disclose.

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Table 1 Treatment Guidelines Recommended by PERC

Treatment with intramuscular (IM) ACTH

Days	Dose – ACTH
1-14	75 U/m^2 twice daily
15-17	30 U/m^2 in the morning
18-20	15 U/m^2 in the morning
21-23	10 U/m^2 in the morning
24-29	10 U/m^2 every other morning (3 total doses)

#If there is no clinical response by day 14, consider alternative treatment.

Treatment with oral prednisolone

Days	Dose – prednisolone
1-14	10 mg oral 4 times daily*#
15-19	10 mg oral 3 times daily*
20-24	10 mg oral 2 times daily
25-29	10 mg oral daily

*If there is no clinical response after day 7 (i.e. no 24 hour period free of infantile spasms), the dose can be increased to 20 mg three times daily. If done, the taper schedule from day 15-19 would be 10 mg 4 times daily and then proceed as in the table beginning on day 20.

#If no clinical response by day 14, consider alternative treatment.

Treatment with oral vigabatrin

Days*#	Dose – Vigabatrin
1 - 3	50 mg/kg/day divided 2 times daily
4 - 6	100 mg/kg/day divided 2 times daily
>7	150 mg/kg/day divided 2 times daily

*Side effects (e.g. sedation, hypotonia) may necessitate slower titration

#If no clinical response by day 14, consider alternative treatment

Table 2: Baseline characteristics by type of spasm treatment

Characteristic		Spasm treatment ACTH N=97	Oral cortico-steroid N=54	Vigabatrin N=47	Other N=32	Total N=230	P-value*
Sex	Male	54 (56)	26 (48)	24 (51)	18 (56)	122 (53)	0.80
Race	Black	12 (14)	8 (17)	4 (9)	7 (24)	31 (15)	0.27
	White	59 (66)	34 (74)	35 (80)	19 (66)	147 (71)	
	Other	18 (20)	4 (9)	5 (11)	3 (10)	30 (14)	
Ethnicity	Hispanic	17 (20)	2 (5)	8 (18)	4 (15)	31 (16)	0.21
Gestational age	Weeks	39 (37,40)	40 (38,40)	39 (37,40)	38 (33,40)	39 (37,40)	0.10
Age at spasm onset	Months	6.0 (4.5, 8.0)	7.0 (4.5,9.0)	6.0 (4.5, 7.7)	7.7 (6.0,10.0)	6.5 (4.5, 8.5)	0.03
First spasm to diagnosis	Days	14 (5,32)	10 (5,18)	14 (4,73)	18 (2,28)	13 (5,31)	0.26
First spasm to treatment start	Days	16 (6,37)	12 (6,21)	21 (6,74)	15 (3,47)	15 (6,37)	0.13
Diagnosis to treatment start	Days	1 (0,2)	0 (0,1)	2 (1,5)	0 (-1,9)	1 (0,2)	<0.001
Prior seizures		19 (20)	17 (32)	19 (40)	20 (63)	75 (33)	<0.001
History of AED use		21 (22)	22 (41)	21 (45)	19 (59)	83 (36)	<0.001
Etiology**	Genetic/metabolic	18 (19)	11 (20)	13 (28)	8 (25)	50 (22)	<0.001
	Prior brain injury	17 (18)	15 (28)	11 (23)	9 (28)	52 (23)	
	MCD/other structural	9 (9)	5 (9)	16 (34)	8 (25)	38 (17)	
	Unknown abnormal	29 (30)	16 (30)	6 (13)	5 (16)	56 (24)	
	Unknown normal	24 (25)	7 (13)	1 (2)	2 (6)	34 (15)	
Developmental issues	None	31 (32)	7 (13)	2 (4)	3 (10)	43 (19)	<0.001
	Mild	10 (10)	6 (11)	4 (9)	1 (3)	21 (9)	
	Moderate	15 (16)	9 (17)	12 (26)	2 (7)	38 (17)	
	Severe	40 (42)	31 (59)	29 (62)	25 (81)	125 (55)	

Values are N (column %) or median (Q1, Q3).

*Chi-square test for categorical variables, Kruskal-Wallis test for continuous variables.

**There were 11 participants with tuberous sclerosis (included in the MCD/other structural etiology group). Eight were on vigabatrin, 1 on ACTH, and 2 Other.

Missing values (N): race (22), ethnicity (35), gestational age (2), age at spasm onset (5), time between first spasm and diagnosis (2), time between first spasm and treatment start (3), time between diagnosis and treatment start (3), and development (3).

Table 3: Characteristics by response to first spasm treatment

Characteristic		Response to treatment: Non-response N=136		Response N=94		P-value*
Sex	Female	63	(58)	45	(42)	0.82
	Male	73	(60)	49	(40)	
Race	Black	20	(65)	11	(36)	0.91
	White	89	(61)	58	(40)	
	Other	18	(60)	12	(40)	
Ethnicity	Hispanic	17	(55)	14	(45)	0.44
	Non-Hispanic	102	(62)	18	(51)	
Gestational age	<37 weeks	30	(63)	18	(38)	0.60
	At least 37 weeks	105	(58)	75	(42)	
Age at spasm onset	<12 months	119	(59)	84	(41)	0.97
	At least 12 months	13	(59)	9	(41)	
First spasm to treatment start	Within 4 weeks	93	(61)	59	(39)	0.35
	> 4 weeks	41	(55)	34	(45)	
Prior seizures	Yes	55	(73)	20	(27)	0.002
	No	81	(52)	74	(48)	
History of AED use	Yes	58	(70)	25	(30)	0.013
	No	78	(53)	69	(47)	
Etiology	Genetic/metabolic/unknown abnormal	66	(62)	40	(38)	0.070
	Prior brain injury/MCD/other structural	56	(62)	34	(38)	
	Unknown normal	14	(41)	20	(59)	
Developmental issues	None/Mild	30	(47)	34	(53)	0.025
	Moderate/Severe	103	(63)	60	(37)	
Treatment	ACTH	44	(45)	53	(55)	<0.001
	Oral corticosteroid	33	(61)	21	(39)	
	Vigabatrin	30	(64)	17	(36)	
	Other	29	(91)	3	(9)	

Values are N (row %)

*Chi-square test

Missing values (N): race (22), ethnicity (35), gestational age (2), age at spasm onset (5), time between first spasm and diagnosis (2), time between first spasm and treatment start (3), time between diagnosis and treatment start (3), and development (3).

Table 4: Relative risk of response, by treatment, etiology, and development

Covariate		Crude Relative Risk (95% CI)	Adjusted* Relative Risk (95% CI)	Adjusted** Relative Risk (95% CI)
Treatment	ACTH	5.81 (4.10, 9.40)	5.50 (3.83, 9.18)	5.24 (3.59, 8.70)
	Oral corticosteroid	4.15 (2.78, 6.76)	4.11 (2.78, 6.52)	3.88 (2.63, 6.46)
	Vigabatrin	3.91 (2.60, 6.45)	3.92 (2.64, 6.50)	3.69 (2.55, 6.18)
	Other	Reference	Reference	Reference
Etiology	Genetic/metabolic/unknown abnormal	Reference	Reference	---
	Prior brain injury/MCD/other structural	1.00 (0.69, 1.43)	1.06 (0.98, 1.16)	---
	Unknown normal	1.56 (1.04, 2.22)	1.39 (0.89, 1.99)	---
Development	None/Mild	1.42 (1.04, 2.01)	---	1.23 (0.86, 1.72)
	Moderate/Severe	Reference	---	Reference

Relative risks, or relative probabilities, of treatment response between groups were estimated using the method of Kleinman and Norton applied logistic regression models; confidence intervals estimated via bootstrapping

*Model including treatment and etiology as covariates

**Model including treatment and development as covariates

Table 5: Etiology, Development, and Treatment effect on Response

Characteristic	Treatment	Response to treatment: Non-response N=136		Response N=94		Predicted Probability of response* (95% CI)
Etiology						
Genetic/metabolic/unknown abnormal	ACTH	25	(53)	22	(47)	49% (37, 62)
	Oral corticosteroid	15	(56)	12	(44)	35% (23, 50)
	Vigabatrin	13	(68)	6	(34)	33% (20, 50)
	Other	13	(100)	0	(0)	8% (3, 24)
Prior brain injury/MCD/other structural	ACTH	10	(39)	16	(62)	55% (40, 68)
	Oral corticosteroid	15	(75)	5	(25)	40% (26, 56)
	Vigabatrin	16	(59)	11	(41)	38% (24, 54)
	Other	15	(88)	2	(12)	10% (3, 27)
Unknown normal	ACTH	9	(38)	15	(63)	65% (48, 80)
	Oral corticosteroid	3	(43)	4	(57)	51% (30, 71)
	Vigabatrin	1	(100)	0	(0)	49% (26, 72)
	Other	1	(50)	1	(50)	15% (4, 41)
Developmental issues						
None/Mild	ACTH	17	(42)	24	(59)	61% (47, 73)
	Oral corticosteroid	7	(54)	6	(46)	47% (30, 64)
	Vigabatrin	3	(50)	3	(50)	44% (26, 64)
	Other	3	(75)	1	(25)	13% (4, 35)
Moderate/Severe	ACTH	26	(47)	29	(53)	51% (39, 63)
	Oral corticosteroid	25	(63)	15	(38)	37% (25, 52)
	Vigabatrin	27	(66)	14	(34)	35% (23, 50)
	Other	25	(93)	2	(7)	9% (3, 25)

Values are N (row %)

*Predicted probabilities of response to treatment (expressed as a percentage) were estimated via two logistic regression models: (1) model containing etiology (overall p-value p=0.29) and treatment (p=0.0016) as covariates, (2) model containing development (p=0.24) and treatment (p=0.0023) as covariates. ~~Once adjusted for treatment, etiology (p=0.29) and development (p=0.24) were no longer significant predictors of treatment response.~~