DR. SCOTT DEMAREST (Orcid ID : 0000-0002-4544-3724)

DR. RENÉE A. SHELLHAAS (Orcid ID : 0000-0002-3175-3908)

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Title: The Impact of Hypsarrhythmia on Infantile Spasms Treatment Response: Observational cohort study from the National Infantile Spasms Consortium

Authors: Scott T. Demarest, MD[1], Renée A. Shellhaas, MD, MS[2], William D. Gaillard, MD[3] Cynthia Keator, MD[4], Katherine C. Nickels, MD[5], Shaun A. Hussain, MD, MS[6], Tobias Loddenkemper, MD[7], Anup D. Patel, MD[8], Russell P. Saneto, DO, PhD[9], Elaine Wirrell, MD[5], Iván Sánchez Fernández, MD[7], Catherine J. Chu, MD, MMSc, MA[10], Zachary Grinspan, MD, MS[11], Courtney J. Wusthoff, MD, MS[12], Sucheta Joshi, MD, MS[2], Ismail S. Mohamed, MD[13], Carl E. Stafstrom, MD, PhD[14], Cynthia V. Stack, MD[15], Elissa Yozawitz, MD[16], Judith S. Bluvstein, MD[17], Rani K. Singh, MD[18], Kelly G Knupp, MD[1] and the Pediatric Epilepsy Research Consortium

[1] Departments of Pediatrics and Neurology, School of Medicine, University of Colorado Anschutz Medical Campus

[2] Departments of Pediatrics & Communicable Diseases (Division of Pediatric Neurology), University of Michigan

[3] Center for Neuroscience, Children's National Health System

[4] Jane and John Justin Neurosciences Department, Cook Children's Hospital

[5] Departments of Neurology and Pediatrics, Mayo Clinic Rochester

[6] Department of Pediatric Neurology, Mattel Children's Hospital at UCLA

[7] Division of Epilepsy and Clinical Neurophysiology, Department of Neurology, Boston Children's Hospital, Boston, MA, USA

[8] Departments of Neurology and Pediatrics, Nationwide Children's Hospital and the Ohio State University College of Medicine

[9] Department of Neurology/Division of Pediatric Neurology, Seattle Children's Hospital University of Washington

[10] Department of Neurology, Massachusetts General Hospital / Harvard Medical School

[11] Departments of Healthcare Policy & Research and Department of Pediatrics, Weill Cornell Medical Center, New York, NY

[12] Division of Child Neurology, Stanford University

[13] Division of Neurology, Department of Pediatrics, University of Alabama, Birmingham

[14] Departments of Neurology and Pediatrics, Johns Hopkins Hospital, Baltimore Maryland

[15] Departments of Pediatrics and Neurology, Division of Child Neurology, Lurie Children's Hospital of Chicago, Northwestern University Feinberg School of Medicine

[16] Departments of Neurology and Pediatrics, Montefiore Medical Center, Albert Einstein College of Medicine

[17] Departments of Neurology and Pediatrics, NYU School of Medicine

[18] Department of Neurology, Carolinas Healthcare System

Corresponding Author:

Scott T. Demarest MD

Assistant Professor, Departments of Pediatrics and Neurology
University of Colorado School of Medicine
Children's Hospital Colorado
13123 East 16th Avenue, B155
Aurora, CO 80045
720-777-1003
Fax: 720-777-7285
Scott.demarest@childrenscolorado.org

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SUMMARY

Objective:

The multicenter National Infantile Spasms Consortium prospective cohort was used to compare outcomes and phenotypic features of infantile spasms patients with and without hypsarrhythmia.

Methods:

Patients two months to two years were enrolled prospectively with new onset infantile spasms. Treatment choice and categorization of hypsarrhythmia was determined clinically at each site. Response to therapy was defined as resolution of clinical spasms (and hypsarrhythmia if present) without relapse three months after initiation.

Results:

82 percent of patients had hypsarrhythmia but this was not associated with gender, mean age, preexisting developmental delay or epilepsy, etiology or response to first-line

therapy. Infants with hypsarrhythmia were more likely to receive standard treatment (adrenocorticotropic hormone, prednisolone, or vigabatrin (OR 2.6, 95% CI: 1.4 – 4.7) and pre-existing epilepsy reduced the likelihood of standard treatment (OR 3.2, 95% CI: 1.9 – 5.4). Hypsarrhythmia was not a determinant of response to treatment. A logistic regression model demonstrated that later age of onset (OR 1.09 per month, 95% CI: 1.03 – 1.15) and absence of preexisting epilepsy (OR 1.7, 95% CI: 1.06 – 2.81) had a small impact on the likelihood of responding to the first line treatment. However, receiving standard first-line treatment increased the likelihood of responding dramatically (OR 5.2 (95% CI: 2 – 13.7) for vigabatrin, OR 8 (95% CI: 3.1 – 20.6) for prednisolone, OR 10.2 (95% CI: 4.1 – 25.8) for adrenocorticotropic hormone).

Significance:

First-line treatment with standard therapy was by far the most important variable in determining likelihood of response to treatment of infantile spasms with or without hypsarrhythmia.

Introduction

West Syndrome (WS) is the electroclinical syndrome consisting of epileptic spasms (a seizure type characterized by sudden proximal muscle predominant, flexion or extension [1]) and hypsarrhythmia [2] on electroencephalogram (EEG) and is typically associated with existing or evolving developmental delay [3–5]. West syndrome has an incidence of 2-4.5 per 10,000 live births [6–10] and is associated with numerous etiologies. Infantile spasms is a broader term that can encompass any patient with onset of epileptic spasms during infancy, approximately 75% of whom have hypsarrhythmia at the time of diagnosis[9, 11]

Hypsarrhythmia is the EEG findings of random or chaotic high amplitude slow waves with intermixed multifocal spikes [5]. Controversy exists regarding the specific amplitudes (>200uV or >300uV) required and the frequency and distribution of spikes [5,11–15]. This variability likely accounts, at least in part, for poor interrater reliability when classifying hypsarrhythmia [16]. Nevertheless, this continues to be considered an important clinical biomarker of a poor prognosis [13,15,17–20]. Even greater controversy

exists regarding specific definitions and utility of modified hypsarrhythmia patterns [15,19] . Separating hypsarrhythmia from the associated epileptic spasms and the underlying pathology has been challenging. Cohort studies of infantile spasms patients without hypsarrhythmia suggests that they have varied outcomes and respond to similar treatments as those with hypsarrhythmia [21–24] . However, patients with and without hypsarrhythmia have never been compared systematically within the same data set.

In 2012 the multicenter Pediatric Epilepsy Research Consortium created the National Infantile Spasms Consortium (NISC) database which has allowed for a systematic, prospective evaluation of response to various first and second line therapies [14,25] The NISC enrolled patients with infantile spasms with and without hypsarrhythmia making it a useful database to determine the effect of hypsarrhythmia on response to treatment. In this study, we used the NISC database to evaluate a cohort of patients with infantile spasms without hypsarrhythmia and compare them to those with hypsarrhythmia in terms of phenotypic features and outcomes. The primary aim was to determine (1) whether patients without hypsarrhythmia should be treated with different medications than those with hypsarrhythmia and (2) if they have a different likelihood of responding to their first-line treatment. Additionally, we evaluated the association between hypsarrhythmia and the phenotypic features age (particularly less than 3 months at onset of infantile spasms [22]), development, pre-existing epilepsy, sex, time interval from onset to diagnosis and underlying etiology. Finally, we assessed the influence of hypsarrhythmia on treatment choice.

Methods

After obtaining written informed consent, patients between 2 months and 2 years with new onset infantile spasms (defined by the occurrence of epileptic spasms) were enrolled to the NISC multicenter database prospectively as described previously [14,25,26] . Patients with early infantile epileptic encephalopathy (Ohtahara Syndrome) or early myoclonic epilepsy were excluded from the study. Those with incomplete data were also excluded.

Sex, age of spasm onset, diagnosis, and treatment initiation, developmental status prior to spasm onset, prior use of any anti-seizure drug (ASD), use of ASDs at the time of diagnosis and etiology was noted for each patient. Etiology was grouped into

seven main categories: genetic/ metabolic, neonatal, neurocutaneous, stroke, structural and unknown cause with either normal development or abnormal development prior to onset of infantile spasms. Development was determined by treating physicians and was grouped into normal or near normal and clearly abnormal [14] .

There was no specific variable for pre-existing epilepsy. Therefore, as a surrogate we utilized whether a patient was already taking an anti-seizure medication at the time they were diagnosed with infantile spasms. It would be unlikely that infants with clear epilepsy prior to onset of infantile spasms would have been weaned off treatment prior to the onset of infantile spasms. This variable is referred to as preexisting epilepsy for convenience throughout the results.

Hypsarrhythmia was defined as random or chaotic high voltage (>200 μV) slow waves with intermixed multifocal spikes and was determined by the referring epileptologist at each site. Modified hypsarrhythmia was noted in the database but there was no clear definition provided for modified hypsarrhythmia. Modified hypsarrhythmia and hypsarrhythmia were grouped for the purposes of this study given the poor interrater reliability in determining hypsarrhythmia and modified hypsarrhythmia [16] . Hypsarrhythmia has been defined broadly in this database [5] .

Physicians at each site determined the therapy for each patient based on their own clinical judgement, but standard dosing recommendations were made for adrenocorticotropic hormone (ACTH), oral corticosteroids (prednisolone) and vigabatrin as described preciously[14]. These treatments were defined as standard therapies for treatment of infantile spasms. All other treatments were considered non-standard treatments. Non-standard treatment includes nine different treatments, with the three most common being (levetiracetam, topiramate and clobazam). Response to therapy was defined as resolution of clinical epileptic spasms and resolution of hypsarrhythmia (if present) within 2 weeks of initiating therapy without relapse at 3 months post initiation. Patients who had incomplete response, no response or relapse were considered non-responders [14] . None of the patients enrolled to NISC during this time period received combinatorial therapy with more than one standard therapy.

All parents provided written informed consent according to center-specific institutional review boards (IRBs) and the study was approved by all participating

institutions' IRBs. Data used in this study were collected between June 2012 and November 2016.

Statistical Analysis

The associations between hypsarrhythmia at onset of infantile spasms and categorical variables such as sex, preexisting epilepsy, preexisting developmental delay, etiology and age of onset (<3 months vs ≥3 months) were assessed using chi-square analysis. Student t-test was used to compare age of onset and time from onset to treatment between the two groups. Response to standard vs non-standard therapy was assessed independently in those with and without hypsarrhythmia. Additionally, a multivariable logistic regression model evaluated the impact of age of onset, preexisting epilepsy, prior development, etiology and the presence of hypsarrhythmia on first-line treatment choice. Finally, the association between response and first-line treatment was assessed through a multivariable logistic regression model that adjusted for factors that were found to be potential determinants of treatment choice or potentially predictive of response to therapy including: the presence of hypsarrhythmia, age of onset of epilepsy, preexisting epilepsy and choice of drug (ACTH, prednisolone, vigabatrin or others). The predictors were evaluated for potential collinearity and important interactions. All statistical analysis was performed using SAS version 9.4 and statistical significance was defined as $p<0.05$.

Results

A total of 447 patients were enrolled with infantile spasms; 366 (82%) with hypsarrhythmia and 81 (18%) without hypsarrhythmia. All patients without hypsarrhythmia had abnormal EEG backgrounds. Sex, age of onset, time from onset of spasms to diagnosis, presence of moderate or severe preexisting developmental delay, preexisting epilepsy and etiology were not different in the two groups (Table 1). Although mean age of onset of infantile spasms was the same in the two groups, infants less than 3 months of age at onset of infantile spasms were less likely to have hypsarrhythmia (18 out of 30, 60.0%) compared to those older than 3 months (348 out of 417, 83.5%) (P=0.001).

Chi-square and multivariable logistic regression modeling determined that only hypsarrhythmia and preexisting epilepsy were significantly related to prescription of a

standard medication as first-line therapy. Infants with hypsarrhythmia were 2.6 times more likely (95% CI: 1.4 – 4.7) to be prescribed standard therapy compared with those who did not have hypsarrhythmia. Patients without preexisting epilepsy were 3.2 times more likely (95% CI: 1.9 – 5.4) to receive standard first-line therapy compared to those with previously diagnosed epilepsy (Table 2).

Response to treatment was equivalent in those with and without hypsarrhythmia (Table 1) despite the observation that patients without hypsarrhythmia were less likely to be prescribed standard therapy (72% vs 87%, p<0.0004). Prescription of standard therapy was independently associated with an increased likelihood of responding to the first therapy, both among patients with hypsarrhythmia (P<0.0001) and without hypsarrhythmia (P<0.0001). Of the 81 patients without hypsarrhythmia, 58 patients received one of the standard therapies and 27 patients (47%) responded. None of the 23 patients without hypsarrhythmia who were prescribed non-standard therapy responded (p<0.0001).

Age of onset of infantile spasms and preexisting epilepsy were associated with response to therapy on univariate analysis (p=0.01 and p=0.0007 respectively). In the multivariable logistic regression, odds of response to therapy increased 1.09 (95% CI: 1.03 – 1.15) times for each month increase in age of onset of infantile spasms (p=0.002), after adjusting for relevant clinical factors. There was no significant interaction between hypsarrhythmia and age of onset within this model. Patients without a diagnosis of epilepsy at the onset of infantile spasms were 1.7 (95% CI: 1.06 – 2.81) times more likely to responding to therapy (p=0.027, Table 3).

The presence of hypsarrhythmia did not impact likelihood of treatment response (p=0.8). Compared to non-standard treatments, First line treatment with ACTH, prednisolone, and vigabatrin increased the odds of response by 10.2 (95% CI: 4.1-25.8, P<0.001), 8 (95% CI: 3.1-20.6, P<0.001) and 5.2 (95% CI: 2-13.7, P=0.0009) times, respectively (Table 3).

Discussion

The results of this study suggest that patients with infantile spasms with or without hypsarrhythmia benefit from the same treatment strategy using one of the first line medications (ACTH, prednisolone, or vigabatrin). None of the patients without

hypsarrhythmia who received non-standard therapy responded. A prescribing bias was also identified, as patients without hypsarrhythmia or with a history of pre-existing epilepsy were less likely to receive standard first-line medications.

The youngest patients (<3 months) were less likely to have hypsarrhythmia at presentation, but patients without hypsarrhythmia were seen at all ages (2 months – 2 years). A similar overrepresentation of patients younger than 3 months was reported previously in a cohort of infantile spasms patients without hypsarrhythmia, where three of sixteen (19%) were less than 3 months of age at onset [22] . In our data, there were no other factors that correlated with absence of hypsarrhythmia. Specifically, there was no difference in the time from onset of infantile spasms to diagnosis of infantile spasms based on hypsarrhythmia. This argues against the theory that patients without hypsarrhythmia have been captured earlier and would develop hypsarrhythmia eventually if left untreated. However, a detailed analysis of subsequent EEGs was beyond the scope of this study. Similarly, there was no difference in the gross assessment of development of infants at the time of infantile spasms diagnosis between the two groups.

Etiology was not associated with the presence or absence of hypsarrhythmia. Etiology is possibly the most difficult factor to analyze in studying infantile spasms because there are likely more than a hundred unique causes [26,27] . To analyze datasets based on each individual diagnosis reduces statistical power to the point of being impractical. We grouped patients into seven categories which cannot capture detailed phenotypic information that may be inherent to a specific etiology. With this caveat in mind the grouping we utilized was not associated with the presence of hypsarrhythmia. The impact of specific etiologies on phenotype and outcomes deserves additional exploration and the use of large multicenter databases, like NISC, will prove invaluable in this effort as the number of enrolled patients continues to grow.

Ultimately, this study reaffirms that the primary predictor of response to therapy is the use of standard therapy (ACTH, prednisolone or vigabatrin). While these treatments were not randomized they were standardized and as reported previously most patients did receive the recommended dosing and duration[14]. NISC is the largest prospective study to date for infantile spasms and clearly demonstrates that earlier age of onset and

preexisting epilepsy negatively impact the likelihood of response to therapy, but this impact is modest when compared to treatment choice. After adjusting for treatment bias hypsarrhythmia is not associated with response to treatment.

The NISC database is limited as a prospective observational study without randomization or long-term follow up [14,25] . While a randomized control trial is ideal for determining the optimal treatment, and adjusting for unmeasured confounders, the NISC database allows for adjustment of many confounders and identification of clinical prescribing biases. Additional study is warranted into the long-term implications of hypsarrhythmia on neurodevelopment. However, most evidence available at this time suggests that each patient has their own range of potential outcomes, heavily influenced by their underlying etiology, but that rapid and effective treatment of infantile spasms likely improves their trajectory within that continuum [28–32] . Data on long-term developmental outcomes would a valuable avenue for future research. We supplement use of an ASD at the time of infantile spasms diagnosis for preexisting epilepsy; while these are likely heavily correlated parameters the significance of “preexisting epilepsy” in this paper should be verified with additional studies. Finally, previously reported poor interrater reliability between EEG readers when evaluating for hypsarrhythmia remains a potential limitation [16] . However, as hypsarrhythmia was classified clinically in our multicenter study, our approach and our data are representative of current clinical practice. Therefore, this study suggests that use of hypsarrhythmia as a clinically meaningful predictor of response to therapy for epileptic spasms in children less than 2 years of age is inappropriate.

This analysis demonstrates that patients who receive ACTH, prednisolone or vigabatrin as first-line treatment have 5-10 times the odds of responding to their initial medication compared to children who are prescribed non-standard treatments. Although early age of onset and preexisting epilepsy had some impact on response, first-line treatment with standard therapy was by far the most important variable in determining likelihood of response to treatment of infantile spasms regardless of the presence or absence of hypsarrhythmia at the time of diagnosis.

Key Points Box

- Hypsarrhythmia is not predictive of response to first-line therapy
- Early age of onset of infantile spasms and a history of pre-existing epilepsy slightly reduce the likelihood of responding to first-line treatment
- Use of standard first-line medications (ACTH, vigabatrin, prednisolone) have by far the largest impact on the odds of response to first-line treatment
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Conflicts of Interest

Dr. Knupp reports grants from American Epilepsy Society and Pediatric Epilepsy Research Fund, during the conduct of the study; grants from Pediatric Epilepsy Research Fund, grants from Zogenix, outside the submitted work. Dr. Gaillard reports grants from Pediatric Epilepsy Research Foundation, during the conduct of the study. Dr. Patel. reports grants from Pediatric Epilepsy Research Foundation (PERF), grants from Upsher-Smith, grants and personal fees from LivaNova, grants and personal fees from GW Pharmaceuticals, grants from Brain Sentinal, personal fees from UCB Pharma, personal fees from Supernus, outside the submitted work. Dr. Loddenkemper serves on the Laboratory Accreditation Board for Long Term (Epilepsy and Intensive Care Unit) Monitoring, on the Council (and as 2nd Vice President) of the American Clinical Neurophysiology Society, on the American Board of Clinical Neurophysiology, as an Associate Editor for Seizure, and as an Associate Editor for Wyllie's Treatment of Epilepsy 6th edition. He is part of pending patent applications to detect and predict seizures and to diagnose epilepsy. He receives research support from the Epilepsy Research Fund, the American Epilepsy Society, the Epilepsy Foundation of America, the Epilepsy Therapy Project, PCORI, the Pediatric Epilepsy Research Foundation, CURE, HHV-6 Foundation, and received research grants from Lundbeck, Eisai, Upsher-

Smith, Acorda, and Pfizer. He serves as a consultant for Zogenix, Upsher Smith and Lundbeck. All other authors have no conflicts of interest to report.

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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Tables:

Table 1. Comparison of Characteristics Based on the Presence of Hypsarhythmia

Characteristic	Hypsarrhythmia N (%) or Mean (SD)	No Hypsarrhythmia N (%) or Mean (SD)	p-value
Overall	366 (82)	81 (18)	

Female	167 (46)	35 (43)	0.69
Preexisting Epilepsy	104 (29)	30 (38)	0.13
Moderate or Severe Developmental Delay	218 (60)	47 (59)	0.85
Average Age of onset (Months)	7.2 (4)	6.9 (4.7)	0.56
Time from onset of spasms to diagnosis (months)	0.97 (1.9)	0.75 (1.1)	0.17
Onset of spasms at less than 3 months age	18 (5)	12 (15)	**0.0013**
Etiology			0.06
Genetic/Metabolic	68 (20)	12 (15)	
Neonatal	49 (14)	14 (18)	
Neurocutaneous	18 (5)	10 (13)	
Stroke	19 (6)	4 (5)	
Structural	44 (13)	16 (20)	
Unknown Abnormal Development	78 (23)	13 (16)	
Unknown Normal Development	68 (20)	10 (13)	
First-Line Treatment Prescribed			
Standard	320 (87)	58 (72)	***0.0004**
Other Treatments	46 (13)	23 (28)	
ACTH	196 (46)	20 (25)	****0.0002**
Prednisolone	85 (23)	18 (22)	
Vigabatrin	66 (18)	20 (25)	
Other Treatments	46 (13)	23 (28)	
Response to Treatment			
Overall			
Responders	148 (40)	27 (33)	0.24
Non-responders	218 (60)	54 (67)	
Standard Treatment			
Responder	142 (44)	27 (47)	0.76
Non-Responder	178 (56)	31 (53)	
Other Treatments			

Responders	6 (13)	0 (0)	0.17
Non-responders	40 (87)	23 (100)	

Characteristics of patients with and without hypsarhythmia at the time of diagnosis. Number of patients within the group (hypsarrhythmia or not hypsarrhythmia) that had that characteristic followed by the percentage in parenthesis.
*Chi-square test comparing prescribing of standard verses other for first-line treatment.
** Chi-square test comparing prescribing of ACTH, Prednisolone, Vigabatrin and Other for first-line treatment.

Table 2. Factors Impacting the Odds of Receiving Standard Therapy

Variable	Odds Ratio	95% Wald Confidence Limits		p-value
Presence of Hypsarrhythmia	2.6	1.4	4.7	0.0015
Preexisting Epilepsy	3.2	1.9	5.4	<0.0001

Multivariable logistic regression model evaluating the association between the variables and likelihood of being prescribed a standard therapy as first-line therapy. Odds ratio with associated confidence intervals and p-values are provided.

Table 3. Factors Impacting the Odds of Response to First-line Treatment

Variable	Odds Ratio	95% Wald Confidence Limits		p-value
Presence of Hypsarrhythmia	0.949	0.54	1.669	0.8556
Age of onset of Infantile Spasms	1.088	1.032	1.148	0.0018
Preexisting Epilepsy	1.728	1.063	2.809	0.0274
ACTH (adrenocorticotropic hormone) vs Nonstandard Therapy	10.247	4.078	25.751	<0.0001
PRL (prednisolone) vs Nonstandard Therapy	7.981	3.092	20.601	<0.0001
VGB (vigabatrin vs Nonstandard Therapy	5.171	1.953	13.688	0.0009

Multivariable logistic regression model evaluating the association between the variables and likelihood of response to first line therapy. Odds ratio with associated confidence intervals and p-values are provided.