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Infantile Spasms of Unknown Cause: Predictors of Outcome and Genotype-Phenotype Correlation

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Abstract

BACKGROUND: No large-scale studies have specifically evaluated the outcomes of infantile spasms (IS) of unknown cause, previously known as cryptogenic or idiopathic. The Epilepsy Phenome/Genome Project aimed to characterize IS of unknown cause by phenotype and genotype analysis.

METHODS: We undertook a retrospective multicenter observational cohort of 133 individuals within the Epilepsy Phenome/Genome Project database met criteria for IS of unknown cause with at least six months of follow-up data. Clinical medical records, imaging, and electroencephalography were examined.

RESULTS: Normal development occurred in only 15% of IS of unknown cause. The majority (85%) had clinically documented developmental delay (15% mild, 20% moderate, and 50% severe) at last assessment (median 2.7 years; interquartile interval 1.71–6.25 years). Predictors of

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Conflicts of interest: Dr. Dlugos has given expert testimony in medical-legal cases. Dr. Sherr is on the advisory board of InVitae, consults for Personalis, and holds stock in Chemocentryx.

Supplementary materials

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positive developmental outcomes included no delay prior to IS ($P < 0.001$), older age of IS onset (median six months old), and resolution of IS after initial treatment ($P < 0.001$). Additional seizures after IS occurred in 67%, with predictors being seizures prior to IS ($P = 0.018$), earlier age of IS onset (median five months old), and refractory IS ($P = 0.008$). On a research basis, whole exome sequencing identified 15% with *de novo* variants in known epilepsy genes. Individuals with a genetic finding were more likely to have poor developmental outcomes ($P = 0.035$).

CONCLUSIONS: The current study highlights the predominately unfavorable developmental outcomes and that subsequent seizures are common in children with IS of unknown cause. Ongoing genetic evaluation of IS of seemingly unknown cause is likely to yield a diagnosis and provide valuable prognostic information.

Keywords

Infantile spasms; Cryptogenic infantile spasms; Developmental outcomes; Epileptic encephalopathy; Epilepsy; Seizures; Epilepsy genetics; Genotype-phenotype

Introduction

Infantile spasms (IS) is one of the most common epileptic encephalopathies with an incidence of 2–4 per 10,000 live births.[1,2] Epileptic spasms typically occur during infancy and are often accompanied by hypsarrhythmia on electroencephalography (EEG) and developmental plateau or regression.[3]

IS carries a poor prognosis, with as few as 15% to 25% of individuals having a normal developmental outcome[4] and rates of autism estimated at 18%–35%.[5] There are a number of well-recognized causes of IS including tuberous sclerosis complex, Down syndrome, cortical malformations, hypoxic ischemic encephalopathy, and central nervous system infection, yet the cause is unknown in over one third of children even after a thorough investigation.[6]

IS of unknown cause comprises patients previously referred to as either cryptogenic or idiopathic.[7] A meta-analysis of IS suggested that 54% of the cryptogenic IS subgroup had favorable neurodevelopment outcomes.[8] However, the investigators highlight the need for further research to identify predictors of neurodevelopment outcomes in IS of unknown cause.

Our study focuses on predictors of developmental and seizure outcomes in children with IS of unknown cause using the multicenter Epilepsy Phenome/Genome Project (EPGP) database.[9] We hypothesize that children with IS of unknown cause will have a high rate of normal developmental outcomes with predictors of normal development being normal development prior to IS onset, treatment initiation within one month of IS onset, and hormonal therapy as first line, as previously reported.[10] Unexpectedly, we report that the majority of IS of unknown cause have a poor prognosis and subsequent seizures are common. Normal development prior to IS and response to first line therapy are predictors of more favorable outcomes. Individuals with a causative *de novo* genetic finding on research whole exome sequencing were more likely to have poor developmental outcomes. Our study

highlights the need for further studies into the underlying mechanisms of IS and identifying biomarkers given the lack of robust clinical predictors of positive outcomes.

Methods

Participants

We undertook a retrospective multicenter cohort study of individuals with IS enrolled in EPGP. EPGP was a multicenter collaborative effort that collected detailed phenotypic and genetic data on a large number of epilepsy patients to try to uncover the role our genes play in the development of certain types of epilepsy.[9] Participants were identified primarily through the EPGP Clinical Centers by screening clinic patients. At the time of enrollment, demographic variables, seizure and relevant medical history, and medical record abstraction were obtained. Site principal investigators reviewed initial information to arrive at a classification of seizure type and epilepsy syndrome before further retrospective analysis by the Data Review Core.[9,11] The local Institutional Review Board approved the study at each of the 26 EPGP clinical centers in the United States and Canada. All participants were enrolled after eligibility criteria were confirmed and their parents or legal guardians provided written informed consent.

The initial inclusion criteria defined by the EPGP study group for the IS cohort consist of (1) a history of epileptic spasms prior to 12 months of age, (2) an EEG with hypsarrhythmia or modified hypsarrhythmia, and (3) the absence of positive genetic or metabolic testing at the time of enrollment. Individuals were excluded if there were found to have severe developmental delay prior to the onset of IS. Severe delay was defined as 50% or more delay in any area (motor, social, language, cognition, or activities of daily living) or global delay, as determined by consensus of the EPGP Phenotyping Core prior to initiation of this study. Additional exclusion criteria were (1) lack of adequate medical records for at least six months after IS onset and (2) structural abnormalities including focal cortical dysplasia on brain magnetic resonance imaging (MRI). Individuals with IS and focal cortical dysplasia on brain MRI would be classified as structural etiology of IS, thus were excluded from our cohort. Two hundred eighty-one individuals were initially identified. Individuals were excluded due to failure to meet our inclusion criteria (19), incomplete medical records (18), focal abnormality on brain MRI (20), and inadequate follow-up data (91). The characteristics of the final cohort (n = 133) were statistically similar to those with inadequate follow-up data (Table 1).

Data review

EEG, MRI, and clinical data were reviewed by expert neurophysiological, imaging, and data review EPGP cores, as previously described.[11,12] All EEGs were reviewed by site investigators and an EEG Core member to assess data quality and inclusion criteria. Brain MRIs were evaluated in a similar manner, reviewed by local investigators and an MRI Core member to exclude a structural lesion. All available medical records were further reviewed by two of the three independent phenotyping reviewers for this report (MRZR, CJY, and KBH). When the two initial evaluators disagreed on any feature, a third review was undertaken, and a consensus opinion was reached. Disagreements were found initially with

reviewer interpretation of inclusion and exclusion criteria only; once this was clarified, interrater agreement was 100%. Records were reviewed for demographic information, family history, and clinical details, including IS, other seizure types as described by the treating physician, antiepileptic medications, developmental and behavioral outcomes, and other neurological features. Initiation of treatment was compared between treatment started within four weeks of onset of IS versus those after 4 weeks of onset, similar to prior studies.[13] We defined remission of spasms as sustained clinical spasms freedom for at least six months after treatment. Responders were defined as remission of clinical spasms for at least six months without reoccurrence of spasms or requiring subsequent medication. Nonresponders were defined as a lack of IS freedom, relapse of spasms within six months after treatment, or requiring subsequent therapy for IS.

Developmental outcome was determined similar to a previously published method.[14] In brief, the phenotyping reviewers retrospectively evaluated all available medical records for specific domains of development. Individuals with insufficient records to make an accurate assessment were excluded for further analysis. Evaluation of overall development, motor, and cognitive status was recorded as normal, mild or equivocal delay, or definite abnormality. Each domain was used to create an overall assessment of development, categorized as normal, mild, moderate, and severe delay. The child was included in the mild developmental delay group if one domain was marked as mild. The moderate developmental delay group consisted of children with two or more domains marked as mild or one domain marked as a definite abnormality, while severe developmental delay included children with two or more domains marked as definite abnormality. Because formal autism spectrum disorder (ASD) testing was not available in our records for the majority of the cohort, the history of an ASD diagnosis was obtained from the primary neurologist's most recent clinical documentation.

Genotype-phenotype and statistical methods

Descriptive statistics were calculated for demographics, family history, and clinical data for both the total cohort and follow-up cohort. Given the retrospective nature of the study, not all data were available for all subjects and each variable was analyzed separately. For phenotypic analysis, the primary results of interest were developmental and seizure outcomes. Characteristics of participants with normal and abnormal developmental outcomes, as well as resolved and subsequent seizures of any type (including recurrence of spasms if this occurred after six months), were compared.

Trio analysis of whole exome sequencing data was available for 100 individuals within the cohort. The sequencing methods and analysis were performed and described previously.[15] *De novo* genetic variants previously associated with epilepsy or epileptic encephalopathy were included in our analysis based upon prior literature[16] and Mendelian Inheritance in Man database entries linked to epilepsy.

Statistical analyses were conducted using SAS v. 9.2. (SAS Institute, Inc., Cary, North Carolina) and Stata v. 13.1 (Stata, Inc., College Station, Texas). Statistical comparisons were performed using *t* tests for continuous variables. Chi-square and Fisher's exact (in case cell

size ≤ 5) tests were used to compare categorical variables. All analyses used two-sided *P* values <0.05 for statistical significance.

Results

Cohort characteristics

A total of 224 children met the inclusion criteria for IS of unknown cause (previously cryptogenic or idiopathic IS) with the demographic and clinical characteristics presented in Table 1. In the cohort, 75 children (56%) were male. The mean age of IS onset when corrected for pre-maturity was 5.25 months (interquartile interval [IQR] four to six months, range 1.5 to 11 months). Twenty-six children (26%) had evidence of mild or moderate developmental delay prior to IS onset, and 17 (13%) had other seizure types prior to the onset of IS. Developmental regression and/or a plateau in development at or after the onset of IS was noted in 76 children (57%). Treatment within one month of IS onset occurred in 78 (70%) of the cohort. As the initial treatment for IS, the majority (65%; n = 85) received a first-line medication for IS, adrenocorticotropic hormone, oral steroids (prednisone or prednisolone), or vigabatrin.

Initial response to treatment

After initial treatment for IS, 31% (23 of 74) achieved IS freedom sustained for at least six months. Hormonal therapy was the only therapy to achieve sustained IS remission as the initial therapy for IS (Table 2). Of those treated with hormonal therapy as initial treatment, 41% (23 of 56) achieved IS freedom sustained for at least six months. Initial treatment with vigabatrin or nonstandard therapies failed to achieve sustained IS remission.

Treatment within one month of IS onset had significantly higher rate of IS resolution compared to those with treatment initiated after one month of IS onset (odds ratio [OR] 13.68, 95% confidence interval [CI] 1.72–108.43). Gender, race, age of onset, developmental delay or seizures prior to IS, or presence of developmental regression and/or plateau did not reach significance in predicting IS freedom after first treatment (Table 2). Taken together, treatment with hormonal therapy within one month of IS onset was the best predictor of sustained treatment response for IS of unknown cause.

Long-term seizure outcome

Seventy-nine (67%) subjects had subsequent seizures after IS. No single seizure type was predominant. Focal (29%), tonic (23%), atonic (17%), myoclonic (17%), and atypical absence (9%) seizures were reported across the cohort with many individuals exhibiting multiple seizure types. Significant predictors of subsequent seizures are presented in Table 3. Earlier age of IS onset (median five months old; IQR three months) was more likely to have additional seizures after IS ($P = 0.02$). Infants with any seizures prior to IS onset were eight times more likely to have subsequent seizures after IS (OR 8.72, CI 1.10–69.03). Children refractory to initial treatment for IS were four times more likely to have additional seizures after IS (OR 4.17, CI 1.56–11.11). Developmental delay prior to IS, timing of treatment, and first-line medication use as initial treatment were not predictors of additional seizure types after IS. The majority (84%) of individuals with additional seizures after IS also had

moderate or severe developmental delays, whereas only 16% of individuals with additional seizures had normal or mild developmental delays at last follow-up.

Developmental outcomes

The median age at last developmental assessment was 2.7 years (IQR 1.71–6.25 years) with the mean age at follow-up of 5.4 years old (range 0.75–43 years). At last follow-up, 15% (n = 20) had no developmental delays (Table 4). After IS, 85% of children had clearly evident developmental delays, either mild (15%; n = 20), moderate (20%; n = 27), or severe (50%; n = 65) delays. Infants with later IS onset (median six months old, IQR two months) were more likely to have no or mild developmental delays ($P = 0.02$).

No infants with delay or seizures prior to IS had a normal developmental outcome. Delay prior to IS was a significant predictor of moderate to severe developmental delays at follow-up (OR 19.19, CI 2.47–148.98). Seizures prior to IS were slightly more common in individuals with severe developmental delay compared to normal and mild delay (OR 5.04, CI 1.07–23.70, $P = 0.0422$). Infants with IS freedom after initial treatment were seven times more likely to have normal development or mild delays compared to moderate and/or severe developmental delays (OR 7.14, CI 2.56–20). History of developmental plateau or regression at the time of IS onset did not predict long-term developmental outcomes. Although time to treatment from IS onset and use of first line medication were predictors of IS freedom, they were not significant predictors of developmental outcomes. Thirty-nine individuals had both normal development prior to IS onset and achieved IS freedom after first medication, of which 25 (64.1%) had normal development at last follow-up. Taken together, the most significant predictors of a positive developmental outcome was older IS onset, normal development prior to IS, and IS freedom after first medication.

The presence or absence of an autism diagnosis was noted by the treating clinician in 48 individuals, of which 20 (42%) had either autistic features or a diagnosis of ASD reported by their treating neurologist. Of the children with ASD, only three had mild developmental delay whereas 17 (82%) had moderate or severe developmental delay (Table 4). No significant predictors of ASD were identified.

Genotype-phenotype correlation

Individuals in the cohort did not have a genetic diagnosis from prior clinical testing. Whole exome sequencing was performed through the EPGP and Epi4K consortium on all trios with adequate samples, n = 100, as described previously.[17] A total of 105 *de novo* variants were identified in 62 individuals, most of which have yet to be reconfirmed as causative associations with IS and/or epilepsy. Pathogenic *de novo* variants in genes associated with epilepsy were found in 15% of those sequenced (Table 5). Of the 15 individuals, 14 were considered severely delayed at follow-up (Table 4). The one individual with age appropriate development at follow-up had a *PTEN* variant considered pathogenic (Table 5). She had congenital macrocephaly (head circumference of 49 cm at five months and 52 cm at 11 months) with IS onset at four months of age and mild developmental regression but responded to therapy with no significant developmental delays at follow-up. The three individuals with *STXBP1* variants had an early age of IS onset (three to four months of age)

and all had subsequent seizures after IS with only one exhibiting seizures prior to IS onset. Overall, delays prior to IS or seizures prior to IS were not more common in individuals with a genetic finding. Individuals with a genetic finding were seven times more likely to have moderate to severe developmental delays compared to those with no or mild delays (OR 7.25, CI 1.2–79.4).

Discussion

We describe the largest cohort of children with IS of unknown cause. Improved understanding of factors underlying the pathogenesis and affecting clinical outcomes in IS is crucial in this devastating childhood epilepsy. Children with IS of unknown cause are often a small subset of a larger cohort. Through the multisite EPGP, this study provides important insight in the clinical characteristics of IS of unknown cause and identifies predictors of developmental and seizure outcomes in this population.

Only 15% of infants with IS of unknown cause had normal developmental outcomes at last clinical assessment. Normal development prior to IS onset, lack of seizures prior to IS, later age of IS onset, and IS freedom after initial treatment were significant predictors of normal developmental outcomes. Our study confirms previous findings that those with no seizures and normal development prior to IS have a better prognosis.[3,10,18]

The developmental outcomes in our cohort were less favorable than those reported in smaller studies of children with IS of unknown cause or subgroups within larger studies of IS of all causes.[3,14,18,19] Normal developmental outcome were seen in 54% for IS of unknown cause from a recent meta-analysis, whereas prior studies had extreme variability (standard deviation ± 30%; range 0%–100%).[8] Variability in outcome measures across prior studies may amount for these differences. For consistency with recent studies, we used a clinical scoring method similar to the prospective National Infantile Spasms Consortium study.[14,20] Duration of follow-up likely contributes to the variability in outcomes as well. In our study, the longer follow-up may have picked up developmental abnormalities only evident later in life and not apparent in studies with shorter follow-up.

IS of unknown cause represents a heterogeneous group. Genetic etiology is likely responsible for IS of unknown cause,[6] with the list of genes implicated in IS continually growing.[7,16] In the current study, we performed a genotype-phenotype correlation using genes previously associated with epilepsy. We identified a causative *de novo* genetic variant in 15% of those sequenced. Our decision to phenotype only individuals with a negative initial IS evaluation (i.e., excluding individuals with a prior genetic diagnosis or abnormalities on brain MRI), likely contributed to the lower rate of causative genetic variants in our study than recently reported.[21] We also excluded candidate genes in our analysis to prevent over interpretation of genetic findings that would likely not rise to the level of pathogenic findings on clinical testing.

We identified several genes previously implicated in IS and epileptic encephalopathy.[15,22] In addition to these genes, *PTEN* has been associated with epilepsy but not specifically IS. This *PTEN* variant was previously associated with Lhermitte-Duclos disease, or dysplastic

gangliocytoma of the cerebellum, and abnormal PTEN signaling.[23] Upon clinical review, this individual had congenital macrocephaly, which is often a feature of the *PTEN* phenotype, supporting the variant as pathogenic. *TUBB2A* is associated with IS and cortical malformations.[24,25] The individual with the *TUBB2A* variant had a normal MRI. It is possible that subtle malformations were not seen on an MRI before 2 years of age with incomplete myelination. We found that individuals with a genetic etiology on whole exome sequencing were more likely to have severe developmental delays and overall a poor prognosis. It is possible that individuals with no or mild delays are caused by novel genes, somatic variants, or epigenetic changes requiring future study. Our study highlights the importance of ongoing genetic evaluation of IS of seemingly unknown cause that can yield a diagnosis and provide valuable prognostic information.

The high rate of additional seizure types after IS in our cohort (67%) is similar to that reported previously.[5] Predictors of seizures after IS included younger age of IS onset, seizures prior to IS, and refractory IS. It is possible that individuals with increased risk factors for addition seizures may have subtle structural abnormalities, such as focal cortical dysplasia, not seen on initial brain MRI. Positron emission tomography, although not routine for the IS evaluation, has been shown to increase yield of identifying focal abnormalities in cryptogenic IS.[26] Recent studies show repeat imaging after complete myelination may identify lesions not detected on initial imaging.[27] Consideration of early positron emission tomography or repeat brain MRI of infants with refractor IS may provide additional insight into the etiology of this subset of individuals.

We found that IS freedom after the first medication was highly predictive of normal development and a negative predictor of subsequent seizures. Predictors of IS freedom included initiation of treatment within one month of IS onset and use of first line therapies, in line with prior studies.[14,28,29] First-line therapies were predictors of IS resolution but were not significant predictors of developmental or seizure outcomes in the current study. Given the variability in first medication used, it is likely that our study was underpowered to detect this effect. Prospective studies have demonstrated the importance of first-line therapies with adrenocorticotropic hormone or steroids achieving high rates of IS freedom.[13,14,30,31] A recent study showed up to an 88% response rate with combination hormonal treatment with vigabatrin in children with IS of unknown cause.[32] Taken together, these findings underscore the importance of prompt treatment of IS upon diagnosis and use of the most appropriate medication to achieve IS freedom.

Predictors of response to therapy for IS were medication used and lag time to treatment. The clinical characteristics such as age of onset, developmental delay, or seizures prior to IS did not predict response to therapy. These findings support the notion that current therapies likely treat the electroclinical features of IS but may not be specific to the underlying etiology. As precision medicine advances, future targeted therapeutics may achieve a higher response rate and better clinical outcomes.

There are notable limitations to this study. Given the retrospective nature of our cohort, records span several decades of IS treatment over which changes occurred in clinical practice recommendations.[33,34] The severity and nature of the developmental delay, autistic

features, and seizure characterization were limited to clinical records. Patients were recruited for this study from EPGP centers with specialized pediatric epilepsy divisions, potentially biasing selection toward more severely affected or refractory patients. However, individuals with severe developmental delays prior to IS were excluded in the current study and careful analysis of clinical records was done to exclude symptomatic IS. Finally, our phenotype-genotype analysis only included *de novo* variants in epilepsy genes and does not evaluate inherited pathogenic variants or copy number variants. Future studies on prospective cohorts with clinically confirmed genetic findings may further refine the genotype-phenotype correlations of IS.

Conclusions

Our study of a large cohort of IS of unknown cause in the EPGP database demonstrated poorer outcomes than previously noted. Normal development prior to IS, lack of seizures prior to IS, later age of IS onset, and the response to first treatment for IS are positive prognostic factors. These findings are important for clinicians to appropriately counsel families about IS outcomes, including individuals with an unrevealing initial evaluation for an etiology of IS. Whole exome sequencing revealed a genetic diagnosis in 15% of the sequenced individuals highlighting the utility of genetic testing for IS. Individuals with a pathogenic *de novo* variant in a known epilepsy gene had a worse prognosis. Further studies on the underlying mechanisms of IS may better inform prognosis and develop more targeted therapies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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TABLE 1.

Clinical Characteristics of Infantile Spasms of Unknown Cause

	Cohort of Infantile Spasms of Unknown Cause		
Characteristic	**Final Cohort (n = 133)**	**Inadequate Follow-up (n = 91)**	***P* Value**
Age of IS onset (months)	n = 126	n = 91	0.3290
Median (IQR)	5.25 (2.00)	5.00 (2.00)	
Range	(1.50, 11.00)	(1.00, 10.00)	
Gender			0.2201
Male	58 (43.6%)	48 (52.7%)	
Female	75 (56.4%)	43 (47.3%)	
Race			0.4672
White	81 (62.8%)	58 (64.4%)	
Black	4 (3.1%)	3 (3.3%)	
Hispanic	19 (14.7%)	18 (20.0%)	
Other	25 (19.4%)	11 (12.2%)	
Prior to IS onset			
Developmental delay (yes/no)	26/76 (25.5%/74.5%)	13/66 (16.5%/83.5%)	0.1506
Seizures (yes/no)	17/112 (13.2%/86.8%)	10/79 (11.2%/88.8%)	0.8347
Developmental plateau/regression (yes/no)	76/57 (57.1%/2.9%)	58/33 (63.7%/36.3%)	0.3352
Treatment			
Lead time			0.1386
<1 month from IS onset	78 (70.3%)	68 (80.0%)	
>1 month from IS onset	33 (29.7%)	17 (20.0%)	
Initial therapy used for IS			
First line medication (ACTH/steroids/VGB) (yes/no)	85/45 (65.4%/34.6%)	64/26 (71/l%/28.9%)	0.3836
Hormonal medication (ACTH or steroids) (yes/no)	81/49 (62.3%/37.7%)	59/31 (65.6%/34.4%)	0.6702

Abbreviation:

ACTH = Adrenocorticotropic hormone

IQR = Interquartile interval

IS = Infantile spasms

VGB = Vigabatrin

The final cohort included those that met criteria for IS of unknown cause with at least six months of follow-up data after IS onset. The final cohort did not differ from those with less than six months follow-up data (Inadequate Follow-up). Subcategory totals differ based on available data.

TABLE 2.

Clinical Characteristics Associated With Response to Initial Treatment

Characteristic	IS Freedom with Initial Treatment			Odds Ratio (95% CI)	*P* Value*
	Yes (n = 23)	No (n = 74)	Total (n = 118)		
Age of IS onset (months)					0.1143
Median (IQR)	6.00 (2.00)	5.00 (3.00)	5.25 (2.50)		
Range	(2.00, 9.50)	(1.50, 11.00)	(1.50, 11.00)		
Gender					
Male	15 (65.2%)	46 (62.2%)	61 (62.9%)	1.14 (0.43–3.04)	1.0000
Female	8 (34.8%)	28 (37.8%)	36 (37.1%)	Ref	
Race					0.1962
White	18 (78.3%)	39 (54.9%)	57 (60.6%)		
Black	1 (4.3%)	3 (4.2%)	4 (4.3%)		
Hispanic	1 (4.3%)	12 (16.9%)	13 (13.8%)		
Other	3 (13.0%)	17 (23.9%)	20 (21.3%)		
Prior to IS onset					
Developmental delay					
No	16 (84.2%)	42 (76.4%)	58 (78.4%)	0.61 (0.15–2.41)	0.7472
Yes	3 (15.8%)	13 (23.6%)	16 (21.6%)	Ref	
Seizures					
No	22 (95.7%)	60 (84.5%)	82 (87.2%)	0.25 (0.03–2.03)	0.2819
Yes	1 (4.3%)	11 (15.5%)	12 (12.8%)	Ref	
Developmental plateau/regression					
No	12 (52.2%)	31 (41.9%)	43 (44.3%)	0.66 (0.26–1.69)	0.4730
Yes	11 (47.8%)	43 (58.1%)	54 (55.7%)	Ref	
Treatment					
Lead time					
<1 month from IS onset	22 (95.7%)	37 (61.7%)	59 (71.1%)	13.68 (1.72–108.43)	0.0023
>1 month from IS onset	1 (4.3%)	23 (38.3%)	24 (28.9%)	Ref	
First-line medication (ACTH/steroids/VGB)					<0.0001
Yes	23 (100.0%)	36 (48.6%)	59 (60.8%)		

Characteristic	IS Freedom with Initial Treatment			Odds Ratio (95% CI)	*P* Value*
	Yes (n = 23)	No (n = 74)	Total (n = 118)		
No	0 (0.0%)	38 (51.4%)	38 (39.2%)		
Outcome measures					
Additional seizures after IS					
No	13 (56.5%)	15 (23.4%)	28 (32.2%)	4.17 (1.56–11.11)	0.0081
Yes	10 (43.5%)	49 (76.6%)	59 (67.8%)	Ref	
Developmental outcome					0.0009
No delay	7 (30.4%)	7 (9.6%)	14 (14.6%)		
Mild	8 (34.8%)	8 (11.0%)	16 (16.7%)		
Moderate	2 (8.7%)	16 (21.9%)	18 (18.8%)		
Severe	6 (26.1%)	42 (57.5%)	48 (50.0%)		
Autism spectrum disorder					
No	11 (55.0%)	8 (72.7%)	19 (61.3%)	0.46 (0.09–2.25)	0.4516
Yes	9 (45.0%)	3 (27.3%)	12 (38.7%)	Ref	

Abbreviations:

ACTH, adrenocorticotropic hormone

IQR = Interquartile interval

IS = Infantile spasms

VGB = Vigabatrin

IS freedom with initial treatment was defined as resolution of IS after first treatment without IS recurrence for at least six months. Total number includes all individuals with response to initial IS treatment data. Subcategory totals differ based on available data.

**P* value represents chi-square analysis for those without a calculated odds ratio.

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TABLE 3.

Characteristics Associated With Risk of Subsequent Seizures After IS

Characteristic	Additional Seizures After IS				
	Seizures (n = 79)	Seizure Free (n = 39)	Total (n = 118)	Odds Ratio (95% CI)	*P* Value*
Age of IS onset (months)					0.0222
Median (IQR)	5.00 (3.00)	6.00 (2.00)	5.25 (2.25)		
Range	(1.50, 10.00)	(3.00, 11.00)	(1.50, 11.00)		
Gender					
Male	46 (58.2%)	22 (56.4%)	68 (57.6%)	1.08 (0.50, 2.34)	1.0000
Female	33 (41.8%)	17 (43.6%)	50 (42.4%)	Ref	
Race					0.7925
White	45 (60.0%)	27 (69.2%)	72 (63.2%)		
Black	3 (4.0%)	1 (2.6%)	4 (3.5%)		
Hispanic	10 (13.3%)	5 (12.8%)	15 (13.2%)		
Other	17 (22.7%)	6 (15.4%)	23 (20.2%)		
Prior to IS onset					
Developmental delay					
No	39 (69.6%)	29 (85.3%)	68 (75.6%)	Ref	
Yes	17 (30.4%)	5 (14.7%)	22 (24.4%)	2.53 (0.84, 7.65)	0.1298
Seizures					
No	61 (81.3%)	38 (97.4%)	99 (86.8%)	Ref	
Yes	14 (18.7%)	1 (2.6%)	15 (13.2%)	8.72 (1.10, 69.03)	0.0180
Developmental plateau/regression					
No	37 (46.8%)	15 (38.5%)	52 (44.1%)	Ref	
Yes	42 (53.2%)	24 (61.5%)	66 (55.9%)	1.41 (0.65–3.13)	0.4346
Treatment					
Lead time					
<1 month from IS onset	18 (29.5%)	10 (25.6%)	28 (28.0%)	0.82 (0.33, 2.04)	0.8200
>1 month from IS onset	43 (70.5%)	29 (74.4%)	72 (72.0%)	Ref	
First-line medication (ACTH/steroids/VGB)					
Yes	50 (65.8%)	28 (71.8%)	78 (67.8%)	0.76 (0.33, 1.76)	0.6736

Characteristic	Additional Seizures After IS				
	Seizures (n = 79)	Seizure Free (n = 39)	Total (n = 118)	Odds Ratio (95% CI)	*P* Value*
No	26 (34.2%)	11 (28.2%)	37 (32.2%)	Ref	
IS freedom with initial treatment					
Yes	10 (16.9%)	13 (46.4%)	23 (26.4%)	Ref	
No	49 (83.1%)	15 (53.6%)	64 (73.6%)	4.17 (1.56–11.11)	0.0081
Other outcome measures					
Developmental outcome					<0.0001
No delay	4 (5.1%)	14 (36.8%)	18 (15.4%)		
Mild	9 (11.4%)	10 (26.3%)	19 (16.2%)		
Moderate	18 (22.8%)	5 (13.2%)	23 (19.7%)		
Severe	48 (60.8%)	9 (23.7%)	57 (48.7%)		
Autism spectrum disorder					
No	14 (48.3%)	10 (71.4%)	24 (55.8%)	Ref	
Yes	15 (51.7%)	4 (28.6%)	19 (44.2%)	2.68 (0.68, 10.53)	0.1991

Abbreviations:

ACTH, adrenocorticotropic hormone

IQR = Interquartile interval

IS = Infantile spasms

VGB = Vigabatrin

Subsequent seizures included focal, tonic, atonic, myoclonic, and atypical absence seizures occurring after IS onset. Total number includes all individuals with data on the presence or absence of subsequent seizures after IS. Subcategory totals differ based on available data.

**P* value represents chi-square analysis for those without a calculated odds ratio.

TABLE 4.

Clinical Characteristics Associated With Developmental Outcomes

Characteristic	Developmental Outcome				Total (n = 132)	No/Mild vs Moderate/ Severe Delay OR (95% CI)	Fisher's Exact *P* Value*
	No Delay (n = 20)	Mild Delay (n = 20)	Moderate Delay (n = 27)	Severe Delay (n = 65)			
Age of IS onset (months)							0.0202
Median (IQR)	6.00 (2.00)	6.00 (2.00)	5.00 (2.00)	5.00 (3.00)	5.50 (2.00)		
Range	(3.00, 8.00)	(4.00, 10.00)	(1.50, 11.00)	(2.00, 10.00)	(1.50, 11.00)		
Gender							
Male	10 (50.0%)	9 (45.0%)	18 (66.7%)	38 (58.5%)	75 (56.8%)	1.72 (0.81–3.63)	0.1826
Female	10 (50.0%)	11 (55.0%)	9 (33.3%)	27 (41.5%)	57 (43.2%)	Ref	
Race							0.4786
White	14 (70.0%)	13 (65.0%)	16 (61.5%)	38 (61.3%)	81 (62.8%)		
Black	0 (0.0%)	0 (0.0%)	2 (7.7%)	2 (3.2%)	4 (3.1%)		
Hispanic	1 (5.0%)	4 (20.0%)	6 (23.1%)	8 (12.9%)	19 (14.7%)		
Other	5 (25.0%)	3 (15.0%)	2 (7.7%)	14 (22.6%)	24 (18.8%)		
Prior to IS onset							
Developmental delay							
No	19 (100.0%)	14 (93.3%)	15 (88.2%)	28 (54.9%)	76 (74.5%)	19.19 (2.47–148.98)	<0.0001
Yes	0 (0.0%)	1 (6.7%)	2 (11.8%)	23 (45.1%)	26 (25.5%)	Ref	
Seizures							
No	20 (100.0%)	18 (90.0%)	24 (92.3%)	49 (79.0%)	111 (86.7%)	3.90 (0.85–17.97)	0.0904
Yes	0 (0.0%)	2 (10.0%)	2 (7.7%)	13 (21.0%)	17 (13.3%)	Ref	
Developmental plateau/regression							
No	10 (50.0%)	11 (55.0%)	12 (44.4%)	23 (35.4%)	56 (42.4%)	1.80 (0.85–3.81)	0.1306
Yes	10 (50.0%)	9 (45.0%)	15 (55.6%)	42 (64.6%)	76 (57.6%)	Ref	
Treatment							
Lead time							
<1 month from IS onset	16 (80.0%)	14 (73.7%)	15 (68.2%)	32 (65.3%)	33 (30.0%)	1.69 (0.70–4.17)	0.2818
>1 month from IS onset	4 (20.0%)	5 (26.3%)	7 (31.8%)	17 (34.7%)	77 (70.0%)	Ref	
First-line medication							
Yes	14 (70.0%)	13 (68.4%)	17 (65.4%)	41 (64.1%)	85 (65.9%)	1.23 (0.56–2.78)	0.6878

Characteristic	Developmental Outcome				Total (n = 132)	No/Mild vs Moderate/ Severe Delay OR (95% CI)	Fisher's Exact *P* Value*
	No Delay (n = 20)	Mild Delay (n = 20)	Moderate Delay (n = 27)	Severe Delay (n = 65)			
No	6 (30.0%)	6 (31.6%)	9 (34.6%)	23 (35.9%)	44 (34.1%)	Ref	
IS freedom with initial treatment							
Yes	7 (50.0%)	8 (50.0%)	2 (11.1%)	6 (12.5%)	23 (24.0%)	7.14 (2.56–20)	0.0001
No	7 (50.0%)	8 (50.0%)	16 (88.9%)	42 (87.5%)	73 (76.0%)	Ref	
Other outcome measures							
Additional seizures after IS							<0.0001
No	14 (77.8%)	10 (52.6%)	5 (21.7%)	9 (15.8%)	38 (32.5%)		
Yes	4 (22.2%)	9 (47.4%)	18 (78.3%)	48 (84.2%)	79 (67.5%)		
Autism spectrum disorder							0.0561
No	7 (100.0%)	5 (62.5%)	5 (38.5%)	11 (55.0%)	28 (58.3%)		
Yes	0 (0.0%)	3 (37.5%)	8 (61.5%)	9 (45.0%)	20 (41.7%)		
Genetic diagnosis							
Yes	1 (6.2%)	-	-	14 (29.2%)	15 (15.0%)	0.14 (0.01–0.82)	0.0348
No	16 (93.8%)	13 (100%)	22 (100%)	34 (70.8%)	85 (85.0%)	Ref	

Abbreviations:

IQR = Interquartile interval

IS = Infantile spasms

Total number includes all individuals with data on developmental outcomes for at least six months after IS onset. Subcategory totals differ based on available data.

Genetic diagnosis represents findings from whole exome sequencing show in Table 5.

* *P* value represents chi-square analysis for those without a calculated odds ratio.

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TABLE 5.

Epilepsy-Related Genes Identified in IS Patients Within the Cohort.

Gene	Variant Effect	hg19 coordinates (chnposition)	Ref/Alt Alleles	Gender	Age of IS Onset (Months)	Additional Seizures	Delay Prior to IS	Developmental Outcome
ALG13	Missense	chrX:110928268	A/G	F	4	Yes, after IS	No	Severe delay
DNM1	Missense	chr9:130982295	G/C	M	6	Yes, after IS	-	Severe delay
GABRA1	Missense	chr5:161322690	C/T	M	-	Yes, after IS	Yes	Severe delay
GNA01	Missense	chr16:56385396	T/C	F	-	Yes, before and after IS	Yes	Severe delay
GRIN1	Missense	chr9:140057118	A/C	F	4.5	Yes, after IS	No	Severe delay
KCNQ2	Missense	chr20:62076674	C/T	F	-	Yes, before and after IS	Yes	Severe delay
KCNQ2	Missense	chr20:62044825	G/C	M	5	No	No	Severe delay
KCNT1	Missense	chr9:138671246	C/T	F	-	Yes, before IS	Yes	Severe delay
PTEN*	Missense	chr10:89717712	C/T	F	4	No	No	No delay
SCN2A	Missense	chr2:166198975	G/A	F	10	-	-	Severe delay
SCN8A	Missense	chr12:52082568	G/A	M	3.5	Yes, after IS	No	Severe delay
STXBP1	Missense	chr9:130434370	C/T	M	4	Yes, after IS	Yes	Severe delay
STXBP1	Missense	chr9:130444768	G/A	M	3	Yes, before and after IS	No	Severe delay
STXBP1	Stop gained	chr9:130428484	C/T	M	3	Yes, after IS	-	Severe delay
TUBB2A†	Missense	chr6:3154698	A/C	M	6	-	Yes	Severe delay

De novo variants in epilepsy-related genes identified on whole exome sequencing of patients within the current cohort. All variants are pathogenic or likely pathogenic using the American College of Medical Genetics and Genomics (ACMG) interpretation criteria (PS2, PM2, PP2, and PP3). Genes listed in bold have variants noted to be “damaging” in PolyPhen-2 and “deleterious” in SIFT (Sorting Intolerant From Tolerant).

*The PTEN variant has been previously described as pathogenic.[23]

†The TUBB2A variant was considered “probably damaging” in PolyPhen-2, “deleterious” in Provean and “possibly pathogenic” in Mendelian Clinically Applicable Pathogenicity (M-CAP). F = female, M = male, (−) records without enough information.

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