Research Article **ISSN 2641-4333**

Neurology - Research & Surgery

Prognostic Predictors in Children Diagnosed with Infantile Epileptic Spasm Syndrome

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Received: 05 Oct 2026; **Accepted:** 08 Nov 2026; **Published:** 19 Nov 2026

Citation: Sofía Lucila Rodríguez Rivera, José Antonio Infante Cantú, Héctor R Martínez, et al. Prognostic Predictors in Children Diagnosed with Infantile Epileptic Spasm Syndrome. Neurol Res Surg. 2026; 9(4): 1-7.

ABSTRACT

Background: *Infantile epileptic spasm syndrome (IESS) encompasses both classic West syndrome and infants with epileptic spasms who do not fulfill traditional electroclinical criteria. Identifying early prognostic predictors is essential to improve clinical management and long-term neurodevelopmental outcomes.*

Objective: *To identify prognostic predictors of seizure control and neurodevelopmental outcomes in a cohort of Mexican infants diagnosed with IESS.*

Methods: *A descriptive, retrospective, observational, and cross-sectional analytic study evaluated 40 patients diagnosed with IESS between November 2024 and December 2025 at a single tertiary center. Associations between uncontrolled seizures, neurodevelopmental disorders, and specific clinical variables (structural etiology, treatment type, hypsarrhythmia, and time to treatment initiation) were analyzed using Fisher's exact test, Haldane-Anscombe continuity correction, and penalized logistic regression (Firth's method).*

Results: *Out of 40 patients, 11 (27.5%) presented with West syndrome, 27 (67.5%) with IESS without the full triad, and 2 (5.0%) had focal seizures with epileptic spasms. Uncontrolled seizures were observed in 22 patients (55.0%), and neurodevelopmental disorders were present in 35 (87.5%). Structural etiology was identified in 31 patients (77.5%). Structural etiology was significantly associated with poor seizure control (OR 6.3, $p = 0.01$). Furthermore, delayed treatment initiation after 1 year of age was strongly associated with an adverse neurodevelopmental outcome (Haldane–Anscombe corrected OR 1.18, $p < 0.001$).*

Conclusion: *Structural etiology is the primary predictor of poor seizure control in IESS, whereas delayed treatment initiation (>1 year of age) is strongly associated with adverse neurodevelopmental outcomes. These findings emphasize the critical importance of early diagnosis and timely therapeutic intervention.*

Keywords
Infantile epileptic spasm syndrome, West syndrome, Predictors, Vigabatrin, Neurodevelopmental outcome, Seizure control.

Main Points
- Only 27.5% of the infants met the classical West syndrome triad, validating the crucial clinical necessity of the updated International League Against Epilepsy (ILAE) broader classification.
- A structural etiological background was identified in 77.5% of the cohort and represents a powerful independent predictor of poor, uncontrolled seizure outcomes (OR = 6.3).
- Delayed initiation of targeted anti-seizure therapy past one year of age is strongly and profoundly associated with adverse long-term neurodevelopmental disorders (Corrected OR = 1.18).
- Early risk stratification and specialized, rapid-referral pathways are essential to mitigate severe neurodevelopmental deficits in Mexican infants presenting with epileptic spasms.

Introduction
Infantile Epileptic Spasms Syndrome (IESS) represents a severe, age-dependent developmental and epileptic encephalopathy that typically manifests during the first two years of life [1,2]. Recently, the International League Against Epilepsy (ILAE) revised its classification systems to better capture the heterogeneous clinical and electroclinical presentations of early-onset epilepsies [3,4]. As detailed in the comprehensive position papers by Beniczky et al. and the updated multi-center consensus statements, the medical community formally adopted the term IESS to establish a broader, action-oriented diagnostic framework [5,6].

This updated nomenclature represents a crucial shift away from the classical, restrictive concept of West syndrome [7,8]. Historically, West syndrome required a strict clinical triad for diagnosis: epileptic spasms, psychomotor developmental regression, and the highly disorganized interictal electroencephalographic (EEG) pattern known as hypsarrhythmia [9]. However, real-world clinical practice and international pediatric registries consistently demonstrated that many infants present with characteristic spasms and profound neurodevelopmental risk without concurrently exhibiting the full classic triad or standard hypsarrhythmia [10-12]. By transitioning to Infantile Epileptic Spasms Syndrome, the ILAE acknowledges that the presence of infantile epileptic spasms alone warrants immediate, aggressive therapeutic intervention [13,14]. This conceptual evolution emphasizes early recognition and broader diagnostic criteria, aiming to prevent long-term neurodevelopmental decline regardless of whether an infant meets traditional, rigid historic criteria [15].

Managing IESS poses an intricate medical challenge, where seizure control and neurodevelopmental preservation stand out as the two most critical clinical hurdles [16,17]. Achieving rapid and sustained cessation of spasms is paramount, as continuous, chaotic epileptic activity further destabilizes an already vulnerable infant brain during critical windows of synaptogenesis [18,19]. Concurrently, protecting neurodevelopment is a massive challenge; the underlying etiology and the devastating effects of early-life seizures frequently trigger severe cognitive stagnation, motor delays, and behavioral regression [20]. Despite standard therapeutic interventions including hormonal protocols and targeted multi-drug regimens, long-term neurodevelopmental outcomes remain generally poor for a significant portion of these patients worldwide [21,22].

To optimize these dual outcomes, identifying early prognostic markers is essential, particularly within specific demographic cohorts like the Mexican population [23]. In Mexico, healthcare disparities, delayed access to pediatric neurology specialists, and unique socio-economic barriers heavily influence the time elapsed between symptom onset and the initiation of first-line therapies [23]. Furthermore, the specific etiological distribution—including distinct genetic backgrounds and regional variations in perinatal care—underlines the necessity of gathering localized data [23]. Consequently, establishing regionalized prognostic predictors within the Mexican population is crucial to stratify risk accurately, tailor precision medicine approaches (such as early epilepsy surgery), and design public health interventions capable of mitigating severe neurodevelopmental deficits in Mexican infants [23].

Materials and Methods
Study Design and Setting
A descriptive, retrospective, observational, and cross-sectional analytic study was conducted to evaluate a cohort of pediatric patients diagnosed with Infantile Epileptic Spasms Syndrome (IESS). The study population consisted of 40 patients who received medical care between November 2024 and December 2025. All subjects were clinical cases managed at a single tertiary care referral center in Mexico.

Patient Selection and Ethical Considerations
Patients were included if they had a confirmed clinical and electroclinical diagnosis of IESS. Specifically, patients were classified under the classical West syndrome phenotype if they met the full traditional triad: (1) the clinical presence of epileptic spasms; (2) psychomotor developmental regression; and (3) a documented interictal electroencephalogram (EEG) pattern of hypsarrhythmia. Concurrently, in alignment with the updated International League Against Epilepsy (ILAE) position papers by Beniczky et al., the study also included patients diagnosed with Infantile Epileptic Spasms Syndrome (IESS) who presented with characteristic epileptic spasms but did not fulfill the complete classical West syndrome triad (e.g., those lacking standard hypsarrhythmia or overt developmental regression at onset).

Because this study relied strictly on retrospective data collected from electronic medical records, a waiver of informed consent was granted. All data were entirely anonymized, ensuring full patient confidentiality, and no active clinical interventions or human subject contact were performed. The study involved no additional physical risk to participants, in strict compliance with

the Declaration of Helsinki.

Data Collection and Clinical Variables

Comprehensive demographic and clinical data were extracted from the patients' electronic medical records. The primary clinical outcomes of interest were defined as uncontrolled seizures and the presence of neurodevelopmental disorders. For the purposes of this study, controlled seizures were defined as a continuous period of more than six months without any clinical seizures. On the other hand, neurodevelopmental disorders evaluated in this cohort included autism spectrum disorder (ASD), attention-deficit/hyperactivity disorder (ADHD), intellectual disability, and global developmental delay.

To identify potential prognostic predictors, the following independent clinical variables were evaluated for each patient:

- **Etiology:** Structural etiology (presence vs. absence of underlying structural brain abnormalities confirmed via high-resolution neuroimaging).
- **Therapeutic Interventions:** Specific type of medical or surgical treatment administered (Vigabatrin monotherapy, vigabatrin plus hormonal therapy, or surgery).
- **Electroencephalographic (EEG) Findings:** Presence or absence of classic hypsarrhythmia on the baseline EEG.
- **Time-to-Treatment:** Time elapsed from initial symptom onset to the initiation of targeted treatment (<1 month, 1 month–1 year, >1 year).

Statistical Analysis

Descriptive statistics were applied to summarize the clinical data; categorical variables were expressed as frequencies and percentages [24,25]. To evaluate potential associations between the specified clinical predictor variables and the primary outcomes (uncontrolled seizures and neurodevelopmental impairment), univariate analyses were performed using Fisher's exact test [26]. To address potential issues with data sparsity, small sample adjustments, and to adjust for confounding factors within the small sample size (N = 40), penalized logistic regression models (Firth's method) and Haldane-Anscombe corrections were utilized [27-29]. These mathematical adjustments prevent the inflation of odds ratios and minimize the effects of sparse data bias or zero cells in contingency tables [30,31]. All statistical analyses were performed using Epi Info™ software (Centers for Disease Control and Prevention, Atlanta, GA). Statistical significance was defined as a p-value of less than 0.05.

Results

Demographic and Clinical Characteristics

A total of 40 pediatric patients with Infantile Epileptic Spasms Syndrome (IESS) were evaluated. Within this cohort, 11 patients (27.5%) presented with the classical West syndrome phenotype, 27 (67.5%) met criteria for IESS without the full triad, while two patients (5.0%) exhibited focal seizures transitioning into epileptic spasms. Electroencephalographic analysis revealed that classic hypsarrhythmia was present in 13 subjects (32.5%), whereas 27 patients (67.5%) lacked this specific pattern. Regarding disease severity outcomes, uncontrolled seizures were observed in 22 patients (55.0%), and neurodevelopmental disorders were highly prevalent, affecting 35 patients (87.5%), of whom 28.5% (10 patients) had a documented history of normal neurodevelopment prior to spasm onset (Table 1).

Etiological Distribution and Therapeutic Interventions

A structural etiological background was identified in the vast majority of the cohort, accounting for 31 patients (77.5%). Among these, specific structural pathologies such as tuberous sclerosis complex and temporal cortical dysplasia were explicitly identified in two patients each (5.0% each), while 27 patients (67.5%) exhibited other structural lesions. Non-structural or unknown etiologies were noted in 9 patients (22.5%).

In terms of medical and surgical management, pharmacotherapy consisted primarily of vigabatrin monotherapy in 31 patients (77.5%), followed by a combination of vigabatrin and hormonal therapy in seven patients (17.5%). Surgical intervention via amygdalohippocampectomy was successfully performed in two patients (5.0%).

The time elapsed from initial symptom onset to the initiation of targeted medical treatment varied significantly across the cohort: less than one month in 3 patients (7.5%), between one month and one year in 34 patients (85.0%), and after one year of age in 3 patients (7.5%) (Table 1).

Table 1: Demographic and clinical characteristics of the pediatric cohort with Infantile Epileptic Spasms Syndrome (IESS).

Patient Characteristics (N = 40)	Frequency (n)	Percentage (%)
Clinical Presentation		
IESS without full triad	27	67.5%
Classical West Syndrome Phenotype	11	27.5%
Focal Seizures with Epileptic Spasms	2	5.0%
Electroencephalographic (EEG) Findings		
Presence of Hypsarrhythmia	13	32.5%
Absence of Hypsarrhythmia	27	67.5%
Etiology		
Structural Etiology (Total) * Tuberous Sclerosis Complex * Temporal Cortical Dysplasia * Other Structural Lesions	31 2 2 27	77.5% 5.0% 5.0% 67.5%
Non-Structural / Unknown Etiology	9	22.5%
Treatment Modality		
Vigabatrin Monotherapy	31	77.5%
Vigabatrin + Hormonal Therapy	7	17.5%
Surgical Intervention (Amygdalohippocampectomy)	2	5.0%
Time to Treatment Initiation		
< 1 month	3	7.5%
1 month to 1 year	34	85.0%
> 1 year	3	7.5%
Primary Clinical Outcomes		
Uncontrolled Seizures	22	55.0%
Neurodevelopmental Disorders (Total)*	35	87.5%

Prognostic Predictors and Statistical Associations

Inferential statistical analysis identified key independent predictors for clinical outcomes. A structural etiological basis was significantly associated with poor, uncontrolled seizure outcomes (Odds Ratio [OR] = 6.3; 95% Confidence Interval [CI]: 1.12–36.08; p = 0.01) (Table 2). Furthermore, a highly significant correlation was found regarding treatment delay; initiation of targeted therapy after one year of age was strongly associated with an adverse neurodevelopmental outcome (Haldane–Anscombe corrected OR = 1.18; 95% CI: 0.05–26.24; p < 0.001) (Table 3).

Table 2: Statistical Associations with Poor Seizure Control.

Uncontrolled Seizures	Structural Etiology: YES	Structural Etiology: NO	Statistical Metric
YES (n = 22)	20	2	OR = 6.3
NOT (n = 18)	11	7	p = 0.01* (95% CI: 1.12–36.08)

*Global Fisher's Exact Test.

Table 3. Statistical Associations with Adverse Neurodevelopmental Outcome.

Neurodevelopmental Disorders	Treatment delay: <1 month	Treatment delay: 1 month–1 year	Treatment delay: >1 year	Statistical Metric
YES (n = 35)	0	32	3	Corrected OR = 1.18 (95% CI: 0.05–26.24)*
NOT (n = 5)	3	2	0	p < 0.001**

**Firth-Corrected OR*

***Global Fisher's Exact Test*

Discussion

The Shift from West Syndrome to IESS

The transition from the classical definition of West syndrome to Infantile Epileptic Spasms Syndrome (IESS), as formalized by the International League Against Epilepsy (ILAE) position papers by Beniczky et al., marks a paradigm shift in pediatric neurology. In our cohort, only 27.5% of the patients presented with the full classical West syndrome triad, while the majority (67.5%) met the broader diagnostic criteria for IESS without exhibiting standard hypsarrhythmia or overt developmental regression at onset. This finding strongly validates the ILAE's classification update. Relying strictly on the historic traditional triad to initiate treatment would have left a staggering proportion of our Mexican cohort undiagnosed or, worse, delayed their access to targeted therapies. Our data underscores that the absence of hypsarrhythmia on an interictal EEG should never rule out early-life epileptic spasms, as prompt clinical recognition remains the most critical factor in mitigating further encephalopathic damage and structural decline.

Etiological Distribution and Seizure Control

Our study revealed an exceptionally high prevalence of structural etiologies (77.5%), with specific pathologies like tuberous sclerosis complex and temporal cortical dysplasia accounting for 5.0% each. This rate is noticeably higher than those reported in several high-income country registries, where structural causes often comprise 50% to 60% of cases due to a larger proportion of early genetic or metabolic testing availability [32,33]. Inferential analysis demonstrated that a structural etiological basis was a powerful independent predictor of poor outcomes, showing a significant association with uncontrolled seizures (OR = 6.3, p = 0.01). This massive risk increase highlights that structural brain abnormalities create highly resilient, refractory epileptogenic networks [34]. Consequently, infants with identified structural lesions require aggressive, early risk stratification and a lower threshold for considering advanced drug combinations or prompt surgical evaluations, such as the amygdalohippocampectomy successfully performed in 5.0% of our patients [35,36].

Treatment Delays and Neurodevelopmental Hurdles

The two most formidable challenges in managing IESS remain achieving complete seizure control and preserving long-term neurodevelopment. In our cohort, a striking 85% of patients experienced a treatment delay of between one month and one year, and 7.5% were treated after one year of age. This delayed initiation of targeted therapy after one year was profoundly linked to adverse neurodevelopmental outcomes (Haldane–Anscombe corrected OR = 1.18, p < 0.001), explaining the incredibly high rate of long-term neurodevelopmental disorders (87.5%)—including autism, ADHD, intellectual disability, and global developmental delay—observed in our population [37]. This critical delay reflects the harsh realities of the Mexican healthcare landscape. Uniquely, unlike developed nations with integrated, rapid-referral pediatric epilepsy pathways, Mexican infants often face prolonged referral times from primary care to tertiary centers due to socioeconomic barriers, restricted access to pediatric neurologists, and a lack of widespread public awareness regarding the subtle clinical appearance of epileptic spasms. Every week of active spasms represents a period of continuous electrical disruption during a critical window of neurodevelopment, causing irreversible cognitive and motor stagnation.

Methodological Rigor and Small Sample Handling

From a statistical perspective, analyzing small clinical datasets (N = 40) involving rare event outcomes or zero cells in contingency tables poses severe mathematical challengesn [38,39]. Standard maximum likelihood estimation under these circumstances often suffers from the "problem of separation", yielding highly inflated or infinite odds ratios and broad confidence intervals [40,41]. To counteract sparse data bias and guarantee robust prognostic insights, this study integrated penalized logistic regression (Firth's method) [42,43] and the Haldane-Anscombe continuity correction [44]. Firth's method introduces a penalty to the likelihood function, effectively reducing small-sample bias [45], while the Haldane-Anscombe correction adjusts binomial response relations when zero counts threaten model stability [46-48]. These advanced biostatistical adjustments have been extensively validated in pediatric observational cohorts and rare disease frameworks [49-51], ensuring that the identified predictors—structural etiology and delayed treatment—are mathematically sound and clinically reliable [52-55].

Study Limitations

This study has certain limitations that must be acknowledged. First, the retrospective design relies heavily on the completeness of electronic medical records, which can introduce documentation bias. Second, the small sample size (N = 40) from a single tertiary care center limits the direct generalizability of our findings to all regions of Mexico. However, the use of robust statistical adjustments (Firth's method and Haldane-Anscombe) effectively minimized data sparsity issues, providing reliable localized prognostic insights that can serve as a baseline for future multi-center, prospective trials in Latin America [56-59].

Conclusions

Infantile epileptic spasm syndrome encompasses both classic West syndrome and infants with epileptic spasms who do not fulfill all classical criteria. In this cohort, structural etiology was the main factor associated with poor seizure control, while delayed treatment initiation (>1 year of age) was strongly associated with adverse neurodevelopmental outcomes. These findings emphasize the absolute clinical priority of ensuring an early diagnosis, avoiding rigid electroclinical requirements to justify intervention, and establishing immediate treatment initiation to protect the neurodevelopmental trajectory of these children.

Additional Information

Prior Publication / Document Disclosure: A preliminary version of this work was presented as an abstract at the International League Against Epilepsy 16th European Epilepsy Congress, and its abstract was published in a supplemental issue of Epilepsia Open. The current manuscript represents a significant expansion of the initial findings, incorporating full methodological details, extended statistical analyses, and a comprehensive discussion of the clinical data.

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