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Immediate outcomes in early life epilepsy: A contemporary account

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yebeh.2019.05.011.

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Abstract

Rationale: Early-life epilepsies (ELEs) include some of the most challenging forms of epilepsy to manage. Given recent diagnostic and therapeutic advances, a contemporary assessment of the immediate short-term outcomes can provide a valuable framework for identifying priorities and benchmarks for evaluating quality improvement efforts.

Methods: Children with newly diagnosed epilepsy and onset <3 years were prospectively recruited through 17 US hospitals, from 2012 to 2015 and followed for 1 year after diagnosis. Short-term outcome included mortality, drug resistance, evolution of nonsyndromic epilepsy to infantile spasms (IS) and from IS to other epilepsies, and developmental decline. Multivariable analyses assessed the risk of each outcome.

Results: Seven hundred seventy-five children were recruited, including 408 (53%) boys. Median age at onset was 7.5 months (interquartile range (IQR): 4.2–16.5), and 509 (66%) had onset in the first year of life. Of 22 deaths that occurred within one year of epilepsy diagnosis, 21 were children with epilepsy onset in infancy (<12 months). Of 680 children followed ≥6 months, 239 (35%) developed drug-resistant seizures; 34/227 (15%) infants with nonsyndromic epilepsy developed IS, and 48/210 (23%) initially presenting with IS developed additional seizure types. One hundred of 435 (23%) with initially typical development or only mild/equivocal delays at seizure onset, had clear developmental impairment within one year after initial diagnosis. Each outcome had a different set of predictors; however, younger age and impaired development at seizure onset were broadly indicative of poorer outcomes. Type of epilepsy and early identification of underlying cause were not reliable predictors of these outcomes.

Conclusion: Early-life epilepsies carry a high risk of poor outcome which is evident shortly after epilepsy diagnosis. Onset in infancy and developmental delay is associated with an especially high risk, regardless of epilepsy type. The likelihood of poor outcomes is worrisome regardless of specific clinical profiles.

Keywords

Drug resistance; Developmental delay; Infantile spasms; Mortality

1. Introduction

Many of the most severe forms of epilepsy first present in the first few years of life. These early-life epilepsies (ELEs) are associated with drug-resistant seizures, developmental and cognitive disability, and dysregulation of other functions controlled by the nervous system including gross motor, fine motor, gastrointestinal, autonomic, sleep, and behavior [1]. They are also associated with a high risk of early mortality [2]. Most research emphasis and clinical guidelines focus on specific electroclinical syndromes such as West syndrome or infantile spasms (IS) and Dravet syndrome [3–8]; however, nearly half of very young children with ELE have nonsyndromic presentations, and their epilepsies are due to a wide variety of causes, each of which is extremely rare [9–12]. Evaluation, diagnosis, and treatment of ELE have changed substantially over the years with the introduction of high-resolution magnetic resonance imaging (MRI), genetic testing, and a variety of new therapeutic options [13]. There is relatively little information available concerning the seizure and developmental outcomes or mortality in the very young with epilepsy as it is currently diagnosed and treated. The most recent studies focused on patients diagnosed 10 to almost 40 years ago, many prior to modern MRI and all prior to the current availability of next generation sequencing (NGS) testing [9–11]. We sought to understand the initial outcomes in the full spectrum of ELE as they first present and are diagnosed and treated in a contemporary series of children prospectively recruited through US pediatric epilepsy centers. Such information can provide indications for areas to target for quality improvement and policy prioritization and provides an initial baseline for future interventions and comparisons.

2. Methods

2.1. Study design and eligibility

Data are from a prospectively identified and recruited cohort of infants and toddlers who were diagnosed for the first time with epilepsy when they presented at 17 US pediatric epilepsy centers (2012–2015). Epilepsy was defined and operationalized according to recent recommendations [14]: occurrence of two or more unprovoked seizures at least 24 h apart (consistent with the traditional criteria [15]), or the diagnosis of a specific epilepsy syndrome, or the occurrence of a single seizure (or cluster of seizures on a single day) with a high perceived risk of recurrence leading to initiation of treatment [14].

To be eligible, a child's first qualifying seizure had to occur before the third birthday. We targeted consecutive eligible children seen from March 2012 to April 2015, although different centers began recruiting at different times during this period. Information concerning evaluations, diagnoses, therapies, and outcomes was collected from medical records at the time of initial evaluation and up through one year after. With the exception of mortality, children had to have follow-up information covering at least the first six months after initial diagnosis to be included in the analyses of outcomes.

2.2. Prognostic factors

The primary clinical prognostic factors that we considered were the following:

a. Age at onset, which was generally considered the age at the first unprovoked seizure; however, this was applied more flexibly than previously under the traditional criteria [15] in light of certain syndromic criteria, particularly Dravet syndrome, which typically presents with a prolonged febrile seizure.

b. Underlying etiology was derived from all relevant sources including any history explanatory of the child's underlying etiology, neurological examination, neuroimaging findings, metabolic testing, and genetic testing. No specific diagnostic tests were required for inclusion in this observational study, and all evaluations were performed at the discretion of the epilepsy provider according to what was deemed clinically appropriate. The use and yield of genetic testing and of neuroimaging in this cohort have been previously reported in detail [16,17]. For these analyses, we included etiology based on all information known prior to or revealed as a result of the initial diagnostic evaluations, even if it took some time for the results to be returned to the physician. Further evaluations performed during the course of follow-up revealed etiologies in additional patients; however, such investigations were usually done *in response* to poor clinical outcomes. As our goal was to predict clinical outcomes based on initial evaluations, etiologies identified as a result of testing initiated after the initial diagnostic evaluation are not studied as prognostic of outcome in these analyses.

c. Seizure types and epilepsy type/syndrome followed recommendations at the time [18] and captured both the type of seizures and whether focality was present. Electroclinical syndromic diagnoses followed recognized criteria [19,20]. Diagnoses as made by the treating provider were used after being centrally reviewed and returned for clarification when necessary. Epilepsies that did not fit a clear electroclinical pattern were categorized according to presentation (focal, generalized, mixed/unclear) and whether or not an underlying cause had been found.

d. Initial developmental status was categorized as typical, mild–equivocal delays (including isolated speech delay) versus definite (moderate to severe) delay. This information was taken from the treating neurologists' characterization based on the initial neurodevelopmental examination.

Because we used the new criteria for epilepsy [14], there were children who, in earlier studies, would not have qualified as having newly diagnosed epilepsy. We considered the extent to which their inclusion may have influenced our results.

Over the course of a year following the initial diagnostic evaluation, children were followed through their medical records. There was ongoing review of incoming data; questions were returned to research coordinators and physician-investigators at each site to clarify, correct, or supply additional information.

2.3. Outcomes

We considered five outcomes: (1) Mortality was recorded if reported to the treating epilepsy center. (2) Drug resistance was operationalized consistent with international

recommendations [21], failure of two appropriate antiseizure medications used in adequate trials to bring seizures fully under control. (3) Evolution from nonsyndromic epilepsy to IS was determined based on the seizure type occurring after the initial diagnosis of epilepsy and entry into the study. Hypsarrhythmia was not an obligatory criterion as this is not required for the diagnosis of IS and is not part of the guidelines for treatment [7]. (4) Appearance of new seizure types in children who initially presented with a diagnosis of IS. (5) Developmental decline was determined based upon a comparison of the initial designation of developmental status and the 12-month designation. Worsening from within normal or mild–equivocal delay to definite (moderate or severe) delay was considered a decline.

2.4. Data management and analysis

Data were maintained in a centralized REDCap© [22] database at Northwestern University. Analyses were performed in Statistical Analysis Systems (SAS) 9.4©. Techniques included standard univariate and bivariate methods for descriptive analysis and assessment of bivariate associations. For multivariable analyses, we employed a generalized linear mixed model approach in Proc GLIMMIX and adjusted for site as a random variable. Rather than modeling odd ratios, we modeled the absolute risk for developing the outcome of interest. This allows one to estimate the absolute probability that a child will experience an outcome based on the combination of risk factors present. In determining which variables to keep in the model, we referred to the p-values (with <0.05 as a minimal criterion of statistical significance); 95% confidence intervals (CI) are presented for all estimates. For parsimony across multivariable models, age was ultimately collapsed to <1 versus ≥ 1 year, and mild/equivocal delays were combined with typical development (with the exception of worsening development). In no case did these adjustments obscure statistically significant effects.

2.5. Informed consent

Parents were approached at the time of initial diagnostic visit or shortly thereafter and invited to participate. An informed consent process was followed and documented by a signed informed consent form as required by each clinical site. All procedures were approved by the IRB of Ann & Robert H Lurie Children’s Hospital of Chicago and each of the participating hospital centers.

3. Results

3.1. Cohort characteristics

A total of 775 children were recruited from the 17 centers, which contributed between 4 and 131 patients each (median of 33 patients). There were slightly more boys (408, 53%) than girls (367, 47%). The mean age at onset was 11.1 months (standard deviation (SD) = 9.4); however, the median age was 7.5 months (interquartile range (IQR): 4.2 to 16.5) with 509 (66%) having their first seizures in the first, 151 (20%) in the second, and 115 (15%) in the third year of life.

In the total cohort, etiologies were identified in 333 (43%) children based upon initial diagnostic evaluations. These were grouped as follows: brain malformations (N = 107,

14%), neurocutaneous disorders (N = 32, 4.1%), acquired injuries (N = 94, 12.1%), metabolic diseases (N = 15, 1.9%), other genetic disorders (N = 66, 8.5%), and other disorders (N = 19 2.5%).

The initial type of epilepsy was grouped as IS (N = 231, 29.8%), other specific electroclinical syndromes (N = 49, 6.3%), and nonsyndromic epilepsy (N = 495, 63.9%). In the nonsyndromic group, the overall presentation was focal in 261, generalized in 148, and mixed or undetermined in 86.

Information about developmental status was missing for 14 children. In the other 761, moderate to severe developmental delay was present at initial evaluation in 272 (35.7%). Mild or equivocal delays were noted in 118 (15.5%), and development was considered within normal limits for 371 (47.8%) children.

Traditional criteria for epilepsy (2 unprovoked seizures separated by at least 24 h) were not met in 101 (13%) of patients. These children were included having met the new criteria including a flurry of seizures on a single day (N = 62) or a single seizure with perceived high risk of further seizures (N = 27), febrile seizures (some with diagnostic suspicion of Dravet syndrome, N = 9), and other circumstances (N = 7).

3.2. Mortality

During the one year of observation, there were 22 (2.9%) deaths in the cohort. These occurred at a median of 161 days (IQR: 92 to 237) after diagnosis, and 14 occurred within the first six months. Deaths occurred in 21 children with onset of epilepsy in the first year of life. Underlying etiologies in children who died included neurometabolic conditions (Leigh N = 3, Zellweger, N = 2, other N = 1), Walker–Warburg syndrome (N = 1), other brain malformations (N = 6), other genetic (N = 3), and other individual factors (N = 5). One of the deaths involved a child who was developmentally delayed and did not have an identified etiology for the epilepsy. No deaths occurred in children with unknown etiology and who were developing normally at the time of initial evaluation. Specific causes of death were not available.

3.3. Six-month follow-up

Overall, 680 (88.4%) children were followed for at least 6 months and constitute the group for whom the other clinical outcomes were studied. With the exception of a slightly greater loss to follow-up in older children, the distribution of clinical factors described above did not differ significantly between the full and followed cohorts (Supplemental Table 1). These factors were strongly intercorrelated (Table 1). Age at onset was strongly correlated with the type of epilepsy, development, and identification of the underlying etiology. Type of epilepsy was further correlated with development and etiology, and etiology and development were strongly correlated with each other.

3.4. Drug resistance

Overall, 239/680 (35%) of the cohort followed ≥6 months met criteria for drug-resistant seizures in the year after epilepsy diagnosis. Drug resistance was associated with onset <1

year (181/452, 40%) versus ≥1 year (58/228, 25%) (p = 0.0007), identified (123/292, 42%) versus unknown (116/338, 30%) etiology (p = 0.0009), and developmental delay (119/246, 50%) versus mild delay (33/107, 31%) or no delay (85/328, 26%) at initial evaluation (p = 0.0001) (Supplemental Table 2). Drug resistance was marginally associated with type of epilepsy (IS, 83/210 (40%) versus nonsyndromic epilepsy, 137/427 (32%) and other, 19/43 (44%), p = 0.08). The new versus traditional criteria for epilepsy did not greatly influence risk of drug resistance overall.

In a multivariable analysis (Table 2A), only age at onset and developmental delay were independently predictive of drug resistance. The lowest risk group identified by this model was for children who were typically developing and ≥1 year at onset of epilepsy, 21% (CI: 14% to 27%). The risk of drug resistance was greater by 12% (CI: 4%–19%) for infants and by 21% (CI: 14%–29%) for those with moderate to severe developmental delay. Predicted risks of drug resistance could thus be estimated from this model as 21% in the referent group (≥1 year and not developmentally delayed). The presence of developmental delay would increase the risk by 21% to 42%; onset in the first year would increase the risk by 12% to 33%. A developmentally delayed infant would thus have an estimated risk of 54% (21% + 21% + 12%).

In infants only (onset <1 year, Table 2B), type of epilepsy, developmental delay, and traditional versus new criteria for epilepsy were independent predictors of drug resistance. Those who did not present with IS did not have clear developmental delay, and who met the traditional criteria for epilepsy had an estimated risk of drug resistance of 38% (CI: 31%, 46%). Developmental delay was associated with an additional 23% (CI: 14%, 33%) increased risk of drug resistance. Children with IS had a risk that was 10% less (CI: −20%, −1%), however, than children with nonsyndromic epilepsy and other syndromes. Further, children who were included under the new criteria for epilepsy also had a risk of drug resistance that was 17% less (CI: −25%, −10%) than those who met traditional criteria. In children ≥1 year at onset (Table 2C), only developmental delay was correlated with a greater risk of drug resistance (23% if not delayed and 43% if delayed, p = 0.0009).

3.5. Evolution from nonsyndromic epilepsy to infantile spasms

A total of 38 children developed IS after the initial onset of epilepsy including 34/227 (15%) infants who initially presented with nonsyndromic epilepsy. Three others were older than 1 year, and one infant evolved from early myoclonic encephalopathy. We focused on evolution to IS in infants with nonsyndromic epilepsy (Supplemental Table 3). Age at onset of nonsyndromic epilepsy within the first year of life was associated with the likelihood of evolution to IS. The observed risk ranged from 21% (<3 months at onset), 18% (3–5 months), 10% (6–8 months), to 0% (9–11 months, p = 0.004 for trend). Developmental delay at initial diagnosis and identified etiology were each modestly predictive of evolution to IS. Notably, none of 7 children with hypoxic ischemic encephalography (HIE) and only 1/11 with intraventricular hemorrhage (IVH)/periventricular leukomalacia (PVL) evolved to have spasms.

On multivariable analysis (Table 3), developmental delay and age at onset remained significant correlates of evolution to IS. In the referent group (age 0–2 months and no or

only mild/equivocal delay), the predicted risk was 19% (CI: 11%, 27%). Developmental delay was associated with an increase in the risk by 15% (CI: 5%, 25%) of evolution to IS. The risk decreased an estimated −7% (CI: −11%, −2%) with each increment in 3-month age group (from 0–2 to 9–11). Children with the highest predicted risk (~34%) had epilepsy onset at 0–2 months and presented with developmental delays.

3.6. New seizure types emerging after initial presentation with infantile spasms

New seizure types developed in 48/210 (23%) children who initially presented with IS. This included 46/197 (23%) children with initial spasms onset in infancy and 2/13 (15%) with older onset. Children who were developmentally delayed at initial diagnosis were more likely to develop new seizure types than those who had mild/equivocal delays or who were considered to have typical development (37/120 (31%) vs. 11/89 (12%), $p = 0.007$, Supplemental Table 4). Overall, the presence of an identified etiology was only modestly associated with the risk of new seizure types evolving ($p = 0.04$). On multivariable analysis, only developmental delay was associated with the likelihood of developing new seizure types, 13% if not delayed and 31% if delayed ($p = 0.002$, Table 4).

3.7. Developmental delay appearing after initial diagnosis

Of 435 children noted to have typical development or only mild–equivocal delays at initial epilepsy diagnosis, 100 (23%) had definite delays newly recognized during the first year of follow-up. Children considered to have equivocal or mild delays at initial evaluation were more likely to have moderate to severe delays after a year than children with initially typical development (38% vs. 18%, $p < 0.0001$). Other factors associated with decline in development were onset in infancy, an identified etiology, initial epilepsy type, and drug resistance (Supplemental Table 5).

In the multivariable analysis (Table 5), independent predictors of developmental decline included onset in infancy, identified etiology, evidence of mild or equivocal delay, and the impact of drug resistance with onset in infancy (but not onset ≥1 year). Having qualified for the study under the new epilepsy criteria [14] was also associated with a modest but significant *additional* risk of +14% ($p = 0.009$). Adjusted for these other factors, IS were not associated with developmental decline. Using the estimates from the model, we can identify a group with a very low risk of developmental decline; children with onset after infancy, who were typically developing initially, had no identified etiology, who did not have drug-resistant seizures, and who met the traditional criteria for epilepsy. Of the 72 in the group defined by these features, only two experienced developmental decline.

At the other extreme, the profile of children with the highest risk were those with onset in the first year of life, mild or equivocal delay at initial evaluation, an identified etiology and drug-resistant seizures, and who did not meet the traditional criteria for epilepsy. The estimated risk of developmental decline for this profile was 91%. This is a theoretical estimate, however; no child actually had all of these features.

4. Discussion

Our data, from a contemporary cohort evaluated and treated for the most part consistent with current recommendations for neuroimaging [23], increased use of genetic testing [24], and treatment of IS [4,7], demonstrate the continued poor outcomes for the ELEs. A third developed drug resistance, highly similar to the proportion reported by others previously [10,11]. Drug-resistant seizures, developmental impairment, and further developmental declines as well as significant risk of increased mortality, and a host of other morbidities remain common. The most recent studies prior to ours highlight the high risk of drug resistance and developmental impairment [10,11]. Our sobering findings suggest that there has been no major changes in the general outlook for these ELEs, which are especially challenging [2,6,9–13]. Currently, there are few evidence-based guidelines or recommendations for the evaluation and treatment of these serious disorders. Most focus on IS [3,4,7] or Dravet syndrome [8]. Yet, about half with onset in infancy and over half with onset ≥1 year, even after evaluation by a pediatric epileptologist, had epilepsies that did not conform to defined electroclinical syndrome criteria; they are nonsyndromic. There remain major knowledge gaps in multiple domains of diagnosis and treatment for ELE; most patients are treated without evidence-based or even consensus-based guidelines.

In this series, onset in the first year of life had a more serious prognosis than onset in the second and third years for all outcomes but most especially early mortality. Several of the deaths we ascertained occurred in association with neurometabolic conditions. Although we did not have access to the cause of death, a previous analysis based on four independent studies demonstrated that most deaths in children with these epilepsies are rarely secondary to seizures but rather to infections or the consequences of the underlying disease [25]. Seizure-related mortality including from sudden unexpected death in epilepsy (SUDEP), while it does occur, manifests itself over the broader age range of people living with epilepsy.

Our findings highlight that the poor seizure and developmental outcomes are as pressing in nonsyndromic epilepsies as they are in IS. Epilepsy onset in the first year of life was associated with a greater risk of drug resistance, evolution from nonsyndromic epilepsy to IS, and developmental decline. Importantly, infancy is when IS, Dravet syndrome, and other extremely rare developmental encephalopathies with epilepsy arise. These well-known syndromes, however, accounted for only about half of all epilepsy in infants, and outcomes in infantile-onset nonsyndromic epilepsy were not substantially different than for other syndromes. Epilepsy with onset in the first year of life should always be viewed as a high-risk situation until proven otherwise [26].

Development is already impaired in many children at initial epilepsy presentation, largely in association with underlying causes of their seizures. There is a literature, however, demonstrating developmental declines in the very young in association with poorly controlled seizures [27–29]. Consequently, our finding of a strong effect on development of drug resistance in infants, even with our very short-term follow-up and crude measures of developmental decline, is in line with current understanding of the impact of early life seizures on the developing brain.

There are some important limitations to our study. First, it is not population-based, and data are subject to selection bias given all participating sites are epilepsy specialist centers. We attempted to protect against referral bias by including only children with newly presenting epilepsy that was newly diagnosed at the participating centers (and not referrals for second opinions or specialist care). Our general findings (proportion under 1 year versus 1–2 years, proportion with identified etiologies, mortality risk, and overall proportion pharmacoresistant) are consistent with what has been described in other cohorts recently [9–11]. On the other hand, the evaluations and treatments received in these centers could potentially have reflected a higher adherence to the few available guidelines than what might be seen in population-based studies in which treatment may be provided by less specialized clinicians. In that context, it is notable that children in our study with IS had slightly better seizure outcomes, in the short term, than those with nonsyndromic epilepsies. Possible explanation is the increased standardization of IS treatment approaches with current optimal therapies reaching affected children [3,4,7]. By contrast, no clear guidelines have been promulgated in the US that would help to standardize the approach to children with nonsyndromic epilepsy. The National Center for Clinical Excellence guidelines for epilepsy care in the UK represent an important step yet to be taken in the US [30].

Our follow-up period was limited to 12 months, allowing assessment only of the immediate responses and outcomes. In the extremely severe ELEs, drug resistance tends to declare itself very early [10,31]. Developmental delays also become apparent over a longer period of time than we captured. Our measures of development were relatively crude, a clinician's assessment based on routine neurological examination. Nonetheless, these are assessments that pediatric neurologists are specifically trained to make, and they may reflect the tip of a much larger iceberg of cognitive deficits to come.

A handful of children had other electroclinical syndromes which we could not individually evaluate as there were typically only a few in each category (see Supplemental Table 1). To understand in depth these very rare disorders, different study designs are required. In the era of ubiquitous electronic health records, leveraging documentation from large multicenter associations in a learning healthcare system may provide novel opportunities to rapidly identify children with such rare diseases to invite them to participate in clinical research.

There are also some unique aspects to our study that add important new information to the literature. Specifically, we included some outcomes that are infrequently addressed such as the evolution to IS and the development of new seizure types in children who initially presented with spasms. Evolution to IS from nonsyndromic epilepsy is especially important to those who might benefit from early interventions to prevent spasms from occurring in the first place [32]. Our model was able to distinguish children with virtually little to no risk for subsequent IS (older infants without developmental delay) from those whose risk was roughly 1/3 (the youngest infants with developmental delays). Lastly, we are unaware of any evaluations of the new criteria for epilepsy which include more patients than the traditional criteria (two unprovoked seizures on separate days). With minor and not especially robust exceptions, we did not find evidence that the use of the new criteria altered the assessment of outcomes for children with new-onset ELE. We note that children included under the new criteria were more likely to decline in development than those who met the traditional

criteria. Their inclusion by their treating neurologists may reflect clinical concerns about the patient that were not reflected in the variables that we studied. Our findings support the extension of the new criteria of epilepsy to infants and toddlers with single seizures and other risk factors.

Overall, our findings demonstrate the distinctly guarded prognosis for infants and toddlers with new-onset epilepsy. Younger age at onset and developmental concerns at the outset remain red flags for poor prognosis. Given our findings that the short-term outcomes of IS and nonsyndromic epilepsies are not markedly different, it is critical to emphasize the seriousness of all new-onset seizures in the very young, not just those that fit a well-defined syndrome. All ELEs potentially pose serious risks and are equally deserving of concerted efforts. There is an urgent need for rigorous studies designed to establish an evidence base for standard clinical care with a goal of optimizing these critical early outcomes [26].

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Declaration of Competing Interest

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He is part of patent applications to detect and predict seizures and to diagnose epilepsy. Dr. Loddenkemper is coinventor of the TriVox Health technology, and Dr. Loddenkemper, and Boston Children's Hospital might receive financial benefits from this technology in the form of compensation in the future. He received research support from the Epilepsy Research Fund, NIH, the Epilepsy Foundation of America, the Epilepsy Therapy Project, the Pediatric Epilepsy Research Foundation, and received research grants from Lundbeck, Eisai, Upsher-Smith, Mallinckrodt,

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Dr. Coryell, Dr. Gaillard, Dr. Keator, Dr. Massey, Dr. Valencia, and **Dr. Wusthoff** report nothing to disclose.

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Table 1

Distributions and associations among the primary clinical factors at the time of initial diagnosis for the primary analytic sample (N = 680).

	Epilepsy type			Development			Etiology	
	Infantile spasms	**Other**	**NSE**	**Within normal**	**Mild/equivocal delay**	**Delayed**	**None identified**	**Identified**
Age at onset (years)								
<1 (452)	197 (44%)	28 (6%)	227 (50%)	201 (45%)	68 (15%)	177 (40%)	221 (49%)	231 (51%)
1 (136)	11 (8%)	5 (4%)	120 (88%)	62 (46%)	29 (22%)	43 (32%)	92 (68%)	44(32%)
2 (92)	2 (2%)	10 (11%)	80 (87%)	65 (71%)	10 (11%)	17 (18%)	75 (82%)	17 (18%)
p-Value	<0.0001 *			<0.0001 *			<0.0001 *	
Epilepsy type								
Infantile spasms (210)				53 (25%)	36 (17%)	120 (57%)	83 (40%)	127 (60%)
Other ** (43)				29 (69%)	5 (12%)	8 (19%)	30 (70%)	13 (30%)
NSE ** (427)				246 (58%)	66 (16%)	109 (26%)	275 (64%)	152 (36%)
p-Value				<0.0001 *			<0.0001	
Development ***								
Within normal (328)							260 (79%)	68 (21%)
Mild/equivocal delay (107)							61 (57%)	46 (43%)
Delayed (237)							63 (27%)	174 (73%)
p-Value							<0.0001 *	

* p-Value was <0.0001 for the full table on 2 or 4 degrees of freedom as well as for the Mantel–Hansel chi-square test for trend.

** Other = Other electroclinical syndrome; NSE = nonsyndromic epilepsy.

*** 8 children were missing information about development at the time of initial epilepsy evaluation.

Table 2

Multivariable model of risk of drug resistance.

	Risk	95% CI	p-Value
A. Overall			
Referent group[a]: age ≥1 year and no definite developmental delay	0.21	0.14, 0.27	<0.0001
Under 1 year	0.12	0.04, 0.19	0.002
Developmental delay	0.21	0.14, 0.29	<0.0001
Risk equation: estimated risk = 0.21 + 0.12 (if < 1 year) + 0.21 (if developmentally delayed)			
B. <1 year at onset of epilepsy			
Referent group[a]: NSE or other[c] syndrome, no definite developmental delay[b], standard criteria for epilepsy	0.38	0.31, 0.46	<0.0001
Infantile spasms	−0.10	−0.20, −0.01	0.04
Developmental delay	0.23	0.14, 0.33	<0.0001
Nonstandard criteria	−0.17	−0.25, −0.10	0.03
Risk equation: estimated risk = 0.38–0.10 (if infantile spasms) + 0.23 (if delayed) − 0.17 (if nonstandard criteria)			
C. ≥1 year at onset of epilepsy			
Referent group[a]: no definite developmental delay	0.20	0.13, 0.26	<0.0001
Developmental delay	0.23	0.09, 0.34	0.0009
Risk equation: estimated risk = 0.20 + 0.23 (if delayed)			

[a]Other = Other electroclinical syndrome; NSE = nonsyndromic epilepsy.

[b]11 children followed 6+ months were missing information about development at the time of initial epilepsy evaluation.

[c]Referent group if the group identified by the null value of each of the variables retained in the model. Results are adjusted for site as a random variable.

Table 3

Clinical correlates of evolution to infantile spasms in infants initially presenting with nonsyndromic forms of epilepsy (N = 227).

B. Multivariable model for evolution to spasms from a nonsyndromic epilepsy presentation in infants			
	Risk	**95% CI**	**p-Value**
Referent group: not delayed, age <3 months	0.19	0.11,0.27	0.003
Developmental delay	0.15	0.05, 0.25	0.004
Age at onset (per 3-month increment in age)	− 0.07	−0.11, −0.02	0.004

Risk equation: estimated risk = 0.19 + 0.15 (if delayed) − 0.07 (for each 3-month increment in age above 0–2 month category).

Table 4

Clinical correlates of developing new seizure types arising in children initially presenting with infantile spasms (N = 210).

Multivariable model for risk of developing new seizure type in children who initially presented with spasms			
	Risk	**95% CI**	**p-Value**
Reference group: no definite developmental delay	0.13	0.04, 0.22	0.002
Developmental delay	0.18	0.07, 0.29	0.002

Risk equation: estimated risk = 0.13 + 0.18 (if delayed).

Table 5

Factors predictive of developmental delay during the year after the diagnosis of epilepsy in children considered within typical limits or having only equivocal or mild delays initially (N = 435).

B. Multivariable model for developmental decline			
	Risk	**95% CI**	**p-Value**
Reference group: unknown etiology, development typical, not pharmacoresistant, onset ≥ 1 year	0.01	0, 0.09	0.88
Known etiology	0.19	0.11,0.27	<0.0001
Mild delay	0.14	0.06, 0.23	0.0006
Drug-resistant[a]	0.06	−0.08, 0.20	0.37
< 1 year at seizure onset[a]	0.08	0.00, 0.17	0.05
Interaction between age and pharmacoresistance[a]	0.29	0.12,0.46	0.0008
Nonstandard criteria	0.14	0.04, 0.24	0.009

Risk equation: estimated risk = 0.01 + 0.19 (if known etiology) + 0.14 (if mild delay) + 0.06 (if drug resistant) + 0.08 (if <1 year at onset) + 0.29 (if <1 year AND drug resistant) + 0.14 (if nonstandard criteria).

[a]The term for pharmacoresistance represents the effect in children ≥1 year, that for <1 year represents the risk in children under a year who are not pharmacoresistant. The Interaction between the two represents the impact in children under a year and who have pharmacoresistant seizures. Note that nonsignificant terms must be retained because of their “interaction” term, which is significant.