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Evolution and course of early life developmental encephalopathic epilepsies: Focus on Lennox-Gastaut Syndrome.

Anne T. Berg, PhD^{1,2}, Susan R. Levy, MD^{3,4}, and Francine M. Testa, MD^{3,4}

¹Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, Illinois

²Department of Pediatrics, Northwestern-Feinberg School of Medicine, Chicago, Illinois

³Department of Pediatrics, Yale School of Medicine, New Haven, CT

⁴Department of Neurology, Yale School of Medicine, New Haven, CT

Abstract

Objectives: Developmental encephalopathic epilepsies (DEE) are characterized by refractory seizures, disability, and early death. Opportunities to improve care and outcomes focus on West Syndrome/infantile spasms (WS/IS). Lennox-Gastaut syndrome (LGS) is almost as common but receives little attention. We examined initial presentations of DEEs and their evolution over time to identify risk and indicators of developing LGS.

Methods: Data are from the Connecticut Study of Epilepsy, a prospective, longitudinal study of 613 children with newly-diagnosed epilepsy recruited in 1993–1997. Central review of medical records permitted classification of epilepsy syndromes at diagnosis and reclassification 2, 5, and 9 years later. DEEs were compared to other epilepsies for seizure and cognitive outcomes, and mortality. Analyses examined the evolution of DEE syndromes after initial presentation with specific comparisons made between WS/IS and LGS. Statistical analyses were performed with t-tests and chi-squares.

Results: Fifty-eight (9.4%) had DEEs, median onset age=1.1y (interquartile range (IQR)= 0.3, 1.3) in DEEs and 6.0y (IQR=3.0, 9.0) in other epilepsies ($p<0.001$). DEEs versus other epilepsies had more pharmacoresistance (71% versus 18%), intellectual disability (84% versus 11%), and mortality (21% versus <1%; all $p<0.001$). During follow-up, the form of epilepsy evolved in 33 children. WS/IS was the most common initial diagnosis ($N=23$) and 5 children later evolved to WS/IS. LGS was diagnosed initially in 4 children (1 later revised) and in 22 by the end of follow-up, including 7 evolving from WS/IS and 12 from nonsyndromic generalized, focal or

Correspondence to: Anne T. Berg, Ph.D., Epilepsy Center, Mail stop 29, Ann & Robert H. Lurie Children's Hospital of Chicago, 225 East Chicago Avenue, Box 29, Chicago, Illinois 60611-2605, Phone: 312.227.4542, Fax: 312.227.9644, atberg@luriechildrens.org.

Ethics Affirmation:

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

Disclosure and conflicts of interest.

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undetermined epilepsies. Evolution to LGS took a median of 1.9 years. LGS developed in 13% of infants, including 9% of those who did not initially present with WS/IS.

Significance: DEEs account for disproportionate amounts of pharmacoresistance, disability, and early mortality. LGS often has a window between initial presentation and full expression. LGS, should become targeted for early detection and prevention.

Keywords

Prognosis; Prevention; West Syndrome; Infantile Spasms

The first few years of life represent an especially active time in the developing brain and a period when the incidence of new-onset epilepsy is particularly high. It is also the time when some of the most devastating forms of epilepsy, “early life epilepsies” or ELE, first arise.^{1, 2} Seizures associated with these epilepsies are often refractory to multiple trials of pharmacological therapy, surgery or diet. They often persist into adulthood, and affected individuals are typically developmentally and intellectually disabled. There is an increased emphasis on early diagnosis and the potential for early interventions that could ameliorate the course of some of these diseases.^{3–6} Few data, however, are available to describe the evolution of these individual disorders from initial onset of epilepsy and their long-term seizure and cognitive outcomes, and mortality. A Canadian study demonstrated the poor long-term outcomes in this group with 24% mortality in the first 2–3 decades of life and refractory seizures and disability in the majority of the remainder.⁷

West syndrome/infantile spasms (WS/IS), the most common of the severe epilepsies that occur in early life, has been the focus of considerable research,^{8–10} interventional studies,^{11–13} quality metrics,¹⁴ guidelines and recommendations,^{15, 16} and an awareness campaign by the Child Neurology Foundation.³ Although West Syndrome is defined by developmental delay, epileptic spasms, and hypsarrhythmia on the EEG,^{17, 18} the epileptic spasms are the focus of diagnostic and therapy recommendation because hypsarrhythmia may not be present and development may initially be normal. In fact, much of the work on WS/IS emphasizes the importance of early recognition and optimum treatment to lessen impact of the underlying “epileptic encephalopathy”^{19, 20} on the child’s development.

LGS, by contrast, has not received similar attention although it affects almost as many children in the population as WS/IS.^{7, 21} LGS is typically first diagnosed between the ages of 2–5 years. Criteria include cognitive impairment, slow spike and wave, multifocal spikes or both on the EEG, and multiple seizure types almost always including tonic seizures but also including myoclonic, atypical, absence, atonic, and tonic-clonic seizures. Unlike with spasms, there is no definition of LGS that does not include developmental impairment. Both LGS and WS/IS arise from many different etiologies, and the disordered EEG signatures and refractory seizures seem to meet the definition of true epileptic encephalopathy in which the developmental and cognitive disability are thought to arise, at least in part, from disruption of developmental process as a result of seizures and dysregulated brain activity.^{19, 20} Further, there is a link between these two syndromes as some children with WS/IS subsequently develop LGS. A better understanding of the natural history of LGS and the timing of when

the features of the syndrome become apparent could allow identification of at risk infants and young children and facilitate the development of future pre-emptive early interventions.

Here we focus on children in the Connecticut Study of Epilepsy who, either at the time of initial presentation with epilepsy or over the course of time from initial presentation, were diagnosed with a form of developmental encephalopathic epilepsy (DEE). The initial presentation and the evolution of these conditions, the underlying etiologies -as understood in the 1990s – and the presentations over time are described with an emphasis on potential opportunities for early identification of infants and children at risk of developing LGS.

Methods:

The Connecticut Study of Epilepsy (CSE) was a prospective, community-based study of children with newly diagnosed epilepsy recruited at the time of initial diagnosis and systematically followed forward for 20 years. Details of the study methods have been published previously^{22–24} and are described here briefly. The initial diagnosis of epilepsy was made by the referring neurologists (16 of 17 practicing in the State during this time participated). Parents participated in initial baseline interviews. Medical records were reviewed by three pediatric epileptologists based on information collected as part of the initial diagnostic evaluation, and then accumulated through 2, 5, and 9 years after diagnosis.²⁴ We used the ILAE classification of the Epilepsies from 1989²⁵ with specific criteria for epilepsy syndromes as described in Roger et al.¹⁸ We consider most syndromes and types of epilepsies from the 1989 classification report²⁵ that were included under the headings of “cryptogenic” or “symptomatic” generalized epilepsies (the terms used at the time) as DEEs. In the 1989 classification, Doose syndrome (myoclonic astatic -or atonic - epilepsy, MAE) and myoclonic absence epilepsy were considered “generalized cryptogenic;” however, opinions vary somewhat and they are now considered part of the generalized “idiopathic” or genetic epilepsy spectrum.¹⁷ Consequently, we did not include either in the DEE group. Specific syndromes, particularly, Dravet and Landau-Kleffner, both of which were placed in the category for “undetermined with both focal and generalized features” were also considered DEEs.

Reasons for changes in epilepsy diagnosis were characterized and included evolution of the epilepsy based on seizure types and EEG findings as well as new results that clarified a diagnosis. The date of the change was estimated from key EEG reports obtained from the medical records and reports of new seizure types. All information was reviewed centrally by the study investigators.

Follow-up was conducted by calling parents every 3–4 months and reviewing seizure occurrence and medication changes. Additional longer interviews and assessments were conducted in the cohort at 5 and 9 years after entering the study and at study closure in 2014. Throughout the study, there was on-going review of all neurological medical records approximately every six months. Cognitive/developmental levels were ascertained from parent-report, administration of the Vineland Adaptive Behavior Scales yearly through five years of age, medical records, school system evaluations when they were included in the medical record, and for those who were able, the Wechsler Intelligence Scales for Children

conducted for research purposes approximately 9 years after study entry were all used to assign a level of cognitive function to each child,²⁶ which we ultimately dichotomized into clear intellectual disability (consistent with an IQ less than 60) versus mild, borderline, or no ID (consistent with full-scale IQ ≥ 60). Remissions and relapses were recorded by the PI based upon parent report of seizure dates and review of the medical records. At the 9-year medical record summary review, the number of seizure days, seizures, and longest time seizure-free during each year of follow-up were also summarized. This information was used to assign levels of seizure occurrence for each of the first 9 years of follow-up: seizure-free (no seizure days), 1–10 seizure days/year, 11–50/year, 51–300/year, and more than 300 seizure/year. If follow-up was terminated during a year, the number of seizure-days was prorated for the time for which a child was followed that year. Medications and doses were reported by the parents and verified in the medical records. Seizures were considered pharmacoresistant if two trials of therapy had failed to control seizures fully. A treatment trial was considered a failure if a drug (a) exacerbated seizures or (b) failed to bring seizures under complete control for a minimum of 1 year provided the drug was given an adequate trial. An adequate trial meant that the drug was appropriate for the type of epilepsy and seizures; that it was used as directed with good adherence; and that the dose was escalated past the initial target dose to the point of provoking dose-related side-effects or the clinical decision was made of inefficacy for controlling seizures.²⁷ Pharmacoresistance at last contact required that the child meet the criteria for pharmacoresistance (2 treatment failures) and have seizures in the last year of follow-up.

Analyses were performed in SAS ©. Statistical tests for bivariate analyses of dichotomous, polychotomous, and ordered categorical variables were performed with Chi2-tests and Mantel-Hanzel Chi2-tests for trend. T-test and ANOVAs or their nonparametric counterparts when necessary were used for comparing means of continuously distributed variables across groups.

Consent and assent:

Initially, parents provided written informed permission for their children to participate in the study and children provided verbal assent if old enough and able to do so. As children attained the age of majority, those who were able, were recruited as adults. For those under guardianship, parental consent was accepted. All procedures were approved by the relevant institutional IRBs at the time and data analyses continue under the auspices of the Ann & Robert H Lurie Children's Hospital IRB.

Results:

From 1993 to 1997, we recruited 613 children into the original cohort. Of these, 300 (49%) were girls, and the mean age at onset was 5.8 years (SD= 4.0).

Fifty-eight (9.5%) children met criteria for a developmental encephalopathic epilepsy either at initial diagnosis or over the course of the study.

DEE compared to other childhood epilepsies:

Median follow-up duration was 17 years in the non-DEE group and 16 in the DEE group. Within the DEE subgroup, only 3 children, including two who died, were followed for less than 2 years. Overall, 13 children in the DEE subgroup were followed less than 5 years; in 10, this was due to early death.

Age at epilepsy onset was substantially younger in DEE versus other epilepsies and outcomes substantially worse (Table 1, Figure 1). A higher proportion of DEE versus other epilepsies met criteria for pharmacoresistance and were pharmacoresistant at last contact; a smaller proportion was in 5-year remission off medications at the end of follow-up. Intellectual disability was much more common in the DEE group overall. This held when the comparison was limited to children with onset in infancy.

Developmental Encephalopathic Epilepsies:

Etiology:

In the DEE group, all but two children had some form of neuroimaging either initially or later in follow-up. These included CT scan only (N=3), an MRI done for clinical purposes (N=46), and a research MRI (N=7).²⁸ Of the two without any imaging, one had Down syndrome and the other had an abnormal neurological and developmental exam without any specific cause identified. Sanger sequencing tests were not routinely available during the mid-1990s, and next generation sequencing panels were not routinely available until near the end of the follow-up period of the study. Consequently, such testing was not used to identify etiology.

An underlying etiology was identified in 30 (52%) children with DEE. Etiologies were characterized as intracranial infection (N=2), hypoxic-ischemic encephalopathy or intraventricular hemorrhage (N=5), hypoglycemic encephalopathy (N=1), chromosomal-genetic syndromes (N=5, including Down (2) Angelman (1), Rett (1) Dubowitz (1) syndromes), malformations of cortical development (N=7, including 2 lissencephaly, 2 pachygyria, 1 focal cortical dysplasia, 1 heterotopia, and 1 holoprosencephaly), neurocutaneous syndromes (N=5 including 3 tuberous sclerosis complex, 2 neurofibromatosis), and neurometabolic diseases (N=5, including 2 Menkes syndrome, 1 Batten disease, 1 complex IV deficiency and 1 presumed metabolic disease that was not fully diagnosed). Of the 28 children with no identifiable etiology, 23 (40% of the total DEE group) had unremarkable neurological examinations and were developing typically for age at the time of the initial diagnosis of epilepsy.

Types of Epilepsy:

Based upon the initial evaluation for epilepsy, syndromes and types of epilepsy were classified as WS/IS (N=23), LGS (N=4), other specific syndromes (N=4, 1 each Doose, Dravet, Othahara, ESES), and nonsyndromic epilepsies (N=27, including 11 focal, 10 generalized, and 6 undetermined).

By the end of the study, these numbers were WS/IS (N=9), LGS (N=22), other specific syndromes (N=5), and nonsyndromic epilepsies (N=22, including 8 focal and 14 generalized) (Figure 2). Over time, there were no changes to the initial syndromic epilepsy diagnosis for 21 of the children (1 each of Dravet, Ohtahara, and ESES), 6 with nonsyndromic generalized presentations, 3 with LGS and 9 with WS/IS. In this last group, 2 children (1 of whom died) were lost to follow-up very early while the others were in complete remission at the end of the study. In four children, a revision to the initial diagnoses was made. One child initially assigned to Doose syndrome was reassigned the diagnosis of LGS. The initial diagnosis of Doose syndrome was uncertain, and the child's clinical picture was equally consistent with a nonsyndromic generalized form of epilepsy which then evolved into LGS. Another child initially assigned a diagnosis of LGS based on the seizure types and EEG was removed from that category because the early course was extremely atypical for LGS. The child responded to treatment rapidly, and seizures completely resolved within 6 months of diagnosis until death four years later. In this instance, the epilepsy diagnosis was revised to nonsyndromic generalized epilepsy secondary to holoprosencephaly. Finally, two children with undetermined nonsyndromic presentations were later diagnosed with Dravet syndrome.

Changes due to evolution of epilepsy occurred in 33 children. When children's epilepsy presentations evolved, we usually observed only one clear change to the next and final presentation. In six, however, some distinct intermediate stages were noted. These included 3 children who first passed through WS/IS before further evolving to LGS (N=1) and nonsyndromic focal (N=1) or generalized (N=1) presentations. The evolution of epilepsy presentation in those whose syndromes evolved over time took a median of 1.8 years (interquartile range (IQR): 0.4 to 2.7 year) before the first (and typically the only) change was identified (usually a combination of new EEG findings and new seizure types).

Seizure course:

There was year-to-year variability for many of the DEE patients in the number of seizure days that were reported in the first 9 years of follow-up. Several children had hiatuses from seizures in some years only to relapse and continue having seizures after that. Another group, many with WS/IS became seizure-free early on and remained that way. The majority, however, had weekly to daily seizures with little reprieve from year to year (Figure 3).

Comparison of WS/IS and LGS:

WS and LGS were the two most common types of epilepsies within the DEE subgroup. WS/IS tended to be the initial presentation for the majority (23/28) of affected children. This was not the case for LGS, and 19/22 children who ultimately had the LGS diagnosis did not receive the diagnosis until a median of 1.9 years (IQR: 0.3 to 2.4 year) after the initial diagnosis of epilepsy. All 22 LGS patients taken together, the median age at diagnosis of epilepsy was 0.75 years (IQR = 0.32 to 2.25) whereas the median age at the time LGS diagnosis was 3.3 years (IQR = 2.4 to 4.8). Children who developed LGS after their initial presentation were first diagnosed with infantile spasms (N=6), nonsyndromic focal epilepsy (N=4), nonsyndromic generalized epilepsy (N=4, one of whom first passed through a period of WS/IS before manifesting LGS), nonsyndromic epilepsy of undetermined nature (N=4,

one of whom developed focal features before developing LGS), and one misdiagnosed as having Doose syndrome.

Cognitive and Seizure outcomes:

Children with LGS (whether evolved from WS/IS or not) had worse seizure control and poorer cognitive outcomes than children with WS/IS without LGS (Table 2). Specifically, 91% of the LGS group versus 52% in the WS/IS group met criteria for pharmacoresistance ($p=0.005$), and 77% versus 38% were pharmacoresistant at last contact ($p=0.009$). A similar proportion in both groups had no identifiable underlying etiology for their conditions and were typically developing at the time of initial diagnosis (38% for WS/IS alone and 45% for LGS +/-WS/IS). There was no clear evidence for differences in the types of underlying causes in children with WS/IS versus LGS. Definite ID was present in 100% of the LGS group (including all 10 children with typical development at onset of epilepsy) and 76% of the WS/IS only group ($p=0.01$). The three children in the WS/IS group who did not have definite ID had all been typically developing at the time of epilepsy onset.

Risk of developing LGS:

Of all young children 5 years-old at initial onset of epilepsy who did not initially present with LGS, 19 of 335 (5.7%) went on to develop LGS. These included 6/23 (26%) who initially presented with WS/IS, 4/12 (33%) with generalized, 4/212 (2%) with focal, and 4/51 (8%) with undetermined nonsyndromic presentations at the time of initial diagnosis ($p<0.001$). The risk of developing LGS, if a child did not first present with it was 13% for infants. Even in infants who did not first present with WS/IS, the risk of developing LGS was still 9%. In 1 and 2-year olds, 5% went on to develop LGS, and only 2 of 146 (1.4%) older children evolved to LGS after the initial diagnosis of epilepsy (both 5 years-old).

Discussion:

Early life developmental encephalopathic epilepsies represent some of the most difficult forms of epilepsy to manage; they account for a disproportionate amount of refractory epilepsy, intellectual disability, and early death seen in children with epilepsy. In our series they represent nearly 10% of all epilepsies diagnosed during the first 16 years of life in the general population and nearly half of all epilepsies diagnosed in infancy, highly comparable to findings from another large population-based study.⁷ While most of these epilepsies are rare, West and Lennox-Gastaut syndrome represent the two most common forms of DEE.

Importantly, whereas most children who have West syndrome present with it as their initial epilepsy diagnosis, most children who have Lennox-Gastaut syndrome initially present with another form of epilepsy. In our series, only 4 children (0.7%) were initially diagnosed with LGS (one perhaps in error), but during the subsequent years, this rose to 3.4% of the total cohort. This represented 6.4% of all pre-school-aged children and 13% of all infants. In the Nova Scotia cohort, only 4 (0.6%) of all children were initially diagnosed with LGS, and this rose to 17 (2.7%) after several years.⁷

Similar to what was reported in children recruited from 1976 through 1993²¹, those with WS/IS, especially in the absence of specific identified etiologies or insults, had moderately

better outcomes than children with LGS in that many were seizure-free and a proportion did not have intellectual disability. Most LGS patients continued with refractory seizures and, regardless of identified etiology and all were intellectually disabled. Importantly, not all children with LGS in our study continued to have refractory seizures; this has been reported in other studies of this syndrome.^{21, 29} The deterioration in developmental status is also well-described.³⁰ The potential reversibility, or at least amelioration, of the intellectual disability following successful surgical therapy for seizure control, supports the impression that the seizures themselves contribute to the cognitive decline and disability.^{20, 31}

WS/IS affects up to 1500 children per year in a country the size of the US³² and has long been acknowledged as an important form of epilepsy to recognize and treat early. Effective treatment is not with standard anti-seizure medications but with steroids (prednisone, prednisolone) or hormones (ACTH) or vigabatrin. Guidelines, recommendations, and most recently, quality metrics provide strong support for rapid, optimum treatment of this condition.^{14–16, 33} Early intervention may improve longer-term developmental outcomes, as suggested in the UKISS trial³⁴ although the underlying etiologies also have a substantial impact.^{21, 34} The potential for modifying disease progression through pre-emptive interventions has led to the pre-treatment trial now underway in the tuberous sclerosis community,³ and the Child Neurology Foundation's "STOP Spasms" campaign.³⁵

Dravet syndrome, affecting roughly 200 infants each year in the US,³⁶ has not yet received the benefits of professional society-promulgated guidelines; however, a recent expert consensus panel reported recommendations for therapies to use and avoid,⁴ and there is evidence that accurate genetic diagnosis can help guide optimal therapy and possibly reduce the severity of the disease and the impact of uncontrolled seizures.³⁷ Even for one of the most recently recognized channelopathies, KCNQ2, which recent data suggest may be present in perhaps only 100 neonates per year in the US,³⁸ there are preferred best first-line therapies based on a limited number of case reports and supportive laboratory studies of the mechanisms and pharmacological responsiveness.^{39, 40} Finally, Batten Disease or neuronal ceroid lipofuscinosis, estimated to affect only about 50 children per year in the United States, now has an FDA-approved therapy. Its availability has spurred efforts to diagnose affected children at the time of the first presentation with epilepsy before all of the features of the disease are apparent, obtain a genetic diagnosis, and proceed to therapy immediately.⁴¹

In light of all of the work done on other extremely rare and devastating conditions, it is perhaps notable that LGS is about as common as WS/IS,^{7, 21} yet there are no similar efforts aimed at early detection and prevention. There appears to be a lag-time in most patients between initial presentation of seizures and development of the full syndrome, including the intellectual disability. In light of this, future efforts should prioritize early identification of children who are on the path to developing LGS before all of the features of LGS are manifest and encourage investigation into early, disease-modifying interventions. This could result in substantial improvements in patient outcomes and reduction in the costs and burdens associated with LGS. Admittedly, the lag time we observed in our study was a combination of how the child was followed by the neurologist and the actual presentation of

the signs of LGS. Nonetheless, there appears to be a window of opportunity in which interventions to prevent evolution to LGS might be considered.

Our data are from the 1990s and do not reflect the recent advances in genetic testing that have occurred since then; some of the children, including those with LGS of unknown cause could have a genetic diagnosis today. LGS, like WS/IS, remains a clinical syndrome however and is not dependent on any specific etiological finding. Further, clinical diagnostic criteria for LGS have not greatly changed during the period when children in the Connecticut study were recruited, and there was still uncertainty about distinguishing Dooze syndrome from LGS.^{42–45} The one child initially considered to have LGS and whose epilepsy was reclassified represents a philosophical conundrum: should the outcome be used to determine the diagnosis? While this would generally lead to self-fulfilling prophecies, in this particular case, the LGS features resolved so rapidly, that the investigators felt the diagnosis was inappropriate. Others might have approached this particular case differently.

Our cohort members were evaluated and followed in community and hospital-based practices, although all records were reviewed centrally by study investigators. Ideally, we would have children evaluated in tertiary pediatric epilepsy programs with video-EEG to get the best possible data. Our data, however, reflect the real world and how most patients were evaluated then and many, perhaps most, still today.

It is time to pay greater attention to careful follow-up and surveillance of children at high risk of evolving to LGS, a common developmental encephalopathic epilepsy about as frequent as WS/IS. This could facilitate the development and testing of disease modifying approaches to prevent the evolution of LGS and its consequences. Therapeutic trials for LGS are directed toward patients with established disease.^{46–48} Given the life-long burden in terms of refractory seizures and disability, prevention of the evolution to LGS in at risk young children, or rapid effective treatment of the underlying encephalopathy in children who present with LGS, as is the practice for WS/IS, could lead to substantial reductions in the population burdens associated with developmental encephalopathic epilepsies.^{49, 50}

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Key points:

- 1) Developmental encephalopathic epilepsies account for disproportionate amounts of refractory epilepsy, disability, and mortality in the pediatric age-range.
- 2) Lennox-Gastaut Syndrome is the most common developmental encephalopathic epilepsy after West syndrome/infantile spasms.
- 3) Although rarely present at the initial onset of epilepsy, Lennox-Gastaut-syndrome accounts for over 10% of infant-onset epilepsy and ~5% in 1- and 2-year olds.
- 4) Lennox-Gastaut Syndrome evolves over time, with a potential window for early intervention between initial epilepsy diagnosis and development of LGS.
- 5) Increased efforts at early detection of high risk children and intervention efforts should target this common developmental encephalopathic epilepsy.

Figure 1:
Distribution of ages at onset in the full cohort and the numbers at each age who presented with or developed a developmental encephalopathic epilepsy (DEE) and those who did not (non-DEE).

Figure 2:

Evolution over the course of follow-up of 58 children who initially or in time developed features consistent with a developmental encephalopathic epilepsy. GEN=Nonsyndromic Generalized Epilepsy, FOC=Nonsyndromic Focal Epilepsy, UND=Nonsyndromic Epilepsy of undetermined nature, LGS=Lennox-Gastaut Syndrome, West=West Syndrome/Infantile Spasms.

Figure 3:
Course of seizure frequency burden (frequency) during the first 9 years after initial diagnosis of epilepsy and type of epilepsies and syndromes initially and over time. Children lost to follow-up before 9 years are designated with an "L" in the year they were lost and those who died with a "D".

Table 1:

Comparisons of Developmental Encephalopathic Epilepsies to other childhood-onset epilepsies

Feature	Developmental Encephalopathic Epilepsies (N=58)	Other epilepsies (N=555)	p-value
Age at onset of epilepsy in years, median (IQR [*])	1.1 (0.3, 1.3)	6 (3 to 9)	<0.001
Onset < 1 year, N (%)	42 (72%)	46 (8%)	<0.001
Death during follow-up, N (%)	12 (21%)	5 (<1%)	<0.001
ID [*] N (%)	49 (84%)	61 (11%)	<0.001
ID in infants only, N (%)	36/42 (86%)	6/46 (13%)	<0.001
Pharmacoresistant	41 (71%)	102 (18%)	<0.001
Pharmacoresistant at last contact	33 (57%)	44 (8%)	<0.001
5-years seizure-free and off medication ^{**}	12/45 (27%)	313/521 (60%)	<0.001

^{*} IQR, Intern-quartile range; ID, Intellectual disability consistent with full-scale IQ <60

^{**} Only children followed at least 5 years are included in these calculations.

Table 2:

Comparison of outcomes in children with West Syndrome/Infantile Spasms (WS/IS) and Lennox-Gastaut Syndrome (LGS)

	WS/IS only (N=21)	LGS +/- WS/IS (N=22 [*])	
Pharmacoresistance			
No	10 (48%)	2 (9%)	0.005
Yes	11 (52)	20 (91%)	
Pharmacoresistance at last contact			
No	13 (62%)	5 (23%)	0.009
Yes	8 (38%)	17 (77%)	
Intellectual disability			
IQ ≥ 60 (not ID)	5 (24%)	0	0.01
IQ < 60 (ID)	16 (76%)	22 (100%)	
Identified cause			
None	12 (57%)	10 (45%)	0.44
Cause attributed	9 (43%)	12 (55%)	
No cause identified <u>and</u> initial presentation was normal/ unremarkable with typical development for age			
No	13 (62%)	12 (55%)	0.64
Yes	8 (38%)	10 (45%)	

^{*} 7 Children who either initially presented with WS/IS or evolved to WS/IS from another initial presentation are included in the LGS group.