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FULL-LENGTH ORIGINAL RESEARCH

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

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Summary

Objectives: Developmental encephalopathic epilepsies (DEEs) 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 at 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-square tests.

Results: Fifty-eight children (9.4%) had DEEs, median onset age = 1.1 years (interquartile range ([IQR] 0.3-1.3) in DEEs and 6.0 years (IQR 3.0-9.0) in other epilepsies ($P < 0.001$). DEEs vs other epilepsies had more pharmacoresistance (71% vs 18%), intellectual disability (84% vs 11%), and mortality (21% vs <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 in 5 children WS/IS evolved later. 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 non-syndromic generalized, focal, or 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 present initially 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
infantile spasms, prevention, prognosis, West syndrome

1 | INTRODUCTION

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 ELEs, first arise.[1,2] Seizures associated with these epilepsies are often refractory to multiple trials of pharmacologic 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 intervention 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 WS is defined by developmental delay, epileptic spasms, and hypsarrhythmia on electroencephalography (EEG),[17,18] the epileptic spasms are the focus of diagnostic and therapy recommendations 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 the impact of the underlying "epileptic encephalopathy"[19,20] on the child's development.

Lennox-Gastaut syndrome (LGS), in 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 and 5 years. Criteria include cognitive impairment; slow spike and wave, multifocal spikes, or both on 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] Furthermore, there is a link between these 2 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 preemptive early interventions.

Key Points

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

Here, we focus on children in the Connecticut Study of Epilepsy (CSE) 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 who are at risk of developing LGS.

2 | METHODS

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 of Connecticut during this time participated). Parents participated in initial baseline interviews. Medical records were reviewed by 3 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 International League Against Epilepsy (ILAE) Classification of the Epilepsies from 1989,[25] 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 report[25] 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 an ongoing review of all neurologic medical records approximately every 6 months. Cognitive/developmental levels ascertained from parent report, administration of the Vineland Adaptative Behavior Scales yearly through 5 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 (ID; consistent with an IQ <60) vs 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 the 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 days/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 2 trials of therapy had failed to control seizures fully. A treatment trial was considered a failure if a drug (1) exacerbated seizures or (2) 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 beyond 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 (Cary, North Carolina). Statistical tests for bivariate analyses of dichotomous, polychotomous, and ordered categorical variables were performed with chi-square tests and Mantel-Haenszel chi-square tests for trend. *t* Test and analyses of variance (ANOVAs) or their nonparametric counterparts, when necessary, were used for comparing means of continuously distributed variables across groups.

2.1 | 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 review boards (IRBs) at the time and data analyses continued under the auspices of the Ann & Robert H Lurie Children's Hospital IRB.

3 | 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 (standard deviation [SD] 4.0).

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

3.1 | 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 2 who died, were followed for

<2 years. Overall, 13 children in the DEE subgroup were followed <5 years; in 10, this was due to early death.

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

3.2 | Developmental encephalopathic epilepsies

3.2.1 | Etiology

In the DEE group, all but 2 children had some form of neuroimaging either initially or later in follow-up. These included computed tomography (CT) scan only (N = 3), magnetic resonance imaging (MRI) done for clinical purposes (N = 46), and a research MRI (N = 7).[28] Of the 2 patients without any imaging, one had Down syndrome and the other had an abnormal neurologic and developmental examination 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.

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[a])	1.1 (0.3, 1.3)	6 (3-9)	<0.001
Onset <1 y, N (%)	42 (72%)	46 (8%)	<0.001
Death during follow-up, N (%)	12 (21%)	5 (<1%)	<0.001
ID[a], 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[b]	12/45 (27%)	313/521 (60%)	<0.001

[a]IQR, interquartile range; ID, intellectual disability consistent with full-scale IQ <60.

[b]Only children followed at least 5 years are included in these calculations.

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], and Dubowitz [1] syndromes), malformations of cortical development (N = 7, including lissencephaly [2], pachygyria [2], focal cortical dysplasia [1], heterotopia [1], and holoprosencephaly [1]), neurocutaneous syndromes (N = 5, including tuberous sclerosis complex [3] and neurofibromatosis [2]), and neurometabolic diseases (N = 5, including Menkes syndrome [2], Batten disease [1], complex IV deficiency [1], and one case of 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 neurologic examinations and were developing typically for age at the time of the initial diagnosis of epilepsy.

3.2.2 | Types of epilepsy

Based on 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, Ohtahara, and Electrographic Status Epilepticus of Sleep (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, whereas the others were in complete remission at the end of the study. In 4 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 type and EEG was removed from that category because the early course was extremely atypical for LGS. The child responded to treatment rapidly, and seizures resolved completely within 6 months of diagnosis until death 4 years later. In this instance, the epilepsy diagnosis was revised to nonsyndromic generalized epilepsy

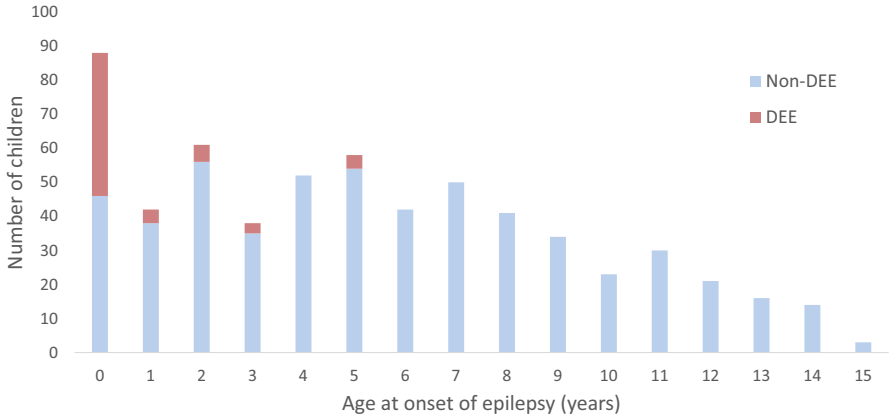

FIGURE 1 Distribution of ages at onset in the full cohort and the numbers of patients at each age who presented with or developed a developmental encephalopathic epilepsy (DEE) and those who did not (non-DEE)

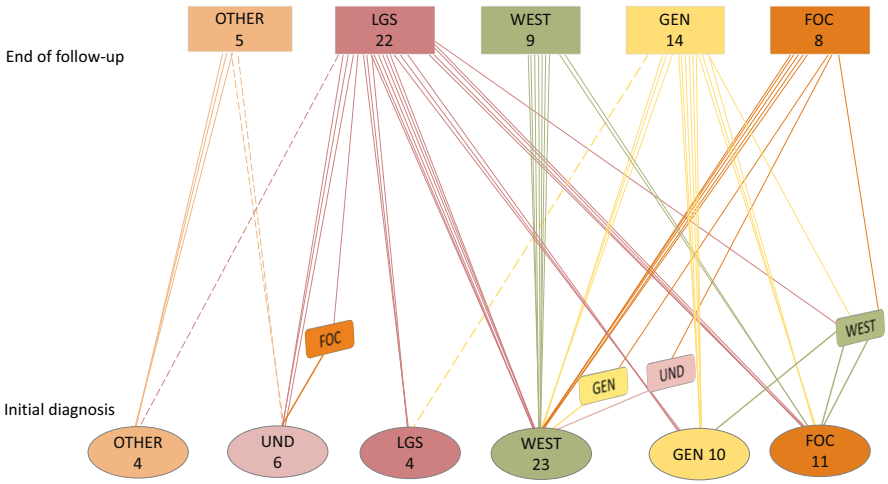

FIGURE 2 Evolution over the course of follow-up of 58 children who initially or in time developed features consistent with a developmental encephalopathic epilepsy (DEE). GEN, nonsyndromic generalized epilepsy; FOC, nonsyndromic focal epilepsy; UND, nonsyndromic epilepsy of undetermined nature; LGS, Lennox-Gastaut syndrome; West, West syndrome/infantile spasms

secondary to holoprosencephaly. Finally, 2 children with undetermined nonsyndromic presentations were later diagnosed with Dravet syndrome (Figure 2).

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 6 children, 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] 0.4-2.7 year) before the first (and typically the only) change was identified (usually a combination of new EEG findings and new seizure types).

3.2.3 | Seizure course

There was year-to-year variability for many of the DEE patients in the number of seizure days 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).

3.3 | Comparison of WS/IS and LGS

WS and LGS were the 2 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 of 22 children who ultimately had the LGS diagnosis did not receive the diagnosis until a median of 1.9 years (IQR 0.3-2.4 year) after the initial diagnosis of epilepsy. With all 22 LGS patients taken together, the median age at diagnosis of epilepsy was 0.75 years (IQR 0.32-2.25), whereas the median age at the time LGS diagnosis was 3.3 years (IQR 2.4-4.8). 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 was misdiagnosed as having Doose syndrome.

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 overtime. 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"

3.3.1 | 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 vs 52% in the WS/IS group met criteria for pharmacoresistance ($P = 0.005$), and 77% vs 38% were pharmacoresistant at last contact ($P = 0.009$).

A similar proportion in both groups had no identifiable underlying etiology for their conditions and was 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 vs 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 3 children in the WS/IS group who did not have definite ID had all been developing typically at the time of epilepsy onset.

3.3.2 | Risk of developing LGS

Of all young children ≤5 years of age 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 of 23 (26%) who presented initially 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).

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[a])	
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 and initial presentation was normal/unremarkable with typical development for age			
No	13 (62%)	12 (55%)	0.64
Yes	8 (38%)	10 (45%)	

[a]Seven children who either presented initially with WS/IS or evolved to WS/IS from another initial presentation are included in the LGS group.

4 | DISCUSSION

Early life DEEs represent some of the most difficult forms of epilepsy to manage; they account for a disproportionate amount of refractory epilepsy, intellectual disability (or ID), 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] Although most of these epilepsies are rare, West and Lennox-Gastaut syndromes represent the 2 most common forms of DEE.

It is notable that, 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 subsequent years, this rose to 3.4% of the total cohort. This represented 6.4% of all preschool-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 1993,[21] 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 ID. Most patients with LGS continued with refractory seizures and, regardless of identified etiology, all were intellectually disabled. It is important to note that 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 ID 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 affect up to 1500 children per year in a country the size of the United States[32] and have long been acknowledged as an important form of epilepsy to recognize and treat early. Effective treatment is not with standard antiseizure medications but with steroids (prednisone, prednisolone) or hormones (corticotropin [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 United Kingdom Infantile Spasms Study trial,[34] although the underlying etiologies also have a substantial impact.[21,34] The potential for modifying disease progression through preemptive interventions has led to the pretreatment 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 United States,[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 United States,[38] there are preferred best first-line therapies based on a limited number of case reports and supportive laboratory studies of the mechanisms and pharmacologic 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 a Food and Drug Administration (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 ID. 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 etiologic finding. Furthermore, clinical diagnostic criteria for LGS have not changed greatly during the period when children in the Connecticut study were recruited, and there was still uncertainty about distinguishing Doose 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? Although 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 DEE 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 lifelong 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 DEEs.[49,50]

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DISCLOSURE

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Drs. Levy and Testa have no conflicts of interest or disclosures. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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