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Abstract

The magnitude and causes of death among a cohort of children with epilepsy were determined. A follow-up study with a population-based cohort of 10-year-old children in the metropolitan Atlanta area with epilepsy was conducted. The National Death Index and linkage to State of Georgia death certificates were used to identify deaths. The authors estimated the expected numbers of deaths by applying mortality rates adjusted by age, race, and sex for the entire state of Georgia to the population for the follow-up period. Among the 688 children who were in the final epilepsy cohort, 64 deaths occurred; 20.6 deaths were expected (mortality ratio adjusted for age, race, and sex = 3.11). The mortality ratios for children with Lennox-Gastaut syndrome and infantile spasms were 13.92 and 11.91, respectively. Children and adolescents with epilepsy, especially those with Lennox-Gastaut syndrome or infantile spasms, have an increased risk of death.

Keywords

Lennox-Gastaut syndrome, infantile spasms, mortality, epilepsy

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Children with epilepsy make up a diverse group of childhood epilepsy syndromes, each manifested by different seizure types, electroencephalogram (EEG) findings, clinical features, and outcomes. About half of children with epilepsy experience a spontaneous remission before adulthood, and about two thirds of children with epilepsy are seizure free on antiseizure drugs. However, children whose seizures continue and do not respond to medication—those with intractable epilepsy—experience an increased risk of morbidity and impaired quality of life. Epilepsy is the most common serious neurological disorder in children worldwide. The prevalence of epilepsy among 10-year-old children in developed countries is about 6 per 1000¹; the prevalence of intractable epilepsy (estimated about 2 per 1000 or about one third of children with epilepsy) is about the same as the prevalence of juvenile diabetes mellitus during childhood.²

Previous studies have demonstrated a modest increased risk of death among children with epilepsy compared with children without epilepsy.³⁻⁷ However, most of these previous studies evaluated childhood epilepsy as a single diagnostic entity—combining children having relatively benign epilepsy syndromes with those having intractable epilepsy into a single heterogeneous group for analysis. Clinical series of children with epileptic encephalopathies, such as infantile spasms and

Lennox-Gastaut syndrome, have reported a high percentage of children with serious injuries, mental retardation, and other comorbid conditions, and possibly an increased risk of death.^{8,9} While no previous studies have examined mortality in persons with infantile spasms or Lennox-Gastaut syndrome ascertained from the general population, Riikonen¹⁰ did find a mortality rate of 19.6% in a cohort of Finnish children with infantile spasms.

Among children with infantile spasms, the onset of clinical spasms (the seizure type among children with infantile spasms) typically occurs between 2 and 12 months of age. Children with infantile spasms have a high risk of serious cognitive impairment and mental retardation, regardless of whether the

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infantile spasms are successfully controlled with medication.¹¹ Lennox-Gastaut syndrome is characterized by multiple types of seizures, including generalized tonic seizures, “drop attacks” (atonic seizures, tonic seizures, or massive myoclonic jerks with falls), and atypical absence seizures associated with slow (<2.5 Hz) spike-wave and a slow background on EEG.¹² Most experts consider cognitive impairment as essential for the diagnosis of Lennox-Gastaut syndrome, and more than 90% of children with Lennox-Gastaut syndrome have mental retardation (IQ < 70).¹³ Children with Lennox-Gastaut syndrome typically experience the onset of the syndrome between the ages of 3 and 11 years.^{13,14}

We report an analysis of the mortality of persons with diagnosed Lennox-Gastaut syndrome and/or infantile spasms ascertained from the general population of metropolitan Atlanta.

Methods

Cohort

The Metropolitan Atlanta Developmental Disabilities Study was a population-based study of children born in 1975 to 1977 with mental retardation, cerebral palsy, epilepsy, hearing impairment, and/or visual impairment who were ascertained at 10 years of age using a multiple-source surveillance system with expert clinician review of systematically abstracted data. Data were abstracted from special education public school records and records at hospitals, clinics, state service facilities, and other clinical providers for children with developmental disabilities.^{1,15} The epilepsy surveillance system also used a surveillance system that included 21 EEG laboratories in metropolitan Atlanta that performed EEGs on children in the 1980s. Additional medical and educational data were obtained on the children who had EEGs, who were also born in the years of interest.¹ Within this cohort of children with epilepsy born in 1975 to 1977 in metropolitan Atlanta, children with Lennox-Gastaut syndrome¹³ and children with infantile spasms¹⁶ were identified for separate analyses. The identification of children with Lennox-Gastaut syndrome¹³ and with infantile spasms¹⁶ included the study pediatric neurologist (E.T.) reviewing the children’s EEGs to verify that EEG aspects of diagnostic criteria for these epilepsy syndromes were met.

The study cohort consisted of different case types. *Active incident* cases were children who were born in the metropolitan Atlanta study area and lived in the study area at age 10 years. *Inactive incident cases* were children born in the study area who died or who migrated out of the study area before 10 years of age. *Prevalent cases* were not born in the study area but lived in the study area when they were 10 years of age. Prevalence was reported on this epilepsy cohort at 10 years of age in a previous report¹ using the active incident cases, plus the prevalent cases (543 cases) in the numerator and the total population of 10-year-old children in the study area in the denominator. For this analysis of death among children with epilepsy, we included the additional inactive incident cases (153 cases) for a total of 696 children with epilepsy ascertained in the surveillance system. Of the 696 children with epilepsy, only 8 children had a race that was neither white nor black; these 8 children, none of whom had died and none of whom had infantile spasms or Lennox-Gastaut syndrome, were excluded from the analysis, yielding a total of 688 children in the final epilepsy cohort for this analysis. Table 1 provides the demographic

Table 1. Demographic Characteristics of Cohort

	N	%
Total children with epilepsy	688	-
Race		
White	438	63.7
Black	250	36.3
Sex		
Male	383	55.7
Female	305	44.3
Epilepsy syndrome		
Lennox-Gastaut ^a	34	4.9
With infantile spasms	11	1.6
Without infantile spasms	23	3.3
Infantile spasms ^a	24	3.5
Non-Lennox-Gastaut and infantile spasms	641	93.2
Co-occurring disabilities		
Epilepsy only	453	65.8
Multiple disabilities with epilepsy	235	34.2
Mental retardation	192	27.9
Cerebral palsy	134	19.5
Hearing impairment	14	2.0
Vision impairment	39	5.7
Number of co-occurring disabilities		
Two	121	17.6
Three	85	12.4
Four	28	4.1
Five	1	0.1
Case type		
Active incident	376	54.7
Inactive incident	153	22.2
Prevalent	159	23.1

^a Some of the children with Lennox-Gastaut also had infantile spasms prior to meeting diagnostic criteria for Lennox-Gastaut syndrome.

characteristics of the epilepsy cohort under study. Figure 1 shows how the cohort was developed.

Approach

We matched the names of the 688 children from the epilepsy cohort to the National Death Index to determine which of these now young adults had died from 1979 to 2001. The National Death Index uses a probabilistic matching procedure that assigns a score to the match, indicative of the likelihood of a true match.¹⁷ We also matched, deterministically, our study data to the Georgia death certificates for 1975 to 1978 to ascertain deaths occurring prior to 1979 in this cohort. We obtained death certificates for all the decedents identified by the National Death Index and Georgia death certificate linkage as probable matches, and these death certificates were reviewed by study investigators to verify that the match identified by the National Death Index was a true match. These death certificates were also reviewed by the study pediatric neurologist/epileptologist, along with available medical record data from the surveillance system, which included the type of epilepsy from the medical records.

The follow-up period was 1975 to 2001. We used a modified life table analysis to construct mortality ratios to assess excess mortality in this cohort relative to the general population and adjusted for age, race, and sex. This technique has been used in a prior mortality study on this cohort that focused on all developmental disabilities under

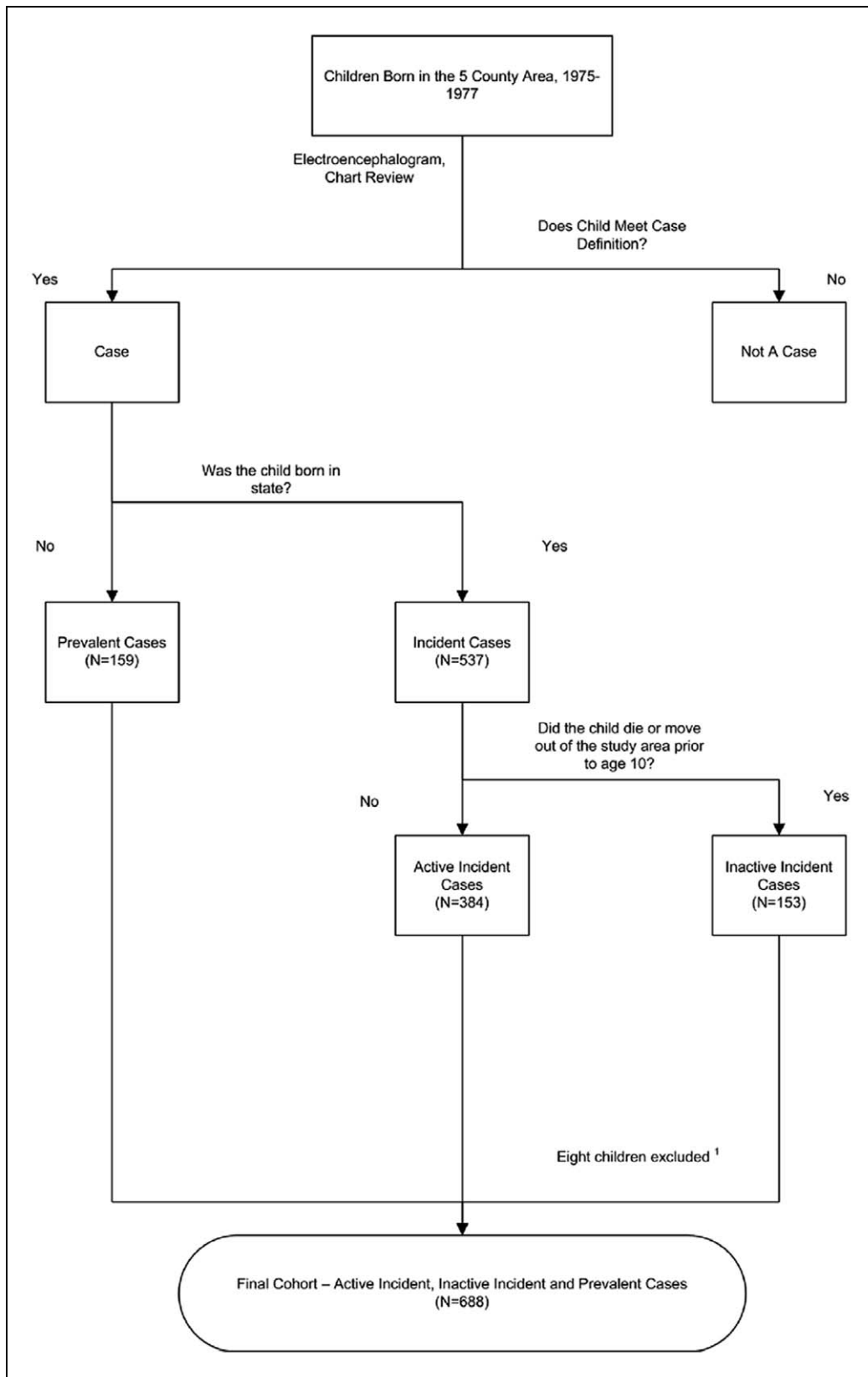


Figure 1. Derivation of Epilepsy Cohort.

¹None of the eight excluded children had infantile spasms or Lennox-Gastaut Syndrome.

Table 2. Mortality Ratios for All Children With Epilepsy

	Mortality rate ^a	Observed	Expected	Mortality ratio	95% confidence limits
Race					
White	3.35	36	10.60	3.40	(2.37-4.70)
Black	4.68	28	9.96	2.81	(1.87-4.06)
Sex					
Male	4.39	41	13.76	2.98	(2.13-4.04)
Female	3.11	23	6.81	3.38	(2.14-5.07)
Age					
<1 year	4.36	3	9.40	0.32	(0.07-0.93)
1-4 years	4.06	11	1.83	6.00	(2.99-10.74)
5-9 years	3.58	12	1.19	10.09	(5.21-17.61)
10-14 years	4.89	16	0.96	16.68	(9.53-27.09)
15-19 years	3.11	10	3.26	3.07	(1.47-5.65)
20-24 years	3.58	11	3.35	3.29	(1.64-5.89)
25-34 years	2.26	1	0.58	1.74	(0.04-9.68)
Overall	3.82	64	20.57	3.11	(2.39-3.98)

^a Per 1000 person years.

investigation in the Metropolitan Atlanta Developmental Disabilities Study.⁶ To obtain expected deaths, we applied the mortality rates for the state of Georgia for the entire period 1979 to 2001 to the observed person years lived; 1979 is the earliest date for which statewide mortality rates are available.

Based on review of the National Death Index output and the death certificates, we estimated expected deaths using statewide mortality rates by broad underlying cause of death categories defined by the National Death Index. For deaths occurring before 1999, we used the *International Classification of Diseases, Ninth Edition* codes. For deaths occurring in 1999 and later, we used the *International Classification of Diseases, Tenth Edition* codes. The cause of death categories selected and the *International Classification of Diseases* codes that correspond to them were identified by the National Death Index.¹⁸ These categories, selected based on the number of deaths that occurred in each and on their general relationship to the condition under study (epilepsy), are as follows: cardiac deaths, 390-459 (*International Classification of Diseases 9*) and I00-I99 (*International Classification of Diseases 10*); neurological deaths, 320-389 (*International Classification of Diseases 9*) and G00-G98 (*International Classification of Diseases 10*); and external causes of death (eg, violence, poisoning), E800-E999 (*International Classification of Diseases 9*) and V01-Y89 (*International Classification of Diseases 10*). The remaining deaths were categorized as "Other" causes of death, including infections, tumors, and so on. The pediatric neurologist/epileptologist reviewed the death certificates and the medical records information to ascertain the underlying comorbid medical and nonmedical events associated with death and estimated as causal factors. The study received appropriate institutional review board approval from the Centers for Disease Control and Prevention (CDC) institutional review board and from local, community review boards.

Statistical Analysis

We applied the age-, race-, and sex-specific mortality rates to the observed person years lived to estimate the expected numbers of deaths. Ratios of observed-to-expected deaths were computed and 95% Poisson confidence limits were calculated using the Statistical Analysis Battery for Epidemiologic Research.

Results

About 64% of the children were white, and 56% were male (Table 1). In all, 34 children had Lennox-Gastaut syndrome; 11 of them also had infantile spasms (32.4%) prior to meeting diagnostic criteria for Lennox-Gastaut syndrome. Twenty-four children had infantile spasms (Table 1). The majority of the cohort only had isolated epilepsy (66%), and the most frequent co-occurring disability was mental retardation (27.9%).

There were 64 deaths yielding an overall mortality ratio of 3.11, after adjusting for age, race, and sex. Most of the deaths in this cohort occurred between 10 and 14 years of age. White children had a slightly elevated mortality risk relative to black children, and females had a slightly higher mortality risk than males (Table 2). In all, 12 deaths occurred among children with Lennox-Gastaut syndrome, and 8 deaths occurred among children with infantile spasms.

Children with Lennox-Gastaut syndrome were 14 times more likely than children in the general population to die from any cause (Table 3). Similarly, children with infantile spasms were 12 times more likely than children in the general population to die from any cause. Although not reaching statistical significance, the presence of infantile spasms caused a small rise in the mortality ratio associated with Lennox-Gastaut syndrome (Table 3). Children with multiple developmental disabilities had higher mortality ratios than did children with isolated epilepsy. An upward trend was noted between increasing numbers of developmental disabilities and increasing mortality ratios in the all-causes-of-death category. Neurological comorbid conditions such as prolonged seizures and status epilepticus were the most significant cause of death (mortality ratio of 19.4; Table 3). This effect was most pronounced in children with Lennox-Gastaut syndrome (mortality ratio of 179) but was also noted in children with infantile spasms, albeit to a lesser degree (mortality ratio of 97; Table 3). When children who had infantile spasms prior to meeting diagnostic criteria for Lennox-Gastaut syndrome were compared with

Table 3. Mortality Ratios by Cause of Death Type

	Mortality ratio (95% confidence limits)				
	All causes	Cardiac	Neurological	External causes	Other
Total children with epilepsy	3.11 (2.39-3.98)	3.40 (0.70-9.92)	19.36 (10.00-33.82)	0.64 (0.21-1.50)	7.38 (5.36-9.91)
Epilepsy syndrome					
Lennox-Gastaut syndrome	13.92 (7.19-24.31)	29.90 (0.76-166.57)	178.97 (58.11-417.67)	0.00 (0.00-11.81)	24.43 (8.97-53.18)
Lennox-Gastaut with infantile spasms	15.24 (4.15-39.02)	0.00 (0.00-355.21)	119.73 (3.03-667.08)	0.00 (0.00-39.27)	38.48 (7.94-112.44)
Lennox-Gastaut without infantile spasms	13.34 (5.75-26.27)	43.37 (1.10-241.64)	204.24 (55.64-522.93)	0.00 (0.00-16.89)	17.90 (3.69-52.32)
Infantile spasms	11.91 (5.14-23.47)	0.00 (0.00-132.12)	96.99 (11.75-350.36)	4.09 (0.10-22.81)	20.56 (5.60-52.65)
Non-Lennox-Gastaut and infantile spasms	2.49 (1.83-3.29)	2.40 (0.30-8.68)	10.35 (3.80-22.53)	0.55 (0.15-1.40)	6.43 (4.50-8.90)
Co-occurring developmental disabilities					
Isolated epilepsy	1.41 (0.85-2.19)	1.72 (0.04-9.56)	2.45 (0.06-13.68)	0.77 (0.21-1.98)	3.33 (1.77-5.69)
Multiple developmental disabilities	6.37 (4.64-8.52)	6.64 (0.80-23.98)	51.76 (25.83-92.61)	0.38 (0.01-2.14)	15.09 (10.25-21.42)
Number of co-occurring developmental disabilities					
Two	2.93 (1.46-5.25)	6.17 (0.15-34.35)	8.93 (0.22-49.75)	0.00 (0.00-2.59)	8.29 (3.79-15.74)
Three	7.47 (4.50-11.66)	9.19 (0.23-51.20)	52.39 (14.28-134.13)	1.08 (0.03-6.02)	17.47 (9.30-29.87)
Four	18.53 (10.13-31.09)	0.00 (0.00-124.81)	255.14 (93.69-555.72)	0.00 (0.00-14.84)	36.49 (15.15-71.89)

those who had Lennox-Gastaut syndrome without infantile spasms, there was a slight increase in the mortality ratio among those children who had infantile spasms diagnosed prior to development of Lennox-Gastaut syndrome. External causes of death (eg, injuries, poisonings) were associated with relatively low mortality ratios for all the children with epilepsy except for infantile spasms, for which a mortality ratio of 4.09 was observed, but this mortality ratio was not statistically significant.

Discussion

In this population-based cohort of children with epilepsy, 64 deaths occurred among 688 children, yielding a mortality ratio adjusted for age, race, and sex of 3.11. An overall increased risk of death among children with epilepsy has been previously reported.^{3,6} However, this is one of the first studies to compare the mortality associated with Lennox-Gastaut syndrome and infantile spasms with other epilepsy syndromes from the same population. Previous studies have also found elevated mortality risks of children with epilepsy.^{3,19} Observed mortality rates for children identified through the Metropolitan Atlanta Developmental Disabilities Study were generally in agreement with other published mortality rates for children with epilepsy.¹⁹

We postulated that the risk of death among children with Lennox-Gastaut syndrome and infantile spasms would be significantly higher than the risk of death among children with epilepsy overall. The risk of death among children in our cohort with Lennox-Gastaut syndrome was 14 times greater than what is expected in children, adolescents, and young adults without epilepsy in the same age group, with most deaths resulting from neurological causes. Similarly, the risk of death among children

with infantile spasms was about 12 times greater than among children, adolescents, and young adults without epilepsy in the same age group. In a Finnish cohort of children with infantile spasms followed until death or until 20 to 35 years of age, one third died before 3 years of age.⁹ The high risk of death among children with Lennox-Gastaut syndrome is consistent with the previously published cohorts from clinical centers.⁸

In our cohort, the definition of infantile spasms required the presence of hypsarrhythmia on EEG.¹⁶ Children with clinical spasms without hypsarrhythmia may represent a less severely affected group, as studies that did not use hypsarrhythmia as a requirement for the diagnosis of infantile spasms have tended to report better cognitive outcomes than those studies that did require hypsarrhythmia for the diagnosis of infantile spasms.¹¹ Whether children with clinical spasms without hypsarrhythmia on EEG have lower risk of death is not known and cannot be determined from our data.

The high risk of death among children with infantile spasms and Lennox-Gastaut syndrome from our cohort further emphasizes the significance of these epileptic encephalopathies despite their relatively low prevalence. More than 90% of children with Lennox-Gastaut syndrome in our cohort had severe-to-profound mental retardation diagnosed prior to age 11 years.¹³ Children with Lennox-Gastaut syndrome and infantile spasms from this cohort at 10 years of age accounted for 17% of all 10-year-old children with severe-to-profound mental retardation in the metropolitan Atlanta study area.^{13,16}

The risk of death from external causes, the most prevalent cause of death in the same age groups in the general population, was lower than expected (mortality ratios of less than one) in all subgroups except for infantile spasms, for which a marginal,

albeit insignificant elevation was noted. This apparent protective effect might be due to reduced exposure to circumstances that can cause death from external causes (eg, motor vehicle accidents) in the more severely disabled persons in the cohort, particularly children with Lennox-Gastaut syndrome and infantile spasms.

The review of death certificates among children with Lennox-Gastaut syndrome and infantile spasms revealed that the causes of death listed were often the very literal immediate cause of death (eg, cardiac arrest); after chart review, it was clear that the death was often precipitated by an epilepsy-related event (eg, status epilepticus resulting in aspiration pneumonia and respiratory failure). Additionally, 4 deaths were consistent with sudden unexplained death in epilepsy; none of the death certificates captured this finding.

The majority of causes of death in our cohort of children with epilepsy were neurological in origin, frequently with seizures reported in medical records as a precipitating factor. This finding suggests that better control of the seizures might lead to reduced mortality in persons with epilepsy, particularly Lennox-Gastaut syndrome and infantile spasms. In most cases, the cause of death listed on the death certificate did not fully capture this information, and these findings could only be ascertained from detailed medical record review. This finding highlights the need for clinicians to thoughtfully review the underlying cause of death information placed on the death certificate and further magnifies the need for medical review of deaths of patients with a history of epilepsy.

This study has several limitations. First, the number of deaths among children with Lennox-Gastaut syndrome was small (12 total deaths, 5 of which were neurological in origin), as were the number of deaths among children with infantile spasms. These small numbers make the confidence intervals very wide for these epilepsy syndromes. Second, nationwide mortality information was only available back through 1979. We obtained mortality information from the state of Georgia only for 1975 to 1978. It is possible that some deaths occurred out of state during 1975 to 1978 and these deaths would therefore not be captured by the current identification procedures; therefore, our estimate of mortality during 1975 to 1978 may underestimate the true number of deaths.

This study has several strengths. Chief among them is the fact that this was a population-based study with a long follow-up period. Furthermore, because we had clinical and identifying information, such as parent's name, for these children, we were able to confirm the National Death Index-identified match by a manual review of the death certificates obtained. The review of EEG recordings by a pediatric neurologist as part of the classification of epilepsy syndromes in a population-based study is also a strength.

Although infantile spasms and Lennox-Gastaut syndrome are relatively rare, their impact on morbidity and mortality in childhood is significant. The association of the high risk of death with seizure-related events in these children further underscores the need to develop new therapies for these severe epileptic encephalopathies. Additional studies of potential etiologies, perhaps using newer technologies to study

genetic-environmental interactions, are also needed, with the hope of finding potentially modifiable risk factors. The relatively high risk of death among children with infantile spasms and Lennox-Gastaut syndrome should influence parental counseling by both neurologists and pediatricians.²⁰

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Declaration of Conflicting Interest

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