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Cause-specific mortality among children and young adults with epilepsy: Results from the U.S. National Child Death Review Case Reporting System ★

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Abstract

We investigated causes of death in children and young adults with epilepsy by using data from the U.S. National Child Death Review Case Reporting System (NCDR-CRS), a passive surveillance system composed of comprehensive information related to deaths reviewed by local child death review teams. Information on a total of 48,697 deaths in children and young adults 28 days to 24 years of age, including 551 deaths with epilepsy and 48,146 deaths without epilepsy, was collected from 2004 through 2012 in 32 states. In a proportionate mortality analysis by official manner of death, decedents with epilepsy had a significantly higher percentage of natural deaths but significantly lower percentages of deaths due to accidents, homicide, and undetermined causes compared with persons without epilepsy. With respect to underlying causes of death, decedents with epilepsy had significantly higher percentages of deaths due to drowning and most medical conditions including pneumonia and congenital anomalies but lower percentages of deaths due to asphyxia, weapon use, and unknown causes compared with decedents without epilepsy. The increased percentages of deaths due to pneumonia and drowning in children and young adults with epilepsy suggest preventive interventions including immunization and better instruction and monitoring before or during swimming. State-specific and national population-based mortality studies of children and young adults with epilepsy are recommended.

★Disclaimer: The findings and conclusions in this study are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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Conflicts of interest

Niu Tian does not have any conflicts of interest to disclose.

Esther C. Shaw does not have any conflicts of interest to disclose.

Matthew Zack does not have any conflicts of interest to disclose.

Rosemarie Kobau does not have any conflicts of interest to disclose.

Heather Dykstra does not have any conflicts of interest to disclose.

Theresa M. Covington does not have any conflicts of interest to disclose.

Keywords

Epilepsy; Mortality; Death; Infant; Child

1. Introduction

The mortality rate in all persons with epilepsy is up to three times higher [1] and in children with epilepsy, five to ten times higher [2,3] than that in the general population. However, limited information has been published about the causes of death in children with epilepsy. Epilepsy is the most common childhood neurologic disorder [4], and epilepsy-related deaths in children are important concerns for parents and guardians. In North America, several regional population-based cohort studies and one recent state population-based study have described the risk factors and causes for death in children with epilepsy[2,3,5,6]. The goal of this study was to investigate cause-specific mortality among children and young adults with epilepsy based on mortality data in 32 states participating in the U.S. National Child Death Review Case Reporting System (NCDR-CRS).

2. Methods

2.1. Data source

Data for this study came from the U.S. National Child Death Review Case Reporting System NCDR-CRS, version 2.2S [7], operated by the National Center for the Review and Prevention of Child Deaths at the Michigan Public Health Institute. This system records conditions and causes associated with child deaths. The NCDR-CRS is a web-based, passive, voluntary surveillance system. Participating states convene multidisciplinary child death review teams that meet regularly to share information regarding causes of mortality and to make recommendations for preventing child deaths. Although every state and the District of Columbia have a child death review system, the scope of the system varies by the amount of local resources, administrative structure (e.g., affiliation with child welfare agency vs. affiliation with health department), legislative authority (e.g., review of sudden deaths only vs. both sudden and medical deaths; age limits), and other factors (e.g., professional composition of child death review team members) [8]. This system includes death information on children and young adults from birth to 24 years of age (mostly from birth to 18 years of age). The NCDR-CRS, 2.2S version, contains over 1800 data elements from many sources, including death scene investigations, reports from coroners/medical examiners/police departments, medical records, and death certificates. Because of differences in local administrative, legislative, and other factors associated with implementation of children death review, data from the NCDR-CRS do not include all deaths from child and young adults occurring in states or specific jurisdictions. Despite this limitation, this unique system covers a large geographic area and is currently used by 43 of the 50 U.S. states [8,9].

2.2. Study subjects

The NCDR-CRS collected information on 68,817 deaths among children and young adults 0–24 years of age from 2004 through 2012 in 32 reporting states. Cause of death data for

subjects come from the death certificate (natural, accident, suicide, homicide, undetermined and other causes), and by primary underlying cause of death determined by the NCDR-CRS during the review process (e.g., deaths due to external events, medical conditions, undetermined if related to external events or medical conditions, and unknown). Since this study was designed to compare the causes of deaths in children and young adults with and without epilepsy, we excluded 19,231 deaths in neonates <28 days old because the definition of epilepsy excludes seizures occurring in neonates under 28 days [10]. Of the remaining 49,586 deaths (72% of 68,817), we noted that 857 deaths were grouped as “neurological/seizure disorders,” as an underlying cause of death because the NCDR-CRS does not distinguish seizure disorders from other neurological disorders. Including this group in the proportionate mortality analysis (see the Methods section 2.3) would distort the comparison by underlying causes of death between those with epilepsy and those without epilepsy. Because the proportion of deaths due to “neurological/seizure disorders” in those with epilepsy exceed that in those without epilepsy and because the distribution of all causes of death in both groups totals 100%, the proportion of deaths due to other causes of death in those with epilepsy would be less than that in those without epilepsy. Excluding deaths due to “neurological/seizure disorders” makes those with epilepsy and those without epilepsy comparable with respect to the underlying causes of death.

In the remaining 48,729 deaths (71% of 68,817), we identified cases of epilepsy or seizure disorder in two ways. We first searched for the terms, “epilepsy” or “seizure”, in the following three NCDR-CRS text files describing characteristics of cases:

- 1) Section A, Question 20, that specified the kinds of physical disabilities, mental disabilities, or both;
- 2) Section F, Question 2, that specified other medical conditions from a list of medical causes; and
- 3) Section F, Questions 3 and 4, that provided information from death certificates of infants.

The second way to identify cases of epilepsy or seizure disorder required “Yes” answers from two of the following four questions: a) Section A, Question 48 (“At any time prior to the infant’s last 72 h, did the infant have a history of seizures or convulsions?”); b) Section A, Question 49 (“In the 72 h prior to death, did the infant have seizures or convulsions?”); c) Section G4 (asked only of asphyxia cases) (“Did this person have a history of seizures?”); and d) Section G5 (asked only of sudden infant death syndrome cases) (“Did this person have a history of seizures?”).

To refine the definition of those with epilepsy or seizure disorder in the 583 deaths identified so far from the above two ways, we excluded 32 more deaths with the following diagnoses: status epilepticus; febrile seizures; seizures associated with meningitis, hypoxic/ischemic brain injuries, other severe brain injuries, or multiorgan system failure; early infantile epileptic encephalitis; cases that may not be epilepsy but only acute seizures from other symptomatic causes (for example, “history of fall resulting in skull fracture and seizures”); and other possibly misclassified cases (for example, terms such as “febrile” and “seizure

disorder” in different text fields). The final analytic sample of 48,697 deaths included 551 deaths with epilepsy and 48,146 deaths without epilepsy.

2.3. Statistical analysis

We performed a chi-squared test to check whether age, sex, and race differed statistically significantly between deaths with epilepsy and deaths without epilepsy. We then compared the proportionate mortality for the deaths with epilepsy and for those without epilepsy by official manner of death from the death certificate (natural, accident, suicide, homicide, undetermined, and others) and by primary underlying causes of death defined by the NCDR-CRS (external events, medical conditions, undetermined if related to medical or external events, and unknown). For both decedents with epilepsy and decedents without epilepsy, we included in the category “Other” all causes of death in which the number of deaths was five or fewer (see footnotes d and f of Table 2). We defined statistically significant differences between the proportion of deaths with epilepsy and the proportion of deaths without epilepsy [the reference group] as a 95% two-sided confidence interval of this difference in proportions that excluded 0.

3. Results

3.1. Sample characteristics

In the final analytic sample, 36% of deaths were in infants less than one year old, 18% in children one through four years old, 9% in children five through nine years old, and 37% in children and young adults 10 through 24 years old. Sixty-one percent were male; 63%, whites; 24%, African-Americans; 5%, other races, and 8%, missing race. Since children with epilepsy who died represent only 1.1% (551 out of 48,697) of all children who died, the characteristics (e.g., the percentage of age and sex) of those without epilepsy who died are almost identical to the percentages in the final analytic sample. Compared with children and young adults without epilepsy who died, children and young adults with epilepsy who died were older and more often male.

3.2. Proportionate mortality

Decedents with epilepsy had a significantly higher percentage of natural deaths but significantly lower percentages of accidental deaths, homicides, and undetermined deaths compared with decedents without epilepsy (Table 1). Decedents with epilepsy had significantly higher percentages of deaths due to pneumonia and congenital anomalies and other medical conditions but lower percentages of deaths due to asphyxia and weapon use compared with those without epilepsy. Decedents with epilepsy also had a significantly higher percentage of drowning deaths and a lower percentage of deaths categorized as “Unknown” compared with those without epilepsy (Table 2).

4. Discussion

In this study, higher percentages of deaths of children and young adults with epilepsy were due to natural conditions or many medical conditions including pneumonia and congenital anomalies and due to accidental drowning compared with deaths of children and young

adults without epilepsy. Children and young adults with epilepsy who died were older and more often male.

The mortality rate in children with epilepsy is five to ten times higher than that in the general pediatric population [2,3]. Findings from a few studies examining causes of death in children with epilepsy are inconsistent. One recent long-term, population-based, prospective cohort study from Finland found that epilepsy itself or deaths related to the occurrence of seizures, especially sudden unexpected death in epilepsy, were the major cause of death in childhood-onset epilepsy [11]. However, most other studies in different populations from Europe and North America found that underlying diseases, especially underlying neurological disorders or other epilepsy unrelated diseases, mainly caused deaths in children with epilepsy, rather than epilepsy or deaths related to the occurrence of seizures [2,3,5,6]. Nevertheless, some of these studies had only a few cases (deaths), covered only a small geographic area, and took place in different time periods. In contrast, our study identified 551 deaths of children and young adults with epilepsy from a large sample of deaths in 32 U.S. states from 2004 through 2012 and suggests that natural or medical conditions were more likely to cause early deaths in children and young adults with epilepsy (55% of deaths in those 9 years old or younger) than in those without epilepsy. This supports the conclusion from other relevant studies indicating that deaths in children and young adults with epilepsy are associated more with other underlying diseases than with epilepsy itself.

Pneumonia in this study was found as an important cause of death for children and young adults with epilepsy or seizures and has long been recognized as a common cause of death in those with epilepsy [12]. Why the pneumonia mortality rate in those with epilepsy significantly exceeds that in the general population (especially in older adults with epilepsy) is still unclear. One study found that the average age of patients with epilepsy who died of pneumonia was 81.3 years [13] and assumed that elderly patients may be more susceptible to pneumonia because of higher rates of associated diseases and suppression of the immune system [14]. In our study, however, a threefold increased pneumonia mortality risk occurred even in children and young adults with epilepsy who died, suggesting that immunizations against pneumococcal pneumonia and influenza in children and young adults with epilepsy may reduce pneumonia-related mortality.

In our study, congenital anomalies occurred as an underlying cause of death in those with epilepsy significantly more often than in those without epilepsy. This result is consistent with a recent finding from the state of South Carolina, the first population-based, state mortality study in children with epilepsy in the U.S. [6]: developmental conditions (congenital malformation, chromosomal abnormalities, intellectual disability, and cerebral palsy) were the most common underlying causes of death (17.5% of premature deaths) among children with epilepsy (0–18 years).

Preventing accidental drowning is important for patients with epilepsy because their risk of drowning is five times higher than that in the general population [15]. Even though children and young adults with epilepsy who died in our study had a significantly lower percentage of accidental deaths overall, they had a significantly higher percentage of deaths from accidental drowning. This finding again strongly suggests the need for teaching swimming

skills, closely watching swimmers in or around the water, and learning cardiopulmonary resuscitation to reduce the risk of drowning in persons with epilepsy [16].

The lower percentages of deaths caused by accidents, homicides, asphyxia, and weapon use in this specific young group with epilepsy might reflect children's better oversight by families. Finally, significantly lower percentages of deaths from the categories "Undetermined" (Table 1) and "Unknown" (Table 2) among children and young adults with epilepsy who died imply that more detailed and accurate medical records may be available in those decedents with epilepsy.

This study has several limitations. First, as mentioned before, because the NCDR-CRS is a passive surveillance system, sampling of deaths is not based on a random sample of deaths and, therefore, is not representative of the population of all deaths in participating states. Second, despite standardized protocols in the NCDR-CRS, different states in this study may have contributed different amounts of information during the study period leading to biased results. Even so, the NCDR-CRS is the only system that provides child death review teams with a valuable tool for capturing, analyzing, and reporting on comprehensive information related to a child's death and plays an important role in research and prevention interventions in U.S. states. In the current study, children with epilepsy who died were older and more often male compared with children without epilepsy who died, consistent with a recent U.S. national profile of childhood epilepsy, indicating that the prevalence of epilepsy was higher in older children and boys [17]. Third, because the underlying causes of death due to seizures could not be distinguished from deaths from other neurological conditions in the NCDR-CRS, we had to exclude both kinds of deaths so as not to distort our proportionate mortality analyses, thus preventing us from analyzing causes of death due to neurological disorders. However, underlying neurological disorders are major causes of death in children with epilepsy [2,3,5,6]. Fourth, because of the limitation of the NCDR-CRS, it was not possible for us to correlate causes (such as due to pneumonia or drowning) or risks of death with specific seizure types or epilepsy syndromes nor could the risk of death be correlated with whether the child with epilepsy history was seizure-free or not. We also could not identify or classify if some deaths in these children and young adults were sudden, unexplained deaths. Finally, our attempt to ascertain deaths from epilepsy by inclusions and exclusions may have misclassified epilepsy deaths.

5. Conclusions

In summary, this study of cause-specific mortality in children and young adults with epilepsy identified the main causes of death as natural (related to primary medical conditions including pneumonias and congenital anomalies) rather than accidental deaths. The most prominent cause of accidental death was drowning. This study is valuable for clinicians' counseling parents about epilepsy-related causes of death. Measures in children and young adults with epilepsy to prevent pneumonia such as pneumococcal immunization and to prevent drowning such as better instruction and monitoring before or during swimming and learning of cardiopulmonary resuscitation may reduce their increased mortality risks. Further efforts to study mortality in children and young adults with epilepsy, on a population basis in states or nationwide, are recommended. Epilepsy stakeholders can contact their state

Child Death Review program [18] to learn about opportunities to support or participate in the review system and to develop educational programs focused on mortality in children with epilepsy for their communities.

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Abbreviations

NCDR-CRS National Child Death Review Case Reporting System

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Table 1

Proportionate mortality by official manner of death in children and young adults (28 days to 24 years) with epilepsy and in children and young adults without epilepsy, U.S. National Child Death Review Case Reporting System^a, 2004–2012.

Official manner of death	Decedents with epilepsy		Decedents without epilepsy		Diff. %	95% CI, %	p < 0.05*
	No.	%	No.	%			
Natural	370	67.15	16,801	34.90	32.25	(27.91, 36.60)	*
Accident	84	15.25	16,544	34.36	-19.12	(-22.54, -15.69)	*
Suicide	7	^b	2890	6.00	N/A	N/A	
Homicide	33	5.99	5112	10.62	-4.63	(-6.89, -2.37)	*
Undetermined	45	8.17	5869	12.19	-4.02	(-6.60, -1.44)	*
Others ^c	12	2.18 ^d	930	1.93	0.25	(-1.10, 1.59)	
Total	551	100.00	48,146	100.00			

N/A: not applicable.

^aData came from 32 U.S. states.

^bEstimates are considered unstable when their relative standard errors are > 30%.

^c“Others” include deaths whose official manner are pending and unknown. In addition, nonresponsive (or considered missing) data are also included in this group.

^dRelative standard error is > 20% but < 30%.

* p < 0.05, Z-test for statistically significant differences between the proportion of deaths with epilepsy and the proportion of deaths without epilepsy [the reference group] based on a 95% two-sided confidence interval of this difference in proportions that excluded “0”.

Table 2

Proportionate mortality by underlying causes of death^a in children and young adults (28 days to 24 years) with epilepsy and in children and young adults without epilepsy, U.S. National Child Death Review Case Reporting System^b, 2004–2012.

Underlying causes of death	Decedents with epilepsy		Decedents without epilepsy		Diff. %	95% CI, %	* p < 0.05
	No.	%	No.	%			
Related to external events							
Motor vehicle	7	^c	8254	17.14	N/A	N/A	
Drowning	44	7.99	2260	4.69	3.29	(0.84, 5.74)	*
Asphyxia	25	4.54	4977	10.34	-5.80	(-7.81, -3.79)	*
Weapon	24	4.36	5380	11.17	-6.82	(-8.80, -4.83)	*
Falls, crush injuries	6	^c	662	1.37	N/A	N/A	
Poisoning	9	^c	1371	2.85	N/A	N/A	
Other ^d	6	^c	866	1.80	N/A	N/A	
Related to medical conditions							
Cardiovascular	25	4.54	1394	2.90	1.64	(-0.25, 3.53)	
Congenital anomaly	51	9.26	2991	6.21	3.04	(0.41, 5.68)	*
Pneumonia	48	8.71	1234	2.56	6.15	(3.65, 8.64)	*
Infection	19	3.45 ^e	1274	2.65	0.80	(-0.86, 2.47)	
Perinatal ^f	7	^c	211	0.44	N/A	N/A	
Other ^g	208	37.75	3693	7.67	30.08	(25.79, 34.36)	*
Undetermined	7	^c	426	0.88	N/A	N/A	
Undetermined if related to medical or external events	33	5.99	3379	7.02	-1.03	(-3.24, 1.18)	
Unknown	32	5.81	9774	20.30	-14.49	(-16.81, -12.81)	*

N/A: not applicable.

^aUnderlying causes of death were defined by the U.S. National Child Death Review Case Reporting System. Cases with an underlying cause of death attributable to “neurological/seizure disorders” were excluded from the analysis because neurological causes cannot be distinguished from seizure disorders in this system.

^bData came from 32 U.S. states.

^cEstimates are considered unstable when their relative standard errors are ≥ 30%.

^dUnderlying causes of death related to external events, with five or fewer deaths regrouped into the category “Other”. Specific causes regrouped into the category “Other” include the following: external injury – fire, burn, and electrocution; external injury – bite; external injury – exposure; external injury – undetermined; and external injury – unknown. In addition, nonresponsive (or considered missing) data are also included in this group.

^eRelative standard error is ≥ 20% but <30%.

^fRefers to those perinatal conditions as the cause of deaths but in which the child lived for 28 days or older before dying.

^gUnderlying causes of death related to medical conditions, with five or fewer deaths regrouped into the category “Other”. Specific causes regrouped into the category “Other” include the following: asthma; cancer; human immunodeficiency virus infections (HIVs), acquired

immunodeficiency syndrome (AIDS); influenza; low birth weight; malnutrition, dehydration; prematurity; sudden infant death syndrome; and unknown cause of death.

* $p < 0.05$, Z-test for statistically significant differences between the proportion of deaths with epilepsy and the proportion of deaths without epilepsy [the reference group] based on a 95% two-sided confidence interval of this difference in proportions that excluded "0".

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