Mortality Risks in New-Onset Childhood Epilepsy

WHAT'S KNOWN ON THIS SUBJECT: Seizure-related death, including sudden death, is a frightening prospect. In part because risk and prevention are poorly understood, neurologists tend to avoid discussions of sudden death with families and young patients.

WHAT THIS STUDY ADDS: Most deaths in children with epilepsy are not seizure related. Relative to the population, however, sudden and seizure-related deaths alone double overall mortality. In uncomplicated epilepsy, such deaths occur at rates comparable to individual leading causes of death in young people.

abstract

OBJECTIVES: Estimate the causes and risk of death, specifically seizure related, in children followed from onset of epilepsy and to contrast the risk of seizure-related death with other common causes of death in the population.

METHODS: Mortality experiences from 4 pediatric cohorts of newly diagnosed patients were combined. Causes of death were classified as seizure related (including sudden unexpected death [SUDEP]), natural causes, nonnatural causes, and unknown.

RESULTS: Of 2239 subjects followed up for >30 000 person-years, 79 died. Ten subjects with lethal neurometabolic conditions were ultimately excluded. The overall death rate (per 100 000 person-years) was 228; 743 in complicated epilepsy (with associated neurodisability or underlying brain condition) and 36 in uncomplicated epilepsy. Thirteen deaths were seizure-related (10 SUDEP, 3 other), accounting for 19% of all deaths. Seizure-related death rates were 43 overall, 122 for complicated epilepsy, and 14 for uncomplicated epilepsy. Death rates from other natural causes were 159, 561, and 9, respectively. Of 48 deaths from other natural causes, 37 were due to pneumonia or other respiratory complications.

CONCLUSIONS: Most excess death in young people with epilepsy is not seizure-related. Mortality is significantly higher compared with the general population in children with complicated epilepsy but not uncomplicated epilepsy. The SUDEP rate was similar to or higher than sudden infant death syndrome rates. In uncomplicated epilepsy, sudden and seizure-related death rates were similar to or higher than rates for other common causes of death in young people (eg, accidents, suicides, homicides). Relating the risk of death in epilepsy to familiar risks may facilitate discussions of seizure-related mortality with patients and families. *Pediatrics* 2013;132:124–131

AUTHORS: Anne T. Berg, PhD,^a Katherine Nickels, MD,^b Elaine C. Wirrell, MD,^b Ada T. Geerts, PhD,^c Petra M.C. Callenbach, PhD,^d Willem F. Arts, MD, PhD,^c Christina Rios, BA,^e Peter R. Camfield, MD,^f and Carol S. Camfield, MD^f

^aEpilepsy Center, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, Illinois; ^bEpilepsy and Child and Adolescent Neurology, Mayo Clinic, Rochester, Minnesota; ^cNeurology, Erasmus Medical Center, Rotterdam, Netherlands; ^dNeurology, University Medical Center Groningen, University of Groningen, Groningen, Netherlands; ^ePediatrics, Yale Medical School, New Haven, Connecticut; and ^fPediatrics, Dalhousie University, Halifax, Nova Scotia, Canada

KEY WORDS

children, epilepsy, mortality, SUDEP

ABBREVIATIONS

CI—confidence interval

PY—person-years

SIDS—sudden infant death syndrome

SUDEP—sudden unexpected death in epilepsy

Dr Berg is principal investigator for the Connecticut Study of Epilepsy, planned and conducted the pooled analysis, and drafted the initial manuscript; Dr Nickels is the lead author on the Rochester study, provided follow-up time and characterized patient deaths and seizure outcomes, and participated in revising the manuscript; Dr Wirrell is the senior investigator of the Rochester study, contributed to conceptualizing the analysis, participated in review of medical charts to define epilepsy variables and characterize patient deaths, and participated in revising the manuscript; Dr Geerts is 1 of the lead authors from the Dutch study, provided follow-up time information and information about causes of death, and participated in revision of the manuscript; Dr Callenbach is 1 of the lead authors from the Dutch study, provided information about the study and causes of death, and participated in revision of the manuscript; Dr Arts is 1 of the senior investigators of the Dutch study, provided review of causes of death, and participated in revision of the manuscript; Ms Rios is the project coordinator for the Connecticut study, developed and executed the approaches for ascertaining death and causes of death, and participated in revising the manuscript; Dr P.R. Camfield is a co-principal investigator for the Nova Scotia study, provided additional information about the Nova Scotia study, reviewed causes of death, and participated in revising the manuscript; and Dr C.S. Camfield is a co-principal investigator for the Nova Scotia study, provided additional information about the Nova Scotia study, critiqued the approach, and participated in revising the manuscript. All authors read and approved the submitted version.

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Mortality rates in people with epilepsy are 2 to 4 times higher overall^{1–4} and 5 to 10 times higher in pediatric epilepsy.^{5–9} This increased risk occurs for several reasons: (1) lethal neurometabolic conditions that present with epilepsy; (2) systemic complications associated with neurodisability; (3) indirect factors resulting in higher mortality (eg, suicide); and (4) deaths shown or presumed to be directly due to the occurrence of a seizure. This last group includes sudden unexpected death in epilepsy (SUDEP), which has been the center of an international awareness campaign¹⁰ and many conferences, as well as the focus of several grant initiatives. Although increasing evidence is clarifying the sequence of events leading to SUDEP, many of which may have implications for prevention, there is still a reticence among neurologists to raise the subject of SUDEP with patients and families. A summary of the National Institutes of Neurologic Disorders and Stroke conference on SUDEP highlighted the importance of conveying information to families and patients about the risk of death in general and SUDEP in particular.¹¹ Concerns were expressed that these discussions might cause anxiety or depression and that there is a need to distinguish between “low” risk and “no” risk. Further research was suggested to determine

how best to provide information about SUDEP and how to overcome the reluctance of health professionals to present this information. This reluctance stands in sharp contrast to the situation in pediatrics, where pediatricians are trained and provide professional support in discussing these risks with parents beginning with the risk of sudden infant death syndrome (SIDS).¹²

One barrier in discussing SUDEP or seizure-related death is the paucity of data on which to base an accurate risk estimate, particularly in children and most especially at the time of initial diagnosis when the topic might reasonably first be raised. This lack of data exists in part because the risk is statistically very low and thus hard to determine in a single study. To address this knowledge gap, we pooled data from 4 large pediatric cohorts to obtain direct estimates of the mortality risk overall and from specific causes of mortality, particularly seizure related and SUDEP.

METHODS

The authors of 4 published pediatric cohort studies combined data regarding mortality.^{5–9} Methods for each study are outlined in Table 1. For 1 study, results are updated here from an earlier report based on an additional 8 years of follow-up.⁵

Deaths were ascertained systematically within each study. Methods included report of parents to study staff during scheduled follow-up calls⁵; report of treating physicians to study staff^{5,6,8}; review of national death indices, health registries, and other administrative databases depending on the study^{5–8}; and an active population-based surveillance program.⁹ Epilepsy in association with lethal neurometabolic or neurodegenerative conditions was explicitly excluded from 1 study.⁷ To be consistent, children with such conditions were excluded from the other 3 studies for these analyses.

Epilepsy presentation was considered “complicated” if there was a known structural brain lesion, significant intellectual disability, or abnormal result on neurologic examination; it was considered “uncomplicated” if these factors were absent.^{5,6,8,9} Children with autism generally had intellectual disability and were thus included in the complicated group. For 1 study, the distinction was based solely on the absence or presence of cognitive or neurologic disability.⁷ This information was extracted from the medical records as recorded by the child’s treating neurologist. In 1 study, research MRIs and neurocognitive testing were performed in more than one-half of the cohort,⁵ and the results were used to

TABLE 1 Description of 4 Studies

Variable	Nova Scotia ⁷	Netherlands ^{6,8}	Connecticut ⁵	Rochester ⁹
Years of recruitment	1977–1985	1988–1992	1993–1997	1980–2009
Methods and patient source	Prospective, population based	Prospective, regional	Prospective, community based	Retrospective, population based
Inclusion criteria	Newly diagnosed epilepsy; ≥ 2 unprovoked seizures Evidence of progressive neurologic disease was grounds for exclusion	Newly diagnosed epilepsy; ≥ 2 unprovoked seizures	Newly diagnosed epilepsy; ≥ 2 unprovoked seizures	Newly diagnosed epilepsy; ≥ 2 unprovoked seizures or single seizure with brain injury and treatment initiated
Age at onset	1 mo–16 y Mean $\pm$ SD: 6.2 ± 4.5 y	1 mo–16 y Mean $\pm$ SD: 5.6 ± 4.1 y	1 mo–16 y Mean $\pm$ SD: 5.8 ± 4.0 y	1 mo–17 y Mean $\pm$ SD: 6.9 ± 5.1 y
Age at time of analysis in survivors	Mean: 19.2 y	5.3–33.5 y Mean $\pm$ SD: 20.7 ± 4.7 y	14.5–35.0 y Mean $\pm$ SD: 23.3 ± 4.3 y	0.2–45.4 y Mean $\pm$ SD: 16.7 ± 9 y
Age at death	0.5–30 y Mean $\pm$ SD: 12.0 ± 7.3 y	2.1–26.9 y Mean $\pm$ SD: 11.8 ± 7.5 y	1.8–28.7 y Mean $\pm$ SD: 11.2 ± 8.8 y	0.2–21.7 y Mean $\pm$ SD: 8.2 ± 6.5 y
Ascertainment of deaths	Provincial health registry and other clinical sources	Physician report to study, national health records	Family report to study, Social Security Death Index	Rochester Epidemiology Project surveillance system

supplement clinical assessment. Person-years (PY) of follow-up were calculated for each patient as the time from study entry (diagnosis) to either death or, for survivors, date of last contact (Table 1).

All studies obtained copies of death certificates and, if performed, copies of autopsy reports. In some instances, eye witness accounts or emergency department or in-patient reports from terminal visits or hospitalizations were available and contributed to assignment of cause of death. Information about cause of death was compiled from death certificates, autopsy reports, and other medical records. Collaborating investigators reviewed the information, and a consensus was reached on how to best categorize each death.

Causes of death were grouped as SUDEP, other seizure related, other natural, and nonnatural (Table 2). In the absence of any information, the cause of death was characterized as unknown. SUDEP was further categorized into definite, probable, and possible SUDEP according to recent recommendations.¹³ In children with significant neurologic compromise, we considered an otherwise unexplained sudden death attributed to cardiac or cardiopulmonary arrest to be possible (not probable) SUDEP in the absence of an autopsy report that definitively excluded infections or other sources of airway compromise.

Death rates with 95% confidence intervals (CIs) are reported as number per 100 000 PY and were calculated by using standard techniques.¹⁴ Poisson regression was performed in SAS Proc Genmod (SAS version 9.2, SAS Institute, Inc, Cary, NC) to test for differences between studies and between complicated and uncomplicated epilepsy. We performed sensitivity analyses to examine the impact of the following: (1) counting possible SUDEP as seizure related; and (2) counting unknown cause as being seizure related or even SUDEP. For

TABLE 2 Definitions of Causes of Death

SUDEP	Sudden unexpected death in someone with epilepsy occurring in benign circumstances for which no specific cause can be identified. Level of certainty regarding the designation of SUDEP was determined with reference to the unified definition. ¹³
Definite	Sudden unexpected witnessed or unwitnessed nontraumatic, nondrowning death occurring in benign circumstances in someone with epilepsy with or without evidence of a seizure in which a postmortem examination does not reveal a cause of death.
Probable	Sudden unexpected witnessed or unwitnessed nontraumatic, nondrowning death occurring in benign circumstances in someone with epilepsy with or without evidence of a seizure having occurred. No postmortem examination is performed or results are unavailable.
Possible	A competing cause of death is present. Complications from severe neurodevelopmental disability was considered a potential competing cause of death in the absence of postmortem results.
Seizure related, not SUDEP	Any death that resulted from documented complications of a seizure (e.g., aspiration during seizure), iatrogenic complications as the result of treating acute seizures, or status epilepticus.
Other natural	Any death not attributable to a seizure or SUDEP and that could specifically be attributed to an acute or chronic medical condition. These could include conditions related to the epilepsy (e.g., brain tumors), consequences of neurodevelopmental impairments (aspiration pneumonia not due directly to a seizure), infections, or other conditions (e.g., cancer). Complication of treatment of a medical condition (e.g., shunt malfunction) are considered in this category.
Nonnatural causes	Any death attributable to homicide, suicide, or accidental death.
Unknown	Inadequate information available to make an attribution of the specific cause of death or to group it into the scheme above

approximate comparisons, death rates in the first 3 decades of life from the 3 countries in which the studies were performed were obtained from vital statistics registries in each country.^{15–18}

All procedures were approved by the ethics committees at all participating institutions. The Connecticut, Dutch, and Canadian studies obtained written informed consent for participation in the original studies. The Rochester Epidemiology Project functions under a community consent protocol.

RESULTS

The 3 studies included 2239 patients with childhood-onset epilepsy (onset <16 years of age^{5–8} or ≤17 years of age⁹). Ten children with lethal metabolic conditions (2, Menkes kinky hair disease; 4, neuronal ceroid lipofuscinoses; 1, Zellwegger syndrome; 2, mitochondrial disorders; 1, Niemann-Pick disease) were excluded from further consideration.

The remaining 2229 subjects were followed for a total of 30 284 PY, and 69 deaths occurred (14–26 per study). The crude death rate per 100 000 PY for all subjects combined was 228 (95% CI: 174–282). Point estimates of the crude rates varied somewhat among the 4 studies, but their CIs overlap (Table 3). A formal test of these differences indicated that they were not overall statistically significant. Within complicated and uncomplicated groups, these differences were greatly reduced. Data adequately fit assumptions for a Poisson distribution.

The death rate in the complicated group (743 [95% CI: 557–930]) was substantially higher than in the uncomplicated group (36 [95% CI: 11–61]) ($P < .0001$).

Causes of Death

Ten deaths were attributed to SUDEP (5 definite with autopsy confirmation, 3 probable, and 2 possible). Three seizure-related deaths occurred (1 status epilepticus, 1 iatrogenic complications

TABLE 3 Mortality Figures Overall and for Complicated and Uncomplicated Epilepsy Presentations

Study	Nova Scotia ⁷	Netherlands ^{6,8}	Connecticut ⁵	Rochester ⁹	Total
<i>N</i> (<i>n</i> subsequently excluded ^a)	686	472 (3)	613 (5)	468 (2)	2239 (10)
PY	8918	6763	10 047	4556	30 284
Average follow-up (y)	13.0	14.4	16.5	9.8	13.6
No. of deaths	26	15	14	14	69
Crude death rate/100 000 PY (95% CI)	292 (179–404)	222 (110–334)	139 (66–212)	307 (146–468)	228 (174–282)
Complicated	<i>n</i> = 173	<i>n</i> = 136	<i>n</i> = 149	<i>n</i> = 163	<i>n</i> = 621
PY	2249	1877	2381	1700	8207
Deaths	23	14	11	13	61
Crude death rate (95% CI)	1023 (605–1441)	745 (355, 1137)	462 (189–735)	765 (349–1180)	743 (567–930)
Uncomplicated	<i>n</i> = 513	<i>n</i> = 333	<i>n</i> = 459	<i>n</i> = 303	<i>n</i> = 1608
PY	6669	4886	7665	2857	22 077
Deaths	3	1	3	1	8
Crude death rate (95% CI)	45 (0–96)	21 (0, 61)	39 (0–83)	35 (0–104)	36 (11–61)

CI, confidence interval.

^a Number with neurometabolic diseases who are reported in the tallies for these cohorts in the literature but who have been subsequently excluded from further analyses.

from treatment of status epilepticus, and 1 aspiration during a seizure). Other natural causes accounted for 48 deaths (pneumonia [*n* = 35], sepsis [*n* = 3], ventriculoperitoneal shunt malfunction [*n* = 3], tracheotomy malfunction [*n* = 1], pulmonary embolism [*n* = 1], cerebral hemorrhage [*n* = 2], cancer [*n* = 2], and cardiomyopathy [*n* = 1]). Five deaths were due to nonnatural causes (2 nonseizure-related accidents, 2 suicides, and 1 homicide). No information was available regarding cause of death for the remaining 3 individuals.

Death rates according to types of cause were calculated overall and for complicated and uncomplicated presentations (Table 4). For potentially seizure-related deaths, we calculated rates for SUDEP (*n* = 10), definite and probable SUDEP (*n* = 8), all seizure-related death (*n* = 13

[10 SUDEP and 3 other]), and seizure-related deaths plus unknown (*n* = 16 [SUDEP, other seizure-related, and unknown]). All causes of death were substantially higher in the complicated group compared with the uncomplicated group. The rate of seizure-related deaths in the complicated group (122 per 100 000 PY) was multiples of the total population death rates in the first 3 decades of life and higher than SIDS rates in developed countries (Table 5). The comparable figure for the uncomplicated group (14 per 100 000 PY) was in the same range as or slightly higher than the single leading causes of death for young people in the population (depending on the country), at the low end of the range for SIDS in developed countries, and higher than 1 estimate of sudden death in the 1- to 30-year-olds.

Patient Profiles Associated With Mortality

Deaths occurred on average 7.5 ($\pm$ 4.9) years after diagnosis (Table 6). In the complicated group, there was a moderate trend suggesting that older onset was associated with a longer time to death (Fig 1).

Average age at death was 11.6 years and was similar across most causes of death. Male and female subjects were approximately equally represented across cause of death categories. Given the small numbers involved, formal tests were not conducted. Data are presented for descriptive purposes only.

Most of the deaths (*n* = 61 [88%]) occurred in participants with complicated presentations, and almost all of these individuals had mild (*n* = 5) or more severe (*n* = 51) cognitive impairment. Drug resistance (57%), lack of seizure freedom in the past year (74%), and a history of convulsive seizures (68%) and of status epilepticus (48%) were all more common than reported for these cohorts in previous publications.^{5–9} No seizure-related deaths occurred in children with the generally pharmacoresponsive and often self-limited syndromes such as childhood absence epilepsy or benign rolandic epilepsy. Two accidental deaths occurred; neither was seizure related.

TABLE 4 Estimated Mortality Rates for All Study Participants and for Uncomplicated and Complicated Epilepsy Presentations for Total Mortality and Cause-Specific Mortality in the 4 Combined Cohorts

Mortality	Overall	Complicated	Uncomplicated
Overall mortality	228 (174–282)	743 (557–930)	36 (11–61)
SUDEP	33 (13–53)	98 (30–165)	9 (0–22)
Definite and probable SUDEP	26 (8–45)	73 (15–132)	9 (0–22)
Any seizure-related death	43 (20–66)	122 (46–197)	14 (0–29)
Any seizure-related death and unknown ^a	53 (27–79)	146 (63–229)	18 (0–36)
SUDEP and unknown ^a	43 (20–66)	122 (46–197)	14 (0–29)
Other natural causes	159 (114–203)	561 (399–722)	9 (0–22)

All estimates are reported per 100 000 PY with 95% CIs.

^a Added to seizure-related deaths to determine the impact of the 3 unknown cases on seizure-related death. The difference between figures calculated with and without the unknown deaths reflects the potential error in estimating this figure due to the missing information for these 3 individuals.

DISCUSSION

Compared with death rates for 1- to 29-year-olds in the United States, Canada, and the Netherlands, the overall death rates in young people followed from their initial diagnosis of childhood-onset epilepsy were substantially elevated. Most of the excess risk occurred

in association with complicated epilepsy presentations, particularly with neurologic and intellectual disability. The crude mortality rate in this group (743 per 100 000) exceeded recent reports for infant mortality rates in the same countries from which the cohorts came (Table 5). Most of the deaths were secondary to infections

and complications from underlying neurologic disability, which by itself confers a substantial mortality risk.^{19–25} Prevention of such deaths, when possible, likely lies in the arena of long-term supportive care and infection control, not seizure management per se. Inclusion of 10 children with diagnosed neurometabolic syndromes with a known lethal course yielded a higher death rate overall (261 [95% CI: 203–318]), particularly in the complicated group (861 [95% CI: 661–1062]). As with the neurodisability group, prevention of deaths associated with these diseases has little to do with seizure management. Comparable to reports from other researchers,^{2,22,26} the death rate in the uncomplicated epilepsy group did not seem substantially greater than expected for the general population.

TABLE 5 Mortality Rates by Age and for Specific Causes in the United States, Canada, and the Netherlands

Mortality Age Group or Cause	United States ¹⁵	Canada ^{16–17}	The Netherlands ¹⁸
Infant	630	510	439
SIDS	57	35	9
1- to 29-year-olds ^a			
Overall	55	34	26
Accidental	24.6	14.2	7.0
Homicide	7.5	2.0	0.9
Suicide	6.8	6.9	3.0
Cancers	4.3	4.5	3.9
Heart/circulatory	3.2	2.5	1.9

Rates are given per 100 000 per year.

^a Weighted average based on age-specific brackets.

TABLE 6 Characteristics of Young People who Died (Overall and Grouped According to Cause of Death)

Characteristic	Overall (N = 69 ^a)	SUDEP (n = 10)	Other Seizure Related (n = 3)	Other Natural (n = 48)	Nonnatural (n = 5)
Median age at onset	2.0 y	2.7 y	4.6 y	1.3 y	12.0 y
IQR (minimum, maximum)	6 mo–7.0 y (1 mo– 15.7 y)	1.3–11.8 y (1 mo–12.3 y)	(8 mo–9.8 y)	0.3–3.7 y (1 mo–12y)	11.4–14.0 y (3.4–15.3 y)
Median age at death	11.0 y	13.7 y	7.8 y	8.3 y	18.2 y
IQR (minimum, maximum)	5–17 y (7 mo–30 y)	5.5–20 y (2.0– 27.9 y)	(5.0–15.8 y)	4.0–13.7 y (7 mo–28.6 y)	18.0–19.2 y (13.9–30.0 y)
Median time to death	7.0 y	9.2y	6.3 y	5.3 y	8.3 y
IQR (minimum, maximum)	3.2–11.7 y (5mo– 20.2 y)	3.2–12.8 y (5 mo– 15.9 y)	1.3–6.9 y	2.8–11.6 y (8 mo–20.2 y)	7.5–10.4 y (4.0–14.5 y)
Gender, n (%)					
Male	37 (54)	5 (50)	2 (67)	23 (48)	4 (80)
Female	32 (46)	5 (10)	1 (33)	45 (52)	1 (20)
Presentation of epilepsy, n (%)					
Complicated	61 (88)	8 (80)	2 (67)	46 (96)	3 (60)
Uncomplicated	8 (12)	2 (20)	1 (33)	2 (4)	2 (20)
Cognitive level, n (%)					
Normal	13 (19)	3 (30)	1 (33)	4 (8)	4 (80)
Mildly impaired	5 (7)	3 (30)	1 (33)	1 (2)	0 (0)
Moderately/severely impaired	51 (74)	4 (40)	1 (33)	43 (90)	1 (20)
Type of epilepsy, n					
Nonsyndromic-focal	33	6	3	19	4
Nonsyndromic-generalized, mixed	20	1	0	17	0
West, LGS, Ohtahara, Dravet syndromes	13	3	0	10	0
Other	3	0	0	2	1
Drug resistance, n (%)	39 (57)	6 (60)	3 (100)	27 (56)	3 (60)
Epilepsy surgery, n (%)	3 (4)	2 (20)	0 (0)	1 (2)	0 (0)
Seizure in last year, n (%)	51 (74)	9 (90)	3 (100)	34 (71)	3 (60)
Convulsions, n (%)	47 (68)	9 (50)	3 (100)	31 (65)	3 (60)
Status epilepticus, n (%)	33 (48)	5 (50)	3 (100)	24 (50)	1 (20)

A version of this table with CIs is available online as Supplemental Information. For seizure control, an indicator for <1 versus ≥1 year seizure-free at time of death or at last contact was adopted because this factor could be accurately applied in all patients given the variability in coding of information across studies. Pharmacoresistance was defined fairly consistently across the studies with only minor variations. All studies required failure of at least 2 or 3 medications to meet the criteria for pharmacoresistance. IQR, interquartile range; LGS, Lennox-Gastaut syndrome.

^a Three subjects with unknown causes are not included beyond the overall summary information.

FIGURE 1

Association between age at onset of epilepsy and time to death in complicated and uncomplicated groups. The correlation between age at onset and years to death was 0.25 ($P = .05$) in the complicated group and -0.20 ($P = .63$) in the uncomplicated group.

Sudden death is of particular concern for people with epilepsy and their families.¹⁰ In young adults (aged 20–40 years), the rate of sudden death in people with epilepsy is estimated to be 24 times that seen in the general population.²⁷ The crude death rate from SUDEP alone in our combined series (33 per 100 000 PY overall and 26 per 100 000 PY for definite/probable SUDEP) is similar to the total population death rate in the first 2 decades of life (excluding infancy) (Table 6). In participants with complicated presentations, however, the SUDEP rate was 2 to 3 times the overall death rates seen in the general population. In fact, others have found a preponderance of SUDEP in association with complicated epilepsy.^{28–31}

In young people with uncomplicated epilepsy, the death rates from SUDEP (9 per 100 000 PY) and all seizure-related deaths (14 per 100 000 PY) are comparable to the leading cause of death (accidents) and higher than other common causes of death, including homicide, suicide, cancer, and heart disease (Table 5). Our estimated SUDEP and seizure-related death rates are in the same range as SIDS death rates in developed countries (9 per 100 000 [Japan] to 80 per 100 000 [New Zealand]).³²

Our point estimates, even for uncomplicated epilepsy, are greater than the rate for all sudden deaths reported in the Netherlands in 1- to 30-year-olds (2.26 per 100 000 PY).

SUDEP risk is age related and is higher in adults, both in adult-onset epilepsy³⁰ and in adults with childhood-onset epilepsy.³³ No firm data are available, but anecdotal reports¹⁰ and identified risk factors³⁴ suggest that the transition time for adolescents and young adults, who may not fully understand the importance of good sleep and nutrition patterns, avoidance of excess alcohol and use of drugs, and adherence to prescribed treatment for preventing seizures, may pose some risks that could be modified. Transition from pediatric to adult care is complicated and particularly so in children with chronic neurologic conditions.³⁵

Somewhat less appreciated is that SUDEP also occurs in infants and young children. A recent survey of parents whose children had Dravet syndrome reported a series of 31 deaths, 19 of which were attributed to SUDEP. The majority of the children were aged <5 years at the time of their deaths.³⁶ Current thinking suggests there is a spectrum of sudden death in the very young beginning with

SIDS, of which SUDEP may be a part and which involves a variety of mechanisms including brainstem serotonergic dysfunction and heart channelopathies.^{32,37–39} Whether mechanisms involved in SUDEP in very young children differ from those in older individuals is under investigation.

The absence of definite seizure-related accidental deaths was encouraging. Potentially, the 3 deaths for which the causes were unknown could have been due to seizure-related accidents; however, including these 3 deaths still places an upper limit on such deaths in our combined cohorts. The low or absent risks we observed in no way indicate that the potential risks are not real. We speculate that common sense measures to prevent seizure-related accidents and accidental deaths in young persons may be having an impact.

The suicide rate was also comparable to that in the general population. Our estimate could be higher if any of the deaths with unknown causes were due to suicide. Relationship to medication use was not available in all studies; however, as reviewed elsewhere, the risks associated with uncontrolled seizures far outweigh the risk of suicide and any potential increased risk of suicide associated with medication use, a risk that has largely been disproven.⁴⁰

Our study has several advantages. We assembled perhaps the largest series of population-representative pediatric epilepsy patients followed from initial diagnosis for ≥ 10 years. All studies independently took very similar approaches to defining entry criteria and targeted the same age-at-onset range. All studies had systematic approaches to determine that a death had occurred and obtained death certificates and, when available, autopsy reports. Hospital records and eye witness accounts were also reviewed when available. We used the recent recommendations on SUDEP definitions and determined

the level of certainty regarding that designation.¹³

There are inevitable weaknesses. Studies were performed in different populations during largely non-overlapping time periods. We were not able to combine data at an individual level because files were no longer available for 1 study. We could not make precise comparisons with population death rates because studies were performed in different countries and over different time periods. However, such comparisons are always approximate. We present them to place our mortality findings in a larger context.

Unlike SIDS, for which there has been a major public health campaign aimed at providers and parents and advanced through the American Academy of Pediatrics¹² and other organizations, discussion of SUDEP still seems to encounter a certain reluctance on the part of neurologic care providers.¹¹ Parents, however, generally do want to be informed of these risks,⁴¹ and

parents who have lost children wish they had been offered such information.¹⁰ Although this reluctance and unease among neurologists will surely change,⁴² it seems that pediatricians who have overcome the barriers of discussing such risks with their families and young patients might be well positioned, if provided with reasonable information about SUDEP, to broach these topics and to address parents' concerns. Ways of preventing SUDEP are unclear and not as advanced as with SIDS. The main risk factor for SUDEP is lack of seizure control, which highlights the importance of adherence to recommended medication schedules.^{43,44} Children with seizures during sleep may also be at increased risk depending on their epilepsy and seizure type, and families may benefit from discussion about this particular concern. Reasonable supervision and precautions may also mitigate some of the risk.⁴⁵ These issues can be emphasized with parents of young children with epilepsy as well as with adolescents acquiring greater

autonomy and transitioning to adult care.³⁵

CONCLUSIONS

Most mortality in young people with epilepsy is secondary to factors associated with neurodisability. Sudden and other seizure-related death does occur at rates higher than in the general population, although most of the risk occurs in association with complicated epilepsy. Demystifying the risk by measuring it and placing it in the context of other risks of childhood death faced by all parents may facilitate discussion of seizure-related death. Pediatricians may benefit those families who have a child with epilepsy by discussing these issues frankly. Generally, they can offer reassurance regarding the actual magnitude of the risk. Providing families with such information as well as an understanding of the importance of medication adherence and other common sense measures is a role appropriate for primary care providers.

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Address correspondence to Anne T. Berg, PhD, Epilepsy Center, Ann & Robert H. Lurie Children's Hospital of Chicago, 225 East Chicago Ave, Box 29, Chicago, IL 60611. E-mail: atberg@luriechildrens.org

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