Mortality in Childhood-Onset Epilepsy

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Objective: To evaluate mortality in children with newly diagnosed epilepsy, to determine the risk of death, and to identify predictors of death from the point of diagnosis.

Design: Prospective community-based cohort of 613 children with newly diagnosed epilepsy. The outcome measure was death. Chi² Tests were used for bivariate analyses and the Cox proportional hazards model for multivariable analyses. Standardized mortality ratios were used to quantify the excess mortality in the cohort relative to the population.

Results: Thirteen deaths occurred during 4733 person-years of follow-up, for a crude death rate of 2.7 per 1000 person-years (0.52 per 1000 person-years in those with nonsymptomatic epilepsy and 12.6 per 1000 person-years in those with symptomatic epilepsy). Ten deaths were associated with the underlying cause of the seizures, 2 were associated with the occurrence or probable occurrence of seizures, and 1 was unrelated to seizures or the underlying disorder. On multivariable analysis, symptomatic etiology (rate ratio, 10.2; 95% confidence interval [CI], 2.1-49.6) and epileptic encephalopathy (rate ratio, 13.3; 95% CI, 3.4-51.7) were independently associated with mortality. The overall standardized mortality ratio for the cohort was 7.54 (95% CI, 4.38-12.99). In children with symptomatic epilepsy, the standardized mortality ratio was 33.46 (95% CI, 18.53-60.43), and in those with nonsymptomatic epilepsy, it was 1.43 (95% CI, 0.36-5.73).

Conclusions: Children with epilepsy have an increased risk of death. Most deaths occur in children with severe underlying conditions and are not directly related to the occurrence of seizures.

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Mortality rates are elevated in people with epilepsy. Some of the increased risk of death is attributable to the underlying cause of the epilepsy, some to seizures (including sudden unexpected deaths presumably related to the occurrence of seizures), and some perhaps to comorbid conditions that may be linked to epilepsy or whose course may be affected by epilepsy. Large-scale studies have reported on death in people with epilepsy followed from the time of their initial diagnosis. These studies focused on mixed age groups. Other authors have considered death (in particular, sudden death) in clinic-based and postsurgical samples of adults. Others have looked at death associated with epilepsy in a cross-sectional manner. This last approach can help put the issue into a population context, but is insufficient for the purposes of considering individual risk and timing of risk after diagnosis. To our knowledge, there are only 2 large prospective studies and 1 smaller study of mortality in children followed from the time of their initial diagnosis of epilepsy. We now report the results of a large community-based study of newly diagnosed epilepsy in children that has been conducted in Connecticut.

Methods

The Connecticut Study of Epilepsy is a prospective cohort of children who were recruited and followed starting from the day on which they were first diagnosed as having epilepsy. Children were recruited from 1993 to 1997. The study’s original intent was to determine the risk and predictors of different outcomes in children studied from the time of their initial diagnosis of epilepsy. Children were recruited from the practices of 16 of the 17 child neurologists practicing in the state and selected pediatricians and adult neurologists who indicated that they occasionally provided all initial care for a child with newly diagnosed epilepsy without referral to a pediatric neurologist. Although not strictly population-based, this is a community-based study and reflects community practice in the state. Eligible children were between the ages of 1 month and 15 years at the time of the ini-
tial unprovoked seizure, had at least 2 unprovoked seizures on separate days (the accepted minimum criterion for epilepsy), and were newly diagnosed as having epilepsy by the referring physicians during the recruitment period.

Seizures, underlying etiology, and epilepsy syndromes were reviewed and classified independently by 3 pediatric neurologists (S.S., F.M.T., and S.R.L.) based on all clinical information available at the time of initial diagnosis. Any discrepancies were reviewed and a consensus was reached. This process was repeated for each child 2 years after initial diagnosis based on all information that accumulated during the subsequent 2 years and all baseline information. Revised diagnoses of syndromes, etiologies, and seizure types were made.16 Because many of the changes became apparent soon after diagnosis, we used the syndromes and etiologies as we classified them 2 years after initial diagnosis.

Epilepsy was classified as symptomatic if an identified neurological abnormality associated with an increased risk of epilepsy (eg, cortical dysplasia or prior stroke) or evidence of a presumed intrauterine insult (eg, cerebral palsy) was found. Children who were, according to all available evidence, neurologically normal (aside from having epilepsy) were considered to have cryptogenic or idiopathic epilepsy, depending on whether their syndrome conformed to the criteria for an idiopathic syndrome. This is consistent with the recommended standards for epidemiological research in epilepsy.9 For this report, we have simply categorized etiology as symptomatic or not. Syndromes were identified and classified according to published criteria.11,12 For the analyses presented here, we focused on syndrome groups (eg, idiopathic generalized or symptomatic partial) and not on specific syndromes. Children with any of the syndromes in the categories for generalized cryptogenic or symptomatic epilepsies or for generalized symptomatic epilepsies (largely reflecting West and Lennox-Gastaut syndromes, although many other syndromes fall in this category) and those in the category for undetermined epilepsies with both generalized and partial features (these include severe myoclonic epilepsy of infancy and Landau-Kleffner syndromes) were considered to have one of the epileptic encephalopathies.13 This designation is new and still under consideration by the International League Against Epilepsy Task Force on Classification and Terminology14; however, it has been largely accepted in the epilepsy community. These are syndromes in which it is believed that there may be an interaction between the level of brain development, the underlying cause of the seizures, and the seizures themselves, which often leads to the apparent progressive nature of these forms of epilepsy. Epileptic encephalopathies include, but are not limited to, syndromes that had previously been referred to as minor motor seizures.

Early intractability was defined as failure of at least 2 appropriate antiepileptic drugs with at least 1 seizure a month on average during an 18-month period and no more than a 3-month seizure-free hiatus during the 18 months.11,12 In addition, these criteria had to be met within 3½ years after study entry to count as early-onset intractability.13 Because of the 18-month criterion, 14 children who were not followed for a minimum of 18 months are not classifiable with respect to this outcome.

Causes of death were grouped as (1) directly due to (eg, neurodegenerative disorder) or attributable to (eg, aspiration pneumonia) consequences associated with the underlying cause of the epilepsy, (2) due to or presumably due to the occurrence of seizures, or (3) unrelated to either the underlying cause or to the occurrence of seizures. Sudden unexpected death in epilepsy was defined according to the following published criteria: ‘‘sudden, unexpected witnessed or unwitnessed nontraumatic, non-drowning death in someone with epilepsy with or without evidence of a seizure and excluding documented status epilepticus, in which postmortem examination does not reveal a toxicologic or anatomic cause of death.’’16(p56) Classification of definite sudden death requires that an autopsy be done and demonstrate no immediate cause of death. Probable sudden death is diagnosed if there is no autopsy confirmation but the death otherwise conforms to this definition. Status epilepticus was defined as continuous or intermittent seizure activity lasting 30 minutes or longer without return to baseline during that time.17 Classification of status epilepticus present before or by the time of the initial diagnosis of epilepsy included status epilepticus during neonatal and prior provoked seizures as well as status epilepticus that occurred as one of the initial unprovoked seizures.18

Children were followed by telephoning their parents every 3 months and by rereviewing the medical records for additional information every 6 months. Informed written permission of the parent was obtained, as well as informed written or verbal consent as appropriate and when possible from the child. All procedures were approved by the institutional review boards of participating institutions. All methods conform to standards for responsible conduct of research with human subjects. Analyses of risk factors for death were performed using χ² tests for bivariate comparisons and the Cox proportional hazards model for multivariable analyses. To determine the standardized mortality ratios (SMRs) for our cohort, we used the population mortality rates reported in Connecticut from 1995 through 1997. Neonatal deaths were subtracted from the population figures, because children in our cohort had to have survived the first month of life to be eligible for entry into the cohort. Person-years spent in each age bracket (<1, 1 to <5, 5 to <10, 10 to <15, 15 to <20, and 20-24 years) were calculated for each child in the study and then summed to give the total number of person-years of observation for the study in each age category. We did this because mortality rates change across these age brackets, and our cohort members aged during the time we followed them. We used indirect standardization and applied the age-specific Connecticut mortality rates to the person-years in our study to obtain an expected number of deaths. The SMR is the ratio of the observed to the expected number of deaths. The standard error of the SMR was calculated according to standard methods.19

RESULTS

Seven hundred seventy eligible children were identified. Of these, 103 declined participation, 30 had language barriers or no telephone (requirement for a telephone-based follow-up study), 11 were not recommended for inclusion in the study for other reasons by their neurologist, and 13 were unreachable. The remaining 613 children (79.6%) were recruited into the study. There were 307 boys and 306 girls. The median age at study entry was 6.1 years (age range, 1 month to 16 years). At the time of reporting, the median follow-up was 7.9 years, and 90% of the cohort had been followed for at least 5 years, with 4733 person-years of follow-up. The median age at last follow-up was 14.1 years (age range, 0.8-26.5 years). Eighty-three children have been lost to follow-up or the families have refused to continue participation after a median of 4.2 years of follow-up. The remaining children have been actively followed or have died.

DEATHS

Thirteen study participants had died 7 months to 7 years (median, 4.2 years) after diagnosis (Figure 1) as of Janu-
ary 2004. The age at death ranged from 1.8 to 16.5 years (median, 6.0 years). Death was attributable to the underlying cause of epilepsy or considered a complication associated with the underlying cause in 9 cases. In 1 child who was seizure-free but had a severe brain malformation and died of an infection, the death may have been in part related to the underlying cause. Cause of death in 2 children was attributed to the occurrence or probable occurrence of seizures. One of these 2 children died during a witnessed seizure that may have been status epilepticus, although there is incomplete confirmation of the seizure’s duration. The other’s death was considered a definite sudden death in epilepsy with autopsy confirmation. The last death was unrelated to both the underlying cause of epilepsy and the occurrence of seizures (Table 1).

BIVARIATE ASSOCIATIONS

Children with remote symptomatic etiology, those whose epilepsy syndrome could be characterized as being one of the epileptic encephalopathies, those who were younger than 2 years at onset, those who had experienced 1 or more episodes of status epilepticus by the time they were initially diagnosed as having epilepsy, and those who became intractable early in the course of their epilepsy were at increased risk of death (Table 2 and Figure 2). Status epilepticus required further consideration. Children with episodes of status epilepticus during a provoked seizure before the onset of epilepsy were at high risk of death. These were episodes of status epilepticus that occurred in the context of intracranial infections and other insults. One child with severe myoclonic epilepsy in infancy had status epilepticus in the context of a febrile illness. Aside from that one instance, there were no deaths associated with febrile status epilepticus or with unprovoked status epilepticus as one of the initial presenting seizures. Sex and the presence of generalized tonic-clonic seizures were not significantly associated with mortality.

MULTIVARIABLE ANALYSIS

Age at onset was strongly correlated with syndrome type, which was in turn strongly correlated with etiology and seizure outcome. In a multivariable Cox proportional hazards model, remote symptomatic epilepsy (rate ratio [RR], 10.2; 95% confidence interval [CI], 2.1-49.6; P = .004) and epileptic encephalopathy (RR, 13.3; 95% CI, 3.4-51.7; P < .001) were independently associated with mortality.

If the death that was not clearly associated with the underlying cause of epilepsy or presumed to be associated with seizures is excluded, the rate ratio for symptomatic epilepsy was 7.7 (95% CI, 1.6-37.7; P = .01). After adjustment for etiology and epileptic encephalopathies, those who met criteria for early intractability had an elevated risk, although it did not achieve conventional levels of statistical significance (RR, 4.1; 95% CI, 0.9-17.5; P = .06).

We examined the group of syndromes referred to as the epileptic encephalopathies and its relation to death in each of the 2 strata defined by etiology (symptomatic or not). This syndrome group was significantly associated with death in both the symptomatic and the nonsymptomatic groups. The finding in the nonsymptomatic group, however, was based on only 1 death. Poor seizure outcome was also associated with death in the symptomatic group, although the effect did not attain conventional levels of statistical significance (RR, 3.7; 95% CI, 0.9-15.4; P = .08).

STANDARDIZED MORTALITY RATIOS

We compared the mortality experienced by the participants in our cohort with that in the population of Connecticut. The overall death rate in Connecticut for persons 1 month to 25 years of age was 0.47 per 1000 per year. The overall rate among members of our cohort was several times higher, 2.7 per 1000 person-years (0.52 per 1000 person-years in the nonsymptomatic group and 12.6 per 1000 person-years in the symptomatic group). The SMR for the overall cohort compared with the Connecticut population was 7.54 (95% CI, 4.38-12.99). In children with nonsymptomatic forms of epilepsy, the SMR was 1.43 (95% CI, 0.36-5.73); and in those with symptomatic epilepsy, it was 33.46 (95% CI, 18.53-60.43).

COMMENT

Our study finds that deaths in this age group are mostly confined to children with severe forms of epilepsy and serious underlying disorders. They are rarely attributable to the occurrence of seizures themselves. Few deaths occur in neurologically normal children. Comparison of our findings with those of Camfield and Callenbach and their colleagues confirms these conclusions (Table 3). The Canadian study found that mortality was many times greater than in the population for children with neurological dysfunction but was not significantly elevated in neurologically normal children. In the Dutch study, all deaths occurred in children with severe neurological conditions. The 3 studies together indicate that mortality in children is only minimally, if at all, elevated in children who are neurologically normal, that almost all of the excess risk is in children with severe neurological conditions, and that little of the risk is due to seizures them-
This basic pattern was also reported in the large community-based cohort study of epilepsy in people of all ages from the United Kingdom. That study reported an SMR of 1.3 in neurologically normal individuals. This represented a modest nonsignificant increase in risk over that in the general population. By contrast, the SMR in

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. (%) of Cohort</th>
<th>No. (%) of Deaths</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epileptic syndrome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Idiopathic partial</td>
<td>66 (10.8)</td>
<td>0</td>
<td>&lt;.001 *</td>
</tr>
<tr>
<td>Symptomatic</td>
<td>79 (12.9)</td>
<td>2 (2.5)</td>
<td></td>
</tr>
<tr>
<td>Cryptogenic</td>
<td>220 (35.9)</td>
<td>1 (0.5)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Idiopathic generalized</td>
<td>136 (22.2)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Epileptic encephalopathy</td>
<td>66 (10.8)</td>
<td>10 (15.2)</td>
<td></td>
</tr>
<tr>
<td>Unclassified</td>
<td>46 (7.5)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Underlying etiology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cryptogenic or idiopathic</td>
<td>492 (80.3)</td>
<td>2 (0.4)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Symptomatic</td>
<td>121 (19.7)</td>
<td>11 (9.1)</td>
<td></td>
</tr>
<tr>
<td>Age at onset, y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2</td>
<td>130 (21.2)</td>
<td>9 (6.9)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>≥2</td>
<td>483 (78.8)</td>
<td>4 (0.8)</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td>.77</td>
</tr>
<tr>
<td>Male</td>
<td>307 (50.1)</td>
<td>6 (2.0)</td>
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</tr>
<tr>
<td>Female</td>
<td>306 (49.9)</td>
<td>7 (2.3)</td>
<td></td>
</tr>
<tr>
<td>Seizure control†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early evidence of intractability</td>
<td>60 (10.0)</td>
<td>8 (13.3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Not immediately intractable</td>
<td>539 (90.0)</td>
<td>4 (0.7)</td>
<td></td>
</tr>
<tr>
<td>Tonic-clonic seizures‡</td>
<td></td>
<td></td>
<td>.68</td>
</tr>
<tr>
<td>Absent</td>
<td>270 (44.0)</td>
<td>5 (1.9)</td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>343 (56.0)</td>
<td>8 (2.3)</td>
<td></td>
</tr>
<tr>
<td>Status epilepticus at initial diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>557 (90.9)</td>
<td>8 (1.4)</td>
<td>.002</td>
</tr>
<tr>
<td>Present</td>
<td>56 (9.1)</td>
<td>5 (8.9)</td>
<td></td>
</tr>
</tbody>
</table>

*Versus all other syndrome groups combined. No other group difference was statistically significant.
†Required at least 18 months of follow-up to ascertain. To be considered immediately intractable, a child had to have failed trials of 2 appropriate medications, have a minimum average of 1 seizure per month for 18 months, and have been seizure free no more than 3 months consecutively during that time. To have early evidence of intractability, the child had to meet these definitions within 3 ½ years after initial diagnosis.
‡Generalized onset or partial onset with secondary generalization present at initial diagnosis or within the first 2 years of follow-up.

Figure 2. Cumulative probability of survival as a function of underlying etiology (A), epilepsy syndrome (B), and seizure control (C).
the neurologically abnormal group was 3.7. Those with “congenital” causes for their epilepsy had the highest risk (SMR, 25). This last group corresponds approximately to the same high-risk groups described in the Connecticut, Canadian, and Dutch children’s studies.

These findings also may help explain why other population-based studies, one from Holland started in the 1960s and a more recent one from Geneva, found that relative to older age groups, the impact on mortality of epilepsy was greater in childhood-onset epilepsy. The types of symptomatic causes of epilepsy in children may produce a high mortality rate. Furthermore, against the background of a low mortality rate in children, the relative impact can be enormous. Only after adjustment for etiology does the low risk in most children who are neurologically normal become clear.

The evidence to suggest that status epilepticus before diagnosis was associated with an increased risk of death during follow-up was almost entirely limited to children whose status epilepticus occurred in the context of a severe insult. Status epilepticus poses a risk of mortality, especially in adults. For the 2 most common contexts in which status epilepticus occurs in children, febrile seizures and unprovoked seizures, status epilepticus tends to have a low morbidity and mortality. Although status epilepticus in the context of an acute insult was associated with an increased risk of death, we suspect that the association is due to this factor being a marker for an underlying cause or syndrome, or to the severity of the brain insult. Such possibilities have been suggested by findings in other studies.

In adults with epilepsy, sudden death occurs at an estimated rate of 0.35 to 7.5 per 1000 person-years depending on how the sample was selected. Little is known about this outcome in children. A population-based study in Ontario identified 27 cases of sudden death in children with epilepsy younger than 18 years during a 10-year period, but no population denominators were provided. In the combined 3 pediatric series reviewed here, only 2 definite cases occurred, for an estimated overall sudden death rate of approximately 0.13 per 1000 person-years (0.19 per 1000 person-years if the probable case is included). Sudden death is rare in this age group, and these findings provide reassurance concerning the low risk of sudden death in children with epilepsy.

Many adults with intractable partial epilepsy, a group at particularly high risk of sudden death in studies of adults, often have the onset of epilepsy during childhood. In a study of adults, young age at onset was associated with an increased risk of sudden death. All the cases of sudden death observed in the Finnish study also occurred once study members had reached adulthood. Other factors that play major roles in adults are uncontrolled seizures, multiple medications, and generalized tonic-clonic seizures. Although our study found evidence suggesting an independent role of seizure control in the risk of mortality (adjusted RR for intractable epilepsy, 4.1; 95% CI, 0.9-17.5), this was not the most important factor in this age group.

None of the children in our cohort or in the Canadian or Dutch cohorts died as a result of household accidents, including drowning, that are generally preventable by appropriate supervision. Because most of the deaths were inevitable (associated with fatal neurodegenerative conditions) or associated with severe neurological dysfunction, prevention of mortality translates into prevention of the underlying causes and, to an extent, better control of seizures. Unfortunately, this is one of the hardest areas in which to make progress.

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People with epilepsy have an increased risk of death relative to the general population. Little is known specifically about the risks, predictors, and causes of death in children with epilepsy, and there are no prospective studies from the United States, to our knowledge.

This study demonstrates that mortality in childhood-onset epilepsy is largely confined to children with severe underlying neurological conditions and epileptic encephalopathies. Poor seizure control may contribute to the risk independent of these factors. In the age group studied, few deaths are directly attributable to the occurrence of seizures, and sudden unexplained death associated with epilepsy is rare in children.

What This Study Adds

notated many administrative aspects of the study for us. This study would not be possible without the generous participation of the many parents and their children in this study.

REFERENCES