Current Literature
In Clinical Science

How Dangerous Is Epilepsy?

Long-Term Mortality in Childhood-Onset Epilepsy.

BACKGROUND: There are few studies on long-term mortality in prospectively followed, well-characterized cohorts of children with epilepsy. We report on long-term mortality in a Finnish cohort of subjects with a diagnosis of epilepsy in childhood. METHODS: We assessed seizure outcomes and mortality in a population-based cohort of 245 children with a diagnosis of epilepsy in 1964; this cohort was prospectively followed for 40 years. Rates of sudden, unexplained death were estimated. The very high autopsy rate in the cohort allowed for a specific diagnosis in almost all subjects. RESULTS: Sixty subjects died (24%); this rate is three times as high as the expected age- and sex-adjusted mortality in the general population. The subjects who died included 51 of 107 subjects (48%) who were not in 5-year terminal remission (i.e., ≥5 years seizure-free at the time of death or last follow-up). A remote symptomatic cause of epilepsy (i.e., a major neurologic impairment or insult) was also associated with an increased risk of death as compared with an idiopathic or cryptogenic cause (37% vs. 12%, P<0.001). Of the 60 deaths, 33 (55%) were related to epilepsy, including sudden, unexplained death in 18 subjects (30%), definite or probable seizure in 9 (15%), and accidental drowning in 6 (10%). The deaths that were not related to epilepsy occurred primarily in subjects with remote symptomatic epilepsy. The cumulative risk of sudden, unexplained death was 7% at 40 years overall and 12% in an analysis that was limited to subjects who were not in long-term remission and not receiving medication. Among subjects with idiopathic or cryptogenic epilepsy, there were no sudden, unexplained deaths in subjects younger than 14 years of age. CONCLUSIONS: Childhood-onset epilepsy was associated with a substantial risk of epilepsy-related death, including sudden, unexplained death. The risk was especially high among children who were not in remission.

Commentary
When patients are first diagnosed with epilepsy, they are often most concerned about disruptive effects on their everyday lives and potential disability. Nonetheless, uncontrolled epilepsy also carries significant safety concerns. These include accidents caused by seizures, death directly resulting from status epilepticus or severe seizures, and sudden unexpected death in epilepsy (SUDEP). Those with epilepsy also have a higher risk of suicide, and a subgroup may die from the underlying neurological conditions, such as brain tumors, that cause the seizures.

Reported epilepsy mortality rates are greatly influenced by study design. Death risk varies greatly depending on the characteristics of the selected patient group. For example, estimates of SUDEP incidence have ranged from 0.09 per thousand patient years in a community cohort with newly diagnosed epilepsy (1) to 9.3 per thousand patient years in a group of patients referred for consideration of epilepsy surgery (2). In population-based studies, the overall epilepsy mortality rate ranged from 2.7 to 3.8 per thousand patient years (3–5), with the risk being 5.3 to 7.5 times that of people without epilepsy.

The risk was 23 times higher in patients with remote symptomatic epilepsy compared with those with idiopathic/cryptogenic epilepsy (3). In addition, the characterization of mortality is likely affected by the duration of follow-up. For example, in a population-based study of new onset epilepsy followed for a relatively short 7-year period (6), mortality was predominantly the direct result of the underlying causes of the symptomatic epilepsy. In longer term studies, seizure-related death may well assume a greater relative contribution. Finally, because medical providers may not be informed when a patient expires, a thorough review of independent death records is an essential supplement to medical record review. Without this, mortality rate may be underestimated. A high autopsy rate is also needed to accurately assess cause.

This prospective population-based study by Sillanpää and Shinnar contributes significantly to knowledge of epilepsy-related mortality because of its methodological strengths. The 245 patients made up all children younger than age 16 living in the vicinity of Turku University Hospital in Finland seen for epilepsy from 1961 to 1964, excluding febrile seizures, other provoked seizures, and isolated unprovoked seizures. These patients had an initial in-patient hospital evaluation and follow-up examinations every 5 years up to 2002.
How Dangerous Is Epilepsy?

The overall autopsy rate was 70%. The detailed evaluations and follow-up allowed for classification of epilepsy into idiopathic, cryptogenic, and remote symptomatic types as well as identification of those who had achieved seizure remission for 5 or more years.

This work provides a somewhat different perspective on epilepsy mortality than past reports. It demonstrated a markedly higher overall mortality rate, 6.9 per thousand patient years. A majority of deaths, 33 out of 60, were seizure-related. This was the case for both the idiopathic/cryptogenic (9 of 15 deaths) and remote symptomatic (24 of 45 deaths) epilepsy subgroups. Even using a conservative definition of SUDEP, as sudden death of unknown cause without evidence of a seizure (9), this was the cause of most seizure-related mortality (18 deaths).

Lack of seizure control was an extremely strong predictor of mortality. The only independent predictor of both overall and seizure-related mortality on multivariate analysis was failure to achieve at least 5 years free of seizures by the last follow-up assessment (terminal remission). Other predictors of mortality on univariate analysis—remote symptomatic epilepsy, history of status epilepticus, and severe cognitive impairment with remote symptomatic epilepsy—were simply predictors of failure to attain seizure remission. There were 109 individuals (44.5%) who did not reach 5-year terminal remission. Of these, 51 (46.7%) died, for a rate of 1.59% per year. This represents 85% of all deaths in the entire study. Of the patients who did achieve terminal remission, only 4 of 103 not on medication died (3.9%), while only 5 of 35 on medication did (14.3%).

The fact that so many of these deaths are seizure-related provides justification for aggressive medical and surgical treatment of epilepsy. This is supported by a study demonstrating that long-term mortality rates are decreased to the level of the general population in patients attaining seizure freedom after epilepsy neurosurgery (8). Because SUDEP risk increases with higher seizure frequencies (9), even treatments that only partially reduce seizures might also reduce mortality.

Gowers (10) wrote in 1885 that “the danger to life of patients with epilepsy is not great.” Sillanpää and Shinnar, by meticulous identification and characterization of deaths over a 40-year period, have disproved this traditional view and revealed the true risk of death in epilepsy. The accumulation of such high mortality in those who continue to experience seizures over decades is disturbing. Uncontrolled epilepsy is dangerous. The more carefully the long-term natural history of epilepsy is scrutinized, the more apparent this becomes. The purpose of seizure treatment is not only to improve the quality of life, but also to save it.

by John W. Miller, MD, PhD

References
Instructions
The purpose of this form is to provide readers of your manuscript with information about your other interests that could influence how they receive and understand your work. Each author should submit a separate form and is responsible for the accuracy and completeness of the submitted information. The form is in four parts.

1. **Identifying information.**
Enter your full name. If you are NOT the main contributing author, please check the box “no” and enter the name of the main contributing author in the space that appears. Provide the requested manuscript information.

2. **The work under consideration for publication.**
This section asks for information about the work that you have submitted for publication. The time frame for this reporting is that of the work itself, from the initial conception and planning to the present. The requested information is about resources that you received, either directly or indirectly (via your institution), to enable you to complete the work. Checking “No” means that you did the work without receiving any financial support from any third party – that is, the work was supported by funds from the same institution that pays your salary and that institution did not receive third-party funds with which to pay you. If you or your institution received funds from a third party to support the work, such as a government granting agency, charitable foundation or commercial sponsor, check “Yes”. Then complete the appropriate boxes to indicate the type of support and whether the payment went to you, or to your institution, or both.

3. **Relevant financial activities outside the submitted work.**
This section asks about your financial relationships with entities in the bio-medical arena that could be perceived to influence, or that give the appearance of potentially influencing, what you wrote in the submitted work. For example, if your article is about testing an epidermal growth factor receptor (DGFR) antagonist in lung cancer, you should report all associations with entities pursuing diagnostic or therapeutic strategies in cancer in general, not just in the area of EGFR or lung cancer.

Report all sources of revenue paid (or promised to be paid) directly to you or your institution on your behalf over the 36 months prior to submission of the work. This should include all monies from sources with relevance to the submitted work, not just monies from the entity that sponsored the research. Please note that your interactions with the work’s sponsor that are outside the submitted work should also be listed here. If there is any question, it is usually better to disclose a relationship than not to do so.

For grants you have received for work outside the submitted work, you should disclose support ONLY from entities that could be perceived to be affected financially by the published work, such as drug companies, or foundations supported by entities that could be perceived to have a financial stake in the outcome. Public funding sources, such as government agencies, charitable foundations or academic institutions, need not be disclosed. For example, if a government agency sponsored a study in which you have been involved and drugs were provided by a pharmaceutical company, you need only list the pharmaceutical company.

4. **Other relationships**
Use this section to report other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work.
American Epilepsy Society  
Epilepsy Currents Journal  
Disclosure of Potential Conflicts of Interest  

Section #1 Identifying Information  
1. Today’s Date: ____February 9, 2011_____________________________  
2. First Name ____John______    Last Name ____Miller______    Degree __M.D., Ph.D.___  
3. Are you the Main Assigned Author? __x__ Yes    ____ No  
   If no, enter your name as co-author ___________________________________________  
4. Manuscript/Article Title: ____How dangerous is epilepsy?____ _______________________
5. Journal Issue you are submitting for: ________11.3_____________________________________________  

Section #2 The Work Under Consideration for Publication  
Did you or your institution at any time receive payment or services from a third party for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?  

Complete each row by checking “No” or providing the requested information. If you have more than one relationship just add rows to this table.  

<table>
<thead>
<tr>
<th>Type</th>
<th>No</th>
<th>Money Paid to You</th>
<th>Money to Your Institution*</th>
<th>Name of Entity</th>
<th>Comments**</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Grant</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Consulting fee or honorarium</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Support for travel to meetings for the study or other purposes</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Fees for participating in review activities such as data monitoring boards, statistical analysis, end point committees, and the like</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Payment for writing or reviewing the manuscript</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. Provision of writing assistance, medicines, equipment, or administrative support.</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. Other</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* This means money that your institution received for your efforts on this study.  
** Use this section to provide any needed explanation.
Section #3 Relevant financial activities outside the submitted work.
Place a check in the appropriate boxes in the table to indicate whether you have financial relationships (regardless of amount of compensation) with entities as described in the instructions. Use one line for each entity; add as many lines as you need by clicking the “Add” box. You should report relationships that were present during the 36 months prior to submission.

Complete each row by checking “No” or providing the requested information. If you have more than one relationship just add rows to this table.

<table>
<thead>
<tr>
<th>Type of relationship (in alphabetical order)</th>
<th>No Money Paid to You</th>
<th>Money to Your Institution*</th>
<th>Name of Entity</th>
<th>Comments**</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Board membership</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Consultancy</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Employment</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Expert testimony</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Grants/grants pending</td>
<td>x</td>
<td>NIH</td>
<td>Various, including clinical trials and animal research relevant to medical and surgical treatment of epilepsy</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>King Pharmaceuticals; UCB Pharma</td>
<td>Various industry sponsored drug studies</td>
<td></td>
</tr>
<tr>
<td>6. Payment for lectures including service on speakers bureaus</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. Payment for manuscript preparation</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8. Patents (planned, pending or issued)</td>
<td>x</td>
<td></td>
<td>Device to treat intractable epilepsy; seizure detection programs</td>
<td></td>
</tr>
<tr>
<td>9. Royalties</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10. Payment for development of educational presentations</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11. Stock/stock options</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12. Travel/accommodations/meeting expenses unrelated to activities listed.**</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13. Other (err on the side of full disclosure)</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* This means money that your institution received for your efforts.
** For example, if you report a consultancy above there is no need to report travel related to that consultancy on this line.

Section #4 Other relationships
Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?

_x__ No other relationships/conditions/circumstances that present a potential conflict of interest.
___ Yes, the following relationships/conditions/circumstances are present:
______________________________________________________________________________________________
______________________________________________________________________________________________
______________________________________________________________________________________________

Thank you for your assistance.

*Epilepsy Currents* Editorial Board