



How Dangerous Is Epilepsy?

Long-Term Mortality in Childhood-Onset Epilepsy.

Sillanpää M, Shinnar S. *N Engl J Med* 2010;363:2522–2529.

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. To ensure the most complete possible identification of deaths, the lists of subjects was compared with the Finnish National Death Register, except for five subjects who emigrated from Finland.



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

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