

## THE NATURAL HISTORY OF EPILEPSY: SPONTANEOUS REMISSION AND MORTALITY

**Natural History and Mortality of Chronic Epilepsy in an Untreated Population of Rural Bolivia: A Follow-Up after 10 years.** Nicoletti A, Sofia V, Vitale G, Bonelli SI, Bejarano V, Bartalesi F, Tran DS, Preux PM, Zappia M, Bartoloni A. *Epilepsia* 2009;50(10):2199–2206. **PURPOSE:** To evaluate the natural history and mortality of chronic epilepsy in an untreated prevalence cohort of people with epilepsy (PWE) in a rural area of Bolivia. **METHODS:** During 1994–1996 we carried out an epidemiologic survey in a sample of 9,995 subjects in the Cordillera province. At the end of the survey we identified 130 PWE, of whom 118 were classified as having “active epilepsy.” We revisited this cohort 10 years after the prevalence survey. **RESULTS:** We were able to trace 103 (87.3%) of the 118 PWE previously identified. Ten of the 103 subjects died during the follow-up period. Of the 93 PWE still alive, adequate information on the occurrence of seizures was available for 71 subjects, of whom 31 (43.7%) were seizure-free for more than 5 years; only 3 of these 31 subjects have taken an antiepileptic drug (AED) for more than 1 year. Generalized seizures were associated with a better prognosis. Mortality rate in our prevalent cohort was 10.0/1,000 person-year at risk [95% confidence interval (CI) 5.5–18.3], without a significant increased risk respect to the general population [standardized mortality rate (SMR) 1.34; 95% CI 0.68–2.39]; a significant increased risk of death was found for patients with remote symptomatic epilepsy (SMR 3.0; 95% CI 1.2–6.3) but not with idiopathic epilepsy. Three of the 10 subjects died of causes possibly related to epilepsy. **DISCUSSION:** Our data suggest that spontaneous remission of epilepsy occurs in a substantial proportion of untreated patients affected by chronic epilepsy; concerning mortality, we found a three-fold increased mortality in patients with remote symptomatic epilepsy.

### COMMENTARY

For many years, the natural history of epilepsy was unknown. Since 1990s, a small number of studies have emerged involving groups of people with untreated and under-treated prevalent epilepsy, mostly from resource-poor countries. The International League Against Epilepsy (ILAE) Guidelines for Epidemiologic Studies defines prevalent epilepsy as: a person with epilepsy who has had at least one epileptic seizure in the previous 5 year, regardless of AED treatment. A case under treatment is someone with the correct diagnosis of epilepsy receiving (or having received) antiepileptic drugs (AEDs) on the prevalence day. These studies have shown that short-term spontaneous remission occurs in a sizeable proportion of people with prevalent epilepsy. Furthermore, spontaneous remission is inferred from the inverse association between duration of epilepsy and the number of people with epilepsy (PWE) in a given population (1) or is estimated by the percentage of seizure-free individuals in the past year (2,3) or by the percentage of those with prevalent epilepsy who are seizure-free during a short-term follow-up (4). Despite slightly different inclusion criteria, results are fairly consistent. A 1–2 year spontaneous remission occurs in 20% to 44% of prevalent epilepsy. Information on spontaneous, long-term seizure freedom and predictors of spontaneous remission has been absent. The study by Nicoletti and colleagues presents a 10-year follow-up of a Bolivian cohort with prevalent active epilepsy (using the ILAE definition of at

least one seizure in the past 5 years) and focuses upon remission and mortality.

During the 10-year Bolivian cohort follow-up, 43.7% of people with prevalent epilepsy became seizure-free for at least 5 years, on or off AEDs, although only 10% had taken an AED for more than 1 year. If prevalent cases lost to follow-up were considered to still have active seizures, then conservatively 30% of the cohort could be considered seizure-free for at least 5 years. This estimate is similar to that reported for short-term, spontaneous remission (1–4). Several potential predictors of achieving seizure freedom were examined, including age, duration of seizures, neurocysticercosis, remote symptomatic etiology, seizure type, and any previous AED treatment. None of these factors was statistically significantly associated with spontaneous remission, but the cohort studied was relatively small.

In incident cohorts of PWE in both developed and resource-poor countries, mortality is consistently significantly increased in the first few years after diagnosis for remote symptomatic seizures, but not consistently increased for idiopathic/cryptogenic seizures (5,6). In an Ecuadorian study, the mortality rate for incident epilepsy was 6.1/1,000 person-years, and the standardized mortality ratio (SMR) was 6.3 (95% confidence intervals (CI): 2.0–10.0) compared to expected deaths in the general population (6). In developed countries, the SMRs range from 1.6 to 3.0 (5). The SMR compares the observed number of deaths to that expected when the mortality rate of the general population is applied to the study population. Because the mortality rate of the general population in resource-poor countries is higher than in developed countries, an SMR of

2 reflects a higher overall annual mortality in epilepsy populations from resource-poor countries than from developed countries. Mortality in prevalence cohorts is less studied, but the expectation would be that mortality is not increased, because prevalent cohorts consist of people who have had epilepsy for some time and most deaths occur in the first few years after epilepsy diagnosis.

Over the 10-year follow-up of the Bolivian cohort reviewed here, the overall SMR was 1.34 (95% CI: 0.68–2.39). Surprisingly, the SMR was significantly increased in prevalent remote symptomatic seizures 10 years after identification of prevalent active epilepsy (SMR = 3.0; 95% CI: 1.2–6.3). This finding is unexpected because studies of mortality in incident cohorts suggest that deaths are increased in remote symptomatic seizures only in the first years after the epilepsy diagnosis. However, the distribution of causes of remote symptomatic seizures in these incident cohorts (e.g., stroke, dementia) differs from that reported in the Bolivian study.

In the current report, neurocysticercosis was present in five of the six people (83%) who died in the remote symptomatic group, which represents half of the total deaths (one of the five people also had comorbid mental retardation). In contrast, though the duration of epilepsy was lower in the Ecuadorian follow-up study of an incident cohort, with an 8% prevalence of neurocysticercosis (7), no deaths occurred among those with neurocysticercosis (7). The prevalence of neurocysticercosis was examined in the Bolivian cohort on November 1, 1994 (8). Among those with prevalent active epilepsy, 32 of 118 (27.1%) were considered to have neurocysticercosis, based upon epidemiological criteria and clinical manifestation. Of note, 18.6% of 112 people with assays showed antibodies against *Taenia solium*, and 31 of 105 with CT scan examinations (29.5%) revealed cysts or calcifications.

Based upon the data presented in Nicoletti et al. and the other Bolivian paper (8), it is possible to approximate the effect of neurocysticercosis on mortality in those individuals with prevalent epilepsy. Comparing the prevalence of neurocysticercosis in the deaths (50%) to its prevalence among those still alive (approximately 23%) reveals that neurocysticercosis, identified 10 years earlier, was about twofold more common among the individuals who died than in people with active epilepsy who were still alive. The case fatality for neurocysticercosis, identified 10 years earlier, can also be approximated as an estimated 16% (5 deaths in 32 of those with neurocysticercosis).

Studies of mortality associated with cysticercosis are few. Mortality rates for cysticercosis identified on the death certificate is low, ranging from 0.32 deaths per 1 million people to 1.16 deaths per 1 million people in Brazil (9) and from 0.006 per million for U.S. Caucasians to 0.56 per million for U.S. Latinos (10). Case fatality is estimated to range from 6% to 10% (11,12). Thus, the case fatality of neurocysticercosis,

observed 10 years after identification, among a cohort first identified with active epilepsy in Bolivia may be higher than expected.

About 50 million people worldwide are estimated to have epilepsy. Approximately 80% of these people are thought to live in resource-poor countries (2). The distribution of causes of epilepsy is different in these countries compared to the developed world, with a greater proportion being due to infectious causes (13). The study by Nicoletti and colleagues suggests that mortality may also differ, with increases occurring long after epilepsy onset, potentially associated with neurocysticercosis. Further work is needed to better understand the long-term mortality of epilepsy in resource-poor countries.

by Dale C. Hesdorffer, PhD

## References

1. Watts AE. The natural history of untreated epilepsy in a rural community in Africa. *Epilepsia* 1992;33:464–468.
2. Tuan NA, Tomson T, Allebeck P, Chuc NTK, Cuong LQ. The treatment gap of epilepsy in a rural district of Vietnam: A study from the EPIBAVI project. *Epilepsia* 2009;2320–2323.
3. Placencia M, Sander JWAS, Roman M, Madera A, Crespo G, Cascante S, Shorvon SD. The characteristics of epilepsy in a largely untreated population in rural Ecuador. *J Neurol Neurosurg Psychiatry* 1994;57:320–235.
4. Keränen T, Riekkinen PJ. Remission of seizures in untreated epilepsy. *BMJ* 1993;307:483.
5. Forsgren L, Hauser WA, Olafsson E, Sander WAS, Sillanpaa M, Tomson T. Mortality of epilepsy in developed countries: A review. *Epilepsia* 2005;46(suppl 11):18–27.
6. Carpio A, Bharucha NE, Jallon P, Beghi E, Campostrini R, Zorzetto S, Mounkoro PP. Mortality of epilepsy in developing countries. *Epilepsia* 2005;46(suppl 11):28–32.
7. Carpio A, Hauser WA, Lisanti N, Roman M, Aguirre R, Pesantez J. Etiology of epilepsy in Ecuador. *Epilepsia* 2001;42(Suppl. 2):122.
8. Nicoletti A, Bartoloni A, Sofia V, Bartalesi F, Chavez JR, Osinaga R, Paradisi F, Dumas JL, Tsang VCW, Reggio A, Hall AJ. Epilepsy and neurocysticercosis in rural Bolivia: A population-based survey. *Epilepsia* 2005;46:1127–1132.
9. Hasiak-Santo A. Cysticercosis-related mortality in the state of São Paulo, Brazil, 1985–2004: A study using multiple causes of death. *Cad Saude Pública Rio de Janeiro* 2007;23:2917–2927.
10. Sorvillo FJ, DeGiorgio C, Waterman SH. Deaths from cysticercosis, United States. *Emerging Infectious Dis* 2007;13:230–235.
11. Sorvillo FJ, Waterman SH, Richards FO, Schantz PM. Cytricerco-sis surveillance: Locally acquired and travel-related infections and detection of intestinal tapeworm carriers in Los Angeles County. *Am J Trop Med Hyg* 1992;47:365–371.
12. Dixon HBF, Lopscomb FM. *Cysticercosis: An Analysis and Follow Up of 450 Cases. Medical Research Council Special Report Series, vol. 299.* London: Her Majesty's Stationary Service, 1961.
13. Senanayake N, Roman GC. Epidemiology of epilepsy in developing countries. *Bull World Health Org* 1993;71:247–258.