Prognosis of epilepsy in a community-based study: 8 years of follow-up in an Argentine community

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Objective – To assess the prognosis of epilepsy, the possibility of achieving remission of seizures, in patients who were identified in a population-based study carried out in Junín, a city of about 70,000 inhabitants in Buenos Aires Province, Argentina. On January 1, 1991 (prevalence day), 106 people had epilepsy, including 64 (60%) with the condition active. *Methods* – Eight years later, we revisited the patients identified in the prevalence study. We analyzed risk factors in relation to remission of seizures. We also confirmed the specific cause of death. *Results* – Ninety-six patients were revisited (10 were completely lost to follow-up). We divided them into two groups: the group in terminal remission (defined as a seizure-free period that extended from prevalence day until the visit day in 1998) which included 64 people (66.7%), and the group of those who continued to have seizures which included 32 (33.3%) patients, of whom eight (25%) died. The overall standardized mortality ratio was 2.45; the rate was two and a half times that of the general national population. *Conclusion* – The better prognosis was observed in the group with generalized idiopathic epilepsy syndrome. Patients with epilepsy secondary to underlying structural causes had the worst prognosis, with higher mortality.

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The most important aspect of prognosis in epilepsy is the possibility of achieving terminal remission of seizures. Studies on prognosis of epilepsy have been difficult because of methodological problems and because epilepsy may be due to many different underlying etiologies (1–4). There are few reports on prognosis of epilepsy in developing countries (5, 6). In this study, we report a follow-up of patients who were identified as having epilepsy in a population-based study. The survey was conducted in the city of Junín, Buenos Aires Province, Argentina (7, 8). The prevalence found was similar to previous results in developed countries and showed differences with some developing countries probably due to use of different methodologies (8–17). The main purpose of this study was to investigate epilepsy prognosis in our population. Data from the first 8 years of follow-up are reviewed and expanded (8) to include remission and mortality, and to examine the factors that may be predictive of outcome.

Methods

Background

Patients with diagnosed epilepsy were originally identified from a community-based study in 1991. This survey was conducted in Junín, a city of about 70,000 inhabitants in Buenos Aires Province, Argentina (8). Systematic sampling was used to select 5839 dwellings (sampling fraction ~25%); 5648 (97%) participated, including 17,049 people. The initial stage of the study involved a case-finding strategy consisting of a two-stage screening approach in the selected households; household screening was followed by neurological examinations. Neurologists examined subjects who screened positive or who reported a diagnosis of epilepsy and ascertained whether or not the diagnosis was epilepsy, using defined diagnostic criteria. A diagnosis of epilepsy required the occurrence of two or more unprovoked seizures or seizure episodes (18). Subjects who had experi-

enced only a single seizure, neonatal seizures, febrile seizures or provoked seizures were excluded.

Epilepsy was defined as definite if 1) a clear description and history of seizures were obtained from the subject, the subject's relatives, or the subject's physician or medical records; or 2) a description and history suggestive of seizures were corroborated by electroencephalographic (EEG) findings. Epilepsy was defined as possible if a description and history suggestive of seizures were obtained without EEG confirmation. The epilepsy was active (AE) if either the subject was taking antiepileptic medication on prevalence day, and at least one seizure occurred in the 5 years preceding that day; or if the subject was not taking antiepileptic medication on prevalence day, and at least one seizure had occurred in the year prior to that day. In all other instances, epilepsy was deemed inactive (IE).

As of January 1, 1991 (prevalence day), 106 people had epilepsy, 64 (60%) of whom the condition was active. Among those with AE, nine (14%) were newly diagnosed by the survey neurologists, and 50 (78%) were already on antiepileptic treatment at the time of the survey. The neurologist classified the seizure types according to the ILAE 1981 classification (19). In those with AE the seizure type was generalized in 37 (58%) people and partial in 24 (38%). In those with IE, the seizure type was generalized in 33 people (79%) and partial in seven (17%).

The lifetime prevalence of epilepsy was 6.2 per 1000 population. For active epilepsy, the point prevalence (per 1000/people) was 3.8 overall (4.0 for females and 3.5 for males). Prevalence peaked at ages 40–59 years for females and 0–4 years for males. The frequency of seizures was as reported at the time of survey.

Study design

In 1998, 8 years later, we revisited the patients with diagnosed epilepsy who had been identified in the prevalence study. Recall of seizure occurrence was enhanced by the fact that the patients now knew that they had epilepsy. Additionally, all the patients with AE continued to visit the assistance centers of the region. The neurologists from the research team interviewed all patients apart from 10 who were lost to follow-up. We analyzed the population in two groups; the group in Terminal remission (TR) included all patients in remission since the prevalence day until the visit day in 1998, whether or not they were originally classified as AE or IE. The other group included those who continued having seizures (S).

Factors associated with the remission of seizures were analyzed.

In the present report, in addition to the classification of seizure types on prevalence day, epilepsy was also classified by syndrome (ILAE 1989) (19), except that we considered idiopathic and cryptogenic epilepsy as one group (20). We had some limitations to establish the etiology in all the patients, because the neuroimaging studies were performed in the majority of persons but not in the whole population. We also incorporated the term 'symptomatic epilepsy' when an etiological factor could be identified but when it was not possible to determine whether the seizure was partial or generalized onset (20). *The effect of age* on prognosis was assessed using the following age groups: < 10, 11–20, 21–50 and > 50 years. The *etiological category* was also included: idiopathic seizures were defined by the failure to identify a cause, and included patients with idiopathic generalized epilepsy as well as those with cryptogenic location-related epilepsies. Remote symptomatic seizures were defined as seizures caused by an identified cerebral lesion or etiology such as a tumor or chronic cerebrovascular disease. Acute symptomatic seizures were considered to include all patients in whom the first seizure had occurred within 3 months of the cause, and congenital neurodeficits was defined as epilepsy that had arisen in association with a neurological abnormality presumably present at birth, such as cerebral palsy. We also *reviewed the antiepileptic drugs (AEDs)* the patient was receiving at the time of the follow-up visit.

If we were informed that any of the subjects had died, we established the specific cause of death from the death certificate, hospital record and/or family doctor. The standardized mortality ratio (SMR) (the number of observed deaths compared with the number of deaths expected in that time period in the observed population, if it experienced age-specific mortality rates of the background population) was calculated (21).

Statistical analysis

Chi-squared test or Fisher's exact test was performed for categorical variables and logistic regression for analysis of risk factors using SPSS (version 12; SPSS Inc., Chicago, IL, USA).

Results

Follow-up

Of a total of 106 subjects, 96 were revisited; 10 patients were lost to follow-up (eight with AE and

two with IE). In the AE group (56 patients), 24 (42.9%) were in *remission of seizures* and 32 (57.1%) continued to have seizures. In the IE group (40 patients), all continued in remission. Sixty-four people (66.7%) were included the group TR, and 32 (33.3%) were included in the group S, of whom eight (25%) had died.

The seizure type was classified according to International League Against Epilepsy (1981 ILAE) (19). The majority (49/61 of those classified, 80.3%) of patients who were in TR had generalized tonic–clonic seizures or absences. The majority (17/27 of those classified, 62.9%) of those from the group S had partial seizures. Comparing type of seizure, the risk of ongoing seizures was seven times more for patients with partial seizures than for those with generalized seizures (OR 6.9, 95% confidence interval 2.5–18.9, $P < 0.001$). We found similar results in the epilepsy syndromes; the majority of (39/49 of those classified, 79.6%) patients who were in TR had generalized syndrome. The majority (17/27, 3%) of those from the group S had partial seizures. Comparing syndromes, the risk of ongoing seizures was six times more for those with partial syndromes than for those with generalized syndromes (OR 6.6, 95% confidence interval 2.3–18.8, $P = 0.001$).

There were no significant influences of the *effect of age* of first seizure on prognosis, for both groups, as most patients began their epilepsy ≤10 years.

More than 70% of patients in the TR group had idiopathic epilepsy. The rest had remote symptomatic causes, the most common of which were central nervous system infections (9%), head injury (6%), and vascular disease (6%). In the S group half of people had idiopathic epilepsy, and the rest had remote symptomatic causes, the most common of which were tumors (16%), vascular disease (13%), and others (mental handicapped) (9%). Logistic regression showed that patients with symptomatic epilepsy were more likely to have ongoing seizures than those with idiopathic or cryptogenic epilepsy (OR 2.7, 95% confidence

interval 1.1–6.7, $P = 0.02$). Fisher's exact test showed that patients with a tumor were significantly more likely to have ongoing seizures than those without (two-sided $P = 0.007$) (Table 1).

The analysis of the *treatments* the patients were undergoing on the visit day showed that only one patient in the group in remission and one in the group with ongoing seizures had never been treated. In group in remission the drugs most widely used in monotherapy were PB and CBZ (11/10). Polytherapy with two AEDs was used by 24 patients in remission and by eight patients with ongoing seizures, and polytherapy with three AEDs was taken by three patients in remission and by six subjects with seizures. There were no significant differences between both groups.

In the group with ongoing seizures, all with AE on prevalence day, eight patients (25%) died during the follow-up period, while the *expected number of deaths* was 3.27 adjusted for age (22). An SMR of 2.45 implies a mortality rate 2.5 times that of the general population. Six of the patients who died had remote symptomatic seizures: four had tumors and two had suffered a stroke. The cause of death was undetermined in two patients (one with a diagnosis of cerebral palsy). In half of the patients who died (four patients), epilepsy began at >50 years. The patients' ages at the time of death was >50 for six patients and between 30 and 49 for two patients. The group of patients who died included three patients with generalized seizures (one of whom had idiopathic generalized syndrome and the other two generalized symptomatic syndrome), four patients with partial seizures (one of whom had partial idiopathic syndrome and the other three partial symptomatic syndrome), and one patient who was not classified.

Discussion

In recent years our understanding of many aspects of epilepsy epidemiology, including prognosis, has been improved by different population-based studies. In general terms, there are few population-based studies devoted to the prognosis of epilepsy, and most were performed in developed countries. The overall prognosis in terms of seizure remission for patients with epilepsy is good. In the present research, almost half the patients with AE at screening achieved at least an 8-year remission period. Such a finding is similar to that reported by Hauser et al. (10). All patients with IE in 1991 were still in remission 8 years later.

One of the most relevant data we found was the difference in the prognosis as regards seizure types and epileptic syndromes. The risk of ongoing

Table 1 The etiology of patients in relation to prognosis

	Remission	With/S
Stroke	4 (6.25%)	4 (12.5%)
Tumor	0	5 (15.6%)
CNS infection	6 (9.37%)	2 (6.2%)
Head injury	4 (6.25%)	1 (3.1%)
Others (Mental Handicape)	3 (4.68%)	3 (9.3%)
Idiopathic	47 (73.43%)	17 (53.1%)
Total	64 (100%)	32 (100%)

seizures was seven times greater for those with partial seizures as those with partial syndromes. Probably because of few patients with synthomatic or idiopathic syndromes we could not observe significant differences between these populations (11, 23).

We also considered the prognosis in relation to age of onset of epilepsy and found no significant differences (24).

We found significant difference between the TR and S groups. The identification of an etiological factor doubled the chances of continuing to have seizures.

With regards to treatment, no significant differences were found in relation to prognosis of the disease.

Of the total population analyzed in the follow-up (96 patients), eight patients in the S group died. We found an SMR of 2.45, which means that the rate was two and a half times that of the general national population, adjusted for age. This finding is similar to previous reports (21, 25, 26). In our population, the major causes of death were tumor and stroke. However, we need a higher number of patients to compare the rate as adjusted by etiology groups with the general Argentine population (22). The mortality rates in particular are liable to be an expression of more lethal underlying conditions; therefore, an analysis of prognosis of epilepsy should be more informative with regard to the underlying etiologies.

Conclusion

Our data shows no significant differences in epilepsy prognosis with published results from developed countries. In agreement with these studies, we found that patients with epilepsy generally have a good prognosis. The better prognosis is observed in the group of patients with generalized epilepsy and generalized idiopathic syndrome.

The better outcome in this group does not seem to be associated with the use of a particular AED. On the other hand, patients with epilepsy secondary to underlying structural causes, have a worse prognosis, being at significant risk of premature death. In conclusion, the prognosis of epilepsy seems to correlate, to a great extent, with its etiology.

References

1. JACOBY A, BAKER GA, STEEN N, POTTS P, CHADWICK DW. The clinical course of epilepsy and its psychosocial correlates: findings from a UK Community study. Epilepsia 1996;**37**:148–61.
2. COCKERELL OC, JOHNSON AL, SANDER JW, SHORVON SD. Prognosis of epilepsy: a review and further analysis of the first nine years of the British National General Practice Study of Epilepsy, a prospective population-based study. Epilepsia 1997;**38**:31–46.
3. SANDER JW. The epidemiology of epilepsy revisited. Curr Opin Neurol 2003;**16**:165–70.
4. KWAN P, SANDER JW. The natural history of epilepsy: an epidemiological view. J Neurol Neurosurg Psychiatry 2004;**75**:1376–81.
5. BHARUCHA NE. Epidemiology of epilepsy in India. Epilepsia 2003;**44**(Suppl. 1): 9–11.
6. SHORVON SD, FARMER PJ. Epilepsy in developing countries: a review of epidemiological, sociocultural, and treatment aspects. Epilepsia 1988;**29**(Suppl. 1): S36–54.
7. ANDERSON WA, MELCON MO, VERGARA RH. Methods for a prevalence survey of neurological disorders in Junín, Buenos Aires, Argentina. Neuroepidemiology 1995;**14**:110–22.
8. MELCON MO, KOCHEN S, VERGARA RH, ANDERSON DW. Prevalence of epilepsy in an Argentine community. Neuroepidemiology 2002;**21**:209.
9. SHORVON SD. Epidemiology, classification, natural history, and genetics of epilepsy. Lancet 1990;**336**:93–6.
10. HAUSER WA, ANNEGERS JF, KURLAND LT. Prevalence of epilepsy in Rochester, Minnesota: 1940–1980. Epilepsia 1991;**32**:429–45.
11. JALLON P, LOISEAU P, LOISEAU J. Newly diagnosed unprovoked epileptic seizures: presentation at diagnosis in CAROLE study. Coordination Active du Reseau Observatoire Longitudinal de l' Epilepsie. Epilepsia 2001;**2**:464–75.
12. ROCCA WA, SAVETTIERI G, ANDERSON DW et al. Door-to-door prevalence survey of epilepsy in three Sicilian municipalities. Neuroepidemiology 2001;**20**:237–41.
13. HAERER AF, ANDERSON DW, SCHOENBERG BS. Prevalence and clinical features of epilepsy in a biracial United States population. Epilepsia 1986;**27**:66–75.
14. PLACENCIA M, SANDER JW, ROMAN M et al. The characteristics of epilepsy in a largely untreated population in rural Ecuador. J Neurol Neurosurg Psychiatry 1994;**57**:320–5.
15. SOMOZA MJ. Epilepsia. Abstracts from the 21st International Epilepsy Congress Sydney, Australia, Vol. 36, Suppl. 3, 1995.
16. NICOLETTI A, REGGIO A, BARTOLONI A et al. Prevalence of epilepsy in rural Bolivia: a door-to-door survey. Neurology 1999;**53**:2064–9.
17. OUN A, HALDRE S, MAGI M. Prevalence of adult epilepsy in Estonia. Epilepsy Res 2003;**52**:233–42.
18. Commission on Epidemiology and Prognosis, International League Against Epilepsy. Guidelines for epidemiologic studies on epilepsy. Epilepsia 1993;**34**:592–6.
19. COMMISSION ON CLASSIFICATION AND TERMINOLOGY OF THE INTERNATIONAL LEAGUE AGAINST EPILEPSY. Proposal for revised clinical and electroencephalographic classification of epileptic seizures. Epilepsia 1981;**22**:489–501. Commission on

Classification and Terminology of the International League Against Epilepsy. Proposal for revised classification of epilepsies and epileptic syndromes. Epilepsia 1989;**30**:389–99.

20. ILAE Commission Report. The Epidemiology of the Epilepsies: Future Directions. Epilepsia 1997;**38**:614–8.

21. COCKERELL OC, JOHNSON AL, SANDER JW, HART YM, GOODRIDGE DM, SHORVON SD. Mortality from epilepsy: results from a prospective population-based study. Lancet 1994;**344**:918–21.

22. GOBIERNO DE LA PROVINCIA DE BUENOS AIRES. Censo Nacional de Población y Vivienda 1991 en la Provincia de Buenos Aires. La Plata: Provincia de Buenos Aires, Dirección General de Estadísticas, 1993.

23. MURTHY JM, YANGALA R. Etiological spectrum of symptomatic localization related epilepsies: a study from South India. J Neurol Sci 1998;**158**:65–70.

24. DOHERTY MJ, JAYADEV S, MILLER JW, FARRELL DF, HOLMES MD, DODRILL CB. Age at focal epilepsy onset varies by sex and hemispheric lateralization. Neurology 2003;**60**:1473–7.

25. WALCZAK TS, LEPPIK IE, D'AMELIO M et al. Incidence and risk factors in sudden unexpected death in epilepsy: a prospective cohort study. Neurology 2001;**56**:519–25.

26. RAFNSSON V, OLAFSSON E, HAUSER WA, GUDMUNDSSON G. Cause-specific mortality in adults with unprovoked seizures. A population-based incidence cohort study. Neuroepidemiology 2001;**20**:232–6.