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SHORT COMMUNICATION

Premature mortality in a Georgian cohort of people with epilepsy

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Summary Mortality in people with epilepsy has not previously been estimated in Georgia. We identified a prevalent cohort of people with epilepsy from a tertiary referral centre in Tbilisi, Georgia and attempted to establish survivorship status for all. One-way sensitivity analysis estimating mortality rates in those lost to follow-up was also used. Of 1952 people, 1250 (64%) were located; 93 (7%) had died over a median of 11 years follow up. The main cause specific Proportional Mortality Ratios were: underlying diseases (39%) and accidental death (9%). One SUDEP was confirmed with a further 4 possible, but the cause of death was unknown in 47%. The overall SMR was 1.4, with much higher SMRs (up to 12) in young people. The sensitivity analysis suggested an SMR of 3.0.

Introduction

Epilepsy is a common chronic neurological disorder affecting over 60 million people world-wide (Ngugi et al., 2010). It is associated with a 2—3 times increased risk of premature death (Gaitatzis and Sander, 2004), with even higher rates in resource-poor countries (Carpio et al., 2005). Currently epilepsy care in Georgia is provided by several private institutions, which do not cooperate closely with each other; there is one state programme, based at the only tertiary centre for epilepsy in Georgia, with an estimated coverage of up to 20% of the population with epilepsy. The treatment gap among people with epilepsy, over 70% in Georgia (Lomidze et al., 2012), could play a role in premature mortality. As no previous estimation of mortality amongst people with epilepsy in Georgia is available, we attempted to establish basic epidemiological parameters related to epilepsy mortality in a Georgian population.

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Materials and methods

Target population

A retrospective prevalent cohort was identified from people with epilepsy attending the tertiary epilepsy centre in Tbilisi for diagnosis and management between 2005 and 2008. In all cases the diagnosis of epilepsy was confirmed by a multidisciplinary team. Survivorship was established through face-to-face or telephone interview with the individuals or their family members or carers. Additional information was obtained from the State Public Registry (death certificates, residency status) and Emergency Medical Service databases. When it was established that an individual had died, possible causes were identified through death certificates. This was supplemented by information obtained at post mortem examination, when available, and from verbal autopsy. Verbal autopsy used structured questionnaires completed at interviews with family members or witnesses to the terminal event. The questionnaire included sections on demographics, on illnesses and events leading to death (particularly injuries or accidents) and previously known medical conditions. Using all information available, putative causes of death (ICD10) were allocated during a moderation session. When circumstances were unclear or if the death certificate was uninformative then the death was categorized as being of unknown cause.

Estimation procedure

During the preliminary stages of the study, in reviewing medical records at the centre, it became clear that many people had been lost to follow-up. Additional information was then obtained from the Department of Statistics and from the records from large Primary Health Care centres responsible for many of the referrals to the tertiary centre. We were then able to trace a further 150 individuals. We used all available data to estimate mortality among people with epilepsy. As a sensitivity analysis, we repeated the estimation assuming that the mortality rate in those still lost to follow-up was double that in those subsequently found having previously been lost to follow-up. An additional sensitivity analysis was also conducted reflecting the worst possible scenario — assuming that all those lost to follow-up had died.

Statistical analysis

The Case Fatality Rate (CFR) was estimated as the number of known deaths in the cohort during follow-up divided by the number of people in the cohort.

Cause-specific Proportional Mortality Rates (PMRs) were estimated as the proportion of deaths due to a specific cause in the cohort.

Person-years were calculated for each age group (the sum of the years of follow-up contributed by each person in each group). Age-adjusted Standardized Mortality Ratios (SMRs) with 95% Confidence Intervals (CIs) were estimated as the ratio of the observed number of deaths in the cohort to those expected if age-specific rates were the same as in the standard population (indirect standardization). The standard population was derived from data from the 2008 Georgian population census. One-way sensitivity analysis was conducted to adjust for the influence on mortality estimation of people who were lost to follow-up. Analysis was carried out in SPSS (v17).

Table 1 Demographics and epilepsy characteristics of those initially traced.

	Alive ($n = 1157$)	Died ($n = 93$)
Male *n* (%)	574 (50)	72 (78)
Age in years at study end		
Mean (SD)	29.6 (16.2)	44.4 (17.7)
Median	26	46
Follow up (person years)		
Mean (SD)	13.7 (10.9)	15.3 (15.4)
Median	11	9.5
Onset age in years		
Mean (SD)	15.7 (14.5)	29.1 (21.2)
Median	13	26.5
Type of epilepsy		
Idiopathic *n* (%)	201 (17)	3
Symptomatic/cryptogenic *n* (%)	956 (83)	90 (97)

Results

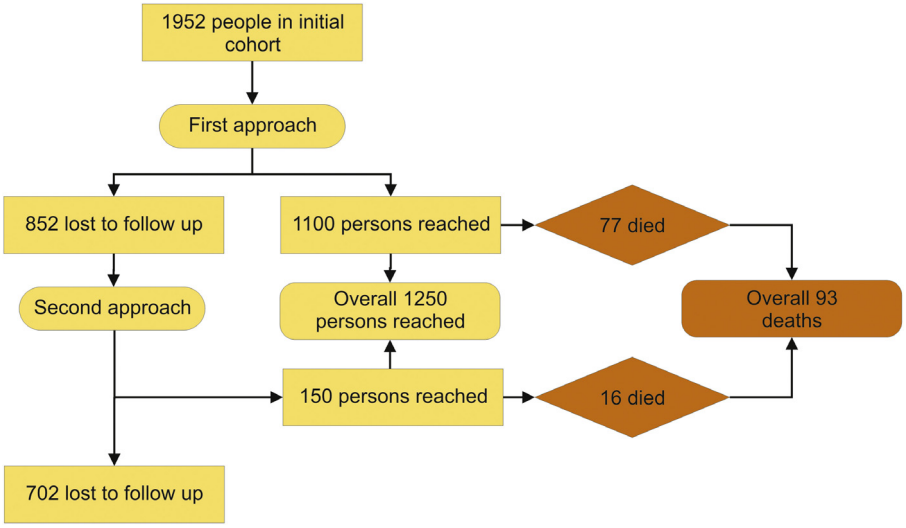
The cohort comprised 1952 people. We were able to locate and establish survivorship in 1250 people (64%) (for more details see participant flow chart, Box). There were 17,094 person-years of follow-up, and 93 people had died (Table 1).

CFR was 7% over a median of 11 years follow-up. Of the 93 people known to have died, 57 (61%) had symptomatic epilepsy; in 40% (23 people) the underlying cause was cerebrovascular disease, in 25% (14 people) the underlying cause was brain tumour, and in ten percent each (six people each) the cause was head trauma or perinatal pathology. The cause-specific PMRs are shown in Table 2.

SUDEP was diagnosed in one person and possible SUDEP was diagnosed in another four. The definite SUDEP was in a male, who died immediately after a witnessed seizure with

Table 2 Cause specific PMRs in 93 people with epilepsy.

Cause of death	*n* (%)
Cerebrovascular events	21 (23)
Brain tumours	14 (15)
Myocardial infarction	1 (1)
Accidental death (all occurred in males)	8 (9)
Drowning	3 (3)
Road traffic accident (2 were drivers)	3 (3)
Head injury from seizure	2 (2)
SUDEP — definite	1 (1)
SUDEP — possible	4 (4)
Unknown cause	44 (47)



Box Box participant flow chart.

nothing found on post mortem examination. The four possible SUDEP cases (who had no post-mortem examination, but in whom verbal autopsy was performed) were: a female who lived with her family who was found dead in bed in the morning, without evidence of a preceding seizure; a male who lived with his family and found dead with no witnessed seizure; a male found dead sitting in a chair; and a female who lived alone found dead by relatives. None had evidence of accidental injury or any other injury.

The overall SMR for people with epilepsy was 1.4 (95% CI 1.1, 1.7). The age-specific SMR (95% CI) for the 5—9 age group was 10.2 (3.5, 30.1), for the 10—14 age group was 12.2 (4.6, 32.4), for the 15—19 age group was 7.5 (3.4, 16.5) and for the 20—24 age group was 3.7 (2.0, 7.0). Significantly elevated SMRs were also observed in age groups 30—34, 40—44, 45—49 and 55—59. For people aged 60 years and above mortality rates were not significantly different from those in general population (Fig. 2). No deaths occurred in the 0—4 year age group or the 75—79 year age group.

After the first sensitivity analysis, assuming that those lost to follow-up had twice the mortality rate of those found in the tracing procedure, 26,252 person/years and 242 probable deaths were considered. The adjusted SMR was 3.05 (95% CI 2.7, 3.5) with similarly higher age specific SMRs in the younger age groups. The second sensitivity analysis assumed that all individuals lost to follow-up had died; 795 probable deaths were considered. The adjusted SMR was 10.04 (95% CI 9.35, 10.76).

Discussion

Premature death among people with epilepsy is probably more common in resource poor-countries, where some data suggest mortality rates three to five times as high as in the general population (Mu et al., 2011; Ding et al., 2013). Among people who were located we found a significantly increased overall premature mortality compared with the general population in Georgia. The increase was not, however, as dramatic as in other studies; this may be due to the retrospective nature of the study design as this type of study tends to miss fatalities during the early years after onset,

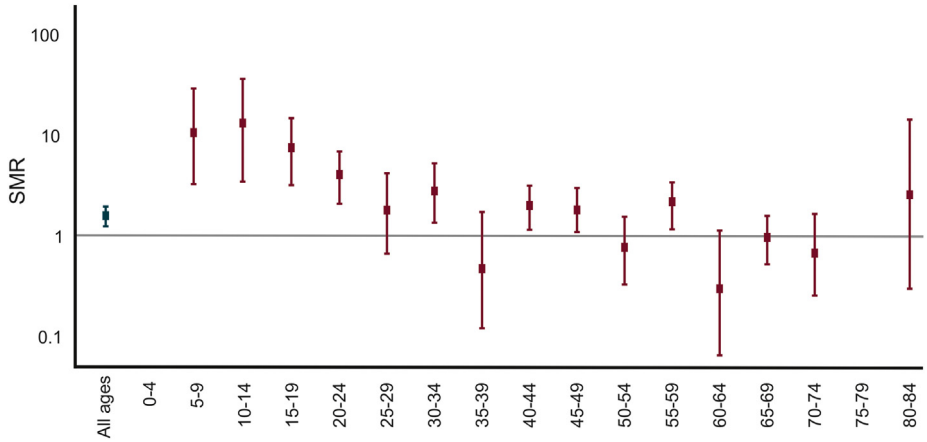


Figure 1 Age-specific standardized mortality ratios among people located. Age-specific SMRs of epilepsy adjusted for the 2008 census. *Y* axis is adjusted to logarithmic scale; bars represent 95% CIs.

when mortality is higher (Neligan et al., 2011). Another possible reason for the low SMR could be a high mortality rate in the general population. The mortality rate in the Georgian population was 9.8 per 1000 inhabitants at the end of 2008. The mean mortality rate in the European Union in the same period was 6.96 per 1000 population. Data from Eastern Europe are, however, comparable to those observed in Georgia (e.g. mortality rate per 1000 population: Hungary — 9.26; Romania — 9.64; Latvia — 10.07; Lithuania — 10.34) (OECD/European Union, 2010). One striking finding was that in the 5—19 year age groups the mortality rate was up to twelve times higher than in the general population. This is in agreement with other studies (Ding et al., 2013; Mu et al., 2011).

The mean age of epilepsy onset among those who died is higher than in those who survived. This may be due to the higher proportion of idiopathic epilepsies (17%) (Table 1) with young age of onset and a similar mortality rate to the general population, among those who survived; among those who died, most had symptomatic epilepsy.

The gender difference in the mortality rate in our study could be explained by the fact that accidental death occurred only in males (Table 2), perhaps because they more often engage in dangerous activities. Another explanation could be that cerebrovascular diseases, the most prominent causes of death, are more common among males.

The high rate of loss to follow-up is problematic for retrospective cohorts (Grimes and Schulz, 2002). In our study 36% people from the initial cohort were lost. We tried to account for this through sensitivity analysis. Taking this into account the SMR suggested a three-fold increased risk of premature mortality in people with epilepsy and this is similar to data from other countries (Mu et al., 2011). When we considered the worst case scenario, assuming all those lost to follow-up had died, the mortality rate was ten times as high as in general population. We consider, however, that the sensitivity analysis assuming double the mortality rate amongst those lost to follow-up is more realistic.

One important cause of death in people with epilepsy is the underlying disease (Shackleton et al., 1999). In our cohort the leading causes of death were neoplasia and cerebrovascular events. Accidents, including drowning, were the leading causes of probable epilepsy-related death.

SUDEP is considered a common cause of death in people with epilepsy (Langan et al., 2002). We identified five deaths that could be attributed to SUDEP, but in only one case had a post mortem been carried out. In 44 cases ascertainment of the cause of death was impossible due to insufficient data about events prior to death. It is possible that some of those categorized as dying of unknown cause had SUDEP.

Suicide seems to be a relatively common cause of death in people with epilepsy (Bell et al., 2009); we did not, however, find any deaths due to suicide. In Georgia there is both social stigma (as suicide is associated with mental illness) and religious intolerance (as those committing suicide are not allowed a religious funeral) towards suicide that encourages relatives to hide suicide and declare that the death is due to acute illness or other causes.

Data from this study should challenge decision makers. Lack of treatment may be a significant factor for the premature mortality of people with epilepsy in Georgia. In our study mortality was assessed based on those who attended the tertiary centre, where the treatment gap is probably much lower than in the general population with epilepsy; thus data presented here should be considered the minimum estimation of mortality in the population with epilepsy in Georgia. Another consideration in reducing premature mortality could be the reduction of accidental death (with special attention to road traffic accidents; in two cases the person with epilepsy was driving the car, which is not against the law in Georgia). Considering the number of accidental deaths (which could be preventable), we have the potential to reduce mortality among people with epilepsy by at least 10%. Efforts should be made throughout the country to improve epilepsy care and reduce the treatment gap as well as to provide regulations for driving in people with epilepsy.

Mortality studies provide valuable data about the course of diseases at population level that is important for health care professionals and decision makers. Retrospective cohort studies have problems locating individuals, but this relatively cheap method can provide useful data and should be considered when resources are limited. A population based prospective study with properly established follow-up procedures should be conducted to obtain a more precise picture of mortality in people with epilepsy in Georgia.

Conflict of interest

None of the authors has any conflict of interest to disclose in relation to this work.

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