Chapter 37

The mortality of epilepsy

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It has been consistently shown in population studies that the risk of premature death is two to three times higher in people with epilepsy than in the general population. This mortality risk is highest in the early years following diagnosis. The risk is stratified by aetiology with people with remote symptomatic epilepsy and neurological deficits having persistently higher risks. Other factors of relevance have been gender, age, a previous episode of status epilepticus, frequency and severity of seizures and antiepileptic drug (AED) compliance.

Long-term population-based prospective incident cohort studies provide the most reliable means of examining the risk of premature mortality and the way it changes over the course of the condition[1], although there are very few studies with follow-up of more than 20 years.

The estimates of the risk of premature death have varied between studies, and case ascertainment can be an issue depending on the methodology used. Mortality studies in epilepsy should be community-based studies of incident cohorts. Studies of people with prevalent epilepsy may underestimate the short-term mortality (as the mortality in people with epilepsy has consistently been shown to be highest in the early years following diagnosis) while simultaneously overestimating the long-term mortality (as those who have gone into remission may not be included in the cohort)[2]. The risk of premature death in people with epilepsy has been studied using death certificates, hospital or institutional records and through follow-up of community cohorts. Death certificates have been shown to be an unreliable source, with epilepsy being recorded on the death certificate in only 7% of patients known to have had seizures[3]. This figure increased to 17% in those with frequent seizures. In a community-based study of mortality in children with epilepsy, epilepsy was recorded on the death certificate in 55% of deaths directly attributable to epilepsy[4].

The most commonly reported measures of mortality in epilepsy studies comparing deaths between the study and a control population are the proportional mortality ratio (PMR) and the standardised mortality ratio (SMR). The PMR gives the proportion of deaths caused by a specific cause in the cohort and compares it with a control group. This is not a direct measure of mortality but rather gives the proportion of deaths due to one specific cause and can be influenced by the rates of other causes of death. The SMR is the ratio of the observed deaths in the study population to the expected deaths if the group had experienced the same age and sex-specific death rates as the population from which they came.

What is the risk and who is at risk?

Studies have consistently shown that males with epilepsy have higher mortality rates, with no clear explanation for this difference. The SMR tends to be high in children but this relates principally to the underlying cause of the epilepsy (remote symptomatic, perinatal insults) rather

than to the epilepsy itself. The lowest SMRs are reported in the 75+ age group; this relates in part to the fact that this age group in the population has a high mortality rate.

Few studies have looked at the risk of mortality after a single seizure. Two retrospective studies have investigated mortality after a single unprovoked seizure; one provided an SMR of 2.3 (95% confidence interval [CI] 1.5, 3.3)[5] and the other an SMR of 1.1 (95% CI 0.1, 4.0) for single idiopathic seizures[6]. In the NGPSE, people with an acute symptomatic seizure (provoked seizure) had an SMR of 3.2 (CI 2.4, 4.3) after more than 20 years of follow up[7]. Overall the SMR in people with a newly diagnosed unprovoked seizure ranges from 2.5 to 4.1 with the highest rates in children and those with symptomatic aetiology[8].

Reported SMRs in mortality studies from developed countries range from 1.6 to 4.1[9]. In the Rochester study[5], the SMR for the total group after 29 years' follow-up was 2.3, with the most significant increase in the first 10 years. In the NGPSE the SMR was 2.5 after median 6.9 years with the highest SMR in the first year (5.1)[10]. The SMR further decreased to 2.1 after 11 to 14 years of follow up[11], and remained stable but persistently elevated after a median follow-up of 22.8 years[7]. The highest SMRs were estimated in people with remote symptomatic epilepsy (SMR 3.7; 95% CI 3.1, 4.6) and epilepsy due to a congenital neurological deficit (SMR 19; 95% CI 7.0, 49.7)[7], which remained elevated throughout follow-up. In contrast people with idiopathic/cryptogenic epilepsy (defined as aetiology not determined) did not have a significantly increased long-term mortality rate (SMR 1.3; 95% CI 0.9, 1.9)[11] in the initial stages of follow-up, a finding that has been replicated in community-based studies in Iceland[6] and France[12]. The French study, which examined the short-term mortality in people with epilepsy, is the only study to have used the categories idiopathic and cryptogenic epilepsy as defined by the ILAE, with no significant differences between the two groups. Interestingly, mortality was significantly elevated in people with idiopathic/cryptogenic epilepsy in the NGPSE during the last 10 years of follow-up[7].

Data on premature mortality in people with epilepsy is more limited from resource-poor countries. Findings from a prevalent cohort study with a follow-up of 6.1 years gave an overall SMR of 2.9 (95% CI 2.6, 3.4)[13], although the SMR reported earlier, after the first 25 months of follow-up, was higher (SMR 3.9, 95% CI 3.8, 3.9)[14]. A much higher SMR was found in young people (aged 10–29 years) (SMRs 28 to 37). Death from drowning was a significant risk (overall SMR 39; 95% CI 26.4, 55.5), but was more critical for people living in a waterside area than for those living in the mountains (HR 3.9; 95% CI 1.7, 9.2, $P = 0.002$)[14]. A similar prevalent cohort with a follow-up of median 28 months found an overall SMR of 4.9 (95% CI 4.0, 6.1), with higher SMRs in young people[15].

Overall, people with epilepsy have been found to have a reduction of life expectancy which is greatest at the time of diagnosis. This reduction can be up to two years in people with idiopathic/cryptogenic epilepsy and up to 10 years in people with symptomatic epilepsy[16].

Mortality in population-based studies is summarised in Table 1.

Causes of death

Causes of death in people with epilepsy can be divided into epilepsy-related and non-epilepsy-related deaths. For people with symptomatic epilepsy (both remote and progressive) the excess mortality risk relates primarily to the underlying cause of the epilepsy rather than to the epilepsy itself. In a study of 692 children with epilepsy followed up over an average of 13 years, the SMR

was 5.3, with functional neurological deficit being the only independent predictor of mortality (occurring in 85% of cases)[17].

In a Finnish cohort of 245 children with epilepsy identified between 1961 and 1964 and followed up prospectively, 44 had died by the follow-up in 1992. Of these 75% had remote symptomatic epilepsy[18] (similar to that found in childhood mortality studies from Australia[4] and Nova Scotia[17]). Most (89%) of those who died were not in remission at the time of death, with a relative risk of death in those with active epilepsy compared with those in remission of 9.3 (95% CI 3.8, 22.7). The cause of death was definitely or probably related to a seizure in 45% of cases. There were three cases of sudden unexplained death in epilepsy (SUDEP) in people with idiopathic epilepsy, none of whom was in remission at the time of death[18]. In the extended follow-up of the cohort up to 2002, 60 (24%) had died, of whom 51 (85%) were not in terminal remission (≥ 5 years seizure free) at the time of death. Those with a remote symptomatic aetiology were three times as likely to die as those with idiopathic/cryptogenic aetiologies (37% vs 12%). Of the 60 deaths, 33 (55%) were felt to be epilepsy related, including 18 deaths from SUDEP, giving a cumulative risk of SUDEP of 7% at 40 years (12% for those not in terminal remission and not taking AEDs[19]).

Table 1. Population studies of mortality in people with epilepsy with standardised mortality rates (with 95% confidence intervals).

Country	**SMR**	**Ages**	**Comments**
Poland[41]	1.8	All	Retrospective prevalent cohort
United States[5]	2.3 (1.9, 2.6)	All	Historic incident cohort (Rochester)
United States[22]	2.1 (1.9, 2.5)	All	SMR for IHD elevated in those <65 years
Iceland[6]	1.6 (1.2, 2.2)	All	Historic incident cohort
France[12]	4.1 (2.5, 6.2)	All	Prospective, incident cohort 1 year mortality
Sweden[55]	2.5 (1.2, 3.2)	≥17 years	Prospective incident cohort with first seizure
Canada[17]	5.3 (2.3, 8.3)	<17 years	Historic incident cohort
China[13]	2.9 (2.6, 3.4)	>2 years	Prospective prevalent cohort
United Kingdom[7]	2.6 (2.2, 2.9)* 2.2 (2.0, 2.5)**	All	Prospective incident cohort (NGPSE) 1984–2009

*definite epilepsy
**definite and possible epilepsy

In a Dutch study of mortality in people with epilepsy followed for over 40 years the SMR was 16 in the first two years decreasing to 2.8 thereafter[20]. After two years, approximately one-third of deaths were directly or indirectly attributable to epilepsy. Common non-epilepsy causes of death cited in mortality studies include pneumonia, cerebrovascular disease, malignancy and heart disease. SMRs and PMRs are consistently elevated for these causes in population-based studies and often markedly so in the first few years of follow-up. In a Swedish study looking at cause-specific mortality in over 9000 adults with epilepsy, the overall SMR was 3.6 (95% CI 3.5, 3.7), with SMRs being increased for specific causes such as cancer (SMR 2.6; 95% CI 2.4, 2.8), respiratory disease (SMR 4.0; 95% CI 3.6, 4.5), heart and cerebrovascular disease (SMR 3.1; 95% CI 3.0, 3.3) and accidents and poisoning (SMR 5.6; 95% CI 5.0, 6.3)[21]. The risk of premature death from heart disease in people with epilepsy was found to be elevated in those aged 25 to 64 but not for those aged 65 years and over in the Rochester cohort[22], and also in the NGPSE cohort during the last five years of follow-up[7]. Bronchopneumonia is an important cause of mortality in people with epilepsy of all ages, not just the elderly, and was associated with the highest SMR (6.6) in the NGPSE[7]. This may be related to aspiration during seizures but this is unproven, or it may be the terminal event.

The influence of mental retardation (MR) and epilepsy was investigated in a Swedish study. The SMR was 1.6 (95% CI 1.3, 2.0) in people with MR only but this increased to 5.0 (95% CI 3.3, 7.5) for those with MR and epilepsy, with the increase in mortality associated with seizure type and frequency[23]. In studies from institutions and hospitals, where people have presumably more severe epilepsy, epilepsy-related deaths are more common. In one study, PMRs were cancer (26%), bronchopneumonia (25%), circulatory diseases (24%), seizure-related deaths (other than SUDEP) (12%) and SUDEP (6%)[24].

SMRs and PMRs for cancer have been consistently elevated in people with epilepsy even after excluding CNS neoplasms. Cancer mortality was compared between two cohorts with epilepsy, one from an institution with more severe epilepsy (SEC) and the other, a community-based population with milder epilepsy (MEC). The SMR for all cancers was elevated in the SEC (SMR 1.42; 95% CI 1.18, 1.69) but not in the MEC (SMR 0.93; 95% CI 0.84, 1.03). The SMR for brain and CNS neoplasms was significantly elevated in the group with milder epilepsy[25].

Two recent studies from Finland[26] and Austria[27] have looked at cause-specific mortality in people with epilepsy, and both demonstrate that the majority of deaths are due to non-epilepsy-related causes. In the Finnish study[26], which was based on a nationwide register-based cohort study of people aged 10 years or older diagnosed with epilepsy between 1990 and 1994, the predominant causes of death were CNS cancer (17%), other cancers (15%), ischaemic heart disease (11%) and cerebrovascular diseases (10%), which may have been related to the probable underlying aetiology. In contrast the proportion of deaths attributable to epilepsy was small with 3.9% of deaths attributable to accidents, 3.4% for alcohol-related diseases and 1.6% for suicides. The Austrian study[27] comprised all adults (≥18 years) treated for epilepsy at a single centre (Innsbruck) between 1970 and 2009. In the overall cohort there were 4295 people, with 822 deaths (overall SMR 1.7; 95% CI 1.6, 1.9). The highest cause-specific SMRs in the overall cohort were for congenital abnormalities (SMR 7.1; 95% CI 2.3, 16.6), suicide (SMR 4.2; 95% CI 2.0, 8.1), alcohol dependence syndrome (SMR 3.9; 95% CI 1.8, 7.4), malignancy of the oesophagus (SMR 3.1; 95% CI 1.2, 6.4) and pneumonia (SMR 2.7; 95% CI 1.6, 4.2). The cause-specific SMRs were broadly similar in those with newly diagnosed epilepsy (1299 individuals with 267 deaths) with an overall SMR of 1.8 (95% CI 1.6, 2.1).

The risk of premature mortality is similarly elevated in people with drug-resistant epilepsy[28]. In a prevalent cohort of 433 people with drug-resistant epilepsy (at least one seizure per month despite treatment with two or more AEDs), with median duration of epilepsy 25 years at study entry who were followed up for six years, the cumulative probability of death was 8.7% (95% CI 6.2, 12.1) with an overall SMR of 2.4 (95% CI 1.7, 3.3). The mortality was largely driven by those with a known epilepsy aetiology; the SMR was 3.1 (95% CI 2.0, 4.6) in people with a remote symptomatic or progressive aetiology and 1.7 (95% CI 0.8, 2.8) in people with an unknown aetiology). The excess mortality in those with known aetiology was not eliminated by exclusion of those with progressive aetiology (SMR 2.5; 95% CI 1.4, 3.8).

Epilepsy-related deaths

Deaths directly related to epilepsy include SUDEP, status epilepticus, consequences of seizures (including accidents, drowning and aspiration pneumonia), iatrogenic (drug toxicity and idiosyncratic) and suicide.

The case fatality following status epilepticus typically ranges from 10−22%[29] (Rochester 21%[30]), with some lower case fatality rates in Europe, possibly as a result of the exclusion of deaths due to status epilepticus following anoxic encephalopathy.

The primary determinant of prognosis in status epilepticus is aetiology[31] but other factors such as age and seizure duration are important in determining outcome[32]. There is some suggestion that the case fatality following status epilepticus may be decreasing (although the evidence is conflicting)[33] and is particularly low in children[34].

SUDEP is defined as a sudden, unexpected death in an individual with or without evidence of a seizure where post mortem does not reveal a specific cause of death[35]. Estimates of SUDEP rates are heavily influenced by the population under study, with much higher rates in those with severe or refractory epilepsy. Identified risk factors for SUDEP include younger age of onset, long duration of epilepsy and refractory epilepsy[36]. The incidence of SUDEP was 0.35 per 1000 person years in the Rochester cohort[37], while an incidence of 1:295 per year was found in children with more severe epilepsy and learning difficulties[38]. SUDEP is reviewed in greater detail in Chapter 38.

People with epilepsy may die as a result of an accident during a seizure. Based on attendance records of four accident and emergency (A&E) departments, the risk of injury as a result of a seizure was estimated to be 29.5 per 100,000 population per year[39]. Many seizure-related injuries tend to be minor, with an increased risk related to background seizure frequency[40], but some injuries can be fatal.

In a one-year population-based study (using inpatient records, doctors' claims and A&E visits) the annual incidence of injuries was higher in people with epilepsy, with 20.6% of people with epilepsy having at least one injury compared with 16.1% among people without epilepsy ($P < 0.001$). In particular, people with epilepsy were more likely to have fractures, crushing injuries, intracranial and other head injuries[41]. Similarly over a two-year period, people with epilepsy were more likely to have injuries inflicted on them by others (odds ratio 1.46; 95% CI 1.04, 2.03) after adjustment for co-morbidities; they were slightly more likely to have motor vehicle accidents and completed or attempted suicide[42].

People with epilepsy have an increased risk of drowning (15- to 19-fold) compared with the general population. In a meta-analysis of the risk of drowning, the total SMR was 18.7. The SMR varied depending on the population under study, with an SMR of 5.4 in community-based incident cohorts, 18 in people with prevalent epilepsy, 25.7 in people with epilepsy and learning disability and 96.9 for people in institutional care[43].

People with epilepsy have been shown to be at increased risk of suicide in some studies[13,21,44] but not in others[5,11]. In a meta-analysis, the SMRs for suicide in people with epilepsy were markedly elevated, particularly for those with temporal lobe epilepsy[45]. In a population-based control study from Denmark, 2.3% of people with epilepsy committed suicide compared with 0.7% in the general population, corresponding to a three-fold increased risk (risk ratio 3.2; 95% CI 2.9, 3.5). This risk was particularly high in people with co-morbid psychiatric illness and in the first six months following diagnosis[46]. A more recent meta-analysis found that the overall SMR for suicide in people with epilepsy was 3.3 (95% CI 2.8, 3.7), with the highest rates being in those following temporal lobe excision (SMR 13.9), following other forms of epilepsy surgery (SMR 6.4) and in people with temporal lobe epilepsy (SMR 6.6)[47].

In a study[48] looking at the role of psychiatric comorbidity in premature mortality in people with epilepsy, people diagnosed with epilepsy in Sweden between 1969 and 2009 were identified through the National Patient Register (n = 69,995) and compared with age-matched and sex-matched controls (n = 660,869) and unaffected siblings (n = 81,396) for risks and causes of premature mortality. During follow-up 6155 (8.8%) people with epilepsy died. A total of 972 people with epilepsy (15.8%) died from 'external causes' (suicide, accidents or assault) with a high adjusted odds ratio (aOR) for non-vehicle accidents (aOR 5.5; 95% CI 4.7, 6.5) and suicide (aOR 3.7; 95% CI 3.4, 4.2). While 75% of those who died from external causes had comorbid psychiatric disorders with strong associations in individuals with depression (aOR 13.0; 95% CI 3.16, 6.0) and substance abuse (aOR 22.4; 95% CI 18.3, 27.3) compared to people without epilepsy and no psychiatric comorbidity, the risk was also increased in people with epilepsy but no depression (aOR 3.3; 95% CI 3.0, 3.7) or substance abuse (aOR 2.2; 95% CI 1.9, 2.6).

AEDs and increased mortality

It has been suggested that antiepileptic treatment with more than two AEDs increases the risk of SUDEP[49], though other studies have not shown an increased risk of SUDEP with any AED in monotherapy or in combination therapy[50]. Moreover the risk of suicide in people taking AEDs, although increased, appears to be low[51].

It has been reported that long-term use of AEDs is associated with an increased risk of fractures, particularly in women, with the risk increasing with the duration of treatment[52].

The response to treatment has been suggested as a determinant of mortality, with people who continue to have seizures despite treatment having an increased risk of premature death compared with those rendered seizure free where no such risk was observed[53].

Non-adherence to antiepileptic medication has been shown to be associated with an over three-fold increased risk of death (hazard ratio 3.3; 95% CI 3.1, 3.5) after controlling for possible confounding factors. Non-adherence was also associated with 86% increased risk of hospital admission and a 50% increased risk of A&E attendance[54].

Conclusions

It is clear that a diagnosis of epilepsy is associated with an increased risk of premature death, particularly in the early years following diagnosis. Up to one-third of such deaths can be directly or indirectly attributable to epilepsy. This risk is decreased but probably not eliminated by rendering the person completely seizure free by treatment.

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