The mortality of epilepsy revisited

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ABSTRACT – Epilepsy carries a significant mortality that, on average, is 2-3 times higher than in the general population. Causes of death in epilepsy are presented. Mortality in epilepsy is assessed by means of particular parameters; the mortality rate, the standardised mortality ratio, and the proportional mortality rate. An overview of their use and significance is given here. A number of epidemiological studies have assessed mortality in people with epilepsy in the general population and in populations from hospitals, out-patient departments, and epilepsy centres. Methodological issues concerning the study of mortality in these populations are discussed. Epidemiological data are presented to describe the overall and cause-specific mortality, as well as determinants of mortality in epilepsy, such as epilepsy and seizure types, time from diagnosis, and age. It has become clear from population studies with long-term follow-up that epilepsy has a higher mortality in the first few years after diagnosis that tends to decrease over time. The pattern of mortality in epilepsy can reflect the underlying conditions causing epilepsy or be associated with the effect of seizures. Emphasis is given to preventable causes of death in epilepsy, such as sudden unexpected death in epilepsy and suicide, which are discussed more extensively. The size of the problem and measures to avoid more deaths in epilepsy are discussed in the light of recently published data.

KEY WORDS: epilepsy, mortality, SMR, SUDEP

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Despite an overall good prognosis for seizure control [1, 2], epilepsy is a potentially life-threatening condition and is associated with increased mortality. This is consistently shown, both in population-based studies and in studies of more selected populations, such as institutionalised patients and clinic attendees [3, 4].

People with epilepsy have a *mortality rate* (the number of deaths that occur in a defined population divided by the person-years at risk in that population) 2-3 times higher than that of the general population [4]. This is better expressed as the *standardised mortality ratio* (SMR), which is the ratio of the observed number of deaths in an epilepsy population to that expected based on the age- and sex-specific mortality rates in a reference population, in a given time [5].

Causes of death in people with epilepsy can be classified into 3 groups: deaths that are unrelated to epilepsy; those that occur as a result of the cause of epilepsy; and those in which the epilepsy itself is the cause of death *(table 1)* [3].

The proportion of deaths due to a particular cause in a cohort of patients in a given period can be described by the *proportional mortality rate* (PMR), which compares the relative contribution of various causes to the overall mortality in this population [4, 6]. PMR is not a direct measurement of the ratio of rates of death between

Table 1. Causes of death in epilepsy (adapted from Nashef *et al.,* 1995 [8]).

Unrelated deaths
Neoplasms outside the central nervous system
Ischaemic heart disease
Pneumonia
Others

Related to underlying disease
Brain tumours
Cerebrovascular disease
Cerebral infection-abscesses and encephalitis
Inherited disorders, e.g. Batten's disease

Epilepsy-related deaths
Suicides
Treatment-related deaths
Idiosyncratic drug reactions
Medication adverse effects
Seizure-related deaths
Status epilepticus
Trauma, burns, drowning
Asphyxiation, aspiration
Aspiration pneumonia after a seizure
Sudden unexpected death in epilepsy

populations, and does not express the risk of members of a population contracting or dying from a disease. Comparisons of PMR between groups or populations can be meaningful only if the cause-specific mortality rates are known so that differences between populations relate to variations either in the number of deaths of interest (numerators) or the total number of deaths (denominators) [4]. For example, an observed excess of a particular cause of death in an epilepsy group may represent a true increased risk, but may also merely represent a deficit of deaths due to other causes.

The underlying disease, of which epilepsy is a symptom, is the main cause of death in newly diagnosed cases, and is associated with increased mortality whether epilepsy is present or not [7]. Epilepsy itself, and probably to a very much lesser extent, its treatment, is a major cause of death in chronic epilepsy [8]. It has been suggested that the long term use of antiepileptic drugs (AEDs) increases the incidence of malignant neoplasia and osteoporosis, thereby potentially affecting long-term mortality rates in people with epilepsy [7].

Abbreviations: SMR = standardised mortality ratio; PMR = proportional mortality rate; SUDEP = sudden unexpected death in epilepsy; TLE = temporal lobe epilepsy; AEDs = antiepileptic drugs.

Measurements and methods

Methodological difficulties permeate studies of the mortality of epilepsy. Definitions of epilepsy and classification of seizures may differ between studies, as well as the accuracy of epilepsy diagnoses and the classification of causes of death. The International League Against Epilepsy (ILAE) has published guidelines for epidemiological research [5], which deal with the issue of definition and classification, and are based on the ILAE classification of epileptic seizures and syndromes [9, 10]. For example, until recently, the term cryptogenic was interchangeable with idiopathic. In the new classification, the term "idiopathic" is reserved for seizures occurring in epilepsy with a presumed genetic origin, and "cryptogenic" characterises seizures occurring in otherwise normal people, with no clear cause. Other problems included the exact definitions of sudden unexpected death in epilepsy (SUDEP) and other seizure-related deaths [11], as well as the inclusion in the epilepsy group of patients with acute symptomatic seizures, – a category known to be associated with increased mortality [8].

The accuracy of information on the cause of death depends on the collecting methods employed. Death certificates can be an unreliable source [12-14] and, although autopsy and supplementary clinical data improve accuracy, they are subject to bias and error [8]. In the ongoing, UK National General Practice Study of Epilepsy [15], epilepsy was mentioned in 10 of 181 patients with definite epilepsy (Dr. Gail Bell, personal communication). Furthermore, SMR cannot be calculated in studies utilising registers of death certificates because the number of person-years at risk in the study population is usually not known. Diagnostic inaccuracy in life may be as high as 15-20%, owing to confusion with syncope and psychogenic attacks or as a result of overinterpretation of EEGs [16, 17]. Case ascertainment is subject to bias: retrospective studies based on hospital records may significantly underestimate the number of cases in the community [17], especially in the elderly, the very young and individuals whose seizures were not witnessed [18]; and population-based studies may include people without epilepsy [19].

In addition to the small number of mortality studies in epilepsy, different study types and reference populations have been used, rendering comparison between studies and application to the general population even more problematic [20]. Studies from selected populations, such as hospital-based case series [16, 21-24], residential epilepsy centre [25-27] and epilepsy centre case series [28] offer the advantage of more reliable diagnoses and accurate classification of cause of death. Their disadvantages are that most include small numbers of patients and, most importantly, suffer from selection bias, as they tend to represent more severe and chronic cases. This is likely to exaggerate mortality and epilepsy-related deaths, and re-

sults cannot be applied to the general epilepsy population. Cross-sectional and prevalent population studies fail to ascertain new cases of epilepsy and therefore miss the high initial mortality of epilepsy, and can misrepresent particular causes of death such as brain tumours [18]. Insurance cohorts [29, 30] represent highly selected, prevalent cases and utilise the lower mortality rates of non-rated policy holders as the standard [7].

The heterogeneity between studies was evident in a recent attempt at a meta-analysis of comparative studies investigating mortality in epilepsy patients [20]. The authors performed a detailed quantitative review of relevant follow-up studies conducted in the last 100 years, in order to investigate the extent and causes of the differences found in studies of mortality in epilepsy. Nineteen studies matched their criteria, assessing community, general medical and institutional populations. However, a summary estimate could not be calculated because of considerable variation in mortality risk ratios of the studies. This variation was explained mainly by differences in the "source population" (that characterises the setting from which patients were recruited), and secondarily by case selection.

The ideal approach is one of large scale, general population-based, prospective incidence studies with comprehensive case ascertainment, accurate diagnosis, sound aetiological assignment, long follow-up and efficient tracing of patients [17]. The National General Practice Study of Epilepsy (NGPSE) studies in the UK [18, 31], the study conducted in Rochester, Minnesota [14], and the

study in Västerbotten County in Northern Sweden [32] appear to fulfil these criteria to a great extent.

Overall mortality

Premature mortality in patients with epilepsy is reported to be significantly higher than in the general population [20]. SMRs for community-based studies range between 1.3 and 3.1 (1.6 and 2.6 for studies using incident cases) (table 2).

A community-based study of mortality in children aged 1-14 years, using a state-wide paediatric mortality surveillance system in Victoria, Australia found an all-cause SMR of 13.2 (95% confidence interval [CI]: 8.5-20.7) [33]. A long-term study in which a cohort of 245 Finnish children with epilepsy were followed up for more than 30 years reported an increased risk of death and decreased probability of survival in those who had not entered remission [34]. A community-based cohort study in Nova Scotia, Canada, which followed 692 children who developed epilepsy between 1977 and 1985, reported SMRs > 5 in the first 15-20 years after diagnosis [35]. The majority of deaths in *people whose seizures start in childhood* occur in adulthood [34, 36, 37].

Studies of selected populations tend to have higher SMRs. In a large cohort study of all patients over 15 years old, in whom a diagnosis of epilepsy was recorded at discharge from any hospital in Stockholm during 1980-1989, an SMR of 3.6 (CI 3.5-3.7) was estimated [16]. This cohort

Table 2. Community-based studies of overall mortality of epilepsy.

Study	Setting	Method	Age at entry	Person-years	SMR (95% CI)*
Alström 1950 [21]	Sweden	Clinical series	23 yrs	N/A	2.4 (2.0-2.8)
Voute 1967 [104]	Europe	Insurance policy holders	Adults	N/A	3.1
Zielinski 1974 [12]	Warsaw	3-yr prevalence cohort	All	~ 20,000	1.8
Hauser et al., 1980 [14]	Rochester, MN, USA	29-yr retrospective incidence cohort	All	8,233	2.3 (1.9-2.6)
Olafsson et al., 1998 [40]	Iceland	30-yr retrospective incidence cohort	N/A	6,308	1.6 (1.2-2.2)
Loiseau et al., 1999 [86]	Gironde, France	1-yr prospective incidence cohort †	All	804	9.3 (7.9-10.9)
Lindsten et al., 2000 [32]	Sweden	11-yr prospective incidence cohort	≥ 17 yrs	850	2.5 (1.2-3.2)
Lhatoo et al., 2001 [31]	United Kingdom	14-yr prospective incidence cohort	All	11,400	2.1 (1.8-2.4)‡
Camfield et al., 2002 [35]	Nova Scotia, Canada	> 15-yr retrospective incidence cohort	28d-16yrs	N/A	8.8 (4.1-13.4)

* CI denotes confidence interval.
† Early mortality was assessed.
‡ The NGPSE study [18, 31] included patients with symptomatic and unprovoked seizures.

comprised a total of 53,520 person-years and 4,001 deaths. In a retrospective study of the survival status of out-patients seen in a Dutch epilepsy centre over a 40-year period (38,665 person-years, 404 deaths), the SMR was 3.2 (CI 2.9-3.5) [28]. In a cohort of adult outpatients with epilepsy at a tertiary referral centre in the UK (1849 patient-years), the SMR was 5.1 (CI 3.3-7.6) [38]. SMRs for institutionalised populations (i.e., patients living in residential epilepsy centres) range between 1.9 and 3.0 [20, 26, 27].

Risk factors determinants of mortality

The higher risk of premature death does not apply equally to all people with epilepsy and serves only as a summary measurement, masking important differences in mortality among the population with epilepsy. Studies of mortality in epilepsy calculate mortality rates according to aetiology, duration and type of epilepsy, age, and sex. In its published guidelines for epidemiological studies, the ILAE proposed that the epilepsies and epileptic seizures be categorised into aetiological groups: idiopathic, cryptogenic, acute symptomatic, remote symptomatic, and progressive symptomatic. [5]. No studies to date have strictly adhered to the new classification scheme. Prior to this new scheme, the three major aetiological groupings usually included the idiopathic (or cryptogenic, or primary) group, the remote symptomatic (or postnatally acquired secondary epilepsy) group, and the (congenital) neuro-deficit group.

Idiopathic (and/or *cryptogenic*) *epilepsy* has the lowest, long-term mortality, with SMRs ranging from 1.5 to 1.8 in population studies [14, 21, 39], suggesting that mortality rates in this group are above those of the general population by 50-80%. Other studies however, failed to show a significant increase in mortality in this group [31, 32, 40]. Studies in children follow the same population trends in mortality, in idiopathic and cryptogenic cases [24, 33, 34] as well as in cases without severe neurological deficit [35].

Although the overall chances of achieving remission are similar in patients with remote symptomatic epilepsy and idiopathic epilepsy, the same is not true of their relative risk of premature death [2]. Long-term mortality is greatly increased in remote symptomatic epilepsy with reported SMRs of 2.2 (CI 1.8-2.7) in the Rochester study [14], 2.3 (CI 1.4-3.5) in an Icelandic study [40], 3.7 (CI 2.9-4.6) in the NGPSE [31], and 3.3 (CI 2.4-4.5) in the Västerbotten County study [32]. Considering people with symptomatic epilepsy, the risk of death appears to be over ten times higher for those with congenital neurological deficit or CNS tumours, and 2-3 times higher in patients with cerebrovascular disease or alcohol abuse [31]. The reported SMR in a prevalent paediatric population with epilepsy in Australia was 49.7 (CI 31.7-77.9) for remote symptomatic

epilepsy [33]. In a population-based study, children with disorders sufficient to cause functional neurological deficit were 22 times more likely to die prematurely than those without [35]. The authors concluded that children with remote symptomatic epilepsy and no neurological deficit are unlikely to die as a result of seizures [35].

The neuro-deficit group, consisting of patients with gross neurological deficit and/or learning difficulties presumed to have been present or acquired at birth, has the highest long-term mortality, with reported SMRs in the range of 11.0 (CI 6.9-16.4) [14] and 25 (CI 5.1-73.1) [31]. The excess mortality is attributed to the small number of deaths expected in the young age group and the high death rate among children with neurological deficit, irrespective of the presence of epilepsy [7].

Seizure type also plays a role: patients with absence seizures do not appear to be at greater risk of death [14], while those with generalised tonic-clonic seizures carry SMRs of 3.5-3.9 for the first 5-10 years from diagnosis [14, 32] and those with myoclonic seizures, 4.1 [14]. The SMR for complex partial seizures was not significantly increased in the Rochester study [14], but was reported as 2.1 (CI 1.2-3.6) in the Vsästerbotten County study [32].

Mortality risk increases with severity of epilepsy, usually assessed by seizure frequency. In one study, patients with "severe" epilepsy or frequent seizures had significantly higher SMRs compared with patients with "slight" epilepsy or free from seizures [23]. Patients whose seizures responded to AED treatment exhibited lower mortality than people with poorly controlled seizures (SMR 2.13 versus 3.77 respectively) [23]. In the Rochester study [14], patients entering remission had an SMR of 2 for the first five years of seizure freedom, but the SMR was not significantly elevated thereafter. These results were corroborated in two recent studies assessing long-term mortality in cohorts of patients who underwent epilepsy surgery [19, 41] SMRs in patients with persistent seizures were 4.69 (CI 2.33-7.75) [19] and 7.4 [41], with a reported rate of death of 1.37 per 100 person-years [19]. In contrast, mortality in patients who became seizure-free post-operatively did not differ from that of the general population [19, 41].

Age-specific SMRs show increased death rates at all ages among people with epilepsy, although this increase is more pronounced in people under 50 years of age and declines sharply after age 60 [12, 14, 16, 23, 28, 31, 40]. SMRs of between 6 to 8 have been reported for age groups up to 50 years, in comparison to SMRs of < 2 for patients older than 70 years [3, 14, 23]. This may be explained by the high mortality in patients with neurological deficit at birth and in young patients with remote symptomatic epilepsy due to head trauma and brain tumours, as well as the highly increased risk of sudden death in younger adults with epilepsy [7, 14]. An important factor contributing to the high SMRs in the young is also the very low mortality

observed in children and the younger age groups in the general population.

Mortality rates in epilepsy vary over time, being higher in the first years after diagnosis. SMRs reported for all cases for the first year were 3.8 in the Rochester study [14], 6.6 in the NGPSE study [31], and 7.3 in the Västerbotten County study [32]. SMRs for the first four years ranged between 2.0 and 3.1 [3, 14, 40]. Mortality rates declined to near normal in years 4-9 in the NGPSE study [31], in years 2-9 in the Västerbotten County study [32], and after the first ten years in the Icelandic [40] and Rochester studies. Rates increased again in years 25-29 of follow-up in the Rochester study [14], in years 9-14 in the NGPSE (but not in the idiopathic epilepsy group) [31] and in years 9-11 in the Västerbotten County study [32]. Trends in the Rochester study [14] persisted for the three aetiological groups (idiopathic, remote symptomatic, neurodeficit) when analysed separately, with much higher initial SMRs for the neurodeficit group. Results similar to this last group were reported by a study of mortality in attendees of a Dutch epilepsy centre cohort [28].

Higher SMRs have been reported in males than in females in some studies [14, 23, 28, 39, 42], but not in others [19, 27, 31, 32, 38].

Cause-specific mortality

Cause-specific mortality refers to deaths occurring in the population or a cohort due to a particular cause.

Epilepsy-related deaths

Deaths attributed to epilepsy itself include suicide, treatment-related deaths, SUDEP, and seizure-related deaths, such as deaths occurring in status epilepticus (SE) and accidents caused by seizures such as drowning and burns (table 1). The proportion of deaths due to epilepsy is described by the PMR, which tends to be higher in selected population studies, ranging between 18 and 41% [22, 23, 25-28, 43], than in community studies where it is between 1 and 13% [12, 14, 31, 33, 34)]. However, two community studies of children in Finland [34] and Victoria, Australia [33] found the epilepsy PMR to be 45% and 22% respectively. A review of the literature from 1910 to 1974, which consisted mainly of studies in institutionalised patients, reported an average epilepsy PMR of 42.7% [44]. The wide range of the epilepsy PMR may be explained by differences in patient characteristics and population selection, diagnostic criteria, duration of follow-up, and classification of causes of death.

Deaths as a result of SE follow similar population trends and comprise up to 12.5% of all deaths. SE appears to be an important cause of death, especially for patients in epilepsy hospitals and centres [25, 27, 43]. The case-fatality rate in SE may be as high as 20%, but can be much higher in patients with acute symptomatic seizures, myoclonic seizures, and in elderly patients (especially those > 65 years) [45, 46]. In a study of cases of generalised convulsive status epilepticus, the case fatality rate was highest in patients with a diagnosis of anoxia, CNS infection, or stroke [46]. The long-term mortality of SE was assessed in patients who survived at least 30 days after a first episode of SE, in Rochester, Minnesota [45]. The overall SMR was 2.8 (CI 2.1-3.5), but the SMR was significantly elevated in all subgroups with symptomatic SE: acute [3.8 (CI 2.5-5.4)], remote [3.0 (CI 1.8-5)], and progressive [3.1 (CI 1.6-5)]. SE was considered progressive symptomatic in the presence of non-static central nervous system (CNS) conditions, such as CNS tumours and degenerative neurological disorders [45]. There was no increase in mortality in patients without an underlying cause of SE (i.e., idiopathic/cryptogenic), suggesting, according to the authors, that SE by itself does not alter long-term mortality [45]. This finding is further supported by other studies, which report that patients who develop status following discontinuation of AEDs or as part of unprovoked epilepsy, and children with epilepsy, have low mortality rates [47-50].

Accident-related deaths comprise between 1.2 and 6.5% of all deaths in community-based studies [12, 14, 31, 34] and between 7.3 and 42% in selected population studies, with SMRs ranging from 2.4 -5.6 [16, 20, 22, 23, 25-27, 39, 43]. People with epilepsy may sustain a fatal accident either during a seizure or as a consequence of a seizure. These could be due to traffic accidents, burns, trauma, aspiration or drowning. The uniformly elevated SMRs and PMR suggest that all people with epilepsy are at higher risk of dying due to accidents, than the general population. People with symptomatic epilepsy may be particularly at risk as is suggested in a population-based incidence cohort study in Iceland. The authors reported that the SMR for deaths due to accidents, poisonings and violence was 7.27 (CI 1.96-18.62) for male patients with remote symptomatic epilepsy and 1.76 (CI 0.47-4.51) for those with idiopathic/cryptogenic seizures [39]. In countries where bathing is favoured over showering, a higher rate of death from drowning might be expected although this has never been properly investigated.

SUDEP is defined as a sudden, unexpected, witnessed or unwitnessed, non-traumatic and non-drowning death in patients with epilepsy, with or without evidence of seizure and excluding documented SE, in which post-mortem examination does not reveal a toxicological or anatomical cause of death [51]. Specific criteria may be applied to classify SUDEP into definite, probable and possible. Patients who do not meet these criteria can be classified as non-SUDEP deaths, and there is also a category of insufficient data [52]. In the UK it is estimated that 500 deaths per annum are SUDEP [53]. Reported risk factors for SUDEP include frequent generalised tonic-clonic seizures; age 20-40 years; acquired epilepsy (primarily from

traumatic brain injury or encephalitis/meningitis), intractable epilepsy, frequent changes of AEDs, and early-onset epilepsy, with seizure severity being the strongest factor [54-59]. AED polytherapy may be an additional, independent factor in adults [56], but not in children [60]. Most sudden epilepsy deaths are unwitnessed and occur during sleep [61]. When witnessed, most deaths occur in association with a seizure, and respiratory compromise is a prominent feature [55]. In some cases, the patient begins recovering from the seizure, but then has a secondary, cardiac arrest, possibly related to hypoventilation [62]. Proposed mechanisms for SUDEP include central and obstructive apnoea and cardiac arrhythmia, although the exact mechanism remains unknown. SUDEP has been reported to be responsible for 2-18% of all deaths in epilepsy [44, 59, 63]. Interestingly, SUDEP accounted for 6 of 11 deaths in a selected group of patients with recurrent seizures following epilepsy surgery [19]. Its incidence rates range from 0.35-1.2 per 1,000 person-years in population-based studies [55, 58, 63-68] to 5 per 1,000 in referral populations [26, 38, 54, 56, 69-71], and to 1 per 100 in surgical series [19, 72]. In a well-designed study, the SMR for SUDEP was 23.7 (CI 7.7-55.0), compared with sudden death in the general population [58]. The risk in children remains uncertain, although a rate of 1:1,500 has been estimated [11]. Children of school age with severe epilepsy and learning difficulties appear to be at high risk of SUDEP, with an incidence of sudden death 1:295 cases per year [68]. The overall age, and sex-standardised mortality ratio in this young cohort was 15.9 (CI 10.6-23).

It has been reported that people with epilepsy are at higher risk of committing suicide than the general population [22, 25, 39] [16, 27, 28, 43, 73] but other investigators have been unable to demonstrate such an increase [14, 18, 26, 74]. In these studies, the suicide PMRs range between 0 and 20% and the SMRs between 1 and 5.8. Incidence cohorts [14, 31] are known to have lower mortality rates than prevalence cohorts because they include small numbers of cases with symptomatic or severe epilepsy, which are over-represented in prevalence cohorts and which are associated with higher mortality. In addition, people who attend hospitals have higher morbidity and mortality than community cohorts. In the large prevalence study of 9,061 adult patients, who were once hospitalised for epilepsy in Sweden, the SMR for suicide was 3.5 (CI 2.6-4.6) [16]. The rate of suicide may be extremely high among depressed patients with epilepsy. Major depression in epilepsy has been associated with significantly decreased, self-reported quality of life, increased disability and missed work, increased medication and medical costs [75, 76]. Mental illness, drug addiction, early onset of epilepsy (particularly onset during adolescence), and personality disorder have been associated with increased risk, with some evidence that risk of suicide may decline with duration of epilepsy [73, 77]. People with epilepsy were re-

ported to have a five fold-increased risk of suicide attempts compared with the general population. Anticonvulsants, particularly barbiturates, were used in most cases of self-poisoning [78]. A literature review based on studies published up to 1983 concluded that patients with severe epilepsy had a suicide rate 5 times higher, and patients with temporal lobe epilepsy (TLE) 25 times higher, than the general population [73]. A later meta-analysis by the same group concluded that the overall SMR for death due to suicide in epilepsy was 5.1 (CI 3.9-6.6). This was based on studies mostly published in the 1970s and 1980s, and mainly including patients with TLE, institutionalised patients, patients from surgical series, and out-patients [79]. In this analysis, the highest suicide rates were observed in patients with surgically-treated TLE whose risk was increased by a factor of 80 [SMR 87.5 (CI 35-180)] [79]. However, this was estimated on the basis of earlier surgical series published in 1968 [80] and 1969 [81] that do not reflect current standards of treatment and/or patient selection criteria. Rates from these early studies may be higher than we would expect today with modern management and decreased use of barbiturates. The recently published follow-up results of the UK NGPSE study with a total of 11,400 patient-years, did not show any excess of suicides [31]. Another recent study reported five suicides in a 12-year period in a total of 10,739 patients with epilepsy seen at a single US centre from 1987 to 1999 [82]. This number is comparable with the average number of suicides in the general US population of about one per 10,000 people per year. All suicide cases had a history of early onset (mean age 9.5 years), long-standing CPS (mean duration 29 years) and very high seizure frequency (often daily). Suicide occurred in all patients after a short interval (3 months to 3 years) of having obtained full seizure control for the first time after temporal lobectomy (3 patients), vagal nerve stimulation, or medication. These patients had been diagnosed with interictal dysphoric disorder (IDD), a syndrome described previously by the authors [83]. IDD comprises intermittent affective and somatoform symptoms, presenting with intense depressive moods with suicidal intensity in some, and with psychotic features and dysphoric symptoms (i.e., irritability, fear, anxiety) in others [84]. According to the authors, suicide in epilepsy results from specific neuropsychiatric disorders (including IDD and post-ictal depression) associated with epilepsy rather than as the result of unfortunate psychosocial difficulties imposed by the chronicity and severity of epilepsy [83]. Management of specific psychiatric disorders and, hence, prevention of suicide in epilepsy can be attained by appropriate use of antidepressant (tricyclic antidepressants and selective serotonin receptor inhibitors), and psychotropic medication [82]. People with epilepsy and previous psychiatric history, including a history of attempted suicide or suicidal thoughts, should be referred to a neuropsychiatrist with experience in epilepsy.

Deaths unrelated to epilepsy

Most deaths are not attributed to epilepsy and can be related or unrelated to the underlying cause of epilepsy *(table 1)*. Deaths in the remote symptomatic group most commonly occur as a result of the underlying cause of epilepsy or from a complication of it [14, 24, 31, 33-35]. Causes include neoplasia, cerebrovascular disease (CVD), ischaemic heart disease (IHD), and pneumonia. The first three causes do not contribute to mortality in child populations [24, 33, 34].

Malignant neoplasia accounts for 16-29% of deaths in community- and hospital-based studies and carries increased mortality with SMRs ranging from 1.7-4.8 [12, 14, 16, 20, 31, 39, 85]. SMRs are significantly higher in patients with remote symptomatic seizures than in patients with seizures of unknown origin [39]. Epilepsy centre studies probably under-represent neoplasia, as these patients tend to be admitted to other facilities [26].

Brain tumours are an important cause of epilepsy as well as cause of death, and may contribute to between ¼ to 1/3 of all deaths due to neoplasia in epilepsy [14, 16, 31]. It is estimated that the incidence of primary brain tumours among patients with epilepsy is 22 times higher than in the general population [86]. Reported SMRs range from 3.4-5.4 [20, 27, 32], although in one study, hospitalised patients with epilepsy appeared to be at much higher risk, with a reported SMR of 29.9 [16]. The question of brain tumour association with anticonvulsant exposure and/or duration of seizures was raised in a number of reports [87-94]. It appears that the excess numbers of brain tumours occurred within 5-10 years of the seizure disorder diagnosis and decreased significantly over time, which suggests that the brain tumours account for the seizures and are not due to AED exposure [27, 86, 95, 96]. The SMR for neoplasia remains at 1.4-2.5 even when CNS tumours are excluded [14, 16, 27, 28, 31]. No specific tumour type or site showed significant excess of deaths in large studies [14, 16, 27], with the exception of studies showing excess deaths due to lung [28, 31] pancreatic and hepatobiliary cancer (although the latter could be an artefact due to the small numbers involved) [26]. There may be a small risk of developing cancer following exposure to AEDs, and a relationship between lung cancer and barbiturates and between non-Hodgkin's lymphoma and phenytoin has been shown in two large studies [96, 97]. The incidence of non-CNS cancers in a population-based cohort of patients diagnosed with seizure disorder in Rochester, Minnesota was not found to be elevated in comparison to the general population [86]. In the same study, there was no association between cancer incidence and duration of seizures or use of AEDs.

People with learning difficulties and epilepsy are subject to mortality rates that are 5-16 times higher than in the general population [38, 98]. The risk of death appears to be highest in those with generalised seizures (SMR 8.1, CI 5.7-11.5), lowest in people with partial seizures without secondary generalisation (SMR 3.7, CI 1.0-13.6), and intermediate in people with secondarily generalised seizures [98]. In comparison, people with learning difficulties and no epilepsy have an SMR of 1.6 (CI 1.3-2.0) [98]. These results indicate that, in this group of patients, mortality is either increased as a result of the seizures or reflects the severity of the underlying condition. The risk of death among children with epilepsy and learning difficulties or cerebral palsy was reported as 1 per 100 person-years in one study [39].

Cerebrovascular disease (CVD) PMR is 14-16% in population-based series [12, 14, 31, 39] and in a large hospital-based series [16], and 5-6% in referral populations [20, 23, 25-27]. SMRs range between 1.8 and 5.3 reflecting a mortality spectrum from epilepsy centre cohorts to general population cohorts, with hospital cohorts in the middle [14, 16, 20, 27, 31, 32]. CVD is the major cause of epilepsy among the elderly [99], and in a large Swedish hospital-based study it accounted for 44% of deaths in people with epilepsy over 75 years in whom the SMR was almost 4 [16]. Patients with remote symptomatic epilepsy are at particular risk [14, 31], suggesting that the underlying pathology is responsible for deaths in this group. This is supported by the finding that people with idiopathic epilepsy in the Rochester Study had an SMR for CVD of 1.4 (0.6-2.6) [14].

PMRs for ischaemic heart disease (IHD) are similar to those for CVD [12, 14, 23, 25, 27, 28, 31, 43]. IHD events include angina pectoris, myocardial infarction and sudden cardiac death. The latter is defined as death in individuals who had no previous clinical diagnosis of IHD and who died within 24 hours of onset of symptoms suggestive of acute coronary insufficiency [100]. The vast majority of IHD deaths in epilepsy occur in patients over 45 years [16]. Mortality rates for IHD are not significantly increased overall for people with epilepsy, with SMRs reported in most studies between 1.1 and 1.6 [14, 27, 28, 31, 39, 101]. In contrast, an SMR for heart disease of 2.5 (CI 2.3-2.7) was reported in a cohort of hospitalised persons over 15 years old diagnosed with epilepsy [16]. Raised SMRs for heart disease in epilepsy have also been reported for patients under 65 years old [101], for patients with remote symptomatic epilepsy [31, 101] and patients with neurodeficit [14, 101]. In the Rochester study [101], there was an increase in the incidence of myocardial infarction both in patients with idiopathic and remote symptomatic epilepsy, and of sudden cardiac death in patients with remote symptomatic epilepsy. There was no relationship between the use of AEDs and incidence rates for IHD or sudden cardiac death [101]. In the Västerbotten County study of a cohort with newly diagnosed unprovoked seizures, myocardial infarction was not associated with a significantly increased SMR in epilepsy [1.5 (CI 0.73-3.2)] [32].

Pneumonia is a common cause of death in epilepsy, especially in institutionalised patients, and often reflects a terminal event in patients with poorly controlled seizures, poor general condition and debilitation [12, 16, 25-27, 31]. PMRs for pneumonia range from 25% in studies of inpatients in epilepsy institutions and hospitals [12, 25-27, 31] to 5% in studies of patients in the community [12, 14, 74], as well as in series based on hospital admissions and epilepsy centre attendance [16, 28]. SMRs range between 3.5 and 10.3 [14, 16, 27, 28, 31]. The majority of deaths due to pneumonia occur in elderly patients [12, 16, 26, 31], which may denote increased susceptibility to pneumonia in this epilepsy population [16, 18]. Pneumonia, however, is an important cause of death in children with epilepsy, especially those with remote symptomatic seizures [33], infantile spasms and severe psychomotor retardation [24]. Pneumonia accounted for 30% of deaths in a study of children with epilepsy in the community [33], as well as in another study of a population with onset of seizures in childhood [34]. The SMR due to pneumonia in young age groups appears to be higher than in the elderly [16, 28], reflecting the low incidence of this cause of death in the corresponding age group in the general, non-epilepsy population, and the severity of the underlying condition or its complications in children and young adults with epilepsy. In a large, hospital-based study, the overall SMR for pneumonia was 4.2 (CI 3.6-4.8) with 40% of deaths due to pneumonia occurring in patients > 75 years, in whom the SMR was 2.4 (CI 1.9-2.9).

The size of the problem

In the UK, at any one time, there are at least 300,000 people being treated for epilepsy [53]. The recently published National Sentinel clinical audit of deaths in people with epilepsy in the UK, commissioned by the National Institute for Clinical Excellence (NICE), looked at the post-mortem investigations and medical care received by patients who had died and who had epilepsy mentioned in the death certificate [53]. The audit found 2,412 deaths with epilepsy on the death certificate among all individuals who died in the UK between September 1999 and August 2000, although it could not establish the true number of deaths in people with epilepsy from national data. Epilepsy was considered to be the probable cause in 812 of these deaths (~ 34%) based on examination of the death certificate and clinical notes from primary and secondary care as well as post-mortem findings. The audit identified a series of shortcomings in the patients' care that "may have contributed to a substantial number of potentially avoidable deaths". Findings included poor record keeping throughout primary and secondary care, deficient management (such as inadequate access to specialist care, inadequate drug management in 20% of adults and 45% of children, lack of appropriate investigations, and inconsistent follow-up), poor information to patients and their families, and inadequacies in the investigations of deaths. There were particular problems in the management of epilepsy in patients with associated problems such as learning difficulties. It is notable that only 3% of the patients who died (none of them children) were known to be seizure-free at the time of their last visit to a physician, but 7% of patients were not on antiepileptic treatment at the time of death. The audit estimated that deaths in 39% of adults and in 59% of children were "potentially or probably avoidable".

Specific measures for the prevention of SUDEP have been proposed elsewhere based on the findings of this audit [102]. Patients at risk should be identified, and they and their families educated about this possibility. Early and aggressive treatment should be directed to patients with continuing seizures (especially generalised convulsions) and should include measures to promote compliance and identification of seizure precipitants. Patients with seizures not responding promptly to treatment should be referred early to a neurologist for the classification of seizure type and epilepsy syndrome, appropriate diagnostic work-up, and development of a patient-specific treatment plan. Patients whose seizures are refractory to treatment for more than 2 years, despite best efforts, should be referred to an appropriate epilepsy centre for re-evaluation with the possibility of surgery, or other treatments such as vagal nerve stimulation and clinical trials of AEDs under development. Finally, pathologists should be educated about SUDEP and alert to its possible occurrence.

Conclusion

Patients with epilepsy are subject to higher standardised mortality rates than people in the general population, with overall SMRs of between 2 and 3. Although numbers may vary due to differences in methodology and the population studied, findings have been fairly consistent across studies. Mortality is significantly higher in people with symptomatic epilepsy, especially those with an accompanying neurological deficit, in which case it tends to follow the mortality of the underlying cause of epilepsy. SMRs are higher in the first 5-10 years after diagnosis of epilepsy, and in younger people due to the low, expected mortality in this age group. People with idiopathic epilepsy and people who enter long-term remission also seem to be affected, but to a much lesser extent. Major contributors to death in patients with epilepsy are brain tumours, cerebrovascular disorders, and pneumonia in elderly or institutionalised patients. SUDEP is the most important cause of epilepsy-related deaths, particularly in the young, and people with frequent seizures and/or suboptimal AED treatment. Despite the adverse prognosis for particular groups of patients, it is important to realise that a proportion of seizure-related deaths, as well as SUDEP, can be prevented by optimising treatment and care for these patients. In addition, patients and their families need to be

aware of the risk of death associated with epilepsy. In the event of death, appropriate post-mortem investigations should be carried out in order to classify the cause of death. The circumstances of death and the medical care received should be looked at in order to identify any management inadequacies. □

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