The mortality of epilepsy

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Epilepsy is often assumed to be a benign condition with a relatively low mortality. There is, however, plenty of evidence to the contrary. Consistent increases have been reported in the mortality of people with epilepsy, especially among younger patients and those with severe epilepsy. Age, sex, race, socioeconomic status, interval from diagnosis, seizure frequency and seizure type have all been suggested as relevant factors. Estimates have, however, varied from study to study. Case ascertainment may pose difficulties because of errors in the diagnosis of epilepsy and problems with the definitions, as well as with assignment and reporting of the causes of death. Inherent methodological problems and unsuspected selection bias may markedly influence mortality rates and account for some of the differences in reported mortality rates.

Two methods are used to compare death rates in patients and control populations:

- *Proportional mortality ratio (PMR)*. This ratio gives the proportion of deaths due to a specific cause amongst a study population and compares it with a control group. It is not a direct measure of the death rate.
- *Standardised mortality ratio (SMR)*. This is the ratio of the observed number of deaths in a study group to that expected during the same period if the group in question had experienced the same age and sex-specific death rates as the control population.

Who is at risk?

Higher SMRs for males than females have been reported but to date no convincing explanation has been advanced for this. The highest reported SMRs are in the 0–40 year age group, a group which has the lowest mortality in the general population. The lowest SMRs are reported in the 75+ age group.

In two community studies, overall SMRs were 2–3 times higher than those of the general population and this increased risk seems to be largely limited to the first ten years after diagnosis[1,2]. In the first of these studies the SMR was 3.8 in the first year after diagnosis, falling to 1.4 after 20 years. This may suggest that this increased mortality is due to the underlying cause of epilepsy (brain tumours, head injury, vascular events, etc) rather than to any other factor. A similar pattern was seen in the second study[2].

Seizure type also seems to be relevant. In the community studies[1,2], the SMR of patients with absence seizures only was no different from the general population while myoclonic seizures carried an SMR of 4.1 in one of the studies[1]. Convulsive seizures, primary or secondarily generalised, have a higher SMR (2.4 overall but 3.5 in the first year after diagnosis). Complex partial seizures only were not associated with a significantly elevated SMR[2]. Studies have also shown increased mortality in patients with idiopathic epilepsy[3-6].

An SMR of 3.8 in patients with severe epilepsy was reported in one study and this was significantly higher than the SMR of 1.8 for those who were seizure free (but who still had an excess mortality)[7]. Another study has also reported an excess mortality in patients with well controlled seizures or in long-term remission[1].

Higher mortality rates for non-whites of either sex, both for deaths due to and related to epilepsy, have been reported in the USA[8]. This might, however, be due to socioeconomic factors rather than race. For example, the infant mortality rate (a well-accepted measure of socioeconomic deprivation) among Afro-Americans is almost twice that of whites.

Causes of death

Common causes of death in people with epilepsy include chest infections, neoplasia, epilepsy-related death and accidents. Reported SMRs for bronchopneumonia have varied between 1.7 and 7.9 and consistently high PMRs have also been reported. Bronchopneumonia is an important cause of death of people with epilepsy especially, but not only, in the elderly age group[1,2,4,9]. A predisposing factor for this increase, at least in the younger age groups, might be pneumonias secondary to aspiration during seizures, although this hypothesis has not yet been formally tested.

The SMRs and PMRs for cancer have been uniformly elevated in all studies, whether or not primary brain tumours were included, and it is likely that death due to cancer is more frequent in people with epilepsy than in the general population[1,2,9,10]. Some studies have, however, reported that this excess number of deaths appears to be related to a diagnosis of a neoplasm prior to the diagnosis of epilepsy rather than the other way round[1,4,8]. A high SMR for hepatobiliary neoplasms has been reported in studies of small selected institutionalised groups[9], although numbers were small.

Epilepsy-related death

Epilepsy as a cause of death is usually subdivided into different categories: status epilepticus, sudden unexpected death (SUDEP) and accidents. There is extensive literature on death in status epilepticus and a fatality rate of 10–20% is often quoted. However, most series have failed to differentiate between individuals with epilepsy and those with no previous seizures[8,11].

SUDEP is defined as a sudden, unexpected, witnessed or unwitnessed, non-traumatic and non-drowning death occurring in a person with epilepsy who had been previously relatively healthy and for whom no cause of death is found, even after a thorough post-mortem examination[12–15]. This is reviewed in more detail in Chapter 40.

People with epilepsy may die because they have an accident during, or as a consequence of, a seizure. There is little doubt that they are at a higher risk of being involved in accidents, but the extent of this is not known. SMRs and PMRs for traumatic death are uniformly elevated, strongly suggesting that accidents and trauma are a more frequent cause of death in people with epilepsy than in the general population[1,4,7,9–11,20,21].

SMRs and PMRs suggest that people with epilepsy may die as result of drowning[11,20,22]. Location, patient selection, swimming capabilities, season and frequencies of seizures all seem to be relevant. In countries where bathing is favoured over showering there may be a higher death rate from drowning, although this has never been properly investigated.

SMRs and PMRs indicate that people with epilepsy are at a higher risk of committing suicide than the general population[1,4,7,10,11,22]. Patients with temporal lobe epilepsy, and those with severe epilepsy, or epilepsy with a handicap have a greatly increased risk of suicide, 25 times greater in the case of temporal lobe epilepsy and five times greater for severe epilepsy[23,24]. There seems to be some evidence that risk may decline with duration of the condition[22].

The role of AEDs

It has been suggested that regular antiepleptic drug (AED) intake might increase the risk of death, although it is very difficult to prove any relationship between death and long-term treatment with AEDs[10,19,21]. Idiosyncratic side effects of AEDs, however, have been associated with death of patients. These are very rare events and usually happen in the early stages of treatment rather than in the long term.

Patients may take intentional or non-intentional overdoses of AEDs and die, but to date there have been few published cases. SUDEP has been associated with non-therapeutic AED levels[25].

It has been suggested that long-term use of AEDs could have oncogenic potential[26]. The drugs implicated have been the barbiturates and hydantoins. Lifetime administration of phenobarbitone in mice and rats has been shown to be carcinogenic and there have been sporadic reports of an association with malignant lymphomas[27]. This point, however, needs clarification and further long-term studies are necessary.

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