

REVIEW

Mortality in paediatric epilepsy

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The reasons for premature death in paediatric epilepsy are reviewed with reference to recent studies reported in the literature. Ways of informing families of children with epilepsy about the risk of death are discussed, and recommendations for personal practice given.

The phenomenon of SUDEP is reported to account for 3–31% of all deaths in people with epilepsy, or to be responsible for approximately 500 deaths per year—almost one death in every 260 people with epilepsy. The incidence in children is not known but is thought to be considerably less.

Most children who have epilepsy have an excellent outcome and have a normal life expectancy. However, long term follow up studies have shown that patients with epilepsy, including children, have an increased mortality rate when compared with the general population.^{1–3} There are many recognised reasons for this increased mortality risk and rate including:

- As a complication of epilepsy or its treatment (for example, traumatic or burn related injury, drowning, suffocation, aspiration of gastric contents)
- As a consequence of convulsive status epilepticus
- As a result of an underlying static or progressive neurological or anatomical cause for death (for example, cerebral dysgenesis, late infantile neuronal ceroid lipofuscinosis, or brain tumour).

Most of the excess mortality occurs in patients who have a symptomatic epilepsy (due to a known cause and frequently in association with physical and/or learning difficulties) and that is refractory to treatment,^{7, 8, 12} in young adults (20–40 years), males, and within the first 10 years following diagnosis. However, deaths have also been reported in other groups including those with apparent idiopathic epilepsy (without any accompanying physical or learning difficulties), children, and also girls. Unfortunately, there are very few mortality studies in epilepsy, including SUDEP, in children.^{13–15} Furthermore, it may not be appropriate to apply adult data to children. Importantly, this is not simply an issue of academic interest. When epilepsy, in its broadest and most holistic sense is discussed with the parents of children with epilepsy (and whenever possible, the children themselves), it is important that the information given is accurate and that any counselling is appropriate and realistic. This should address a number of issues, including the likelihood of achieving seizure control and the possible future withdrawal of any antiepileptic drugs, and the potential hazards of seizures, including injuries and drowning. Many in the medical, nursing, and lay arena feel strongly that the risk of death should also be included in these discussions, although this view is not unanimous. For obvious reasons it is important that, wherever possible, discussion of these issues should be based on accurate and reliable evidence and information.

However, there remains a proportion of patients, including children, with epilepsy whose death cannot be adequately explained, and it is to this group that the syndrome of “sudden, unexplained [unexpected] death due to epilepsy (SUDEP) has been ascribed”.^{4–9} SUDEP has received, and continues to receive much attention in both the medical and lay press and was, erroneously, considered to be the main focus in the recently published NICE endorsed National Sentinel Clinical Audit of Epilepsy-Related Death,¹⁰ whereas the primary aim was to establish whether any deficiencies in the clinical or overall management of patients with epilepsy could have contributed to the deaths. There are different definitions of SUDEP, but the following one is considered to be the most comprehensive:

“The sudden, unexpected, witnessed or unwitnessed, non-traumatic and non-drowning death in patients with epilepsy, with or without evidence for a seizure and excluding convulsive status epilepticus in which post-mortem examination does not reveal a toxicological or anatomical cause for death.”¹¹

THE EVIDENCE

Most general, “all age” population studies have reported a standardised mortality ratio (SMR) in patients with epilepsy of 2 or 3.^{1, 3} Paediatric studies have suggested a higher SMR for all children with epilepsy of 7–13.2;^{14, 16–18} however, in these studies the SMR for those children who have idiopathic epilepsy without any additional neurological or cognitive deficits is reported to be no higher than their respective reference, non-epileptic populations.

The findings of two recent paediatric population studies both confirm, but also add to these earlier data. In the Dutch Study of Epilepsy in Childhood, nine of 472 children who developed epilepsy between the ages of 1 month and 16 years and followed up from diagnosis, died during the five year follow up.¹⁷ Importantly,

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no deaths occurred in 328 children with idiopathic epilepsy, including patients with typical absence, juvenile myoclonic, and benign rolandic epilepsy. All nine children died from an underlying static or progressive neurological disorder (usually accompanied by physical and learning difficulties) and in addition, it was considered that none had died from SUDEP. No patients died from drowning. Children with symptomatic epilepsy had a 22-fold increased mortality risk compared to the general paediatric population, with a mortality of 11.5/1000 person-years compared to the general population of approximately 0.5/1000 person-years.

In a study conducted in a single province in Canada (Nova Scotia), a cohort of children who developed epilepsy between 1977 and 1985 were reviewed in 1999.¹⁸ Twenty six of 692 children with epilepsy had died by 1999, the rate of death 5.3 and 8.8 times higher than the reference populations in the 1980s and 1990s respectively. Only five deaths occurred in children without “severe neurological deficit”, a figure that did not differ from the estimated (expected) rate for the reference population. No child drowned. Only one of 98 patients with absence epilepsy died; this was an 18 year old girl who committed suicide. Children with disorders causing functional neurological deficits were over 22 times more likely to die than those without a deficit—a figure that was almost identical to that in the Dutch study. Four of the 26 deaths were unexpected, all in young adults aged 18–30 years and without any neurological deficits. Postmortem examination revealed that one was a homicide and two were suicide deaths. The remaining death, which the authors considered to be due to SUDEP, was in a 21 year old woman with tuberous sclerosis and mild learning difficulties who was poorly compliant with antiepileptic medication. The authors found that 20 years after the onset of epilepsy, the mortality of patients with epilepsy without severe neurological deficits was approximately 0.7/1000 person-years, which was no different from the reference, non-epileptic population but approximately 15/1000 person-years for those with epilepsy and severe neurological deficits. The rate of SUDEP was very low at 1.1/10 000 patient years. It was concluded that although children with epilepsy had more than five times the risk of dying than the general population in the first 15–20 years after the diagnosis, most of the deaths were related to co-morbid neurological deficits and not to the epilepsy.¹⁸

The objectives of the Dutch and Canadian studies were respectively to “determine the mortality of children who have epilepsy in comparison with the general population”,¹⁶ and to “establish the risk factors and frequency of death in childhood epilepsy to enable provision of appropriate counselling and reassurance for families”.¹⁷

The objectives of the National Sentinel Clinical Audit of Epilepsy-Related Death^{10 19} were twofold: “to understand better the circumstances that may contribute to epilepsy deaths by auditing the implementation of existing guidance relevant to the prevention and investigation of deaths and by advising on preventative strategies and appropriate treatment of relatives”. The Department of Health specifically requested that the Audit try and identify possible “preventative strategies”. The Audit therefore focused on the following three key areas:

- The investigation into epilepsy related deaths (pathology, and specifically, postmortem procedures)
- The care the patients received prior to death (primary care [general practice] and secondary care)
- The contact with the bereaved families following the death.

Epilepsy Bereaved, the voluntary organisation that initially conceived this proposal, together with endorsement and

support of the Royal Colleges, had originally requested that epilepsy related deaths should be investigated as a Confidential Enquiry. This would have ensured that all primary and secondary medical care and pathological information would have been made available for analysis. In contrast, disclosure of medical information to a National Sentinel Audit is voluntary. Therefore, had this study been a Confidential Enquiry, all 81 children who died during the 12 month audit period would have been investigated, instead of only 22 deaths where the medical information was made available to the Audit team. As in the Dutch and Canadian deaths, the majority of the children in this Audit had learning and/or physical difficulties and what was thought to be symptomatic epilepsy. In addition almost 50% had developed epilepsy by 12 months of age and at least 16 of the 22 were experiencing monthly or more frequent seizures at the time of death.¹⁰ SUDEP was considered to have been a possible cause of death in at least six patients. However the medical, and particularly the pathological (postmortem) data on these children were extremely limited, which militated against providing a definite diagnosis of SUDEP.

Finally, it was considered that the care received by the children prior to death could potentially have contributed to their death in over half (17 of the 22 patients). Although the methodology and consequently the results of the Audit could be criticised on the basis of the data collection, the small number of patients audited and the lack of a control or reference group, this should not detract from the principal findings and potential implications of the study. The Chief Medical Officer (CMO) for England recommended in his Annual Report for 2001 that within three months of the publication of this Audit, the Department of Health should issue an action plan and that in the interim, local NHS clinicians and organisations should review (or, perhaps more likely), establish policies and practices for both the management of epilepsy and also epilepsy related deaths. The Royal College of Paediatrics and Child Health has responded to this request by the CMO and has recommended the following framework to improve the care of children with epilepsy:

- A managed clinical network that identifies and brings together key professionals to improve the lives of young people with epilepsy
- A well defined clinical pathway for primary to secondary care, secondary to tertiary care and tertiary to quaternary care (epilepsy “centres” including facilities and expertise for epilepsy surgery)
- The provision of appropriate clinical guidelines and information for each relevant step in the care pathway.

INFORMING FAMILIES ABOUT EPILEPSY AND DEATH

Discussing mortality and the possibility of death is not easy^{21 22} and frequently conflicts with simultaneously trying to encourage children with epilepsy and their families to adopt a positive attitude and to lead as normal a life as possible. Although this is a potential (if not real) dilemma and the discussions may be difficult and traumatic, they need to be undertaken. There are many reasons why families may need to know. Firstly, because premature death may occur in epilepsy for the reasons outlined above. Secondly, although SUDEP is very rare, is never entirely predictable, or can always be prevented, the phenomenon may nevertheless be associated with recognised risk factors, including the irregular use or acute withdrawal of antiepileptic medication. Thirdly, because families may themselves find out from other, less reliable and more “sensationalist” sources, including the media (for example, the British Broadcasting

Corporation's drama, *The Lost Prince*, in January 2003, of Prince John, a member of the Royal family who appeared to die during a seizure). In addition, it has been appropriately pointed out that "it is the right of people with epilepsy and their families to know the facts as anyone who suffers from a chronic condition with an increased risk for premature death".^{20, 21} In contrast, there would appear to be little justification supporting the opposite view of not mentioning (that is, withholding information about) epilepsy and death; the inherent difficulty in raising and discussing the issue does not constitute a justifiable reason. The findings of the recent Audit¹⁰ would suggest that there is a marked reluctance to discuss this issue. In only one of the 22 families was there written evidence that the possibility that epilepsy could be fatal had been discussed with the family and in no case notes was there written evidence that the potential hazards of seizures (including injuries) had been discussed.¹⁰ It must be emphasised that most of the children in the Audit had severe epilepsy and additional neurological problems, the specific group that has been found to be associated with an increased risk of dying prematurely.^{6, 13, 14, 16–18} Finally, the Audit also found that the parents and families of people who had died with epilepsy expressed concern and some anger that at no point had they been informed that epilepsy was a potentially fatal condition, whether from status epilepticus, SUDEP, or other causes.

One of the problems is that "epilepsy" is not a single disorder but a group of disorders (or syndromes) with different clinical phenotypes, different causes, and different prognoses. This is of fundamental importance when discussing epilepsy and the risk of death with families and emphasises the inappropriateness of continuing to discuss epilepsy as though it were a single disorder. Diagnosing the specific epilepsy syndrome and the cause of the epilepsy may, as shown by the findings of the Dutch¹⁷ and Canadian¹⁸ studies (and to a lesser extent the National Sentinel Clinical Audit), better inform doctors about the risks of premature death and SUDEP for individual children—which can then be shared with the family.

A number of factors are important in trying to minimise any trauma and misunderstanding that might arise from talking about epilepsy and the risk of death, including an understanding of the child's epilepsy syndrome and any underlying cause, a doctor-family relationship that facilitates a trusted and open discussion, and recognising the best timing for such a discussion.²² For many families, it may be appropriate to discuss this issue during the consultation when the diagnosis of epilepsy is first "disclosed";²³ for others a more appropriate time may be some weeks later. How the information is given is also very important and may influence how families respond to what they have been told. Support from a nurse specialist in epilepsy or epilepsy counsellor may often make this process easier. The provision of appropriate written information is also important for families to read after any consultation.

Although the concept and process of communicating risk to families is important, it may be misunderstood and may not necessarily be helped by using terms such as "negligible", "very low", or "high" to describe levels of risk.²⁴ Data from the National Statistics Office for 2001 (www.statistics.gov.uk) showed that the mortality rate for children with epilepsy aged 0–14 years was 37 per million, giving a "very low" level of risk.²⁴ Comparisons with other potentially fatal diseases may also be unhelpful, particularly because most other chronic diseases that families may have heard about, such as asthma and diabetes, are relatively homogeneous compared to "epilepsy". Using the same National Statistics data for 2001, the mortality rate for asthma was 11 per million, giving a "minimal" level of risk.²⁴ Individual families

want to know about, and are concerned about their child and their condition, and not any other condition; "putting things into perspective" (implicit in using comparisons), is also not necessarily helpful or relevant. A detailed analysis of this issue is outside the remit of this article but the concept is reviewed in detail by Calman²⁴ and a more comprehensive discussion can be found at the following website: www.doh.gov.uk/pointers.htm, "Communicating about risks to public health".

PERSONAL PRACTICE

Within the epilepsy clinic at Alder Hey, the issue of epilepsy and risk of death:

- Is spontaneously raised and discussed with the families of all children with symptomatic epilepsy, with or without additional neurological and learning difficulties and in children with an apparent idiopathic (cryptogenic) epilepsy syndrome with drug resistant tonic-clonic seizures
- Is not spontaneously discussed with the families of children who have benign familial infantile convulsions, childhood onset absence epilepsy, or benign partial epilepsy with either centro-temporal or occipital spikes
- Is always discussed if the family themselves ask questions such as: "can you die from a fit" or "can epilepsy kill you", irrespective of their child's epilepsy syndrome, underlying cause of the epilepsy or seizure frequency
- Is discussed on the basis of the epilepsy syndrome the child has, the presence of any additional learning or physical difficulties and the cause of the epilepsy; these factors will determine exactly what is said to the family in terms of risks
- Whenever death is discussed, a generic information sheet on "epilepsy and death" is given to the family and the epilepsy nurse specialist is informed of this discussion before her initial contact with the family—which is either on the day of, or generally within two weeks of the medical consultation.

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ARCHIVIST.....

Pimecrolimus cream for atopic dermatitis

At least half of young children who develop atopic dermatitis (AD) do so within the first 6 months of life and there is evidence that early treatment might affect prognosis. Topical corticosteroid preparations are often used but the possible adverse effects are well known. Pimecrolimus, an inhibitor of proinflammatory cytokines, has been used successfully, apparently with minimal systemic absorption after topical application. Now a larger, multicentre trial (Vincent C Ho and colleagues. *Journal of Pediatrics* 2003;**142**:155–62) has confirmed the benefit.

A total of 186 children aged 3–23 months with mild or moderate AD were randomised (2:1) at 25 centres in six countries to pimecrolimus 1% cream or placebo twice daily for six weeks. After that all patients were given open label pimecrolimus for 20 weeks. At the end of the first six weeks 55% (pimecrolimus) versus 24% (placebo) were rated clear or almost clear of AD. By day 8 pruritus was considered absent or mild in 70% versus 37% and by day 43 in 72% versus 33%. Patients transferred to pimecrolimus in the open label phase did equally well and benefit was maintained throughout this phase. Adverse events were usually mild and not thought to be related to treatment.

Pimecrolimus 1% seems to be effective and safe treatment for young children with AD.