A National Surveillance Study of Childhood Epilepsy Mortality in the United Kingdom and Ireland

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Abstract

Background: Patients with epilepsy are significantly more likely to die prematurely than the general population, with causes ranging from associated co-morbidities to Sudden Unexpected Death in Epilepsy (SUDEP). We aimed to estimate UK and Ireland incidence of childhood epilepsy deaths, and to describe case demographics and clinical characteristics.

Methods: This was a prospective, population-based surveillance study using established active surveillance methodology designed by the British Paediatric Surveillance Unit (BPSU).

Results: Eighty-eight confirmed cases were reported with overall annual incidence of 0.65 per 100,000 children aged less than 16 years (95% CI: 0.52-0.81). More cases were male (65%) and cases fell across all age groups, with more deaths reported in older children. Twenty-five per cent of deaths were epilepsy related (including SUDEP) ; 75% of deaths were non-epilepsy related. SUDEP was the most common cause of seizure related deaths, accounting for 13 out of 17 children (76%). An underlying epilepsy syndrome was present in 36% of deaths, and 88% had global developmental delay. In addition, 90% of the children had co-morbid conditions in addition to epilepsy.

Conclusions: In this study, we have demonstrated that death in children diagnosed with epilepsy occurs mainly in 'complicated epilepsy' secondary to factors associated with neurodisability, consolidating previous data. SUDEP is also a significant cause of paediatric epilepsy mortality that needs further attention. There is clear need to better understand and reduce the number of epilepsy deaths in children in the UK, and national surveillance of SUDEP is warranted to better understand this entity in paediatric populations.

Introduction

Epilepsies are a group of disorders with a variety of etiologies, seizure types, underlying syndromes, ages at onset, and as a result variable prognoses [1]. Collectively epilepsy is the most common chronic central nervous system (CNS) condition affecting around 600,000 people UK-wide [2]. It is associated with significant NHS burden, economic and personal costs and suffering. People with epilepsy are 2 to 3 times more likely to die prematurely than the general population [3-4]. Children with epilepsy can die from various causes such as seizure complications (e.g. aspiration, injury or drowning), co-morbid conditions and sudden unexpected death in epilepsy (SUDEP) [5-6].

SUDEP is defined as "the sudden, unexpected, witnessed or unwitnessed, non-traumatic or non-drowning death of people with epilepsy, with or without evidence of a seizure, excluding documented status epilepticus and in whom postmortem examination does not reveal a structural or toxicological cause for death" [7]. SUDEP is further subclassified into definite, probable and possible SUDEP. In probable SUDEP an autopsy is not required and in possible SUDEP a competing cause of death is present. Although we are not yet sure what causes SUDEP, the most important risk factor in adults is the occurrence of seizures – the risk of death increases with more frequent seizures [8]. In fact, the risk of SUDEP was reported to be 23 times higher in people with poor seizure control compared to people with well controlled seizures in a case control study [9]. In addition to the frequency of seizures, the type of seizure is important, with generalised tonic clonic seizures (GTCS) consistently shown to be the major risk factor associated with SUDEP. Children with learning disability and difficult

to control epilepsy may be even more at risk of SUDEP, with one previous study showing a mortality rate almost 16 times higher than expected [10].

Studies of epilepsy mortality are complicated by differing definitions of epilepsy, diagnostic accuracy and epilepsy prevalence in the study population. Given that many existing studies are mainly local case series and retrospective in design, there is a clear need for our study; one-year prospective surveillance of deaths in UK and Republic of Ireland (ROI) children with epilepsy using the reporting system designed by the British Paediatric Surveillance Unit (BPSU). We report case demographics and clinical characteristics, and estimates of incidence on a national level. Our aim was to undertake a comprehensive descriptive study of paediatric epilepsy deaths in UK children over a 13 months surveillance period, to better inform families and their clinicians of the true burden of epilepsy mortality, and to provide a platform for future studies characterising those children at higher risk of death.

Methods

Surveillance methodology (BPSU)

Since 1986, the BPSU has been an established centre for rare paediatric disease surveillance. Consultant general paediatricians and tertiary specialists (95% of UK and Irish Paediatricians in 2013, including paediatric neurologists) receive reporting cards every month [11]. Response rates are consistently above 90% (93.3% in 2012). Paediatric epilepsy mortality surveillance ran from November 2016 to November 2017. Paediatricians reporting relevant cases were sent a data questionnaire requesting full details of the reported case.

Case definition

Paediatricians were expected to report all children aged less than 16 years who died and had been diagnosed with epilepsy. The child must have had seizures or been treated with antiepileptic medication within the last 5 years. Paediatricians were asked to report all suspected cases, even if the results of investigations were pending.

Data Questionnaire

In order to identify duplicate reports, minimal patient identifiers (date of birth, gender, NHS number, hospital number, partial postcode) were collected. The UK Census 2001 categories were used for reporting ethnicity [12]. Further details regarding clinical presentation, co-morbid conditions, diagnostic tests and management decisions were requested.

Denominator data

Incidence of epilepsy mortality was calculated using data from UK Office for National Statistics and Irish Central Statistics Office; namely mid-2016 population estimates [13,14]. Of note, population data stratified by ethnic group was only available for young people aged less than 14 years in England, ROI and Wales, using 2011 estimates [13,14].

Statistical analysis

Data with an approximately normal distribution are summarised using means and standard deviations. For data with a non-normal distribution, medians and interquartile

ranges were used instead. The Poisson method was used for calculating confidence intervals around estimates of incidence. StataSE 13.1 was used to perform all analyses.

Ethical approval

The London Central Research Ethics Committee provided ethical approval (Ref: 16/LO/1265. In order to collect patient identifiers without the need for consent, approval was obtained from the Confidentiality Advisory Group (Ref: 16/CAG/0093).

Results

In total there were 131 notifications, with 88 confirmed cases. Fourteen were duplicate notifications, and nine were excluded as they did not meet case criteria (Figure 1). We could not ascertain case status for 20 notifications (12%), because the clinicians were unable to remember patient details (n=6) or did not respond after multiple reminders (n=14). Analysis was performed on the 88 confirmed cases. The estimated annual incidence of childhood epilepsy deaths was 0.65 per 100,000 children aged 0–15 years (95% CI: 0.52-0.81) (Table 1). More cases were male (65%), (Table 2). The cases fell across all age groups, with more deaths reported in older children. Age at death ranged from 3 months to 15 years 11 months and the median age at death was 8.0 years (IQR: 3-12). The median age of onset of epilepsy (first seizure) was 1.0 years (IQR: 0.5-4).

The clinical profile and management of all cases is shown in detail in table 3. For the thirteen cases of SUDEP, eight children were male (62%), and ten were from white ethnic groups (77%) (Table 4). Age of death ranged from 18 months to 15 years 11 months and the median age of death was 7 years (IQR: 2.8-12.5). The median age of

first seizure was 0.4 years (IQR: 0.1-7.3). Table 5 shows the clinical profile and management in detail for reported SUDEP cases.

Epilepsy related deaths, including SUDEP, occurred in 25% of children (namely status epilepticus, accidental death and aspiration of gastric contents during a seizure) and 75% of deaths were non-epilepsy related. Pneumonia and lower respiratory infections accounted for 36% of non-epilepsy related deaths and sepsis caused death in an additional 20% of patients. SUDEP was the most common cause of seizure related deaths, accounting for 13 out of 17 children (76%).

Twenty-seven children (36%) had an underlying epilepsy syndrome; the most common were Dravet syndrome (n=4), remote symptomatic epilepsy (n=4), Lennox-Gastaut syndrome (n=3), West syndrome, (n=3), Retts syndrome (n=3), Juvenile Myoclonic Epilepsy (n=2). Forty-six children did not have an underlying epilepsy syndrome (64%). With regards SUDEP cases, there was an underlying epilepsy syndrome in six patients (46%); seven children did not have an underlying epilepsy syndrome (54%).

Discussion

We report UK national incidence estimates of epilepsy deaths in the paediatric population using a prospective national active surveillance methodology. Most previous studies of paediatric epilepsy mortality are standardized case series or retrospective case control/cohort studies. Child mortality data has been published in some cohort studies of epilepsy patients in addition to surveys of mortality but often this paediatric data is difficult to tease out from adult data [3,15]. In our study, childhood epilepsy deaths occurred with an annual incidence of 0.65 per 100,000

children aged 0-15 years (95% CI: 0.52-0.81).

Patient Profile Associated with Mortality

In our cohort, 65% of children were male, and median age at death was 8.0 years. In a study combining four large cohorts, the analysis demonstrated children with new-onset epilepsy had an average age of 11.6 years at death and this was similar across most causes of mortality [16-19]. Seventy per cent where of white ethnicity and 19% of South Asian ethnicity. In light of 2011 UK census ethnicity data (ethnic breakdown; white 86%, asian 7.5%, black 3.3%, mixed 2.2%, other 1.0%), our incidence figures suggest that the incidence of epilepsy mortality may be higher in children from minority ethnic groups than those from white backgrounds (table 1).

Death in children with epilepsy can be directly seizure related or completely unrelated to the seizure disorder. Within the category of non-epilepsy related deaths, they are often related to an underlying neurological disability secondary to diffuse brain injury. In our study epilepsy related deaths including SUDEP, occurred in 25% of children. SUDEP was the most common cause of seizure related deaths. These findings are supported by the literature; 75% of deaths were due to non-epilepsy related causes in the previously mentioned combined analysis of four cohorts of children with new-onset epilepsy - 2239 children and follow up of over 30,000 person years [16-19]. Pneumonia resulted in 35 of 48 (73%) deaths, whilst septic shock and ventriculoperitoneal shunt obstruction or malfunction accounted for a further 6% of deaths each. SUDEP was noted to account for 10 out of 13 (77%) of epilepsy related deaths in the study combining cohorts and, in a Finnish cohort, 18 out of 33 (55%) of seizure related deaths

[20].

Of particular relevance, an underlying epilepsy syndrome was present in 36% of children who died during our 1-year surveillance period and 88% had global developmental delay. In addition, 90% of the children had co-morbid conditions in addition to epilepsy, the two most common being cerebral palsy and neonatal encephalopathy. This is consistent with other studies that have determined that 'complicated' epilepsy is the strongest mortality risk factor. In comparison to children in the uncomplicated group, children with complicated epilepsy in the combined cohort [16-19] had significantly higher natural cause related rates of death (561 compared to 9 per 100,00 person-years), seizure-related death (122 compared to 14 per 100,000 person-years), and SUDEP (98 compared to 9 per 100,000 person-years).

Paediatric SUDEP incidence and risk factors

There remains uncertainty in the literature regarding paediatric SUDEP incidence; recently published practice guidelines by the American Academy of Neurology (AAN) and American Epilepsy Society (AES) on SUDEP reported its incidence per 1,000 epilepsy person-years as 0.22 (95% CI 0.16–0.31) in children and 1.2 (0.64–2.32) in adults, concluding that patients should be counseled that SUDEP risk is rare in children but small in adults [21]. However, Sveinsson *et al* reported similar SUDEP incidence rates for children and adults [22], which was replicated in a recent Canadian cohort [23]. Using a multifaceted surveillance system for identifying SUDEP cases in the Canadian cohort, 17 children were initially identified, in addition to 4 more after capture-recapture analysis with an adjusted incidence of definite and probable SUDEP

of 1.45 per 1,000 paediatric epilepsy person-years (CI 0.90–2.22).

In our study, SUDEP accounted for 13 (19%) of deaths in all children with epilepsy. Thirteen other children with epilepsy died of unknown cause; classified under the category of 'undetermined' due to the absence of a postmortem/autopsy. As SUDEP incidence is often underestimated, the number of deaths attributable to SUDEP in children in our study is likely to be greater than we have reported. Whilst paediatric SUDEP is rare, this would be in keeping with more recent literature suggesting that it is more common in children than previously thought [24].

Strengths and limitations

The main strengths of the study include its national coverage, high response rates and its active surveillance approach. Nevertheless, any non-compulsory surveillance system will likely lead to a degree of under-reporting. The lack of an alternative case ascertainment source makes it difficult to estimate the full extent of potential under reporting. However, we expect it to be low with regular monthly reminders to all consultant paediatricians. Clinicians did not always have access to the case notes at the time of reporting due to the processes surrounding child death in the UK, and were not always the primary clinician managing the child's epilepsy, which led to some delays and may have been a source of bias. Due to BPSU methodology restrictions, it was not possible for us as researchers to obtain full notes for case notes review on the notified children, and we relied on the reporting clinicians to fill in the questionnaires as accurately as possible. This is demonstrated for instance by a lack of information in the completed questionnaires about the frequency of specific seizures subtypes rather than

overall frequency of seizures.

Conclusions

Mortality rates for UK children remain worse in comparison to many European countries in spite of a decrease in child mortality over the last ten years [25]. A number of widely reported cases of epilepsy deaths and concerns regarding high rates of missed diagnosis has led to recent focus on optimising care for children with epilepsies [26,27]. Numerous initiatives, including the Epilepsy12 National Audit have tried to address these concerns with a special focus on execution of recommendations by the National Institute of Clinical Excellence (NICE) [28] and Scottish Intercollegiate Guideline Network (SIGN) [29].

Our UK national surveillance study has attempted to address an important gap in knowledge regarding a topic of considerable public health importance. Consistent with previous data, our study demonstrates that mortality in children with epilepsy occurs mainly in 'complicated epilepsy' secondary to factors associated with neurodisability. SUDEP is also a significant cause of paediatric epilepsy mortality that needs further attention. We hope our findings will stimulate further robust epidemiological studies into childhood SUDEP and epilepsy mortality, and encourage health care providers, advocacy groups, social services and others concerned with improving epilepsy outcomes in children to work together to reduce their risk for premature death.

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Declarations of interest

We declare no competing interests. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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