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Short communication

The reliable measurement of temporal trends in mortality attributed to epilepsy and status epilepticus in Northern Ireland between 2001–2015

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ABSTRACT

Purpose: Epilepsy mortality is of considerable public health concern, as a leading cause of premature neurological death. Recent English and Welsh mortality data suggests a falling mortality rate where epilepsy was the underlying cause of death, predominantly due to a reduction in status epilepticus (SE) mortality. We sought to validate this finding in Northern Ireland.

Methods: Officially recorded death certificate data related to epilepsy and SE were obtained from the Northern Ireland statistics and research agency. Data were analysed from 2001 to 2015. The outcomes were the age-adjusted mortality rate for epilepsy and SE. External validation of SE deaths was carried out using data from an intensive care national audit and research centre database.

Results: From 2001 until end of 2015, epilepsy was recorded at death certification in 1484 cases. 458 deaths were considered due to epilepsy. Among 75 in whom SE was recorded, SE was the cause of death in 46 patients. External validation found 103 total deaths related to SE in ICU departments in Northern Ireland, suggesting an overall under-ascertainment of officially recorded statistics. With respect to the 2013 European Standard Population, the mean age-adjusted mortality rate for epilepsy was 1.9 (95% C.I. 1.73–2.07) per 100,000 person years. For SE the mean age-adjusted mortality rate was 2.1 (95% C.I. 0.15–0.27) per 100,000 person years.

Conclusions: Death certification in SE is likely to be an underestimate of the reality. Further efforts are urgently needed to determine the extent of SE-related deaths and all deaths in patients with epilepsy.

1. Introduction

Despite a falling total mortality rate in many western populations, total neurological deaths have increased over the last several decades. This is due to increased longevity, and increased prevalent neurological disease, better modern diagnostic approaches and greater detection of the neurological disease burden [1]. These trends in mortality have major implications for public health and neurological services, as greater comparative funding should follow any increasing burden of disease.

Epilepsy is one of the most common and serious neurological disorders and a leading cause of premature death [2,3]. One of the major epilepsy-related causes of death is SUDEP (sudden unexpected death in epilepsy) [4]. Access to adequate epilepsy medical expertise is likely to have a bearing on SUDEP risk as frequent convulsive seizures are one of the major modifiable risk factors. Addressing risk factors may reduce SUDEP risk [5]. Status epilepticus (SE) is an extreme manifestation of epilepsy, but presents *de novo* in persons without epilepsy, and has a case fatality rate of between 2–40% [6].

Two recent studies in England and Wales have highlighted epilepsy-related mortality rates in other regions of the UK [7,8]. Our aim was to determine the temporal trends in the epilepsy mortality rates in Northern Ireland, where healthcare is also delivered by the National Health Service (NHS) model. We carried out an external validation of SE death certification data by audit of recorded deaths in intensive care units.

2. Methods

The Northern Ireland Statistics and Research Agency (NISRA) collate death certification data in Northern Ireland. We retrieved data relevant to epilepsy and SE deaths for the years 2001–2015. Mid-year estimates for the Northern Ireland population provided annual denominators [9]. Relevant deaths were coded as either “epilepsy (not

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otherwise specified)", and other deaths were coded as "status epilepticus". The World Health Organization introduced the International Classification of Diseases tenth edition (ICD-10) in 2001, and we took this as the starting point for our study.

Death certificate data was classified into two groups, those in which SE or epilepsy were the underlying primary cause of death, or a contributory cause. We compared the SE death certificate data with cases identified through audit data held by the Intensive Care National Audit and Research Centre [ICNARC]) which classifies admissions to critical care based on a primary or secondary admission diagnosis. The audit database was reviewed from 2001 to 2015, with participation of all intensive care units in Northern Ireland. The primary or secondary diagnosis in this case is not necessarily equivalent to death certification part I and part II. However it is assumed that the primary or secondary diagnosis would indicate either a likely direct cause of death, or at least part of the casual sequence to be the listed in an ICU admission in which death was the outcome. If patients improved from SE during their ICU stay but subsequently died in the hospital admission, we excluded these deaths unless clear evidence was available to indicate the primacy of SE in resulting in death. This approach aimed to develop as conservative an estimate as possible.

Detailed statistical analysis was not advised due to the small numbers involved, and rather trends are presented. 95% confidence intervals were calculated. Different versions of the European Standard population (ESP) 1976 and 2013)were used to allow comparison with previous data.

3. Results

From January 2001 until December 2015 there were 1484 patients for whom epilepsy was recorded on the officially recorded death certificate. Of these 458 deaths were considered due to epilepsy. SUDEP accounted for 46 cases of the epilepsy deaths. SE was mentioned as contributing to death in 75 deaths; in 46 it was considered the direct cause of death (See Table 1 and Fig. 1).

The mean number of epilepsy deaths per annum was 31 (95% CI 23–41). The mean number of SE deaths per annum was 3 (95% CI 2–5). The crude mean annual mortality rate for epilepsy was 1.71 (95% CI 1.55–1.89) per 100,000 person-years over the 15 year period. For SE the crude mean mortality rate over the course of the study was 0.17 (95% CI 0.12–0.22) per 100,000 person-years.

With use of the 1976 ESP the mean age-adjusted mortality rate for epilepsy (as underlying cause) was 1.59 (95% CI 1.45–1.72) per 100,000 person years. For SE the mean age-adjusted mortality rate (as underlying cause) was 0.15 (95% CI 0.11–0.19) per 100,000 person years. With respect to the 2013 ESP, these rates were 1.97 (95% CI 1.79–2.15) and 0.21 (95% CI 0.15–0.27) per 100,000 person years, respectively.

Table 1 and Fig. 1 show the age-adjusted mortality rate associated with epilepsy and SE both for the direct underlying cause of death and where it is mentioned as a contributory cause on the death certificate. Table 1 and Fig. 1 represent the data analysis of the 1976 and 2013 ESP respectively.

Using the 1976 ESP as reference, epilepsy as a contributory cause of death showed a trend for increasing mortality over time. For the 2013 ESP we identified that epilepsy as a contributory cause, as well as an underlying cause of mortality increased over time. In both population models, SE failed to display any clear temporal trends.

The ICNARC database prospectively recorded 103 total deaths occurring in intensive care units across Northern Ireland, where SE was the primary or secondary diagnosis (see supplementary table). The ages of all patients in the audit were not provided and thus an age-adjustment was not possible. Of the 103 deaths, 19 were determined to have cerebral anoxia. Of these SE was deemed the primary cause of death in 3 and the secondary cause in 16. In 32 results returned from one centre the distinction between primary or secondary diagnosis was not available.

4. Discussion

In this study from Northern Ireland over a 15 year period, we identified a trend for increased mortality from epilepsy related deaths, as well as instances where epilepsy was a contributory factor. No clear trends associated with SE mortality were seen, however external validation of death certification data suggests potential under-ascertainment.

Two recent UK based studies used 1976 ESP [7], and 2013 ESP data [8] have been carried out. The former found significant reduction in all epilepsy deaths mainly as a result of decline in SE deaths. The latter combined both underlying and contributory causes of epilepsy death and reported a direct age-adjusted epilepsy mortality rate between 2003–2005, as 6.1 per 100,000 population and as 8.1 per 100,000

Table 1
Summary of officially recorded mortality data for epilepsy and status epilepticus in Northern Ireland (2001–2015). (95% confidence intervals represented in brackets).

Year	Total population	Total Epilepsy deaths	Crude epilepsy mortality (per 100,000)	Underlying epilepsy cause of death age-standardized mortality rates (per 100,000)	Total epilepsy (underlying and contributory) age-standardized mortality rate (per 100,000)	Total SE deaths (% of total of combined deaths)	Crude SE mortality (per 100,000)	Underlying status epilepticus cause of death age-standardised mortality rate (per 100,000)	Total Status epilepticus (underlying and contributory) age-standardized mortality rate (per 100,000)
2001	1,688,800	21	1.24	1.22 (0.70–1.74)	3.47 (2.63–4.32)	2 (9%)	0.12	0.11 (−0.04–0.26)	2.42 (0.05–4.79)
2002	1,697,500	20	1.18	1.14 (0.64–1.64)	3.72 (2.84–4.60)	6 (23%)	0.35	0.31 (0.06–0.56)	3.56 (0.92–6.20)
2003	1,704,900	22	1.29	1.29 (0.75–1.83)	3.47 (2.60–4.33)	5 (19%)	0.29	0.23 (0.03–0.43)	4.79 (1.82–7.76)
2004	1,714,000	31	1.81	1.72 (1.11–2.33)	3.86 (2.99-4.74)	1 (3%)	0.06	0.06 (−0.06–0.18)	2.47 (0.05–4.89)
2005	1,727,700	30	1.74	1.62 (1.04–2.20)	4.43 (3.50-5.37)	1 (3%)	0.06	0.04 (−0.04–0.12)	0.42 (−0.40–1.24)
2006	1,743,100	30	1.72	1.62(1.04–2.20)	4.71 (3.75–5.66)	3 (9%)	0.17	0.16 (−0.02–0.34)	3.77 (0.98–6.57)
2007	1,761,700	33	1.87	1.83 (1.21–2.45)	4.55 (3.61–5.48)	2 (6%)	0.11	0.11 (−0.04–0.26)	1.63 (−0.21–3.47)
2008	1,779,200	32	1.8	1.69(1.10–2.28)	4.13 (3.25–5.01)	2 (6%)	0.11	0.11 (−0.04–0.26)	1.62 (-0.21-3.45)
2009	1,793,300	33	1.84	1.67 (1.10–2.24)	5.51 (4.50–6.51)	2 (6%)	0.11	0.10 (−0.04–0.24)	1.64 (0.03–3.25)
2010	1,804,800	27	1.5	1.41 (0.88–1.94)	4.27 (3.38–5.16)	4 (13%)	0.22	0.19 (0.00–0.38)	2.58 (0.52–4.65)
2011	1,814,300	33	1.82	1.57(1.03–2.11)	4.79 (3.88-5.70)	4 (11%)	0.22	0.21 (0.00–0.42)	3.19 (0.64–5.74)
2012	1,823,600	41	2.25	2.01 (1.39–2.63)	5.71 (4.71–6.70)	4 (9%)	0.22	0.17 (0.00–0.34)	2.7 (0.72–4.81)
2013	1,829,700	39	2.13	1.88(1.29–2.47)	6.17 (5.13–7.20)	2 (5%)	0.11	0.09 (-0.03-0.21)	0.95 (−0.37–2.26)
2014	1,840,500	30	1.63	1.45(0.93-1.97)	5.53 (4.60–6.47)	5 (14%)	0.27	0.21 (0.03–0.39)	2.62 (0.68–4.55)
2015	1,851,600	36	1.94	1.67 (1.12–2.22)	6.33 (5.32–7.34)	3 (8%)	0.16	0.17 (−0.02–0.36)	2.08 (0.04–4.12)

*One hospital had no electronic records before 2008, and a manual search of records was not feasible.

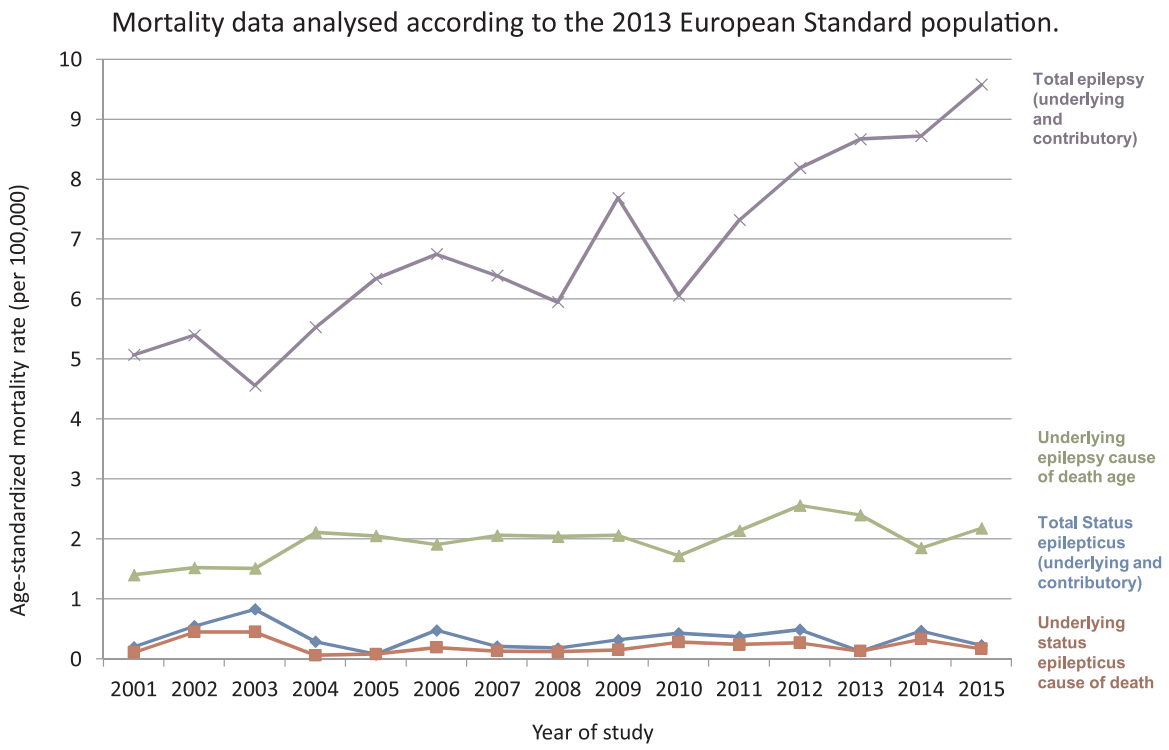

Fig. 1. Northern Irish age-standardised mortality rate between 2001 to 2015 (derived from the 2013 European standard population).

population for 2012-2014. In Northern Ireland, the comparative figures would be 5.5 per 100,000 population, and 8.5 per 100,000 population respectively, suggesting that epilepsy mortality is increasing. This is unlikely to reflect changes in the death certification process [10], but may reflect changes in a relative ageing of the population of Northern Ireland in comparison to England and Wales (see Supplementary Figure) [11].

In 15 years only 46 SUDEP cases were recorded, which is likely to be a substantial underestimation if SUDEP occurs with a frequency of 1.2/1000 patient-years (95% CI 0.64–2.32) in adults [4], and that the lifetime prevalence of epilepsy is 7.60 per 1000 persons (95% CI 6.17–9.38) [12]. Given that the sentinel audit was only published in 2002, it is likely that awareness of SUDEP increased over the time period of the study [13].

Published incidence figures on SE report 10–20/100,000 cases and case fatality rates of 2–40%. These estimates would predict 3–144 deaths from SE per year in Northern Ireland [6]. Over the period of the study, death certification listed 46 cases where SE was the underlying cause of death, and in 75 patients as either an underlying or contributory cause. Our external validation identified 103 deaths occurring in intensive care units. This seemingly represents an under ascertainment by 27% of deaths. However, if known cerebral anoxia patients are excluded from this analysis, the under ascertainment is more conservative at 14%. Furthermore this external validation attempt did not look at SE deaths which could have occurred in nursing homes, palliative care settings, inpatient medical wards where escalation to an intensive care unit was not considered appropriate, or indeed intensive care unit patients in whom non-convulsive status epilepticus in coma may not have been identified.

It is unclear why the SE mortality trend is not increasing in a similar way to epilepsy mortality. Perhaps ascertainment is limited to the acute symptomatic cause, and SE is not being included in the causal sequence due to poor recognition. We know that old age is a risk factor for poor outcome in SE, and the aging population might have predicted an increasing mortality rate. Indeed the lack of a trend for increased mortality may reflect better intensive care case selection, better management, or improved prehospital care.

Under-ascertainment of epilepsy related deaths from death certification has previously been demonstrated in the National General Practice Study of Epilepsy [14], indicating that this is a widespread problem, with likely multiple causes, potentially including lack of confidence with neurological decision making in primary care [15]. It is not a problem restricted to the post-mortem diagnostics as inaccurate coding also occurs in antemortem clinical practice [16].

Limitations of this present study include potential under-estimation of the rate of cerebral anoxia deaths, as one centre did not provide data on SE aetiology, precluding the ability to determine if SE was primary or secondary diagnosis in 32 cases. Despite this we would consider that if SE occurred as a primary or secondary diagnosis, in all likelihood it would still be documented on the death certificate at least in a contributory role. We did not have the incidence of epilepsy in NI during this time period, and accurate outpatient coding would allow this to be captured, for future public health planning. The expansion of neurology services (from 7 to 18 consultant neurologists, electroencephalography now in 5 of 9 intensive care units, and wide services provided at district general hospitals) in the study period will have enhanced the diagnostic capacity, and likely resulted in greater capture of the disease burden, which may be a confounder to the apparent increased mortality rate. In terms of limitations of the database validation, we did not have detailed descriptions of the sequence of events leading towards death. We were unable to differentiate between subtypes of SE or determine the care they received for their status epilepticus.

One of the strengths of these data is that we have highlighted an under-ascertainment from an external validation study. These data provide an estimate of the frequency of SE related intensive care unit admissions, who subsequently died during or shortly after that admission in Northern Ireland.

5. Conclusion

We identified an increasing trend for epilepsy related mortality in our population, and identified an under-ascertainment of the officially

recorded number of epilepsy related deaths. A robust attempt to improve future services through assessment of risk factors associated with epilepsy-related deaths is advised. Stringent coding selection with external validation is urgently required.

Future major investment needs to be considered for this service in Northern Ireland, to prepare for the ageing population and the increasing burden of epilepsy in this population.

Ethical approval

Ethics is not required for the general data analysis as all of these data are available in the public domain. In terms of the audit - this was carried out with local audit department approval where requested, and access to ICNARC data was granted by each departmental head in the relevant Intensive Care Departments.

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Competing interests

MK: Received salary support from UCB paid via his home institution for a 6 month period of sabbatical work in the last year, unrelated to this present study.

JC/MOM: No conflicts relevant to this work.

Authorship

MK conceived the idea, analysed the data and wrote the first and final revision. MOM and JC provided advice and edited the manuscript.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.seizure.2018.11.017.

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