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Does intellectual disability increase sudden unexpected death in epilepsy (SUDEP) risk?

Charlotte Young [a], Rohit Shankar [a,b,*], Joanne Palmer [c], John Craig [d], Claire Hargreaves [a], Brendan McLean [c], David Cox [a], Richard Hillier [a]

[a] Cornwall Partnership NHS Foundation Trust, Chy Govenek, Threemilestone Industrial Estate, Truro TR4 9LD, United Kingdom
[b] Exeter Medical School, United Kingdom
[c] Royal Cornwall Hospital Truro Cornwall, United Kingdom
[d] Belfast Health Trust, United Kingdom

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ABSTRACT

Purpose: An estimated 1.4 million people in the United Kingdom (UK) have intellectual disability (ID) with 210,000 having severe or profound ID. Of these, approximately 125,000 have epilepsy, representing one quarter of all patients with epilepsy in the UK. For those with full scale intellectual quotients (FSIQs) of less than 50, half have epilepsy, with half of these having treatment resistant epilepsy. One of the two major causes of mortality within this population is sudden unexpected death in epilepsy (SUDEP).
Methods: We performed a literature review exploring the extent to which ID was considered as a risk factor for SUDEP. We also considered whether there was any relationship between the types of health care system in which the studies were conducted and whether ID was considered in studies of SUDEP.
Results: We identified 49 studies which had explored risk factors for SUDEP, of which, approximately 50% (n = 23) considered ID in the planning stages. Of these studies 60% (n = 14) found ID was a risk factor for SUDEP. 60% of all the studies were conducted in countries where the health care system was publicly funded.
Conclusions: Overall we found ID definitions and specified standardized mortality rates and impact of institutionalization to be quite poorly presented.

1. Introduction

Epilepsy is a major global health problem affecting an estimated 50 million people worldwide[1] and around 400,000 people in the UK.[2] In relatively unselected populations, most studies in both the developing and the developed world have found the point prevalence of active epilepsy to lie between 4 and 10/1000; rates for chronic epilepsy of around 5 to 10/1000 are probably applicable to all general populations in both the developed and developing world.[3]

Many people find that their epilepsy does not get in the way of their everyday life but up to 30% develop treatment resistant epilepsy.[4] Epidemiological studies consistently report a standardized mortality rate (SMR) of 2–4 for epilepsy. In chronic epilepsy the main cause of excess mortality is death during a seizure in particular sudden unexpected death in epilepsy (SUDEP). SUDEP is estimated to account for 500 deaths a year in the UK.[5]

The incidence of sudden death appears to be 20 times higher in patients with epilepsy compared with the general population, and SUDEP is the most important directly epilepsy-related cause of death. However, the risk varies markedly between different epilepsy populations. SUDEP is uncommon in patients with new onset epilepsy and in patients in remission where the incidence has been estimated to 0.1–0.35 cases in 1000 person years in population-based cohorts of epilepsy patients. It is considerably higher in patients with chronic epilepsy, 1–2 per 1000 person years, and highest among those with severe, refractory seizures, 3–9 per 1000. SUDEP may occur at all ages, with highest rates between 20 and 40 years. In most cases SUDEP appears to be seizure-related.[6]

SUDEP as a cause of death is obtained by exclusion of other potential causes. In UK and many other first world countries SUDEP can only be determined by the coroner following an extensive investigation of the death. The operational definition for SUDEP is

* Corresponding author at: Cornwall Partnership NHS Foundation Trust, Chy Govenek, Threemilestone Industrial Estate, Truro TR4 9LD, United Kingdom. Tel.: +44 1872221553.
E-mail address: Rohit.shankar@nhs.net (R. Shankar).

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provided by Nashef[7] and Anneger[8,9] for classifying SUDEP as definitive (all 6 criteria of the operational definition satisfied after an autopsy), probable (Autopsy was not performed but there is no other plausible explanation for death) and possible (all six criteria met without an autopsy). Table 1 lists the criteria for classifying SUDEP deaths.

Various risk factors have been looked for and intellectual disability (ID) is considered a higher risk though estimates vary.[10]

Intellectual disability (ID) or Learning disability or mental retardation is a disability characterized by significant limitations in both intellectual functioning and in adaptive behaviour, which covers many everyday social and practical skills. This disability originates before the age of 18 years and persists lifelong.[11,12]

ID occurs in 2.5–3% of the general population. Standardized tests need to be undertaken to ascertain the reasoning ability in terms of mental age which is represented as Intelligent Quotients (IQ). ID is defined as IQ score below 70–75. Adaptive skills are the skills needed for daily life and are significantly faulty in people with ID. ID varies in severity. The Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (*DSM-IV*)[12] and the WHO classification system, International Classification of Disorders (ICD 10)[11] are the diagnostic standards. They classify ID into mild, moderate, severe, and profound. These categories are based on the functioning level of the individual. People with mild ID, account for 85% of total ID population, have an IQ range of 55–75 and are reasonably self-sufficient. Those with moderate ID representing 10% of the total ID population have IQ scores between 35 and 55 manage simple tasks of daily living but struggle with more complex tasks and require significant supervision. About 3–4% of the ID population is severely impaired. Severe ID individuals have IQ scores of 20–40. They may master very basic self-care skills and some communication skills. 1–2% of people with ID who have profound ID with IQ scores lower than 25 and they lack basic living skills and/or communication skills. Both severe and profound ID people need a high level of structure and supervision.

The prevalence of people with ID in the UK is estimated to be 1.4 million.[13] 26% of patients with epilepsy have ID.[14] Half of patients with IQs of less than 55 i.e. moderate to profound ID have epilepsy and 50% of these have treatment resistant epilepsy.[15] This population also has a significantly higher representation of mental health and physical health comorbidities and are vulnerable to both acute and chronic health problems and issues with communication making it difficult to make informed choices. The two major epilepsy related causes of death in ID are, sudden unexpected death in epilepsy (SUDEP) and status epilepticus are significantly over represented in this population.[16] With regard to SUDEP and ID, Tellez-Zenteno et al. in their systematic review found the risk to be 3.4 times higher than the general population with epilepsy.[17] Walczak et al. in their cohort study identified a 5 times higher risk of SUDEP, with ID being an independent risk factor.[18] However, in both studies the sample size was quite limited ($n = 5$ for IQ < 70). It is therefore uncertain as to whether intellectual disability is a risk factor for SUDEP. Given that 25% patients with epilepsy have ID it is therefore important issue to determine if ID is a risk factor for SUDEP to help keep people safe, to structure person centred services and to manage health costs. The costs of healthcare in countries which are primarily funded by personal insurance are high and good insurance coverage is unaffordable for many. In 2012, The United States Census Bureau stated that 15.4% of people were uninsured; this infers that around 48 million people are not satisfactorily covered for appropriate health care.[19] Equally in 'socialized medicine' countries such as the UK where the health care is state sponsored concerns exist of systemic rationing of treatment. Thus the nature of healthcare adopted by a country could impact profoundly on managing long term conditions such as epilepsy in vulnerable people with ID and influence mortality outcomes. This paper looks to explore the available evidence of the links between ID, epilepsy and SUDEP and its links with different healthcare systems with a view to gaining insights around current risks and care patterns.

We looked to understand the ID and SUDEP and Epilepsy connection by investigating

1. Do studies looking at risk factors in SUDEP consider ID?
2. Do studies which look for ID as a risk factor in SUDEP find it?
3. Does the type of healthcare funding influence researchers exploring ID as a risk factor for SUDEP?

Table 1
SUDEP: sudden unexpected death in epilepsy: definition and criteria Annegers et al.[8,9]

1The victim suffered from epilepsy, defined as recurrent unprovoked seizures
2The death occurred suddenly (in minutes), when known
3The victim died unexpectedly, while in reasonable state of health
4Death occurred during normal activities and benign circumstances
5An obvious medical cause of death was not found
6Death was not directly caused by a seizure or status epilepticus

Definite = all 6 and autopsy, Probable = all 6, SUDEP autopsy not performed but no other explanation, Possible = all 6, SUDEP Autopsy not performed and there could be an alternate explanation.

2. Methods

A literature search was undertaken in two phases using all available data published with no date constraints. The search included both original research and review articles. Only articles published in English were used. The review was a detailed literature review looking into mainstream scientific literature available to the search engines mentioned below. It did not take into account grey literature, unpublished works etc. It was not a systemic review as specified by Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[20]

In the first phase PubMed was utilized using search terms 'sudden' 'death', 'mortality', 'epilepsy', 'SUDEP', 'risk factor', 'protective factor', 'learning disability', 'mental retardation', 'neurological impairment', 'intelligence' and 'intellectual disability' in different permutations and combinations. Papers were excluded if they explored only one risk factor for SUDEP such as cardiac anomalies, intractable epilepsy, asthma and accidental deaths (drowning and asphyxia) or excluded those with ID. Studies were not included if they purely examined the paediatric population. Febrile convulsions were not included.

Articles were deemed appropriate if they either explored at least one risk factor for SUDEP without excluding the ID population or had considered a range of possible risk factors for SUDEP. Microsoft Excel was utilized to record the findings. Each paper was examined to see if:

a. When studies were designed did they consider ID as a possible risk factor?
b. Did the studies define ID if they included it as a risk factor? Did they define ID using International Classification of Diseases 10[11] or DSM 4[12] i.e. mild, moderate, severe or profound ID?
c. Did the authors comment on standardized mortality rates?
d. Did any of the studies consider ID as a protective factor? e. Did the studies find ID to be a risk factor for SUDEP A second stage of exploration then commenced once these questions were addressed?

We researched what countries the studies were conducted in and linked it to the type of health care utilized in the country of

investigation. Countries were then categorized into 'Private', 'Public' or 'Dual' types of healthcare after researching Government policies online.

- 'Private' health care was defined as using a private insurance based system to provide the majority of the nation's care.
- 'Public' healthcare was defined as the Government providing the majority of the nation's care through taxation.
- 'Dual' healthcare we have defined as using both private insurance based as well as state funded healthcare – this reflected varying ratios within countries therefore this is an umbrella term for countries such as Australia. This was clarified by reading government official websites.

Descriptive analysis was performed using counts and frequencies. Associations were assessed using Fisher's Exact test looking at type of healthcare and whether or not they looked for ID and whether they found this or not. Statistical significance was set at $p < 0.05$. Data were analyzed using IBM SPSS statistics for Windows version 19.[21]

3. Results

On applying our search strategies, 311 papers were identified. Once the exclusion and inclusion criteria were applied, 49 articles were deemed appropriate and examined. Both original research and review articles were part of the results and were scrutinized. Care was taken to include a study only once to avoid duplication. Of the included studies that explored general risk factors for SUDEP, about half ($n = 23$, 46.9%) considered ID in their planning stages. Of the 23 studies which explored ID approximately 60% ($n = 14$) found it to be a risk factor for SUDEP (Table 2). Only 2 studies used ICD 10 criteria to define the nature and degree of ID.[18,22] Seven studies commented on the type of ID.[18,22–27] One used the definition, 'Intelligent quotient less than 70'[18] and another classified ID as 'severe or profound'.[22] The remaining studies used terms like 'neurological deficit',[22] 'enrolled at a residential school'[25] or 'neurodeficit' defined as mental retardation, cerebral palsy, hypotonia,[26] etc. without expanding any further on what they meant by these terms.

Of the 49 studies examined, 10 (20.4%) studies commented on Standardized Mortality Rates (SMRs) associated with risk factors in SUDEP.[16,23,25–32,56] The remit of comment and investigation of SMR of risk factors of these 10 studies was ambiguous and diverse. Some articles commented on epilepsy SMR in people without ID and some reported on epilepsy SMR in the background of ID or CP or neurological damages.

In terms of SMRs related directly to ID as a risk factor, 4 (8%) studies made specific comment. Nashef et al. commented that the standardized overall mortality ratio was 15.9 with 20 of 28 deaths considered epilepsy related.[25] Forsgren et al. found that the SMR for people with epilepsy and ID was as high as 5.0 (95% CI: 3.3–7.5); if they had cerebral palsy, the SMR increased to 5.8 (95% CI:3.4–9.7) and the highest mortality (SMR = 8.1; 95% CI: 5.7–11.5) was seen in those who had a generalized epilepsy from the onset.[32] Forsgren[30] stated that the highest mortality was found in patients with epilepsy and 'neurodeficits' present since birth, including ID or cerebral palsy (SMRs ranging from 7 to 50). Sperling[32] stated that the mechanism underlying this increase remains to be elucidated, but it is consistent with the known high standardized mortality rates in ID populations.[31]

Kiani[16] studied SUDEP and ID whilst utilizing the Leicestershire Intellectual Disability Register database between 1993 and 2010. 244 deaths (27%) occurred in people with ID and epilepsy of the 898 adults with ID who had died over the 18-year study period. Of the 109 deaths due to probable or definite SUDEP in that period across all populations, 26 (23.4%) were people with ID which was the second most common cause of death among adults with ID and epilepsy. The SMRs for SUDEP in patients with ID were 37.6 for men (95% CI: 21.9–60.2) and 52.0 for women (95% CI: 23.8–98.8). The degree and aetiology of ID was reported where available but case files for those people who died without ID of SUDEP was not analyzed.

The remaining 6 studies made comment about general SMRs in reference to the other risk factors that they had explored but not ID specifically. The studies were conducted in various settings and the impact of institutionalization on epilepsy in particular and health in general was not considered by any individual study.

No studies found ID to be a protective factor. However, Duncan and Brodie[24] found that night supervision when associated with ID was protective. Shankar et al. in their review of SUDEP risk factors found limited evidence that ID was a risk factor for SUDEP[10] but recognized that this could have been due to poor study designs and lack of statistical power. Shankar et al. in their 9-year systemic examination of all SUDEPs in the county of Cornwall identified only 3 ID patients in 48 SUDEPs. However the presence of a specialist ID epilepsy service in Cornwall could have influenced the results significantly.[33]

The second phase of the literature review considered the country of origin and the type of healthcare associated with that country (Table 3).

Of the 49 studies reviewed, approximately 60% ($n = 29$) were conducted in countries with publically funded healthcare systems such as the UK, Sweden and Canada. Fifty five percent ($n = 16$) of publically funded studies ($n = 29$) considered ID, with 75% ($n = 13$) of those considering ID finding ID to be a risk factor for SUDEP.

Twenty-seven percent ($n = 13$) of the studies originated from countries with privately funded healthcare systems like the USA. Of these 30% ($n = 4$) considered ID as a risk factor for SUDEP, with 50% ($n = 2$) finding this to be the case. Fourteen percent ($n = 7$) of the studies were from countries with dual type of healthcare systems like the Netherlands and Australia. Of these, 43% ($n = 3$) explored if ID was a risk factor in SUDEP, with none of these studies finding it to be (Table 3).

Analysis of the above data showed that the undertaking of investigation of ID as a potential risk factor by the examined studies ($n = 23$) did not depend on the type of health care system from which the studies originated ($p = 0.173$). However, when the papers ($n = 23$) were examined to see if there was association between the type of healthcare and their finding of ID as a risk factor, papers emerging from publicly funded health systems were more likely to find ID as a risk factor than either dual or private health systems ($p = 0.040$).

Table 2
Summary of results looking at studies exploring ID as a risk factor in SUDEP: sudden unexpected death in epilepsy
(n = identified studies).

	Number of studies n	% of all studies
Literature search using stated search terms	311	
After exclusion criteria applied[2,16–18,22–32,34–60]	49	
Number of studies which considered ID as a risk factor in SUDEP[2,16–18,22–27,30,31,35,38–42,45,46,51,55,56]	23	46.9
Number of studies which found ID to be a risk factor in SUDEP[16–18,23–27,30,31,41,42,55,56]	14	28.6
Number of studies who found ID to be a protective factor in SUDEP	0	

4. Discussion

The premature mortality in particular SUDEP caused by epilepsy is a subject of topical importance. The literature on

Table 3
Summary of studies (*N*) who looked for and found ID as a risk factor in SUDEP: sudden unexpected death in epilepsy.

Type of healthcare	*n* = 49	Looked for ID (*N* = 23)	% of total	Found ID *n* = 14	% of total (*n* = 23)
Private[18,22,26,31,32,48,49,54,59,62,64–66]	13	4[18,22,26,31]	17	2[18,31]	8.69
Public[2,16,17,23–25,27–30,34,36,39–43,45,47,50–53,55–57,60,63,67]	29	16[2,16,17,23–25,27,30,39–41,43,45,51,55,56]	70	12[16,17,23–25,27,30,41,42,45,55,56]	52.1
Dual[35,37,38,44,46,58,61]	7	3[35,38,46]	13	0	0

SUDEP is growing, however our prime findings highlight that ID though overrepresented in patients with epilepsy has not been looked at in any sufficient detail to enumerate its risk for SUDEP. This is confirmed by the fact that when looked for by researchers it has come up as a significant factor. Studies in the literature searched appeared to vary in their interest in exploring the role of ID within SUDEP. From the little research available the ID population is more impacted by the consequences of epilepsy including SUDEP. Donoghue et al. stated that the general risk of SUDEP for people with epilepsy was between 1:500 and 1:1000 person-years. Donoghue et al. goes on to explain that the risk increases to 1:200 person years for those with a neurological impairment.[27]

The over representation of SUDEP in the ID population is a major issue of concern.[16] The cognitive impairment and communication difficulties intrinsic to ID could leave many people with ID vulnerable to difficulties in making informed choices around treatment. In addition they could have poor understanding of the potential interventions and investigations (such as EEG, blood tests, etc.). They are also predisposed to higher levels of distress and anxiety leading to potential behaviour disturbances. Thus assessment and diagnosis due to these considerations are made significantly more difficult and leaves the vulnerable individual exposed to misdiagnosis and potential inadvertent harm. Unfortunately very few studies explore ID as a risk factor and fewer still analyze its impact.

Epilepsy occurs at a higher incidence and is more prevalent in people with an intellectual disability. It is well recognized that health and social needs and their outcomes for people with ID vary significantly based on their level of ID. This makes it important to know if differentiation was made between mild, moderate, severe and profound ID as is current good practice when health and social care is delivered. No study has looked satisfactorily into this issue. The majority of studies of SUDEP and ID have been focused on presence or absence of ID and not looked at issues from the perspective of the organization and availability of health and social services for people with ID.

It appears the research of ID being examined as a risk factor for SUDEP is not skewed by the nature of healthcare systems across the globe. However we are mindful that given the small number of studies available there is scope of a potential type 2 error due to lack of power. When studies examine for ID as a risk factor it appears public supported health systems are more likely to find them than private or mixed care health systems. While on the face of it this suggests more representation of people with ID in the SUDEP deaths in public health systems it is difficult to hypotheses' this with any confidence given the potential bias of unclear definition, poor and unclear case selections and low power.

The data on the health system is weak and given to potential error in interpretation. Firstly the methodology used was an indirect representation of the nature of health care (i.e. using classification based on origin of scientific papers). Secondly the number of studies which discuss SUDEP let alone ID and SUDEP is far from satisfactory. Thirdly, the type of care the patients got was not looked into. However, it illuminates and interesting unsearched area in the care of people with ID and epilepsy.

A major associated area not looked at by any of the studies was the confounding effects of institutionalization and inherent cognitive impact of epilepsy. There is robust evidence[68] to suggest that prolonged institutionalization has an impact on intellectual, physical, behavioural, and social–emotional functions leading to a range of children and people who would not have an inherent ID sublimating to a range of ID functioning.

As all of the studies looked at people dead as a result of SUDEP it is a matter of concern that ID was not thought relevant enough or the individuals suspected to have ID not further investigated to examine comprehensively for nature and degree of ID. This reflects a possible professional gap and lack of comprehension of issues of ID in investigating teams which pre-dominantly were of neurological origin. People with ID are living longer and various good practice charters[13] exist to ensure they have equal rights as any other citizen of their country. However fundamental gaps exist in the care provided, led by ignorance and indifference[69].

Known areas of high medical risk, such as epilepsy which is significantly over represented in ID population needs to be handled in a person centred and proactive manner in vulnerable adults with ID. Three potential models of enabling this in research and care settings could be suggested. Clinicians and researchers working in Epilepsy could avail bespoke training on ID specific issues including skill development in mental capacity issues, communication issues and frequent co-morbidities (such as sensory problems, Autism, behavioural disturbances, etc.). There could be involvement of ID professionals in developing epilepsy studies and models of care. Alternately, ID clinicians could be up skilled with epilepsy competencies. However, the best results could be a mix of all three where there is strong conjoined working between Epilepsy and ID professionals at both research and clinical care levels. A broad based multi-professional development of skills with shared competencies would significantly protect and risk minimize vulnerable individuals with ID from the devastating consequences of Epilepsy such as SUDEP.

Conflict of interest statement

None declared.

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