Title page

Article title: Paediatric Sudden Unexplained Death in Epilepsy (SUDEP): is it truly unexplained?

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Abstract:

Sudden Unexpected Death in Epilepsy (SUDEP) is an increasingly recognised cause of death in children and young people with epilepsy. Although paediatric SUDEP is thought to be a rare event, it may be more common than previously thought, with incidence estimates ranging from 0.22-6 per 1000 person years. Limited clinician experience and knowledge about paediatric SUDEP has impaired the ability to inform children and their families about their individual risk and means to reduce it. Although many questions remain, in the past two decades our understanding of paediatric SUDEP has greatly increased. The pathophysiology of paediatric SUDEP remains poorly characterised, with distinct respiratory, cardiac, and central mechanisms all likely to be involved. Recent cohort studies have allowed major risk factors to be identified, including frequent generalised tonic-clonic seizures, nocturnal seizures, and lack of supervision. Optimising seizure control, alongside the early detection and supervision of seizure activity, are possible risk reduction strategies. Evidenced-based

discussions about paediatric SUDEP should form part of routine care for children and young people with epilepsy.

Key words: Paediatric Sudden Unexplained Death in Epilepsy, SUDEP, epilepsy, epidemiology, risk factors

Paediatric Sudden Unexplained Death in Epilepsy (SUDEP): is it truly unexplained?

Case summary

The stimulus for conducting research in this most challenging of area, was a phone call one of us received (AS) by a family under their care. Their daughter, aged just 2.5 years, had been found dead in her cot that morning 'out of the blue'. The death was adjudged to be due to Sudden Unexpected Death in Epilepsy (SUDEP). No Paediatrician wants to receive a such a call. Two other colleagues in North London lost a patient each from SUDEP soon afterwards. This was both a very sad and difficult time. This piece was written with the aim of educating clinicians on SUDEP, to inform practice based on the available research evidence.

Introduction

Caring for children and young people with epilepsy (CYPwE) is a staple part of the life of every Paediatrician. Epilepsy is currently the most common chronic central nervous system condition affecting children with a prevalence of 0.5- 1%. Advances in our understanding of childhood epilepsy, anti-seizure medication, and support for CYPwE and their families, has greatly improved long-term epilepsy management, allowing many CYPwE to live successfully with epilepsy. Despite this, the overall age-matched mortality rate in children with epilepsy remains 5-10 times greater than that in the general population (1). Although there are multiple known causes of death in children with epilepsy, including status epilepticus, drowning and injury, SUDEP represents the most common cause of epilepsy related-death.

SUDEP is a challenging condition to research, with small numbers of cases, the majority of which being unwitnessed. Over the past two decades, cohort studies describing the characteristics of childhood SUDEP deaths has developed our understanding of possible mechanisms and risk factors, yet there is still a paucity of evidence. Understanding the risk factors, pathophysiology and circumstances associated with paediatric SUDEP would aid paediatricians in several ways. Firstly, it will empower clinicians to approach discussions about SUDEP risk in an evidence-based manner. Secondly, targeting modifiable risk factors will help create personalised management plans to reduce SUDEP incidence.

Defining SUDEP

Establishing a clear definition of SUDEP is challenging with cases based on a diagnosis of exclusion. Inconsistent definitions of SUDEP have previously made comparison between epidemiological studies difficult. Two complementary definitions, published by Annergers et al and Nashef et al, have since been unified in the following definition:

"Sudden, unexpected, witnessed or unwitnessed, nontraumatic and nondrowning death in patients with epilepsy, with or without evidence for a seizure and excluding documented status epilepticus, in which post-mortem examination does not reveal a toxicologic or anatomic cause of death".

SUDEP is now subclassified into Definite, Probable and Possible SUDEP. This takes into account whether an autopsy has been performed and if a competing cause of death is present **(table 1).**

SUDEP Subtypes	
Definite	Sudden, unexpected, witness or unwitnessed, non-traumatic and non-drowning death, occurring in benign circumstances, in an individual with epilepsy, with or without evidence for a seizure and excluding

	documented status epilepticus, in which post-mortem examination does not reveal a cause of death.
Probable	Same as Definite SUDEP **but without autopsy.** The victim should have died unexpectedly while in a reasonable state of health, during normal activities, and in benign circumstances, without a known structural cause of death.
Possible	A competing cause of death is present.

Table 1: Unified classification of SUDEP.

Epidemiology of SUDEP

Determining the incidence of paediatric SUDEP is necessary to allow counselling of CYPwE and their families on SUDEP risk, alongside establishing its size as a public health problem. The ability to accurately estimate paediatric SUDEP incidence has been limited by small case numbers and variation between population groups studied. Estimates of adult SUDEP incidence have ranged by a factor 100 with the incidence rate is thought to range between 0.9 to 2.3 per 1000 person-years. Higher rates are seen in those with refractory epilepsy.

The incidence of SUDEP in children remains uncertain. An initial report by the American Academy of Neurology suggested that paediatric SUDEP is less common than adults, quoting an incidence of 0.22 vs 1.2 per 1000 epilepsy person-years. Subsequent cohort studies have disputed this assumption, finding comparable incidence rates between children and adults. In total estimates of paediatric SUDEP incidence ranges from 0.22-6 per 1000 person years. This may reflect SUDEP incidence being underestimated in children due to deaths being classified as 'undetermined', as a result of an absence of a post-mortem / autopsy. Overall, SUDEP is rare in children, yet may be more common than initially thought. Importantly, the precise SUDEP incidence within subgroups of childhood epilepsy is not known.

Mechanisms of SUDEP

With the majority of SUDEP cases being unwitnessed, the evidence basis supporting mechanisms of SUDEP death in children were initially driven by findings at autopsy, alongside descriptions of the circumstances of death. More recently, analysis of SUDEP deaths occurring whilst an individual is being monitored with EEG, video-telemetry and cardiorespiratory vital signs, has provided further insights. Our understanding remains largely derived from adult studies.

With the majority of witnessed SUDEP deaths occurring in close proximity to a seizure event, many of the hypothesis regarding the pathophysiology of SUDEP are drawn from what is already known about the physiological changes that occur during a seizure and within the post-ictal period. Seizures can induce cardiac arrhythmias alongside respiratory depression that may be severe enough to cause hypoxia. Therefore, three broad mechanisms for SUDEP have been proposed **(figure 1).**

Respiratory

Witnessed SUDEP deaths have commonly reported that individuals developed abnormal breathing patterns or breathing difficulty. The exact mechanisms of respiratory compromise have not been established. Airway obstruction induced by seizure activity has been hypothesized as one potential mechanism, which may arise from asphyxiation, severe postictal laryngospasm, or neurogenic pulmonary oedema. Seizure-induced hypoventilation is thought to be another important mechanism. Video-EEG recordings of adult patients who have died from SUDEP have shown respiratory insufficiency and central hypoventilation in the postictal state. One study witnessed

apnoea (59%) and oxygen desaturation (55-83%) in the majority of cases. Autopsies of children who have died from SUDEP showed that over 20% had evidence of acute hypoxic changes in the brain with pulmonary oedema noted in all 8 patients who had undergone complete autopsy (4). This suggests that, even if respiratory dysfunction is not the primary cause of death, it is likely to be involved.

Cardiac

The lack of an identifiable cause of death at post-mortem is suggestive of a cardiac arrhythmia. This is thought to be precipitated by central autonomic dysfunction, alongside catecholamine release, induced by seizure activity. Similarly, hypoxia and hypercapnia induced prolongation of cardiac repolarisation can also contribute to the formation of a dysrhythmia. Thus, there is debate surrounding whether the cardiac arrhythmia is the primary cause of death.

Several dysrhythmias have been observed during seizures. Sinus tachycardia is the most common, with transient bradyarrhythmias also occurring often in the presence of apnoea. QT interval changes have been observed, however given several anti-seizure medications may prolong the QT interval, this complicates interpretations. Changes in heart-rate variability are also well documented in childhood epilepsy. Despite this, reports of malignant tachyarrhythmias are rare in monitored settings. Seizure-induced cardiac asystole, on the other hand, is seen infrequently and may be a possible contributor to SUDEP.

Given the likely role of a cardiac mechanism in SUDEP, studies have looked to establish whether an underlying cardiac risk factor may predispose an individual with epilepsy to SUDEP. It has been suggested that genetic mutations associated with channelopathies may confer increased risk, with mutations commonly affected in Long QT Syndrome being observed in adult cases. Whether structural cardiac abnormalities can predispose an individual to SUDEP is not known, however architectural changes, such as myocardial fibre hypertrophy, have been observed at autopsy in children.

Central

Proposed central mechanisms of SUDEP initially centred on central hypoventilation second to “cerebral shutdown” or postictal generalised EEG suppression (PGES). However, the involvement of PGES in SUDEP remains controversial and its occurrence in children is largely unknown. An alternative central SUDEP mechanism was proposed and described by the MORTEMUS study (3). This was a retrospective worldwide evaluation of cardiorespiratory arrests occurring on epilepsy monitoring units. Of 90,000 monitored patients, the study identified 16 cases of definite or probably SUDEP. Cardiorespiratory data available from 10 of these cases discovered a new pattern of cardiorespiratory dysregulation in which individuals developed rapid breathing after a GTCS, followed by transient or terminal cardiorespiratory dysfunction. This pattern of cardiorespiratory dysfunction is yet to be described in CYPwE.

With increasing surveillance and witnessed SUDEP events in monitored settings, our understanding of the possible mechanisms of SUDEP has increased. It is likely that SUDEP represents a constellation of syndromes, each with a distinct pathophysiology. There are still several questions that remain unanswered, particularly with respect to the timing and relative contribution of respiratory, cardiac and central components. Furthermore, the mechanisms we have described centre on events induced either during, or in close proximity, to a seizure. SUDEP has been reported to occur in the absence of a seizure in adult settings. Importantly, it remains unknown whether the mechanisms seen in adults are comparable to that in children.

SUDEP risk factors: early learnings from Adult SUDEP

Up until recently, most large population-based case-control studies have focused on SUDEP risk factors in adults. Initial analysis produced conflicting results. This was attributed to several factors including inconsistent definitions of SUDEP cases, small numbers of cases, inappropriate choice of controls and bias in the methods by which cases were attained. In 2011, the Task Force on Epidemiology of the International League Against Epilepsy (ILAE) pooled data from four major case-control studies of SUDEP to more accurately describe SUDEP risk factors. They found the following risk factors were associated with a statistically significant increased risk of SUDEP.

1. Increased frequency of generalised tonic-clonic seizures (GTCS)
2. Longer duration of epilepsy
3. Young age at onset
4. Polytherapy
5. Male gender

Of these factors, the frequency of GTCS was determined as the strongest risk factor for SUDEP. A further study performed in Sweden identified that nocturnal seizures alongside lack of nocturnal supervision were additionally strongly associated.

SUDEP risk factors in CYPwE

Only a small number of controlled studies have looked at risk factors associated with SUDEP in CYPwE.

Demographics

Analysis of the case demographics of CYPwE who have died from SUDEP shows a diverse patient group including all ages and genders. Studies have suggested a slight male predominance, as seen in adults. Accurate analysis of ethnic or geographic variation in paediatric SUDEP has not been achieved. The age of death from SUDEP has been found to be evenly distributed across childhood.

Aetiology of Epilepsy:

Understanding SUDEP risk by epilepsy subtype is critical for providing accurate information to CYPwE and their families about SUDEP risk. Associations between epilepsy subtypes and SUDEP may also provide further insights into SUDEP pathophysiology.

SUDEP has been reported in all types of childhood epilepsy. This includes those due to structural, metabolic, immune, and genetic (previously termed idiopathic) causes. In adult literature, the previously termed symptomatic epilepsies, encompassing structural, metabolic and immune causes, have been reported to have higher rates of SUDEP. This was primarily from traumatic brain injury or encephalitis/ meningitis. Similarly, in a systematic review, 33% of SUDEP cases had symptomatic epilepsy vs 21% idiopathic, despite idiopathic epilepsy being the most common childhood epilepsy subtype (4). Alongside symptomatic epilepsy, SUDEP has also been more strongly associated with epilepsy syndromes in children, with Dravet syndrome being shown to confer the greatest increase of SUDEP risk. Precise incidence rates of SUDEP amongst epilepsy subtypes have not been calculated.

It is already known that the all-cause mortality rate in paediatric epilepsy is substantially higher (x20) in those with complicated epilepsy, defined as that being associated with neurodisability or brain lesions. In fact, one study has shown that children with uncomplicated epilepsy did not have a significantly increased all-cause mortality risk when compared to the general population (1). The extent to which this increased mortality risk is attributed to an increased risk of SUDEP is debated. It

is thought the majority of these deaths are due to secondary factors associated with neurodisability. Yet, pooling of several cohort studies showed the rate of SUDEP to be 2-3x higher in patients with complicated epilepsy. Similarly, the link between SUDEP and intellectual impairment and developmental delay is complex as these are in turn associated with complex, medically refractory epilepsy and their associated increased risk of all-cause mortality. Many patients with intellectual impairment and refractory epilepsy are cared for in residential institutions where they have greater supervision. This may be protective against risk of SUDEP.

Finally, there is controversy surrounding the incidence of SUDEP in benign epilepsies, such as benign epilepsy with centrotemporal spikes (BECTS). Typically, children with BECTs have been considered to have a uniformly good prognosis. However, case reports have suggested that SUDEP can occur in BECTs, albeit infrequently. Whether it is necessary to discuss the risk of SUDEP in these cases is debated.

Type of Seizures

In adult studies, generalised tonic-clonic seizures (GCTS) and an increased seizure burden have both been strongly associated with elevated risk of SUDEP. These findings are mirrored in CYPwE. GTCS has been shown to be one of the leading risk factors for paediatric SUDEP; 88% of cases in a systematic review were found to have GTCS (4). Having said this SUDEP has been reported in children with simple or partial complex seizures. Importantly, increased seizure burden has been shown to confer substantially higher SUDEP risk, as seen in adult cases. This reinforces the importance of epilepsy control. Interestingly, studies have also demonstrated that SUDEP is associated with an early age of onset of seizures, with the majority of paediatric SUDEP cases having a seizure-onset below age 5. This may reflect both the severity of subsequent epilepsy in these children, alongside known associations between SUDEP and specific syndromic epilepsies.

Anti-seizure medication

The relationship between types of anti-seizure medication and SUDEP is complicated and with no proven relationships elicited in CYPwE. In adult studies, there have been contradictory reports regarding the association between specific anti-seizure medications and increased SUDEP risk. So far, no specific anti-seizure medication has been strongly associated with increased risk of SUDEP. Similarly, although polypharmacy has been linked to SUDEP in adults, there is no definitive association between number of anti-seizure medications and SUDEP in CYPwE. Importantly, poor compliance with anti-seizure medications has been linked with increased risk of SUDEP in adults with subtherapeutic anti-seizure medication levels being noted in several studies. This finding has been replicated in children. This again emphasises the importance of optimising anti-seizure medications to gain adequate seizure control.

Circumstances and Positioning

Having established that SUDEP is likely to occur in close proximity or during a seizure-event, it is thought that the timing and positioning of a patient during the seizure may confer an increased risk of SUDEP. In adult studies, the presence of nocturnal GCTS in the previous year were associated with a 15-fold increased risk of SUDEP. Similar associations have been seen in children, with 51% of SUDEP cases being found in bed (4). Prone positioning has also been associated with SUDEP in both adults and children. It is thought that this may increase the risk of asphyxiation, and subsequently risk of SUDEP. The association with nocturnal seizures is therefore likely to represent a combination of the child being more likely to be unsupervised and in a prone position, alongside potentially having a higher seizure burden.

Genetic predisposition

Investigation into the role of a genetic predisposition in paediatric SUDEP has been limited by sample size. Studies have largely focussed on adults. No single gene has been strongly associated with all SUDEP cases, however several candidate genes have been identified with varying levels of association. These pathogenic variants were predominantly found in ion channel subunits, such as *SCN1A*, seen in Dravet syndrome. Whether this confers increased risk through a predisposition to fatal cardiac arrhythmias is not known. Thus, although a genetic susceptibility may play a role in paediatric SUDEP, it has not yet been characterised and the overall cause of SUDEP is likely multifactorial.

Discussing SUDEP with CYPwE and Caregivers

Relatives of CYPwE with SUDEP consistently indicate they wished they had been informed about the risk of SUDEP. They describe 'guilt' from not having the opportunity to employ risk-reduction measures. Both NICE and the American Academy of Neurology (AAN) guidelines state that CYPwE should be provided with information on SUDEP. Unfortunately, on average <30% of healthcare professionals routinely discuss SUDEP with their patients (4). Discussing the possibility of death with CYPwE can feel conflicting when simultaneously encouraging them to think positively about living with epilepsy. Clear guidance detailing the content of discussion, alongside the most appropriate timing and setting is therefore required **(table 3).**

Stratifying risk discussions

Our increasing understanding of the prevalence, risk factors and potential mechanisms of SUDEP can shape evidence based personalised discussions about SUDEP. A stratified approach to addressing a CYPwE's relative risk of SUDEP is sensible. In adults the SUDEP seizure and safety checklist has been developed by Shankar et al allowing individuals to determine an individual baseline risk rating based on 19 factors. Although this is not validated in CYPwE, it is useful to consider which of the established paediatric risk factors are present in each individual, and their relative risk of SUDEP **(table 2)**. It is important to distinguish that the risk of SUDEP is higher in those with poorly controlled epilepsy with a high frequency of generalised tonic-clonic and nocturnal seizures. Regardless, one should reassure that paediatric SUDEP is rare event.

Increased risk	**Lower risk**
Demographics	
- Male - Intellectual disability	- Normal intellect - No significant comorbidities
Epilepsy features:	
- High seizure frequency - GTCS - Nocturnal seizures - Early onset age - Polytherapy	- Uncomplicated epilepsy - New onset - Monotherapy
Circumstances and positioning:	
- Prone positioning - Unsupervised	- Supervision

Table 2: A guide for classifying paediatric SUDEP risk factors.

Reducing the risk of SUDEP

Based on our understanding of paediatric SUDEP risk factors, several sensible suggestions for reducing a CYPwE's SUDEP risk have been put forward. Patients may therefore be empowered with personalised information on possible risk reduction measures that can be taken.

Given that the most important risk factor for paediatric SUDEP is uncontrolled GCTS, optimising a patients epilepsy management is critical. Patients should be counselled on the importance of seizure control to reduced SUDEP risk, alongside being encouraged to reduce seizure provoking factors such as non-adherence to treatment or poor sleep. From a clinician perspective, optimising a CYPwE epilepsy management is key, which involves timely referral to an epilepsy specialist and adjusting medications as required. If adequate seizure control cannot be achieved using medication, non-pharmacological interventions should be considered, such as the ketogenic diet, epilepsy surgery and vagal-nerve stimulation, where appropriate.

Alongside optimising epilepsy control, reducing the frequency of unsupervised seizures is important. Although it may not always be practical, advising nocturnal supervision or the use of nocturnal listening devices may further reduce the risk imposed by nocturnal seizures. It may also be reasonable to encourage CYPwE to sleep in a supine position or use pillows to create a safer sleep environment. Furthermore, ensuring supervision in the post-ictal phase until full consciousness is restored may be protective regardless of seizure timing. Technological advancements in seizure detection devices, which include both EEG and non-EEG based systems, may provide further means of reducing the risk of unsupervised seizures and thus reduce the risk of SUDEP.

Timing and setting of SUDEP risk discussions

The optimum timing of this discussion may vary between individuals. Most caregivers suggest this discussion should happen at or close to the time of epilepsy diagnosis, however CYPwE often recognise that the healthcare professional may be best placed to determine whether the person is ready. SUDEP risk discussions may be incorporated into general discussions about the importance of seizure management or be a stand-alone conversation. Repeat discussions or providing information in chunks, may aid long-term understanding. Although written information should never replace a discussion, supplementing discussions with written information in the form of leaflets or links to online resources is helpful. The charity SUDEP Action has many educational resources for CYPwE, alongside sources of support for those bereaved due to SUDEP. There is little evidence to support which age is best to involve a child, however usually from age 12-13 onwards children are included in discussions (4).

The setting and clinicians involved in SUDEP risk discussions is also important to consider. Discussions are generally best received face-to-face in a clinical or home setting. It is best that the clinician undertaking the discussion has good rapport with the child alongside knowledge of SUDEP. It is worth considering involving allied health professionals, such as specialist nurse practitioners, to help support the family.

Content
What is SUDEP? Prevalence and mechanisms: • *"We know that sometimes individuals with epilepsy may die where the cause of death is unexplained: this is called Sudden Unexplained Death in Epilepsy or SUDEP"* • *"The exact incidence of SUDEP in children is unknown but it is thought to be a rare event"* • *"We are beginning to understand more about the mechanisms of SUDEP. It is likely that a seizure causes a disturbance in a child's heartbeat or breathing. We do not know exactly how this occurs…"*

Personalised risk factors: stratifying risk • *"So far, we know that the key risk factors for SUDEP are… (see table 2)"* • "*In your case, you have……. This puts you at a slightly higher/ lower risk of SUDEP"*
Personalised risk reduction measures: • *"Based on what we know about SUDEP, reducing seizure frequency is the most important way to reduce the risk of SUDEP"* • "*Encouraging CYPwE to sleep face up, alongside finding means to supervise them at night, may also be helpful, if this is practical to do so"*
Delivery
Setting: • Clinical or home environment Timing: • Ideally near to Epilepsy diagnosis • Clinician who knows CYPwE may be best placed to judge when most appropriate Personnel: • Clinician with a good rapport • Consider involving wider MDT Other: • Consider supplementing with written information

Table 3: SUDEP discussion checklist. This table provides a framework for discussing SUDEP with CYPwE and their families.

Conclusion and practice points

Over the past 20 years, our awareness and understanding of paediatric SUDEP has dramatically increased. Yet more is needed to be done. The development of the North American SUDEP Registry in the United States and Canada will continue to provide prospective surveillance allowing improved characterisation of paediatric SUDEP incidence and risk factors. Paediatric SUDEP must be recognised as an important public health problem with appropriate development of services designed to support bereaved families. Based on the available evidence, SUDEP risk discussions should form part of routine epilepsy care of any CYPwE. Ultimately, optimising seizure control remains the central means by which SUDEP incidence can be reduced, however further characterisation of paediatric SUDEP risk factors will allow clinicians to better tailor personalised risk reduction strategies. The potential for technological advances in seizure monitoring and detection devices provides great hope for the development of further means to reduced paediatric SUDEP incidence.

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Further Reading

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Figure captions

Figure 1: Proposed mechanisms for SUDEP. Respiratory, Cardiac, and Central dysfunction results in death, most often triggered seizure activity. SUDEP may represent several syndromes each with a distinct pathophysiology. The mechanisms of SUDEP in the absence of seizure activity are poorly understood.