Sudden Unexpected Death in Epilepsy (SUDEP) - What Pediatricians Need to Know

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Sudden unexpected death in epilepsy (SUDEP) is a devastating complication in children with epilepsy. Children with generalized tonic-clonic convulsions, nocturnal seizures, and co-morbid developmental delay/intellectual disability are at higher risk of SUDEP. The pathogenic mechanisms are incompletely understood and involve cardiac, respiratory, autonomic and cerebral dysfunction. Prone positioning is also significantly associated with SUDEP and may be a target for SUDEP prevention. Good epilepsy control also attenuates the risk; hence, it is important to provide adequate antiepileptic drug therapy with stress on drug compliance as well as early surgical referral for seizure control, wherever necessary. It is recommended that parents of children with epilepsy be counseled about the risk factors for SUDEP and potential measures of SUDEP prevention. We herein provide a pediatric perspective of the problem and guidance about parental counselling for its prevention.

Keywords: *Counselling, Morbidity, Outcome, Prevention, Uncontrolled epilepsy*.

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Mortality in children with epilepsy is significantly higher than the general population [1]; although, most deaths in children with epilepsy are not related to seizures or epilepsy [2]. The higher risk is explained by several factors: respiratory illness with underlying neurological condition that presents with seizures, systemic comorbidities, indirect factors as well as deaths presumably or demonstrably due to seizures. Sudden unexpected death in epilepsy (SUDEP), which belongs to the last group, has gained prominence as a cause of death in epilepsy in recent years.

DEFINITION

SUDEP is defined as a "sudden unexpected witnessed or unwitnessed, non-traumatic, non-drowning death in a patient with epilepsy with or without evidence of a seizure and excluding documented status epilepticus in which post-mortem examination does not reveal a toxicological or anatomical cause of death [3]." This definition requires a postmortem examination to diagnose SUDEP, which is not available in the majority of instances. Hence, criteria have been described for definite, probable and possible SUDEP [4] (***Box* I**).

BURDEN

The incidence rates of SUDEP in children have been reported to be 0.36-0.43 per 1000 person-years [5-7]. Although SUDEP rates have been reported to be lower in children compared to adults, the American Academy of Neurology (AAN) practice guidelines on SUDEP established the incidence rate of SUDEP in children with epilepsy to be 0.22/1000 patient–years (95% CI 0.16-0.31) after a systematic review of 12 class I studies [8]. Due to imprecision in incidence data results, random-effect meta-analysis was further performed. SUDEP was found to affect 1 in 4,500 children with epilepsy in one year, making the risk of SUDEP rare.

Risk Predictors

There are very few studies assessing risk factors in childhood SUDEP and most of the data is derived from larger studies in adults.

- The presence and frequency of generalized tonic-clonic seizures (GTCS) is an important risk predictor for SUDEP [8].
- The relative risk of SUDEP is 7.7 times higher in patients with onset of epilepsy between 0-15 years compared to onset after the age of 45 years [9].
- All-cause mortality, including SUDEP, is also higher in children with developmental delay [10].
- Children with uncontrolled seizures have a higher risk [11].
- SUDEP has also been shown to increase with the duration and severity of seizures, with 15-fold risk

Box I Classification and Definition of Subtypes of Sudden Unexpected Death in Epilepsy (SUDEP)

Definite SUDEP

- Sudden, unexpected, witnessed 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 postmortem examination does not reveal a cause of death.

Probable SUDEP

- 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 SUDEP

- SUDEP cannot be ruled out but a competing cause of death is present. If a death is witnessed, a cutoff of death within one hour from acute collapse is suggested.

with more than 50 GTCS per year, nocturnal seizures and the occurrence of GTCS [12], as well as prolonged tonic state leading to post-ictal immobility [13].

- Postictal generalized EEG suppression beyond 50 seconds also may have a predictive role in SUDEP and is associated with sleep, shorter duration of clonic phase, symmetric tonic extension posturing and terminal burst-suppression after a seizure [14].
- Symptomatic epilepsy has a higher risk of SUDEP compared to idiopathic generalized epilepsy. Patients with Dravet syndrome are also at a higher risk of death [15].

SUDEP shares certain features with the syndrome of sudden infant death (SIDS), suggesting possible common mechanisms. SIDS is sudden and unexpected death that occurs in infants below the age of one year. Both SIDS and SUDEP are diagnoses of exclusion, and autopsy findings are usually not revelatory. Deficiency in arousal response to rise in carbon dioxide in both syndromes may contribute to death, suggesting that these two entities may lie on a continuum [16].

PATHOPHYSIOLOGY

The pathophysiology of SUDEP is not well elucidated and is believed to arise from an interaction between predisposing factors and triggers. Predisposing factors include effects of long-standing seizure disorder such as altered autonomic function, etiology of epilepsy (*e.g.* symptomatic, familial), factors related to drug therapy such as abrupt withdrawal or polypharmacy *etc*. A triggering seizure leads to preterminal events including cardiac, respiratory, autonomic and cerebral dysfunction. The various mechanisms (***Fig.* 1**) include the following:

Cardiac dysfunction: Sudden cardiac arrest is a proposed mechanism with certain ion channel abnormalities being implicated in both epilepsy and cardiac arrhythmia. The most widely implicated is the sodium channel abnormality, which may also explain the higher rates of SUDEP in Dravet syndrome [17]. Another link is the association between long QT syndrome and familial epilepsies, both of which are channelopathies.

Respiratory dysfunction: Severe peri-ictal hypoxia occurs in one-fourth of patients with SUDEP [17]. Autopsy changes of pulmonary edema have also been observed in SUDEP cases, but this is likely an effect than a cause of SUDEP.

Autonomic dysfunction: Various autonomic abnor-malities have been described in patients with refractory epilepsy and include lower parasympathetic and higher sympathetic tone, increased vasomotor tone and impaired heart rate variability [18]. Changes in ictal heart rate also suggest autonomic dysfunction, with tachycardia occur-ring in up to 60% of seizures and bradycardia in 6% of focal seizures [17,19]. As per the Mortality in epilepsy monitoring units study (MORTEMUS), an initiative that assessed cases of SUDEP and near-SUDEP in patients admitted for video-EEG monitoring, post-ictal centrally mediated cardiac and respiratory depression associated with post-ictal generalized EEG suppression was a strong mechanism leading to SUDEP [20]. The switch from parasympathetic to sympathetic state, combined with sympathetic over-drive that accompanies the state of drug withdrawal that accompany seizures may be a possible precipitant.

Channelopathies: Channelopathies are disorders characterised by dysfunction of ion channels. Traditionally channelopathies have been considered genetic defects *eg*., long QT syndrome and Dravet syndrome. In inherited channelopathies, the same ion channel abnormalities are expressed in the heart as well as the brain. Hence, these epilepsies are associated with an arrythmia-prone cardiac condition.

Recently, there is an emerging concept of acquired channelopathy *i.e.*, channel dysfunction in patients with chronic epilepsy. Animal studies have shown that epilepsy alters the expression of sodium, potassium, calcium and cationic channels in the heart. In these

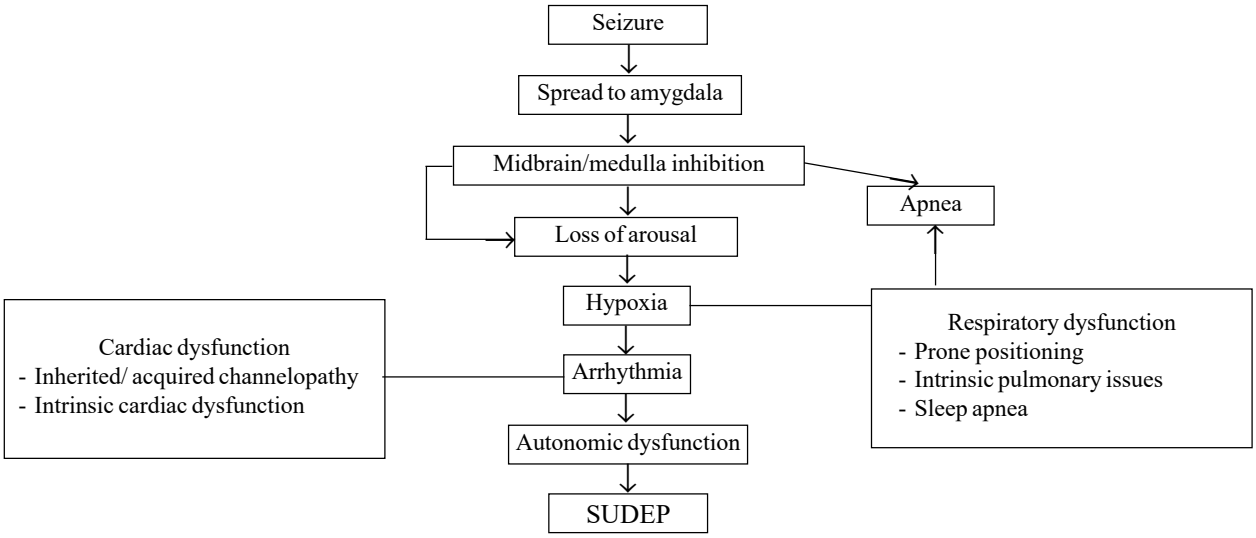

Fig. 1 *Various pathophysiological mechanisms leading to sudden unexpected death in epilepsy (SUDEP).*

acquired cardiac channelopathies, epilepsy increases the pro-arrhythmic state increasing predisposition to sudden death [21].

Cerebral dysfunction: SUDEP occurs more often in sleep and almost all cases are nocturnal and associated with the prone position. Various neurotransmitter abnormalities have been reported in association with SUDEP including low serotonin state [22] and excessive opioid [23] and adenosine activity. Brainstem serotonin modulates respiratory drive and has also been implicated in sudden infant death syndrome [24]. It may contribute to SUDEP by a similar mechanism.

INTERVENTIONS FOR PREVENTION

As uncontrolled epilepsy is a known risk factor, effective epilepsy treatment to reduce frequency and duration of seizures as well as GTCS should be targeted. Nocturnal supervision was found to be protective in one case-control study [25] and may be combined with seizure detection devices, but clinching evidence in SUDEP prevention is lacking. It is of potential benefit in children with uncontrolled or nocturnal seizures. In India, nocturnal supervision of children is generally culturally acceptable as co-sleeping of children with their parents is common. A blanket 'back to sleep' advice to avoid prone positioning may be recommended, with the caveat that it is the post-ictal turning prone which is usually responsible. Hence parents should be counseled to turn the child to a lateral position and avoid prone position after the seizure. The use of lattice or safety pillows may reduce the contribution of prone position to post-ictal cardiorespiratory distress.

In terms of preventive drug therapy, it has been observed in mouse models of SUDEP that selective serotonin reuptake inhibitors (SSRI) such as fluoxetine may decrease apnea risk [26]. Serotonergic neurons in the brainstem are believed to be responsive to rise in CO_2 and fall in pH levels in the blood and thereby stimulate respiration and arousal. In a retrospective study on adults with focal seizures [27], it was noted that patients on SSRIs (for co-morbid mental health problems) had a reduced likelihood of post-ictal oxygen desaturation as compared to patients who were not on SSRIs. Recently, two randomized controlled trials have been completed to evaluate the role of fluoxetine to prevent post-seizure apneas and desaturation; however, the results have not been published yet. Massive release of endogenous opioids and adenosine is induced by seizures and helps in seizure termination [28]. However, this surge can also lead to post-ictal apnea. Naloxone is currently under a randomized trial for this purpose. Adenosine antagonists may also be beneficial for this purpose.

These therapies; however, are still in the emerging phase and currently being tried in adults. More evidence is needed before the data can be extrapolated to children.

Parental Counseling

Counseling of caregivers and sensitization towards SUDEP is imperative. Caretakers should be educated regarding the importance of adherence to treatment, nocturnal supervision, especially to avoid prone position after seizures, as well as basic life support training imparted to willing caregivers. However, whether all patients with epilepsy should be counseled about the risk

of SUDEP or only high-risk patients remains a matter of debate, and scientific data till date does not permit the establishment of evidence-based guidelines for the same. However, disclosure of SUDEP risk to all epilepsy patients has been endorsed by multiple neurological societies, including a joint task force of the American Epilepsy Society and the Epilepsy Foundation and the American Academy of Neurology (AAN) [29], and in India by the joint consensus document on parental counseling by Association of Child Neurology (AOCN) and Indian Epilepsy Society (IES) [30]. In a study on parental views regarding the counseling of SUDEP risk, parents generally expressed a preference for receiving routine SUDEP counseling at the time of the diagnosis of epilepsy [31]. In another study from Malaysia (32% of participants were of Indian origin), 70.9% of parents felt that receiving SUDEP information was positive [32]. Most parents did not report any impact on their own functioning. However, increasing numbers over time reported an impact on the child's functioning. In a study from UK, 74% of pediatric neurologists conveyed SUDEP information to a select group of patients only. In contrast, 94% of parents of children with epilepsy expected the physician to provide SUDEP information [33].

In India, many neurologists and pediatricians feel that imparting the knowledge of SUDEP may increase parental anxiety and stress levels, which may be unwarranted as the complication is so rare. However, it is also known that many parents are afraid their child would die when they witness the child having a seizure for the first time. The information that the risk of death is very low may be reassuring. Also, the knowledge of this condition may improve drug compliance, as seen in studies from outside India. In an Indian study of SUDEP counseling of adults with epilepsy and their caregivers, it was shown to increase drug adherence without any increase in anxiety or stress levels in either the patients or their caregivers [34]. More experience is needed in this field to understand parental perceptions and reactions.

CONCLUSION

SUDEP is an under-recognized but important threat in patients with epilepsy. It is important to assess SUDEP risk in all epilepsy patients, particularly in those with generalized tonic-clonic convulsions, nocturnal seizures, as well as co-morbid developmental delay. Appropriate antiepileptic drug therapy with stress on compliance, early surgical referral for surgically remediable epilepsies, avoiding post-seizure prone positioning, and caretaker counseling and support will go a long way in the prevention of this condition.

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