Sudep-------The Unsolved Mystery

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ABSTRACT

SUDEP (Sudden Unexpected Death in Epilepsy) is really a medical mystery till now. A lot of possible explanations are contributed to it. These being cardiac, respiratory, autonomic,drugs, nature of epilepsy etc. It still remains one of the most important cause of death in epilepsy patients apart from status epilepticus, trauma.
The incidence of SUDEP is estimated to be 0.35 per 1000 person-years of follow-up in this population. Known associated demographic risk factors for SUDEP include male gender and an average age of 28-35 years.

Key Words—epilepsy, cardiac, respiratory, autonomic, drugs, status epilepticus

Introduction

Patients with epilepsy have a mortality rate 2-3 times higher than that of the general population because of epilepsy-related deaths. The phenomenon of SUDEP usually accounts for 8-17% of deaths in patients with epilepsy .[1]

Defination:

SUDEP is defined as sudden, unexpected, nontraumatic, nondrowning death in an individual with epilepsy, witnessed or unwitnessed, where postmortem examination does not reveal an anatomical or toxicological cause for the death.

The US Food and Drug Administration (FDA) and Burroughs-Wellcome developed the following criteria for SUDEP in 1993.

1. The patient has epilepsy, which is defined as recurrent unprovoked seizures.
2. The patient died unexpectedly while in a reasonable state of health.
3. The death occurred suddenly (ie, within minutes).
4. The death occurred during normal and benign circumstances.
5. An obvious medical cause of death could not be determined at autopsy.
6. The death was not the direct result of a seizure or status epilepticus.

Classification of SUDEP:

1. Definite SUDEP: Cases meet all criteria and have sufficient descriptions of the circumstances of the death and a postmortem report.
2. Probable SUDEP: Cases meet all criteria but lack postmortem data.
3. Possible SUDEP: SUDEP cannot be ruled out but evidence is insufficient regarding the circumstances of death and no postmortem report is available.
4. Not SUDEP: Other causes of death are established clearly or the circumstances make the diagnosis of SUDEP highly improbable.

Frequency:

1. Race : SUDEP usually occurs more commonly in African American than Caucasians.
2. Sex : Male-to-female ratios as high as 7:4 have been reported.
3. Age: Most cases of SUDEP have been observed in patients with epilepsy who are in their third to fifth decade (ie, age 20-40 years), with a higher incidence at the younger end of the age range. The average age

Patient-related	1. Young (25-35 y) 2. Male 3. Developmentally delayed
Seizure-related	1. Symptomatic epilepsy 2. Seizure type - Generalized tonic-clonic 3. Younger age of seizure onset 4. Duration of seizure disorder -Longer than 10 years 5. Higher number of seizures 6. Recent seizures
Treatment-related	1. Subtherapeutic serum level of antiepileptic medication 2. Higher number of antiepileptic medications 3. Recently changed 4. Other treatment 5. Surgery 6. Higher serum levels of carbamazepine

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is estimated to be 28-35 years. It is very rare in children.

Risk Factors: Table 1. Possible Risk Factors for SUDEP

Pathophysiology

Unfortunately a very small portion of definite SUDEP cases have been documented as witnessed. Langen et al [2] have reported 15 cases of witnessed SUDEP and 80% of these patients had a seizure immediately before death. Terrence reported 24% and Leetsma reported 38% of witnessed deaths to be an immediate consequence of a seizure attack. [3,4] Kloster reported evidence of recent seizures (ie, witnessed, oral trauma, cyanosis) in 67% of victims.[5]. The immediate event before death was respiratory arrest (obstructive and central) in a few witnessed cases. The majority of victims were reported to have difficulty breathing before death. Attempts at cardiopulmonary resuscitation were unsuccessful. Different pathophysiological events may contribute to SUDEP. The mechanism is probably multifactorial.

Respiratory Factors:

1. Neurogenic pulmonary edema

Possible Mechanisms.

A. Massive alpha-adrenergic response,
B. generalized vasoconstriction,
C. pulmonary hypertension.
D. The high protein content of the alveoli which indicates severe damage to the endothelial membranes leading to increased pulmonary permeability.

2. Central sleep apnea (cessation of spontaneous respiratory drive during sleep)

Possible Mechanisms.

A. Seizures are known to cause central apnea by direct propagation of the electrical discharge to the respiratory center. Episodes of apnea lasting 10-63 seconds, accompanied by a significant fall in oxygen saturation, have been documented.
B. In addition, cardiac arrest can cause secondary cardiopulmonary arrest. So et al documented a case of near-SUDEP due to postictal apnea.[6]

3. Asphyxiation

Possible Mechanism

A. Prone position affecting ventilation by obstructing the upper respiratory tract as well as increasing the chances of aspiration. [5,7]

Cardiac and Autonomic factors

Cardiac arrhythmias also may play an important role as an underlying mechanism of SUDEP. Fatal arrhythmias can occur both during the ictal attack and interictally. These sudden fatal arrhythmias cause acute cardiac failure and death. [8,9,10] Arrhythmias preceding SUDEP have been postulated to be the underlying cause of death. Lathers documented the synchronization of ictal and interictal spikes with cardiac sympathetic activity. Ictal tachycardia has been documented in 83% of seizure attacks, and bradycardia can accompany as many as 4% of seizures. During the attack, patients presented with prolonged decreases in heart rate, which lasted beyond the seizure attack in most cases. The majority of patients had decreased brain perfusion with potentially fatal outcome. [11]

Potential Mechanisms

A. Propagation of the electrical activity to the amygdala, which has efferent connections, via the central nuclei, to the cardioregulatory centers in the medulla. Arrhythmia can be a consequence of this event.
B. Massive sympathetic surge during a seizure attack and
C. vagal inhibition might be other potential mechanisms for increased ectopic ventricular activity. Also, extreme vagal stimulation might cause heart blocks
D. Hypofunction of the autonomic cardiovascular reflexes is postulated to be more prominent in patients who also were at high risk for SUDEP and in patients with a more refractory seizure disorder.
E. Interictal sympathetic-mediated dysregulation of cerebral blood flow is another possible mechanism for SUDEP. [12]

In summary, although autonomic dysfunction is known to be associated with epileptogenic activity, its importance as a contributory risk factor to potential fatal outcomes for this population is yet to be determined. Evaluation of autonomic cardiovascular and respiratory reflexes in patients with epilepsy can provide us with valuable information on the mechanism of SUDEP.

Medications

1. Levels of antiepileptic medications have been shown to be subtherapeutic in most SUDEP cases, indicating poor compliance with medications.
2. Patients on multiple antiepileptic drugs had a significantly higher rate of SUDEP.
3. Carbamazepine has been the antiepileptic used more frequently among these patients compared

with other patients with epilepsy. Some side effects such as cardiac arrhythmias or sedation might be contributing.A study of the cardiovascular reflexes in 24 patients with epilepsy, documented increased heart rate variability that was, at least partially, attributed to carbamazepine.[10] Other researchers have reported similar findings.

Autopsy Findings in Sudep Cases

Autopsy, per the definition, fails to reveal the underlying cause of death; however, several autopsy reports confirm the following findings in the organs of patients with SUDEP.

Brain: [5,7]

1. Cerebral edema was reported in the majority of both childhood and adult cases. However, none of the cases showed mass effect due to edema.
2. Hypoxia in the hippocampal area were noticed in a few instances.
3. Sclerosis of the amygdala has been documented in patients with SUDEP.

Lungs:

1. The lungs were heavier than expected in all patients in different studies; lung weights were 110-190% of normal.[3]
2. Mild to moderate pulmonary edema with protein-rich fluid.
3. alveolar hemorrhage were seen in all specimens in this study.

Heart: Fibrosis of the conductive system in some cases.

Liver:

1. Increase in weight and venous congestion, indicating right cardiac failure, were documented in the majority of cases.

Prevention

1. Patient education plays a significant role in preventing sudden death.
2. To identify high-risk patients, and suggest means to reduce risk of SUDEP. The issue needs to be discussed specifically with patients and caregivers.
3. Increasing awareness of the caregivers might improve the ease that physicians discuss this possibility with their patients and help prevent this outcome.
4. Optimal seizure management with effective monotherapy decreases the risk for SUDEP.
5. Compliance with medication
6. Avoiding periods of decreased coverage during changes in medication regimens are essential.
7. Avoiding alcohol, drugs, seizure-provoking situations, and high-risk situations (eg, driving, swimming) needs to be emphasized.
8. Proper training of the caregivers in acute management of tonic-clonic seizures, including positioning the patients during and after the attack and delivering cardiopulmonary resuscitation. Respiration needs to be monitored during the postictal period. Stimulating the patients postictally also is believed to reduce the chances of apnea.

Conclusion;

Irrespective of lot of research, SUDEP still remains a medical mystery. Treating physicians of epileptic patients should be well aware of this entity and take adequate steps for its prevention. It seems wise to include the patients and their caregivers in the strategy to combat SUDEP.

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