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Increasing awareness about sudden unexplained death in epilepsy- a review

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Summary
Sudden unexplained death in epilepsy (SUDEP) is the commonest cause of epilepsy-related death and most of the presumed risks factors associated with it are probably avoidable. In Nigeria most deaths in individuals with epilepsy occurred at home and so were never reported. Therefore, autopsies are usually not carried to determine the cause of death. This article hopes to reawaken the attention of clinicians to this important, yet not so well known phenomenon, with a view towards addressing problems highlighted Literatures and research publications on SUDEP were systematically reviewed. Case definition, criteria for diagnosis, risk factors, pathophysiology and treatment options for SUDEP and possible methods towards decreasing its incidence was discussed. Incidence of SUDEP increases with the severity of seizure, early onset epilepsy, poor seizure control, generalised tonic-clonic seizure, multiple antiepileptic medications and frequent adjustment of antiepileptic drugs (AEDs). The pathophysiology of SUDEP is not yet clearly elucidated, but it seems to involve interplay of several factors. At the centre of this, is the impaired cardio-respiratory reflexes leading to central apnoea, hypoxia and oedema along with cardiac arrhythmias. Education of patients, relatives and caregivers is crucial to reducing the incidence of SUDEP. Optimal seizure management with an effective monotherapy where possible, should be the goal of the managing physician. In cases of intractable epilepsy, vagal nerve stimulation and neurosurgery should be considered early.

Keywords: *Epilepsy-SUDEP –epilepsy death -risk factor -prevention.*

Résumé
La mort subite et inexplicable due aux epilepsies est la cause commune des deces et les facteurs a rsique associes sont probablement inevitable. Au Nigeria, La mort des epileptiques sont dans leur maison et jamais enregistree ni d autopsie. Cette etude eveillel'attention des emdecins sur 'importance moins connu. Cette revue systematique des cas , des criteres de diagnsostie, des facteurs a risque , patholgie et les options de traitement des epileptiques etait faite et le methodes possible pour decroire les incidences sont discutees. Suite a la severite des crampes et des crises precose d'epilepsie des multiples antiepileptiques et regimen diverse, la pathophysiologie de cette maladie resten a elucider, mais apparit une comme une combination de plusieurs facteurs avec un refelexe cardio-respiration impair suivit de l'apnoeee centrale , l'hypoxie et d'oedeme cardiaque.L'education des patients, de la famille et des corps medicale est crucial pour reduire cette incidence. Le menagement des crampes optimales par la monotherapie effective doit etre le but du medecin. Dans les cas d'epilepsie intracable, la stimulation du nerf vagale et la neurochirugie precose doivent etre considerees.

Introduction

SUDEP is the sudden, unexpected, non-traumatic and non-drowning death in an individual with epilepsy, witnessed or unwitnessed, in whom post-mortem examination does not reveal a toxicologic or anatomic cause for the death [1,2].

The first publication linking epilepsy and sudden unexplained death appeared in 1910 [3], although the relationship between epilepsy and unexplained death had been know since the 18th century [4]. Thereafter several studies had been carried out on sudden unexplained death in epilepsy (SUDEP) [5-7]. The term "unexplained death" which was first used in American literatures is now preferred internationally to "unexpected death", since the International Workshop on Epilepsy and Sudden Death was held in London in 1996 [2,8].

Six criteria have been developed by the US Food and Drug Administration (FDA) and the Burroughs-Wellcome in an attempt to standardised the diagnosis of SUDEP [9].

- The patient has epilepsy, which is defined as recur rent unprovoked seizures
- The patients died unexpectedly while in a reason able state of health.
- The death occurred suddenly (i.e. within minutes).
- The death occurred during normal and benign cir cumstances.
- No obvious medical cause could be determined during autopsy.
- The death was not the direct result of a seizure or status epilepticus.

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It is important to note that evidence of a recent seizure does not exclude the diagnosis of SUDEP as long as the death did not occur during the seizure.

Case definition and terminologies used in SUDEP are as below:

I. Definite SUDEP: Cases meeting all criteria and have sufficient descriptions of the circumstances of the death and a post-mortem report.
II. Probable SUDEP: Cases meeting all criteria but lack post-mortem report.
III. Possible SUDEP: SUDEP cannot be ruled out but evidence is insufficient regarding the circumstances of death and no post-mortem report is available.
IV. Not SUDEP: other causes of death are established clearly or circumstances make the diagnosis of SUDEP highly impossible.

Evidence from several studies strongly suggest that SUDEP is a seizure related phenomenon, and it is the most common cause of seizure related death [10-13]. In about 75% of SUDEP cases the death occured during normal activity with majority being found dead in bed [10] and in almost all cases, seizure was reported before the demise [14].

The only available study on SUDEP from Africa during this write-up was from Cameroon. The study found that status epilepsy, SUDEP and drowning were the three most common causes of epilepsy-related death [15], while non-usage of AEDs resulting in uncontrolled seizures was the most significantly associated risk factor for SUDEP.

In Nigeria, there is a dearth of data on SUDEP and the risk factors for epilepsy-related deaths. This is because most deaths in individuals with epilepsy occurred at home, and so were never reported. Therefore, autopsies were not carried in order to determine the cause of death making it difficult if not impossible to determine the incidence of this phenomenon. Likewise the treatment gap of epilepsy (i.e. the percentages of patients in a defined population on any one day, with active epilepsy, not receiving anticonvulsant medication) in developing countries like Nigeria, remains high due to lack of manpower, finance, inadequate knowledge and erratic drug supply [16]. Since most of the presumed risks factors for SUDEP are probably avoidable, this review article hopes to reawaken the attention of clinicians to this important but not so well known condition, with a view towards addressing problems highlighted.

Epidemiology

Generally people with epilepsy have an increased risk of sudden unexplained death compared to the general population [10,17] This is highest in those with uncontrolled generalised tonic-clonic epilepsy [17]. SUDEP accounts for between 2-25% of all deaths in patients with epilepsy depending on the population studied [7,10]. The incidence of sudden unexplained death is estimated to be 24-fold greater in epileptics than in the general population [18] and close to 40 times in young adults (between third to fifth decades) than among those without seizure [19] Data from a cohort study found the incidence of SUDEP to be 9 per 1000 among drug-resistant epileptics compared to 5 per 1000 in those with controlled seizure [11]. Generally, SUDEP is said to be rare in children compared to adult and a Male-to-female ratio as high as 7:4 has been reported generally [20].

Risk factors

The causes of SUDEP are as of yet not precisely known but few witnessed cases, circumstantial clinical and autopsy reports seem to suggest that this phenomenon is seizure-related [10]. Several works have emphasised a higher risk in early onset epilepsy, frequent generalised tonic-clonic seizures, chronic epilepsy (> 30 years), severe refractory seizures, polytherapy with AEDs in adults (but not in children) [21], frequent AEDs dose adjustments, epilepsy associated with injuries other than the central nervous system [11,22-26]. Also dementia and mental retardation have been cited as important risk factors for SUDEP [23].

Table 1: Summary of Possible Risk Factors for SUDEP

Variable	High risk
Patients-related risk factors	
Age	28-35 years
Sex	Male
Seizure-related	
Aetiology	Symptomatic
Type	Generalised tonic-clonic
Age of onset	Younger
Duration of seizure disorder	> 10years
Severity of seizure	Increased number of attack
Treatment-related	
AED serum level	Subtherapeutic
Number of AED	>2
AED regimen	Recently changed

Although, several studies had demonstrated an association between alcoholism and SUDEP, a case-control study on risk factors for SUDEP refuted this claim [11]. Report by Nilsson *et al* showed that the relative risk of SUDEP increases with the number of seizures per year [10]. It is ten times more in patients with greater than fifty seizures per year when compared to those with less than two per year [10] and also rises with increasing number of antiepileptic drugs (AED) taken simultaneously [10,13,23].

Pathophysiology

Although the exact pathophysiologic mechanisms leading to death in SUDEP have not been fully unravelled, three mechanisms have been proposed: cardiac arrhythmias, neurogenic pulmonary oedema, and postictal suppression of brain stem respiratory centres leading to central apnoea [27].

Clinical, pathological and experimental evidences have implicated a precipitation by cardio-respiratory reflexes leading to central apnoea, hypoxia and oedema along with secondary cardiac dysfunction from arrhythmias or ischemia [7,28-30]. Studies in which electroencephalogram and electrocardiogram heart rate changes were correlated with clinical data, showed increased autonomic stimulation during seizures especially while sleeping in patients with SUDEP compared to clinically similar group of patients with refractory seizures [4,8]. Corroborating this is the finding of lowered mortality rate and SUDEP up to two years after vagal nerve stimulation in epilepsy [31]. A study have also demonstrated that intermittent stimulation of the left vagal nerve resulted in the reduction of seizure frequency by more than 50% in 35-43% of patients with medically refractory partial onset seizures [32].

Vagal nerve stimulation, although palliative, result in reduction of heart rate and is being suggested as a treatment modality for intractable epilepsy and secondarily generalized seizures, especially where no "curative" epilepsy surgery is available [33]. The technique of vagal nerve stimulation involves implantation of a pacemaker-like device in the anterior chest wall with stimulating electrodes connected subcutaneously to the left vagus nerve at the carotid bifurcation [32,33].

Few post-mortem reports have shown the presence of subendocardial fibrosis in epileptic patients with an apparently normal heart [34,35]. This finding supports the arrhythmia hypothesis, because similar small areas of myocardial fibrosis have been shown to be responsible for malignant arrhythmias in the presence of heart disease [36].

The possibility that SUDEP could have been due to mass effect from cerebral oedema has also been refuted [36]. As autopsy reports from brain of patients with SUDEP found cerebral oedema in only those with symptomatic epilepsy secondary to a primary cerebral pathology, and none of the cases showed pressure effect from cerebral oedema [37,38].

There are also speculations that certain yet unidentified genes might possibly increase an individual's susceptibility to developing SUDEP but this is yet to be fully elucidated [39]. The risk/benefit of AEDs in epilepsy and SUDEP has been a subject of controversy. Some studies have reported the likelihood of antiepileptic medications, especially carbamazepine use, its toxicity and frequent rapid change in it levels, to be associated with SUDEP [11,40]. Reasons adduced to this effect, was the possibility of carbamazepine promoting rhythmic instability from its effect on autonomic responses and cardiac conduction. However, this evidence has been refuted by more recent works that have shown that there is no increased risk associated with carbamazepine use or any other particular AED [41]. Conflicting data exist with regard to AED blood levels in SUDEP. Some have related subtherapeutic drug level while others increased AEDs serum levels to SUDEP [42,43]. The finding of subtherapeutic AED blood level was thought to be due to recent drug withdrawal or a non-compliance with drug regime. Thus, suggesting that low drug level predisposed to SUDEP by enhancing electrophysiologic instability of the myocardium [44]. Another experimental data had demonstrated that blood level of phenytoin declined after death [45], which revealed post-mortem drug degradation. Therefore post-mortem serum AEDs level may be unreliable in determining antemortem drug compliance. Other studies have now proved that normal postmortem drug levels and high AED at the last therapeutic drug monitoring before the onset of death can be associated with SUDEP [45,46]. These findings might possibly explain pro-arrhythmic properties of AED.

To conclude from available evidences, the pathophysiology of SUDEP is most likely multifactorial. Tigaran *et al* have postulated a provocative deduction of a complex pathophysiologic interplay between the heart, antiepileptic medications, and the central nervous system, especially in temporal lobe epilepsy [8]. These interactions may probably be responsible for impairment in cardiac function, thus providing an explanation for the unravelled SUDEP phenomenon.

Conclusion

SUDEP is not rare among patients with uncontrolled epilepsy especially in young adults, and because continued generalised seizure is one of the most important risk factors for SUDEP [47]. Early and aggressive seizure control along with optimising AEDs and prescribing few medications as necessary should be aimed at. Cases of refractory seizures should be referred early to the neurologist for proper epilepsy and epilepsy syndrome classification with appropriate treatment instituted. At present there is no strong reason to avoid any particular AED. Further studies are needed to unravel the potential role of each AED in SUDEP and establish its clinical relevance, if any.

Strategies at promoting compliance with antiepileptic medications, as well as regular follow-up attendance should be emphasised to both the patients and relatives. Patients whose seizures have persisted for more than 2 years despite best and optimum dosage should be considered for vagal nerve stimulation and neurosurgery, which worldwide is presently under-utilised, though probably the best treatment for intractable epilepsy.

In industrially developing countries, there is urgent need to improve-on both the manpower and resources needed to cope with the 21st century challenges of intractable epilepsy. Autopsy reports on the causes of death in

epileptic patients should be encouraged. Relatives and caregivers also need to be trained in acute management of tonic-clonic seizures, the right way to position the patients during and after an attack and delivering cardiopulmonary resuscitation.

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