Emergency Critical Care for Epilepsy in Sleep

Saniye Doğan¹, Kristina Polat¹, Yunus Emre Sarikaya¹ and Enes Akyüz²*

¹Faculty of Medicine, Yozgat Bozok University, Turkey
²Department of Biophysics, Faculty of Medicine, Yozgat Bozok University, Turkey

*Corresponding Author: Enes Akyüz, Department of Biophysics, Faculty of Medicine, Yozgat Bozok University, Turkey.

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Abstract

Epilepsy is characterized by neuronal discharges leading disruption of the excitatory and inhibitory balance of the brain and the underlying mechanism of the disease is not fully known.

Approximately 40% of the cardiac pathology associated with epilepsy and the prevalence of it in our country have made the disease necessary to inform patients and their relatives about sudden unexpected death in epilepsy (SUDEP) and possible cardiac/respiratory investigations.

Epileptic seizures increase more frequently in non-rapid (non-REM) stages of sleep, leading to difficulties in the direct diagnosis and treatment of seizures in sleep. Recently, it has been found that cardiac involvement during sleep causes death in epilepsy. In order to be aware of the seizures developing during sleep and to prevent sudden deaths, the interest in the warning devices informing the relatives of the patients has increased. In this review, studies and recommendations related to the occurrence of epilepsy in sleep state were discussed.

Keywords: Epilepsy; SUDEP; EEG; ECG; Emergency

Introduction

Epilepsy is a neurological disorder with recurrent seizures and the seizure in epilepsy is defined as sudden electrical activity in the brain. This causes the messages in the brain to interfere or temporarily stop [1].

Epilepsy is different from other serious neurological conditions because seizures are short and rare, therefore almost all patients are not affected by seizure activity. Although seizure activity is rare, disability and sudden death may occur as a result of the uncertainty of epilepsy. These unpredictable conditions adversely affect the quality of life of both patients and their relatives.

Epidemiology and mortality

It has been reported that approximately 2% of the population has epilepsy and has a seizure at least once in their lives [2]. The prevalence of active epilepsy is generally between 4 and 12 per 1000, regardless of geographical location. However, a sub-standard health system, poor hygiene circumstances, an increased infection and previous traumatic brain injury may contribute to the development of the disease [3-5].

Although essential advances in the treatment of epilepsy, considerable resistance to drugs is still alive [6]. Sudden unexpected death in epilepsy (SUDEP) is one of the leading causes of mortality in drug-resistant young-adult patients and approximately 40% of these patients have been reported to have one or more abnormalities of cardiac function [7,8]. Awareness of deaths due to epilepsy needs to be increased because patients have a 24-fold higher risk of sudden unexpected death than the normal population [9,10].

**Pathophysiology**

Epileptogenesis is the process of transforming non-epileptic neuronal cells into the cell that can produce spontaneous and recurrent seizures. The disease is mainly caused by an imbalance in excitatory and inhibitory systems in neuronal network. The imbalance both disrupts normal neuronal processing and leads to disruptions in the functioning of neighboring networks [3,11,12].

The mechanisms of epileptogenesis include genetic, epigenetic, molecular and structural changes in neuronal cells. Although various mechanisms develop during seizures, most mechanisms develop on the pre-ictal and post-ictal periods [13,14].

Several structural changes shown in animal models have also been contributed to epileptogenesis. Hyperexcitability in brain tissue might be given as neuronal and glial plasticity [14,15]. The structural abnormalities are generally thought to lead to focal epilepsy and genetic abnormalities to generalized epilepsy [16]. In addition, the presence of focal epilepsies caused by genetic mutations has been identified [17,18].

As a result of genetic or structural changes count as essential to the onset, progression or aggravation of epileptic seizures.

**Epilepsy and autonomic nervous system**

Epilepsy is closely associated with disorders in the autonomic nervous system (ANS) because the centers of the autonomic nervous system are located within the cerebral cortex. Patients with epilepsy show autonomic system disorders during ictal and/or interictal periods. As neuronal discharges affect ANS, various symptoms such as bradycardia, tachycardia, apnea, tachypnea, abdominal discomfort, nausea, vomiting and hypersalivation occur during seizures [19].

In 2019, sympathetic and parasympathetic changes were examined in temporal lobe epilepsy patients. Accordingly, autonomic symptoms (orthostatic intolerance, gastromotor, pupillomotor, vasomotor, secretomotor symptoms) and orthostatic hypotension were observed. Coherency, sympathetic skin response (SSR) amplitude was found to be higher in epilepsy patients. Changes in RR interval values (RR-IV%) during rest, deep inspiration and Valsalva maneuver were also significantly lower in the patient group [20]. According to these results, an epileptic seizure seen in temporal lobe affects autonomic nervous system parameters. Furthermore, in a study conducted by Devinsky., et al. it was shown that tonic-clonic seizure, one of the generalized seizure types, may cause autonomic function in pre-ictal, ictal or post-ictal processes and cause cardiac arrhythmias so this is a crucial approach for SUDEP mechanism [21,22].

It is known that even if no significant cardiac dysfunction or electrophysiological abnormality on the basis of acute neurological events including epilepsy, it may cause cardiac pathologies. Cardiac rhythm and conduction disorders have been reported to be common in seizures, especially in resistant and generalized epilepsies [7,23].

Heart rate variability (HRV) is an essential indicator of autonomic function abnormalities and clinical epilepsy studies shows autonomic changes in chronic epilepsy [24]. HRV is a defined parameter for the assessment of cardiac autonomic regulation, a balanced sympathetic-parasympathetic activity. In 2018, patients with epilepsy including abnormal HRV could be associated with sudden unexpected death during interictal periods.

Long QT syndrome (LQTS) is one of the most common causes of epilepsy. LQTS is a clinical and genetic heterogeneous syndrome that is prone to ventricular arrhythmias with long QT intervals on ECG, Torsades de pointes and ventricular fibrillation [25]. As examining the causes of SUDEP, LQTS has been frequently studied. The use of ECG during routine EEG recording may be useful in early diagnosis of epileptic seizure-like conditions and in determining treatment plan changes in epilepsy patients [26].

**Epilepsy and SUDEP**

SUDEP is the most common cause of death in epileptic patients at an early age and directly related to epilepsy. The incidence rate is age-dependent and is 0.22 per 1000 patients (per patient) in children with epilepsy and 1.2 per 1000 patients in juvenile [27]. Epilepsy patients between the ages of 20-40 have been reported to be at the highest risk group for SUDEP. In a significant number of cases, SUDEP was a fatal complication after tonic-clonic seizures [28].
SUDEP usually occurs as seizures are not witnessed or at night [29]. In majority of cases, it occurs following tonic-clonic seizures during sleep or as individuals are usually in the prone position. The predicted mechanisms of SUDEP include post-seizure suppression of brain activity and stimulation associated with impaired respiration, autonomic and cardiac function [30]. Therefore, the measurement of brain functions and cardiovascular values during sleep in epilepsy patients counts as crucial contribution to reducing the risk of SUDEP.

SUDEP is probably a reason of the peri-ictal coupling of a number of different predisposing and precipitating factors. Among these, the presence of a seizure before the fatal event is the only feature appearing to be constantly present. Different mechanisms such as cardiac arrhythmia, respiratory dysfunction, systemic or cerebral circulation disorder have been proposed as potential physio-pathological mechanisms. In addition, clinical data suggest that SUDEP occurs during sleep. In most studies, the incidence of possible sleep-related SUDEP has been shown to be higher than 40%.

In 2019, the most essential risk factor for SUDEP was the presence and frequency of generalized tonic-clonic seizures. The risk may vary further under the genetic effects associated with both heart and epilepsy. A better understanding of the genetic factors affecting SUDEP risk may potentially help in understanding the underlying pathophysiology of SUDEP (Figure 1).
Sleep and epilepsy

The relationship is based on two main factors: epilepsy and sleep stage. Sleep is generally divided into three stages. The stages are as follows: alertness, non-rapid eye movements (NREM) period and rapid eye movements (REM) period [31]. It is known that during the NREM sleep, the connection between neurons is strengthened and in the REM phase dream is occurred.

According to the American Academy of Sleep Medicine (AASM), NREM sleep is divided into three stages. The first two stages are known as mild sleep, third stage is deep sleep or slow wave sleep (SWS) (Kryger, 2005). In the first stage of NREM sleep; muscles relax and the situation lasts for about 10 minutes, the second stage is seen to slow down breathing and heartbeat. The second stage lasts approximately 20 minutes [32] and epileptic patients are known to have seizures in the second sleep stage. The seizures were characterized by sudden, jerky and unusual movements of the arms and legs. Life-threatening complications such as injuries and bone fractures or even SUDEP may occur as a result of concussions if sleep epileptic seizures are not timely intervened [33].

Common situations in which sleep and epilepsy may mediate certain electrical oscillations of brain networks and share the same internal cellular properties. The sleep represents physiological brain rhythms, while seizures cause normal oscillations to become pathological patterns. Sleep and seizures also share the brain cortex, thalamus/reticular thalamic nucleus, brain stem and the same neuronal network including modulation of systems rising from the forebrain [34]. Known sleep disorders in epileptic patients cause worsening of seizures due to insufficient sleep. Sleep disturbance and the increase of seizure numbers may lead to various harmful effects such as memory, learning, attention, behavior and increased daytime fatigue [35]. The literature show that epileptic seizures increase more frequently in non-rapid (non-REM) stages of sleep. During sleep, especially frontal lobe seizures develop, so seizures in sleep might be confused with other sleep disorders such as tooth grinding, drowsy, moaning and sleepwalking (Figure 2). This situation causes difficulties in the diagnosis and treatment of epilepsy.

![Figure 2: The underlying causes and consequences of epileptic seizures in sleep are shown.](image-url)

Video electroencephalography (vEEG) recordings are required to detect episodes of epilepsy in sleep and differentiate from other sleep disorders. In the method, brain waves are recorded all night and the patient’s movements and behaviors in sleep are filmed. EEG is the most valuable method for the diagnosis of epilepsy, classification of patients with epilepsy, selection of appropriate treatment/prognosis and follow-up of the disease. In addition, ictal/peri-ictal arrhythmia types detected during vEEG recordings such as tachycardia, bradycardia and asystole may give an idea about the localization of the epileptic focus. It has been shown that cardiac pathology is...
associated with 25% of patients with epileptic seizures [36]. Accordingly, the presence of ECG recordings during routine EEG imaging may be a practical and early solution in the diagnosis and treatment plans of patients diagnosed with epilepsy or in whom EEG is requested with a preliminary diagnosis of epilepsy. Therefore, in several centers, recordings of cardiac variability are taken by using simultaneous ECG electrodes during routine EEG recording [37].

**Conclusion**

Informing the patient ictal period of the seizure to the relatives immediately may help points below:

- Negative consequences of epileptic seizures will be prevented.
- The quality of life of the patients will be improved.
- Increased costs due to non-prevention of seizures will be prevented and financial gain will be provided.

As suggestion, the points below might be offered for emergency critical care of epilepsy and other diseases:

- With the planned device, relatives of patients with heart diseases might be informed and brain waves may be analyzed.
- A system measuring respiratory function as well as ECG and EEG might be developed with a much more powerful device. With this system, not only heart diseases but also respiratory disorders may be targeted in epilepsy patients.
- In order to convince the patient and the relatives of the patient, sudden unexpected death in epilepsy; SUDEP” concept might be applied to raise awareness.
- This device could easily be used in diseases/syndromes (such as long QT syndrome, short QT syndrome).

Given the severity of seizures and sudden death in epilepsy patients, EEG and ECG recordings, especially during sleep, are crucial. It is assumed that the simultaneous seizure of the records to relatives of the patient/physician might prevent worsening of the course of epilepsy and/or prevent sudden death. In view of all the situations, a need for devices providing simultaneous alert transmission (eye patch, etc.) stands out.

Until recently, seizure warning devices have been constructed with studies on seizure prediction. It is known that seizure warning devices have a transmission system via movement. However, the devices are inadequate to detect epileptic seizures in which the patient does not have any body movement during sleep. In this case, it is assumed that the planned device will be effective in measuring EEG/ECG parameters in determining sleep seizures and thus preventing sudden death.

**Bibliography**


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