DOI:10.4274/tnd.2019.56254
Turk J Neurol 2019;25:109-116

Review / Derleme

Seizures with Autonomic Symptoms and Sudden Unexpected Death in Epilepsy (SUDEP)

Otonom Semptomlu Nöbetler ve Epilepside Beklenmeyen Ani Ölümler (SUDEP)

Rabia Gökçen Gözübatık Çelik[1], Çiğdem Özkara[2]

[1]Istanbul Bakirkoy Dr. Mazhar Osman Mental Health and Neurological Diseases Training and Research Hospital, Clinic of Neurology, Istanbul, Turkey

[2]Cerrahpasa Faculty of Medicine, Department of Neurology, Istanbul, Turkey

Abstract

The autonomic nervous system, formerly the vegetative nervous system, is a division of the peripheral nervous system that supplies smooth muscle and glands, and thus influences the function of internal organs. The hypothalamus is the main center responsible for the autonomic functions in the central nervous system. Other anatomical structures can be listed as cingulate gyrus, amygdala, paraventricular nucleus. The central autonomic network involved in the pathophysiology of autonomous epilepsy is represented in the non-dominant hemisphere. Autonomic seizures are shown in temporal and insular lobe epilepsies commonly. Blood pressure changes, heart rhythm disturbances (tachycardia, bradycardia, arrhythmia, asystole), respiratory changes (apnea, hypopnea, bradypnea), salivation increase, vomiting/retching, pilo-erection, sweating increase, mydriasis/miosis, spitting, water drinking, genital automatism, intestinal motility disorders are clinical signs in autonomic epilepsy. SUDEP (sudden unexpected death in epilepsy) is defined as sudden, unexpected, nontraumatic, non-drowning death in an individual with epilepsy, witnessed or unwitnessed, in which post-mortem examination does not reveal an anatomical or toxicological cause of death. The vast majority of SUDEPs occur in the aftermath of a generalised tonic-clonic seizure. It's responsible for 17% of deaths in epileptic patients. Witnessed recorded SUDEP cases involve postictal cardiorespiratory dysfunction with failure of arousal. It is reported that the threshold value of SpO_2 is 80-86% for the risk of sudden death. While patients who have had seizures remotely and have had successful epilepsy surgeries also carry the SUDEP risk, the most important risk factor is a history of generalised tonic-clonic seizures.

Keywords: Autonomic seizures, epilepsy, SUDEP

Öz

Otonom sinir sistemi bilinçli kontrolün olmadığı bir sistemdir. Sempatik ve parasempatik olmak üzere iki bölümden oluşur. Santral sinir sisteminde otonom sistemden sorumlu ana merkez hipotalamustur. Otonom nöbet semiyolojisinde rol alan diğer anatomik yapılar singulat girus, amigdala, paraventriküler nükleustur. Otonom epilepsilerin fizyopatolojisinde yer alan santral otonom ağ non-dominant hemisferde temsil edilirken otonom bulgular temporal ve insuler lob epilepsilerde sıktır. Hastalarda klinik olarak; kan basıncı değişiklikleri, kalp ritim bozuklukları (taşikardi, bradikardi, aritmi, asistoli), solunumsal değişiklikler (apne, hipopne, bradipne), tükürük artışı, kusma/öğürme, pilo-ereksiyon, terleme artışı, midriazis/miyozis, tükürme, acil miksiyon, su içme, genital otomatizm, barsak motilite bozuklukları nöbet öncesi/sırası/ve sonrasında görülebilen otonom semptomlardır; temporal lob epilepsisinde daha sıktır. Otonom nöbetli hastaların ani ölüm riski de diğer epilepsi hastalarına göre daha fazladır. Epilepside ani beklenmedik ölüm (SUDEP); epilepsi hastasında boğulma, travma ve status epileptikus dışlandıktan sonra; ani, beklenmedik, görgü tanığı ya da ölüm sırasında nöbet kanıtı olsun olmasın meydana gelen; postmortem incelemelerde ölüme neden olan yapısal veya toksik bir sebep saptanmayan ölüm olarak tanımlanır; epilepsideki ölümlerin %17'sinden sorumludur. SUDEP'nin etiyolojisinde; altta yatan postiktal kardiyorespiratuvar disfonksiyon olduğu öne sürülür. Ani ölüm riski için SpO_2 eşik değerinin %80-86 olduğu bildirilirken, iktal olaylar, otonom sistemin kronik aktivasyonu nedeniyle ölümcül aritmileri tetiklerler. Özellikle uykuda olan jeneralize tonik klonik nöbetler, dirençli epilepsiler SUDEP ile ilgilendirilen risk faktörlerindendir. Kardiyorespiratuvar bulgulu otonom semptomlu nöbetlere bu risklere katkıda bulunabileceği açısından dikkat edilmelidir.

Anahtar Kelimeler: Otonom nöbetler, epilepsi, SUDEP

Address for Correspondence/Yazışma Adresi: Rabia Gökçen Gözübatık Çelik MD, Istanbul Bakirkoy Dr. Mazhar Osman Mental Health and Neurological Diseases Training and Research Hospital, Clinic of Neurology, Istanbul, Turkey
Phone: +90 554 937 00 87 E-mail: gokcen3@hotmail.com ORCID: orcid.org/0000-0002-8186-8703
Received/Geliş Tarihi: 22.10.2018 **Accepted/Kabul Tarihi:** 15.02.2019

Introduction

The Autonomic Nervous System and Cerebral Function of the Autonomic Nervous System

The autonomic nervous system is a system that regulates the physiologic processes of human beings without conscious control. It consists of two systems that work as antagonists to each other, namely the sympathetic and parasympathetic systems. The terminal neurons of the sympathetic and parasympathetic system are in the ganglions. Ganglions, consisting of a large number of nerve cells, are located outside the central nervous system (CNS). Most internal organs can be innervated from both sympathetic and parasympathetic fibers. Stimulation of sympathetic fibers increases heartbeats and cardiac output, reduces bowel motility, relaxes the bronchi and gallbladder, and causes contraction in the sphincters of the digestive tract. Stimulation of the parasympathetic fibers has an antagonist effect on the body.

The main center responsible for the autonomic nervous system is hypothalamus in the CNS. The hypothalamus is considered to be an upper center that controls lower autonomic centers, especially in the brain stem and spinal cord. The hypothalamus coordinates the responses from external and internal inputs, visceral and pain afferents, humoral signals, circadian states, limbic system, and cognitive states through this system. It also provides body homeostasis by controlling neuroendocrine and somatomotor system responses (sphincter, respiratory motor neurons).

Parasympathetic responses are induced by stimulating the anterior part of the hypothalamus, and sympathetic responses arise with the stimulation of the posterior part. The vasopressor, vasodilator, cardioaccelerator, cardio-decelerator, and respiratory areas forming the body autonomic system are found in the reticular formation in the brain. It is suggested that the main control between these systems is provided by the connections between the ascending and descending pathways in the CNS. The neurons involved in the main control of these connections are found in the thoracolumbar segment of the sympathetic system and in the craniosacral segment of the parasympathetic system (1).

Apart from the hypothalamus, many central connections play a role in autonomic functions. These can be summarized as the insular cortex, anterior cingulate cortex, amygdala, preoptic area, periaqueductal area, parabrachial nucleus, solitary tract nucleus, ventrolateral medulla, and medullary raphe nucleus (Table 1) (1).

The Autonomic Nervous System and Epilepsy

Epilepsy is a chronic neurologic disorder caused by increased excitability of nerve cells in the brain and that may require prolonged or lifelong treatment. The International League Against Epilepsy described epileptic seizures as a temporary symptom and/or finding due to excessive and synchronous activity of neurons in the brain, and epilepsy as a brain disorder that may cause epileptic seizures along with neurobiologic, cognitive, psychological, and social consequences (2,3). Epileptic seizures are based on hyperexcitability due to hypersynchronous and repetitive activation of neurons (4,5).

Seizures have different semiologic characteristics related to the affected area in the brain. In this review, it is aimed to examine the conditions with marked autonomous findings.

The anatomic structures involved in autonomic seizure semiology are usually the cingulate gyrus, amygdala, paraventricular nucleus, and lateral hypothalamus. Cardiovascular, respiratory, gastro-intestinal, cutaneous, pupillary, genital, and urinary system findings may be observed during an autonomic seizure (6). The clinical autonomic symptoms that can be seen before, during or after seizure include changes in blood pressure, heart rhythm disturbances (tachycardia, bradycardia, arrhythmia, asystole), respiratory changes (apnea, hypopnea, bradypnea), hypersalivation, vomiting/retching, piloerection, excessive sweating, mydriasis and myosis, spitting, urgent urination, drinking water, and bowel motility disorders (7,8).

Nowadays, with the help of functional imaging studies, the presence of many networks with different features has been determined in the brain and it is understood that the brain performs its functions through these networks (9). The central autonomic network involved in the pathophysiology of autonomic epilepsies is mainly represented in the non-dominant hemisphere, and autonomic findings are common in temporal lobe epilepsies (TLE) and insular lobe epilepsies (10).

A. The Cardiopulmonary System and Autonomic Epilepsy

The underlying pathologies related to the cardiac and pulmonary system in patients with epilepsy may cause further

Table 1. Central components of the autonomic nervous system

Anatomic structures	Functions
Insular cortex	Visceral pain and temperature sensation integration
Anterior cingulate cortex	Modulation of autonomic responses including the goal-directed behaviours
Amygdala	Adjusting the intensity of sensory stimulation
Preoptic area of the hypothalamus	Homeostasis, integrating endocrine and behavioural responses to provide immune modulation
Periaqueductal gray matter	Integrate responses for autonomic somatic and pain modulation
Parabrachial nucleus	Sending somatic and visceral inputs to the hypothalamus, thalamus, and amygdala
Solitary tract nucleus	Controlling taste and visceral afferents and providing reflex response to other areas
Ventrolateral medulla	Vasomotor control of blood pressure and the respiratory system
Medullary raphe	Control of the sympathetic (vasoconstriction) and thermoregulation in the skin

symptoms due to deterioration during seizures. However, autonomic changes such as cardiac arrhythmia, asystole, bradypnea-apnea, hyperventilation, and blood pressure changes may also occur during the seizure without any underlying pathology (11).

Epileptic seizures are often among the differential diagnosis in patients with cardiac diseases and syncope (especially convulsive syncope). Therefore, studies investigating these similarities are available in the literature starting from the 1970s. In one of these studies, cardiac arrhythmia was found in 20% of patients who presented to the neurology department with a possible diagnosis of epilepsy (12).

Convulsive syncope is a frequent clinical condition that occurs due to autonomic dysfunction and that is mistaken for epileptic seizures. The term "convulsive syncope" was first described as "slow pulse, dizziness, and mild epileptic attacks" (13), and it was later named as Adams-Stokes syndrome. The prevalence of convulsive syncope was reported as 0.03% in a study of blood donors (14). In addition, cardiac monitoring during long-term video-electroencephalography (VEEG) also contributes to the exclusion of psychogenic seizures. In studies, it was found that sympathetic tone was significantly higher in epileptic seizures than in non-epileptic seizures. Therefore, detailed VEEG and ECG monitoring play an important role in the differential diagnosis (15,16).

Although there are different rates in the literature, heart rate varies between 38-100% during epileptic seizures. In a meta-analysis, the prevalence of ictal tachycardia was reported as 82%. According to this study, no significant difference was observed in the presence of ictal tachycardia for focal (64%) and generalized seizures (71%), and cardiac rhythm changes were determined, especially in temporal seizures (17). Although younger case samples (average 26 years) were frequently shared in the literature, it was reported in another meta-analysis that the tendency of heart rhythm variability was significant for those age more than 30-40 years (18,19).

The pathophysiology under autonomic involvement in patients with epilepsy has been investigated in many studies, but no definitive conclusion has been reached. It has been reported that epilepsy is associated with sympathetic activation, vagal activation, sympathetic-vagal suppression, and vagal suppression (which is a risk factor for arrhythmias), that some antiepileptic drugs (AED) could lead to cardiac arrhythmia and affect cardiac excitability and conduction, and that AEDs contributed to the impaired autonomic cardiac effect (20,21). In particular, the detection of lower vagal tone in refractory epilepsies supports this condition (22). Animal studies also showed that vagal nerve activity was suppressed during seizures, and cardiac inhibition was observed in the postictal period by disabled baroreflexes (21).

Selective activation of parasympathetic or sympathetic centers by electrical dissipation of seizures may explain the ictal cardiac changes. It is thought that changes in ictal heart rate are not due to seizure-related physical or psychological effects, but are due to underlying autonomic system disorders. Heart rate variances are more frequently observed especially in refractory epilepsies. In 64% of generalized seizures and 71% of focal seizures, tachycardia is observed during seizures. Bradycardia is a less common autonomic symptom and is often detected in children (23).

According to the hypothesis of lateralization, bradyarrhythmias are observed more frequently on the left side and tachyarrhythmias on the right side (24). Electrical stimulation of the left insular cortex triggered bradycardia caused by a parasympathetic mediated pathway, and stimulation of the right insular cortex triggered tachycardia, thus although the dominance of the right hemisphere has been claimed in cardiac sympathetic regulation, this hypothesis has not been proven due to different lateralization findings in many case reports in the literature (25).

In another study examining nine seizures detected in deep stereotactic VEEG, the authors found that the ictal activity of the anterior hippocampus and amygdala were closely related to tachycardia; however, they found that it was independent of ictal insula activity. Although there is no change in cardiac rhythm in generalized or focal seizures, an earlier and faster rhythm may be observed, especially in TLE originating from the right hemisphere. The underlying mechanism is not clear, but sympathetic hyperactivity and decrease in parasympathetic tone are among the hypotheses. It has been argued that there is no value of lateralization for ictal tachycardia (23).

Iodic asystole is a fatal, autonomic symptom encountered during seizures. In a meta-analysis, the rate of ictal asystole was found as 0.22-0.4% and it was reported that this rate increased to 16% during VEEG recordings in refractory epilepsy. Although central autonomic dysregulation plays a role in the pathophysiology of this finding, mostly in focal, left-sided TLE, it may be associated with neuronal networks in patients with chronic epilepsy. In addition, the presence of cardiac pathology and female sex are significant risk factors for ictal asystole in patients with newly diagnosed epilepsy, and a 30% risk of recurrence of ictal asystole in these patients was emphasized (26).

Blood pressure changes are also observed during seizures. In one study, ictal hypertension was observed at a rate of 26.3% and hypotension at a rate of 8.7%, 60% of these patients had temporal onset seizures, and both systolic and diastolic blood pressures significantly increased in the ictal and pre-ictal periods. Ictal bradycardia was recorded in a patient with temporal seizure (27).

In conclusion, the underlying mechanisms of ictal cardiac arrhythmias are still unclear and most patients have no underlying cardiac risk factors. Ictal arrhythmias are often detected incidentally during simultaneous VEEG and ECG monitoring. Many studies have been conducted to date and many studies are ongoing to improve the early diagnosis and clinical awareness of this potentially fatal condition. Potential genomic biomarkers identified for this purpose and channelopathies that play a role in epileptogenesis and cardiorespiratory pathophysiology (i.e. neurocardiac genes) are among the most promising developments. There is currently no clinical guideline for ictal bradycardia/asystole, and seizure control, indicating the type of epilepsy syndrome or permanent pacemaker implantation. However, the implantation of pacemakers in the treatment of ictal asystole, a potentially fatal risk, is reported as a common recommendation by most investigators, including patients who are clinically stable (28).

Another system that plays a role in autonomic regulation is the pulmonary system. In autonomic seizures, findings related to the pulmonary system such as apnea and hypopnea are also seen. The best known of these is peri-ictal apnea and its prevalence is

47%. Patients are generally unaware of apnea prior to seizure, so a polysomnographic record should be made in the diagnosis (29). The frequency of peri-ictal apnea increases with focal seizures or automatic motor focal seizures with impaired consciousness. As in the cardiac system, pulmonary autonomic disorders are more common in TLE. It is frequently associated with severe apnea and hypoxia for longer than 60 seconds (SpO_2 <75%) (29).

B. Sudden Unexpected Death in Epilepsy (SUDEP)

SUDEP is defined as sudden, unexpected death in a patient with epilepsy that is not caused by drowning, trauma or status epilepticus, regardless of whether there is an eyewitness and evidence of seizures. No structural or toxic cause of death is detected in postmortem examinations.

Patients with epilepsy have higher mortality rates than the general population. Among the known causes of death are seizure-related complications such as status epilepticus, accidents, drowning, suicide and pneumonia, and SUDEP is another leading cause of death due to epilepsy (30). Studies have shown that the incidence of SUDEP is 27 times higher in young adult patients with epilepsy (20-45 years) than in control populations (31), and another study in the United States found that the second most important neurologic cause of deaths after stroke was SUDEP (32). The annual incidence of SUDEP in patients with chronic epilepsy was 1-2/1000 patients in cross-sectional studies and the incidence of SUDEP in newly diagnosed epilepsy is estimated to be 1/10,000 patients per year. In patients with refractory epilepsy, a higher incidence (500 times patient/year) of SUDEP has been reported. The incidence in children is lower than in other age groups (approximately 0.2/1000 patient-year) (33). In 2017, a systematic review and practice guide developed by the American Academy of Neurology and the American Epilepsy Society found that SUDEP affected an average of 4500 children and 1/1000 adults each year, according to intermediate evidence (Level B). This guideline also reports that major risk factors for SUDEP are the presence and frequency of generalized tonic-clonic seizures (34).

There are definite, probable, possible, near-SUDEP, and not SUDEP definitions for SUDEP (35):

- Definite SUDEP: sudden, unexpected, witnessed or unwitnessed, nontraumatic and nondrowning 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 reveals no cause of death.
- Probable SUDEP: same as Definite SUDEP but without autopsy.
- Possible SUDEP: a competing cause of death is present.
- Near-SUDEP: a patient with epilepsy survives resuscitation for more than 1 h after a cardiorespiratory arrest that has no structural cause identified after investigation.
- Not SUDEP: a clear cause of death is known.
- Unclassified: incomplete information available; not possible to classify.

If a concomitant condition other than epilepsy is identified before or after death and if the death may have been due to the combined effect of both conditions, this is called "SUDEP Plus". The SUDEP classification is prefixed to this term such as "Definite SUDEP Plus" or "Probable SUDEP Plus".

The etiology of SUDEP is not yet known. The four main mechanisms with relatively strong evidence leading to SUDEP are cardiac dysfunction, pulmonary dysfunction, brainstem stimulation system dysfunction, and neurotransmitter and neuromodulator system dysregulation. Although the left insular region pathology associated with autonomic dysfunction is hypothesized anatomically, several gene mutations have been identified that genetically increase the risk of SUDEP and contribute to the pathophysiology (33,36,37,38).

Since the initial definition of cardiovascular dysfunction, it has been recognized as the leading mechanism for SUDEP. Chronic, recurrent activation of the autonomic nervous system in patients with epilepsy may also lead to sympathovagal disorder, which may eventually induce lethal arrhythmias during or between ictal events. Various types of cardiac arrhythmias occur during or after seizures. Sinus tachycardia is the most common, but supraventricular/ventricular tachycardia, bradycardia, atrioventricular block, and asystole are the other observed arrhythmias (11,39). The incidence of tachyarrhythmias during or after the seizure was 57% and 2%, respectively (16,17). In another study, ictal asystole was observed in 0.27% of patients during video electrographic monitoring (39). In a large population study in terms of risk of cardiac death, it was observed that the mortality risk increased in patients with OTC >470 or <393 msec in ECG. In seizure-recording studies performed with VEEG, it was shown that OTC and SPO_2 were independent risk factors for SUDEP. Although different opinions have been reported, it is hypothesized that these two parameters may guide in detecting patients with epilepsy at risk of sudden death (11). The presence of generalized tonic clonic seizure (GTCS) is one of the major risk factors for the risk of sudden death in all patients with epilepsy. Regardless of GTCS, 1-2 seizures per year without GTCS increase the risk of SUDEP by 5-fold and 3 or more seizures by 15-fold (40). Low vagal and high sympathetic tonuses are known to be serious risk factors for cardiovascular disease and SUDEP, in particular, the presence of bradycardia and arrhythmias during interictal sleep (22). Therefore, studies have shown that the risk of sudden death of patients with epilepsy under vagal nerve stimulation (VNS) treatment has decreased significantly in the long term (41). Reducing seizure duration by decreasing the severity of respiratory, cardiac, and cerebral dysfunction with early intervention reduces the risk of SUDEP (11,42,43).

Pulmonary dysfunction was not considered as a mechanism for SUDEP in the initial studies. In a study conducted in 1996 using respiratory and continuous VEEG monitoring, it was found that 59% of patients had apnea and 35% of patients oxygen desaturation (55-83%) during seizures (44). Obstructive and mixed apneas reported during seizures have been shown to cause cardiac repolarization abnormalities (long or short QT intervals) as a result of ictal hypoxemia (45). Oxygen desaturation correlates with the duration of the seizure and postictal immobility. Oxygen saturation may decrease more than 33% in all seizures, whether generalized or not (46). Therefore, SPO_2 monitoring is very important during seizure recording and the SPO_2 threshold value is reported as 80-86% for the risk of sudden death in studies (11). In a retrospective study (MORTEMUS) of the Epilepsy Monitoring Unit that included

93,791 patients and 11 definite cases of SUDEP, sudden death was found to be associated with respiratory dysfunction, bradycardia, and arousal dysfunction in postictal periods. The authors also observed transient tachyarrhythmias in some patients with SUDEP, but they stated that these were followed by bradycardia and asystole (47). The arousal system in the brain is located in the brainstem and is a nucleus producing a group of neurotransmitters that controls the alertness and consciousness with the effects of serotonin, norepinephrine, histamine, dopamine, and acetylcholine (48,49). In research in patients with epilepsy based on the study of serotonergic system-related animal models, selective serotonin re-uptake inhibitors have been found to reduce postictal oxygen desaturation in focal seizures but not in generalized seizures (50). The loss of protective reflexes such as coughing and movement in postictal periods exposes patients to increased risk of death due to airway obstruction and aspiration (49). The brainstem stimulation system also has neurons that control cardiovascular, respiratory, and autonomic neurons. Therefore, spread of seizures to the brainstem may also affect the function of these three systems.

Nowadays, biomarker research is underway for the diagnosis of SUDEP. These markers include other biomarkers and gene polymorphisms of nocturnal seizures, prolonged post-ictal suppression, ictal/post-ictal hypoxemia, mood disorders, and serotonergic dysfunction (51).

Serotonergic neurons are central chemoreceptors that stimulate the airway and cause waking from sleep in response to hypercapnia. They are also important in preventing asphyxia by airway closure during postictal apnea. Therefore, serotonergic therapies have the potential to reduce the risk of SUDEP (38). Other brainstem neurotransmitters and neuromodulators may also play an important role in the pathophysiology of SUDEP. There is a significant relationship between increasing and decreasing levels of serotonin, noradrenaline, acetylcholine, and glutamate-secreting brain stem neurons and their functions. It is thought that these brainstem neurons are part of the ascending arousal system associated with awakening control and also regulate all respiratory and carbon dioxide chemoreceptors. Adenosine is another neurotransmitter that may pose a risk for SUDEP. Caffeine, an adenosine receptor agonist, decreases the seizure threshold by increasing cortical excitability (52).

GABA and opioid receptor activation inhibit cardiorespiratory control centers by inhibiting respiration and may pose a risk for SUDEP. Decreased projections during seizures and activation of these receptors with medication or recreational drugs (including alcohol) may increase the likelihood of postictal cardiorespiratory inhibition. In conclusion, although optimal pharmacologic targets remain unclear, drugs that modulate serotonin, adenosine or other neurochemical systems are thought to help prevent SUDEP.

Many genetic mutations have been reported to be associated with an increased risk of SUDEP through multiple mechanisms, including increased severity of epilepsy, increased postictal parasympathetic activity, altered autonomic function, prolonged suppressed levels of consciousness after seizure, and impaired brainstem cardiorespiratory control (38,53,54). Mutations that cause epileptic encephalopathies (e.g. Dravet's syndrome, the *SCN1A* gene) and cardiac channelopathies (e.g. long QT syndrome) are examples of these genes (55,56). In children, SUDEP is associated with all of the aforementioned risk factors and has similar clinical and pathologic features with sudden infant death syndrome (SIDS) and sudden unexplained death in childhood. All three conditions usually occur during sleep in male patients, and the prone position is known as a risk factor. The hypothesis mechanisms of SIDS include heart, respiratory, and arousal dysfunction such as SUDEP and are associated with defects in the serotonin system similar to SUDEP (38).

Other risk factors for SUDEP include early-onset epilepsy, young age, male sex, the prone position, nocturnal seizures, mental retardation, drug-resistant seizures, frequent seizures, rapid drug change, low antiepileptic drug levels, psychotropic drug use, and alcohol or substance abuse (11,57).

The first step among the various strategies for preventing SUDEP is to raise awareness of this situation. In 2014, the SUDEP awareness survey, which included 1150 American and Canadian neurologists, revealed that less than 7% of neurologists were able to consider SUDEP and that 11.6% had no information about SUDEP (58). In another study by Canadian pediatricians, it was found that only 33% of physicians had heard of SUDEP (37,59). For this reason, increasing awareness of SUDEP and encouraging studies are the primary prevention methods. Better control of seizures with options such as VNS, epilepsy surgery, phrenic nerve electrode, and diaphragmatic pacer may prevent SUDEP, but it should be remembered that these are patient-specific options (60). In addition, epilepsy, a chronic disease, continues to pose a risk of SUDEP in patients with seizures in remission. This also applies to patients who have undergone successful epilepsy surgery. Cases with generalized seizures in the pre-operative period and those with recurrent disease in the late period carry more risk for SUDEP (61,62). Several studies in animals and humans showed that serotonin dysfunction increased the risk of SUDEP and that treatment that increased serotonin activity had the potential to reduce SUDEP. Among these possible treatments, selective serotonin reuptake inhibitors are the most investigated medical therapies. In the future, other drugs that alter the function of the brainstem stimulation system may create an option to prevent SUDEP. Reporting of deaths due to SUDEP and encouraging postmortem examinations of patients who died of SUDEP will also help to clarify the pathophysiology. However, it should be kept in mind that effective control of seizures is the only effective strategy for preventing SUDEP, and the greatest goal in the future is to reduce both the incidence of SUDEP and the SUDEP threat to patients and their families (57).

C. Other Autonomic Findings Related to Seizure

Other autonomic symptoms observed before and after seizures include vomiting, spitting, coughing, piloerection, sweating, and genital automatism. In the literature, there are many studies in the guiding feature of lateralization and localization of the findings. As in other autonomic findings, these symptoms are also frequently demonstrated in patients with TLE.

Ictopic vomiting is an autonomic symptom associated with anterior temporal and insular involvement that can be seen in focal and generalized seizures. Left mesiotemporal and bilateral insular involvement was found in patients (63), and there was also evidence of epileptiform activity in the right TLE. In addition, ictal vomiting may also occur only with the involvement of

amygdala and other mesial structures without the insula being affected (64). It is hypothesized that the pathophysiology originates from the tonic activation of the cortex and from the inhibition of deactivation in the subcortical structures, the dorsal vagal complex of the reticular area, and central pattern generators (64). In Panayiotopoulos syndrome, which is associated with hyperexcitable central autonomic networks, ictal vomiting is an autonomic symptom (65).

Ictal spitting is a rare (0.3-0.6%) autonomic symptom that frequently indicates non-dominant hemisphere (66). There are cases that indicate dominant hemisphere involvement (67), ictal spitting has been associated with the involvement of operculoinsular cortex and therefore with a bad taste in the mouth in the SEEG study (68), but there are also opposing views (69).

Peri-ictal coughing is also known as an autonomic finding, which is more frequently observed in TLS with non-dominant hemisphere involvement (70).

Piloerection is another rare autonomic finding that can be detected by careful examination before/during seizures. Bilateral piloerection has no localizing or lateralizing value, whereas unilateral piloerection indicates the ipsilateral epileptogenic area (71). Amygdala and insula-related central autonomic network disorder is considered responsible for its pathophysiology. Although it is usually detected in the left hemisphere and especially in TLE (72), it was also observed in a case of medial frontal lobe epilepsy (73).

Unilateral sweating is another rarely seen autonomic symptom. It has been noted that unilateral sweating often occurs in seizures that occur at the ipsilateral left temporal/temporoparietal or posterior insular region (74).

Genital automatisms are more common in men with an increasing prevalence with increasing age. Genital automatisms, which can be considered relatively rare (4-11%), are frequently observed in ipsilateral TLE. They are associated anatomically with the perisylvian cingulate gyrus and paracentral lobe. Genital sexual auras are observed in parietal lobe seizures (75).

Autonomic dysfunction has been reported in seizures associated with autoimmune encephalitis. Autonomic findings such as peritoneal gastrointestinal findings, piloerection, ictal fever, urinary urge, and cough have been reported to be more frequent in the autoimmune antibody-positive group. Ictal fever was associated with voltage-gated potassium channel (VGPC) complex antibody, and pilomotor seizures were associated with gamma aminobutyric acid antibody (GABAAR) (76). For this reason, autoimmune encephalitis should be considered in patients with epilepsy with status epilepticus and/or psychiatric disorders and peri-ictal autonomic seizures.

AEDs are used for the treatment of epilepsies with autonomic symptoms. However, as a result of this pathophysiology, natural vagus stimulation for seizure control may be proposed as a treatment choice. Physiologic methods such as reducing psychological stress, slow breathing exercises, meditation, music (Mozart K488), forgiveness exercises, laughing, positive emotion and social contact, exercise, nutrition (omega 3, fasting, probiotics), massage, washing the face with cold water, and lying on the right side can be counted among them (77). When using VNS therapy in resistant seizures, it can be thought that it may be useful in this respect.

Frequent and prolonged seizures increase the risk of SUDEP. Therefore, the choice of correct and effective treatment in patients with epilepsy is important to reduce this risk. However, some AEDs may cause sudden death due to their cardiac adverse effect profiles. The best-known ones are carbamazepine (CBZ) and intravenous phenytoin, which have severe cardiotoxic adverse effects such as bradycardia, sinus arrest, and atrioventricular block (21,78). Lamotrigine (LTG) and phenobarbital are other known risky antiepileptics. However, recent publications indicate that CBZ given as monotherapy does not increase the risk of SUDEP. In patients with generalized tonic clonic seizures, LTG monotherapy may cause fatal arrhythmias due to a genetic predisposition, especially in women (79,80,81), but no such symptoms have been found in symptomatic or cryptogenic epilepsies. In addition, carbamazepine, phenytoin, and lamotrigine, which are sodium channel blockers, are known to cause a paradoxic increase in seizure frequency in channelopathy-induced diseases such as Dravet syndrome and generalized epilepsy with febrile seizures plus, and they are also known to have negative effects on myoclonus in juvenile myoclonic epilepsy. Therefore, it would be appropriate not to use the therapies mentioned in patients with risk of SUDEP and those with a diagnosis of genetic epilepsy (idiopathic generalized epilepsy). In cases where these antiepileptics are used due to necessity, care should be taken to use these drugs as a monotherapy and not to use them in conjunction with other cardiotoxic drugs; however, in general, there is no significant relationship between SUDEP and AEDs (82).

In conclusion, autonomic symptoms cannot be observed frequently in seizure semiology. Their lateralization and localization values are not clear. Some autonomic signs may be associated with certain autoantibodies. It should be kept in mind that patients with autonomic seizures with cardiopulmonary symptoms may have a higher risk of SUDEP than other patients with epilepsy. Early diagnosis of symptoms and increased clinical awareness may be life-saving for patients.

Ethics

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Ç.Ö., Concept: Ç.Ö., Design: Ç.Ö., R.G.G.Ç., Data Collection or Processing: R.G.G.Ç., Analysis or Interpretation: R.G.G.Ç., Ç.Ö., Literature Search: R.G.G.Ç., Writing: R.G.G.Ç., Ç.Ö.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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