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Sudden unexpected death in epilepsy (SUDEP) – risk factors

Nagła nieoczekiwana śmierć w padaczce (SUDEP) – czynniki ryzyka

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Abstract

Epilepsy is one of the most common chronic brain disorders, characterised by recurrent unprovoked seizures. It affects over 50 million people worldwide, irrespective of their socio-demographic status. The most common cause of death in both children and adults suffering from this disease is "sudden unexpected death in epilepsy" (SUDEP). It is defined as "the sudden, unexpected, witnessed or unwitnessed, non-traumatic, and non-drowning death in patients with epilepsy, with or without evidence for a seizure, and excluding documented status epilepticus, in which post-mortem examination does not reveal a toxicological or anatomical cause for death". The aim of this review is to expand knowledge about the most common risk factors for this fatal complication of epilepsy, which include the presence of generalised tonic-clonic seizures, high seizure burden, nocturnal tonic-clonic seizures, and early epilepsy onset, as well as disease duration exceeding 15 years. Some uncertain risk factors include male gender and polytherapy; however, the latter is sometimes considered a protective factor of SUDEP, as it enables individuals to overcome the burden of generalised tonic-clonic seizures. A better understanding of those factors could help implement more effective preventive measures, which would lower the incidence of SUDEP.

Keywords: seizures, epilepsy, sudden unexpected death in epilepsy, SUDEP

Streszczenie

Padaczka należy do najczęstszych przewlekłych zaburzeń pracy mózgu, charakteryzuje się występowaniem nawracających, samoistnych napadów. Dotyka ponad 50 milionów osób na całym świecie, niezależnie od ich statusu społeczno-demograficznego. Najczęstszą przyczyną śmierci zarówno u dzieci, jak i dorosłych cierpiących na tę chorobę jest nagła nieoczekiwana śmierć w padaczce (*sudden unexpected death in epilepsy*, SUDEP). Jest ona definiowana jako „nagła, nieoczekiwana, w lub bez obecności świadków śmierć nieurazowa i nie przez utonięcie u pacjentów z padaczką, z lub bez dowodów na wystąpienie napadu, z wykluczeniem udokumentowanego stanu padaczkowego, w której badanie pośmiertne nie ujawnia toksykologicznej ani anatomicznej przyczyny śmierci". Celem niniejszego przeglądu jest poszerzenie wiedzy na temat najczęstszych czynników ryzyka tej śmiertelnej komplikacji padaczki, którymi są: obecność uogólnionych napadów toniczno-klonicznych, wysoka częstość napadów, nocne napady toniczno-kloniczne, wczesny początek padaczki oraz czas trwania choroby powyżej 15 lat. Do niepotwierdzonych dotąd czynników ryzyka zaliczają się płeć męska oraz stosowanie wielu leków w leczeniu padaczki, choć to ostatnie bywa czasami uznawane za czynnik ochronny w przypadku SUDEP, ponieważ pozwala uwolnić pacjentów od obciążenia związanego z uogólnionymi napadami toniczno-klonicznymi. Lepsze zrozumienie tych czynników mogłoby pomóc we wprowadzeniu skuteczniejszych metod zapobiegania, a w rezultacie obniżyć wskaźnik SUDEP.

Słowa kluczowe: drgawki, padaczka, nagła nieoczekiwana śmierć w padaczce, SUDEP

INTRODUCTION

Over 50 million people worldwide suffer from epilepsy, regardless of their socio-demographic status (Chen et al., 2023). To diagnose epilepsy, at least two unprovoked seizures occurring more than 24 hours apart are required. However, it is worth noting that up to 8% of individuals have at least one seizure in their lifetime (Chen et al., 2023). The most common diagnostic test used to diagnose epilepsy is electroencephalogram. Multiple types of seizures can be distinguished in epilepsy, including both focal and generalised. This work focuses on a fatal complication of this disorder – sudden unexpected death in epilepsy (SUDEP). A clear underlying pathological aetiology of this event is yet to be determined (Mesraoua et al., 2022). Overall, trauma, drowning, and anatomical and toxicological causes of death are necessary to be ruled out during post-mortem examination to diagnose SUDEP (Saetre and Abdelnoor, 2018), and SUDEP can be subclassified into definite, probable, and possible categories (Abdel-Mannan et al., 2019). Awareness of this complication is essential, as it is the most common epilepsy-related cause of death in both adults and children (Whitney et al., 2019a). Since the main risk factor is the presence of frequent and uncontrolled generalised tonic-clonic seizures, it is worth considering whether in some cases this fatal complication could be preventable.

The main purpose of this paper is to analyse the available literature with the aim of highlighting the most common SUDEP risk factors.

MATERIALS AND METHODS

A literature search was conducted for this systematic review, using the PubMed and Google Scholar electronic databases. Only these two databases were used, as the aim was to focus on the most accessible journals and search engines. No article types were excluded. No specific language was set, but ultimately only works with English abstracts were included, one of which was written in German. A time filter was set to include works published within the past five years. The keywords used were: "SUDEP + rates" OR "SUDEP + statistics" OR "SUDEP + epidemiology" OR "SUDEP + risk factors" OR "SUDEP + etiopathology" OR "SUDEP + age" OR "SUDEP + age onset" OR "SUDEP + comorbidities" OR "SUDEP + prevention" OR "SUDEP + serotonin" OR "SUDEP + serotonin + prevention" OR "SUDEP + Holter ECG" OR "SUDEP + mechanism" OR "SUDEP + genetics". On Google Scholar, no particular language filter was applied, the results were sorted by relevance, and no specific type of publication was selected. The keywords used were the same as in the PubMed database. The included works were published between 2016 and 2025.

Inclusion criteria:

1. publications on SUDEP;
2. articles focusing on death in epilepsy, including SUDEP.

Exclusion criteria:

1. articles focusing on epilepsy only, without reference to SUDEP;
2. articles focusing on risk factors for death in epilepsy without including SUDEP.

No restrictions regarding the age, sex, ethnicity etc. of individuals described in the papers were set.

A total of 33 articles were identified and synthesised in this review.

EPIDEMIOLOGY AND PATHOPHYSIOLOGY

The overall risk of SUDEP is estimated to be approximately 1 in 1,000 individuals per year (Wartmann et al., 2024; Whitney et al., 2019). This risk is believed to substantially increase in patients with epilepsy experiencing frequent generalised or focal to bilateral tonic-clonic seizures (Whitney et al., 2023a). Overall, the incidence of sudden death in individuals with epilepsy is 20 times higher than in the general population (Whitney et al., 2023a). All in all, there does not seem to be any particular increase in risk in specific countries, nor is there a significant difference or exclusion by age group or gender. Currently, the exact pathophysiology of SUDEP remains unknown (Maguire et al., 2020), but proposed mechanisms have been described, and certain pathogenic genetic variants and neurogenetic

Gene	Disorder	Meaning
SCN1A, *SCN2A*, *SCN8A*, *NPRL2*, *NPRL3*, *KCNA1*	Developmental and epileptic encephalopathies, e.g. Dravet syndrome	High seizure burden, medically refractory epilepsy, altered heart rate variability
DEPDC5	Familial focal epilepsy with variable foci	High seizure burden
KCNQ1, *KCNH2*, *SCN5A, NOS1AP*, *KCNE1*, *ANK2*, *AKAP9*	Long QT syndrome	Prolonged ventricular repolarisation, predisposition to torsade de pointes, ventricular fibrillation, and sudden cardiac death
SCN5A, *HCN4*, *SCN1B*, *CACNAB2*	Brugada syndrome	Fatal cardiac disease
HCN1, *HCN2*, *HCN4*	Familial sinus bradycardia syndrome	Spontaneous rhythmic activity in neurons causing hyperexcitability of the nervous system
CDKL5	X-linked infantile spasm syndrome	High seizure burden in infants
Expansion of alanine repeats in the homeobox gene *PHOX2B*	Congenital central hypoventilation syndrome	Hypoventilation and impaired ventilatory response to hypercapnia and hypoxaemia during sleep

Tab. 1. Examples of pathogenic genetic variants and neurogenetic syndromes associated with an increased risk of SUDEP (Shao et al., 2025; Whitney et al., 2023b)

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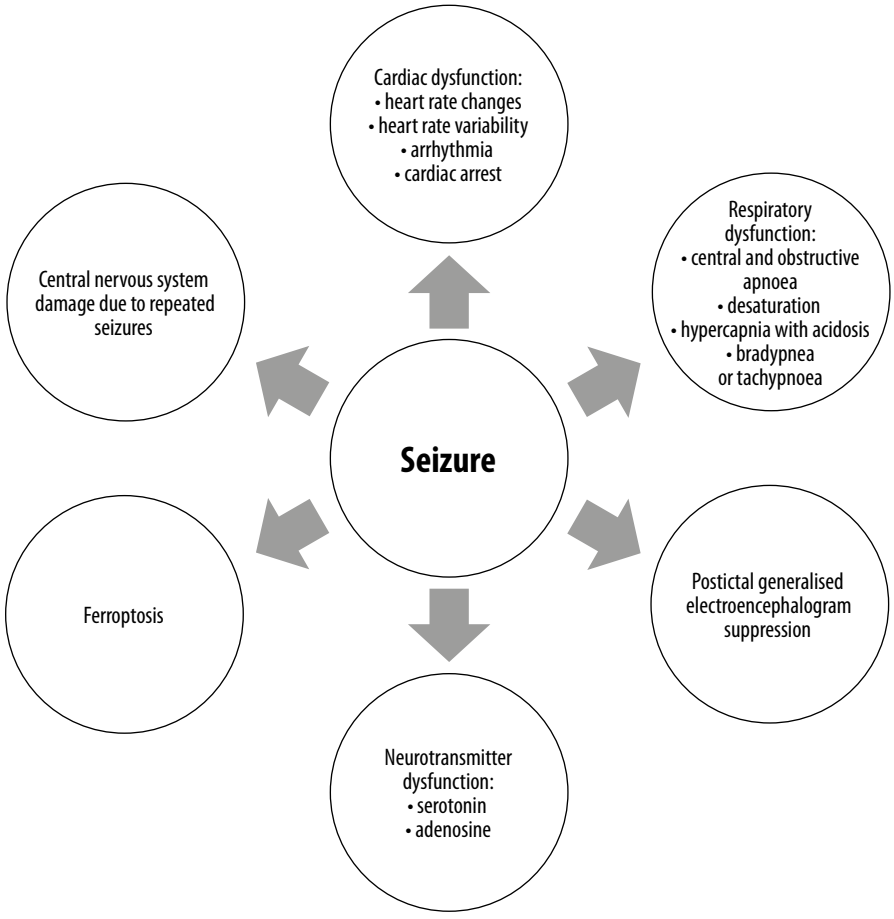

Fig. 1. Current concept of SUDEP (Jiang et al., 2025; Sun et al., 2023)

syndromes correlated with a higher risk of SUDEP can be distinguished (Fig. 1., Tab. 1).

Risk factors

Type of seizures

The authors agree that the occurrence of tonic-clonic seizures, in particular generalised tonic-clonic seizures (GTCS), is the most important risk factor for SUDEP (DeGiorgio et al., 2019; Mesraoua et al., 2022; Sveinsson et al., 2023). The risk is also increased when these seizures remain uncontrolled and occur with a greater frequency (Trivisano et al., 2022). This situation can be observed when patients do not follow the appropriate anti-seizure treatment or suffer from drug-resistant epilepsy. Hence, it is crucial to inform patients and their care partners about the possible risk of SUDEP (Asadi-Pooya et al., 2022; Trivisano et al., 2022).

In addition, as most SUDEP cases occur at night during sleep (Ali et al., 2017), sleep is also considered a risk factor for SUDEP. Some authors link this association to the presence of sleep-onset seizures (Nei and Pickard, 2021; Whitney et al., 2019), while others highlight the importance of the prone position in the immediate aftermath of a GTCS (Ali et al., 2017; Esmaeili et al., 2021; Whitney et al., 2019). Some believe that prone positioning may worsen apnoea following a GTCS and result in impaired arousal, thus contributing to SUDEP (Whitney et al., 2023a).

SUDEP can also be an aftermath of focal seizures, although this is less common (Trivisano et al., 2022). More precisely, in the work of Abdel-Mannan et al. (2019), 53 out of 60 individuals who died from SUDEP had generalised tonic-clonic seizures (88%), and 20 had either simple or partial complex seizures, accounting for 33%. Meanwhile, Sveinsson et al. (2020b) concluded that GTCS in the years preceding SUDEP are associated with a 27-fold increase in risk, and that no excess risk was observed in those with non-GTCS only. Also, Sveinsson et al. (2023) found that post-traumatic epilepsy is associated with a higher risk of SUDEP compared to the genetic aetiology, and that the decisive role seems to be played by the tonic-clonic component of the seizure.

Early onset, long epilepsy duration, and high seizure burden

Other risk factors include early epilepsy onset as well as epilepsy duration, as the longer it lasts, the higher the risk of SUDEP. Overall, greater severity of epilepsy, reflected

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in seizure frequency and seizure type, especially in those with nocturnal GTCS, are predisposing factors to SUDEP (Trivisano et al., 2022). The aforementioned study also noted that the SUDEP rate is classically considered higher in adults than in children, with a greater risk for patients with childhood-onset epilepsy that is chronic and persists into adulthood, but the authors were reluctant to confirm it, suggesting that SUDEP in children tends to be underestimated. Abdel-Mannan et al. (2019) highlighted that the relative risk of SUDEP appears to be 7.7 times higher in patients with early-onset epilepsy (0–15 years) than in individuals with late onset (after 45 years). Multiple studies identify early seizure onset as an independent risk factor for SUDEP (Maguire et al., 2020; Shankar et al., 2017). Interestingly, Sveinsson et al. (2023) suggested that SUDEP risk is highest during the first years after the epilepsy diagnosis. Also, it is worth noting that high seizure burden significantly increases the risk of SUDEP, even having three GTCS per year in comparison to two incidents per year (Abdel-Mannan et al., 2019; Shankar et al., 2017; Whitney et al., 2019).

Age

Overall, the incidence rate of SUDEP is approximately 23 times higher than that of sudden death in the general population of the same age (Saetre and Abdelnoor, 2018). At the same time, Eslami et al. (2021), in their cohort study, concluded that the peak seems to occur in the fourth decade of life, but they admitted that because of the difficulties in making an accurate diagnosis, as well as the likely underestimation of SUDEP occurrence in elderly individuals, more refined classification of SUDEP subgroups is needed to perform epidemiologically relevant comparisons between studies. On the other hand, Trivisano et al. (2022) concluded that the SUDEP rate in children is also unclear, as "it varies depending on the sample population, age range, type of epilepsies, epileptic syndromes or genetic epilepsies, classification systems, follow-up period, diagnosis methods, and recorded cause of death". All in all, it is hard to estimate whether age itself can be considered a risk factor for SUDEP, or whether this risk is instead associated with the duration of epilepsy, since having epilepsy for over 15 years is regarded as a SUDEP risk factor (Maguire et al., 2020).

Lack of antiepileptic drug treatment and polytherapy

As mentioned above, resistance to anti-seizure medications is a predisposing factor for SUDEP (Trivisano et al., 2022). As the high frequency of GTCS is the main risk factor for SUDEP, and the lack of antiepileptic drug treatment leads to a greater number of seizures, it is an indirect risk factor (Shankar et al., 2017). Similarly, non-adherence to prescribed medications – resulting in worsening or loss of seizure control is also considered as indirect risk factor (Shankar et al., 2017). It is worth noting that non-adherence can be both intentional and unintentional (Henning et al., 2019). Also, the risk is significantly increased after not being free from seizures for over five years (Shankar et al., 2017; Whitney et al., 2019).

Abdel-Mannan et al. (2019) concluded that treatment comprising multiple antiepileptic drugs is indeed another SUDEP risk factor, but they acknowledged that they were unable to associate the risk with any specific medication. Still, some authors confidently mention polytherapy as a risk factor (Maguire et al., 2020), while others point out discrepancies in terms of polytherapy being associated with an increased risk of SUDEP (Whitney et al., 2019). Interestingly, there are also studies claiming that polytherapy substantially reduces SUDEP risk (Sveinsson et al., 2020a). All in all, every aforementioned author agrees that achieving freedom from seizures is key to decreasing the risk of SUDEP.

Others: intellectual disability, substance abuse, gender, cardiac problems, lack of nocturnal supervision

The presence of intellectual impairment and developmental delay is associated with medically refractory epilepsy, and an elevated risk of early all-cause mortality (Abdel-Mannan et al., 2019; Garg and Sharma, 2020).

A previous diagnosis of substance abuse or alcohol dependence has been associated with an increased risk of SUDEP (Sveinsson et al., 2020b). On the other hand, Shankar et al. (2017) considered alcohol and other substance abuse as a potential indirect risk factor for SUDEP, as it may affect seizure control.

In terms of gender, Sveinsson et al. (2017) concluded that the SUDEP incidence rate is independent of sex in older age, but that the risk is increased in males under the age of 16. Similarly, Abdel-Mannan et al. (2019) reported an increased risk in male individuals, with 51% of SUDEP cases in their work being male. Maguire et al. (2020) and Shankar et al. (2017) also identify male gender as a risk factor, while Bosch et al. (2024) mention it as a risk factor with weak circumstantial evidence.

At the same time, patients with psychiatric comorbidities are at greater risk of SUDEP, especially women (Sveinsson et al., 2017).

In addition, cardiac problems have been mentioned as potential causes of SUDEP. Baysal-Kirac et al. (2017) concluded that patients with drug-resistant epilepsy present consistently lower heart rate variability (HRV), which may be associated with increased cardiovascular mortality. They highlighted that 24-hour Holter monitoring could be useful to determine increased cardiovascular risk in epilepsy. DeGiorgio et al. (2019) also noted that lower HRV, as well as seizure-induced changes to the QT and corrected QT intervals, may serve as biomarkers for increased SUDEP risk. This underlines the importance of cardiological consultation in SUDEP prevention.

It is worth mentioning that living alone seems to be associated with a fivefold increased risk of SUDEP (Sveinsson et al., 2020b), while, according to some findings, the combination

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of having GTCS and not sharing a bedroom with up to a 67-fold increased risk, compared to a 19-fold risk for those with GTCS who have roommates (Bosch et al., 2024; Whitney et al., 2023a).

Role of serotonin in SUDEP prevention

Serotonin (5-HT) is involved in the regulation of breathing, sleep/wake states, arousal, and seizure modulation (Bhasin et al., 2021; Petrucci et al., 2020). Petrucci et al. (2020) pointed to findings indicating that there are deficits of 5-HT in patients with epilepsy, while Patodia et al. (2022) highlighted that individuals with SUDEP showed focal medullary atrophy along with a reduction in serotonergic neurons. They also mentioned that seizures can modulate serotonergic networks, including 5-HT receptors and serotonin transporters. Co-administration of drugs that increase available 5-HT, such as selective serotonin reuptake inhibitors (SSRIs), may improve seizure control in epilepsy patients (Petrucci et al., 2020), as well as decrease the risk of postictal apnoea (Bhasin et al., 2021). It was reported that postictal hypoxemia was significantly less frequent in patients receiving SSRIs compared to those who were not on SSRIs (Bhasin et al., 2021). Overall, chronic 5-HT enhancement might be a seizure-protective factor (Petrucci et al., 2020), which, as mentioned above, could contribute to a reduced risk of SUDEP.

CONCLUSIONS

SUDEP risk factors include:
1. presence of tonic-clonic seizures;
2. uncontrolled and nocturnal seizures;
3. early onset and long epilepsy duration (>15 years);
4. high seizure burden;
5. comorbidities.

The highest risk of SUDEP was observed in individuals with GTCS who slept unattended (Sveinsson et al., 2020b); therefore, the presence of nocturnal supervision and the use of nocturnal listening devices or nocturnal supervision may help decrease the risk (Maguire et al., 2020; Whitney et al., 2019). Another preventive strategy is adherence to antiepileptic treatment to achieve freedom from seizures, which, if maintained for more than 5 years, significantly lowers the SUDEP rate. Most authors cited in this work point out that SUDEP in children is rarely discussed in comparison to SUDEP in adults, and that it should not be underestimated. This highlights the need for further investigation of this topic, as well as the development of effective methods of SUDEP prevention that are still lacking (Nascimento et al., 2017). Also, Mesraoua et al. (2022) highlighted the significance of multi-faceted education. Firstly, well-educated healthcare professionals are able to contribute to SUDEP prevention both directly and indirectly, not only by optimising the management of epilepsy, but also educating patients and their caregivers about risk reduction behaviours. Secondly, well-informed individuals suffering from epilepsy and their caregivers can contemplate preventive measures in order to reduce risk of SUDEP.

In conclusion, every person involved in the process needs to understand the nature of SUDEP, its burden, and the associated risk factors, with an emphasis on those that are potentially modifiable. Unfortunately, many neurologists still do not discuss SUDEP with all patients with epilepsy and their care partners (Asadi-Pooya et al., 2022; Mesraoua et al., 2022; Whitney et al., 2023a). At the same time, individuals living with epilepsy, as well as their family/friends, feel the need to know the dangers of SUDEP, and positive impact on self-management upon discussing the risks of SUDEP has been reported (Collard and Regmi, 2019; Jiang et al., 2025).

Conflict of interest

The authors do not report any financial or personal connections with other persons or organisations which might negatively affect the content of this publication and/or claim authorship rights to this publication.

Author contribution

Original concept of study; collection, recording and/or compilation of data; analysis and interpretation of data; writing of manuscript; critical review of manuscript; final approval of manuscript: JL.

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