REVIEW ARTICLE

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Bilateral dependence of sleep disorders and temporal lobe epilepsy – literature review

Wzajemna zależność między zaburzeniami snu a padaczką skroniową – przegląd literatury

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Abstract

Introduction. The analysis of sleep and its phases in the context of various pathophysiologies has attracted increasing attention from the scientific community; therfore, this review of the literature focuses on temporal lobe epilepsy (TLE).

Objective. The aim of the review is to systematize and update the knowledge and research currently available on the interplay of sleep deprivation and seizures in TLE, with a focus on MTLE.

Materials and method. The following keyword combinations were used to search the Pubmed, Science Direct and Google Scholar databases: sleep disturbance in mesial temporal lobe epilepsy, sleep in temporal lobe epilepsy, nocturnal temporal lobe epilepsy, temporal epilepsy sleep disturbance. After applying exclusion criteria, 23 papers were selected for the review.

Brief description of the state of knowledge. The publications qualified for the review were divided into 7 categories in terms of the subject of the publication. These categories relate to characteristic brain waves, memory and its consolidation processes, heart and sleep apnea, anti-epileptic drugs, motor disorders and lateralization of the discharges. Articles that did not fit into any of the previously mentioned categories were placed in the 'Other' group.

Conclusions. It is agreed that sleep is an important factor that should be taken into account when selecting the appropriate treatment and researching new AEDs. Moreover, sleep is significant to the patient›s quality of life, has a profound impact on its components, for example, physical and social functions, emotions and leisure, but may also influence the effectiveness of therapy.

Ke words

epilepsy, sleep disturbance, temporal lobe epilepsy

Streszczenie

Wstęp. Analiza snu i jego faz w kontekście różnych patofizjologii przyciąga coraz większe zainteresowanie środowisk naukowych, dlatego w niniejszym przeglądzie literatury skupiliśmy się na padaczce skroniowej (TLE).

Cel pracy. Celem tego przeglądu jest usystematyzowanie oraz zaktualizowanie obecnie dostępnej wiedzy i badań na temat wzajemnej zależności deprywacji snu i ataków padaczkowych w TLE, ze szczególnym uwzględnieniem MTLE.

Materiały i metody. W celu przeszukiwania baz danych Pubmed, Science Direct i Google Scholar użyto następujących kombinacji słów kluczowych: *sleep disturbance in mesial temporal lobe epilepsy*, *sleep in temporal lobe epilepsy*, *nocturnal temporal lobe epilepsy*, *temporal epilepsy sleep disturbance*. Po zastosowaniu kryteriów wykluczających do przeglądu wybrano 23 artykuły.

Aktualny stan wiedzy. Zakwalifikowane do przeglądu publikacje zostały podzielone na 7 kategorii na podstawie tematyki publikacji. Wspomniane kategorie dotyczą charakterystycznych fal mózgowych, pamięci i procesów jej konsolidacji, serca i bezdechu sennego, leków przeciwpadaczkowych, zaburzeń motorycznych oraz lateralizacji wyładowań. Artykuły, które nie pasowały tematyką do żadnej z wcześniej wymienionych kategorii, umieszczono w grupie „Inne".

Podsumowanie. Sen jest ważnym czynnikiem, który powinien być brany pod uwagę przy doborze odpowiedniego leczenia oraz w badaniach nad nowymi AEDs. Ponadto sen ma istotne znaczenie dla jakości życia pacjenta oraz ma silny wpływ na jego elementy składowe, którymi są np. funkcje fizyczne i społeczne, emocje i wypoczynek, ale także może wpływać na skuteczność terapii.

Słowa kluczowe

padaczka, zaburzenia snu, padaczka skroniowa

INTRODUCTION

Sleep, its purpose, physiology and pathologies attract increasing attention from the scientific community. Although the topic is rich in hypotheses, there are still no clear answers. Not only sleep disorders are investigated, but also their impact

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on specific disease entities and their cause-and-effect course. Epilepsy is one of the conditions that have been proven to be associated with sleep [1, 2, 3, 4, 5].

Epilepsy is a common neurological disease and it is estimated that it affects 1% of the world›s population [6]. Its pathophysiology and treatment influence mental health, cognitive and behavioural abilities [7]. Although the incidence of epilepsy is differentiated in terms of demographics, the advantage of focal seizures over generalized seizures has been established both in the group of adults and children [8]. Among focal epilepsy, the most common is temporal lobe epilepsy (TLE) which, unfortunately, is also one of the most resistant epilepsy types [9, 10, 11]. There are two types of TLE: middle and lateral. Middle TLE (mesial temporal lobe epilepsy, MTLE) occurs in the vast majority.

The etiology of TLE is very complex and includes, i.a., brain damage, infections and febrile seizures, as well as idiopathic origin. So far, no genes that could be responsible for it have been identified [12, 13]. One of the main causes of TLE may also be hippocampal sclerosis (HS), which also predisposes to the development of mental diseases such as schizophrenia [14]. The hippocampus makes up the largest part of the middle temporal lobe. Post-mortem examination of the brain of people with TLE shows the presence of markers suggesting the excessive activity of this structure, which leads to its atrophy [14]. In this case, particular attention is paid to the ectopic mossy fibres and cavity cell loss [13]. The mossy fibers form the connection between the dentate gyrus and CA3, and their purpose is to regulate the activity of the hippocampus. It is suspected that their increased proliferation and inappropriate location cause excessive stimulation, and thus lead to the development of epilepsy [14]. On the other hand, a decrease in the number of interneuron cavity cells may result in a loss of balance between excitation and inhibition [13]. There are more factors involved in the pathomechanism of HS and a simplified picture of this pathology is presented here. Moreover, it has been suggested that the characteristic symptoms of TLE, such as the feeling of fear, aura or dreamy states, are caused by disturbances in the amygdala, namely its diminution or hardening (as in the case of the hippocampus), as well as a change in the number of receptors [12].

It is estimated that 20–30% of people suffering from epilepsy do not respond to drug treatment. The alternative is therefore non-pharmacological treatment, which is dominated by surgery which usually consists in locating the source of the discharge and removing it [15, 16]. In the case of TLE, the precise location and early treatment can not only reduce the number of seizures, but also stop them or improve some vital functions of the patient [17, 18, 19]. Of course, it should also be taken into account that the success of the procedure is influenced by many factors, such as age or lateralisation of discharges (and also the one concerning children) [20]. However, the conducted studies are inconsistent with regard to the impact of surgical treatment on the architecture of sleep, and thus its quality [21, 22].

It has been observed that people with epilepsy more often suffer from sleep disorders and related diseases, such as obstructive sleep apnea [23, 24]. Among the most frequently mentioned types of epilepsy that have a significant impact on sleep, frontal lobe epilepsy (FLE), TLE and childhood or adolescent epilepsy can be distinguished [25]. Although nocturnal epileptic seizures occur more frequently in FLE, it has been noticed that in the case of TLE there is a greater disturbance of sleep architecture [26]. It is believed that the circadian rhythm and the length of each sleep phase influence when an attack is likely to occur. Research has confirmed that TLE seizures most often occur in the morning and late afternoon with a characteristic aura and subsequent forgetfulness of the attack [25]. It has also been observed that nocturnal seizures usually appear in the NREM phase, which is characterized by hyper-synchronization of brain waves [25, 27]. In the case of nocturnal TLE seizures, phase 1 of sleep is prolonged and the duration of the REM phase significantly decreases and sleep efficiency decreases [27]. However, the more frequent seizures during the day are preceded by a decrease in the duration of the REM phase [26, 27].

Another factor influencing the quality and quantity of sleep is anti-epileptic drugs (AEDs), and their effect differs depending on the patient [25, 28, 29]. What is certain, however, is that seizures affect the amount and quality of sleep, and sleep affects the frequency of seizures. On the other hand, this dependence is often mediated by illnesses accompanying these diseases.

OBJECTIVE

The aim of the review is to systematize and update the knowledge and research currently available on the interplay between sleep deprivation and seizures in TLE, with a focus on MTLE. This will allow for a better understanding of the subject and more detailed research, thus identifying potential research goals. Characterizing the relationship between epilepsy, sleep, and wakefulness can be very important in properly diagnosing the type of epilepsy, and in determining the prognosis and selecting the appropriate treatment.

MATERIALS AND METHOD

In preparing the literature review, the following key word combinations were used: sleep disturbance in mesial temporal lobe epilepsy, sleep in temporal lobe epilepsy; nocturnal temporal lobe epilepsy, and temporal epilepsy sleep disturbance. For this purpose, Pubmed, Science Direct and Google Scholar databases were searched. The exclusion criteria were: studies from before 2015, conference materials, reviews, meta-analyses and case reports, as well as research works in a language other than Polish and English, or with a study group of less than 10 people, and tests on animals. Based on the adopted criteria and combinations of key words, 23 studies were qualified for the review (Tab. 1).

BRIEF DESCRIPTION OF THE STATE OF KNOWLEDGE

Characteristic discharges. Research by Del Felice et al. [30], Nayak et al. [31], Giorgi et al. [32] focuses on the analysis of interictal epileptiform discharges (IEDs). This characteristic brain activity, which differs from that during an epileptic seizure, is due to different mechanisms activated by specific ligands [33]. Registering IEDs and their assessment is sometimes a difficult task due to technical limitations, and their clinical usefulness is often questioned; nevertheless, it

Table 1. Presentation of the publications included in the review based on their subject matter, group size and rating

Category	Group size	Conclusions	Authors, year
Characteristic discharges	12	Sleep reduces cortical interactions and increases the spread of IEDs. The pattern of spread of IEDs is characteristic of MTLE and neocortical TLE.	Del Felice et al., 2015 [30]
Characteristic discharges	140 (40 with TLE)	The appearance of IEDs depends on the level of synchronization of each sleep phase. AEDs delay the occurrence of IEDs by desynchronizing	Nayak et al., 2018 [31]
Characteristic discharges	13	sleep after prior deprivation is more unstable, and more general IEDs occur in the NREM phase	Giorgi et al., 2017 [32]
Characteristic discharges	140 (40 with TLE)	Excessive synchronization of brain waves in epilepsy during sleep promotes neuronal depolarization.	Nayak et al., 2018 [36]
Memory	25 (16 with TLE)	People with TLE are more likely to be depressed IEDs and hippocampal sclerosis can delay the onset of the REM phase and thus shorten the SWS phase, which adversely affects memory	Miller et al., 2016 [38]
Memory	25 (16 with TLE)	SWS as an important factor in the study of memory and learning processes. Treatment of sleep disorders can improve the health of patients with epilepsy.	van Schalkwijk et al., 2018 [39]
Memory	71	There was no correlation between the perceived sleepiness and cognitive abilities in people with TLE and hippocampal sclerosis.	Vascouto et al., 2018 [40]
Memory	22 (11 with TLE)	SWS does not affect the memory consolidation process in children. Negative correlation of IEDs and consolidation processes. Sleep plays a compensatory role in children›s consolidation processes,	Chan et al., 2017 [41]
Heart reactivity and sleep apnea	50 (4 groups with 10 people in each)	In TLE, a motor episode occurs earlier and lasts longer, compared to parasomnia. TLE awakenings are caused less often by external factors The lowest RRI values in people with TLE compared to other studied groups.	Peter-Derex et al., 2018 [43]
Heart reactivity and sleep apnea	I group – 10 II group – 10	TLE and carbamazepine reduce baroreceptor sensitivity, thus increasing the risk of SUDEP.	Nayak et al., 2017 [44]
Anti-epileptic drugs	I group – 20 II group – 20	Carbamazepine worsens sleep stability.	Nayak et al., 2016 [47]
Anti-epileptic drugs	83	Treatment difficulties may be caused by the more frequent activation of epileptiform discharges during sleep.	Stefanatou et al., 2019 [48]
Motor abnormalities	30 (15 z TLE)	TLE increases the number of minor motor events performed during sleep.	Giuliano et al., 2017 [50]
Motor abnormalities	148 (50 z RTLE, 48 z LTLE)	TLE, especially RTLE, is correlated with the occurrence of RLS.	Geyer et al., 2016 [51]
Lateralization	16	Duration of the REM phase in people with left-sided TLE is shorter than in people with right-sided TLE (although the test should be repeated with a larger group).	Nakamura et al., 2016 [52]
Lateralization	33	Left-sided TLE laterality reduces the time between the onset of a seizure and waking.	Gumusyayla et al., 2016 [53]
Other	15	The miRNA expression profile changes after a bilateral seizure occurs.	Surges et al., 2016 [54]
Other	170	There is a relationship between the type of seizure and the time it occurs.	Gurkas et al., 2016 [55]
Other	56 (34 with TLE)	Epileptiform activity in the brains of people who are sleepy is increased, especially in epilepsy. The incidence of these activities varies between healthy and sick people.	Cartella et al., 2019 [56]
Other	90	Sleep disturbances in people with epilepsy are not directly correlated with epilepsy, but with other comorbidities.	Yang et al., 2016 [57]
Other	56	People with MTLE have a disturbed sleep pattern, which can cause daytime sleepiness and tiredness.	Scarlatelli-Lima et al., 2016 [58]
Other	189 (101 with TLE, 88 with ETLE)	People with TLE have a higher risk of developing obstructive sleep apnea.	Yildiz et al., 2015 [59]
Other	247 (199 with epilepsy)	Patients suffering from epilepsy have a greater chance of developing sleep disorders than healthy people.	Turaga et al., 2016 [60]

is believed that they help in determining the type of epilepsy and its origin [34].

In the study by Del Felice et al. [30] it was noted that IEDs appear more frequently during sleep. The aim was therefore to investigate whether sleep and cortical interactions influence the spread and distribution of IEDs, respectively. Del Felice et al. [30] based their research on a group of 12 people diagnosed with right-sided TLE, on whom measurements of 256-channel EEG were carried out during the day and night. On the day of recording, which was preceded by sleep deprivation, patients were not taking anti-epileptic drugs (AEDs) or stimulants. Sleep deprivation was caused by the N2 recording being made at 03:00. Another recording was made at 13:00 during the patient's nap. The data was then analyzed by two independent neurophysiologists, and 60 IEDs were distinguished in the waking and sleeping states. After averaging the results for each phase and type of epilepsy, the differences between them were marked on the t-map. The authors of the study also sought to determine the source of the abnormal brain activity. The results obtained

indicate a wider projection of IEDs during sleep in TLE. There were also low-amplitude EEG abnormalities in the waking state following the onset of IEDs, which during sleep turned into less frequent high-amplitude abnormalities in people with MTLE, while no abnormalities were observed in people with neocortical TLE during this time. Researchers agreed that MTLE has greater structure synchronization compared to neocortical TLE and therefore assumed that this is why IEDs cause a series of high amplitude deviations. They also noted that sleep reduces discharges and inhibits interactions between specific cortical regions. Despite the lack of used calculations, the authors of the study agree with the statement that the connectivity between the previously mentioned regions is limited, which increases the excessive synchronization of the brain spheres. At the same time, it should be pointed out that the authors emphasize that their research may be distorted by the small study group [30].

Another issue raised withn reference to the characteristic neural discharges is sleep deprivation. In an earlier work by Giorgi et al. [35] it was found that sleep deprivation influences the higher incidence of IEDs. In the study by Giorgi et al. [32], which qualified for the review, the researchers wanted to check whether morning sleep is associated with an increased incidence of IEDs, compared to physiological sleep. Their aim was also to observe any abnormalities in sleep architecture.

Giorgi et al. [32], at the very beginning of the publication, note that in 40% of people with focal epilepsy, IEDs are not observed, but if they do occur, their number increases with sleep deprivation. In the conducted study, polysomnography (PSG) compared single REM/NREM sleep cycles after deprivation sleep and during physiological sleep. The results showed no significant differences in the macrostructure of sleep, but studies of the cyclic alternating pattern (CAP) indicate its significant instability after deprivation, especially in the N2 phase, and a significant predominance of synchronized slow waves. However, there were no significant differences in the number of IEDs after and without sleep deprivation, but only in the overall assessment of the NREM phase, in which the number of IEDs was significantly higher after sleep deprivation. The authors wanted to confirm the hypothesis that morning sleep (after deprivation), which is characterized by greater instability, may cause an increased frequency of IEDs [32]. Nayak et al. [31] focused on the NREM phase in propagating IEDs by assessing these waves during sleep and wakefulness. It should be noted that the studies also took into account the effects of AEDs. In another work by Nayak et al. [36], citing studies proving that excessive cortical synchronization of specific structures leads to the propagation of epileptic seizures, studied and compared the brainwave activity of people with various types of epilepsy with a healthy control group during sleep and wakefulness.

To investigate the NREM phase and the effect of antiepileptic drugs (sodium valproate and carbamazepine) on epilepsy markers Nayak et al. [31] used the timing phase assessment preceding the IEDs. 120 people participated in the study, divided into 3 groups of 40 people each, according to the type of epilepsy. One of these groups consisted of people with TLE. Each group was then divided equally into drug-drug and drug-naive patients. The subjects were subjected to PSG as well as visual assessment of REM tones. The EEG data were filtered and analyzed, and then their synchronization was assessed for delta, theta, alpha and beta waves. As IEDs differ, researchers decided to use multi-level modeling of mixed effects. TLE showed greater synchronization of each wave type during IED compared to extratemporal epilepsy (ETLE). However, in both cases, the greatest synchronization was recorded in the N1 phase. The authors of the study indicate that this may be due to the formation of sleep spindles, but also admit that most sleep spindles are formed in the N2 phase, so there may be a different mechanism behind it. Moreover, it should be noted that due to the limited number of IEDs, the authors could not determine the effect of AEDs on cortical synchronization in the case of the focal epilepsy under study. However, the study emphasizes that the sleep phase has an impact on the level of synchronization preceding IEDs, and on the basis of studies on juvenile myoclonic epilepsy, they confirm that AEDs, by causing wave desynchronization, delay the appearance of IEDs [31].

In another study by Nayak et al. [36], also examining a group of 120 people, 40 of whom had TLE, compared the background of EEG in different types of epilepsy. During the PSG, the synchronization of individual waves was assessed. The results showed an increased synchronization of delta and theta waves in people with epilepsy (including TLE), compared to the control group. Thus, the authors suggest that over-synchronization affects all epilepsy types, promoting the depolarization of neurons [36].

In conclusion, the above-mentioned studies emphasize the important role of sleep synchronization, especially the NREM phase, in the etiology of IEDs and their effects. However, the authors indicate the limitations of their research, such as the small study group or insufficiently sensitive equipment. This is also highlighted in the work of Asadollahi et al. [37], whose results showed a weak positive correlation between IEDs and the frequency of seizures. The authors of this study believe that the standard EEG may not be a valuable tool for people with TLE.

Memory. Another important factor often taken into account in studying the interplay of sleep and epilepsy is the aspect of memory consolidation and pathologies observed in the hippocampus. Because both memory and sleep are believed to be impaired in patients with epilepsy, Miller et al. [38] investigated the effect of nocturnal seizures and damage to the hippocampus on them. In other studies, van Schalkwijk et al. [39], taking into account the significant time differences in the duration of the REM phase in TLE, assessed the memory capacity of these people in terms of the time spent in slow wave sleep and the delay in the REM phase. On the other hand, Vascouto et al. [40] conducted a relatively large study considering people with diagnosed MTLE and hippocampal sclerosis. Their goal was to discover whether there was a correlation between their cognitive abilities and their feeling of sleepiness. Sleep-dependent memory consolidation has also been investigated by Chan et al. [41] in children 6–16 years of age, with consideration of IEDs.

Sleep affects many aspects of our lives, including memory. Miller et al. [38] in their research took into account nocturnal IEDs, damage to the hippocampus, sleep architecture and memory status. A very important factor in these studies is slow-wave-sleep (SWS), which is related to the consolidation of declarative and episodic memory. The authors cite publications showing that sleep deprivation, especially stages 3 and 4 of NREM, which constitute SWS, leads to memory deterioration. 25 people participated in the study, 16 of whom had TLE. Of the people with TLE,

12 had hippocampal lesions. The EEGs performed showed that people with epilepsy spent little time in SWS, and the REM delay (especially in people with nocturnal IEDs) was longer compared to controls. Questionnaires on memory, depression and IQ levels were also conducted. Among the above-mentioned tests, statistically significant results were obtained for depressive states, which were more severe in the study group. It was also observed that people with longer REM delay had a significantly reduced memory index, compared to the group with shorter REM delay. The authors note that the longer the REM phase delay, the less the SWS. However, they indicate that the delay in the REM phase can be influenced by both IEDs and damage to the hippocampus. However, it should be noted that the results could have been influenced by the small study group, subjective memory tests, as well as the choice of the statistical test and the fact that the EEG results were obtained from a one-time test [38].

Two years later, the same research group, van Schalkwijk et al. [39] conducted a similar study, but this time using an objective memory test. The number of patients and the type of factors taken into account did not change. The neurophysiological measurements were based on remembering autobiographical events, i.e. 17 situations from everyday life simulated by the examiners, remembering 24 details of the story, geometric figures and 15 words. The study lasted 2 days during which patients received an ambulatory EEG. The obtained results showed a positive correlation between SWS and verbal learning (15-word test) and a negative correlation between the REM phase delay and the memory of autobiographical events. Declarative memory (storytelling) was worse in people with TLE, more frequent seizures and hippocampal lesions, which also impair autobiographical memory. In contrast, IEDs deteriorated the visual-spatial memory (geometric figure). The authors declare the limitations of their research to be similar to the previous limitations. However, they emphasize that there is a correlation between SWS and verbal memory, and indicate SWS as an important factor in studying memory and the learning process [39].

Vascouto et al. [40] conducted their research on a group of 71 adults diagnosed with MTLE and hippocampal sclerosis. The aim was to investigate the correlation between cognitive ability and perceived sleepiness according to the Stanford Sleepiness Scale (SSS).On the second day of hospitalization, the patients underwent a series of cognitive tests. The results showed a greater sense of sleepiness in the study group compared to the control group, despite a similar average amount of sleep the night before the study. However, the thesis put forward at the beginning that sleepiness and worse cognitive abilities have an influence on each other has not been confirmed. The undoubted limitations of the study were the subjective nature of the SSS test, the language barrier in its performance, and the fact that no alternative test was used that would confirm the obtained results. To sum up, the authors concluded that the sense of sleepiness is not a valuable factor in the case of neuropsychological research [40].

Research by Chan et al. [41] included memory consolidation in 22 children with focal epilepsy, 11 of whom were found to have TLE. Verbal and visual-spatial memory was checked by means of pairs of words and place locations of 2 identical pictures, respectively. The study assumed an improvement in memory with increasing SWS time and its deterioration with increasing IEDs. As the results of the patients were compared individually, the study was conducted in 2 stages: during the day and after sleep. The stages had to be separated by a 24-hour break. The authors reported poorer memory and sleep in people with focal epilepsy compared to controls. However, the memory of the sick was deteriorated only in the daytime tests, while no changes were noticed between the control group and the test group in the bedtime studies. The authors therefore assume that sleep plays a compensatory role in the consolidation process in children with focal epilepsy. This was especially noticeable in children with TLE, who were the worst at the tasks, but their memory improved after a night's sleep. Similar results were seen in people with longer duration of the disease. In addition, patients had less stable sleep, and there was a positive correlation between SWS and memory improvement, but it did not reach statistical significance. Therefore, the authors concluded that SWS does not play a significant role in consolidating memory in children. In the case of IEDs, there was a negative correlation with the consolidation of verbal memory, and thus it was assumed that it is an important sleep disturbance factor that impairs consolidation processes in children, and deserves a more detailed analysis. The authors admit, however, that the greatest weakness of the study was the size of the study group, which made a more detailed analysis of the results impossible [41].

Summing-up, on the basis of the cited publications, it can be concluded that in TLE memory consolidation is influenced by IEDs (negative correlation) and SWS, but only in the case of adult patients (positive correlation). It should be noted, however, that the studied groups consisted of a small number of people and it was difficult for the authors to prove the statistical significance of the results obtained. However, the publications cited indicate that in people with TLE, memory is partially damaged in some way, and in the case of children, sleep may play a compensatory role for these disorders. Very important in this matter is the appropriate selection of objective tests and taking into account the individual characteristics of patients, such as the circadian rhythm, because it may affect the test results.

Heart reactivity and sleep apnea. The aspect of sleep apnea and associated heart disorders is also worth mentioning. These pathologies are a common cause of sudden unexpected death in epilepsy (SUDEP) [42]. Peter-Derex et al. [43] used the heart function in his study and differentiated NREM parasomnia from nocturnal seizures. However, in another study, Nayak et al. [44] point out that sleep apnea, especially in people with epilepsy, can cause significant autonomic instability leading to SUDEP. The aim of the research by Nayak et al. [44] assessed the variability of sinus rhythm in patients with TLE and sleep apnea using PSG. The second part of the study assessed the effect of carbamazepine on the factors mentioned above.

Peter-Derex et al. [43] in their article highlighted the difficulty of distinguishing NREM parasomnia from nocturnal seizures. They assumed that in both cases there is an increased activation of the autonomic system and that it precedes movement disorders. The authors of the publication wanted to find a factor differentiating this agitation, and compared the cardiac reactivity of the above-mentioned disorders in 50 people during awakening, parasomnia, and nocturnal FLE and TLE seizures (10 people in each group). Each patient underwent at least one overnight video EEG (VEEG) examination, and the recordings were assessed by

two independent doctors. Particular attention was paid to the time from the onset of the first movement disorder, its duration and type. Beat-to-beat RR intervals (RRI), heart rate and heart rate variability were also analyzed. Differences were noticed in the time of the onset of a motor episode (NREM phase 2 in patients with epilepsy and NREM phase 3 in people experiencing parasomnia) and in its duration (they lasted significantly longer in the TLE group). Moreover, the analysis revealed significantly lower RRI in people with TLE compared to other groups. The authors assume that this may be due to their appearance before the onset of the motor episode and their longer duration. This lack of correlation is considered in some studies to be an early clinical sign of an impending attack, especially in the context of MTLE. The downside of this publication is its retrospective nature, which resulted in the lack of some data and the use of different procedures for the groups [43].

In the above-mentioned study, no person was reported to have sleep apnea. However, this is an important factor in the context of SUDEP. Nayak et al. [44] studied heart rate variability during apnea in people with TLE using PSG. Moreover, they considered the role of carbamazepine as a factor increasing the risk of arrhythmias. The study therefore consisted of 3 groups of 10 people: TLE without drugs, with TLE treated with carbamazepine, and control. The analysis and comparison of the results included heart rate variability in the 2 minutes before and after the apnea episode, and throughout its duration. Patients were examined using EEG, magnetic resonance imaging (MRI) and questionnaires assessing sleep quality and the occurrence of sleep disorders. The results showed no changes in heart rate in people with TLE and sleep apnea who were not taking their medications, compared to controls. In contrast, in the carbamazepine group, the rate of heart rhythm changes showed a decrease in sympathetic activity and an increase in parasympathetic activity immediately after an apnea episode. The authors concluded that in TLE, baroreceptor activation may be damaged, especially with carbamazepine treatment, and this condition increases the risk of SUDEP. The weaknesses of the study was the small study group and technical limitations [44]. These articles suggest that changes in heart function are not only a valuable diagnostic factor for TLE, but also that changes in heart function indicative of autonomic instability are particularly pronounced during sleep.

Anti-epileptic drugs. The effect of anti-epileptic drugs on sleep varies and depends on a specific compound; however, it has been observed that the classic antiepileptic drugs cause wakefulness disorders and pathological sleep [45, 46].

Nayak et al. [47] gave particular attention to carbamazepine and its influence on sleep architecture. For this purpose, the sleep structure of people with drug-resistant TLE was compared with a group taking carbamazepine in monotherapy. Another study that focused on the treatment of epilepsy and possible interactions with sleep is that by Stefanatou et al. [48], who assessed specific prognostic factors in MTLE, taking into account sleep activity and resistance to treatment. In the above-mentioned work by Nayak et al. [47], the study groups, including patients with TLE without drugs or treated with carbamazepine, consisted of 20 people in each group, and a control group consisted of 40 people. Following PSG, the number of awakenings and spontaneous cortical activity were assessed. A questionnaire was also applied to detect any sleep disorders in the patients. The results indicated that patients with TLE had significantly poorer sleep quality and a greater amount of REM awakenings, compared to the healthy controls. The analysis also showed greater spontaneous cortical activity in the N1 and N2 phases in people with TLE, with the highest overall value recorded in the group treated with carbamazepine. The authors concluded that the studied drug influenced the micro-architecture of sleep by worsening its stability [47].

On the other hand, Stefanatou et al. [48] compared TLE susceptible to treatment and resistant to treatment and to establish prognostic factors. After analyzing the patients' data, 83 people qualified for the study, divided into 4 groups depending on the frequency of epileptic attacks. Each patient underwent an MRI scan and at least 2 EEG tests, one of which was performed at night. The obtained results indicated that a poor response to treatment in TLE is associated with greater activation of epileptiform discharges during sleep. The authors assume that this condition may have been caused by changes in the neural network. However, the factors limiting the study were the small number of people free from seizures, and the duration of the study [48].

In summary, some AEDs may affect sleep by destabilizing it. However, one of the therapeutic actions of AEDs is to counteract hyper-synchronization of the brain waves, which was mentioned in the discussion of the articles on IEDs, while it is assumed that over-activation of epileptiform may be responsible for treatment resistance in TLE, although this hypothesis requires more careful testing. It should be mentioned that recent studies conducted on a group of 12 people, showed a positive effect of eslicarbazepine acetate, a third-generation AED, on the stability of sleep in people with TLE, thus improving its quality [49].

Motor abnormalities. Various motor disorders, such as restless legs syndrome (RLS), also include sleep disorders, including those associated with epilepsy. These are conditions that significantly worsen the quality of sleep and the patient›s well-being.

Giuliano et al. [50] noted in their study that little is known about minor motor events in people diagnosed with MTLE. Their aim, therefore, was to determine the frequency of occurrence of the afore-mentioned pathology in MTLE and to characterize this relationship. A similar study was conducted by Geyer et al. [51], but they focused specifically on restless legs syndrome (RLS). Due to the close proximity of these disorders in the structure of the brain, the researchers wanted to determine the frequency and severity of RLS in TLE and to test the role of RLS as a lateralizing and warning factor.

In a study by Giuliano et al. [50], 15 patients with MTLE were involved (8 men and 7 women) with an average age of 31.8 ± 14.9 years, and 15 healthy volunteers (6 men and 9 women) with an average age of 32.8 ± 11.2 years. Each participant underwent long-term video-EEG monitoring (LTM) measurements with at least 8 channels. The recordings were analyzed by 2 independent observers, and assumed movement patterns lasting up to 4 seconds, with or without accompanying EEG signals, as minor motor events. They were classified into several categories: hand-face movements, oral automatisms, limb dystonias, head turns, pelvic movements, straightening movements, gesture automatisms, and other undefined movements. The sleep phase in which they occurred was also taken into account.

EEG recordings were analyzed at 2 time points – 2 minutes before and during minor motor events. The final results showed that subjects with MTLE performed more than 3 times as many minor movements during sleep, mostly oral automatisms, gestures, limb dystonias and straightening. Movements of MTLE patients were more often preceded by EEG abnormalities, but most minor motor events, both in the control and study groups, were not related to the EEG signal [50]. In the study Giuliano et al. [50], the location of MTLE was not distinguished among the respondents which could have been caused by the small study group. However, in both studies, a more frequent occurrence of motor episodes in MTLE patients was shown (according to Geyer et al. [51] on the right). The authors agree that this could have been influenced by AEDs. Moreover, Giuliano et al. [50] emphasized difficulties in interpreting the results and suggests that more frequent motor episodes in people with MTLE may be caused by greater instability and fragmentation of sleep, whereas Geyer et al. [51] consider this relationship in terms of an aura. The research by Geyer et al. [51] focused on the problem of RLS. People suffering from obstructive sleep apnea, severe speech disorders, cognitive disorders, stroke or strongly predisposed to secondary RLS were excluded from the study, among others, by iron deficiency anaemia or low ferritin levels.

Research has also taken into consideration the location of TLE in terms of RLS occurrence. All epilepsy patients were assigned to RTLE and LTLE groups, either right-sided TLE and left-sided TLE, respectively; those who could not be assigned to one of these groups were excluded from further study. The resulting groups consisted of 50 people with RTLE, 48 people with LTLE and 50 healthy people in whom epilepsy also did not occur in the family. RLS was assessed according to NIH criteria using the International Restless Legs Study Group questionnaire. RLS was detected in 21 out of 50 RTLE patients, of whom 10 had severe symptoms before the onset of epilepsy. In the LTLE group, 7 out of 48 had RLS, of whom one had severe symptoms before the attack. However, in the control group, 5 out of 50 people had RLS. According to these data, there is a correlation between the location of TLE and the occurrence of RLS, the chance of developing RLS in a person with RTLE is 4.6 times higher than in people with LTLE. The correlation of the severity of symptoms and the coming attacks could not be found because of the lack of statistical significance. Statistical significance was also not observed when comparing the control group and the group with LTLE [51].

Lateralization. Epilepsy is an extremely complex and multifactorial disease. Epilepsy and many disorders related to different parts of the brain are correlated. The following studies highlight this aspect, taking into account the location of foci and their relationship with sleep disorders.

Nakamura et al. [52] focused on sleep quality and the location of epilepsy lesions in more detail. The group examined LTM and PSG data from 16 patients, 10 with left-sided and 6 with right-sided lesions. Subjects met the following conditions: they did not experience an attack during the recording, their sleep phases were identifiable by the number of EEG abnormalities allowed, they had not received brain surgery, their studies provided sufficient data, and they did not take gabapentin at a dose of 1,800 mg per day or more or lamotrigine at a dose> 200 mg per day. The final compilation shows that the duration of the REM phase in people with left-sided TLE was significantly lower than in people with right-sided TLE, contrary to the previous results. No statistically significant differences were found in the remaining stages of sleep. The authors explain their results, which differ from the literature, as being caused by the small research group and the lack of a control group. They also emphasize that future studies should include non-epileptic patients with temporal lobe injuries to delineate the specific characteristics of the correlation of damage and the pattern of sleep phases [52].

Gumusyayla et al. [53] investigated the effect of TLE lateralization on the time between epilepsy and awakening. Like Nakamura et al. [52], they used retrospective VEEG and PSG data from 33 patients with diagnosed TLE; distinguished between left (19 patients) and right (14 patients). Seizures in which the location or laterality of the TLE could not be determined were excluded from the study. A total of 64 epileptic seizures occurring at night were distinguished, all in the NREM phase that preceded awakening. The results show that the time between onset of an attack and awakening was significantly longer in people with right-sided TLE, thus laterality appeared to be a factor in the time needed to awaken. A limitation of the study, as indicated by the authors, is the lack of recordings of invasive EEG, because only one person used intracranial electrodes, but no significant data was obtained [53].

Subsequent studies taken into account are thematically very diverse. One of them is the work of Surges et. al. [54] assessing changes in the amount of specific miRNAs in the blood of people with MTLE, with secondary generalized seizures. On this basis, the researchers were able to distinguish differences in the amount of miRNAs, taking into account attacks occurring during the day or at night [54]. Gurkas et. al. [55] checked the relationship between the type and location of epilepsy and the circadian rhythm in children, based on the analysis of electroencephalogram (EEG) results from the last 5 years. Cartella et. al. [56] compared the activity of specific brain structures between a group of healthy people and people diagnosed with MTLE and left hippocampal sclerosis. They based their conclusions on the results of EEG and functional Magnetic Resonance Imaging (fMRI) [56]. Another interesting study is the work of Yang et. al. [57], where the strength of the correlation between insomnia and epilepsy was checked, taking into account depression as a comorbid disease. Whereas Scarlatelli-Lima et. al. [58] subjected people with refractory MTLE to a complex study in terms of sleep. In their study, they assessed, among others, disorders in particular sleep stages based on the wakefulness after sleep onset (WASO) index [58]. In the work of Yildiz et. al. [59] the authors, on the basis of questionnaires, wanted to discover what specific sleep disorders occur in people with TLE and ETLE. Similar studies to assess the most common sleep disorders in people with epilepsy were carried out by Turaga et. al. [60].

The assessment of plasma miRNA level as a biomarker of epilepsy was undertaken by Surges et al. [54]. The study involved 15 patients who met the following requirements: age over 18 years, diagnosed drug-resistant MTLE and unilateral hippocampal sclerosis without other abnormalities in the cranial MRI. Blood samples were taken from them before and after the onset of a bilateral seizure (BCS) – 30 minutes, 3–6 hours, 20–28 hours and 3–6 days after the

attack. MiRNA expression was assessed using quantitative polymerase chain reaction (qPCR). Using for the validation of the expression of samples before and 30 minutes after the attack, due to the statistical significance of these groups, it was proved that the expression level of miR-143–3p, miR-145–3p, miR365a-3p and miR532–5p increased significantly, taking all respondents into account. However, it was noted that the expression differed between patients. In the case of post-BCS miRNA expression during sleep, in 4 of 15 patients it was significantly higher 30 minutes after the seizure, but changes in miRNA expression levels were also detected during the 3–6 and 20–28 hour periods, which were not present during wakefulness. Focusing on these 4 patients, validation by qPCR was then performed and miRNAs with altered expression following an attack were selected. Due to the small group that was formed, only miR-663b achieved statistically significant values. In the discussion, the authors emphasize that the changes in expression are not unique to attacks during sleep, but are more frequent then [54].

In the study by Gurkas et al. [55] on the influence of the position and type of epilepsy on the incidence of the circadian cycle in children, EEG data from 170 patients were used. A total of 909 epileptic seizures were analyzed. Attention was paid to the time of the attack, whether it occurred during the day (06:00–18:00) or at night (18:00–06:00), whether the patient was asleep or not, and the frequency of occurrence at 3-hour time intervals within the stipulated periods. Where possible, the doses of the drugs were limited to children, and depended on the severity and frequency of seizures. Patients and their parents were obligated to press the emergency button when an attack or similar disturbing events occurred. According to the data collected by the researchers, tonic, clonic and hypothermic seizures occurred during sleep, while auras, dialeptic, myoclonic, hypomotor and atonic seizures, and epileptic spasms occurred more frequently when the children were awake. Regarding localization, the temporal lobe experienced a seizure more often at night during sleep (24:00–03:00), the temporal lobe during the day (06:00–09:00 and 12:00–15:00), as did generalized seizures (12:00–18:00) and the occipital lobe (09:00–12:00), in which seizures occurred more often also when the patient was awake (15:00–18:00). Parietal lobe seizures occurred more frequently while patients were awake,. The authors explain this with a small number of parietal seizures, which may have made the results unreliable [55].

The results of the study by Cartella et al. [56] were based on data from 34 patients with TLE and hippocampal sclerosis, and 22 healthy volunteers. Subjects with a history of psychiatric and neurological diseases, disorders while sleep or awake, cardiovascular or thyroid disease, anaemia, and drug users, were excluded from the study. During the week prior to the experiment, all participants were given specific instructions to maintain regular sleep. EEG measurement was then performed. Then, the night before the measurements were taken, the participants slept for only 3–4 hours. Sleep deprivation was assessed using functional magnetic resonance imaging (fMRI) and re-EEG. The number of TLE patients with EEG abnormalities after the decrease in sleep time increased from 15–23. Activities characteristic for epilepsy (imaged by, among others, peaks and sharp waves) were demonstrated in the left fronto-midtemporal region and mainly occurred in the NREM1 and NREM2 stages of sleep. The fMRI results differed between the control group and the study group – in people with epilepsy, increased activity was detected, among others, in the occipital gyrus, insula, left cingulate gyrus, left pre-central gyrus or right superior temporal gyrus. Reduced activity was demonstrated, among others, in the left cuneus, left precuneus, left fusiform gyrus, right supramarginal gyrus and left superior temporal gyrus [56].

Yang et al. examined the severity of sleep disorders, comorbidities and related morbidity in epilepsy. Validated questionnaires were used: Insomnia Severity Index (ISI), Epworth Sleepiness Scale (ESS), and Beck Depression Inventory (BDI), as well as PSG and EEG to detect obstructive sleep apnea. The Apnea Hypopnea Index (AHI) was used to assess apnea. The study did not include people with a history of sleep-related illnesses, recently treated psychiatrically or after suicide attempts, or patients treated with vagal nerve stimulation. An interview was conducted that identified sleep and wake patterns for each participant, symptoms associated with sleep disorders, use of drugs and substances such as caffeine and alcohol. Ultimately, data from 90 patients were used for the results. AHI was normal in 49 patients, elevated (5–10) in 15 and high (> 10) in 26. Scores were above 10 on the Epworth Sleepiness Scale in 31 patients, signifying excessive daytime sleepiness. Regarding ISI, only the BDI, mBDI (modified BDI), ESS and total sleep time showed a statistically significant correlation. Based on the results, the authors concluded that of all factors taken into account, including epilepsy, insomnia is only associated with depression, sleep time and quality. However, the authors did not exclude a relationship between insomnia and epilepsy – they explain the results with the small study group and the cross-sectional nature of the study [57].

Scarlatelli-Lima et al. [58] conducted similar studies, but focused on a specific group of patients – with drug-resistant epilepsy MTLE. Eligible patients (56 people) underwent PSG, VEEG, MRI, neurological, neuropsychological and psychosocial examination, and the Pittsburgh Sleep Quality Index (PSQI), ESS and Stanford Sleep Scale (SSS). Each patient was receiving AEDs; therefore, in order to compare the effects of the drugs, the daily doses were standardized to the ratio of the Prescribed Daily Dose (PDD) and the Defined Daily Dose (DDD). After completing the questionnaires, it was found that 9 patients had clinically significant excessive daytime sleepiness (ESS score> 10). PSQI results indicated poor sleep quality in the last month in 15 patients. Subsequent studies revealed that 30 patients had a delayed REM phase, 49 patients had an increased sleep fragmentation index (WASO), 35 patients had a prolonged NREM phase, 38 patients had a shortened REM phase, and 41 patients had a so-called alpha-delta sleep associated with increased alertness and non-regenerative sleep. IEDs occurred most frequently during the NREM3 sleep phase.

In connection with all the above data, the authors of the publication assume that people with MTLE have a disturbed sleep structure, which may cause daytime sleepiness and fatigue. However, they point out that the patients were reluctant to collaborate enough to create a sleep diary prior to the study, which could lead to them suffering from sleep deprivation. Moreover, no measurements of the respiratory system were performed during PSG, so undiagnosed obstructive sleep apnea may have been missed [58].

With the use of questionnaires, such as the ESS, MOS (Medical Outcome Study Sleep Scale), and SD-SDQ (Sleep

apnea scale of the sleep disorders questionnaire), Yildiz et al. [59] compared the incidence of sleep problems between patients with TLE epilepsy and ETLE. As in previous studies of this type, VEEG measurements were performed. 189 patients were assigned to the TLE (101) or ETLE (88) groups. The results of the sleep quality study showed that patients with temporal epilepsy had a higher risk of coexisting obstructive sleep apnea because the SD-SDQ score was significantly higher (15.9 vs. 14.9, p = 0.04). Although PSG had not been performed, the researchers state that TLE is associated with breathing problems during sleep. Assessment with the use of ESS and MOS scales was not able to show statistically significant differences [59].

The last article included in this review was an observational study by Turaga et al. [60], which compared overall sleep quality in epilepsy and healthy people. The ESS and PSQI questionnaires were used. The study involved 199 epilepsy patients and 48 healthy controls. People with heart, psychiatric and sleep diseases, and the mentally disabled were excluded from the study. Interestingly, the work performed by participants was taken into account, excluding people working shifts or night work, which was not often emphasized by previous research groups. 24.6% of epilepsy patients had sleep disorders, compared to 10.4% in the control group. 10% of people with epilepsy and 6.89% of healthy people achieved the ESS score ≥ 10, and comparison of the mean results in the groups also shows the advantage of the sick (4.96 in patients, 3.60 in the control group). The results of the PSQI questionnaire showed a similar trend – the total PSQI score was statistically significantly higher than in healthy subjects (3.78 vs. 2.43), confirming a positive correlation between epilepsy and sleep disorders [60].

CONCLUSIONS

The analysis of sleep and its phases in the context of various pathophysiologies attracts increasing interest in the scientific community. As mentioned at the outset, the relationship between sleep and epilepsy is known, thus the presented review of the literature focused on a specific group of epilepsy – TLE.

From the presented comparisons, similarities and differences were distinguished in the study results (Tab. 2), as well as the criteria for including patients in the study (Tab. 3). It can be concluded that sleep in people with TLE is more unstable and characterized by a higher fragmentation index. Undoubtedly, a factor that disrupts sleep is IEDs, which are sometimes difficult to record and mentioned as the test limit. In contrast, SWS appears to be an important factor in the consolidation processes in adults, but not in children.

The role of anti-epileptic drugs which influence the brain waves during sleep and desynchronize it, has been emphasized many times. However, due to the variability in the use of AEDs among the subjects, only carbamazepine was analyzed in detail. Its action has also been found to affect heart rate variability in people with sleep apnea. Therefore, analysis of similar studies should also take into account the diseases accompanying epilepsy, such as depression or sleep apnea, and with the use of validated and objective tools to determine the cause of such disorders. Moreover, it should be mentioned that the nature of the changes may be influenced by the hemisphere of the brain in which epileptic discharges occur. However, it should be pointed out that the publications analyzed in the presented literature review, were published only during the last 5 years. The reason for this limitation was the focus on the most recent research examining the relationship between sleep and TLE. Therefore, in the future, the conclusions presented in this review should be extended to include older literature for a more detailed analysis. Moreover, most of the studies analyzed emphasized the problem of too small a group of subjects, which could have influenced the obtained results.

Nevertheless, it is agreed that sleep is an important factor that should be taken into account when selecting the appropriate treatment and researching new AEDs.

Table 2. Similarities and differences in each of the presented categories. Due to the large variety of studies in the 'Other' category, they are not included in the table.

Category	Similarities and differences
Characteristic discharges	Increased neural synchronization in the NREM phase is responsible for an increase in the number of IEDs, or an increased depolarization of neurons during sleep. In the Del Felice et al. [30] study, patients were not taking medication on the day of the study. Giorgi et al. [32] pointed out that after sleep deprivation, the N2 phase shows the greatest instability, and thus an increased number of IEDs. In the study by Nayak et al. [31], the highest synchronization and number of IEDs in the N1 phase were recorded. Nayak et al. [36] exclude IEDs from their research and indicate an increased synchronization of the delta and theta bands, not only in TLE, but also in other types of epilepsy.
Memory	Miller et al. [38] and van Schalkwijk et al. [39] indicate that the longer the REM latency, the lower the percentage of SWS, which results in deterioration of learning and memory. In the Vascuoto et al. [40] study, despite the greater perceived sleepiness of patients with MTLE and hippocampal sclerosis, they did not perform worse on cognitive tests than the control group. According to Chan et al. [41], sleep in children with epilepsy enhances learning.
Heart reactivity and sleep apnea	Nayak et al. [44] suggested a possible change in reflex baroreceptor activation in TLE, and Peter-Derex et al. [43] noticed lower RR interval in patients with TLE.
Antiepileptic drugs	Nayak et al. [47] suggest some AEDs may increase sleep instability. Stefanatou et al. [48] found a link between activation of epileptiform discharges during sleep and treatment resistance.
Motor abnormalities	Giuliano et al. [50] point out a possibility that higher recurrence of arousal, caused by MTLE, can be the cause of nocturnal motor events. Geyer et al. [51] proved RLS is more common in patients with TLE, but did not suggest any cause. However, they did say that RLS can be identified as prodrome and further research on this topic is needed.
Lateralization	Nakamura et al. [52] speculate that the side (site?) of the lesion and it's characteristics could have a specific effect on sleep architecture. Gumusyayla et al. [53] showed similar results. They underline that localization may change the nature and degree of the interaction between sleep and seizure.

Table 3. Patients' classification to the study

Authors, year	Classification
Characteristic discharges	
Del Felice et al., 2015 [30]	Patients with TLE who underwent presurgical evaluation for epilepsy.
Nayak et al., 2018 [31]	Patients with diagnosed TLE attending the neurological services.
Giorgi et al., 2017 [32]	Retrospective selection of patients with TLE who underwent nocturnal PSG and SD-EEG with complete NREM/REM cycle and IEDs occurrence. Patients were excluded if they had epileptic seizures within 72 h before recording, showed a periodic leg movement or were diagnosed with psychiatric illnesses.
Nayak et al., 2018 [36]	Patients with diagnosed TLE attending the neurological services.
Memory	
Miller et al., 2016 [38]	Patients aged 18-60 years with estimated IQ not lower than 80, and without known neurological or psychiatric disorders. Neurologist classified patients based on EEG recordings, neuroimaging and seizure semiology as having TLE or extratemporal epilepsy and assessed possible lesion.
van Schalkwijk et al., 2018 [39]	Patients were diagnosed as having TLE or extratemporal epilepsy based on ambulatory EEG.
Vascouto et al., 2018 [40]	Adult patients with diagnosed refractory MTLE and hippocampal sclerosis confirmed by full interview, specialists examinations, seizure semiology, MRI and ictal video-EEG.
Chan et al., 2017 [41]	Patients were aged 6-16 years and had a diagnosis of drug-resistant focal epilepsy. Children attended mainstream school and planned hospital admission for at least four nights. No apnea or desaturations have been reported in children.
Heart reactivity and sleep apnea	
Peter-Derex et al., 2018 [43]	Patients with definite final diagnosis of TLE (and other types of epilepsy) and at least one nocturnal episode.
Nayak et al., 2017 [44]	Patients with diagnosed TLE without medication or on CBZ monotherapy.
Antiepileptic drugs	
Nayak et al., 2016 [47]	Patients with diagnosed TLE without medication or on CBZ monotherapy.
Stefanatou et al., 2019 [48]	Patients with MTLE (who fulfilled classification criteria of MTLE and underwent EEG or MRI) were divided into groups based on frequency of the seizures.
Motor abnormalities	
Giuliano et al., 2017 [50]	Patients with diagnosis of TLE made according to the 2001 International League Against Epilepsy (ILAE) criteria. Specifically with symptomatic MTLE to be certain of the location of the epileptogenic zone. MTLE diagnosis was made according to clinical, electroencephalographic and neuroimaging evidences. They also recruited healthy controls of similar age.
Geyer et al., 2016 [51]	Patients with diagnosis of epilepsy based on EEG, MRI, functional imaging, semiological features were further categorized into right TLE and left LTE. Patients not reliably categorized or with multipleictal onset zones were excluded from the study.
Lateralization	
Nakamura et al., 2016 [52]	Patients with left and right TLE, with prerequisites mentioned in the article. Authors did not mention how exactly the patients were diagnosed.
Gumusyayla et al., 2016 [53]	Patients diagnosed with unilateral TLE (right or left) according to ILAE criteria, discussed with various specialists considering clinical and electrographic features of seizures, MRI findings and positron emission tomography when available.
Others	
Surges et al., 2016 [54]	Adult patients with MTLE with quantitive MRI features of hippocampal sclerosis without other pathologies.
Gurkas et al., 2016 [55]	Paediatric patients. Video-EEG was performed to classify the epilepsy in terms of location of seizures. Generalized, temporal, frontal, occipital, parietal and multilobar were considered.
Cartella et al., 2019 [56]	Patients with left MTLE and hippocampal sclerosis, all taking anti-epileptic drugs.
Yang et al., 2016 [57]	Adult patients with diagnosed epilepsy.
Scarlatelli-Lima et al., 2016 [58]	Drug resistant MTLE patients, diagnosed according to ILAE, evaluation was conducted considering clinical history, neurological examination, MRI.
Yildiz et al., 2015 [59]	Drug-resistant epilepsy diagnosed in a multi-disciplinary case conference, considering clinical features, MRI findings, positron emission tomography and, if applicable, ictal and interictal single photon emission computerized tomography.
Turaga et al., 2016 [60]	Various epilepsies, most common type of epilepsy was chronic MTLE.

Moreover, sleep is significant fpor the patient›s quality of life, has a profound impact on its components which are, for example, physical and social functions, emotions and leisure, but may also influence the effectiveness of therapy [61].

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