



Sleep disturbances in autoimmune encephalitis

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Autoimmune encephalitis is an inflammatory neurological disorder characterized by psychiatric symptoms, cognitive impairment, and focal neurological deficits or seizures. Sleep disturbances are not a major consideration in the diagnosis and treatment of patients with autoimmune encephalitis. Various types of sleep disturbances are frequent, severe, and long-lasting, which can compromise the recovery and quality of life in patients with autoimmune encephalitis. Sleep disorders in patients with autoimmune encephalitis have received limited attention, and the prevalence and pathophysiological mechanisms of sleep disorders remain unclear. Recent studies have suggested that early recognition of specific sleep disturbances may provide clues for diagnosing autoimmune encephalitis. Furthermore, early diagnosis and treatment of sleep disturbances can promote recovery and improve long-term outcomes in patients with autoimmune encephalitis. In this report, we aimed to provide a comprehensive and extensive understanding of the clinical relevance of autoimmune encephalitis and specific related sleep disorders.

Keywords: Encephalitis, Dysomnia, Sleep disturbances, Polysomnography

Introduction

Sleep is a complex functional process, and almost one-third of a human lifetime is allocated to sleep [1]. In humans, sleep, which is not simply a state of rest, comprises multiple cyclic stages, including slow-wave sleep and rapid eye movement (REM) sleep [2]. Sleep disturbances resulting from insomnia, central disorders of hypersomnolence, sleep-related breathing disorders, and sleep-related movement disorders foster development of cardiovascular or cerebrovascular disorders.

Sleep disturbances are common in antibody-associated diseases of the central nervous system (CNS), also known as autoimmune encephalitis [3]. Sleep problems are commonly severe and persistent even after the acute phase of autoimmune encephalitis. Diverse types of sleep disorders, including sleep-wake disorders (e.g., hypersomnolence and insomnia) and sleep-related breathing disorders, may occur in patients with autoimmune encephalitis. However, sleep disturbances in au-

toimmune encephalitis have received little attention; thorough studies are lacking, as the literature mostly comprises case reports.

In the current review, we aimed to investigate specific sleep-related symptoms and disorders in autoimmune encephalitis and to highlight each sleep disorder reported in association with autoimmune encephalitis.

Assessment of Sleep Disturbances in Autoimmune Encephalitis

Sleep history

Detailed information on sleep history and medical history should be obtained from patients with sleep disturbances. Detailed evaluation of sleep history is mostly restricted in patients with autoimmune encephalitis though sleep apnea may be witnessed by a caregiver. Sleep-related information may

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also be obtained from a caregiver because patients with autoimmune encephalitis, particularly those with cognitive impairment, may not describe their sleep status appropriately. Therefore, simplified and structured questionnaires may be useful to estimate sleep problems in autoimmune encephalitis. Sleep history and questionnaires should focus on the prevalent sleep disturbances, including hypersomnolence, insomnia, parasomnia, and sleep-related breathing disorders.

Sleep questionnaires

The Epworth sleepiness scale (ESS) and Stanford sleepiness scale (SSS) are useful for detecting and quantifying subjective daytime sleepiness [4,5]. The total ESS score ranges from 0 to 24, with a score of 11 or more reflecting excessive daytime sleepiness. The SSS contains a 7-point scale ranging from 1 (very alert) to 7 (very sleepy).

The Pittsburgh Sleep Quality Index (PSQI) is a useful questionnaire for estimating sleep quality and quantity during the previous month [6]. The PSQI consists of 19 self-rated questions used to calculate the seven-dimensional components of sleep, which are evaluated on a scale of 0 to 3 points: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction. Global PSQI score, ranging from 0 to 21, is the sum of the seven component scores, with higher values indicating poorer sleep quality. A cutoff value of 5 for the global PSQI score is used to distinguish poor sleepers (>5) from good sleepers (≤ 5).

The REM sleep behavior disorder screening questionnaire was developed to assess the cardinal features of REM sleep behavior disorders according to the International Classification of Sleep Disorders [7]. The questionnaire contains 10 questions with 13 items that focus on dream enactment behavior and symptoms related to CNS diseases. In the original validation study [8], a cutoff score of 5 was defined in a cohort with heterogeneous REM sleep behavior disorder. The Korean version of the questionnaire is valid and reliable for estimation of symptoms and severity of REM sleep behavior disorder in South Koreans [9]. The REM sleep behavior disorder screening questionnaire can be a useful tool for diagnosis of REM sleep behavior disorder in patients with autoimmune encephalitis who present with vigorous, violent, and jerky movements with talking during sleep.

The STOP-Bang questionnaire (SBQ) and Berlin questionnaire (BQ) were used to identify subjects at risk for sleep apnea [10,11]. The SBQ consists of eight items, ranging in score

from 0 to 8, requiring dichotomous responses related to sleep apnea, snoring, tiredness, witnessed sleep apnea, high blood pressure, body mass index, age, neck circumference, and sex [10]. A cutoff value ≥ 3 denotes a high risk of moderate-to-severe obstructive sleep apnea (OSA), and that < 3 denotes a low risk [12]. The BQ contains 10 questions focused on three categories of snoring behavior (category 1, questions 1–5), daytime sleepiness or fatigue (category 2, questions 6–9), and obesity or hypertension (category 3, question 10). Persistent and frequent symptoms (>3–4 times per week) in at least two of the three categories are considered to denote a high risk for sleep apnea [11].

Overnight polysomnography

Polysomnography (PSG) is a standard diagnostic tool that objectively confirms sleep architecture, sleep patterns, and the presence of sleep disorders. The total sleep time may be shortened due to prolonged sleep latency, frequent arousal, and elevation of wakefulness after sleep onset. For 1 week before the PSG study, the patients are instructed not to drink alcohol or caffeinated beverages and to sleep and wake regularly. The PSG contains a six-channel electroencephalogram (EEG), a four-channel electrooculogram, an electromyogram, and an electrocardiogram. A thermistor, nasal air pressure monitoring sensor, oximeter, piezoelectric bands, and body position sensor are applied to the patient.

Combined polysomnography and video-electroencephalogram monitoring

The standard montage used in overnight PSG, including bilateral frontal, central, and occipital leads, is limited in its ability to differentiate nocturnal seizures and parasomnia compared with extended EEG montages [13,14]. Combined PSG with standard EEG montage utilizing an 18-channel EEG could provide accurate diagnostic value for sleep disorders in both adults and children with epilepsy [13,15].

Sleep Disturbances in Autoimmune Encephalitis

Central disorders of hypersomnolence (excessive daytime sleepiness)

Hypersomnolence is a term that describes the symptom of excessive sleepiness, whereas hypersomnia indicates specific disorders including idiopathic hypersomnia. Scales such as the ESS or SSS can be useful for detecting or quantifying the degree of excessive daytime sleepiness. Severe reduction of total sleep time reportedly occurs at disease onset and is fol-

lowed by hypersomnia during the recovery phase in patients with anti-*N*-methyl-*D*-aspartate (NMDA) receptor encephalitis [16]. Hypersomnia is prevalent in specific autoimmune encephalitides, including anti- α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor encephalitis, anti-di-peptidyl-peptidase-like protein 6 (DPPX) encephalitis, and anti-IgLON5 (immunoglobulin-like cell adhesion molecule 5) disease [3]. Cataplexy is defined as more than one episode of generally brief (<2 minutes) sudden loss of muscle tone with retained consciousness [17]. Excessive daytime sleepiness and cataplexy are core features of narcolepsy type 1. Narcolepsy with cataplexy has been reported in anti-Ma2 encephalitis, especially with involvement of the hypothalamus [18]. Narcolepsy is present in autoimmune encephalitis with anti-aquaporin-4 IgG antibody [19]. However, hypersomnolence remains under-reported in patients with autoimmune encephalitis.

Insomnia

Insomnia is characterized by difficulty initiating or maintaining sleep, resulting in general sleep dissatisfaction [17]. The daily pattern of the sleep-wake cycle can be estimated with a sleep log (sleep-wake diary) or actigraphy, a validated noninvasive accelerometer for objective measurement of sleep parameters and average motor activity over a period of days to weeks. Insomnia is a common sleep-related symptom in autoimmune encephalitis and has been reported in many autoimmune encephalitides, including anti-NMDA receptor, anti-Caspr2, and occasionally anti-leucine-rich glioma inactivated 1 (LGI1) encephalitis [20-22]. Patients with insomnia and autoimmune encephalitis usually present with acute and severe insomnia (sometimes not sleeping for days or weeks), hallucinations, or abnormal behavior.

Sleep-related breathing disorders

Sleep-related breathing disorders include OSA disorders and central sleep apnea syndromes according to the third edition of the International Classification of Sleep Disorders [17]. Apnea is defined as a reduction in the amplitude of airflow by 90% or more, lasting at least 10 seconds. Apnea can be further classified as obstructive or central if inspiratory effort is present or absent, respectively, throughout the period of apnea. Hypopnea is defined as a reduction in airflow of 30% or more, lasting at least 10 seconds, and associated with $\geq 3\%$ oxygen desaturation or arousal [23]. OSA is graded according to the apnea-hypopnea index (AHI): AHI of <5 (events/hour) is normal, AHI of ≥ 5 and <15 is mild OSA, AHI of ≥ 5 and <30 is moderate OSA, and AHI of ≥ 30 is severe OSA.

Patients with autoimmune encephalitis are vulnerable to upper airway obstruction during nocturnal sleep [3]. OSA has been reported in patients with DPPX, LGI1, and IgLON5. Interestingly, patients with anti-IgLON5 disease present with both OSA and nocturnal laryngeal stridor, sleep-related laryngospasm, commonly seen in multiple system atrophy [24,25]. OSA originates from obstruction of the upper airway, such as the pharynx; stridor is evoked from narrowing of the lower airway, including the larynx or vocal cords [17]. Continuous positive airway pressure treatment is effective in eliminating both stridor and sleep apnea [26]. Patients with anti-Hu encephalitis present with central hypoventilation syndromes [27] that may be caused by brainstem dysfunction.

Parasomnia

Parasomnias are abnormal sleep-related complex movements, behaviors, emotions, perceptions, dreams, and autonomic nervous system activity [17]. Parasomnias may occur during REM sleep or non-REM sleep. The differential diagnosis of parasomnias and nocturnal seizures is complex, especially in patients with autoimmune encephalitis. Combined PSG with simultaneous video-EEG monitoring is crucial to enhance diagnostic accuracy.

REM sleep behavior disorder, the most common form of REM-related parasomnia, is characterized by abnormal dream-related behaviors during REM sleep, resulting in injury or sleep disruption. This feature of REM sleep behavior disorder can be observed in several types of autoimmune encephalitis such as anti-DPPX, anti-LGI1, anti-Caspr2, anti-Ma2, and anti-IgLON5 [24,28-31]. In patients with NMDA receptor encephalitis, both REM sleep behavior and non-REM parasomnia such as confusional arousal have been described [16,32].

Sleep-related movement disorders

Sleep-related movement disorders are relatively simple and stereotypical movements that disturb sleep or its onset. Periodic limb movements during sleep (PLMS) are periodic episodes of repetitive, highly stereotyped limb movements, mostly in the lower extremities [17]. PLMS reportedly occurs in patients with anti-IgLON5 disease, anti-DPPX encephalitis, anti-LGI1 encephalitis, and anti-Ma1/Ma2 encephalitis [28,31-33].

Restless legs syndrome, which is closely linked to PLMS, is a sensorimotor disorder with complaint of a strong, irresistible urge to move mostly the lower limbs [17]. New or worsening symptoms of restless legs syndrome were reported in patients with specific autoimmune encephalitis such as anti-LGI1 and anti-Ma1/Ma2 [32].

Specific Autoimmune Encephalitis is Highly Linked to Sleep Disorders

Anti-NMDA receptor encephalitis

Sleep disorders were most frequently reported in the anti-NMDA receptor form of encephalitis [34-36]. During the acute phase, up to 90% of patients show severely reduced quantity of sleep or insomnia [16,22,35,37]. During the recovery phase, a shift of sleep pattern occurs from insomnia to hypersomnia. In video-PSG recordings, abnormal behaviors including hyperphagia, hypersexual behavior, and confusional arousals are frequently associated with anti-NMDA receptor encephalitis.

Morvan syndrome

Approximately 80% of patients with Morvan syndrome have Caspr2 antibodies, some patients have LGI1 antibodies [38], and 50% of those with Morvan syndrome have thymoma [39]. Morvan syndrome is characterized by peripheral nerve hyperexcitability, autonomic dysfunction, encephalopathy with confusion, frequent visual hallucinations, and severe insomnia. The prevalence of sleep disorders is up to 93% in patients with Morvan syndrome [38,39]. Morvan syndrome should be considered if a patient presents with acute-onset severe insomnia, excessive sweating, and 24-hour motor hyperactivation or parasomnia with dreaming or hallucination.

Anti-IgLON5 disease

Anti-IgLON5 disease is characterized by unique sleep disturbances associated with brainstem dysfunction and gait instability. Greater than 80% of anti-IgLON5 disease patients were reported to suffer from sleep disturbances. Many types of sleep disorders, including insomnia, hypersomnia, parasomnia, sleep-related movement disorder, and sleep-disordered breathing, can be observed in anti-IgLON5 disease [24,25,40-42]. Insomnia and hypersomnia may coexist in 70% of patients. Complex sleep behaviors with vocalization are frequently observed during non-REM sleep. The characteristic PSG findings in previous studies are decreased total sleep time and abnormal non-REM sleep architecture with the absence of vertex sharp transients, sleep spindles, K-complexes, and delta slowing [42,43]. Sleep-related breathing disorders such as OSA and nocturnal laryngeal stridor are very frequent in patients with anti-IgLON5 disease [24,41]. REM sleep behavior disorders and PLMS were frequently reported in patients with anti-IgLON5 disease [31,41,44].

Conclusions

Sleep disturbances are a prevalent and crucial component of autoimmune encephalitis. Hypersomnia, narcolepsy, insomnia, OSA, parasomnia, and PLMS are commonly associated with autoimmune encephalitis. Sleep problems should be highlighted to improve the diagnosis and treatment of sleep disorders, which can reduce morbidity and enhance long-term outcomes in autoimmune encephalitis. Further research is required to elucidate the pathophysiology of each type of autoimmune encephalitis and associated sleep disorders.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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