Introduction

Sleep is a fundamental, recurrent behavior exhibiting a physiological state of rest and reduced consciousness [1]. Sleep homeostasis is tightly regulated by complex circadian systems that show roughly a 24-hour pattern in the regular cycle of sleep and wakefulness [2,3]. Sleep plays a crucial role in health, affecting both the nervous system and immune function [4]. Sleep and the immune system are interconnected through the effects of circadian systems on immune functions via the neuroendocrine and sympathetic systems. The immune system responds to such signals by releasing cytokines that influence sleep and circadian mechanisms [5,6]. In addition to understanding the basic physiology of sleep and its connection to the immune system, the recent discovery of novel autoantibodies in neuroimmunological disorders has generated additional interest in the dynamic interaction between sleep and the immune system. In this review, the complex relationship among sleep, immune regulation, and neuroimmunological disorders was examined with emphasis on the vital role of sleep in modulating immune function and its influence on these conditions. This relationship emphasizes the importance of assessments and management of sleep quality in the treatment approaches for neuroimmunological disorders.

Keywords: Sleep, Neuroimmune interaction, Circadian rhythm, Neurologic autoimmune disease
Sleep and immune system interactions

Physiology of interactions between sleep and the immune system

Sleep initiation and control are mediated by complex networks involving hypothalamic brain regions, the arousal system, and the circadian system [17]. The sleep and circadian systems modulate immune responses through neuroendocrine and sympathetic pathways, and the immune system influences these processes through cytokines [3,18]. Growth hormone and prolactin levels peak at night, even in the absence of sleep; however, these peaks can be further enhanced by sleep. Prolactin can play an immunomodulatory role through cytokine receptor modulation, and growth hormones can stimulate the proliferation of T/B cells and the synthesis of immunoglobulins [19,20]. Conversely, cortisol and catecholamines undergo suppression during sleep and are controlled by the activity of the hypothalamus-pituitary-adrenal axis and the sympathetic nervous system, respectively [21,22]. These stress hormones are the key mediators of the connection between sleep and the immune system. Dimitrov et al. [23] showed that circadian rhythms are differentially regulated by cortisol and epinephrine levels based on the number of circulating T cells. Naïve T cell subsets exhibit a negative correlation with cortisol rhythms, peaking during the night, and effector CD8+ T cell counts are positively correlated with epinephrine rhythms, reaching peak levels during the daytime (Table 1). Increases in cortisol during the daytime can cause an increase in CXCR4 expression, which can facilitate the redistribution of naïve T cells to the bone marrow. Daytime elevations in catecholamines may attenuate CD11a/CX3CR1-mediated attachment to the endothelium, potentially promoting the mobilization of effector CD8+ T cells from the marginal pool [23,24]. The circulating natural killer (NK) cell count also peaks in the early morning and is low at night and mediated through CD11a/CX3CR1 signaling [25]. Therefore, during sleep, early-stage immune cells likely circulate in the blood, priming for adaptive immune responses, while cytotoxic effector functions dominate during wakefulness [18].

Cytokine activities exhibit circadian rhythms under neuroendocrine control [3,26,27]. Key proinflammatory cytokines such as interleukin (IL)-6, IL-12, tumor necrosis factor alpha (TNF-α), and interferon gamma typically reach their peak levels at night [26–29]. In contrast, the anti-inflammatory cytokine IL-10 shows sleep-dependent fluctuations, peaking during the daytime. Although these patterns were observed in most studies, discrepancies in IL-6 and IL-10 behavior have been reported [27,30]. Cytokines also can play an important role in sleep regulation; IL-1 and TNF-α were observed to enhance non-REM sleep, while their inhibition can suppress spontaneous sleep [31].

Sleep deprivation and immune function

The intricate interactions among the sleep/circadian system, immune cells, and cytokines are significantly altered by periods of sleep deprivation, which can introduce substantial stress that adversely affects health and immune function [18,32]. Prolonged sleep deprivation has been associated with increased proinflammatory activity, similar to that observed in chronic sleep disturbances. Notable elevations in inflammatory markers such as IL-6, TNF-α, and C-reactive protein have been observed following sleep deprivation [33]. Furthermore, sleep deprivation can lead to decreased cytokotoxic activities in T cells and NK cells along with a reduction of T cell proliferative capacity [34,35]. Research on monocytes shows that sleep loss induces a functional alteration of the monocyte proinflammatory cytokine response [36]. In a previous study, acute sleep deprivation was shown to elevate anti-inflammatory cytokine IL-10 level but to have little effect on the ratio of TNF-α/

Table 1 Variations of immune cells and cytokines related to sleep

<table>
<thead>
<tr>
<th>Variable</th>
<th>During sleep</th>
<th>Daytime</th>
<th>Sleep deprivation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naïve T cell</td>
<td>↑</td>
<td>↓</td>
<td>Reduced proliferative capacity</td>
</tr>
<tr>
<td>Effector cytotoxic T cell</td>
<td>↓</td>
<td>↑</td>
<td>Decreased counts and cytotoxic activity</td>
</tr>
<tr>
<td>Natural killer cell</td>
<td>↓</td>
<td>↑</td>
<td>Decreased cytotoxic activity</td>
</tr>
<tr>
<td>Monocytes</td>
<td>No change</td>
<td>No change</td>
<td>Decreased function of proinflammatory cytokine response</td>
</tr>
<tr>
<td>IL-6</td>
<td>↑</td>
<td>↓</td>
<td>Increased level</td>
</tr>
<tr>
<td>IL-10*</td>
<td>↓</td>
<td>↑</td>
<td>Not altered</td>
</tr>
<tr>
<td>IL-12</td>
<td>↑</td>
<td>↓</td>
<td>Increased level</td>
</tr>
<tr>
<td>TNF-α</td>
<td>↑</td>
<td>↓</td>
<td>Increased level</td>
</tr>
<tr>
<td>IFN-γ</td>
<td>↑</td>
<td>↓</td>
<td>Increased level</td>
</tr>
</tbody>
</table>

↑, increased; ↓, decreased; IL, interleukin; TNF-α, tumor necrosis factor alpha; IFN-γ, interferon gamma.

*Some studies have reported the absence of circadian variation.
IL-10 [37]. In another study that included college students with sleep insufficiency, increased IL-10 levels were observed. Additional research is required to elucidate the contradictory results for IL-10 in the context of sleep deprivation [38]. Despite the diversity in experimental designs and definitions of sleep deprivation in studies, a common finding is that sleep deprivation promotes proinflammatory activity and attenuates immune function. The variations in immune cells and cytokines associated with sleep are presented in Table 1 and Figure 1.

Clinical aspects of sleep and neuroimmunological disorders

Alteration of sleep as a risk factor for neuroimmunological disorders

Due to the relationship between sleep and the immune system and the effects of sleep deprivation on immune function, alterations in sleep can be considered a risk factor for neuroimmunological disorders. This connection is well documented in studies on multiple sclerosis (MS). An association between shift work and subsequent risk of MS has been established; starting shift work before 20 years of age was found to significantly increase MS risk [39]. Other studies in which nurse cohorts were included, a history of night shift work spanning 20 years or more was associated with increased risk of MS [40]. Therefore, beginning shift work at a younger age appears to significantly influence the association between shift work and MS risk. Furthermore, research conducted in Sweden on sleep patterns and risk of MS in adolescence revealed that insufficient sleep and poor sleep quality during adolescence increased the risk of MS in a dose-dependent manner [41]. Thus, adequate sleep at a young age, essential for proper immune function, could be a preventive factor against MS [41].

Sleep loss is associated with the disease activity of many autoimmune conditions, including systemic lupus erythematosus, Sjögren disease, and inflammatory bowel disease [42–44]. Similarly, the outcome of MS is associated with sleep quality; poor sleep quality negatively affects MS outcomes by possibly influencing the efficiency of remyelination processes [45]. In a previous study, sleep disturbance was indicated as a possible trigger for acute MS exacerbation [46]. Sleep should be regarded as an important clinical factor when evaluating the disease activity of neuroimmunological disorders.

Sleep-related clinical features of neuroimmunological disorders

The influence of sleep disturbance on immune regulation is bidirectional, as imbalances in the immune system can contribute to sleep disruptions. Central nervous system (CNS) demyelinating disorders may result in brain lesions in sleep- and/or circadian rhythm-related brain structures, leading to symptomatic sleep disorders. Inflammation within the CNS may be directly related to sleep disturbance, and autoanti-

Figure 1 Interactions between sleep and immune function

NK, natural killer; IL, interleukin; TNF-α, tumor necrosis factor alpha; IFN-γ, interferon gamma.

*There are inconsistent reports in other studies.
bodies targeting neuronal proteins in the brain may cause sleep disorders [47].

Symptomatic narcolepsy cases consist of heterogeneous disease conditions, often involving lesions in the hypothalamus [48]. Although AQP-4 is highly expressed in hypothalamic periventricular regions, MS can present as symptomatic narcolepsy with hypothalamic lesions. NMOSD, which is associated with a disease-specific autoantibody targeting AQP-4, can frequently exhibit hypothalamic lesions accompanied by symptomatic narcolepsy [49]. Patients with MS may be at increased risk of obstructive sleep apnea, especially when they have brainstem lesions [50]. In addition, chronic insomnia is a common issue among MS patients [51]. Fatigue in MS has been the subject of extensive research due to its significant effect on patients. Evaluating sleep quality is essential for assessing fatigue and depression, which are critical factors for quality of life in MS patients [52]. Therefore, sleep evaluation should be included in a clinical assessment for MS patients. Individuals with NMOSD may experience diminished sleep quality from the early stages of the disease [13]. One study using polysomnography in NMOSD cases showed that sleep architectures in NMOSD patients are markedly disrupted [9]. Myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD), for which diagnostic criteria have only recently been established [8], has yet to be extensively studied in terms of sleep. Hypersomnia with hypothalamic lesions was reported in a MOGAD patient [53].

Sleep can be altered in various ways, with all types of sleep disorders potentially arising in autoimmune encephalitis. However, such sleep-related symptoms are frequently unnoticed due to the predominance of other neurological and psychiatric symptoms [7]. Insomnia associated with autoimmune encephalitis, such as anti-NMDAR, anti-Caspr2, and anti-LGI1 encephalitis, is typically acute and severe, often accompanied by hallucinations or abnormal behaviors [54,55]. In patients with anti-NMDAR encephalitis, the disease typically progresses through two main clinical phases: acute and recovery. Sleep disturbances also follow this pattern, with insomnia commonly occurring in the early acute stage and later being replaced by hypersomnia. This transition between clinical phases is closely associated with decreased NMDAR levels, followed by a gradual restoration of NMDAR function. Therefore, NMDAR function plays a key role in the occurrence of insomnia and the subsequent hypersomnia in anti-NMDAR encephalitis [56].

Anti-immunoglobulin-like cell adhesion molecule 5 (IgLON5) disease is characterized by complex sleep disorders. Due to the rarity and gradual progression of this condition, such sleep disturbances may be a key indicator for diagnosis. Ap-

| Table 2 Clinical characteristics of sleep alteration in neuroimmunological disorders |
|---------------------------------|---------------------------------|---------------------------------|
| Disorder                        | Autoantibody                   | Associated brain lesion         | Clinical features                |
| Multiple sclerosis              | None                           | Hypothalamic lesion             | Symptomatic narcolepsy          |
|                                 |                                |                                 | Poor sleep quality               |
|                                 |                                |                                 | Insomnia                        |
| NMOSD                           | Anti-aquaporin4 Ab             | Hypothalamic lesion             | Symptomatic narcolepsy          |
|                                 |                                |                                 | Poor sleep quality               |
| MOGAD                           | Anti-MOG Ab                    | Hypothalamic lesion             | Hypersomnia                      |
| Autoimmune encephalitis        | Anti-NMDAR Ab                  | Reticular activating system     | Insomnia                        |
|                                 | Anti-LGI1-Ab                   | Reticular activating system     | Hypersomnia                      |
|                                 | Anti-Caspr2 Ab                 | Thalamic/hypothalamic lesion    | Insomnia                        |
|                                 |                                | Limbic system                   | Hypersomnia                      |
|                                 | Anti-IgLON5 Ab                 | Reticular activating system     | Morvan syndrome                  |
|                                 |                                |                                 | Insomnia                        |
|                                 | Anti-Hu Ab                     | Medulla neuronal loss*          | RBD                             |
|                                 | Anti-Ma2 Ab                    | Brainstem neuronal loss*        | OSA                             |
|                                 |                                |                                 | Non-REM parasomnia               |
|                                 |                                |                                 | Central hypoventilation          |
|                                 |                                |                                 | Symptomatic narcolepsy          |

Ab, antibody; NMOSD, neuromyelitis optica spectrum disorders; MOGAD, myelin oligodendrocyte glycoprotein antibody-associated disease; NMDAR, N-methyl-D-aspartic acid receptor; LGI1, leucine-rich glioma-inactivated 1; RBD, REM sleep behavior disorder; OSA, obstructive sleep apnea.

*Reported in autopsy studies.
proximately 70% of patients experience insomnia with excessive daytime sleepiness. Laryngeal stridor and unusual behaviors during sleep can be identified [7,57]. In addition, REM sleep behavior disorder is frequently observed, with prominent limb and body jerks. The precise pathomechanisms of anti-IgLON5 disease and its associated sleep disturbances remain unclear. However, some studies have shown that sleep abnormalities in anti-IgLON5 diseases can be modified or normalized after immune therapies, indicating a relationship between the immune system and sleep abnormalities in this disease [57]. Further studies are needed to clarify the pathophysiology of sleep disturbance in anti-IgLON5 disease. Other types of sleep manifestations in neuroimmunological disorders are presented in Table 2 [58].

It is crucial to recognize that drugs used to treat these neuroimmunological disorders can impact sleep. For example, steroids can cause insomnia, neuroleptics can lead to hypersomnia, and certain benzodiazepines may induce abnormal behaviors during sleep. These side effects of treatment are common in clinical practice and should be considered in the management of affected patients.

**Conclusion**

This review has highlighted the complex interconnection between sleep, the immune system, and neuroimmunological disease. Immune cells and cytokines have circadian variations. Notably, inadequate sleep and sleep deprivation can disrupt these rhythms and are potential contributors to the onset and worsening of neuroimmunological disorders. Sleep and neuroimmunological diseases have a two-way relationship, and neuroimmunological diseases can cause sleep disorders. By integrating sleep management into the therapeutic strategy for these conditions, clinicians can offer more targeted and effective treatments, ultimately improving outcomes and quality of life for patients with neuroimmunological diseases.

**Conflicts of Interest**

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

**Author Contributions**

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**References**

potential immunomodulatory therapeutic effect. Cytokine 2023;169:156253.


