

Sleep Disorders in Patients after COVID-19

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Healthy sleep is required to ensure the body's homeostatic stability, the consistency of immunological reactions, and optimum functioning of the internal organs, the nervous system, and cognitive functions. Patterns of changes to the circadian rhythms have been studied in many diseases, though infection with SARS-CoV-2 is a new reality and the basic mechanisms of functioning of the body in this pathology require deeper investigation. Despite the difficulty of analytical investigations in pandemic conditions, experience of the diagnosis of COVID-19 has now been acquired and treatment algorithms have been developed for different clinical situations; vaccines have been developed. Least studied are questions of the long-term sequelae of COVID-19. At the same time, there are good grounds for suggesting that patients need long-term rehabilitation in the post-covid period of SARS-CoV-2, for reasons including damage to the nervous system. Analysis of publications – from descriptions of clinical cases to literature reviews – allows empirical experience to be accumulated, providing the opportunity for future identification of prognostic markers for the disease for effective prevention of long-term sequelae. The results of current prospective studies draw attention to the occurrence of dyssomnia and obstructive sleep apnea not only as a common consequence of coronavirus infection, but also as a factor significantly worsening the prognosis in the acute period of illness. It has repeatedly been shown that sleep deprivation has adverse influences on the body's resistance, including to SARS-CoV-2, and requires correction to improve prognoses in the acute and long-term periods of illness in COVID-19 patients.

Keywords: COVID-19, SARS-CoV-2, sleep disorders, insomnia, dyssomnia, obstructive sleep apnea.

WHO assessments indicate that the situation regarding the incidence of the new coronavirus infection (COVID-19) on May 14, 2021 is >160 million infections and that the number of confirmed deaths has passed 3.3 million, despite the fact that more than 1.264 billion doses of vaccine have now been given. The clinical characteristics of disease in the acute stage and its pathogenesis and complications continue to be actively researched. Least studied are questions of the long-term sequelae of SARS-CoV-2 infection, which is entirely natural and is associated with a multitude of factors, the main one of these indisputably being time. As data have accumulated, more and more new sequelae of the disease become apparent, and many studies detecting the long-term signs of COVID-19 infection have been and are now being conducted.

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The aim of the present work was to analyze information on the effects of COVID-19 infection on the state of patients' sleep.

Sleep Disorders in the COVID-19 Pandemic. Sleep is a physiological state which plays a key role in maintaining homeostasis, immune system functioning, energy metabolism, cognitive functions, and neuronal plasticity [1]. Sleep regimes have undergone significant changes in the modern world, especially when a profession involves night shifts, which produce significant inversion of circadian rhythms [2].

The new coronavirus pandemic produced novel global factors with adverse influences on sleep. Most countries have introduced self-isolation regimes. Fear and uncertainty associated with the infection itself and with thoughts of social wellbeing on the background of restrictions undoubtedly influence people's mental health; lack of socialization and limited contacts with people in general and loved ones

in particular during the pandemic initiate the development of depression and anxiety [3, 4] and adversely influence qualitative and quantitative sleep indicators.

Studies in Google Scholar and PubMed raise interest in a number of studies on the effects of a number of social-demographic characteristics in COVID-19 patients on sleep quality. Thus, work reported by Akinci and Basar [5] included 189 patients (78 women and 111 men) divided into groups depending on Pittsburgh Sleep Quality Index (PSQI) scores. Assessment of the results established that the occurrence of sleep disorders was linked with longer-lasting hospitalization of patients with COVID-19 and higher incidences of depression. A cohort study reported by Huang et al. [6] (1733 patients) addressed all possible sequelae of COVID-19. Division of COVID-19 patients into groups depending on severity in the acute phase of illness on the Ordinal Scale for Clinical Improvement (OSCI), recommended by the WHO, revealed a correlational relationship between severity in the acute phase of illness and the duration of particular symptom complexes in the postcovid period. The most consistent manifestations of the postcovid period were fatigue and muscle weakness (63%). Anxiety and depression were found in 23% of COVID-19 patients and sleep disorders in 26%. Prolonged persistence of these symptoms was found to be typical of patients with severe clinical manifestations in the acute phase, of 5–6 points on the OSCI, but not typical of the group of patients scoring 3 on the OSCI. Similar patterns were reported by Lam et al. [7] in a group of SARS-CoV-1 patients, among whom 40% experienced chronic tiredness or fatigue.

A meta-analysis run by Jahrami et al. [8] established that sleep disorders during the pandemic were found in 35.7% the population, while COVID-19 was diagnosed in 74.8% of patients with dyssomnia. The authors noted that among the methods used for sleep studies, the most sensitive is the PSQI. Assessing the prevalence of sleep disorders in medical workers, the authors found a level comparable with that in the general population – 36%. Current publications have now presented a good number of results from small studies and clinical cases [9–13], also confirming the fact that sleep disorders occur in the postcovid period.

Apart from insomnia, SARS-CoV-2 patients just as frequently show respiratory disorders during sleep (RDDS). The structure of RDDS covers a quite wide spectrum of pathological states [14], though the commonest in this group of disorders is obstructive sleep apnea (OSA). It has been estimated that nearly a billion adults aged 30–69 years have OSA [15], with repeated partial or complete obstruction of the respiratory passages during sleep, leading to impaired respiratory biomechanics, decreased blood oxygen levels, and waking from sleep. An extensive systematic review prepared by Miller and Cappuccio [16] indicated that a multitude of OSA-associated risk factors were linked with unfavorable outcomes of COVID-19. Studies reported by Cariou et al. – the CORONADO study [17] – showed that the occurrence of OSA could be an independent risk factor

for death from COVID-19. However, continuation of the study is required for this to be confirmed.

Pathogenetic Components of the Influence of Sleep Disorders on the Body. Sleep deprivation has various adverse consequences: decreased levels of physical and mental activity, along with increases in the risks of cardiovascular, cerebrovascular, and endocrine organ diseases. While stress can have adverse influences on sleep quality [19], this latter can in turn lead to impairments to immunity [20, 21]. The stress-activated sympathoadrenal system (SAS) has detrimental effects on sleep. Sleep disorders in turn start to stimulate the SAS, triggering a vicious circle [22]. The activated SAS suppresses proinflammatory and anti-inflammatory immune responses [23].

Healthy sleep maintains the regular expression of monocytes, macrophages, and dendritic cells in the immune system during the day. This stability can be impaired in dyssomnias. For example, interleukin-6 release peaks occur in normal conditions at 05:00 and 19:00. However, sleep deprivation can change these times [24, 25].

Chronic dyssomnia can influence the relative distribution of immune cell phenotypes, with decreases in the levels of CD3⁺, CD4⁺, and CD8⁺ cells [26]. Partial or complete sleep deprivation for one night decreases interleukin-2 production by T cells [27–29], while prolonged deprivation was associated with a shift in the balance towards the activity of Th-2 cytokines over Th-1 cytokines, altering the immune response in favor of a predominance of B-cell immunity [30–34]. This shift can have deleterious effects when the body is infected or on vaccination. This was found in one study: even one night with sleep deprivation in experimental conditions decreased the immune response on vaccination against influenza A virus and hepatitis A virus [35].

Approaches to Correcting Sleep Disorders in the COVID-19 Pandemic. Many working groups were formed during the pandemic to solve various strategic problems dictated by the epidemiological situation. Sleep disorders, recognized as serious consequences of SARS-CoV-2 infection, also pose a task for specialists. The Working Group of the European Academy for Cognitive Behavioral Therapy has developed practical recommendations for preventing and treating sleep disorders: cognitive behavioral therapy for insomnia (CBT-I) [36]. The authors proposed methods both for the population as a whole and for particular social groups such as mothers with children and medical workers. A significant drawback of the recommendations is the lack of an indications of the level of evidence supporting the medication therapy proposed. CBT-I is suggested as first-line treatment, as this method has the best evidence base. When CBT-I is ineffective, short-term use of benzodiazepines may be effective. Sedative antidepressants may be useful in the short-term perspective, particularly if comorbid states include anxious and depressive mental disorders.

It should be noted that CBT-I is recognized and recommended by organizations such as the British Associa-

tion for Psychopharmacology and the American College of Physicians [37–41]. Liu et al. [42] suggested an alternative method of treating insomnia, i.e., progressive muscle relaxation. The Jacobson relaxation technique used by patients with confirmed COVID-19 produces improvements in sleep quality and reductions in anxiety levels in five days.

Conclusions. Results from studies summarizing observations made during the SARS-CoV-2 pandemic and published in the non-Russian press point to a link between dyssomnia and both the acute stage of COVID-19 and the period of long-term sequelae. At the same time, generally accepted data on the negative effects of sleep deprivation on the immune system acquire special significance in the context of the new coronavirus infection, whose pathogenesis requires further and deeper investigation. The problem raised here – sleep disorders in coronavirus infections – is of interest both for science and for practical neurology. There is a current need to create favorable conditions for rehabilitation of COVID-19 patients. At the same time, studies of the pathogenetic bases of disorders associated with SARS-CoV-2 will allow the conditions for prompt diagnosis and pathogenetically based treatment of this severe and insufficiently investigated infectious disease, which poses a real threat to humanity, to be created.

The authors declare no conflict of interest.

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