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Infections, Pandemics, and Sleep Disorders

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Studies of the neurological symptoms and signs associated with the acute and late phases of infectious diseases are important in pandemic conditions. The novel coronavirus infection (COVID-19) pandemic has increased the number of patients with sleeplessness, this being an adverse prognostic factor for infections. This review addresses the factors and mechanisms of sleep impairments and their relationship with inflammation and immune system dysfunction in infectious diseases. In particular, impairments to the functioning of the melatoninergic system are discussed as the cause of sleeplessness during pandemics. The relevance of developing measures for rehabilitating patients, particularly use of Sonnovan to restore normal sleep, which plays a fundamental role in supporting people's mental and physical health, is emphasized.

Keywords: sleep impairments, sleeplessness, pandemics, infection, COVID-19, SARS-CoV-2, anxiety, depression, melatonin, Sonnovan.

The body interact with microorganisms from the moment people are born all the way to the end of life. Studies of this question have for many centuries been among the most relevant challenges in medical sciences. Searching in the international PubMed database (February 2021) identified more than 3.5 million scientific articles for the search term "infection," which is significantly greater than the number of publications on, for example, "pain" (fewer than 0.9 million) or "stroke" (fewer than 0.4 million); the number of articles published annually has doubled in the last 10 years to about 0.2 million [1].

On entering the human body, pathogenic microorganisms can produce clinical manifestations or latent infectious diseases (carriership), or slow infections can develop. Any infection can involve the human nervous system in one way or another. Pathological changes arise as a result of direct entry of microorganisms into nervous system tissues, or via actions on their structural components or metabolites, or by means of secondary lesions to the nervous system.

Among the main clinical manifestations of most infections are symptoms evidencing nervous system reactions: fever, elevated fatigue on physical or mental exercise, headache, pain in the limbs or other body parts, paresthesia, itch, changes in appetite, vertigo, sleeplessness, and/or increased sleepiness. Many infectious diseases start with symptoms and signs of CNS involvement. Changes in sleep constitute an important and common symptom, not always obvious to patients or their treating doctors and not always assigned any importance as the focus is on fever, pain, impaired nasal respiration, cough, and stool disorders – all of which prevent normal sleep.

Interest in studies of nervous system damage in infectious diseases increases in epidemics and pandemics.

The current pandemic of the novel coronavirus infection (COVID-19) has raised numerous questions for wide-ranging interdisciplinary collaboration. During the pandemic, the outcome of the infectious disease in any individual depends not only on the results of the interaction between the pathogen and the body and the individual efficacy and safety of the treatment provided, but also on the patient's psychological state and behavior and the local organization of medical care. The outcome of acute infectious diseases during pandemics can influence sleep duration and quality. During reconvalescence, the prognoseis for recovery of impaired functions depends largely on whether or not patients have asthenia, sleepiness, and/or sleeplessness.

Studies of the anatomical, physiological, biochemical, physical, and molecular bases of the regulation sleep and waking have been pursued for many years [2]. Koval'zon

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took the view [3] that sleep should be regarded as a "particular genetically determined state of the human (and warm-blooded animal) body characterized by a consistent sequence of replacement of particular polygraphic patterns in the form of cycles, phases, and stages."

The states of sleep and waking are controlled by neurochemical systems whose main transmitters are acetylcholine, dopamine, noradrenaline, serotonin, histamine, and orexin. Melatonin is important in regulating circadian rhythms, and this has been confirmed by clinical data on the therapeutic efficacy of melatonin formulations in post-infection sleep impairments accompanied by CNS damage [4, 5].

Some groups of cells regulating sleep and waking may be targets for inflammatory processes and are not infrequently involved in infections. Inflammatory cytokines can be expressed in the suprachiasmatic nucleus (SCN) of the hypothalamus: interleukins (IL)-1r and IL-6, tumor necrosis factor α (TNF-α), and interferon-γ (IFN-γ) [6, 7]. IFN-γ and TNF-α are expressed rhythmically [8]. The chemokine CXCL12 and its receptor CXCR4 are expressed in the SCN [9, 10]. CXCR4 expression has been observed in neurons producing melatonin-concentrating hormone (MCH) [11]. Fractalkine (chemokine CX3CL1) and its receptor CX3CR1 are expressed in the thalamus [12]. Chemokine CCL2 and its receptor CCR2 are expressed in the basal nuclei, thalamic nuclei, and raphe nuclei [13, 14]. Experimental studies have shown that neurons producing MCH are sensitive to signal transmission mediated by chemokine CCL2 and can react to administration of lipopolysaccharides (LPS) and components of the outer wall of Gram-negative bacteria [15]. Orexinergic neurons (ON) themselves are evidently not sensitive to inflammation. However, their activity in experimental conditions of LPS-induced lethargy can be suppressed by GABAergic interneurons [16]. On the other hand, ON is sensitive to increased nitric oxide (NO) production, which may be linked with induction of neuronal NO synthase in local inflammatory reactions [17].

In acute infectious diseases, the adaptive response of the neurons, apparent as fever, pain, loss of appetite, and drowsiness, promotes successful functioning of the human immune system on interaction with microorganisms. Drowsiness preserves the energy required for increasing body temperature, which in turn increases leukocyte activity and inhibits microbial multiplication [18]. Experimental studies in animals infected with influenza virus [19], *Staphylococcus aureus* [20] or *Escherichia coli* [21] bacteria, or *Candida albicans* fungi have demonstrated increases in the duration of the subsequent period of decreased slow-wave sleep activity [18] and increases in electroencephalogram (EEG) slow-wave amplitude during sleep. Prostaglandins (PGD) in infections can operate as sleep mediators [19]. Overall, the data indicate that inflammatory mediators generally induce drowsiness. Infectious lesions to CNS structures can lead to long-lasting and profound changes to sleep [22].

The first of the best known studies identifying the causes of sleep impairments in infectious diseases were studies conducted by Constantin von Economo, an Austrian military pilot, neurologist, and psychiatrist. His scientific interest was a mysterious disease at the beginning of the 20th century (1915–1926) characterized by drowsiness, fever, and oculomotor impairments, and which was later termed encephalitis lethargica [23]. Having excluded a multitude of potential causes for this disease, von Economo came to the conclusion that encephalitis lethargica was induced by an unknown virus affecting brain tissue in the same way as poliovirus but not identical to poliovirus [24]. The pathomorphological changes in the brain in encephalitis lethargica are similar to those of microscopic lesions in African sleeping sickness (human African trypanosomiasis), described by Marinescu in 1918 [25]. Although encephalitis lethargica was described as epidemic, as its distribution was similar to that of an infectious disease over a limited period of time, both the principles of its occurrence and the means of transmission continue to remain incompletely understood.

Von Economo proposed the existence of a sleep and waking center in the brain and anticipated a number of contemporary theories on sleep regulation based on the finding of sleep centers in the rostral hypothalamus and waking centers in the posterior hypothalamus. This discovery played an important role in our understanding of the neurobiology of sleep. Knowledge of the key regulatory neural systems of sleep affected subsequent research into the sleep–waking cycle, which was initiated by Frédéric Bremer and Giuseppe Moruzzi and is based on the passive sleep induction theory. These scientists introduced the concepts of "diffuse" and "nonspecific" ascending reticular brainstem arousal systems. This theory led on to the hypothesis that there are different interacting levels – waking centers and sleep centers, as well as active sleep induction [26].

At the same time as the epidemic of encephalitis lethargica at the beginning of the 20th century, Europe and other countries were also affected by the Spanish flu pandemic (1918–1920), which became one of the largest pandemics in human history – affecting about 30% of the planet's population and causing loss of life in at least 2.7% of patients. During the Spanish flu pandemic, steps were taken to strengthen global epidemiological surveillance and develop consistent methods to prevent the spread of diseases: social institutions (schools, churches, courts, theatres) were closed for months in several countries, restrictive measures for visiting shops were introduced, along with mask wearing; shaking hands was banned [27].

One feature of the Spanish flu was damage to the organs of respiration, with rapid progression to hemorrhagic pneumonia. Signs of nervous system pathology were headache, general hypesthesia, memory impairment, sleeplessness, and in some cases psychotic disorders [28].

The ribonucleic acid (RNA) genome sequence of the Spanish flu virus was determined in 1997. A similar virus

(H1N1) produced the Russian flu pandemic in 1977–1978 and the swine flu pandemic in 2009, though the consequences of these pandemics were less catastrophic [29].

CNS lesions associated with H1N1 influenza virus during the last pandemic produced clinical signs – the most significant were memory impairments, sleeplessness, and psychotic disorders. Researchers took the view that increased vascular permeability plays an important role in the pathogenesis of neurological disorders in influenza. Given the seasonal regularity of influenza epidemics, it is difficult to determine susceptibility to novel virus strains and the rate of spread of infection among different ethnic and age groups.

Scientific and technological resources in the 21st century are enormously advanced compared with what was available during the Spanish flu pandemic. However, COVID-19 was a major call to the current world community. The COVID-19 pandemic led to additional health problems, such as anxiety, depression, and sleeplessness, the main provocatory factor for these being distress [30]. Despite successes in the treatment of infectious diseases, nervous system lesions in COVID-19 remain a serious problem with both short-term and long-term sequelae. In particular, underestimation of neurological symptoms can lead to degradation of the outcome of the acute phase of the disease, and also to secondary complications. Thus, a cross-sectional study of 7236 volunteers showed that the overall prevalences of anxiety disorder, depression, and sleep impairment were 35.1, 20.1, and 18.2%, respectively, significantly greater than before the pandemic [31].

The mechanisms of the neurobiological processes occurring in viral infections and which may underlie microorganism-induced functional and structural impairments in the brain, nerves, and muscles are currently under active study. Anosmia, stroke, cranial nerve pathology, encephalopathy, meningitis, and epileptic seizures are among the neurological manifestations described in COVID-19 patients. It remains difficult to identify which of these neurological impairments in COVID-19 are induced by SARS-CoV-2 and which are due to excessive cytokine responses and/or hypercoagulopathy with clot formation. COVID-19 patients not infrequently develop neurological symptoms without that typical respiratory signs such as cough and breathlessness, and without fever [32].

The World Health Organization (WHO) guidelines and government measures during the COVID-19 pandemic have led to numerous restrictions on daily life, including social distancing and self-isolation at home. Although these measures are vitally important for protecting public health, the results show that they have adverse influences on people – they change movement patterns and eating habits. An international online survey was carried out to identify the consequences of COVID-19-associated restrictions, with the accent on physical activity and eating behavior. A total of 1047 responses from the cohort, of which 54% were women, were analyzed; 36% of respondents lived in Asia, 40% in Africa, 21% in Europe, and 3% in other countries; the survey established that being at home had adverse influences on all levels of physical activity. For example, the time spent sitting increased from 5 to 8 h. Food consumption and the nature of nutrition (type of foods, uncontrolled eating, snacks between main meals, number of main meals taken) during isolation became more harmful to health [33].

Analysis of psychological reactions to the COVID-19 pandemic showed an increase in the number of respondents with symptoms of anxiety and depression, not infrequently linked with sleep impairments. It therefore seems appropriate to develop measures seeking to restore normal sleep, as this plays a fundamental role in maintaining people's mental and physical health. The appropriate duration and quality of sleep are needed for people to overcome pandemic-related problems [34].

Introduction of isolation regimes has led to reductions in the time people spend in fresh air and exposure to sunlight, which also has adverse effects on sleep and circadian rhythms. Normal work/rest regimes (getting up at a particular time, going to work, eating and physical exercise at certain times, taking part in social and leisure activities) constitute an important chronometric factor regulating the sleep–waking cycle. At the initial stages of isolation, sleep in some cases became more prolonged, which might seem useful, though sleep quality decreased notably, subsequently having a degrading influence on the sleep–waking cycle, adversely affecting work people's work capacity and health overall [35, 36].

Assessment of the sleep regime using online questionnaires during isolation revealed a shift in the time of going to sleep to later hours on workdays and sleep impairments on rest days. During a week at home, 37.9% of respondents characterized their sleep as being of average quality and 15% rated it as poor; 31.3% reported degradation of sleep quality as compared with their usual lifestyles [37, 38].

Restoration of impaired sleep must be an important component of measures for preserving mental health during pandemics. There is a need to seek to eliminate factors promoting sleeplessness, among which the main are restlessness and loneliness associated with COVID-19, levels of education, virus infection, and prior mental illness [39, 40].

In conditions of the constantly growing worries about COVID-19, lack of sleep may be due to difficulties going to sleep or disordered circadian rhythms. Study data suggest that interconnections between degraded sleep effectiveness and innate immunity make people susceptible to viral infections. An online study of adults (843 respondents) living in the COVID-19 pandemic addressed the effects of self-isolation on sleep, daytime functioning, and mental health in this population (most (67.4%) were women (mean age 52 years) suffered from obesity). A total of 69.4% of respondents reported changes in sleep pattern, fewer than a half (44.7%) retaining good sleep; 45.6% noted higher levels of drowsiness than before isolation. "Sleep disturbance" was the most frequently reported problem (42.3%), "unintentional falling

asleep" was identified by 35.2%), "difficulty going to sleep" and "waking during sleep" by 30.9% and 30.8%, respectively), and "going to bed later" by 30%. Respondents with suspected COVID-19 complained of nightmares and they had anomalous sleep rhythms.

Studies of the connection between psychosocial stress, sleep deprivation, and susceptibility to virus infections continue in relation to the COVID-19 situation. Measures controlling stress, including elimination of sleep-related impairments and sleep hygiene, can have effective influences on immune responses, thus decreasing susceptibility to viral infections [41]. The existence of a correlation between sleep quality and the state of the immune system has been confirmed by a number of previous studies. Thus, comparison of serum anti-influenza antibody levels before and four weeks after vaccination of young healthy people with and without sleeplessness showed that sleep impairment is a risk factor for decreased immunity to influenza virus [42].

Screening of 402 adults who had had COVID-19 (265 men, mean age 58 years) for one month after hospital treatment showed that more than half had symptoms of mental disorders. The level of systemic immune inflammation had a direct relationship with measures of depression, anxiety, and sleep impairment on subsequent observations. Despite lower levels of inflammatory markers, women suffered more from both anxiety and depression. Patients with histories of mental disorders gave worse test results than healthy patients with similar inflammatory marker levels [43].

Attention in the scientific community is currently directed to studies of neurotransmitters and hormones, which are important for understanding the mechanisms of development of nervous system lesions in COVID-19; among these is melatonin.

Melatonin is a multifunctional signal hormone synthesized and secreted mainly by the pineal gland. Melatonin is known to influence many biological processes in the body, including circadian rhythms, the immune system, and neuroendocrine and cardiovascular functions, and plays a key role in preventing age-dependent oxidative stress. The level of melatonin production decreases significantly with age. Some studies have shown that the aging process is closely linked with activation of free-radical reactions and mitochondrial dysfunction. This is one of the causes of the more severe course of COVID-19 in elderly people [44, 45]. Chronic diseases such as obesity, diabetes mellitus, and arterial hypertension are regarded as unfavorable factors in COVID-19. Patients with these have decreased immune activity and levels of endogenous antioxidants and lethality due to COVID-19 increases with increases in the burden of chronic disease and age, when melatonin levels decrease [46, 47]. In this context, melatonin, both endogenous and as the formulation Sonnovan (ZAO Canonpharma Production) is a potential agent with perspectives for overcoming COVID-19 infection and increasing immunity both in healthy people and patients with obesity and diabetes mellitus.

The leading sign of COVID-19 is severe acute respiratory syndrome due to inflammatory reactions at the level of the lungs, accompanied by uncontrolled oxidative stress. Thus far there is no effective treatment for this pathology, especially in elderly people, who make up the main risk group. It is entirely likely that the use of Sonnovan, a powerful antioxidant with immunomodulatory properties, supports increases in melatonin in the human body and may have significant value in viral infections. In any case, the fact that high resistance to SARS-CoV-2 correlates with high melatonin levels was clearly demonstrated experimentally by Heideman et al. and Tresguerres et al. [48, 49].

Studies of the regulation of the melatoninergic pathways may be an important aspect in understanding how viruses control cellular immunity. It is entirely likely that viral suppression of melatonin production promotes the development of the initial "cytokine storm" with impaired regulation of immune cells [50].

A number of studies have demonstrated a general tendency to increases in the number of cases of SARS-CoV-2 infection and low blood melatonin levels in chronic metabolic disorders in elderly people. It may be that melatonin interacts directly with the SARS-CoV-2 membrane or its genetic material. It has been suggested that melatonin may affect the biological activity of viruses. This is confirmed by the fact that melatonin, a small amphiphilic molecule, can easily penetrate biological membranes to enter all cells, reaching subcellular organelles. In addition, data have been obtained showing that melatonin has influences on the regulation of gene expression via primary epigenetic mechanisms, including methylation of deoxyribonucleic acid. Complex molecular studies are required to clarify the ability of melatonin to inhibit the biological activity of SARS-CoV-2 in patients with diabetes mellitus or obesity. Data have now been obtained showing that melatonin has an indirect antiviral action due to its anti-inflammatory and antioxidant, immunomodulatory, and immunostimulatory actions [51].

Further research is needed on the anti-inflammatory effects of melatonin at different stages of SARS-CoV-2; it may act on angiotensin-converting enzyme 2 and protease inhibitors.

Melatonin very probably plays an important role in suppressing SARS-CoV-2, preventing the development of COVID-19. This endogenous antioxidant stimulates general immunity, inhibits cellular apoptosis, blocks the cytokines mediating inflammation in the lungs, and decreases blood vessel penetrability, which limits alveolar edema and prevents pulmonary fibrosis. Thus, Sonnovan may be effective in patients in critical states as, producing the effects described above and promoting normalization of sleep, it can reduce anxiety and depression, which may increase treatment compliance and the ability to improve overall clinical outcomes in COVID-19 patients. It is of note that Sonnovan has a good safety profile.

Thus, melatonin formulations may constitute an important component of adjuvant therapy in the prophylaxis and treatment of viral infections, including those such as COVID-19 [52].

Another important aspect is the common underlying mechanisms of melatonin and vitamin D in relation to modulating and controlling immune responses and oxidative reactions against COVID-19 [53]. Activation of the renin-angiotensin system with subsequent inflammatory reactions plays a leading role in the development of COVID-19; activation can be suppressed by the combination of vitamin D and melatonin.

Conclusions. The interaction between anxiety and immune system dysfunction is actively discussed in the current scientific literature, as are the interaction between immune system dysfunction and sleep impairment and the interaction between anxiety and sleep impairment. These are associated with cognitive disorders and pain, which can be triggered by microorganisms.

It is entirely likely that pain, altered sleep, and anxiety, as manifestations of nervous system responses to the entry of microbes into the body, depend on which pathogen is interacting with the macroorganism, and the nature of the reaction depends on the individual characteristics of the person's immune system, which are determined largely at the genetic level.

In some cases, moderate anxiety, increased sleep duration, and minor pain promote situation-appropriate behavior such that the interaction of the pathogenic microorganism with the person's immune system results in a mild course of the infectious disease or disease does not develop at all.

In other cases, patients manifest symptoms and signs evidencing severe structural damage to the nervous system and/or nervous system dysfunction.

Also clear is that restriction of a person's activity in the prodromal period of infection and increases in sleep duration may prevent manifestation of the infectious disease. This will be the subject of future work.

In patients with COVID-19, some of the commonest and most important complaints are impairment of olfaction and pain, including fibromyalgia, asthenia, cognitive impairment, and sleep impairment.

This supports the view that functional interactions between the human nervous and immune systems in response to entry of a microorganism are evidence of depletion of the regulatory functions of the nervous system due to the actions of SARS-CoV-2 virus and make the development of therapeutic measures for rehabilitation of COVID-19 patients very relevant.

Analysis of data from studies of the mechanisms of the involvement of melatonin in sleep and waking processes, inflammation, and immunity, taking account of our own and worldwide practical experience, suggests that the formulation Sonnovan should be used in patients with sleep disorders at a dose of 3 mg 30–40 min before sleeping during pandemics with prophylactic aims, and also in infections [54]. In elderly people, Sonnovan can be taken 60–90 min before going to bed because of changes in melatonin metabolism and treatment course duration can also be increased.

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