Features of autonomic disorders in patients with COVID-19

Abstract. The spread of coronavirus disease 2019 (COVID-19) caused a pandemic; there are no effective treatments and vaccines for now. COVID-19 also greatly affects many organs and systems of the body, including the heart, intestines, kidneys and brain, despite the fact that pneumonia and pulmonary dysfunction usually predominate in the clinical picture. The study of statistics, structure of morbidity and mechanisms of organ and system disorders in patients with COVID-19 revealed the main pattern: no matter what organ or system is damaged, the disrupted autonomic nervous system affects the outcomes of coronavirus infection. As a result, various biomarkers and conceptual theories have been identified the analysis and generalization of which intensified the need to determine a strategy for the prevention and treatment of autonomic disorders.

Keywords: literature review; pandemic; COVID-19; autonomic disorders; extended autonomic system; stress

The role of the COVID-19 infection in autonomic disorders

During the year of the pandemic, morbidity and mortality statistics increased significantly. Acute cardiovascular diseases and suicides are at the forefront [1–5], and there are still no approved antiviral drugs or effective long-term vaccines to control coronavirus disease 2019 (COVID-19). However, to address this problem around the world, to counter the pandemic, serious efforts have been made [6–9].

This required the genomic characterization of a new human pathogenic coronavirus isolated from a patient with severe acute respiratory syndrome after visiting Wuhan in 2019 [10, 11]. After that, deep metagenomic sequencing and polymerase chain reaction have become fundamental for studying infection of a severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2) and the mechanisms of its mutation, as well as the creation of drugs based on genetic engineering [12–16].

In a healthy person, the stability of the internal environment tends to homeostasis. Homeostasis is not a result but a goal of the whole organism. All organs and systems aim at this [17, 18].

The disease leads to a shift in homeostasis, which is named allostasis in the concepts of integrative physiology. An example of homeostasis can be normotonia of the autonomic nervous system (ANS) (Fig. 1a). Allostasis is a shift of curves for oppositely operating effectors of sympathetic (SNS) and parasympathetic nervous systems (PNS) that leads to regulation of the changeable variable autonomic nervous system at other levels (Fig. 1b).

Purpose: to analyze the pathogenetic features of the autonomic nervous system lesion by coronavirus infection to identify patterns that could predict the disease course and improve treatment.

Evolution of views on stress management

In the process of regulating homeostasis, the main role belongs to neurohumoral regulation, which determines the response to stress. For the first time, stress conceptualization as a non-specific organism reaction to an external stimulus was proposed by Hans Selye as a “general adaptation syn-
drome” (1950). It included stages such as anxiety, resistance and exhaustion [19, 20].

In the 1990s after the proposed theory of the central stress system existence, which would cause activation of a stress syndrome, George Chrousos and Philip Gold of the US National Institutes of Health were the first who proposed the concept of integration of the autonomic nervous system and humoral mechanisms in the regulation of the central stress system components (Fig. 2) [21, 22].

In the short term, activation of this system can greatly shift homeostasis toward allostasis, which can be important for survival in critical situations, without consequences for the body. Long-term activation of ANS in cases that do not threaten human life will cause damage, depleting the body resources [23, 24].

As the preconditions for understanding the problem of autonomic disorders appeared in the early stages of treating patients with COVID-19, researchers began to worry about a more detailed study of what is traditionally named the autonomic nervous system, consisting of parasympathetic nervous system, sympathetic nervous system and intestinal nervous system. Increasing the meaning of the term “autonomic”, they brought to the fore neuroendocrine and neuroimmune systems [22, 23]. Thus, researchers introduced the term “extended autonomic system” (EAS) using some integrative concepts of physiology — homeostasis, allostasis and stress based on which the main assumption was made about the existence of biomarkers of EAS activation [23] (Fig. 3).

Ways of coronavirus infection migration

Numerous researchers suggest that such a massive spread of SARS-CoV-2 and severe autonomic nervous system disorders may be due to its high neurotropism. During the review of various independent scientific studies, two groups of patients were identified depending on the neurological and pathogenetic features [25–31].

The first group consisted of patients in whom SARS-CoV-2 migrated into the brain through the blood penetrating the blood-brain barrier [30–36]. The generalization of the results in this group correlates with SARS-CoV-2 effect on the renin-angiotensin system (RAS) through angiotensin-converting enzyme [37, 40]. Under these conditions, there is often a positive feedback loop between RAS activation and tonic enhancement of ef...
Notes: there is a traditional model of the central stress system regulated by the central ANS (reproduced with permission from the American College of Physicians) on the left side of the scheme; on the right side, there is EAS, consisting of 5 effector components and ending with factors contributing to critical illness or death. A grey bar below PNS may indicate suppression of the PNS. CING — cingulate cortex; AMY — amygdala; Hippo — hippocampus; PVN — paraventricular nucleus of the hypothalamus; HACER — hypothalamic area controlling emotional responses; AVP — arginine vasopressin (same as anti); CRH — corticotropin-releasing hormone; VTA — ventral tegmental area; PAG — periaqueductal gray; LC — locus ceruleus; A5 — A5 noradrenergic cell group; RTN — retrotroapezoid nucleus; RVLM — rostral ventrolateral medulla; AP — area postrema; PBN — parabrachial nucleus; Pre-B ön — pre-B öniger complex; NTS — nucleus tractus solitarii; CVLM — caudal ventrolateral medulla; NA — nucleus ambiguus; DMNX — dorsal motor nucleus of the vagus nerve; RPN — respiratory pattern generator; ACTH — adrenocorticotropic hormone (corticotropin); SNS — sympathetic noradrenergic system (norepinephrine); SAS — sympathetic adrenergic system (adrenaline); PNS — parasympathetic nervous system (acetylcholine); AI — angiotensin I; ACE — angiotensin-converting enzyme; Aldo — aldosterone; ATN — acute tubular necrosis; IL-6 — interleukin 6; TNF — tumor necrosis factor alpha.

Different sympathetic nerve activity. Increased sympathetic activity may stimulate RAS activation, which may further stimulate sympathetic activity (Diaz et al., 2020; Guan et al., 2020; Hoffmann et al., 2020).

The second group included patients with the parasympathetic central nervous system disorders due to possible increased neurotropism, mainly of the vagus nerve and the olfactory bulb. This correlates with the data from other works, which put forward a different route of coronavirus infection migration, directly through the nerve trunks of the vagus nerve and the olfactory bulb [41–44].

Normally, when stimulating chemoreceptors and mechanoreceptors of these nerves, signals are transmitted to the brain stem through the glossopharyngeal nerve and vagus nerve, converging in the NTS. Then signals go to the somatosensory cortex and other higher brain centers, which provide interoception of the internal environment of the body. The processing of these signals in the cerebral cortex causes feelings such as hunger, shortness of breath, or dyspnea [44–48].

Patients with coronavirus infection are likely to have the inhibition of processing these signals.

A randomized, blind, placebo-controlled study of healthy people with non-invasive transcutaneous vagus nerve stimulation indicates a decreasing release of inflammatory cytokines, which provides an anti-inflammatory effect [46–49].

Thus, the pathogenesis of COVID-19 and the proposed theories of SARS-CoV-2 penetration into the brain can be imagined as a homeostasis shift towards the sympathetic nervous system (Fig. 4) where the SNS and PNS disorders are observed, but pathogenetic links and severity of violations are still not known.

Conclusions

1. The study of the autonomic nervous system disorders confirms the proposed theories of the two main routes of coronavirus infection migration.

2. The proposed new approaches to the correction of autonomic disorders in patients with COVID-19 using non-
invasive transcutaneous stimulation need to be correlated with the RAS system study.

3. The results of independent studies confirm the possible neurotropism of the virus by two pathways of migration to the central structures of the brain.

The prospect of further study of ANS disorders in patients with coronavirus infection is to identify the priority routes of coronavirus infection migration, as well as the severity of damage to the autonomic nervous system, which would make it possible to predict and improve treatment outcomes compared to standard methods of treating patients with COVID-19.

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Особливості вегетативних розладів у хворих на COVID-19

Резюме. Поширення коронавірусної інфекції 2019 (COVID-19) спричинило пандемію, ефективних методів лікування й вакцин поки що немає. COVID-19 значною мірою впливає на багато органів і систем організму, включаючи серце, кишечник, нирки та мозок, незважаючи на те, що зазвичай у клінічній картині переважають пневмонія і легенева дисфункція. При вивченні статистики, структури захворюваності та механізмів порушення органів та систем у хворих на COVID-19 виявлено головну закономірність: який би орган або система не були пошкоджені, вегетативна нервова система обов’язково буде порушуватися, а це вплине на результат перебігу коронавірусної інфекції. У зв’язку з цим були виявлені різні біомаркери та концептуальні теорії, при аналізі та узагальненні яких назріла необхідність визначити стратегію профілактики та лікування вегетативних порушень.

Ключові слова: огляд літератури; пандемія; COVID-19; вегетативні розлади; розширення аутономна система; стрес