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Extrapulmonary manifestations of coronavirus disease (COVID-19): current status (a literature review)

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The aim of the study is to analyze the literature data on modern views concerning extrapulmonary manifestations of coronavirus disease (COVID-19).

Based on the analysis of current publications, the article analyzes the clinical manifestations of coronavirus disease (COVID-19) as a multisystem disorder with two main types of clinical manifestations, namely pulmonary and extrapulmonary. Determining pathogenetic mechanisms of extrapulmonary symptoms are, on the one hand, the tropism of SARS-CoV-2 to ACE2 receptors, expressed not only by alveolar epithelial type II cells, but also by cells of the heart, nervous system, vascular endothelium, small and large intestine, basal layer cells of the epidermis, cells of endocrine organs, etc., and on the other hand, immune-dependent mechanisms, in particular the development of "cytokine storm".

It is shown that the spectrum of extrapulmonary manifestations of COVID-19 is very wide, and clinical manifestations are characterized by significant polymorphism. Extrapulmonary symptoms of COVID-19 were analyzed considering the organs of the gastrointestinal tract, nervous, cardiovascular and endocrine systems, skin and others. Attention is drawn to a certain association between definite extrapulmonary manifestations and the severity of COVID-19 course.

Thus, particular extrapulmonary manifestations are associated with a milder course of COVID-19 (anosmia, dysgeusia, etc.), others, vice versa, occur in severe disease (damage to liver, kidney, heart, pancreas). In addition, some extrapulmonary manifestations, especially of the nervous system, may remain in patients even after an acute period of the disease. Some extrapulmonary manifestations, which are currently described in a small number of patients, are also reviewed.

Conclusions. COVID-19 is characterized by a wide range and high frequency of extrapulmonary manifestations, which is explained by both the direct action of SARS-CoV-2 and immune-dependent mechanisms. Some extrapulmonary manifestations are associated with a milder course of COVID-19, others, on the contrary, occur in severe disease.

Key words: coronavirus disease COVID-19, viral infection, extrapulmonary manifestations.

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Позалегеневі прояви коронавірусної хвороби (COVID-19): сучасний стан питання (огляд літератури)

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Мета роботи – проаналізувати відомості фахової літератури щодо сучасних уявлень про позалегеневі прояви коронавірусної хвороби (COVID-19).

На підставі аналізу сучасної наукової літератури проаналізували клінічні прояви коронавірусної хвороби (COVID-19) як мультисистемного захворювання з двома основними типами клінічних проявів: легеневими та позалегеневими. Визначальні патогенетичні механізми виникнення позалегеневої симптоматики, – тропізм SARS-CoV-2 до рецепторів ACE2 (є не лише на альвеолярних клітинах II типу, але й на клітинах серця, нервової системи, ендотелію судин, тонкого і товстого кишечника, клітин базального шару епідермісу, клітинах органів ендокринної системи тощо), а також імунозалежні механізми, зокрема розвиток «цитокінового шторму».

Показано, що спектр позалегеневих проявів COVID-19 дуже широкий, а клінічні прояви вирізняються істотним поліморфізмом. Проаналізували позалегеневу симптоматику COVID-19 з боку органів шлунково-кишкового тракту, нервової, серцево-судинної та ендокринної систем, шкіри тощо. Звернули увагу на певну асоціацію окремих позалегеневих проявів із тяжкістю перебігу COVID-19.

Так, окремі позалегеневі прояви асоціюються з легшим перебігом COVID-19 (аносмія, дисгевзія тощо), а інші виникають у разі тяжкого перебігу хвороби (ураження печінки, нирок, серця, підшлункової залози). Ба більше, деякі позалегеневі прояви, особливо з боку нервової системи, можуть залишатися в пацієнтів навіть після гострого періоду хвороби. Розглянули позалегеневі прояви, що нині описані в невеликої кількості пацієнтів, зумовлюючи необхідність продовження вивчення цього питання.

Висновки. COVID-19 характеризується широким спектром і високою частотою розвитку позалегеневих проявів, що пояснюється прямою дією SARS-CoV-2 та імунозалежними механізмами. Окремі позалегеневі прояви асоціюються з легшим перебігом COVID-19, інші виникають при тяжкому перебігу хвороби.

Ключові слова: коронавірусна хвороба COVID-19, вірусна інфекція, позалегеневі прояви.

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Coronavirus disease (COVID-19) is currently considered a multisystem disorder with two main types of clinical manifestations, namely pulmonary and extrapulmonary [1–4]. Pulmonary manifestations are the most pronounced, as their severity is evidently associated with the severity of COVID-19. Extrapulmonary manifestations of the disease sometimes dominate, especially in the mild course of COVID-19, but can be combined with pulmonary ones in moderate and severe course, which requires individual treatment of patients [1,3,5–7]. To date, much less attention has been paid to the analysis of extrapulmonary manifestations than to pulmonary lesions. In the ongoing COVID-19 pandemic, understanding the spectrum and frequency of extrapulmonary symptoms, pathogenetic mechanisms of their development, associations with the disease severity, will help to increase the effectiveness of early diagnosis and allow timely individualization of comprehensive treatment.

Aim

The aim of the work is to analyze the literature data on modern views concerning extrapulmontary manifestations of coronavirus disease (COVID-19).

It is important to understand the pathophysiological mechanisms of the disease development to recognize the spectrum and features of the extrapulmonary clinical manifestations. The determining factor of extrapulmonary symptoms is the tropism of SARS-CoV-2 to angiotensin-converting enzyme 2 (ACE2) receptors, expressed not only by alveolar epithelial type II cells, but also by cells of the heart, nervous system, vascular endothelium, small and large intestine, basal layer cells of the epidermis, endocrine cells, etc. [8–11]. It is believed that cells on the membrane of which ACE2 expression exceeds 1 % are a target for SARS CoV-2 virus [12]. In addition to the tropism of the pathogen to ACE2 receptors, an important pathogenetic component of the extrapulmonary symptom development is a significant viral load and immune-dependent mechanisms, namely the induction of “cytokine storm” [1].

Gastrointestinal symptoms in a significant number of patients are due to the presence of ACE2 on the cells of the gastric and intestinal mucosa [12]. Confirmation of the role of SARS-CoV-2 in the gastrointestinal tract damage is not only its excretion via the feces [13], but also the presence of viral inclusions in the cytoplasm of intestinal cells [14]. A Chinese retrospective study has shown diarrhea in 75 % of COVID-19 patients and abdominal pain [15]. It is believed that diarrhea at the disease onset is more often associated with mild to moderate disease and is not associated with the risk of severe and fatal one [4]. However, in severe cases, the incidence of anorexia (66.7 % vs. 30.4 %), diarrhea (16.7 % vs. 7.8 %), nausea (11.1 % vs. 9.8 %) and abdominal pain 8.3 % vs. 0.0 %) is higher in patients needing intensive care [16]. In this category of patients, clinical manifestations of the gastrointestinal tract are associated not only with the direct viral action, but also with immune-dependent mechanisms of damage via “cytokine storm”, as evidenced by histological data, namely the presence of numerous lymphocytic infiltrates and interstitial edema of the gastric and intestinal lamina propria layer [14].

Liver injury in COVID-19 patients are due to the presence of ACE2 on liver cells, however the expression of ACE2 by cholangiocytes is 20 times higher than on the membrane of hepatocytes [17], which supports the retrograde type of liver damage due to SARS-CoV-2 infection [18]. Liver injury in patients with COVID-19 is confirmed by changes in functional tests due to the development of hyperenzymemia with increased levels of alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase [2]. According to the results of a meta-analysis, the cumulative prevalence of acute liver injury in patients with COVID-19 is estimated at 23.7 % [19]. Risk factors for liver involvement in the pathological process include young age, high levels of interleukin-6 and ferritin [20]. This study also reports that in COVID-19 patients with gastrointestinal manifestations such as diarrhea, nausea, vomiting, anorexia and abdominal pain, the risk of the liver involvement in the pathological process is higher than in patients without these symptoms [2]. The appearance of liver symptoms is associated with a worse prognosis and increased risk of mortality [2]. Liver injury was most commonly reported in patients with severe COVID-19 as well as lethal outcomes: 58 % and 78 %, respectively [17]. In severe and critical course of COVID-19, immune mechanisms are also important, namely the induction of “cytokine storm”, in the development of which there is a damage to many organs, including the liver [17]. This confirms the detection of focal centro-lobular necrosis (90.2 %) and foci of lymphocytic-leukocyte infiltration of liver lobes (7.3 %) in the pathomorphological examination of the liver from patients who died from COVID-19 [20]. In the clinical interpretation of liver injury signs, it should also be borne in mind that some medications, including antivirals, are hepatotoxic and can lead to drug-induced hepatitis. In addition, the presence of concomitant chronic liver disease in a patient should be excluded [21].

In studying the features of the COVID-19 clinical manifestations, attention was immediately drawn to the early neurological symptoms, which were more characteristic of the mild disease course. These manifestations included anosmia and dysgeusia (18.2 %) [5], headache (13.1 %) and dizziness (16.8 %), insomnia [6]. It is believed that the appearance of early neurological manifestations can be explained by the direct effect of SARS-CoV-2 on extracellular domain of ACE2 receptors in the neuroepithelium and the subsequent ability of the virus to access the brain and thalamus via the axons of olfactory neurons [22]. It is reported that these neurological manifestations in some cases may persist even after negative results of polymerase chain reaction [6].

Data on the neurotropic nature of SARS-CoV-2 explain the development of acute and long-term psychoneurological effects in COVID-19 [23]. The development of neuropsychiatric symptoms is explained by the ability of SARS-CoV-2 to cause demyelinating processes in brain cells, which affects the cognitive and behavioral spheres [24]. Concomitant cardiovascular diseases, diabetes and other diseases accompanied by microvascular lesions may further contribute to the neuroinvasion of SARS-CoV-2 and, accordingly, increase the risk of virus-associated psychoneurological symptoms [25]. Therefore, most often in people with concomitant vascular pathology, especially the elderly, as well as in patients with severe COVID-19, neuropsychiatric symptoms, including delirium, depression,

anxiety, memory impairment develop in the acute period of the disease. And in some convalescents, these symptoms may persist for a long time [26]. A British study has showed a change in mental status in 31 % of patients with encephalopathy or mental disorders, which were more common in young people [27]. According to a US multicenter study, 13.5 % of hospitalized patients with COVID-19 developed psycho-neurological disorders, including encephalopathy, stroke, which led to higher mortality rates [28]. The development of psychosis in individual patients associated with direct action of SARS-CoV-2 on brain cells also has been described [29]. To date, there are descriptions of individual clinical cases of peripheral nervous system lesions in patients with COVID-19, such as Guillain–Barre syndrome [30]. In patients with severe and critical COVID-19, late-stage neurological disorders develop as a consequence of thromboembolic complications, leading to ischemic stroke in 2.5 % of patients [7].

The appearance of dermatological manifestations in patients with COVID-19 is associated with the presence of ACE2 receptors in the cell membrane of the basal layer of the skin [1]. The role of SARS-CoV-2 in the signs of COVID-19 skin manifestation has been proven by the detection of the virus by polymerase chain reaction in skin samples [31]. The incidence of cutaneous extrapulmonary manifestations of COVID-19 according to various researchers varies widely. So, according to the authors [32], one in five patients (20.4 %) had skin manifestations of COVID-19, while other researchers reported that only 1.5 % of patients had these symptoms [33], and the authors [34] report only isolated cases from their practice. In addition, it should be noted that the spectrum of clinical signs of extrapulmonary manifestations of COVID-19 described in the literature is characterized by significant polymorphism. Namely, the researchers have found elements of maculopapular rash, different variants of erythema, pernio like changes and different combinations of such manifestations, and so on. Attention was drawn to the fact that skin changes had a clinical manifestation both concomitantly with respiratory symptoms and before signs of the respiratory system damage in some patients [32–34]. Today it is believed that the appearance of cutaneous extrapulmonary manifestations of COVID-19 is more characteristic of mild and moderate infection [1,32–34]. For the correct interpretation of skin changes as extrapulmonary signs of COVID-19, it is necessary to exclude side effects when using drugs for treatment of these patients [1].

Cutaneous extrapulmonary manifestations of COVID-19 are characterized by significant clinical polymorphism with special attention paid to the development of various types of alopecia in these patients, namely telogen, focal and androgenic, etc. [28,35]. There are even special changes in the nails of patients with COVID-19, which are characterized as polydactyl erythronychia or symptom “COVID red crescent” with the appearance of red crescent-shaped stripes surrounding the distal part of the nail hole, indicating microvascular damage [36].

In severe and critical COVID-19, kidney injury deserves special attention due to the direct action of SARS-CoV-2, as ACE2 receptors are expressed by cells of both the glomerular and tubular apparatus, and on the other hand, the development of “cytokine storm” [37]. Renal injury in patients with severe disease is accompanied by proteinuria (65.8 %) and hematuria (41.7 %), and acute kidney disease with elevated blood creatinine increases the risk of hospitalization in intensive care units and the risk of death [38]. In those who died from COVID-19, renal pathomorphological changes are characterized by focal necrosis of the renal tubular epithelium (73.2 %), focal lymphocytic-leukocyte infiltration (12.2 %) and renal microvascular thrombosis (17.1 %) [20]. Patients with comorbid chronic kidney disease have a significantly higher risk of acute kidney injury, leading to higher mortality rates among such patients [39].

The cardiovascular system is naturally involved in the pathological process in the severe and critical course of COVID-19 with the development of such manifestations as arrhythmia, most often paroxysmal atrial fibrillation, hypertension, cardiomyopathy, myocarditis, myocardial infarction [40–42]. Today, it is believed that myocardial damage in patients with COVID-19 is secondary to systemic causes and is not the result of direct action of the virus [43]. The combination of “cytokine storm” with respiratory dysfunction and hypoxemia results in damage to myocardial cells [41]. In this case, myocardial damage, which may be clinically manifested by arrhythmia or acute coronary syndrome, is clearly linked to severe COVID-19 and worsening prognosis [41,44,45]. Confirmation of the dependence of heart disease on the severity of COVID-19 is the results of meta-analysis, which showed significantly higher levels of troponin I in patients with severe disease treated in intensive care units compared with milder disease, as well as cases of myocardial infarction among patients with severe and critical disease [46]. Heart damage is also confirmed by the detection of elevated natriuretic propeptide hormone in patients with COVID-19 who are treated in intensive care units [47].

There are numerous reports in the literature demonstrating the endocrine system involvement in the pathological process of COVID-19 due to both the expression of ACE2 receptors on the target cell membranes and the immune-mediated mechanism of “cytokine storm” damage. Of particular note is the pancreatic injury, which is occurred in 22.9 % of patients with newly diagnosed signs of hyperglycemia [48] and 6.4 % of patients with previous decompensation of diabetes mellitus [49]. The high risk of these violations is associated only with direct action SARS-CoV-2 on beta-cells of the pancreas, but also with the development of “cytokine storm” caused by a high release of pro-inflammatory cytokines, which leads to beta-cell dysfunction and apoptosis, and consequently insulin production is decreased [3]. Patients with diabetes are at risk for more severe COVID-19 [3].

Some studies have shown the development of thyroid dysfunction [1,50], including those with a high frequency of these violation detection (64 %) [50]. In the study [51], the authors have described the clinical case of acute adrenal insufficiency that developed in a patient with severe COVID-19. The authors explained the development of this condition within the “cytokine storm”, namely the influence of interleukin-1, interleukin-6, tumor necrosis factor-α in high concentrations on the axis of the hypothalamic-pituitary-adrenal system [51,52].

Studies focusing on the dysfunction of the reproductive endocrine glands have drawn attention to the significantly higher incidence of lesions in men than in women [53], due

to the expression of ACE2 by spermatogonia cells (1.4 %) as well as Leydig and Sertoli cells (4.24 %) [54]. Testicular dysfunction was manifested by a decrease in plasma testosterone levels in 37.5 % of patients, a decrease in luteinizing hormone in 29 % of patients, and a decrease in the testosterone-to-luteinizing hormone ratio [55], and in the study [56] testicular dysfunction was recorded in 91 % (11 of 12) of patients.

Of particular interest are studies examining the issue of placental abruption and, accordingly, the risk of COVID-19 vertical transmission [57]. Detection of SARS-CoV-2 virions in syncytiotrophoblasts of placental villi has been reported using electron microscopy [58] and polymerase chain reaction [59]. In placental cells, the expression of ACE2, necessary for the viral S-protein binding to the target cell [60,61], however, an extremely low level of transmembrane serine protease 2 expression was found, needed for virus penetration into the cell and subsequent replication [61,62]. This explains the low risk of SARS-CoV-2 infection vertical transmission. For example, in a study involving 435 newborns from women with COVID-19, no vertical transmission of SARS-CoV-2 infection was recorded [63]. According to another study including 201 newborns from mothers with COVID-19, polymerase chain reaction showed a positive test of nasopharyngeal mucus in the first 48 hours of life in 2.4 % of cases, but they had no signs of pneumonia according to visualization methods, and a negative PCR test result was recorded a week later [64].

ACE2 receptors may even be present in some tissues of the eye, which explains the appearance of conjunctivitis in some patients [65,66]. It is believed that clinical signs of conjunctivitis may appear at the disease onset due to direct exposure to SARS-CoV-2 through airborne droplets, and at the later stage of the disease, due to virus damage to eye cells via the systemic circulation [67,68].

Some studies have noted the presence of generalized bone and muscle pain in patients with COVID-19 due to the direct action of SARS-CoV-2 on ACE2 in the skeletal muscle and cortical bone cells [69,70].

Conclusions

1. Coronavirus disease (COVID-19) in addition to lung injury, is characterized by a wide range and high frequency of extrapulmonary manifestations involving various organs and systems. The appearance of these signs is explained by both the direct action of SARS-CoV-2 and immune-dependent mechanisms.

2. Certain extrapulmonary manifestations are associated with a milder course of COVID-19 (anosmia, dysgeusia, etc.), others, on the contrary, occur in severe disease (liver, kidney, heart, pancreas), and some ones can persist even after the acute period of the disease (neuropsychiatric disorders).

3. Summarizing current data on extrapulmonary manifestations of COVID-19 will allow general practitioners to improve early diagnosis of the disease and timely individualize complex treatment.

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