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PATHOMORPHOLOGY OF ADRENAL LESIONS IN CORONAVIRUS INFECTION

(Review article)

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Abstract. COVID-19 has been shown to affect numerous organ systems, including the adrenal glands, which play a central role in the body's stress response. Clinical reports describing early-onset hypocorticism and acute adrenal insufficiency following SARS-CoV-2 infection suggest that the adrenal glands may be compromised either directly by the virus or indirectly through systemic disease mechanisms. The purpose of this review is to summarize and evaluate current evidence regarding structural, functional, and pathophysiological alterations of the adrenal glands associated with COVID-19.

Autopsy findings consistently demonstrate vascular abnormalities—including thrombosis, infarction, hemorrhage, and severe endothelitis—represent another recurrent pattern and highlight substantial microcirculatory disruption. Additional findings such as cellular hyperplasia, necrosis, lipid degeneration, and focal adrenalitis further support the notion of notable adrenal involvement. Although expression of ACE2, TMPRSS2,and other viral entry–associated proteins in adrenal tissue provides biological probability for SARS-CoV-2 infection of adrenal cells, the limited number of virus-positive cells observed suggests that direct cytopathic injury is unlikely to be the primary mechanism.

Collectively, the available literature underscores the multifactorial nature of adrenal involvement in COVID-19 and highlights the necessity for further research to better define the prevalence, underlying mechanisms, and long-term consequences of adrenal dysfunction in affected patients.

Keywords: COVID-19, adrenal glands, endocrine glands, adrenal insufficiency, hypocorticism, sepsis.

ПАТОМОРФОЛОГИЯ ПОРАЖЕНИЙ НАДПОЧЕЧНИКОВ ПРИ КОРОНАВИРУСНОЙ ИНФЕКЦИИ.

(Обзорная статья)

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Аннотация. Было показано, что COVID-19 поражает множество систем органов, включая надпочечники, которые играют центральную роль в реакции организма на стресс. Клинические данные, описывающие ранний гипокортицизм и острую надпочечниковую недостаточность после инфекции SARS-CoV-2, позволяют предположить, что надпочечники могут быть поражены как непосредственно вирусом, так и опосредованно через механизмы системного заболевания. Цель данного обзора —

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обобщить и оценить современные данные о структурных, функциональных и патофизиологических изменениях надпочечников, связанных с COVID-19.

Результаты аутопсии неизменно демонстрируют сосудистые нарушения, включая тромбоз, инфаркт, кровоизлияние и тяжёлый эндотелит, которые представляют собой ещё один рецидивирующий паттерн и указывают на существенное нарушение микроциркуляции. Дополнительные признаки, такие как клеточная гиперплазия, некроз, липидная дегенерация и очаговый адреналит, дополнительно подтверждают представление о значительном поражении надпочечников. Хотя экспрессия ACE2, TMPRSS2 и других белков, ассоциированных с проникновением вируса в ткань надпочечников, обеспечивает биологическую достоверность инфицирования клеток надпочечников SARS-CoV-2, ограниченное количество наблюдаемых вирус-позитивных клеток позволяет предположить, что прямое цитопатическое повреждение вряд ли является основным механизмом.

В совокупности имеющиеся литературные данные подчёркивают многофакторный характер поражения надпочечников при COVID-19 и указывают на необходимость дальнейших исследований для более точного определения распространённости, основных механизмов и долгосрочных последствий дисфункции надпочечников у пациентов с этим заболеванием.

Ключевые слова: COVID-19, надпочечники, эндокринные железы, надпочечниковая недостаточность, гипокортицизм, сепсис.

Introduction. It is known that under the influence of COVID-19, along with most organs, the adrenal gland is also affected. The appearance of symptoms of hypocorticism due to adrenal insufficiency shortly after the onset of SARS-CoV-2 infection indicates damage to this organ by the virus. Adrenal crisis and long-term consequences of HPA axis dysfunction should be considered to prevent adrenal crisis in patients receiving antiviral drugs and/or steroids for COVID-19. The aim of this review is to analyze published findings on adrenal gland damage associated with SARS-CoV-2 infection

Discussion. Autopsy studies by Waldemar Kanczkowski and colleagues revealed pronounced local inflammation in the adrenal glands of COVID-19 patients. While some investigations reported only mild or sporadic focal inflammatory changes, others observed substantial infiltration of $CD3^+$ and $CD8^+$ lymphocytes throughout various layers of the adrenal cortex and in perivascular regions. One study noted cellular hyperplasia in the zona fasciculata in 86% of cases, suggesting potential disruption of adrenal hormone production. Nonetheless, vascular injury appears to be the most consistently reported complication, including acute fibrous necrosis of adrenal arterioles, apoptotic debris, and severe endothelitis in periadrenal and parenchymal tissues. Histological and imaging studies further identified thrombosis, infarctions, and hemorrhages in the adrenal glands of patients with severe COVID-19. Bilateral acute adrenal infarction was detected in 23% of critically ill individuals, while another study reported unilateral and bilateral infarctions in 13.4% and 2.6% of 343 patients, respectively. Although adrenal insufficiency was not formally evaluated, these infarctions correlated with prolonged ICU stays and increased mortality, possibly reflecting a procoagulant and

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prothrombotic state. Moreover, diverse pathogens—including fungi, viruses, and bacteria—can compromise adrenal integrity. Infections such as Mycobacterium tuberculosis or cytomegalovirus may directly contribute to Addison's disease, whereas partial adrenal cortex damage may remain below the 90% threshold necessary to elicit clinical symptoms of adrenal insufficiency [4]. All of the above studies prove the occurrence of inflammatory infiltration in the adrenal tissue as a result of coronavirus infection.

The influence of receptors for further development in the adrenal glands can be seen in the studies of Mao Y. et al. According to them for SARS-CoV-2 to infect adrenal cortex cells, the presence of ACE2 and TMPRSS2 proteins, which mediate viral binding and entry, is required. Analyses using bulk and single-cell RNA sequencing, as well as immunohistochemistry, have confirmed the expression of these proteins in human adrenal glands. ACE2 expression was particularly pronounced in stromal cells, small capillaries, and adrenal parenchymal cells, whereas TMPRSS2 was predominantly localized in the adrenal cortex [6].

Severe coronavirus infection resembles sepsis in both its clinical course and pathophysiological mechanisms. Lower-grade infections are characterized by a pronounced systemic inflammatory response, immune dysregulation, and endothelial damage, leading to microcirculatory impairment and organ dysfunction. Patients experience new cytokine storms, coagulopathy, acute respiratory distress syndrome, and multiple organ failure. Sepsis frequently impairs hypothalamic-pituitary-adrenal (HPA) axis function too. Decreased glucocorticoid metabolism and lower levels of corticosteroid-binding globulin (CBG) can elevate cortisol bioavailability, leading to suppression of ACTH secretion. A significant proportion of critically ill patients develop critical illness–related corticosteroid insufficiency (CIRCI), which is defined by reduced morning cortisol concentrations (<10 μg/dL) or by decreased activity of the glucocorticoid receptor α (GRα) resulting from ongoing inflammation. Additionally, adrenal insufficiency may arise from direct cytotoxic injury or hemorrhagic events affecting the HPA axis. Given similarities between bacterial sepsis and severe SARS-CoV-2 infection, adrenal dysregulation and damage may occur in COVID-19 patients. Clinical studies and reports describe various forms of adrenal insufficiency in mild and severe cases [1].

Cortisol synthesis and release are tightly regulated by the hypothalamic-pituitary-adrenal (HPA) axis. In healthy individuals, cortisol secretion exhibits both ultradian and circadian rhythms, driven by pulsatile ACTH release from the pituitary, which is in turn controlled by hypothalamic CRH. Cortisol production is further modulated by metabolic and inflammatory mediators, including angiotensin II, antidiuretic hormone (ADH), prostaglandins, macrophage migration inhibitory factor (MIF), interleukin-6 (IL-6), and various adipokines. The majority of circulating cortisol is bound to corticosteroid-binding globulin (CBG), which limits excessive effects on peripheral tissues [8].

Autopsy studies of patients who succumbed to atypical pneumonia revealed degeneration and necrosis of adrenal cortex cells, suggesting direct viral cytopathic effects. SARS-CoV antigens and genomic sequences were detected within adrenal tissues, indicating that cortisol homeostasis may be disrupted in individuals with atypical pneumonia or COVID-19. Microscopic examination identified adrenal damage in 46% of cases (12 of 28

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patients), even in the absence of clinically diagnosed adrenal insufficiency. Observed pathological changes included nonspecific focal adrenalitis, lipid degeneration, necrosis, vascular thrombosis, hemorrhage, and localized inflammation. These findings emphasize the presence of coagulation abnormalities in COVID-19 and highlight the potential role of anticoagulant therapy. Collectively, the data suggest that SARS-CoV-2 may contribute to acute adrenal insufficiency through thromboembolic mechanisms [3]

Leyendecker et al. found signs of acute adrenal infarction in 23 of 219 patients with severe lung damage (88% bilateral, 8% with adrenal insufficiency) [5].

Several reports have described cases of bilateral adrenal hemorrhage and/or adrenal insufficiency. Even with appropriate management, individuals with adrenal insufficiency exhibit higher morbidity and mortality compared to the general population, potentially due in part to impaired immune function. Current evidence does not indicate an increased risk of COVID-19 in this patient group. In fact, an Italian cohort study reported a lower COVID-19 prevalence (0.8%) among patients with adrenal insufficiency relative to the general population [7].

Yanqing Ding and colleagues employed monoclonal antibodies and molecular probes to detect SARS-CoV antigens and RNA in tissues obtained from deceased SARS patients. Viral components were identified in multiple organs, including the tracheal and bronchial glands, gastric parietal cells, intestinal epithelium, renal tubules, sweat glands, parathyroid, pituitary, pancreas, adrenal cortex and medulla, hepatocytes, and neurons. In contrast, control tissues showed no evidence of viral presence in the esophagus, spleen, lymph nodes, bone marrow, heart, aorta, cerebellum, thyroid, ovaries, uterus, or skeletal muscles [2]. Pathological changes in these organs may result from direct cytopathic effects of local viral replication or systemic reactions to respiratory failure and immune responses triggered by viral infection.

Zinserling V. and colleagues reported that ACE2 receptors are expressed not only in the respiratory system but also in many other organs, including the adrenal glands. They documented the first pathomorphological alterations in adrenal glands of patients with severe COVID-19, characterized by perivascular infiltration of $CD3^+$ and $CD8^+$ T lymphocytes. Adrenal tissues from 10 patients were collected postmortem and subjected to histological and immunohistochemical analyses following standard protocols. No macroscopic abnormalities were observed during autopsy. Paraffin-embedded sections were stained with hematoxylin and eosin, and immunohistochemistry was performed using antibodies against CD3, CD8, and CD20, with antigen retrieval via EnVision FLEX Target Retrieval Solution. Images were captured using a Nikon Eclipse Ni-U microscope (Nikon). The study revealed that adrenal glands may sustain severe damage in COVID-19, likely mediated by $CD8^+$ lymphocyte–driven cytotoxicity. Postmortem analyses identified two main patterns of adrenal injury. Mononuclear inflammatory foci were observed throughout various cortical layers and surrounding tissues, with immunohistochemistry confirming $CD3^+$ and $CD8^+$ lymphocyte presence. Additionally, the adrenal cortex exhibited cellular alterations, including enlarged nuclei and small-cell proliferative foci, resembling patterns seen in pulmonary tissue, suggesting direct effects of SARS-CoV-2 [11]

Given the pivotal role of the adrenal glands in the stress response, these results have important clinical implications, as SARS-CoV-2 infection may profoundly disrupt adrenal

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function under pathophysiological conditions. Various bacterial and viral pathogens can target the adrenal glands and glucocorticoid signaling pathways, employing immunoinvasive strategies to suppress the body's glucocorticoid-mediated stress response. Due to the high sensitivity of adrenal tissues and their crucial role in severe disease, detailed investigation of adrenal morphology in critically ill COVID-19 patients is warranted. This study provides the first systematic morphological characterization of pathoimmunological changes in adrenal glands from autopsies on patients with COVID-19. Additional proteins expressed in adrenal tissue, including furins, neuropilin-1, C-type lectins, and SRB1 scavenger receptors, may facilitate SARS-CoV-2 entry. The virus may also exploit the endosomal pathway, requiring acidic pH and L-cathepsin expression. The presence of these receptors supports the notion that SARS-CoV-2 can infect adrenal cells. Indeed, viral RNA and antigens have been detected in adrenal glands using in situ RNA/DNA hybridization, immunohistochemistry, and RT-qPCR, predominantly in scattered cortical and endothelial cells. Nevertheless, the low number of SARS-CoV-2–positive cells and absence of widespread tissue damage suggest that direct cytopathic adrenal insufficiency is unlikely [9].

Conclusion. Taken together, current data indicate that COVID-19 can compromise adrenal integrity and function through a combination of inflammatory, vascular, and potentially direct viral mechanisms. Given the essential role of the adrenal glands in maintaining homeostasis during stress and critical illness, further research is urgently needed to elucidate the clinical significance of these findings, determine the true prevalence of adrenal insufficiency in COVID-19, and refine management strategies for affected patients.

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