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The endocrine system function disturbances during and after SARS-CoV-2 infection

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Abstract. – Several receptors for the angiotensin-converting enzyme 2 (ACE2), essential for the penetration of SARS-CoV-2 into cells, are located in the tissues of the endocrine glands. Therefore, it has been suggested that SARS-CoV-2 infection results in the development of hormonal disturbances.

To date, several cases of endocrine disturbances related to the dysfunction of all endocrine glands during and after SARS-CoV-2 infection have been described. In this review, we discuss the endocrine system disturbances in patients with COVID-19 and post-COVID-19 syndrome. Based on the case reports described in the literature, patients with COVID-19 may develop endocrine disturbances that are immediately life-threatening. In addition, patients with post-COVID-19 syndrome may develop chronic endocrine disturbances.

In summary, the diagnostics of endocrine system disturbances based on clinical symptoms should be taken into account in both patients with COVID-19 and post-COVID-19 syndrome.

Key Words:
Endocrine system, SARS-CoV-2, COVID-19, Post-COVID-19 syndrome.

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has a similar genome (80%) to Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV). The main clinical symptoms caused by both viruses are also similar. The studies performed after the SARS-CoV epidemic in 2003 showed that this virus may impair both functions of the hypothalamus and pituitary axis, as well as the endocrine organs, especially the adrenal glands, thyroid and pancreas[1-3]. Thus, it has been suggested that SARS-CoV-2 infection may also cause endocrine system disturbances[4]. Indeed, angiotensin-converting enzyme 2 (ACE2) receptors, which mark the location of the penetration of SARS-CoV-2 into cells in large numbers, are localized in the tissues of the endocrine glands[5]. Thus, it has been suggested that infection of SARS-CoV-2 and COVID-19 may result in the development of hormonal disturbances[5].

It is well known that inflammation related to systemic viral infection alters the endocrine system function by several mechanisms, including the activation of the hypothalamic-pituitary-adrenal (HPA) axis. The production of viral proteins, which is induced by the replication and direct damage of endocrine cells, is associated with the immune response and viral gene production and affects the function of the HPA axis. The effect of these pathological processes is the transient or permanent dysfunction of the adrenal glands[6]. On the other hand, the HPA axis plays an important role in the regulation of immune response, influencing the risk and course of infections[4].

As mentioned above, SARS-CoV-2 binds with the ACE2 receptor by domains of the virus located in the C-terminal fragment of the S1 subunit. In addition, in the cells with a low expression of ACE2 receptors, the presence of cofactors facilitating the penetration of SARS-CoV-2 to cells has been shown. One of the cofactors is neuropilin-1 (NRP1). The expression of NRP1 was found in the parathyroid glands, adrenal glands and testes. In addition, the natural endogenous ligand of NRP1 in the vascular endothelial growth factor (VEGF) receptor is localized in the pituitary gland[7].

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The cytopathic effect of viral infection is defined as pathological and morphological changes in cells caused by viruses, including SARS-CoV-2[8,9]. However, it has been observed that the cytopathic effect of SARS-CoV-2 occurs only in specific cell lines[10]. An experimental study performed on cells lines showed that SARS-CoV-2 has a cytopathogenic effect, causing the lysis of a single layer of cells. In other cell lines, a lack of change has been observed despite intensive virus multiplication. Moreover, in the tissues infected by SARS-CoV-2, other changes may occur, such as net-like multinucleated syncytial cells, the formation of giant syncytial cells and the destruction of tight cells junctions, cilia shrinkage and beaded changes. The absence of cilia ordering has also been found[11]. These changes may also occur in the cells of the endocrine glands.

SARS-CoV-2 Infection and Hypothalamic Function

SARS-CoV-2 enters the central nervous system by the hematogenous route or directly by the cribriform plate[12]. The impact of SARS-CoV-2 on the function of the HPA axis occurs in two ways: (1) directly by viral invasion and cells damage, and (2) indirectly by the release and action of cytokines, as well as an increase of circulating cortisol levels. In addition, the infection may cause pituitary inflammation development[13].

The expression of ACE2 receptors was found in the hypothalamic paraventricular nucleus, responsible for fluid homeostasis, and in the choroidal plexus[14]. In patients with SARS-CoV-2 infection, the development of the syndrome of inappropriate antidiuretic hormone hypersecretion (SIADH) has been described. One of the mechanisms involved in the development of SIADH is the non-osmotic stimulation release of vasopressin by the overproduction of cytokines[6]. Moreover, the increased vasopressin synthesis may be related to pneumonia by the mechanism involving insufficient volume of intravascular fluid, low extracellular fluid osmolality, contraction of the pulmonary vessels and abnormal filling of the left atrium. In addition, the increased production of vasopressin may be a consequence of the stress related to infection or psychological stress in the course of COVID-19, activating cortical neurons and stimulating the hypothalamus[15]. A few cases of SIADH in patients with SARS-CoV-2 infection and COVID-19 pneumonia have been described[16-18]. It should also be noted that the development of diabetes insipidus in young women in the course of the post-COVID-19 syndrome was described[19].

SARS-CoV-2 Infection and Pituitary Gland Function

The risk factors of pituitary infarction related to SARS-CoV-2 infection include thrombocytopenia, coagulopathy and platelet dysfunction, as well as tropism of the virus to the endothelium of the cerebral vessels. A few cases of pituitary infarction have been described in patients with SARS-CoV-2 infection[20].

In patients with SARS-CoV infection, pituitary gland endocrine function disturbances, including decreased prolactin, follicle-stimulating hormone, luteinizing hormone and increased thyroid-stimulating hormone secretion, likely related to the damage of adenohypophysis endocrine cells, were observed[21]. Similar disturbances may occur in patients with SARS-CoV-2 infection. However, in patients with SARS-CoV-2 infection, elevated prolactin concentrations related to increased cytokines levels were observed[22]. Moreover, in this group, decreased growth hormone release was also reported[23].

SARS-CoV-2 Infection and Thyroid Gland Disorders

A few cases of subacute thyroiditis (SAT) in the course or after COVID-19 have been described[24-28]. Moreover, in some cases, the SAT symptoms occurred from 17 to 40 days after COVID-19 remission[29]. Furthermore, an increased prevalence of SAT was observed in Italian patients with a severe course of COVID-19[30]. It should also be noted that, in some cases, SAT was the sole symptom of SARS-CoV-2 infection[26,31]. Of interest, cases of SAT after SARS-CoV-2 vaccination have also been described[32,33]. It has also been suggested that COVID-19 increases the risk of thyrotoxicosis related to systemic immune activation induced by SARS-CoV-2 infection[34].

In a Barcelona center, two cases of Grave's disease in patients with SARS-CoV-2 infection were reported. The first case relapsed after 35 years of remission, and the second case was a newly diagnosed disease[35]. Moreover, in a Madrid center, two cases of relapse of Grave's disease were also described[36]. Furthermore, in a Michigan center, one case of Grave's disease in a young woman was described 2 weeks after SARS-CoV-2 infec-

tion[37]. In addition, two cases of Grave's disease caused by autoimmune/inflammatory syndrome induced by adjuvants (ASIA) after SARS-CoV-2 vaccination (Pfizer-BioNTech) were reported[38]. All these cases suggest that COVID-19 acts as an autoimmune trigger for latent or new-onset Grave's disease development.

It should also be noted that cases of primary hypothyroidism related to COVID-19 have been reported[30,34,39]. In addition, in a 49-year-old male with no previous history of thyroid disease, hypothyroidism with abnormal levels of TSH and T3, and the presence of anti-thyroperoxidase antibodies (anty-TPO) 6 months after recovering from COVID-19 were described[40].

SARS-CoV-2 Infection and Parathyroid Glands Function

One case of persistent hyperphosphatemia and hypoparathyroidism in a patient with SARS-CoV-2 infection was described[41].

SARS-CoV-2 Infection and the Insufficiency of the Adrenal Glands

The mechanism of adrenal insufficiency caused by viral infections includes the activation of the HPA axis by cytokines, resulting in increased adrenal perfusion and a higher risk of hemorrhage and immunomodulation toward a Th-2 helper T cell response[42]. In patients infected with SARS-CoV, postmortem histopathological changes in the adrenal gland, including infiltration by the monocytes and lymphocytes, as well as focal necrosis, were described[43]. In 28 autopsies of patients with SARS-CoV-2, infection microscopic lesions (46%), necrosis (25%), cortical lipid degeneration (14%), hemorrhage (7%) and unspecific focal adrenalitis (3.5%) in the adrenal gland were found[44]. It has been suggested that vasculopathy related to a 'cytokine storm' is a cause of adrenal damage[45].

A few cases of acute adrenal infarction caused by bilateral adrenal hemorrhage related to renal vein thrombosis or adrenal microvascular thrombosis have been described in patients with COVID-19[47-49].

The other mechanism of adrenal dysfunction is the production of ACTH-inactivating antibodies. Peptides produced by SARS-CoV are structurally similar to ACTH and may trigger the stimulation of the production of antibodies, which are also destructive for ACTH. The proteins produced by SARS-CoV-2 are 89.1% similar to those produced by SARS-CoV. Therefore, the same mechanism secondary adrenal insufficiency may occur during this infection[46].

Heidarpour et al[50] described a case of an elderly man with COVID-19 admitted to the intensive care unit due to frequent episodes of vasopressor-resistant hypotension, which was ultimately diagnosed as acute adrenal insufficiency. The pathomechanisms of adrenal insufficiency in the course of SARS-CoV-2 infection include the inhibition of ACTH release and alteration of ACTH action in adrenal gland cells by high concentrations of proinflammatory cytokines, such as TNF-alpha, IL-1 and IL-6 ('cytokine storm'). In addition, a low level of HDL-cholesterol found in seriously ill patients may diminish the supply of substrate for cortisol production. The term 'critical illness-related corticosteroid insufficiency' determines the decreased levels of the cortisol binding protein, reduced protein complex cleavage, enhanced cortisol metabolism, and decreased number and affinity of cortisol receptors. These pathomechanisms play a role in functional adrenal insufficiency development[51]. In the severe course of COVID-19, the development of functional adrenal insufficiency may be possible.

SARS-CoV-2 Infection and Disturbances of Pancreas Function

Both endo- and exocrine pancreas cells are characterized by high ACE2 receptor expression[52]. Therefore, it is suggested that the pancreas is susceptible to SARS-CoV-2 infection[53]. This hypothesis was confirmed by the results of an experimental study[54].

A few cases of mild pancreatitis in patients with a severe course of SARS-CoV-2 infection have been reported[52,55]. However, it should be noted that acute onset of type 1 diabetes (T1D) related to damage of pancreatic islets occurred more frequently than pancreatitis in patients with SARS-CoV-2 infection[2]. In addition, hypokalemia occurring during SARS-CoV2 infection may impair insulin secretion[56]. The analysis of data from northwest London showed that new-onset T1D and diabetic ketoacidosis during the COVID-19 pandemic was approximately 80% higher than in a typical year[57]. Moreover, in another study[58], ketosis was found in 6.4% of patients with SARS-CoV-2 infection on admission to the hospital.

Moreover, the 'cytokine storm' related to SARS-CoV-2 infection may inhibit the tyrosine

kinase activity of insulin receptors, resulting in impaired insulin sensitivity[59]. Therefore, it has been suggested that SARS-CoV-2 infection diminishes insulin sensitivity in patients with pre-diabetes[60].

SARS-CoV-2 Infection and Testis Function

The effects of viral infection on testis function include the impact on the hypothalamus-pituitary-testis axis function, local inflammation in the testis and the influence of fever on testicular function[61].

A higher prevalence of hypogonadism was found in patients with SARS-CoV-2 infection. In most of these cases (85%), hypogonadism was secondary[62]. However, the direct effect of SARS-CoV-2 on both hormone and sperm testicular production seems important in the development of hypogonadism. ACE2 receptors were present on both Sertoli and Leydig cells. In addition, a higher expression of NRP1 was found in testicular cells. The presence of ACE2 receptors has also been described in sperm. Thus, it is suggested that SARS-CoV-2 infects not only testis cells but also sperm[7]. Postmortem histopathological analysis of changes in the testes of patients with COVID-19 revealed swelling, vacuolization and cytoplasmic thinning in Sertoli cells; the detachment of tubules from the basement membranes; and a decreased number of Leydig cells[63]. Moreover, two cases of orchitis during SARS-CoV-2 infection (in a 14-year-old boy and a 43-year-old man) have been described[64,65]. In addition, decreased testosterone levels were found in 30% and inhibin-B in 25% of men with a history of COVID-19[66].

The effect of SARS-CoV-2 infection on semen quality has also been described. The mechanisms include the higher activity of ACE2, the effect of proinflammatory cytokines and ROS (Reactive Oxygen Species), as well as the low activity of superoxide dismutase[67]. The results of a prospective study[68] showed azoospermia in 18.6% and oligospermia in 7.0% of men after recovering from COVID-19. Interestingly, SARS-CoV-2 in semen was detected in 26.7% of patients in the acute phase of the infection and 8.7% after recovery[69]. However, the possibility of sexual transmission of SARS-CoV-2 is still debated[70].

Moreover, hypogonadism and impaired endothelial function related to SARS-CoV-2 infection contribute to erectile dysfunction. A higher prevalence of erectile dysfunction in patients with a history of COVID-19 was shown[71]. Moreover, in an international cohort study, sexual dysfunction was frequently observed in men with post-COVID-19 syndrome[72].

SARS-CoV-2 Infection and Ovary Function

ACE2 receptor expression is found in ovarian tissues[73], as well as the uterus, placenta, vagina, and breasts[7]. However, oocytes do not appear to be infected by SARS-CoV-2. This hypothesis is supported by the cases of two women with a positive SARS-CoV-2 PCR test who underwent controlled ovarian stimulation[74].

The results of the retrospective study showed that SARS-CoV-2 infection was associated with a change in menstrual volume and the length of the menstrual cycle regardless of the infection severity[75]. Menstrual disturbances, especially irregular menstruation and unusually heavy periods/clots were also observed in an international cohort study among women with post-COVID-19 syndrome[72].

Coagulopathy During SARS-CoV-2 Infection and its Implications on Endocrine Disturbances

Severe COVID-19 infections frequently manifest coagulation disturbances, such as disseminated intravascular coagulation or thrombotic microangiopathy. It should be noted that the clinical and laboratory changes in the coagulation disturbances in COVID-19 are different than those in the common presentation of coagulopathy. The profound coagulation abnormality in the course of severe COVID-19 infections seems to be caused by coagulation changes induced by inflammation 'cytokine storm' in combination with severe endothelial damage, resulting in a massive release of Willebrand factor and plasminogen activators[76]. These coagulation disturbances increase the risk of hemorrhage[77]. The prothrombotic state related to endothelial damage has also been found in long COVID-19[78]. Coagulopathy in severe COVID-19 infections seems to be related to venous and arterial thromboembolic disease. It has also been suggested that distinct intravascular coagulation syndrome in the course of COVID-19 may need separate diagnostic criteria[79]. The most important differences between abnormalities in homeostasis in the course of the coagulopathy in COVID-19 and DIC include the lower severity of thrombocytopenia and hypofibrinogenemia[80-82].

Coagulopathy in the course of COVID-19 is associated with poor prognosis[83]. One of the causes of shock and death may be acute adrenal insufficiency related to COVID-19 coagulopathy and hemorrhage[42-45]. In addition, COVID-19 coagulopathy may be a cause of SIADH and pituitary infarction[15,20], which are potentially life-threatening conditions.

Conclusions

Among other symptoms and late complications of SARS-COV-2 infection, endocrine dysfunction should be considered. Some complications, such as SIADH, pituitary infarction and acute adrenal insufficiency, can be directly life-threatening. Therefore, hormonal parameters should be monitored in patients with SARS-COV-2 infection and post-COVID-19 syndrome. Post-COVID-19 syndrome occurs in 50-70% of patients hospitalized due to SARS-COV-2 infection up to 3 months after hospital discharge. It is suggested to distinguish the three forms of post-COVID syndrome using the following criteria: acute post-COVID-19, with symptoms from 5 to 12 weeks; long post-COVID, with symptoms from 12 to 24 weeks; and persistent post-COVID-19, in which symptoms occur over 24 weeks after the infection[84]. The symptoms of post-COVID syndrome include neurocognitive, autonomic, gastrointestinal, respiratory and musculoskeletal disturbances. Patients have reported various symptoms, including heart palpitations, chronic rhinitis, insomnia, chest pain, cough, anxiety, nausea, abdominal pain[85], fatigue, headache, attention disturbances, hair loss and dyspnea[86]. Some post-COVID symptoms may be related to endocrine disturbances, such as an impaired function of the hypothalamus, pituitary gland and thyroid gland. The long-term complications of SARS-CoV-2 infection may also include impaired fertility and sexual function, especially in men[87].

There are no recommendations regarding hormonal diagnostics in patients with SARS-CoV-2 infection and post-COVID-19 syndrome. Due to the growing number of people with COVID-19 and post-COVID-19 syndrome, developing minimal diagnostic schemes regarding the types of hormonal determinations and the time intervals in which they should be performed is necessary.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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