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Endocrine impact in infections including COVID-19

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ABSTRACT

Endocrine damage in infectious diseases (bacterial, viral) has been proven for a long time, confirming the disruption of the functions of most endocrine glands via the hypothalamic-pituitary-glandular axis. Endocrine activity takes place in tandem with the activity of the immune system. They intercondition and influence each other, any change in one sector influencing the other (positively or negatively). Severe (critical), bacterial or viral infections go through the stage of sepsis, the background of which is the disruption (disorganization) of the host's response to the infection. The mechanisms by which the endocrine glands are affected are multiple (direct, immunologically mediated, thrombotic) leading to multiple, morphological and functional lesions. The recovery of these injuries takes place over time, and permanent sequelae are possible. The recent pandemic caused by SARS-CoV-2, through the ways of manifestation and evolution of the diseases, justifies the interest regarding the endocrine damage in the SARS-CoV-2 infection, both in the acute and post-acute phase (long COVID evolves with symptoms, some newly appeared, which are also present in non-COVID endocrinopathies).

Material. The arguments regarding the endocrine damage were extracted from the publications mentioned at the end of the work as bibliographic titles.

The results highlight the endocrine damage in infections, especially in severe ones - and the impact on the immediate and late evolution of the illnesses.

Conclusions. In order to understand the pathogenic, physio-pathological and clinical aspects of an infection, attention must be paid to the state of the endocrine system in correlation with the immune system, especially in patients receiving shorter or longer corticosteroid therapy.

Keywords: sepsis, virus, COVID-19, endocrine diseases

INTRODUCTION

The constants of the internal environment – homeostasis – are governed by the neuroendocrine system and the immune system. The immune system is strongly influenced by the functional state of the endocrine glands, especially the adrenal gland and the thymus.

In the case of infections, the first sensor is the native immune system, which in certain situations is oversized, uncontrolled and can lead to sepsis, by producing a large amount of cytokines (cytokine storm) that can affect the morphology and function of various organs, including some endocrine glands, which, in turn, can influence the immune response, immediately and later.

The evolution of an infectious disease is strongly influenced by the immune and endocrine response, which sometimes have either a reparative or a destructive role. This response changes during the course of the infectious disease and beyond. The infectious disease is not cured once the pathogen is eliminated, the immunological and endocrine changes can persist for a long time (weeks, months or even years) with functional consequences of some organs (some even biochemically imperceptible) but with a clinical expression.

Endocrine changes have been described in infectious diseases (bacterial and viral) and before COVID.

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Before COVID

Endocrine changes in SEPSIS

In SEPSIS, changes were observed in all hypothalamo-pituitary-glandular axes [1].

a. Hypothalamic-Pituitary-Adrenal Axis
- hypercortisolemia in the acute phase (stress, adaptation)
- disorders in the Beta Adrenergic system (catecholamines)

b. Hypothalamic-pituitary-thyroid axis
- decrease in triiodothyronine

c. Hypothalamic-Pituitary-Gonadal axis
- hypothalamic amenorrhea

Disruptions in the endocrine system are part of the host response to infection [1].

Endocrine changes in viral infections

Before COVID, the impact of some viral infections on the various endocrine glands with the interest of the hypothalamo-pituitary-glandular axes was noticed [2,3].

a. *Affecting the Hypothalamic-Pituitary-Adrenal axis* – characterized by an increase in the level of cortisol in the first phase (to influence the native immune response (IL 6, TNF) in HSV1, CMV, INFLUENZA infections)

b. *Affecting the Hypothalamic-Pituitary axis* – characterized by a decrease in antidiuretic hormone and the appearance of SIADH with hyponatremia in HSV1, EBV infection

Morphologically, it was noticed at the level of the pituitary gland:
- Ischemia (infarction – apoplexy) in infection with HANTA, FLU
- Hemorrhages in the infection with HANTA, VZV.

In all cases, decreases in the levels of hormones produced by the pituitary gland have been described.

Thyroid damage in viral infections

The following have been described:
- Subacute thyroiditis with hyperthyroidism or hypothyroidism in infections (MUMPS, COXSACKIE, ADENO, INFLUENZA)
- Autoimmune hyperthyroidism in infections with EBV, HIV
- Autoimmune hypothyroidism in infections with PARVO, HSV, HEP C, E, EBV

Adrenal damage in viral infections

The following have been described:
- Multifocal necrosis in infections with FLU (H5N1), EBOLA, ECHO, CMV, HIV (99% die from AIDS)

Pancreas damage in viral infections

It has been described the damage to BETA-insulin-secreting cells with hyperglycemia, type 1 diabetes in MUMPS, HEP.C, COX, CMV infection.

Testicular damage

It was found in MUMPS, ZICA, HIV infections.

Ovarian damage

It was encountered in infections with MUMPS, ZICA, HIV CMV (Ovarian Carcinogenesis).

CORONAVIRUS INFECTION

SARS 1 and SARS-CoV-2 have approximately 80% genomic similarity.

SARS 1 and SARS-CoV-2 use the same receptor ACE2 and TMPRSS2 for human cell entry.

ACE2 is present in all endocrine glands and adipose tissue [6].

In the infection with SARS-CoV-1 (2003), genomic sequences of the virus were detected in the Hypothalamus with a deficiency of: ACTH – with hypocorticism, TSH – with hypothyroidism, as a result of the involvement of the pituitary-thyroid and adrenal axis [4].

Cytopathic effects have been described in the thyroid – correspondingly low levels of T3 (94%) and T4 (46%) – that persist for a long time and in covalescence requiring supplementation with levothyroxine.

Cytopathic effects have also been described in the pancreas (glycemic disorders), adrenal gland (hypocortisolism).

In experimental SARS 1 – necrotic lesions in the adrenal gland and thyroid were described.

Infection with SARS-CoV-2 (COVID-19)

The infection with SARS COV 2 proved to be a systemic disease in which the immune and endocrine systems are strongly involved in the pathogenesis of the infection both in the acute and post-acute phase.

The central (constant) element detected on the biopsy materials is the endothelial damage that favors thrombosis (thrombotic endotheliopathy) with anatomical and functional consequences practically in any sector including the endocrine one [5].

SARS-CoV-2 uses the same ACE2 and TMPRSS2 receptors [6].

Endocrine glands: Pituitary, Thyroid, Adrenal, Pancreas, Testis, Ovary, Thymus express both ACE2 and TMPRSS2 [11,12].

Thus, the endocrine system is vulnerable to SARS-CoV-2 [6].

Patients with COVID have endocrine disorders with an impact on the immediate evolution of the disease as well as post-COVID being able to develop chronic endocrine disorders.

Endocrine disorders contribute to the symptoms developed by the COVID infection in both the acute and post-acute phase.

Pituitary damage in COVID [2,3,6-10]

SARS-CoV-2 was detected in the pituitary gland of those who died.

Morphologically, pituitary apoplexy was described [6].

Hormonally, the following were found:
- Secondary hypocorticism – 40% – low level up to 3 months
- Central hypothyroidism – 5% up to 9 months
- Hyponatremia – 50% caused by antidiuretic hormone dysfunction (SIADH – Syndrome of inappropriate antidiuretic hormone)

Other changes:
- low growth hormone (GH).
- increased level of:
  - prolactin
  - FSH (Follicular Stimulating Hormone)
  - LH (Luteinizing Hormone)

Thyroid damage in COVID [2-4,6-10,12,13]

In severe/deceased forms, there were significant decreases in:

TSH – pituitary hormone

T3 – thyroid hormone

In a group of 287 critically ill patients – 20% – presented thyrotoxicosis correlated with increased levels of IL6 supporting the role of inflammation, and in 5% – hypothyroidism.

Subacute thyroiditis was described in patients with medium forms manifested in: temperature, neck pain, fatigue, tremors, weakness, palpitations that appeared between days 5-42 [12].

Ultrasound appearance of thyroiditis and hypocapture of radioisotopes were described [12].

Patients received corticosteroids with a significant improvement [12].

Thyroid dysfunctions persisted for a long time (in another group of 50 patients, 64% had thyroid dysfunction 3 months after the onset, in another group of 70 patients, thyroid function returned to normal between 3 and 6 months).

Thyroid cell damage can be caused by the direct action of the virus, the viral genome was found in 9 out of 25 (36% autopsied cases). Hashimoto thyroiditis has also been described [10].

In Long Covid, there is fatigue, myalgia, foggy mind, symptoms also found in non-Covid thyroid dysfunctions [6].

Adrenal damage in COVID [3,6-10,13]

Morphological changes were described in the deceased:
- Single or bilateral hemorrhages [6,8].
- Microinfarcts found in 3 cases (33% in a batch of 9 deceased) [12].

From a hormonal standpoint, the following were described:
- hyponatremia – 30% – correlated with SIADH
- low cortisol level in: 38% of cases (84 patients) with moderately severe forms and in 6.8% medium forms

Long Covid symptoms: fatigue, postural hypotension, cognitive impairment are also present in non-Covid adrenal insufficiency.

Pancreas damage [3,4,6-10,12]

The ACE2 receptor was detected in betapancreatic cells.

The virus was detected in insulin-secreting B cells with B-cell lesions.

Biochemically, Denovo Diabetes or worsening of existing Type I Diabetes were found.

Adipose tissue damage [12]

Adipose tissue expresses both ACE2 and TMPRSS2 in high quantity, thus explaining the severe forms in obese.

Testicular damage in COVID [3,4,6-9]

The ACE2 receptor is present in seminiferous tubules, spermatogonia, Sertoli cells, Leydig cells producing testosterone (SARS-CoV-2 genome found in 6 out of 9 cases (67%).

The virus was present in sperm in 6 out of 38 cases examined.

The following were also described:
- reduced spermatogenesis
- maturation and reduced mobility of spermatozoa
- low testosterone level correlated with IL6↗ CRP↗ with immune-mediated hypogonadism

Ovary damage in COVID [3,4,6-9]

The ACE2 receptor is present in the ovaries, uterus, vagina, placenta.

Clinically, menstruation disorders have been described, especially in the post-Covid phase.

Thymus damage in COVID

The thymus is involved in the cellular, humoral, as well as the endocrine immune response.

It is a lymphoid organ responsible for the generation and maturation of T lymphocytes involved in cellular immunity [14].

The thymic hormones Thymopoetin, Thymosin and Thymuline have a role in the differentiation and functions of lymphocytes and are involved in inflammatory and autoimmune processes, including SARS-CoV-2 infection [14].

At the level of the Thymus, epithelia express ACE2, these being the target of SARS-CoV-2 and consequently altering their functions with an important role in the immediate or late evolution of COVID-19 [15,16].

Lymphopenia in the T cell system is one of the elements constantly encountered in COVID and it can be explained by the direct damage to the thymus caused by SARS-CoV-2 [15].

Monitoring the activity/functions of the thymus is useful in evaluating the evolution of the COVID infection.

It is known that the thymus is involved in the clinical picture of Myasthenia Gravis (muscular weakness). This is an autoimmune disease through

the production of antibodies against acetylcholine receptors, preventing the transmission of nerve impulses to the muscles. The main cause resides in the existence of Thymus disease, previous to the infection with SARS-CoV-2.

In COVID, new cases of Myasthenia Gravis were described in people without a history of Myasthenia gravis, which have occurred 2-4 weeks after the onset [26-28]. or the recurrence of crises in people with a known history of Myasthenia Gravis.

Pineal gland damage in COVID [17-20]

The Pineal Gland produces melatonin, a hormone involved in regulating the circadian rhythm and the sleep-wake state. The decrease in the level of this hormone – with age – or other circumstances correlates with sleep disorders (insomnia).

Insomnia and sleep disorders are frequently encountered post-Covid. Exogenous intake of melatonin has been shown to improve sleep and cognitive performance [19].

Melatonin has been proven to have other actions: anti-inflammatory, antioxidant [19-21].

For its multiple properties, melatonin has been proposed as a therapeutic adjuvant in COVID-19 [10,20].

DISCUSSIONS

Severe (critical) bacterial and viral infections sequentially go through the stage of sepsis meeting all the criteria of sepsis (Sepsis 3) [21-25].

Pathogenically and physio-pathologically, this state (stage) is characterized by the presence of two factors: endothelial and thrombotic lesions inducing the dysfunction of many organs [5].

Similar changes, but of lower intensity are also present in medium or mild forms of the disease. These changes can persist long after the acute episode even if it was not an intensely manifest one.

Clinically, these changes (morphological, functional) can generate a series of general or particular symptoms grouped into “Post Sepsis Syndrome” or “Post Covid Syndrome”.

Post Sepsis Syndrome includes both patients with bacterial and viral Sepsis.

Post Covid or Long Covid includes COVID-19 infections, both those with severe sepsis as well as those with medium or mild forms but who show similar symptoms for a long time.

Viral infections produce a series of changes in the structures of the endocrine system in several ways [9]:

- direct cytopathic action
- as a result of the action of cytokines
- viruses can encode the production of specific proteins with the homologous structure of hormones against which antibodies (with both antiviral and antihormonal action) can be developed, triggering an autoimmune reaction even in the early stages of infection
- the products resulting from the cells of virally or immunologically affected cells act upon the cells of other organs at a distance and their suffering is added to those produced directly or indirectly.

Dysfunctions of the endocrine system have an important (decisive) impact in the unfolding of the infectious process.

The monitoring of the functions of the endocrine and immune system during the infection must be done simultaneously, because the medication used in the treatment of the disease (corticotherapy) can influence the two factors.

CONCLUSIONS

Many endocrinopathies have been reported in bacterial and viral infections. They can be transient or even permanent.

These include hypopituitarism, SIADH, central diabetes insipidus, thyroiditis (hyper or hypo functions), hyperglycemia, adrenal insufficiency, testicular and ovarian damage.

Since many of the symptoms induced by these changes are common with those induced by other non-Covid conditions, it is important to collaborate with endocrinologists to quantify the contribution of endocrine disorders in explaining the clinical picture both in the acute period of SARS-CoV-2 infection and in the post-acute period (Long Covid).

This is particularly important in formulating therapeutic schemes, in particular immunosuppressive medication (corticotherapy), which is a hormonal medication.

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