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EFFECTS OF COVID-19 ON THE THYROID GLAND

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SARS COV-2 is a betacoronavirus, which infects human tissues by penetrating cells through the receptor of the angiotensin 2 conversion enzyme. Studies have shown that the receptor of the angiotensin 2 conversion enzyme ACE2 is found in high amounts in the thyroid gland. The thyroid gland and SARS COV 2 are involved in complex interactions through hormones and immunomodulatory signaling molecules. These connections have been established in both physiological and pathological conditions. Clinical research has shown that by associating COVID-19 disease with thyroid disorders, biochemical examination can identify thyrotoxicosis, hypothyroidism, and non-thyroid disease syndrome.

Key words: Thyroid, COVID-19, Hypothyroidism.

INTRODUCTION

Globally, Covid-19 disease caused multiple health problems because the causative agent, SARS COV 2, is spreading in such a rapid manner with outbreaks growing exponentially[1].

SARS COV-2 is known to be a beta-coronavirus that infects human tissues by entering cells through the receptor of the angiotensin 2 (ACE2)[2,3] conversion enzyme. Once inside the host cell, the virus activates the enzyme TMPRSS2. The binding of the spike viral protein to ACE2, together with the cleavage of ACE2 by TMPRSS2, facilitates the penetration of the virus into the cell, viral replication and intercellular transmission[3].

The infection caused by SARS COV 2 has a broad spectrum in terms of clinical appearance, ranging from asymptomatic forms, with frequent respiratory damage and possibility of transmission, to severe and very severe forms[4], leading to acute respiratory distress syndrome, or even multi-organ failure in the cases of patients with high risk factors[5,6].

In this context, studies regarding COVID-19 and thyroid disease have begun and it has been found that ACE2 is present in high amounts. The thyroid gland and SARS COV 2 are involved in complex interactions through hormones and immunomodulatory signaling molecules. These connections have been established in both physiological and pathological conditions[7,8].

Thyroid hormones modulate innate and adaptive immune responses through both genomic and nongenomic mechanisms[7]. Concentrations of L-thyroxine (T4) and 3,3', 5-triiodo-L-thyronine (T3) stimulate the production and release of cytokines, which are components of the "cytokine storm" specific to systemic viral infection[9,10]. Furthermore, thyroid hormones are able to potentiate the antiviral action of IFN-γ (interferon gamma)[9]. Similarly, the immune response to SARS COV2 infection in autoimmune thyroid diseases, alemtuzumab-induced thyroid dysfunction are being studied[10,11,12]. Thus, clinicians have observed that respiratory infections could cause a thyroid storm in patients with decompensated hyperthyroidism, favoring the risk of death. It should be noted that T4, the main hormone secreted by the thyroid gland, is known to activate platelets[13]; this may support the pathological coagulation encountered as a complication of virus infections. This observation further motivates the study of the relationship between COVID-19 and the thyroid gland.

CLINICAL PRESENTATIONS

The binding of the virus to the ACE2 and the activation of TMPRSS 2, will cause the decrease of angiotensin 1-7 with the increase of angiotensin II, which is responsible for immune-mediated lung inflammation and lung parenchyma injury [3,4].

The *in silico* approach shows that ACE2 expression levels in the thyroid gland are positively and negatively related to immune responses and the results of distinct thyroid manifestations. A major group of structural proteins of the plasma membrane that could be involved in the cellular invasion of SARS COV 2 is integrins. SARS COV 2 could affect the thyroid gland because hyperactivity of the immune responses of Th1 / Th 17 and the COVID-19-associated cytokine storm can trigger and disrupt inflammation of the thyroid gland[14].

Patients infected with SARS COV 2 in the study underwent histopathological examinations where interstitial lymphocyte infiltration was observed[15,16]. Follicular epithelial cell disruption has also been observed. However, the significance of histopathological data on the thyroid gland of COVID-19 patients taken in the study is uncertain. It can only be said that two plausible mechanisms could explain changes in the thyroid gland and the hypothalamic-pituitary-thyroid axis: one has an indirect effect, with inflammatory immune responses caused by SARS COV 2, and another is a direct viral effect.

THYROID GLAND DYSFUNCTIONS IN PATIENTS WITH COVID-19

During the epidemic with SARS COV-1, studies were performed, and changes in thyroid function were observed[17,18]. Thus, Wang and colleagues observed that serum levels of TSH, T3 and T4 in patients with SARS COV 1 were significantly lower than those in the control group[17]. They made a positive correlation between the severity of SARS and T3 levels, so the more severe the disease, the lower the T3 level. Moreover, Wang and colleagues observed that depending on the stage of the disease, the levels of T3 and T4 also show changes, namely: in the acute phase of the disease, the level of T3 had decreased in 94% of patients and T4 had decreased in 46% of patients. During convalescence T3 was low in 90% of patients and T4 was low in 38% of patients.

Leow and colleagues reported that the patients studied four months after recovery were hypothyroid, with central hypothyroidism and primary hypothyroidism due to chronic lymphocytic thyroiditis [18].

Correlating the above, we could associate thyroid dysfunction in patients with COVID-19, already having evidence from studies such that the thyroid gland and the hypothalamic-pituitary-thyroid axis could be the target of SARS COV 2 disease. Specifically, associating the disease COVID-19 with thyroid disorders, by biochemical examinations can be identified: thyrotoxicosis, hypothyroidism, as well as non-thyroid disease syndrome [19,20].

THYROTOXICOSIS

Subacute thyroiditis is a disease caused by the viral or postviral inflammatory process. Many viruses can be associated with the development of thyrotoxicosis and evidence of infection can be based on epidemiological or serological data.

It usually has three consecutive phases: the initial phase, in the first few months, followed by hypothyroidism for roughly three months and then by euthyroidism [21].

Another study show that is conceivable that in patients with thyrotoxicosis and COVID-19 atrial fibrillation could be due to both the hormonal excess and the systemic inflammatory response [14]. 32% and 16% of overt thyrotoxic patients with COVID-19 also developed atrial fibrillation and thromboembolic events, respectively. In thyrotoxic patients in-hospital mortality was higher and the duration of hospitalization was longer as compared to COVID-19 patients with normal thyroid function [14].

Thyroid imaging features corresponded to that of classical tyreotoxicosis at the time of destructive thyrotoxicosis. COVID-19-related thyrotoxicosis was similar to thyrotoxicosis secondary to other viruses: in all cases, steroidal and non-steroidal anti-inflammatory drugs were effective to obtain a quick resolution of thyrotoxicosis and normalization of inflammatory markers. Glucocorticoid use in patients with COVID-19 has been proven to be of benefit[22]. Considering the potential cardiovascular complications of both COVID-19 and subacute thyroiditis, a low dose of steroids could have positively impact on the outcome of patients with COVID-19-related subacute thyroiditism.

HYPOTIROIDISM

Similarly to thyrotoxicosis but with lesser extent, hypothyroidism could negatively impact on outcome of COVID-19. Central hypothyroidism is biochemically defined as low FT4 with inappropriately low/normal TSH[23]. In the study by Chen et al. (2020), central hypothyroidism could be diagnosed in 2–6% (one to three out of 50 patients) of patients hospitalized for non-mild COVID-19, who had low FT4 with low/ normal TSH. Reversal of these hormonal changes occurred after recovery from COVID-19, a fact that highlights plausible acute/transitory effects of COVID-19 on HPT axis [24].

ATYPICAL THYROIDITIS (AT)

Atypical thyroiditis is a form of subacute thyroiditis, without neck pain, recognized in COVID-19 patients. It is characterized biochemically by low concentrations of TSH and FT3 along with normal or elevated concentrations of FT4, thus the synonym of "thyroxine thyrotoxicosis"[25]. The study shows that in non-mild COVID-19 patients the absence of neck pain could be due to lymphopenia. Muller et al. (2020) found that 15% (13/85) of COVID-19 patients admitted to high intensity of care unit had atypical thyroiditis. As opposed to classical subacute thyroiditis and COVID-19- related subacute thyroiditism was more frequent in male patients, and this could be partially explained by the gender difference in the immune signatures associated to ACE2 at the thyroid level. The development might have contributed to the more critical conditions compared to patients admitted to HICUs in 2019[25].

CONCLUSIONS

Theoretically, SARS-CoV-2 can involve any organ, affecting even the thyroid gland which is manifested by thyroid disorders and hormonal changes. The severity of COVID-19 appears to be the major determinant of the type of alteration that dominates the thyroid lesion. Specifically, thyrotoxicosis associated with neck pain (i.e., classic subacute thyroiditis) occurs mainly during or immediately after mild COVID-19, throat-free thyrotoxicosis (possibly in the context of non-thyroid disease syndrome) could characterize more severe and critical cases of pneumonia COVID-19.

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