COVID-19 and Hypothalamic–Pituitary Diseases

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Long COVID-19, also known as post-acute sequelae of SARS-CoV-2 infection, is a condition where individuals who have recovered from the acute phase of COVID-19 continue to experience a range of symptoms for weeks or even months afterward. While it was initially thought to primarily affect the respiratory system, it has become clear that Long COVID-19 can involve various organs and systems, including the endocrine system, which includes the pituitary gland. In the context of Long COVID-19, there is a growing understanding of the potential implications for the pituitary gland. The virus can directly affect the pituitary gland, leading to abnormalities in hormone production and regulation.

Long COVID-19 pituitary

1. Introduction

The most recent pandemic declared to date is the coronavirus disease 2019 (COVID-19). In December 2019, Chinese authorities informed the World Health Organization (WHO) about clusters of viral pneumonias detected in the city of Wuhan [1]. The causative virus is severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is a single-stranded positive-sense RNA virus enveloped in the coronavirus subfamily, highly contagious among humans [1]. COVID-19 defines the disease caused by SARS-CoV-2. As of now, over 769 million people worldwide have been infected with COVID-19, and the WHO has recorded more than 6.9 million deaths [2].

SARS-CoV-2, like other coronaviruses, enters cells via the Angiotensin 2 Conversion Enzyme (ACE2) receptor and Transmembrane Serine Protease 2 (TMPRSS2) [3]. The extensive spectrum of SARS-CoV-2-induced lesions is attributed to the presence of the ACE2 receptor in numerous tissues, including the colon, liver, brain, and various endocrine tissues such as the pancreas, thyroid, and gonads [4][5].

Endocrine disorders associated with COVID-19 have been reported in several studies, exhibiting an endocrine phenotype ranging from clinically paucisymptomatic presentations to potentially life-threatening endocrine emergencies [6][7][8]. The pancreas is the endocrine organ most frequently affected by SARS-CoV-2. COVID-19 is responsible for impairing the glycemic balance in diabetic patients and increasing the incidence and severity of inaugural diabetic ketoacidosis during the pandemic [8][9][10][11].

The thyroid is the second most commonly affected endocrine gland in COVID-19. The most common abnormality in patients infected with SARS-CoV-2 is a decrease in thyroid-stimulating hormone (TSH) and free Tri-

iodothyronine. An increased prevalence of thyrotoxicosis and primary hypothyroidism secondary to COVID-19 has also been reported [6][12][13][14][15][16]. Involvement of the adrenal glands by SARS-CoV-2 has been less frequently reported, with preserved adrenal function in the vast majority of patients [17][18][19]. However, primary adrenal involvement by SARS-CoV-2 has been primarily reported due to adrenal hemorrhages and infarctions. It has also been suggested that COVID-19 may play a role in the pathogenesis of Addison's disease [20][21][22].

Gonadal involvement during COVID-19 has been rarely described. In males, it primarily manifests as orchitis-epididymitis and a tendency towards hypergonadotropic hypogonadism. Disturbances in spermatogenesis have also been reported [23][24][25][26][27]. Regarding ovaries, a few studies have concluded the absence of modification in the ovarian hormonal profile [28][29][30][31].

The central nervous system (CNS) is also a frequent target of SARS-CoV-2. A less explored compartment within the CNS in COVID-19 research, relative to other CNS structures, is the pituitary gland. COVID-19 infection has been associated with hypothalamo–hypophyseal (HH) disorders, such as pituitary apoplexy, diabetes insipidus, and hypophysitis [4][32][33][34][35]. In addition to the ongoing global relevance of the viral infection, the long-term impact of SARS-CoV-2 remains poorly understood. Many patients report the persistence or onset of symptoms, such as fatigue and cognitive impairments, several months after infection. This has led to the definition of a new entity, known as 'Post COVID-19 Syndrome,' or more commonly referred to as 'Long COVID-19' [36]. The proportion of patients affected by Post COVID-19 Syndrome varies from low percentages to as high as 93% of SARS-CoV-2-infected individuals [37]. Virological and histological hypotheses analyzing these residual symptoms suggest the persistence of certain post-inflammatory lesions, including vascular issues [38]. Other authors have postulated the theory that nano-antioxidants play a role in the pathogenesis of this syndrome [39][40]. However, when closely examining the remaining symptoms in these patients, some are strikingly similar to those seen in antehypophyseal deficiencies, notably corticotrop and somatotrop. Some studies investigating the HH axis have also identified antehypophyseal deficiencies, particularly corticotrop and somatotrop, during the acute phase of COVID-19 infection and in the late post-infectious phase, several months later [4][41].

Recently, some authors have suggested the involvement of the pituitary gland in COVID-19 infection and in Post COVID-19 Syndrome [4]. Certain symptoms could be explained by these pituitary deficiencies. The ACE2 receptor, which enables SARS-CoV-2 entry into cells, is expressed in the HH axis [4]. The exact mechanisms of viral action on infected cells remain under discussion, but inflammatory and autoimmune mechanisms are primarily implicated. Pituitary exploration during infection and follow-up in Post COVID-19 patients has not been systematically established due to the insidious nature of these lesions [4][41].

2. COVID-19 and Hypothalamic–Pituitary Diseases

Severe acute respiratory syndrome coronavirus (SARS-CoV) and SARS-CoV-2 belong to the coronavirus family [42]. The principal receptor for SARS-CoV-2, ACE2, manifests a ubiquitous expression across the cellular landscape of endocrine organs, notably prominent in the pancreatic and thyroid tissues [43][44]. This receptor has also been

identified in hypothalamo–hypophysial tissues, albeit with a lesser degree of expression compared to other endocrine tissues [45][46].

SARS-CoV has been associated with various endocrinopathies, particularly pituitary-related [45][47]. SARS-CoV-2 has demonstrated a binding affinity to ACE2 10 to 20 times higher than that of SARS-CoV, explaining at least its higher infectious potential [4][48].

Throughout the evolution of the COVID-19 pandemic, several studies have reported hypothalamo–hypophyseal involvement potentially linked to SARS-CoV-2. These mainly include cases of hypophysitis, hypopituitarism, pituitary apoplexies, inappropriate secretion of antidiuretic hormone (SIADH), and diabetes insipidus. Hypothalamic involvement, on the other hand, has been very rarely described [4][8][35][49][50][51][52][53][54]. All these descriptions are summarized in **Table 1**.

Table 1. Types of lesions occurring to hypothalamo–hypophyseal gland during COVID-19 infection.

Type of Lesions	Authors	Year	Country	Results	Study Description
Pituitary apoplexy	Hazzi et al. [32]	2023	Canada	14 cases	Literature review
Syndrome of Inappropriate ADH secretion	Khidir et al. [33]	2022	Sudan	36% of Hyponatremia	Meta-analysis
Hypophysitis	Capatina et al. [4]	2023	Romania	Not precise	Several cases reported but widely underestimated according to the authors [44][45][46][47][48]
Isolated central diabetes insipidus	Yavari et al. [34]	2022	Iran	1 case	Literature review
Hypothalamitis	Facondo et al. [35]	2022	Italy	5 cases	Literature review

2.1. Pituitary Apoplexy

Pituitary apoplexy is a medical emergency that occurs when there is bleeding or impaired blood flow to the pituitary gland, often in the context of a pituitary adenoma. It can cause sudden-onset headaches, visual disturbances, and hormonal imbalances. Patients with severe COVID-19 may be at an increased risk of developing blood clotting disorders, which could potentially lead to conditions like stroke or apoplexy. The virus can trigger an inflammatory response and cause abnormalities in blood coagulation, contributing to the formation of blood clots. The evolution of apoplexy in infected patients is not well evaluated. In common apoplexies, for example, in the study of Falhammar et al., 33 patients had a pituitary apoplexy, 55% of them were men, and the mean age was 46 years. Only 9% of the patients required acute pituitary surgery, while eight patients were operated after more than one week. During follow-up [7.6 ± 4.3 years], none of the hormonal deficiencies regressed, and three patients died from non-related causes [55].

2.2. Hypophysitis

Hypophysitis is an inflammation of the pituitary gland and is a rare cause of hypopituitarism. Autoimmune hypophysitis is a known condition in COVID-19, where the body's immune system attacks the pituitary gland [56]. Determining the actual occurrence rate of hypophysitis following COVID-19 proves to be challenging. Given that a significant number of symptomatic COVID-19 patients undergo glucocorticoid treatment in the early stages of the disease, and in some cases, for extended durations, there exists the potential for a substantial underassessment of hypophysitis diagnoses. In the meta-analysis of Capatina et al., there are only some cases that were reported in the literature, with one case being that of Misgar et al., describing a case of infundibuloneuro hypophysitis, which presented without involvement of the anterior pituitary [4][54].

2.3. Syndrome of Inappropriate Antidiuretic Hormone Secretion and Arginine Vasopressin Deficiency

Initial observational studies indicated that around half of COVID-19 patients experienced hyponatremia [57]. However, a retrospective examination of an extensive global registry tracking hospitalized COVID-19 cases, known as the Health Outcome Predictive Evaluation for COVID-19, identified substantially lower frequencies: hyponatremia in 20.5% of cases, hypernatremia in 3.7%. Both conditions were found to be associated with increased mortality and incidences of sepsis [33].

The prevalent cause of hyponatremia, particularly in individuals with COVID-19 pneumonia, was reported to be SIADH. However, whether SIADH directly results from the viral infection remains unclear. It is noteworthy that in various cases, there were reports of newly developed AVP deficiency either during or, more commonly, shortly after COVID-19 infection. This observation raises the prospect of a potential causal association [33].

2.4. Central Diabetes Insipidus

Several pathophysiological mechanisms have been proposed to explain CDI secondary to COVID-19. Ong et al. verified the expression of ACE2 in the paraventricular nucleus, making it susceptible to SARS-CoV-2 [58]. Iadecola and colleagues noted the presence of ACE2 and transmembrane protease serine on median eminence capillaries [59]. In a review conducted by Haidar et al. on the involvement of SARS-CoV-2 in central nervous system tissue damage, postmortem examinations have identified the presence of the SARS-CoV-2 genome in the hypothalamus, along with observations of degenerated and edematous neurons [60].

There is a variation in the timeframe between the diagnosis of COVID-19 and the onset of CDI. Yavari A et al. documented a case where central DI manifested six weeks after the initial COVID-19 diagnosis [34].

Similarly, Misgar et al. presented a case in which central DI developed eight weeks after the onset of COVID-19 [54].

2.5. Hypothalamic Lesions

There are intricate anatomical and functional interconnection between the hypothalamus and the olfactory bulb. Consistent with prior findings, recent evidence has revealed magnetic resonance imaging (MRI) alterations in the olfactory cortex among COVID-19 patients, underscoring the participation of the olfactory system in viral neuroinvasion [61]. This observation was further elucidated through the utilization of three- and two-dimensional fluid-attenuated inversion recovery images, which delineated cortical hyperintensity in the right gyrus rectus and hyperintensity in the olfactory bulbs [61].

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