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Pituitary and SARS CoV-2: An unremitting conundrum

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There is increased interest related to the impact of coronavirus disease 19 (COVID-19) on the endocrine system and in particular on the pituitary gland. Over the course of the severe infection with acute respiratory syndrome coronavirus 2 (SARS-CoV-2), there are both acute and delayed effects on the pituitary, related to infection and/or treatment. Hypopituitarism, pituitary apoplexy and hypophysitis have been all reported, as well as arginine vasopressin deficiency (diabetes insipidus) and syndrome of inappropriate antidiuretic hormone secretion. Furthermore, patients with acromegaly, Cushing's disease and hypopituitarism are theoretically at increased risk of complications with COVID-19 and require close monitoring. Evidence regarding pituitary dysfunction in patients with COVID-19 continues to be gathered, as the breadth and depth of knowledge also continues to rapidly evolve. This review summarizes data analysis to date on the possible effects of COVID-19 and COVID-19 vaccination on patients with normal pituitary function and patients with known pituitary pathology. Though clinical systems were significantly affected, it seems there is no overall loss of biochemical control in patients with certain pituitary pathologies.

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Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), first identified in late 2019–early 2020, was identified as the cause of the unexpected worldwide spread of coronavirus disease-19 (COVID-19). The subsequent COVID-19 pandemic represented the most serious challenge faced by healthcare systems in modern history and the impact on the quality and continuum of medical care was significant, especially for patients with rare and chronic diseases, including pituitary pathology [1].

SARS-CoV-2 infects host cells by binding of the viral transmembrane spike-protein to the angiotensin-converting enzyme 2 (ACE2) receptor [2]. Angiotensin-converting enzyme 2 mRNA is widely expressed in a variety of tissues hence the infection has the ability to spread rapidly to target organs outside the respiratory system [3]. In particular, ACE2 is expressed in the hypothalamus and pituitary; furthermore, the hypothalamus is a region with particularly high expression of ACE2 [4]. Similarly, receptor expression and consecutive endocrine damage to the thyroid, gonads, and pancreatic islets [5] have been reported in association with COVID-19. In addition, the crucial immune-modulatory role of hormones and their interaction with the immune response contributes to a complex and continuously changing picture of endocrinopathies in the context of COVID-19.

COVID-19 infection as well as the vaccines designed to prevent COVID-19 have been associated with cases of hypothalamo-pituitary dysfunction such as pituitary apoplexy [6], electrolyte imbalances due to Antidiuretic hormone (ADH) related dysfunction [7,8] or hypophysitis [9]; a possible temporal association, but not causation cannot be excluded.

More importantly, patients with pituitary pathology have chronic diseases in need of complex treatments and monitoring. The pandemic disrupted routine patient care and novel solutions (such as telemedicine) emerged and were managed, in part, to cover gaps in optimal standard of care [10]. In addition, some patients with pituitary pathology present with complications and comorbidities that put them at higher risk of being infected or developing a more severe form of COVID-19 [8]. Here we review clinical concerns raised by COVID-19 as they relate to patients with known, or susceptible to, pituitary pathology.

Pathogenesis

Putative mechanisms implicated in pituitary disease in SARS-CoV-2 infection

As previously noted, ACE2 is expressed in both the hypothalamus and the pituitary gland [4]; possible targets for COVID-19 infection. The virus has been hypothesized to enter the brain either via the nasopharyngeal epithelium through the olfactory bulb or via the general circulation and passing through the blood-brain barrier (BBB) [11]. However, the anterior pituitary is located outside the BBB [12] and may be also directly affected by SARS-CoV-2 [13]. Relatively low expression of ACE2 in the pituitary compared to other organs [14] is over compensated by the increased binding affinity of SARS-CoV-2 compared to SARS-(10–20-fold higher) [2].

Theoretically, the impact of SARS-CoV-2 on the function of the hypothalamic-pituitary axis could occur either directly by viral invasion or indirectly by inflammation and the release of cytokines (Fig. 1) [15]. The mechanism is yet unclear and more importantly, there is no evidence to date of a direct mechanism. In a small autopsy series on COVID-19 fatal cases, a patient with multiple subacute pituitary infarcts had undetectable SARS-CoV-2 RNA as measured by quantitative reverse transcription-polymerase chain reaction (qRT-PCR) in pituitary tissue [16]. Lack of immunoreactivity for viral protein in pituitary cells (as measured by immunohistochemistry, which is less sensitive than RT-PCR) has been reported [17,18]. Histologically, no evidence of COVID-19-specific changes were found in the pituitary glands of 50 fatal cases of COVID-19 [18]. Mechanisms could possibly not involve direct viral infection and the potential role of systemic inflammation or cerebrovascular changes needs to be further explored. Nevertheless, numerous case reports taken together indicate COVID-19-induced damage to the hypothalamus and pituitary in different clinical scenarios. An autopsy study on 44 patients who died due to COVID-19 (11 cases in whom extensive sampling of the central nervous system was performed) revealed that SARS-CoV-2 is capable of infecting and replicating within the brain and furthermore, viral replication might persist for several months; of the investigated cases SARS-CoV-2 RNA and protein could

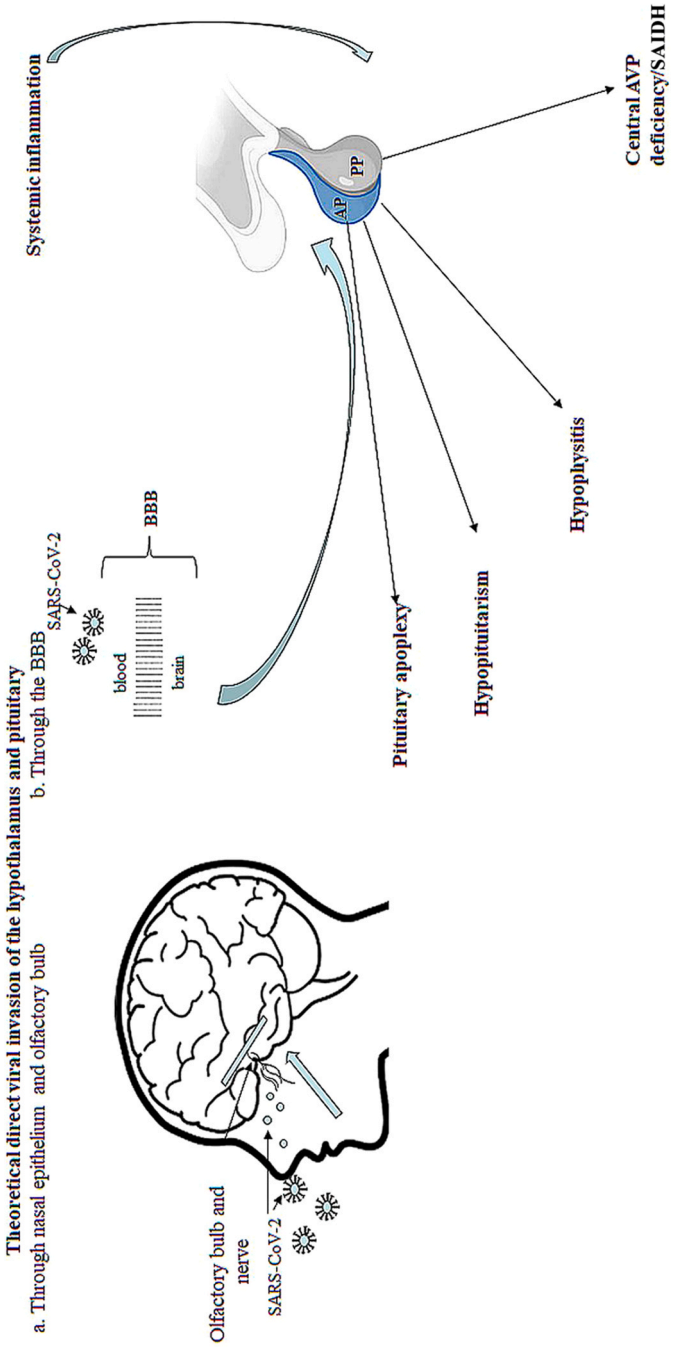

Fig. 1. Potential COVID-19-related dysfunctions of the anterior and posterior pituitary (putative mechanisms and consequences).

be detected in the hypothalamus in only one case [19]. To date there are no predictive markers that could differentiate those COVID-19 cases that are most likely to eventually involve either the hypothalamus or the pituitary.

Pituitary pathology in the context of COVID-19

Pituitary conditions occurring in the setting of COVID 19

Pituitary apoplexy

Numerous potential precipitating factors for pituitary apoplexy (PA) have been described [20], the potential causal link for most being related to coagulation or vascular abnormalities. Therefore, as SARS-CoV-2 infection has been associated with different degrees of coagulopathy [21], COVID-19 theoretically increases the risk of PA.

Indeed, several cases of PA, either during the evolution of COVID-19 or shortly afterwards have been reported [6, 22–26]. This includes a small (8 patient) case series from a single center [6]. In some of these patients, pituitary macro- or microadenoma had been diagnosed before the apoplectic event, while in others it was only discovered in the setting of PA [25,27,28]. A single case reported PA one month after the diagnosis of COVID-19 in the absence of a clearly identifiable pituitary lesion [22], however, causality cannot be, again, proven.

While a fatal outcome was reported in PA cases and very severe forms of COVID-19 [24], recovery was achieved in most patients, either after surgery [26,29] or conservative management [23,25]. One case of PA during late pregnancy was safely managed, conservatively, before elective induction of vaginal delivery and then transsphenoidal intervention [30].

Together these case reports or small series cannot be held up as definitive proof for a causal or coincidence relationship between COVID-19 and PA. However, increased awareness, is justified particularly in patients with known pituitary adenomas, with or without additional predisposing factors during SARS-CoV-2 infection.

Hyponatremia and hypernatremia—syndrome of inappropriate antidiuretic hormone secretion and arginine vasopressin deficiency

Hyponatremia was reported in 30–60% of SARS-CoV-1 infected patients [31] and was also expected to occur in SARS-CoV-2 infections. Early descriptive studies reported prevalence of hyponatremia of approximately 50% among COVID-19 patients [31,32]. A retrospective analysis of a large international registry of hospitalized COVID-19 patients, the Health Outcome Predictive Evaluation for COVID-19 (HOPE) study, revealed considerably smaller percentages; hyponatremia in 20.5%, hypernatremia in 3.7%, both being correlated with mortality and sepsis [33]. Indeed, hyponatremia is correlated with worse outcomes and increased mortality in numerous diseases [34] while its correction is associated with improved outcomes [35]. This also holds true for COVID-19; hyponatremia is associated with more severe disease [31], higher rates of hospitalization, intensive care unit (ICU) admission, use of mechanical ventilation, and death [36,37]. Hyponatremia has been suggested as an independent variable for COVID-19 progression to severe disease, and death [31]. As there is an inverse correlation between serum sodium and serum interleukin 6 (IL-6) levels (with IL-6 being an essential cytokine involved in the fatal outcomes of COVID-19 due to cytokine storm) [38], this is a putative pathogenic link. Also, IL-6 can induce vasopressin secretion [31] and correction of hyponatremia after treatment with IL-6 receptor antibody (tocilizumab) was reported [39].

Syndrome of inappropriate anti-diuretic hormone secretion (SIADH) was the most commonly reported mechanism underlying hyponatremia, especially in patients with COVID-19 pneumonia [40–42]. However, alternative explanations can be present in individual cases (e.g., adrenal insufficiency; AI), excessive diuretics used to treat pulmonary edema, gastrointestinal fluid losses, and kidney damage) [7,8,37]. A rare possible cause is excessive water intake, as a result of either dysgeusia or because patients consider water to be beneficial [43]. A recent systematic literature search confirmed SIADH to be the most common reason for hyponatremia followed by AI and hypovolemic hyponatremia due to gastrointestinal losses [37].

Table 1
Cases of onset arginine vasopressin deficiency in the context of COVID-19.

Age (years)	Male/ Female	Time from COVID-19 diagnosis	Serum sodium	MRI findings	outcome	Reference
68	Male	During acute infection	Hypernatremia	No abnormality	Death	[50]
60	Female	8 weeks	Hypernatremia	Pituitary stalk thickening	Good response to DDAVP	[45]
44	Female	12 days	Normal sodium Concomitant CAI	No abnormality	Good evolution in hospital, lost to follow-up	[46]
28	Male	1 month	Hypernatremia	No abnormality	Concomitant myocarditis Good response to DDAVP	[47]
54	Female	6 weeks	High normal sodium	No abnormality	Good response to DDAVP	[48]
17	Male	3 weeks	Hypernatremia	Disappearance of the normal posterior pituitary bright spot	Good response to DDAVP	[53]

*CAI = central adrenal insufficiency; DDAVP = desmopressin

Whether SIADH is a direct consequence of the viral infection itself is also not clear. Other causes may also contribute to SIADH pathogenesis (e.g., the use of antibiotics, positive pressure ventilation, and stress related to infection [44].

It should be noted that new-onset arginine vasopressin (AVP) deficiency was also reported during or (more frequently) shortly after COVID-19 infection in several cases (Table 1), raising the possibility of a causal relationship [45–50]. Possible putative mechanisms to explain AVP deficiency in this context are hypophysitis or immune-mediated, however, the number of cases reported so far are too few to allow for any sound conclusion. Epidemiological data shows that hypernatraemia is exceedingly rare in these patients outside of a hospital setting; in contrast, the rate of hypernatraemia during hospital admission is significant, particularly in patients with adipsic AVP deficiency [51].

Interestingly, of the cases with AVP deficiency presumably linked to COVID-19 reported so far, only two did not have hypernatremia (one with concomitant AI [46]) while all the others displayed significantly high serum sodium levels (Table 1). However, the most plausible reasons appear to be related not to the impairment of the thirst mechanism, but rather to increase in insensible water losses (caused by fever, hypoxia and sepsis). Extreme caution is needed in the management of these patients as under correction may lead to dehydration, severe hypernatremia and acute kidney failure while hypercorrection might lead to acute pulmonary edema [52].

Hypophysitis

In 2005 Leow et al. reported reversible post-infectious hypophysitis with transient hypocortisolism in 39% of patients who survived a previous (SARS) epidemic [54].

Delayed damage of pituitary function was reported in one case at 2 months after recovery from a confirmed COVID-19 infection with later full remission of both panhypopituitarism and suggestive imaging features of hypophysitis (complete recovery) [9]. Another case of an adolescent diagnosed with hypophysitis (suggestive clinical symptoms and imaging features but normal pituitary function; complete resolution with short-term glucocorticoid treatment) was reported 3 weeks after symptomatic COVID-19 [55]. Misgar et al. reported a case of AVP deficiency (infundibuloneuro hypophysitis), which presented without involvement of the anterior pituitary [45].

Cases are rare and the true prevalence of hypophysitis post COVID-19 is very difficult to establish. Since many symptomatic patients with COVID-19 receive glucocorticoids during initial disease management, sometimes for prolonged periods [56], this might lead to a considerable under evaluation of the diagnosis of hypophysitis.

Hypopituitarism

The most intriguing and somewhat contradictory reports about pituitary function in patients with COVID-19 concern the hypothalamic-pituitary-adrenal (HPA) axis. Initially, increased serum cortisol levels were reported in COVID-19 patients and as prognostic factors for acute mortality rates [57]. Afterwards, serum adrenocorticotropic hormone (ACTH) levels were also reported to be significantly increased in COVID-19 patients compared to normal controls but dramatically decreased in critical cases compared to non-critical patients [14]. A small (28 cases) prospective cohort study reported basal values compatible with mild central AI (no stimulation tests performed) in many patients, especially those with severe forms of infection [58].

A recent meta analysis of published data revealed significantly higher levels of cortisol in patients with severe COVID-19 in comparison with those with mild-to-moderate disease forms [59]. However, cortisol levels were substantially lower in fatal cases of COVID-19 compared to survivors [60]. The apparent contradiction in some of these results might be explained by the heterogeneity of patient samples as well as testing protocols used. Many additional uninvestigated cofactors can influence cortisol metabolism, binding globulin levels or both thus altering the serum cortisol level and misinforming about the adrenal reserve.

Central AI has also been reported during convalescence from mild COVID-19 (not having required any form of medical treatment) [61]. However, just as for hypophysitis, the reports concerning central AI (either during acute phase of COVID-19 or during/after remission) can be significantly biased by the wide use of systemic glucocorticoids in the treatment of cases with moderate or severe COVID-19 [62,63]. In one study up to 30% of patients recovering from COVID-19 received glucocorticoid treatment for at least

6 weeks [56]. Despite ongoing efforts, definitive conclusions regarding the optimal glucocorticoid regimen (drug, timing, dose and duration) are lacking and literature reports exhibit highly variable regimens [64]. Additionally, many interindividual differences also occur. Therefore, it is possible that at least some of the cases labeled as central hypocortisolism secondary to the viral infection are in fact physiologic central AI due to exogenous glucocorticoids administration. The situation is similar to that previously reported in SARS survivors; over one third had transient secondary AI (resolving within 1 year) due either to exogenous glucocorticoid use or direct viral damage [54]. Ritonavir (an antiviral sometimes used in the treatment regimen) markedly inhibits the metabolism of corticosteroids [65], therefore, theoretically there is an increased risk of HPA axis suppression, hence adrenal crisis, in cases of combined use, at the time of discontinuation.

Central AI developing in patients who have recovered from COVID-19 could theoretically be a direct consequence of the viral infection as well (by either direct/vascular damage, inflammation). Molecular similarity between SARS-CoV-2 proteins and human ACTH as well as high titers of anti-ACTH antibodies in patients with long COVID syndrome were also suggested as potential pathophysiological explanations [66].

Patients in whom the pathogenesis of central AI can be clearly separated from exogenous glucocorticoid use are rare. A patient who developed transient but prolonged (more than 1 year) growth hormone (GH) and ACTH deficiency during intensive care for COVID-19 was reported [67]. A case report of new-onset secondary AI one month after recovery from mild COVID-19 (necessitating no treatment) was also reported [68].

Other pituitary axes dysfunctions are also possible. Thyroid dysfunction during acute COVID-19 appears to be rare and mild [69,70]. Although data are scarce (including a rare case with central hypothyroidism) the dysfunction appears to be transient [69,70]. Long-term data are needed for clarification. The transient nature would also be suggested by extrapolating knowledge from the previous SARS pandemic; 4.9% of patients developed central hypothyroidism at 3–6 months post-SARS and the majority of patients were euthyroid by 9 months after infection [54].

Growth hormone deficiency (GHD) was also suggested, but rarely evaluated formally; patients with COVID lung involvement had significantly lower serum insulin-like growth factor 1 (IGF-1) and GH levels versus those without [71,72]. In one study, 3–7 months after the diagnosis of COVID-19 infection, peak cortisol responses to low-dose ACTH test were insufficient in 16.2% patients while 46.5% and 9.3% of patients had inadequate GH and cortisol responses to glucagon stimulation test, respectively [73]. The fact that the GH axis is also affected points more towards a late effect of the infection itself on the pituitary function than towards an effect of the medications received during the acute phase.

Central hypogonadism as a potential consequence of COVID-19 has not been consistently reported. One patient with secondary amenorrhea persisting 6 months after a SARS-CoV-2 infection had hypogonadotrophic hypogonadism, delayed pituitary response to thyrotropin-releasing hormone (TRH) and a gonadotropin increase to the gonadotropin-releasing hormone (GnRH) analog, suggesting a hypothalamic deficiency [74]. In this particular case, no psychological stress could be elicited to explain a functional hypothalamic amenorrhea, no organic cause was found either.

Subclinical central hypogonadism (decreased testosterone, luteinizing hormone; LH and prolactin) was also described in otherwise healthy males in the first months after recovery from COVID-19 with a tendency of testosterone to recover during 3 months of follow-up [72]. Fortunately, serum testosterone levels keep increasing for the first year after infection, but close to 30% of previous COVID-19 patients still have hypogonadal levels at 12 months [75]. The mechanism is yet unclear. In another relatively small study, male hypogonadism (especially secondary) was diagnosed in a significant majority of cases with moderate-to-severe disease during the acute phase of the infection [76].

Despite theoretical considerations about possible mechanisms and benefits of increased prolactin levels in COVID-19 [77] a recent systematic review of the literature found no clear data for a change in prolactin levels in COVID-19 patients [78]. However, there is a significant decrease in testosterone/LH, follicle stimulating hormone (FSH)/LH ratio, and sex hormone binding globulin (SHBG) levels and high levels of LH, and estradiol/testosterone ratio underlining that a complex mechanism is at work, not exclusively at the pituitary level [78].

Rapid-onset obesity, hypoventilation, hypothalamus dysfunction, and autonomic dysregulation syndrome

Rapid-onset obesity, hypoventilation, hypothalamus dysfunction, and autonomic dysregulation (ROHHAD) syndrome is a disease of unknown etiology, course and prognosis. The first viral-associated case was reported, recently, a 4-year-old female who developed a ROHHAD syndrome-like condition several months after a COVID-19 infection, suggesting hypothalamic damage [79].

COVID-19 in patients with pituitary disorders

During the initial waves of pandemic and strict lockdowns in many parts of the world there was a considerable reduction of on-site medical evaluations partly compensated by distance evaluation (by phone, email, and video/telemedicine consults). However, it seems there was no significant decrease in the percentage of controlled patients with certain pituitary pathologies [80]. Nevertheless, strict public health measures imposed by the pandemic increased general stress levels and had a particularly negative impact on patients with chronic diseases [81].

Acromegaly

In the first months of the pandemic the main difficulties in the complex medical care of patients with acromegaly were related to postponing elective surgery, delays in the assessment of treatment efficacy or complications and reduced availability of certain drugs, especially nurse administered injections [8]. However, the pandemic and its consequent limitations did not seem to have affected outpatient access and achievement of good disease control in a sample of 41 acromegalic patients with (signs/symptoms [S], associated comorbidities [A], growth hormone levels [G], insulin-like growth factor 1 levels [I], tumor features [T]), Acromegaly Quality of Life Questionnaire (AcroQoL), and ACROmegaly Disease Activity Tool (ACRODAT) results comparable between 2018 and 2020–2021 assessments [82].

A different perspective was offered by the results of another study; only 21.4% of 84 participating endocrinologists reported no negative impact of the pandemic on diagnostic practice, and only 19.1% reported no negative effect on patient follow-up. More than half reported that remote evaluation actually improved their communication with their patients and 69% intended to continue to use these methods in the future [83]. Similarly, unexpected positive feedback for the new healthcare distance methods for acromegaly patients were also reported in Brazil [84] and presumably this might be the case for patients with other types of pituitary adenomas. Oral medications have also been increasingly used where available [85] in patients who had difficulties traveling to clinic or reduced clinics 'availability.

When exposed to COVID-19, patients with acromegaly (especially those with biochemically uncontrolled disease) may represent a particularly at-risk subgroup due to possible complications and comorbidities: upper airway obstruction, kyphoscoliosis, arterial hypertension and various other cardiovascular complications (up to heart failure), and diabetes mellitus [86].

Possible drug interactions should also be considered, e.g. pasireotide in association with some drugs (hydroxychloroquine, azithromycin) initially used for COVID could induce QT prolongation and increase even more the risk of arrhythmias [8]. Also, pasireotide in combination with high-dose systemic glucocorticoids might significantly increase glycemic levels.

Patients with radiological thoracic vertebral fractures and COVID-19 had worse outcomes when hospitalized for pneumonia [87] thus potentially predicting cardiorespiratory risk. As patients with acromegaly have higher prevalence of vertebral fractures [88], close monitoring for cardiac and respiratory complications is warranted.

Cushing's disease

Hypercortisolism in the presence of COVID-19 raises even more concerns. Although current knowledge about the risk of SARS-CoV-2 infection or severe disease progression in patients with endogenous hypercortisolism is scarce, any viral infection is likely to be more severe and prolonged in a patient with hypercortisolism as a result of decreased anti-infectious defense mechanisms [89].

Also, various possible complications of Cushing' syndrome-hypertension, increased cardiovascular risk profile and diabetes mellitus are recognized as risk factors for negative prognosis of COVID-19 [90].

Hypercoagulability and increased risk of thromboembolic complications, well-known in Cushing's syndrome [91], add to the highly increased risk of severe complications in case of SARS-CoV-2 infection.

Indeed, in a small study performed in Lombardy in the first year of the pandemic, SARS-CoV-2 infection affected 3.2% of patients with CD (small cohort, no statistical analysis possible) compared to none in the control group (pituitary incidentalomas) and only 0.6% of the general population; additionally, patients with CD appeared to develop more severe forms of infection [92].

Single case reports or small case series also seem to suggest that patients with severe florid hypercortisolism may develop severe, even lethal forms of infection while biochemically controlled patients may even experience asymptomatic COVID-19 [93]. Available data seem to indicate that uncontrolled hypercortisolism, as expected, is worse in the setting of COVID-19. Whether the intense medical treatment aimed at controlling hypercortisolism during COVID-19 is likely to improve the prognosis of the infection is also not known and sometimes treatment for CD is temporarily stopped when COVID-19 ensues [94].

Previously well-controlled patients with CD might also develop signs of AI during COVID-19 requiring withdrawal or dose reduction of the medical treatments for hypercortisolism and intravenous replacement with hydrocortisone [95]. The possibility of developing AI should be monitored by surrogate parameters (e.g., blood pressure, heart rate, serum electrolytes, and glucose levels) if serial cortisol measurements are not feasible. The block and replace scheme could diminish the risk of iatrogenic AI and decrease the need for frequent monitoring [85,96]; though suggested by guidelines [97], prospective studies in patients with active CS developing COVID-19 are currently lacking. Nonetheless, biochemical control of hypercortisolism by 'block and replace' regime allowed complete recovery from infection in some cases [98,99]. Intravenous immunoglobulins plus adequate treatment of each comorbidity was also successful in one patient [100].

Various drug interactions should be considered between drugs used to treat hypercortisolism and COVID-19. Possible interactions are mainly related to hypoglycemia, hypokalemia and QT interval prolongation. Therefore, caution should be used when administering hydroxychloroquine, ritonavir or azithromycin and patients should be adequately monitored during treatment. Using systemic glucocorticoids as a treatment for COVID-19 in patients treated with glucocorticoid receptor antagonists (mifepristone) is likely to be less effective [101]. Medications with a stimulating effect on cytochrome P450s (e.g., tocilizumab) [102] will increase the clearance of numerous drugs, including ketoconazole, levoketoconazole and mifepristone, making dose adjustments necessary.

Remdesivir is metabolized by both cytochrome P450 (CYP) and non-CYP enzymes [103] such that drugs that induce cytochrome P450 (e.g., mitotane) might have clinical consequences related to the decreased efficacy of remdesivir. Given the high risk of thrombotic events due to the disease itself, and the procoagulant effects of COVID-19, antithrombotic prophylaxis should be introduced early in the course of the disease. Other important issues to be considered are; optimal control of diabetes mellitus (insulin therapy in uncontrolled patients, avoid metformin in severely ill patients in order to prevent lactic acidosis), need for urgent rehabilitation, risk of severe psychiatric complications, and/or debilitating persistent physical complaints. All should be adequately managed and multidisciplinary management is essential for optimal care of patients both in the acute and post-acute COVID-19 phase [104].

Hypopituitarism and adrenal insufficiency

Patients with known hypopituitarism and, in particular, those with AI have increased mortality compared to the general population and one of the leading causes of death are infections [105]. However, optimal education of the patients and increased medical staff awareness regarding the possibility of adrenal crisis during an infection can dramatically decrease the risk. Indeed, in a retrospective study based on telephonic medical interviews, AI patients adequately treated, monitored and educated reported the same prevalence of COVID-19-suggestive symptoms and disease severity as controls. They did not report adrenal crisis or need for hospitalization [106]. However, in this study the majority of cases had no laboratory confirmation of the infection.

In a similar study performed in the United Kingdom in 2020, 159 hypopituitary patients taking glucocorticoid replacement (97% fully aware of sick-day rules, over 70% having an emergency intramuscular kit) almost 19% reported symptoms compatible with COVID-19 infection. However, only 2/7 tested patients received a confirmatory positive test result. Nevertheless, no mortality or severe cases were reported [107]. Such patients could probably manage without titrating the usual replacement dose if asymptomatic during COVID-19 [108,109].

However, with the increased availability of testing and treatment protocols during the pandemic, more rigorous studies illustrate a different picture. The relative risk for confirmed SARS-CoV-2 infection and hospitalization among patients with AI was 3-fold and 23.8-fold higher, respectively, versus the general population [110]. Older age, known pulmonary disease and higher replacement doses of glucocorticoids were associated with higher risk [110].

This last observation certainly requires further investigation. It is well-known that currently used glucocorticoid replacement regimens are frequently not physiological, not always reliably monitored with adequate markers, and many times overdosed [111]. Therefore, there is a consequent increased risk for metabolic and cardiovascular disorders recognized as risk factors for poor outcomes and death in COVID-19 [112]. This underlines the need for these patients to remain in close contact with their medical provider under all circumstances in order to prevent both underdosage and voluntary overdosage out of fear. In one study half of the AI patients included were hyperconscious of the potential risk of COVID-19 infection and this was significantly associated with increased glucocorticoids dose [113]. The risk is probably lower in cases of central AI, generally milder than primary AI, 10–20 mg daily of hydrocortisone in divided doses is usually sufficient [114], while in patients with primary AI acute adrenal crises have been more consistently described [115,116].

In a brief report of three cases with hypopituitarism admitted for treatment of mild to moderate COVID-19 the evolution was unremarkable and patients were discharged after a few days [117].

The European guideline for the management of AI in the context of COVID-19 pandemic recommends sick-day rules consisting of 4 oral daily doses of hydrocortisone in the presence of "signs and symptoms suggestive of COVID-19" with immediate parenteral self-injection and emergency transfer to hospital in case of clinical deterioration [114].

Arginine vasopressin deficiency and anti-diuretic hormone secretion

In patients with AVP deficiency with intact thirst mechanism and mild COVID-19 symptoms, oral rather than nasal desmopressin (1-desamino-8-D-arginine vasopressin; DDAVP) is preferred, as it is better absorbed in the context of inflamed respiratory airways. In severe COVID-19 cases parenteral desmopressin should be offered. If fever, tachypnea or perspiration are severe and insensible water losses are likely to be significantly increased; intravenous hydration should be recommended if cognition is impaired preventing adequate hydration [52]. These patients, as well as those who need diuretics (to prevent pulmonary edema), or those who do not receive desmopressin as needed are at risk of dehydration and hypernatremia.

They should be managed in close collaboration by an ICU team and endocrinologist and in addition to standard care, pateints should also receive low-molecular-weight heparin during episodes of hypernatremia [52]. If increasing the dose of desmopressin is not effective in correcting hypernatremia, adding furosemide has proven helpful by promoting natriuresis [118].

Management of patients with SIADH who become infected with SARS-CoV-2 can also be challenging; SIADH most frequently develops in the days following discharge from neurosurgical interventions – patients should be advised to limit their fluid intake strictly to thirst, and to report any unusual symptoms or unexplainable weight gain to their primary care physician. The diagnosis and management of SIADH should be made according to current guidelines [119]. Correction of hyponatremia should be undertaken with extreme caution in patients with COVID − 19, especially those with severe hyponatremia, as bolus hypertonic saline might induce pulmonary edema, thus low dose hypertonic saline infusion is considered safer [52].

Pituitary surgery and COVID-19

Consequences of the COVID-19 pandemic for pituitary patients were related to limited access to surgery, the fear that transsphenoidal surgery might be a high-risk procedure in terms of infection (for both patients and medical staff), inaccessibility of health care providers during lockdowns, and community quarantines. This led to disruptions in the continuity of care, testing and monitoring. Therefore, at the onset of the pandemic, general recommendations were released to postpone elective surgical procedures [85] and sometimes surgery was canceled altogether. Thereafter, the Pituitary Society

suggested to prioritize emergent and urgent pituitary procedures, only postponing clearly elective surgeries [10].

Testing for SARS-CoV-2 infection before surgery [120] was widely used to minimize infection risk. Usually patients with proven COVID-19 were denied surgery but successful emergent surgery in patients with COVID-19 started to be increasingly reported [26,29,98]. In all cases, including proven negative COVID-19 patients, and full personal protection equipment (PPE) for surgeons was widely used. A web-based survey of surgeons worldwide proved that standard PPE was used all over the world (with extra precautions in some areas), preoperative screening by reverse transcriptase-polymerase chain reaction (RT-PCR) in all symptomatic cases (and even in asymptomatic cases in certain centers), and use of airborne PPE were inversely associated with COVID-19 transmission during surgery [121]. With adequate presurgical testing and the use of standardized protocols regarding personal protection, pituitary surgery proved safe for patients with negative preoperative COVID-screening [122]. Machine learning could further predict mortality in patients with COVID-19 in the perioperative period undergoing surgery, but also estimate [123] needs for acute pituitary surgeries, and impact of different system stressors [124], including COVID-19.

COVID-19 vaccination and pituitary diseases

Not only SARS-CoV-2 itself but also specific vaccines against it could also potentially induce acute cytokine release [125] thus causing endocrine dysfunction [126]. Rare and isolated case reports raised the possibility of SIADH [127,128] or central AVP deficiency after vaccination. In case AVP deficiency developed one week after BNT162b2mRNA COVID-19 vaccine (BioNTech/Pfizer) administration, with infundibulo-neurohypophysitis on magnetic resonance imaging (MRI) [129].

Hypophysitis has also been described not only after COVID-19 [55,130] but also after vaccination [131,132]. Isolated ACTH deficiency with MRI suggestive of pituitary atrophy instead of hypophysitis has also been described one day after the second mRNA vaccination against COVID-19 [133].

Pituitary apoplexy has also been reported after vaccination [134,135]. However, the causal link between COVID-19 vaccination and the above-mentioned types of pituitary dysfunction cannot be conclusively established based on these rare case reports.

Vaccine efficacy can be deminished in patients under various immunosuppressive and in particular glucocorticoid therapies [136]; however, no such data are available for patients under glucocorticoid replacement. In a survey of Pituitary Society members, most clinicians declared they maintain the current glucocorticoid replacement dose around the time of vaccine administration and only increase in cases of fever (and less than half in case of arthralgias and myalgias) [137]. A more recent prospective study proved that increasing glucocorticoid replacement dose around vaccine administration is not routinely needed [138]. However, a 2–3fold increase in the usual dose is recommended if the patient is experiencing any symptoms after COVID-19 vaccination as acute AI can occasionally occur [139].

A telephone survey about COVID-19 peri-vaccination glucocorticoid coverage patients with AI revealed that 8.3% and 27.5% of patients reported symptoms after the first and second vaccine injection, respectively, and therefore felt the need to escalate the replacement dose. No adrenal crisis occurred regardless of dose titration [140].

In a prospective study doubling the oral glucocorticoid dose was needed in up to 8% of patients, especially after the second vaccine dose, but no parenteral administration was required [138]. Similar recommendations are made by others to prevent adrenal crisis based on single cases [139].

Long COVID and the pituitary gland

Approximately 10% of patients recovering from COVID-19 may experience persistent, sometimes debilitating clinical manifestations. These include neuropsychiatric manifestations such as depression, anxiety, loss of memory, sleep and concentration problems, anosmia, ageusia, and respiratory, such dyspnea, chest pain, persistent cough, and muscle and joint pain, or general (fatigue) symptoms [141]. Similarly, a heterogeneous constellation of symptoms can persist after many other viral illnesses. In the case of COVID-19 this highly non-specific syndrome with unknown pathogenesis has been named long COVID syndrome.

Hormonal changes are thought to be at least partly linked to the development of the persistent symptoms of long COVID [142], with particular attention to the putative connection between HPA axis disorder and post COVID morbidity. It has been suggested that the inability of the HPA axis to recover after the acute illness may represent the pathogenetic basis of long COVID syndrome [143]. It was also hypothesized that HPA axis dysfunction might be the consequence of a neuroinflammatory process [144].

The HPA axis is vulnerable to hypoxia, hypercoagulability, endothelial dysfunction, and autoimmune changes induced by COVID-19 infection. However, as mentioned before, investigating function during or after COVID-19 is highly biased by the disease itself as well as by the treatments received (mainly high-dose systemic glucocorticoids).

Long COVID syndrome shares many clinical characteristics with AI (for example fatigue, myalgia, and depression) and clinicians should pay close attention to distinguish between the two. In one study, in patients investigated at least 3 months after COVID-19 illness had normal adrenal and thyroid function (although almost two-thirds complained of persistent fatigue) [145].

However, AI should be timely diagnosed and treated. Simple biochemical investigation including serum electrolytes, total blood count, glucose, cortisol, and plasma ACTH could aid in diagnosis. It should be noted that the short Cortrosyn (Synachten) test (most commonly used) cannot reliably exclude mild, especially recent forms of central AI. Other useful adjunctive measures could include using the lowest effective dose of glucocorticoids for the shortest interval during acute infection, clinical monitoring for AI after discontinuation, optimal rehabilitation measures, and early assessment for possible infections. Use of routine replacement hydrocortisone is definitely not recommended. This has proven partially useful in occasional case reports with suspicion for AI, e.g., one case of long COVID reported low free cortisol levels and some degree of clinical improvement with hydrocortisone replacement [146].

Conclusions

The COVID-19 pandemic has disrupted every aspect of general life and medical practice, and has undoubtedly represented an unprecedented challenge for doctors, patients, and health authorities. This review underlines evidence for specific involvement of the pituitary gland in the complex endocrine phenotype of COVID-19 in both acute and delayed circumstances. Moreover, details of risk factors for severe forms of COVID-19, as they pertain to the particulars of care for patients with pituitary diseases, (some of whom are prone to numerous comorbidities and complications), are highlighted. A stringent call to collect all available data on pituitary involvement in the setting of the continuing SARS-CoV-2 pandemic is warranted. This will help drive evidence-based recommendations for patient management and the development of tools best suited for the needs of pituitary patients in the face of ever changing and challenging conditions.

Practice points

- Pituitary dysfunction, hypopituitarism, hypophysitis and pituitary apoplexy can rarely develop during or shortly after SARS-CoV-2 infection.
- Patients with acromegaly and Cushing's disease are at increased risk of complications in cases of SARS-CoV-2 infection and require close monitoring and attention to possible drug interactions.
- If a SARS-CoV-2 infection develops, patients with hypopituitarism should maintain close contact with their medical provider and strictly follow sick-day rules to minimize COVID-19 associated risks.
- Severe COVID-19 patients with AVP deficiency or SIADH should be managed in collaboration with an intensive care unit team and endocrinologist.

Research agenda

- Clarifying the mechanisms of viral infection and persistence of viral replication within the pituitary will shed light on SARS-CoV-2 involvement of hypothalamus and/or pituitary.
- Prolonged follow-up of severe and less severe COVID-19 survivors will help clarify the mechanisms behind viral damage persistence and differentiate it from the effect of the medications received during the acute phase.
- International registries of significant cases of pituitary abnormalities linked to COVID-19 could be beneficial.

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