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Review Article

The Pituitary Gland in the COVID-19 Pandemic: A Narrative Review of the Literature

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Abstract

The COVID-19 pandemic has had implications in the central nervous system. COVID-19 infection is characterized by coagulation activation and endothelial dysfunction, causing the endocrine system's ischemic and hemorrhagic vascular syndromes. We aimed to provide an overview of the global literature on the impact of COVID-19 on pituitary function and structure. A narrative, nonsystematic review of the literature retrieved from a significant medical online database (PubMed) between February 1, 2020 and June 30, 2021. The relevant literature was narrated in a concise thematic account. Most specific recommendations for managing endocrine disorders during COVID-19 rely on the same principles of epidemiological safety measures, delaying nonemergency admissions and transforming the routine follow-up to telemedicine clinics. Ongoing medications should be continued. Special attention is required to both primary and secondary adrenal disorders. Corticosteroids are a mainstay of treatment in COVID-19 infection. Therefore, it is essential to consider all aspects of high doses, including adverse metabolic reactions, especially in people with diabetes and prediabetes. Surgery is postponed for nonemergency situations, restricting most planned surgeries, and if required in an emergency, plans should include an additional risk. Sick-day rules should be adhered to strictly. Regular contact with endocrinology teams can be maintained through teleconsultations and virtual clinics. In conclusion, special attention is needed to the interaction between COVID-19 infection and pituitary conditions in a bidirectional manner. The direct impact of COVID-19 on pituitary structure and function is possible and should be recognized timely and treated effectively. Furthermore, appropriate organizational adjustments are needed to maintain a coordinated response within the conventional multidisciplinary management to optimize the care of patients with pituitary conditions among the ongoing COVID-19 pandemic.

Keywords: Acromegaly, COVID-19, Cushing, hypophysititis, hypopituitarism, pituitary apoplexy, pituitary surgery, pituitary tumors, pituitary

Introduction

COVID-19 is a novel coronavirus responsible for a pandemic that emerged in December 2019. Heterogeneous clinical forms are described from asymptomatic to severe hypoxaemic acute respiratory syndrome with multisystem organ failure.[1] COVID-19 infection has tremendously impacted social living and clinical practice, education, and research.[2,3] Almost all organs and systems suffer from COVID19 infection. Endocrine conditions are not an exception, and some endocrine organs are at risk of a direct or indirect damage by COVID-19.[4] Endocrine treatment modifications due to COVID-19 infection are required proactively to avoid decompensation and eventual hospital admission. This case was most evident in diabetes and adrenal insufficiency, in which rapid increase of "replacement" therapy is warranted by adopting the appropriate sick day's rules and easy contact with the health care provider through different telematic modalities.[5]

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Pituitary disorders, albeit not common, have special significance due to their peculiar management requirements under the care of multidisciplinary teams with critical volume to maintain adequate expertise. The care typically involves a multidisciplinary team working in concert to deliver timely, often complex, disease investigation and management, including pituitary surgery.[6-10] COVID-19 has brought about major disruption to the services, limiting access to care and testing, and dramatically reducing the ability to undertake transsphenoidal surgery safely. Therefore, we have reviewed the global literature on the pituitary and COVID-19 to provide a concise thematic account of the subject.

Materials and Methods

This is a narrative, nonsystematic review of the literature retrieved from a major online bibliographic database on June 30, 2021. The PubMed database was searched using a simple search term of (Pituitary and COVID-19) to identify the relevant publications. One hundred twenty-six records were identified, and retrieved articles were examined to confirm their relevance. Selected articles were reviewed and narrated thematically.

We aimed to provide a reasonably concise but adequately representative narration of the global literature on the impact of COVID-19 on the pituitary gland in healthy individuals and on the course and management of preexisting disorders of pituitary structure and function. One author drafted an initial manuscript, and all other authors reviewed and further developed it for intellectual content using a single version loaded online using Google Docs. No statistical analysis was conducted on the data included in the original articles, and detailed numerical presentations were avoided. All types of original articles were included. The final product was refined through several multilateral rounds of discussion. It was not intended to review conditions of the pituitary gland in detail, and older literature was only cited minimally to make some of the arguments.

Results

The themes that evolved from the review of the literature are listed in Table 1. To put these in a clinical context, we discuss them under the following headings: (a) Endocrine involvement in COVID19, (b) Impact of COVID-19 on preexisting pituitary conditions (masses and tumors, Cushing's disease, acromegaly, prolactinomas, and hypopituitarism. (c) Pituitary manifestation of COVID-19 (hypophysitis, pituitary apoplexy (PA), posterior pituitary dysfunction. (d) Practical management of pituitary disease during COVID 19 and (e) impact on pituitary surgery. We will also underscore literature on professional concerns and patient perspectives.

Table 1: The themes emerged from the review of the literature on the pituitary gland in COVID-19 pandemic

Management of specific pituitary conditions during COVID-19 pandemic
Impact of COVID-19 on pituitary function and structure
Pituitary tumors and pituitary surgery
Pituitary apoplexy
Organization of care for pituitary patients
Management of hypopituitarism in COVID-19 infected patients
Monitoring and telemedicine

COVID-19: Coronavirus disease 2019

Endocrine involvement in COVID-19

The interplay between COVID-19 and the endocrine system occurs at multiple levels. The widespread presence of angiotensin-converting enzyme-2 (ACE-2) receptors on various tissues, including different endocrine organs, suggests scope for direct viral infection. The ACE-2 receptors act as the entry gate of the virus to the host cells allowing direct virus damage to these cells. The interactions via the activation of inflammatory mediators and indirect immune-mediated damage are also postulated.[11,12] ACE-2 receptors are expressed in various endocrine glands, including testis, pancreas, thyroid, adrenal, and pituitary glands. Clinical and biochemical manifestations have been recorded in COVID-19 patients, resulting in endocrine dysfunctions, similar to what was observed during the SARS outbreak in 2003. The evidence so far suggests that COVID-19 can lead to functional hypopituitarism by direct and indirect effects on the hypothalamic-pituitary axis resulting in an inappropriate adrenal response during stress. Immune-mediated damage to thyroid glands resulting in subacute thyroiditis has been reported. COVID-19 has been reported to precipitate hyperglycemia in patients with diabetes and uncover insulin resistance in those previously undiagnosed. COVID-19 could trigger Type 1 diabetes with ketosis. The exact mechanism is not well known. However, direct virus-induced and immune-mediated beta-cell damage have been demonstrated. The presence of COVID-19 in semen has unclear clinical significance at present.

Impact of COVID-19 on pituitary disorders

A summary of the impact of COVID-19 on preexisting pituitary conditions and its management implications is presented in Table 2 and is discussed below.

Cushing's disease

Cushing syndrome is a rare condition with an estimated prevalence of around 40 cases per million.[15] Approximately 80% of cases are caused by adrenocorticotropic hormone (ACTH) overproduction, secondary to a pituitary adenoma (Cushing's disease) or ectopic ACTH syndrome, and the remaining 20% of cases are caused by cortisol excess due to adrenal tumor or hyperplasia.[15] Cushing's disease leads to increased cardiovascular, respiratory, metabolic, and infectious risks when the patients fail to achieve biochemical control. In addition to the risk mentioned above, an increase in venous thromboembolism has also been reported in COVID-19 patients with Cushing's disease, particularly in surgical procedures, immobilization, and severe infections.[16] As a result of these risk factors, patients with Cushing's disease could have been prone to severe COVID-19 infection.[17]

Table 2: Summary of the impact of COVID-19 on preexisting pituitary conditions and its management implications

Condition	Impact of COVID-19	Management implications	References
Cushing's disease	Uncontrolled CD are at higher risk of infection due to immune suppression with increased mortality	Strict surveillance and early intervention in suspected COVID-19 severe hypercortisolism	[13]
	Pasireotide use in patients on hydroxychloroquine plus azithromycin may prolong QTc	Pasireotide should be used with caution	
	Increased VTE risk, especially with surgery, immobilization, severe infections, and CVEs		
Acromegaly	Inadequately controlled acromegaly negatively impacts the quality of life and survival due to its systemic comorbidities	Adopt new approaches such as remote communication with patients and use of orally administered octreotide to simplify management during the pandemic	[13]
	Pasireotide use [see above]	It should be used with caution	
Prolactinomas	Increased risk of impulse control disorders and worsening depression	Obtain psychiatric history and drug usage before starting treatment. Begin DAs in small doses and adopt dose titration regimens with close monitoring of blood pressure	[6]
	Increased hypotension risk with DAs use		
Hypopituitarism	Patients with adrenal insufficiency are at risk of adrenal crisis	Supplement HC therapy once a COVID-19 is confirmed and refer to the "sick day rule"	[14]
	Patients with CDI may develop dilutional hyponatremia due to chronic desmopressin intake	Check electrolytes and do teleconsultations regularly	
	Hypernatremia in COVID-19 may be due to excessive insensible water loss due to fever, high respiration rate, diuretics, and inadequate fluid replacement	Monitor urinary osmolarity and volume, plasma osmolarity, and Na regularly until plasma Na returns to safe levels. Avoid nasal desmopressin	

DA's: Dopamine agonists, CD: Cushing's disease, VTE: Venous thromboembolism, CVEs: Cardiovascular events, CDI: Cranial diabetes insipidus, HC: Hydrocortisone, HPT: Hypothalamic-pituitary-testicular, COVID-19: Coronavirus disease 2019

Data from a large Italian series of 61 patients with Cushing disease, included 15 cases of active hypercortisolism, 28 patients in remission with hypoadrenalism, and 18 eucortisolemic subjects, showed 3.2% of them had positive COVID-19 as compared to 0.6% of the general population.[18] Severe clinical presentation was observed primarily in active Cushing disease subjects, indicating that chronic hypercortisolism may be associated with more severe COVID-19 infection and that active Cushing's disease patients should be considered a high-risk population for COVID-19 infection.[18] In another clinical case series of 22 patients with active Cushing syndrome, in which three cases were affected by COVID-19, the clinical course of COVID-19 was dependent on the severity of endogenous hypercortisolism.[19] Furthermore, a young female with Cushing's disease who developed COVID-19 pneumonia was treated with a "block-and-replace" regimen using a combination of steroidogenesis (metyrapone and trilostane) and hydrocortisone, in addition to other treatments that included antiviral therapy. She achieved clinical and biochemical improvement and underwent curative surgery 1 month later (after testing negative for COVID-19).[20] To reduce the risk of COVID-19 infection, diagnostic pathways may need to diverge from their usual recommendations.

When comprehensive differential diagnostic testing and/or surgery is not possible, medical treatment should be started instead, and transsphenoidal pituitary surgery should be postponed achieving better biochemical control of hypercortisolism in these immunosuppressed patients.[21] The medical therapy with block and replace scheme in order has been suggested to avoid the risk of iatrogenic adrenal insufficiency.[13] It is thought that mild hypercortisolemia in the context of COVID-19 for a short time is preferable over adrenal insufficiency.[13] Finally, numerous possible interactions should be considered between Cushing syndrome medications and pharmacological treatment of COVID-19 with the possibility for QT prolongation, hypo- and hyperkalemia, liver toxicity.[22,23]

Acromegaly

Acromegaly is a rare condition characterized by increased growth hormone secretion and consequently, insulin-like growth factor 1 (IGF-1) generally caused by a pituitary adenoma. Current treatment for acromegaly includes neurosurgery, medical therapy, and radiotherapy either as single or combined multimodal therapeutic strategies.[23,24] Treatment aims to achieve biochemical control, reduce tumor mass, normalize mortality, and restore average life expectancy.[24] Therefore, poor disease control negatively impacts the quality of life (QOL) and survival due to its many systemic comorbidities.[25] The management guideline for patients with acromegaly during the COVID-19 pandemic is lacking. The international online survey on the effects of COVID-19 in acromegaly was conducted to clarify the effect of the pandemic on acromegaly care.[26] Most of the respondents reported significant surgical intervention delays with limited presurgery testing access.[26] Other challenges reported in this survey were difficulty in monitoring and hospital visits for octreotide injection.[26] In light of this, the survey suggested that endocrinologists adopt new approaches caring for patients with acromegaly during COVID-19, such as remote communication with patients principally via phone to avoid hospital visits and improve patient care.

Furthermore, orally administered octreotide simplified the management of acromegaly during the pandemic.[13]

Acromegaly-associated comorbidities may negatively affect the course and management of COVID-19 and therefore, must be optimally controlled to avoid increased predisposition to viral infection and complications.[27] If mass effects are not present, somatostatin analogs injections are a good choice, as they may safely defer neurosurgery and radiotherapy. Clinical and biochemical reevaluation should be postponed within 6 months if possible, according to optic pathway status.[28] Finally, due to the higher risk of arrhythmias in patients with acromegaly and an increase of QTc interval, pasireotide should be used with caution in patients treated with hydroxychloroquine and azithromycin, since these treatments could potentially induce QTc prolongation.[23,29]

Gatto *et al*.[30] reported their experience in the management of acromegaly in a large referral center in Italy during a COVID-19 pandemic. They showed a 33% reduction of on-site clinic visits of their patients in 2020 but a compensatory rise in teleconsultation compared with 2019. Interestingly, disease control (based on IGF-1 level) was achieved in about three-quarters of the patients and was not significantly different between 2019 and 2020.[30]

Prolactinoma

Prolactinomas are the most common hormone-secreting tumors of the pituitary.[31] Normalization of prolactin levels and reduction of a tumor mass can be achieved in most patients using dopamine agonists (DAs).[31] Given their association with minimal morbidity and reasonable response to DAs, these drugs currently represent the cornerstone of treatment for prolactinomas. Patients with prolactinoma and with established medical treatment might develop depression as one of the adverse effects of DAs.[32] During the pandemic, mental health issues become more prevalent. Hence, it is crucial to obtain a complete psychiatric history and any concurrent drugs intake before starting DAs.[6]

In addition, COVID-19 patients' blood pressure control may get disrupted. Therefore, considerable caution should be exercised to avoid severe hypotension with the use of DAs. Restricted accessibility to medical appointments and blood testing during the pandemic may hamper the management of these patients, particularly those with larger tumors who might need surgery for drug resistance or intolerance. In a group of patients for whom medical therapy is not possible and surveillance is not acceptable, the risks and benefits of surgical intervention will need to be carefully assessed.[6]

Hypopituitarism

Patients with preexisting hypopituitarism on conventional replacement therapy may be at risk of poor outcomes. Patients should be educated to carefully manage and adjust hormonal replacement therapy, especially in adrenal insufficiency[6] In addition, patients with adrenal insufficiency are at risk of overtreatment as an adverse effect of glucocorticoid (GC) replacement therapy with consequent increased risk for hyperglycemia, hypertension, and obesity, all of which are currently recognized risk factors for poor outcomes and death due to COVID-19.[4] Importantly, to prevent adrenal crisis, patients with central adrenal insufficiency and symptoms suggestive for COVID-19 infection require appropriate steroid coverage (e.g., HC 20 mg, every 6 h).[14] During hospitalization, when clinical deterioration develops, HC should be started intravenously and maintained up to 200 mg/day, continuously or intermittently (e.g., 50 mg every 6 h).[14]

Carosi *et al*.[33] evaluated the prevalence of COVID-19 symptoms and outcomes in a large group of patients with adrenal insufficiency (primary and secondary) and another control group using a phone survey in a large center in Italy. One-fifth of patients with adrenal insufficiency had symptoms highly suggestive of COVID-19, which was not different from the control group. None of those patients needed hospital admission or developed adrenal crisis suggesting that patients with adrenal insufficiency might not be at increased risk of contracting COVID-19 or developing poor outcomes from it. The study's main limitation is that only 12 patients had nasopharyngeal swabs, with only 2 (all in the adrenal insufficiency group) being positive for COVID-19.[33]

Furthermore, when clinical circumstances improve, oral administration may be resumed after gradual steroidal tapering. Another source of concern about adrenal hormones and COVID-19 is the use of ritonavir, which significantly inhibits corticosteroid metabolism and enhances their systemic effects with consequent hypercortisolism.[34] In addition in COVID-19, patients with hypopituitarism should consider adjusting testosterone doses to avoid a pro-inflammatory response observed in hypogonadism and the increased risk of venous thromboembolism associated with higher testosterone levels. While in females, stopping oral contraceptives and continuing use of hormonal therapy in postmenopausal women is advisable.[35] On the other hand, patients with central hypothyroidism may be at risk of thyrotoxicosis due to systemic immune activation by COVID-19 infection, necessitating frequent monitoring and adjustment of thyroid replacement therapy.[36]

Pituitary manifestation of COVID-19

Neurological manifestations

Several clinical reports have confirmed that about 34% of COVID-19 patients develop several neurological manifestations, such as headaches, vomiting, and nausea, indicating an involvement of the central nervous system (CNS) and peripheral nervous system.[37,38] Neuroinvasion of coronaviruses has at least three routes: Retrograde transmission via olfactory sensory neurons, infiltration of immune cells, and entry across the blood–brain barrier.[37] The hypothalamic circuits represent an entry point for the virus via the olfactory bulb. The hypothalamus also reaches out beyond the CNS to the periphery via the hypothalamic-pituitary-adrenocortical (HPA) axis, which plays a vital role in modulating the host's susceptibility to viral infections. The high levels of pro-inflammatory cytokines activate the HPA axis during the early stages of viral infections, which, in turn, stimulates the

release of adrenal GCs to suppress aggressive inflammatory attacks and regulate the immune response. Some studies with SARS patients showed evidence of central hypocortisolism and low dehydroepiandrosterone sulfate levels, indicating damage of the hypothalamic-pituitary circuits. On the other hand, lymphopenia is a key hematological feature of COVID-19 and is strongly associated with HPA activation and GCs levels.[38]

It is noteworthy that SARS-CoV was identified in the adrenal glands, suggesting a direct cytopathic effect of the virus. In addition, autopsies have shown degeneration and necrosis of the adrenal cortical cells; therefore, it was suggested that SARS-CoV might manipulate the stress response and subsequently, cortisol dynamics. This is considered as one of the primary immune invasive strategies to suppress the host's response.[38] However, such studies are lacking on the pituitary gland. Occasional anterior pituitary infarcts have been reported.[37] There were attributed to the COVID19-induced cytokine storm, which causes coagulopathy, in turn resulting in histologic findings of microthrombi, infarcts, hemorrhages, and "neutrophilic plugs." Sepsis and acute respiratory distress are likely to contribute to these findings as well. Nonetheless, they stated that pathologists do not typically evaluate such findings. Perhaps, future studies could focus on detecting the virus in the pituitary and look for pituitary infarction as well.[37]

How much of the inflammatory changes are due to autoimmune phenomena versus direct viral infection or other causes remains unresolved. Cerebral endothelial infection is also present, and a hematogenous infection route is plausible, perhaps even common.[37]

Pituitary apoplexy

PA is a rare medical emergency due to hemorrhage or infarction of the pituitary adenoma and is typically associated with severe headache, visual disturbance, and hypopituitarism. There has been a clear link between COVID-19 and coagulopathy with increased thrombosis and bleeding risks which may put patients with pituitary adenomas at risk of developing PA.[37] Most of the data about PA in the COVID-19 pandemic comes from single case reports except for 1 case series of three patients.[39-45] The details of the cases, COVID-19 context, and outcomes/recommendations are summarized in Table 3.

Overall, about 10 cases of PA were reported, with the majority of patients in their 4–5th decade of life. Nearly all patients presented with classic PA symptoms of acute headache and vision loss, while altered levels of consciousness and cranial nerve deficits were rare. Symptoms of COVID-19 were simultaneously present in the majority at the same time of PA presentation and were confirmed with polymerase chain reaction (PCR) testing. However, in two patients, COVID-19 symptoms were reported either 1 month before PA presentation or 1 day postsurgery. No patients were known to harbor pituitary adenoma before the presentation with apoplexy, and nearly all cases had no classical risk factors for PA. In many cases, there was no clear documentation of the pituitary functions. Almost all cases were due to pituitary macroadenomas with tumor sizes ranging between 0.8 and 6.9 cm. Visual field evaluation by perimetry was rarely reported. Of those with available follow-up data at the time of publication, almost half of the patients underwent transsphenoidal tumor resection with significant or complete vision recovery. Two cases showed some improvement in visual symptoms on glucocorticosteroid; one declined surgery. Of interest, Chan *et al*.[43] reported the only case of PA during pregnancy with complete recovery of vision post trans-sphenoidal surgery (TSP), which was performed after a planned assisted vaginal delivery.[43] Of all reported cases, only one had severe COVID-19 with respiratory distress and hypoxemia who died within 12 h of presentation.

Despite the large number of infected people, the small number of PA cases in patients with COVID-19 does not suggest an increased risk of apoplexy in this population, although underreporting is possible. In addition, most of the reported cases lacked proper hormonal evaluation and visual field (VF) assessment by perimetry. It could be conceivable that the risk of viral transmission during VF evaluation by perimetry outweighs the benefits of this test, especially in the presence of adequate clinical evaluation of visual acuity and VF on examination. However, proper evaluation of pituitary hormone functions is simple and should be performed on all patients. Some of these cases are published in noninternal medicine or endocrine journals might explain the limited data about pituitary functions in the reported cases. Finally, management of PA either through a conservative approach or surgery needs to be individualized. Only rarely and perhaps in resource-limited areas, surgical management of PA on the reported cases was delayed or declined because of the COVID-19 pandemic.

Pituitary insufficiency

Table 4 summarizes the case reports of pituitary insufficiency in association with COVID-19.[48-52] Hypopituitarism *per se* is associated with increased morbidity and mortality, mainly due to cardiovascular disease, a significant risk factor for COVID-19 disease severity.[48] Alzahrani *et al*.[53] concluded that the adrenocortical response in patients with COVID-19 infection was impaired. A significant percentage of the patients had plasma cortisol and ACTH levels consistent with central adrenal inefficiency, as evident by the cases reported by others.[49,50] Furthermore, other workers[48,54] presented the possible mechanisms by which COVID-19 may affect testosterone levels, resulting in compromised male reproductive health. Reports about high luteinizing hormone while diminished levels in COVID-19 patients negate the hypothalamic-pituitary-testicular (HPT) axis mediated lowering of testosterone. Although not evidenced, high testicular expression of ACE2, which aids viral entry into cells, may suggest direct viral-testicular invasion. However, secondary inflammation and oxidative stress, owing to SARS-CoV-2 infection, are more likely to impair steroidogenesis. Moreover, blockage of ACE2-aided angiotensin II into angiotensin conversion may also affect testosterone synthesis. SARS-CoV-2, by mimicking ACTH,

Table 3: Summary of reported cases of pituitary apoplexy in association with COVID-19

Author (year) [reference]	Cases	Context	Outcome
Katti *et al.* (2021)[39]	46 years male with sudden bilateral loss of vision	COVID-19: Symptomatic (fever ×10 days); positive PCR throat swab MRI: 3.4 cm adenoma	Initially, Dx as optic neuritis (before MRI) and was treated with steroids with slight improvement. Surgery deferred due to COVID Perhaps subclinical PA, no hormonal evaluation, awaiting surgery at the time of publication
Bordes *et al.* (2021)[40]	65 years female with progressive headache and emesis. Also, photophobia and phonophobia	PMH: HTN and fibromyalgia COVID-19: 1 month before PA MRI: 1.4 cm SM	Improvement of headache and reduction of SM size after steroids Not a typical PA presentation and prolonged time from COVID-19 till presentation
Ghosh *et al.* (2021)[41]	44 years female with acute headache, vomiting, and blurred vision	COVID-19: Symptomatic (fever <1 week earlier); positive PCR swab; MRI: 3.1 cm cystic solid SM	Declined surgery Partial improvement of vision with steroids
Solorio-Pineda *et al.* (2020)[42]	27 years male with acute headache, altered LOC, and decreased visual acuity	Severe covid pneumonia. CT: 6.8 cm SM	Rapid progression of COVID-10 pneumonia and death 12 h after the presentation
Chan *et al.* (2020)[43]	28 years G5 P1 presented at 38 weeks GA with acute onset headache and blurred vision	COVID-19: Asymptomatic; positive test on routine nasal swab	Vision improved with steroids. Planned elective vaginal assisted delivery followed by TSS. Complete recovery of vision (No classic RFs, No perimetry, No absolute indication for surgery)
LaRoy and McGuire (2021)[44]	35 years male with acute headache and neck stiffness	COVID-19: Symptomatic (fever and SOB) CT: 0.8 cm	No PA RFs. No perimetry. No FU data
Martinez-Perez *et al.* (2021)[45]	54 years female with acute headache and blurred vision	Covid-19: Asymptomatic; positive PCR. MRI: 2.8 cm SM	Significant vision improvement postcraniotomy NFA on pathology
	56 years male with acute headache and diplopia	PMH: HTN, hypothyroidism COVID-19: Symptomatic (chills and myalgia ten days before presentation); positive PCR. MRI: 1.8 cm SM	Complete recovery of vision and CN deficits post-TSS. Lactotroph adenoma
	52 years male with acute headache and progressive vision loss	PMH: HTN COVID-19: Symptomatic (fever and cough 1-day postoperative); positive PCR MRI: macrozadenoma	Complete recovery of vision post-TSS. Lactotroph adenoma (COVID postoperative; not with apoplexy)

SOB: Shortness of breath, VF: Visual fields, PA: Pituitary apoplexy, CT: Computed tomography; MRI: Magnetic resonance imaging, SM: Sellar mass, CN: Cranial nerve, HTN: Hypertension, COVID-19: Coronavirus disease 2019, PCR: Polymerase chain reaction, PMH: Past medical history, LOC: Loss of conciousness, GA: General anaesthesia, RFs: Risk factors, FU: Follow up, TSS: Transsphenoidal surgery

may trigger host antibodies against the ACTH molecules to suppress the host stress response. Moreno-Perez *et al*.[55] analyzed the prevalence of low serum testosterone and impaired fertility potential in COVID-19 male survivors, as well as its association with postacute COVID-19 syndrome (PCS) and QOL. One hundred and forty-three patients were evaluated after disease onset. Low teststerone, was detected in 41 patients. Low levels of Inhibin-B were detected in 25 patients. Obesity and hypokalemia were associated with low teststerone, whereas age >65 was an independent predictor of Sertoli cell dysfunction. Low teststerone, or Sertoli cell dysfunction was not associated with PCS. Patients with low teststerone, had lower scores in 4 domains of QOL. The prevalence of low serum testosterone and impaired fertility potential in COVID-19 survivors is high in the medium term. Melo *et al*.[56] assessed the seroprevalence of COVID-19 antibodies in adult subjects with untreated isolated growth hormone deficiency (IGHD) due to a homozygous null mutation in the GHRH receptor gene. They concluded that the evolution to symptomatic stages of the infection and the frequency of confirmed cases was lower in IGHD patients than in GH-sufficient individuals.

Central diabetes insipidus (CDI) patients admitted to hospitals with COVID-19 have a high risk for mortality due to volume depletion. Specialists ought to supervise fluid replacement and dosing of desmopressin.[57] It is important to emphasize that desmopressin doses may need to be delayed to allow regular periods of free water clearance so that excess water intake does not lead to dilutional hyponatremia.[50,57] Patients should measure their body weight daily and be aware of the symptoms of over and under replacement if they develop them.[57]

Hyponatremia has been associated with higher morbidity and mortality. Berni *et al*.[58] observed that hyponatremia was an independent predictor of in-hospital mortality (2.7-fold increase vs. normonatremia), and each mEq/L of serum sodium reduction was associated with a 14.4% increased risk of death. These results suggest that serum sodium at admission may be

Table 4: Summary of reported pituitary insufficiency in association with COVID-19

Author (year)	Context/case summary	Management and outcome	Comments
Fux Otta *et al.* (2020)[48]	Known case of pituitary insufficiency on daily HC	HC dose was not changed during the infection as the patient was asymptomatic	Individualization of HC dose during COVID-19 infection
Chua and Chua (2021)[49]	47 years male with new-onset central hypocortisolism 1 week post-COVID-19 URTI. Central Hypothyroidism was also diagnosed, with spontaneous recovery after 6 weeks MRI: No pituitary lesions	Started on HC 10-5-0-0 mg 3 weeks after initiation of HC, serum cortisol remained normal	Hypothalamic-pituitary activation during the systemic illness is followed by a rebound decrease in activity after recovery leading to delayed-onset central hypocortisolism
Gaudino *et al.* (2021)[50]	A 9-year-old child with COVID-19 and a recent diagnosis of suprasellar nongerminomatous germ cell tumor with CDI and hypothalamic-pituitary failure	The patient remained asymptomatic and required no change in the replacement therapeutic dosages	A proposal for pediatric patients with COVID-19 and hypothalamic-pituitary failure*
Sheikh *et al.* (2021)[51]	28 years male with myocarditis due to COVID-19 1 month after initial infection; developed CDI on dayS 7; Brain MRI was normal	Recovery on desmopressin' after 16 days in hospital on desmopressin 0.3 mg TID	New-onset CDI as a long-term complication after recovery from COVID-19
Naaraayan *et al.* (2020)[52]	Life-threatening hyponatremia associated encephalopathy in a COVID-19 patient secondary to HCT use for hypertension	Treated with hypertonic saline and desmopressin. Serum cortisol high. Serum Na and mental state normalized over four days	Thiazides should be used cautiously for hypertension during the pandemic

*Recommendations include a. Children with AI should immediately receive parenteral HC 50–100 mg/m2. b. delaying desmopressin doses to allow regular periods of free water clearance to avoid dilutional hyponatremia. CDI: Cranial diabetes insipidus, HC: Hydrocortisone, HCT: Hydrochlorothiazide, MRI: Magnetic resonance imaging, COVID-19: Coronavirus disease 2019, TID: Three times daily, URTI: Upper respiratory tract infection

Table 5: Summary of the salient practice points for management of pituitary disorders during COVID19 pandemic*

Practice points	References
Patients with pituitary disorders should be classified as needing emergent, urgent, or elective care to guide timely intervention	[6]
Use virtual/telemedicine care to assess and follow stable patients with pituitary disorders	[6-9]
Patients with chronic stable pituitary disorders are to be followed less frequently with access to care when needed	[6]
Patients with pituitary disorders on corticosteroids should be counseled on steroid management if they are infected with COVID-19 or sick after the COVID-19 vaccination	[46]
Laboratory samples could be collected by the patient at home when possible, e.g., salivary samples instead of blood samples for cortisol assays. However, one visit for laboratory samples collection may be necessary for most patients after proper virtual assessment	[9,47]
Medical therapy to be utilized when it is an option in place of surgical intervention during the epidemic peak	[6]
Surgical intervention should be done timely without delay when needed to treat pituitary tumors-maintaining the patients' and healthcare personnel's safety to be ensured through proper COVID-19 screening and applying proper isolation before intervention	[6,10]

*The recommendations are based on different sources, COVID-19: Coronavirus disease 2019

considered an early prognostic marker of disease severity in hospitalized COVID-19 patients. De La Flor Merino *et al*.[59] reported a case of a patient with severe hyponatremia due to adrenal insufficiency secondary to hypopituitarism due to pituitary macroadenoma with radiological signs of subacute PA in a patient with COVID-19 infection. Transsphenoidal surgical decompression of the lesion was performed. They pointed out that secondary insufficiency is produced by insufficient hypothalamic-pituitary stimulation, with a deficit of ACTH and GCs, but with a correct mineralocorticoid function and with the renin-angiotensin-aldosterone axis intact. It is not known if this infectious picture has triggered the GC decompensation caused by stress. Endogenous cortisol exerts a tonic inhibitory effect on antidiuretic hormone (ADH) secretion. In GC deficiency, there is a nonsuppressible ADH release despite the existing hyposmolality. GCs produce negative feedback on both corticotropin and ADH release. This corrects the water and electrolyte imbalance and normalizes ADH levels and the renal expression of aquaporin-2 mRNA.

Practical management of pituitary disease during COVID-19

COVID19 pandemic affected patients with pituitary diseases directly but mostly indirectly. Management included organization readjustments and clinical adaptation of the usual practices.[6-10,46,59-61] A summary of the principles and salient practice points for the management of pituitary disorders during the COVID-19 pandemic is presented in Table 5. Some practical aspects are highlighted below.

Graf *et al*.[60] reported that 267 patients (64.8%) experienced a delay or change in the planned care for their pituitary disease, with 100 patients (24.3%) perceiving an impact on their care. It was concluded that, more than half of the cohort were indirectly impacted by the pandemic through a delay or change to their planned care, this is even though only a tiny percentage of patients had confirmed or suspected COVID-19 infection

(6.0% reported having suspected COVID-19 infection and only three received a confirmed positive test result). Of note, no deaths due to COVID-19 were identified.

The Pituitary Society surveyed its membership on GC management in patients with adrenal insufficiency for COVID-19 vaccination.[60] Thirty-six percent recommend that patients automatically increase GC dosage with the administration of the first vaccine injection. The majority of the rest suggested a plan to increase the dose if the patient develops a fever, and others, to a lesser extent, plan to increase the dose if myalgias and arthralgias occur. The disruption of care of patients with pituitary disorders and at large patients with endocrine diseases was also reported by the presidents and representatives of the Asean Federation of Endocrine Societies (AFES) member countries. They reported that the burden of COVID-19 cases and its case fatality rate varies across the AFES member countries, but its impact is almost uniform: It has disrupted the provision of care for patients with endocrine diseases.[7] Telemedicine and innovations have been operational across the AFES countries to cope with the resulting disruptions.

Gupta *et al*.[61] reported a retrospective observational study that included patients with sellar-suprasellar and clival lesions. Management protocols were divided into three phases based on the prevalence of COVID-19 and the number of mandatory preoperative COVID-19 tests being conducted. A total of 31 cases were operated on during this period. During Phase I (low prevalence; no preoperative COVID testing), endonasal surgeries were largely abandoned in favor of transcranial approaches. In Phase II (medium prevalence, one preoperative COVID test), They gradually resumed endonasal surgeries for "emergent" and "essential" cases, and subsequently, in Phase III (high prevalence; two preoperative COVID tests), They had no hesitation in performing "elective" endonasal surgeries with additional barriers for the prevention of aerosol transmission. No patient developed COVID-19 infection postoperatively. Eight health-care workers in their department acquired the disease during this period, none of whom were directly involved in the surgeries for the above cohort of patients. With a strict preoperative COVID testing protocol, adherence to proper drilling techniques, and using additional barriers to prevent droplet and aerosol spread, endonasal surgeries for sellar-suprasellar lesions are safe.

Regarding diagnostic challenges, there is no direct effect of the COVID-19 virus on the accuracy of endocrine tests has been reported. However, the safety processing of salivary samples is a challenge in patients with Cushing's diseases, for example, as it carries a risk for the laboratory personnel if the patient has COVID-19, diagnosed or undiagnosed. Indeed obtaining salivary samples instead of blood samples will benefit patients with, e.g., Cushing's disease or adrenal insufficiency, allowing their treatment to be monitored by posting saliva samples to the laboratory, rather than attending clinics for blood sampling with the attendant risk of contracting COVID-19. Adaway *et al*.[47] reported that heat treatment could be used to inactivate COVID-19 in saliva samples before analysis for cortisol and cortisone. Although the use of microbiological safety cabinets remains the first-line recommendation in all current guidelines, heat inactivation enables samples to be safely handled in laboratories with limited access to microbiological safety cabinets.

For patients with suspected functioning pituitary adenomas, acromegaly, Cushing disease, prolactinomas, and TSHomas; selected and appropriate laboratory testing could be done after telemedicine evaluation.[28] Indeed, the endocrinologic evaluation of such patients is essential since many of these patients have hypopituitarism and/or medical comorbidities that may affect the course and management of COVID-19. Patients with no urgent need for surgery could be treated medically until the pandemic subsides with close monitoring and assessment via telemedicine virtual visits.[9] However, patients with visual impairment due to a pituitary adenoma compressing the optic apparatus should undergo pituitary surgery as soon as possible.[9] Furthermore, in patients with a history of functioning pituitary tumors who are in remission or controlled on medical therapy; follow-up through the virtual clinic is recommended with no change in treatment regimens for 6 months unless there is a clear clinical suspicion of significant changes in response to therapy or the appearance of adverse effects of medications.[9] In patients with pituitary adenomas undergoing pituitary surgery, several measures may be taken before surgery irrespective of symptoms, including screening for COVID-19 and isolation of patients for up to 2 weeks before surgery.[6] For patients with proven COVID-19 infection in whom surgery is indicated, surgery should be delayed if possible until patients no longer have symptoms and have a negative swab test result.[6]

Furthermore, the pituitary society recommended categorizing cases as emergent, urgent, or elective.[6] Patients presented with PA; acute severe visual loss should be operated on in an emergent fashion. However, patients with slowly progressive disease or functioning tumors with aggressive clinical features may benefit from urgent surgery. On the other hand, patients with incidental and asymptomatic tumors can be scheduled as elective cases.[6]

Pituitary surgery in the COVID19 era

Context

Even in ideal circumstances, the performance of safe and effective endoscopic transsphenoidal pituitary surgery requires complicated orchestration of care amongst multiple medical and surgical teams in the preoperative, intraoperative, and postoperative settings.[10]

The challenges imposed by the new reality of the global COVID-19 pandemic have affected all aspects of pituitary surgery, especially the surgical management of pituitary adenomas. Perhaps, the foremost of these challenges is the gap in knowledge and lack of experience in dealing with such a formidable opponent. This has sparked a healthy effort of sharing surgical experience and devising new protocols and

tools for the surgical management of this group of patients. Nevertheless, this commendable effort may fall short of the required standard for drawing evidence-based guidelines. This section seeks to crystalize these challenges and explore the current literature to advise the clinical practice. The challenges facing pituitary surgery in the context of the COVID-19 pandemic are conceptualized under four themes presented in Table 6. These are elaborated below:

A. The rationalization of 'nonurgent or elective surgery would imply restricting surgical procedures for pituitary adenoma.

Challenges

The mounting pressures of this pandemic and the massive drain on health care systems around the globe led to rationalization in health care provisions at every level. Globally, health care facilities were forced to prioritize efforts to contain and manage the complications of the pandemic over other areas of healthcare. In some units, this meant a complete cessation of elective and nonurgent surgical procedures. Other smaller units were forced to shift their focus entirely for combating the pandemic, with anesthetists being recruited for intensive care unit (ICU) care, operating rooms being used exclusively for trauma cases and life/limb-threatening conditions. Pituitary adenomas and skull base procedures were generally viewed as elective procedures and often postponed or cancelled altogether.[62] Furthermore, Mazzatenta *et al*.[63] compared their non COVID19-related workload in the neurosurgery department for 2020 to the 2 previous years. As expected, the surgical procedures in 2020 constituted only 26%–28% of the previous 2 years. The impact of shifting the focus away from other areas of healthcare, although understandable, has arguably compromised the well-being of patients with chronic medical conditions, especially patients in need of elective surgical interventions such as pituitary adenomas.

Solutions

Kolias *et al*.[64] suggested adopting a risk-mitigation approach that would enable surgical teams to operate on selective pituitary and skull base cases based on risk-benefit balance. The group suggested a set of modifications to routine clinical practice to adapt to the potential COVID-19-related risks. This notion was supported by a more extensive multicentre prospective observational study across the United Kingdom.[65] Twelve tertiary neurosurgical units participated between March 23, and July 21, 2020. Overall, a total of 124 patients were included. Preoperative COVID-19 screening was performed in 116 patients (94%), with only one patient detected preoperatively to have COVID-19 infection, and his surgery was delayed until after remission. The performed surgical procedures included (transsphenoidal approach, 97 of 105 [92%]; expanded endoscopic endonasal approach, 19 of 19 [100%]). The group reported no COVID-19-related adverse events postoperatively, and all patients and healthcare staff had no COVID-19-related morbidity. This demonstrated that Endoscopic Endonasal Surgery for pituitary adenomas could be maintained safely during the pandemic. Other authors shared the same experience about the feasibility and the safety of maintaining this clinical service throughout the pandemic (primarily based on the presence of solid clinical indications for urgent surgery).[66-68] On the other hand, Penner *et al*.[69] operated successfully on functional pituitary adenomas (without visual compromise) during the pandemic. They adopted a good preoperative screening program (requiring two negative PCR tests preoperatively) and the use of adequate personal protective equipment during patient contact. Such experiences support the notion that in the face of the lasting effects of the COVID-19 pandemic, the notion of avoiding elective endoscopic procedures has to be revisited.

Table 6: A conceptualization of the challenges facing pituitary surgery in the context of COVID-19 pandemic*

A	The rationalization of 'nonurgent or elective surgery would imply restricting surgical procedures for pituitary adenoma
B	Endoscopic endonasal transsphenoidal surgery is widely accepted as the best available surgical option. Nevertheless, it is feared to expose health care providers to increased risk of cross-contamination due to operating in heavy viral load areas and the risk of areolisation and droplet generation
C	Operating endonasally in infected patients is feared to expose such patients to unmitigated risks due to exacerbating potential respiratory and neurological complications of COVID infection
D	COVID-19 infection and its complications may mimic, alter, or complicate the expected clinical course of pituitary adenoma and its surgical management

*The literature addressing these challenges and possible solutions are reviewed in detail in the main text. COVID-19: Coronavirus disease 2019

B. Endoscopic endonasal transsphenoidal surgery is widely accepted as the best available surgical option. Nevertheless, it is feared to expose health care providers to increased risk of cross-contamination due to operating in heavy viral load areas and the risk of areolization and droplet generation.

Challenges

Endonasal procedures are postulated to carry a significantly higher risk of exposure to the COVID-19 virus due to the higher viral load and risk of viral shedding via generated droplets with such surgical manipulation.[70] Furthermore, Zhu *et al*.[71] reported that 14 of their healthcare providers involved in a COVID-19 case contracted the virus. However, the group highlighted that none of the staff involved in the actual surgery were infected. All documented cases occurred in the postoperative period due to a lack of adequate protective measures by the staff who came in contact with that patient. The risk is postulated to be the highest for procedures involving the respiratory or gastrointestinal tract mucosa due to the known biodistribution of the virus. The use of powdered instruments such as power drills and microdebrider is suggested to increase the risk of airborne viral particles by aerosolization of cerebrospinal fluid (CSF), CNS tissue, and theoretically blood laden with COVID-19 virus.[72]

Among the issues related to this challenge is the typical scenario of asymptomatic COVID-19 cases where the risk of transmission might be exacerbated by the lack of vigilance and the not adapting to the strict contact measures otherwise enforced in known COVID-19-infected cases. Champagne *et al*.[62] explored the neurosurgical practices in different geographical zones stratified according to the prevalence of COVID-19. The group reported a higher rate of viral transmission to healthcare providers in medium prevalence zones than high prevalence zones. This was suggested to be associated with a lower rate of preoperative PCR testing in units in the medium prevalence zone than their counterpart in the high prevalence zone, which arguably led to more asymptomatic COVID-19-infected cases being undetected in 32% of viral transmission cases in healthcare providers.

Solutions

Dhillon *et al*.[73] examined the particle size, concentration, and airborne duration during endoscopic endonasal pituitary surgery in three patients undergoing endoscopic endonasal procedures in a theater setting. Particle image velocimetry and spectrometry with air sampling were used for aerosol detection. The group found that intubation and extubation generated large amounts of tiny particles that remained suspended in the air for relatively long durations and dispersed through theater. Endonasal procedures and pituitary tumor resection generated smaller concentrations of larger particles that were airborne for shorter periods and traveled shorter distances. Accordingly, the group concluded that the risk of aerosolization and increasing airborne viral particles is not unique to endonasal access of powered instruments, which might be reassuring for endoscopic surgeons. The relatively high risk of aerosolization during intubation and extubation was the subject of study by others. Santos *et al*.[74] reported their experience with the University of Mississippi Medical Center airway management algorithm for patients infected with the novel coronavirus who need emergent surgical attention.

Different solutions have been proposed for droplets generating maneuvers and instruments, including minimizing the use of high-speed drills and microdebriders (rongeur and chisels can be used alternatively). Solari *et al*.[75] reported using an improvised face mask, "the nose lid" applied onto the patient's nose during the procedure. The group suggested that such modification to draping can be easily assembled from widely available instruments in OR. It still allowed the smooth introduction of endoscopic equipment in and out of the nasal cavity reducing the risk of aerosolization. Similarly, Arefin *et al*.[76] presented few modifications in draping and nasal preparation that included the use of povidone iodine as mouthwash and nasal spray or irrigation as a disinfectant for both patient and health care providers before the surgery. The authors also reported they used a simple polythene sheet as a barrier drape isolating the patient or operative area to prevent the spread of aerosols in the operating room during surgery as the other component.

Several groups addressed asymptomatic COVID-19 cases by proposing general preoperative screening paradigms and risk stratification based on clinical assessment, routine PCR screening preoperatively, and careful medical history tracking of potential contact with infected individuals. Routine screening appears to alleviate the risk of COVID transmission even in high prevalence areas compared to other areas where such measures were not deployed routinely.[62,70] Furthermore, Iorio-Morin *et al*.[70] stressed adoping a set of general contact precautions in every case, including the use of appropriate PPE, negative pressure operating rooms, limiting traffic through OR, and limiting the number of healthcare providers dealing with infected cases, as well as dedicating a designated anesthetic team to handle such cases.

C. Operating endonasally in infected patients is feared to expose such patients to unmitigated risks due to exacerbating potential respiratory and neurological complications of COVID infection.

Challenges

The first issue in this category is that any surgical intervention in COVID infected patients (mainly asymptomatic) might negatively affect the patients themselves, as suggested by retrospective review from China, which examined 34 asymptomatic patients with COVID-19 who underwent surgery during the incubation period. Of these patients, 44% subsequently required ICU admission for respiratory deterioration, with a noted mortality rate of 20.5%.[77] In addition, when performed in infected patients, these endoscopic procedures can be argued to carry a risk of introducing a higher viral load to the bloodstream when disrupting the nasal mucosa (theoretically causing transient viremia), which may lead to further COVID-related complications. Similarly, in endoscopic skull base cases (for pituitary or other conditions) where CSF leak is encountered accidentally or otherwise, the risk of direct viral inoculation in the CNS is further considered. Lau *et al*.[78] highlighted the neurotropic nature of SARS coronavirus, which has been detected in the CSF of infected patients. This was due to the abundance of ACE-2 receptors in the CNS and the affinity of coronaviruses for binding to ACE-2 receptors. Correia *et al*.[79] suggested that such neurotropic predilection is the driving factor in the development of meningitis or encephalitis in some patients with the COVID-19 virus.

Solutions

The findings of Lei *et al*. 2020[77] were for patients undergoing various surgical procedures that did not include endoscopic endonasal surgery for pituitary adenoma. However, they might be reasonably extrapolated to pituitary cases as they could be related to the need for intubation and general anesthesia and immune system reaction to surgical trauma, which is not procedure specific. Arguably endoscopic procedures might carry even particular risks due to the temporary incapacitation of nasal breathing with nasal packing, higher risk of aspiration postoperatively, and occasionally longer duration, especially

in complex endoscopic skull base cases compared to their open microsurgical alternatives. For these considerations and previously discussed other considerations, the current literature suggests that rigorous preoperative screening is paramount to avoid inadvertently operating on asymptomatic COVID-19 patients.[6] Operating on these patients when detected preoperatively should be balanced against the above potential risks, which remain so far theoretical.

An alternative risk-mitigating strategy in these patients, who may have clinically sound indications for undergoing urgent surgery, is to minimize the mucosal destruction, avoid nasal packing, modify their endoscopic procedures to be shorter, less invasive and avoid CSF leak if at all possible.

However, there is currently no evidence that intraoperative CSF leak in COVID-19 infected patients leads to any added COVID-19 specific morbidity. To the best of our knowledge, there are no dedicated studies that examined this point, but from the current literature, some authors reported inadvertent CSF leak during EES on COVID-19 patients with no reported complications.[71] Another possible solution for operating on urgent pituitary cases during the pandemic is to consider an alternative route (transcranial open surgery) rather than the endoscopic transsphenoidal route. This would arguably avoid traversing the nasal route with all the relevant implications as discussed before and maybe suggested exposing the patients (as well as staff) to lower risks by avoiding all mucosal surfaces, endonasal packing, and much lower risk of CSF leak. Golden *et al*.[81] reported operating trans-cranially on COVID-19 infected patients with giant pituitary adenoma with a good outcome.

D. COVID-19 infection and its complications may mimic, alter, or complicate the expected clinical course of pituitary adenoma and its surgical management.

Challenges

Our knowledge of the full effects and mechanisms of COVID-19 is far from complete. The CNS effects, in particular, seem to be quite varied with the risk of intracranial bleeding, CNS vasculitis, cranial neuropathies, as well as stroke is reported.[79] These CNS manifestations in conjunction with known pituitary adenoma might falsely indicate adenoma progression or apoplexy and mislead the treating clinicians. Nevertheless, Martinez-Perez *et al*.[45] reported a series of genuine PA in COVID-19 infected patients. Although the authors stopped short of suggesting a causative effect, the known COVID-19 micro thrombotic effects might be implicated here, suggesting at least a contributory role for COVID-19, adding a layer of complexity for managing large pituitary adenomas in COVID-19 infected patients. Talmor *et al*.[80] also reported a postoperative complication in COVID-19 patients following CSF leak repair with nasoseptal flap, which was complicated with flap necrosis. The authors suggested this resulted from COVID-19 infection, having inspected the same flap previously and found it healthy before diagnosing the patient with COVID-19. The proposed

Table 7: Description of a risk mitigation approach for pituitary and skull base surgery during the COVID-19 pandemic*

Stage	Practice points
Preoperative	Routine PCR testing of all patients
	In the context of recent infection or clinical symptoms suggestive of COVID-19, patients should have two negative PCR tests preoperatively (for elective cases)
	For urgent cases, PCR tests should be done preoperatively, and results reviewed preoperatively if feasible
	If patients are known to be COVID-19 positive special considerations should be given to delaying surgery for 10-14 days if no clinical harm is expected
	Minimize patient traffic throughout the hospital by coordinating all tests if possible and consider out-of-hours visits to avoid contact with other patients
Intra-operative	Negative pressure ventilation system in OR
	Consider operating in dedicated OR or out-of-hours on COVID-19 infected cases to minimize contact with other patients
	Use of powdered airway purification respirators if possible
	Use of appropriate PPE for all staff coming in contact with the patient
	The use of mechanical or chemical disinfectant strategies (POLIDON) might be considered
	Minimize or avoid altogether (if possible) the use of powered tools endonasal such as drills or shavers, which may generate more viral laden aerosols
	Consider modifying the draping technique to avoid airborne viral aerosols
	Exercise extra caution when removing drapes, which has been shown to generate more airborne droplets of infected tissue/mucus
	Adhere to the clear and systemic guideline for airway management for intubation/extubation by the anesthetic team
	Consider allocating a dedicated anesthetic team for COVID-19 infected cases
	Avoid CSF leak if at all possible
	In case of a CSF leak, consider multi-layered repair, including fat and fascia lata
	Avoid nasal packing
Postoperative	Maintain contact precautions throughout the hospital stay, especially for aerosol-generating procedures such as removal of nasal packing
	Minimize the length of hospital stay
	Consider the added stress of the viral infection for the steroid management in selective cases
	Avoid nasopharyngeal swabs strictly in the immediate postoperative period
	Consider oropharyngeal swabs for follow-up for the first 2 weeks postoperatively
	After 2 weeks, anterior nasal or mid-turbinate nasal swabs can be considered for PCR swabs
	After 6 weeks, nasopharyngeal swabs can be done with caution

*Modified from Kolias *et al*., 2020.[64] PCR: Polymerase chain reaction, CSF: Cerebrospinal fluid, OR: Operating room, PPE: Personal protective equipment, COVID-19: Coronavirus disease 2019

mechanism was microthrombotic events. While this remains a theoretical explanation, it may invite further considerations of such added complications for COVID-19 in this setting.

Solutions

Fleseriu *et al*.[6] suggested a comprehensive protocol for managing various pituitary endocrinopathies in the era of COVID-19. This included managing PA, emphasizing steroid replacement, and the potential increased demand for stress hormones during the viral illness. When focal neurological deficits (visual deterioration, cranial neuropathy) develop in the context of known pituitary adenoma, careful radiological assessment for any changes in the pituitary adenoma should be done to exclude the possibility of apoplexy. As suggested by the experience of Martinez-Perez *et al*.[45] and others, when congruent clinical and radiological manifestations confirm the diagnosis of PA, patients should be managed as per the standard protocols, including offering EES procedures for rapidly deteriorating visual scores or altered mental status due to mass effect. With regards to CSF leak, it is suggested that avoiding CSF leak altogether is the best strategy. However, if an inadvertent CSF leak occurs or intradural procedures are undertaken. A multilayer repair involving fat and fascia lata graft (in addition to mucosal flaps and other artificial dural repair kits) should be considered.

Finally, some practical recommendations and suggestions based on surgical experience managing pituitary patients during the pandemic are summarized in Table 7.

Conclusions

Several factors have been established to increase the risk of hospitalization and death in COVID-19 patients, such as older age, preexisting obesity, hypertension, cardiovascular disease, and diabetes mellitus. A bidirectional relationship seems to exist between COVID-19 and several endocrine disorders. In this review, we focused on the impact of COVID-19 in patients with pituitary disorders. In addition to general comorbidities that may apply to many pituitary patients, they are also susceptible to the following pituitary disorder-specific features: Hypercortisolemia and adrenal suppression with Cushing disease, adrenal insufficiency, and diabetes insipidus with hypopituitarism, and sleep-apnea syndrome and chest wall deformity with acromegaly. We have summarised the available literature on the subject to help practicing clinicians recognize the relationship between COVID19 and the pituitary gland in whichever direction it may occur.

Authors' contribution

All named authors contributed to conception of the article, drafting of their assigned sections and review of the final version of the manuscript.

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Conflicts of interest

There are no conflicts of interest.

Compliance with ethical principles

No ethical approval is required for review type of study.

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