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ABSTRACT

Objective: In December 2019, a novel coronavirus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) caused an outbreak of coronavirus disease 2019 (COVID-19) that resulted in a global pandemic with substantial morbidity and mortality. Currently, there is no specific treatment or approved vaccine against COVID-19. The underlying associated comorbidity and diminished immune function of some pituitary patients (whether caused by the disease and its sequelae or treatment with excess glucocorticoids) increases their risk of contracting and developing complications from COVID-19 infection.

Methods: A review of studies in PubMed and Google Scholar published between January 2020 to the time of writing (May 1, 2020) was conducted using the search terms ‘pituitary,’ ‘coronavirus,’ ‘COVID-19’, ‘2019-nCoV’, ‘diabetes mellitus’, ‘obesity’, ‘adrenal,’ and ‘endocrine.’

Results: Older age and pre-existing obesity, hypertension, cardiovascular disease, and diabetes mellitus increase the risk of hospitalization and death in COVID-19 patients. Men tend to be more severely affected than women; fortunately, most men, particularly of younger age, survive the infection. In addition to general comorbidities that may apply to many pituitary patients, they are also susceptible due 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.

Conclusion: This review aims to focus on the impact of COVID-19 in patients with pituitary disorders. As most countries are implementing mobility restrictions, we also discuss how this pandemic has affected patient attitudes and impacted our decision-making on management recommendations for these patients. (Endocr Pract. 2020;26:915-922)

INTRODUCTION

In December 2019, a novel coronavirus (SARS-CoV-2) was identified as the cause of a cluster of pneumonia cases in Wuhan, China (1), and the World Health Organization designated the disease as coronavirus disease 2019 (COVID-19). The epicenter of infection was linked
to a seafood and exotic animal wholesale market in the city and has since rapidly spread, resulting in a global pandemic. As of May 1, 2020, the ongoing COVID-19 pandemic has infected over 3.3 million individuals and claimed over 230,000 lives (2). Although these grim figures are expected to rise in the coming months, they are still an underestimate of the true numbers as many mild and asymptomatic individuals are not likely going to be diagnosed.

The purpose of this review is to provide an overview on the impact of COVID-19 in patients with pituitary disorders. As most countries are implementing mobility restrictions, we also discuss how this pandemic has changed patient and physician attitudes and impacted decision-making on management recommendations for these patients. In preparation for this manuscript, we conducted an electronic database search of PubMed and Google Scholar of studies published between January 2020 to the time of writing (May 1, 2020) using the search terms 'pituitary,' 'coronavirus,' 'COVID-19,' '2019-nCoV,' 'diabetes mellitus,' 'obesity,' 'adrenal,' and 'endocrine.'

CLINICAL FEATURES OF COVID-19 INFECTION

Amongst confirmed cases, the majority (87%) of patients are aged between 30 and 79 years, and almost 50% of the patients have pre-existing medical conditions, including cardiovascular disease, diabetes mellitus (DM), chronic lung disease, hypertension, and cancer (3). Clinical features vary and include fever, cough, dyspnea, headache, myalgia, general weakness, headache, anosmia, and diarrhea (4,5). The respiratory symptoms can be heterogeneous, ranging from minimal symptoms to severe hypoxia with acute respiratory disease syndrome (ARDS). Older age, obesity, hypertension, cardiovascular disease, and DM increase the risk of hospitalization and death in COVID-19 patients (6). Gender susceptibility has also been observed; men are more frequently affected and more prone to become seriously ill than women (7). Fortunately, most men, especially those of younger age, recover from the infection (8).

RISK FACTORS OF COVID-19 INFECTION TO PITUITARY PATIENTS

The COVID-19 pandemic has brought to light several new challenges to pituitary patients. Many of these patients are already carrying a burden trying to understand and manage the disease themselves, notwithstanding the fact that they have to stay educated to new developments. These patients now have additional concerns about their particular susceptibility, whether their treatments need to be modified to reduce their susceptibility to the infection and, if so, how and what they have to do if they become infected. Table 1 summarizes general and pituitary disorder–specific risk factors relevant to the COVID-19 infection and management recommendations.

(A) General Risk Factors

Pituitary patients particularly with Cushing disease, craniopharyngioma, and growth hormone deficiency are prone to develop central obesity. Obesity is itself associated with hypertension, cardiovascular disease, DM, sleep-apnea syndrome, and certain types of cancers, all of which increases the susceptibility to COVID-19 infection. Of 178 patients with data on underlying conditions, 49.7% had hypertension, 48.3% had obesity, about 35% reported chronic lung conditions such as asthma, and DM and cardiovascular disease were seen in 28% each (9). Obesity is also associated with decreased expiratory reserve volume, functional capacity, and respiratory system compliance, making ventilation more difficult (10). Hypertension is one of the most frequent comorbidities observed in COVID-19 patients who developed ARDS (27%) (11). However, it is unclear whether uncontrolled hypertension is a risk factor for acquiring COVID-19 or whether controlled blood pressure amongst hypertensive patients is or is not less of a risk factor. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) are often utilized for treatment of hypertension but associated with increased pulmonary ACE2 expression that may facilitate entry and proliferation of the SARS-CoV-2 virus (12,13). When the virus gains entry into the host tissue, ACE2 is downregulated, resulting in a reduction in degradation of angiotensin II and unopposed aldosterone secretion with subsequent kaliuresis and hypokalemia (14). This has raised questions about the possibility that these agents could increase the susceptibility and worsen the prognosis in COVID-19 patients. Pituitary patients, particularly those with Cushing disease, acromegaly, and those overtreated with glucocorticoids for adrenal insufficiency (AI) are predisposed to hypertension and may be treated with ACE inhibitors and ARBs. Because there is as yet inadequate evidence to suggest that hypertension is related to COVID-19 outcomes, use of ACE inhibitors and ARBs for hypertension management should not be discontinued (15) until further data become available.

Recent epidemiologic studies have reported an increased risk of COVID-19–related complications in patients with underlying cardiovascular disease (8,11,16). Ruan et al (17) reported that among COVID-19 patients who died, the cause of death was respiratory failure and myocardial injury in 33% of the patients and primary myocardial injury and/or heart failure in 7% of the patients, whereas Shi et al (18) demonstrated higher rates of ventilator requirement and in-hospital mortality in those with cardiac injury. Other reports have found elevated serum troponin levels in 5 to 7% of hospitalized COVID-19 patients, implying concurrent myocardial injury (5). However, it remains unclear whether the association with worse outcomes is simply due to selection of older, more fragile patients that are more vulnerable to ischemia with metabolic abnormalities during critical illness or direct...
myocardial injury caused by the virus or its prothrombotic inflammatory sequelae. Heart failure, arrhythmia, and sudden cardiac death have also been observed in severely ill patients. Zhou et al (8) found that 52% of patients who died had pre-existing heart failure, whereas Arentz et al (16) reported that cardiomyopathy was found in 33% of patients. Conversely, arrhythmias and sudden cardiac death are possibly caused by significant atrial and ventricular arrhythmias precipitated by electrolyte abnormalities (19). Furthermore, some therapies empirically touted to treat COVID-19 infection (e.g., hydroxychloroquine) are associated with QT prolongation (20).

Diabetes mellitus has been shown to be a predictor of severity of disease, ARDS, and increased mortality (11). Potential mechanisms include higher-affinity cellular binding and efficient viral entry due to augmented ACE2 expression in the lung, decreased viral clearance, impaired adaptive immunity, and increased risk of hyperinflammatory cytokine storm. Additionally, hyperglycemia inhibits neutrophil chemotaxis, phagocytosis, and intracellular killing of microbes and impairs adaptive immunity (21). Peripheral CD4+ and CD8+ T-cell counts are decreased, whereas Th17 CD4+ T cells and cytokine levels are increased (21), suggesting that DM exerts decreased antiviral interferon responses (22). Because ACE inhibitors and ARBs are used in DM patients as antihypertensive and renoprotective drugs, a contrary hypothesis is that the increased ACE2 expression caused by these drugs could theoretically increase the risk of contracting COVID-19 infection, although currently this hypothesis remains unproven. Other drugs commonly used in DM patients include statins, calcium channel blockers, and aspirin. Statins have been shown to inhibit nuclear factor–kappa β activation that could dampen the hyperinflammatory cytokine storm (23); calcium channel blockers could decrease the severity of pneumonia by inhibiting cellular calcium influx (24); and aspirin could shorten the length of hospital duration and reduce the development of cardiovascular complications (ClinicalTrials.gov Identifier: NCT04365309). Nonetheless, the precise role of these agents in COVID-19 is not fully elucidated; hence, these drugs should be continued in DM patients until further data are published.

Supraphysiologic doses of glucocorticoids are commonly used in clinical practice to decrease inflammation and prolonged exposure causes immunosuppression that increases the susceptibility to infections and causes fasting and postprandial hyperglycemia (25). Conversely, systemic absorption and side effects associated with local glucocorticoid injections are underrecognized. Administration of supraphysiologic doses of glucocorticoids, either systemically or locally (e.g., intra-articular and epidural), suppresses the hypothalamic-pituitary-adrenal (HPA) axis. For example, the median elimination half-life of triamcinolone injected into the epidural space is almost 9 days (26), causing HPA axis suppression that lasts several weeks. Quantifying systemic dose and risk is challenging, starting with the notion of identifying a threshold of safe number of injections or total milligrams of glucocorticoid injected per year (27). Prolonged adrenal suppression

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| Table 1 | General and Pituitary Disease–Specific Risk Factors for COVID-19 |
|----------|-----------------------------------------------------------------|
| **Risk factors** | **Management recommendations** |
| **General** |  |
| - Obesity | - Optimize weight management |
| - Hypertension | - Optimize blood pressure control |
| - Cardiovascular disease | - Consider anticoagulation, anti-arrhythmic and supportive hemodynamic therapy |
| - Diabetes mellitus | - Optimize glycemic control and manage other diabetes comorbidities |
| - Excess and prolonged glucocorticoid exposure | - Limit glucocorticoid doses and employ caution on the necessity, dosing, and frequency of local glucocorticoid injections |
| **Pituitary-disorder specific** |  |
| - Hypopituitarism (particularly adrenal insufficiency and diabetes insipidus) | - Pay close attention to “steroid sick day” rules and consider prompt “stress dosing,” and maintain adequate hydration |
| - Cushing disease (hypercortisolemia and adrenal suppression) | - Consider initial medical therapy as first-line therapy to achieve eucortisolemia and avoid over-treatment causing adrenal insufficiency, and promptly treat adrenal suppression with glucocorticoid replacement doses |
| - Acromegaly (sleep-apnea syndrome, chest wall deformity, upper airway obstruction and intrathoracic collapse) | - Treat sleep apnea, and seek early medical attention if breathing worsens |

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results in adrenal atrophy, and abrupt withdrawal of glucocorticoids may rapidly lead to adrenal crisis. Many of the signs and symptoms are nonspecific and can be mistaken for symptoms of intercurrent illness, the underlying condition that the patient is receiving treatment for (e.g., weakness/fatigue, nausea, vomiting, diarrhea, headache, fever, and myalgia), or only recognized when exposed to physiologic stressors (e.g., illness, surgery, or injury).

Drug-drug interactions need to be considered in COVID-19 patients since some of the antiviral therapies such as lopinavir-ritonavir are strong cytochrome P450 3A4 (CYP3A4) inhibitors that can decrease metabolic clearance of glucocorticoids and prolong their biologic action. Lopinavir-ritonavir has recently been shown to provide no clinical benefit (28), whereas remdesivir apparently does not affect CYP3A4 activity and has been demonstrated to exert some clinical improvements in treating COVID-19 patients (29). Additionally, the clinical profile of side effects differs between hypercortisolism from an exogenous (usually iatrogenic) compared with an endogenous source (30,31). A meta-analysis of more than 2,000 glucocorticoid-treated patients with nonmalignant diseases showed that the relative risk for infection was 1.5 times that of controls (31). The degree of risk for infection was a complex function of the level and duration of glucocorticoid excess, dosing schedule, clearance of the type of glucocorticoids, presence of co-existing immunosuppressive therapy, and degree of the underlying host disease (31). Exogenous glucocorticoid use may also pose different infection risks in different types of pituitary disorders. For example, the risk of a patient with Cushing disease and concurrent DM treated with supraphysiologic doses of glucocorticoids for adrenal suppression to contract COVID-19 infection is inherently heightened compared to a normoglycemic patient with a pituitary nonfunctioning adenoma and isolated secondary AI on physiologic glucocorticoid replacement doses.

(B) Specific Risk Factors to Pituitary Patients

(I) Hypopituitarism

Infectious diseases and excess mortality are reported in patients with AI (32,33), especially in those with severe AI. This may be related to the association between AI and impaired natural immunity function with defective neutrophil action and natural killer cells (34). Studies have shown an increased risk of viral infections in AI patients, presumably related to an impairment in adaptive cellular immunity (33), whereas patients receiving hydrocortisone replacement therapy administered three times daily have been reported to have selective impairment in natural killer cell toxicity. Conversely, Isidori et al (35) demonstrated that a reduction in glucocorticoid exposure using a once-daily, modified-release hydrocortisone preparation restored counts of natural killer cells and reduced the number of infections, particularly flu-like illnesses. In contrast to the majority of patients with primary AI, the degree of AI in pituitary patients is generally milder due to the presence of some underlying basal cortisol secretion. Consequently, in order to avoid unnecessary immnosuppression in patients with secondary AI, 10 to 20 mg daily of hydrocortisone in divided doses is almost always sufficient, and daily doses greater than or equal to 30 mg should be avoided. However, if the patient with AI is developing an acute COVID-19 infection with persistent fever, oral hydrocortisone stress doses of 20 mg every 6 hours is recommended (36).

The increased rate of infectious diseases may precipitate adrenal crisis (37), leading to increased mortality, and could also be accounted for by insufficient glucocorticoid stress dosing. Conversely, patients with AI may also be at risk of overtreating themselves with glucocorticoids, rendering them hypercortisolemic with the associated risk of hyperglycemia and immunosuppression. Previous studies have demonstrated that glucocorticoid overreplacement is one of the main contributing factors of excess mortality in patients with hypopituitarism (38,39). For these reasons, patients with AI may be at higher risk of developing COVID-19 infection, although to date, there are no data reporting this outcome in such patients. A prospective study evaluating serum cortisol and adrenocorticotropic hormone (ACTH) levels in patients with severe COVID-19 infection is currently underway (ClinicalTrials.gov Identifier: NCT04273321).

For patients with diabetes insipidus (DI), COVID-19 infection may cause increased fluid loss, further compounding dehydration and electrolyte abnormalities, especially if fever, tachypnea, diarrhea, and vomiting are present (40). Finally, cancer patients on immune checkpoint inhibitor therapy are also at heightened risk of COVID-19 infection. Immune checkpoint inhibitor therapy is a new cancer therapy that is used increasingly, but because of its unique mechanistic action, it is associated with immune-mediated hypophysitis (41,42). In patients with hypophysitis, including secondary AI and DI, who are infected with COVID-19, stress-dose glucocorticoid supplementation and judicious water and electrolyte replacement, respectively, are recommended.

(II) Cushing Disease and Acromegaly

Cushing disease patients have multiple risk factors that predisposes them to COVID-19 infection, including chronic hypercortisolism and its sequelae (e.g., hyperglycemia, hypertension, central obesity, prothrombotic diathesis, and immunosuppression) and treatment-induced (surgical or medical) adrenal suppression (43). If pituitary surgery is successful and AI develops postoperatively, glucocorticoid replacement therapy is required and should be tailored to each individual patient’s needs, avoiding over- or underreplacement. Conversely, in patients on medical therapy, dose reductions are needed if overtreatment is suspected. On the other hand, patients in remission owing to surgery or medical therapy might also develop glucocorticoid withdrawal associated with lack of wellbeing and flu-like symp-
toms that mimic AI and COVID-19 infection, which can be challenging to differentiate. One strategy is to supplement glucocorticoids at higher than optimum replacement doses (“stress dosing”) for several weeks after remission, then taper the dose according to individual patient symptomatology to avoid unnecessary prolongation of iatrogenic hypercortisolism. In Cushing disease patients who previously underwent radiation and those on medical therapy that decreases serum ACTH and cortisol levels, they may need to store more hydrocortisone tablets at home in case they develop an illness to avoid adrenal crisis and cannot be seen by their endocrinologist promptly, whereas if the patient is on mifepristone, dexamethasone tablets should be prescribed to the patient.

For acromegaly patients, the comorbidities associated with increased susceptibility to COVID-19 infection include sleep-apnea syndrome, chest wall deformity, upper airway obstruction, and intrathoracic collapse. Mortality due to respiratory disease is reported to be approximately 25% of cases (44). Impaired respiratory function originates from the multiple anatomic changes associated with the disease (e.g., airway anatomy, bones, muscle structure of the chest, and lung elasticity) (44). Patients with acromegaly may have a barrel chest due to changes in vertebral and costal morphology, and they may have upper airway obstruction as a result of macroglossia, prognathism, thick lips, and hypertrophy of the laryngeal mucosa and cartilage. Hypoventilation and hypoxemia may develop from central respiratory depression and kyphoscoliosis (45), thus further predisposing these patients to increased respiratory infections. Studies have shown that with disease remission, it is possible to reverse some of the associated comorbidities, including joint articular cartilage thickness, vertebral fractures, left ventricular function, exercise capacity and endurance, lipid profile, and obstructive apnea events (46). Additionally, improving treatment and reversing the comorbidities can potentially normalize mortality in acromegaly patients comparable to the general population (47), thereby decreasing their risk to COVID-19 infection.

NEUROPSYCHOLOGICAL SEQUELAE OF COVID-19 INFECTION

The COVID-19 pandemic has significantly impacted the mental health in patients and healthcare providers alike, with depression, anxiety, fear of illness, and uncertainty about the future being reported (48). Furthermore, social isolation resulting in loss of structured educational and work activities also threatens to worsen public mental health (49). This is further compounded by several case reports of suicidal deaths possibly related to anxiety of contracting or spreading COVID-19 (50,51).

Pituitary patients, especially those with hypopituitarism on hormone replacement therapies, those who have undergone radiation therapy, and those with functional pituitary adenomas on medical therapy, require laboratory testing and serial magnetic resonance imaging studies to monitor therapeutic dosing efficacy and tumor growth. Due to fears of contracting COVID-19 infection, some patients have understandably been reluctant to undergo any form of testing. This has prompted healthcare providers to modify their decision-making and clinical management strategies to accommodate patient attitude changes, and at the same time, not compromise treatment safety.

For front-line healthcare workers, regular exposure to the infection, protective equipment shortages, and long work hours are added mental stressors (52), and posttraumatic stress was frequently reported negatively affecting overall wellbeing (53-55). Given the global burden of COVID-19 infection and its impact on neuropsychiatric sequelae, the public health implications of such complications will be significant. Understanding the trajectory and characteristics of neuropsychiatric outcomes stemming from COVID-19 infection will be critical, and protecting the mental health of healthcare workers will be important to preserve their long-term psychological and emotional health.

NEUROSURGICAL CONSIDERATIONS SPECIFIC TO PITUITARY PATIENTS

In response to the COVID-19 pandemic, the Centers for Disease Control and Prevention, the United States Surgeon General, and several other medical specialties such as the American College of Surgeons and the American Society of Anesthesiologists have recommended interim cancellations of elective surgical procedures. Although pituitary surgeries are generally considered elective and safe in the hands of an experienced neurosurgeon, such surgeries may not be safe even if urgent during the COVID-19 pandemic. A report of the early experience in China and Italy revealed an increased risk of contagion amongst ear, nose, and throat surgeons and their teams performing aerosol-generating procedures, such as those involving the sinuses (56,57). This raises an issue for pituitary patients awaiting surgeries, of which such surgeries are frequently performed through transsphenoidal and other endonasal transspinus routes. This has led some professional neurosurgical societies to propose alternative routes to the transsphenoidal route (58,59). Fortunately, as most pituitary tumors are slow-growing benign lesions, surgery may be deferred, and close monitoring with serial magnetic resonance imaging studies and formal visual field assessments can be undertaken. For pituitary patients who require urgent surgical intervention, usually due to worsening vision from tumor mass effect on the optic apparatus or the acute presentation of pituitary apoplexy causing rapid visual loss, testing for COVID-19 pre-operatively or performing surgery transcranially to allow access to the pituitary tumor for decompression of the optic apparatus could be considered. One might argue that the risk profile of a craniotomy is higher compared to that of a transsphe-
noidal approach (60); nevertheless, this risk to the neuro-
surgical team performing the surgery is less, a risk that
outweighs the individual risk to the patient. For patients
with functional adenomas such as Cushing disease and
acromegaly, medical therapy could be initiated to induce
biochemical remission, and surgery could be deferred until
this pandemic improves.

MANAGEMENT RECOMMENDATIONS

During this COVID-19 pandemic, proper methods
for infection control and prevention, supportive ther-
api es, and considerations of potential therapies relevant to
the pituitary disorder and any underlying comorbidities
should be undertaken. Optimizing weight management and
blood pressure control are key components, while impor-
tant cardiovascular disease management considerations
include anticoagulation and anti-arrhythmic manage-
ment, and hemodynamic support. For patients with DM,
onal management of hyperglycemia and other diabetic
complications is important to improve the prognosis and
reduce disease burden. If fever, cough, or breathlessness
develops, contacting the primary care physician or nurse
by telephone, e-mail, or telemedicine is mandatory in order
to seek medical guidance concerning measures to avoid the
risk of worsening glycemia and development of diabetic
ketoadidosis. Excess and prolonged systemic glucocorti-
coid exposure should be minimized, whereas for patients
who receive local glucocorticoid injections, consider total
glucocorticoid doses to be used and employ caution on the
frequency of injections. If fever is present, maintenance of
adequate hydration, especially for patients with DI and AI,
is recommended. Patients with AI in particular should moni-
tor themselves closely and implement “sick day rules” even
if symptoms are mild and initiate “stress dosing” promptly.
This should include adequate self-hydration and increas-
ing their glucocorticoid doses, especially if high fever is
present. If vomiting is present, injectable glucocorticoids
should be administered and prompt medical evaluation
and intravenous fluid resuscitation undertaken to prevent
dehydation. Patients should wear their Medic Alert brace-
let at all times and store sufficient glucocorticoid tablets
in order to sustain social isolation if they are well enough to
stay at home. For patients with Cushing disease and acro-
megaly, initial medical therapy may be considered as first-
line therapy to achieve disease control before surgery is
planned at a later date. For patients with acromegaly and
sleep-apnea syndrome using continuous positive airway
pressure (CPAP), continuing CPAP is recommended as the
benefits of treatment outweigh the risk, especially for
key workers, those with safety-critical jobs, and those
with increased workload during the pandemic. If a CPAP
user develops worsening symptoms or has asymptomatic
proven COVID-19, stopping CPAP is reasonable, and they
should seek medical attention early.

CONCLUSION

The complex interactions of COVID-19 and vari-
ous pituitary disorders places these patients at height-
ened risk of severe disease, ARDS, and premature death.
Pituitary patients are urged to request for COVID-19 test-
ing if exposed or repeat testing if prior result was nega-
tive if symptoms persist, utilize telemedicine services for
communication with healthcare providers, closely monitor
blood glucose levels, increase vigilance to symptoms of
AI, maintain healthy nutrition and daily exercise, adhere
to daily medications, and adapt to increased replacement
dosages if clinically indicated. If infected or suspected to be
infected with COVID-19, patients should practice general
preventive measures, such as adhering to social isolation to
prevent transmission to others at the same time monitoring
for clinical deterioration. Additionally, neuropsychiatric
monitoring should be undertaken to fully appreciate and
mitigate the long-term deleterious impacts of COVID-19
on brain and behavior. Ultimately, patients and healthcare
workers need to be vigilant and responsive to collectively
minimize the transmission of this virus and buy some time
for effective therapies to be developed.

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