

# Assessment of Adrenal Function in COVID-19

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## ABSTRACT

Adrenal insufficiency (AI) is a life-threatening but readily treatable condition. The prevalence of AI in coronavirus disease 2019 (COVID-19) is unknown. The objective of this article is to review data regarding AI in COVID-19. We performed a PubMed search in English, Spanish, and French until November 25, 2020. Search terms included AI, adrenal hemorrhage, adrenal infarction, COVID-19. We found only 4 case reports of new-onset AI possibly triggered by COVID-19. Two cases were due to bilateral adrenal hemorrhage, a third patient had pituitary apoplexy, and the fourth case presented with severe hyponatremia. A computed tomography series reported acute adrenal infarction as an incidental finding in 23% of 219 patients with severe and critical COVID-19. Autopsy studies have shown microscopic lesions in the adrenal glands of 46% of patients who died from severe COVID-19. No cases of AI were described after the withdrawal of dexamethasone (6 mg/d for up to 10 days) given to treat patients with COVID-19. We conclude that AI is uncommonly reported in patients with COVID-19 and is likely underdiagnosed. Most cases are due to hemorrhagic infarction of the adrenals or pituitary gland. Further studies are needed to evaluate adrenal function in patients with COVID-19.

**Key words:** Adrenal infarction, adrenal insufficiency, coagulopathy, coronavirus disease 2019, pituitary

## INTRODUCTION

Adrenal insufficiency (AI) is a treatable disorder that can be life-threatening if its diagnosis is missed.<sup>[1]</sup> Many symptoms and signs of AI may overlap with those of coronavirus disease 2019 (COVID-19) such as hypotension, diarrhea, vomiting, and hyponatremia.<sup>[1,2]</sup> Unfortunately, the status of adrenal function is unclear in COVID-19. In turn, in patients who already have AI, the prevalence of COVID-19 is unknown. In one Italian survey of 121 patients with AI ( $n = 40$  with primary AI, and  $n = 81$  with secondary AI), COVID-19 was reported in one patient with primary AI, that is, 0.8% prevalence.<sup>[3]</sup> The main purpose of this manuscript is to review all pertinent studies that evaluated AI among patients with COVID-19. These studies included case reports, imaging, and autopsy investigations.

## CASE REPORTS

Only 4 case reports were found in the literature that described new-onset AI in patients with COVID-19.<sup>[4-7]</sup> Overview of these reports is summarized in Table 1. In the first case Frankel *et al.*<sup>[4]</sup> from Israel reported a 66-year-old woman with a history of primary antiphospholipid syndrome (APLS) who was hospitalized for COVID-19. Her main symptoms included diffuse abdominal tenderness due to bilateral adrenal hemorrhage.<sup>[4]</sup> AI was confirmed by undetectable serum cortisol levels that failed to respond to stimulation by a synthetic adrenocorticotrophic hormone (ACTH).<sup>[4]</sup> The authors attributed this case of primary AI to adrenal hemorrhage due to thrombosis of adrenal veins caused both by APLS and COVID-19.<sup>[4]</sup> In the second report from France, Maria *et al.*<sup>[5]</sup> described another patient with primary APLS who also presented with abdominal pain in addition to diffuse thrombosis in the lower extremity. However, the

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authors did not report the method of biochemical confirmation of AI. Nevertheless, replacement glucocorticoid therapy was given to the patient.<sup>[5]</sup>

In the third report, Gravalos *et al.*<sup>[6]</sup> from Spain described the case of a 59-year-old man admitted to the hospital with COVID-19 and severe hyponatremia [Table 1]. Work-up of hyponatremia revealed secondary AI due to pituitary apoplexy, a form of hemorrhagic infarction in a pituitary tumor.<sup>[5]</sup> In the fourth case, Heiderpour *et al.*<sup>[7]</sup> from Iran reported a 69-year-old man with COVID-19 admitted with COVID-19 pneumonia and refractory hypotension. The authors diagnosed acute AI based on the assumption that serum cortisol levels, although within normal limits, were inappropriate in the face of the stress of COVID-19 pneumonia.<sup>[7]</sup>

Taken together, these 4 reports suggest that new-onset AI may occur in the setting of COVID-19. Although the underlying mechanisms are unclear, it is possible that the coagulopathy that characterizes COVID-19 could have triggered adrenal vein thrombosis,<sup>[4,5]</sup> or pituitary apoplexy.<sup>[5]</sup> Thus, AI appears to be an uncommon complication of COVID-19, but it manifests itself in the presence of a predisposing factor, such as pre-existing APLS or pituitary adenoma.<sup>[4-6]</sup> Meanwhile,

the case of AI reported by Heiderpour *et al.*<sup>[7]</sup> suggests that refractory hypotension may occur in association with severe COVID-19, similar to other causes of severe sepsis. Indeed, the short-term clinical course of the 4 patients described above responded favorably to hydrocortisone therapy and no one died [Table 1].

### Imaging studies

Leyendecker *et al.*<sup>[8]</sup> evaluated the frequency of acute adrenal infarction by unenhanced computed tomography (CT) of chest performed in 219 French patients with severe and critical COVID-19. The authors found that 51 of the 219 (23%) of patients had CT signs of acute adrenal infarction on their initial chest CT, and in 45 of these 51 patients (88%), the adrenal infarction was bilateral.<sup>[8]</sup> In addition, the authors mentioned that 4 patients with bilateral adrenal infarction had “biological” AI defined as a triad of hyperkalemia (>5 mmol/L), hyponatremia (<130 mmol/L) and hypoglycemia (<3.9 mmol/L).<sup>[8]</sup> Moreover, rates of intensive care unit (ICU) admissions were significantly greater in patients with adrenal infarction compared with those without infarction, 67% and 45%, respectively ( $P < 0.05$ ).<sup>[8]</sup> Yet, mortality rates were similar, 27% in each group of patients.<sup>[8]</sup> These data suggest that a common finding in severe and critical cases of COVID-19 is adrenal infarction. The latter may be related to

**Table 1: Studies reporting new-onset adrenal insufficiency (AI) in patients with COVID-19**

Reference	Frankel <i>et al.</i> <sup>[4]</sup>	Gravalos <i>et al.</i> <sup>[6]</sup>	Heiderpour <i>et al.</i> <sup>[7]</sup>	Maria <i>et al.</i> <sup>[5]</sup>
Patient age/sex	66-year-old F	59-year-old M	69-year-old M	48-year-old man
Main symptom	Diffuse abdominal pain	Vomiting, abdominal pain, confusion	Refractory hypotension	Sudden abdominal pain, thrombosis of dorsalis pedis artery
Lowest serum sodium levels	129 mEq/L (135–145)	102 mEq/L (135–145)	135 mEq/L (normal range not reported)	Not reported
Serum cortisol	<1µg/dl (normal range not reported)	3.1 µg/dl (4.8–19.5)	12 µg/dl (normal range not reported)	Not reported
ACTH	207 pmol/L (1.6–13.9)	4.6 pg/ml (7–60)	Not reported	Not reported
Imaging	CT suggested bilateral adrenal hemorrhage	MRI of sella turcica showed pituitary apoplexy in a macroadenoma	Not done	CT showed bilateral adrenal hemorrhage
Treatment of AI	IV hydrocortisone (dose not reported) followed by prednisone 10 mg/d + fludrocortisone 0.1 mg/d	Hypertonic saline (3%) IV. Hydrocortisone 100 mg IV q12, then 100 mg infusion over 24 h	IV hydrocortisone 100 mg followed by 1 mg/h. Maintenance 10 mg prednisolone orally qday	Not detailed “substitutive therapy for adrenal function”
Outcome	Discharge after 11 days	Had transsphenoidal decompression of apoplexy	After 53 days, patient's condition was “good” on supplemental oxygen	Discharge after 27 days
Comments	Patient had history of primary anti-phospholipid syndrome	Long-term outcome was not mentioned	Long-term outcome was not mentioned	Patient had history of primary anti-phospholipid syndrome

F: Female, M: Male, ACTH: Adrenocorticotropic hormone, CT: Computed tomography, MRI: Magnetic resonance imaging, IV: Intravenous

COVID-19 coagulopathy.<sup>[9,10]</sup> Meanwhile, the observation by Leyendecker *et al.*<sup>[8]</sup> that only a minority of patients (4 of 219, or 1.8%) exhibit the laboratory abnormalities characteristic of AI suggest that many cases of AI associated with severe COVID-19 are either subclinical and/or underdiagnosed.

### Autopsy studies

In 28 patients who died from severe COVID-19, Santana *et al.*<sup>[11]</sup> showed that 12 patients (43%) had adrenal lesions. The most common observed lesions were necrosis found in 7 cases, followed by cortical lipid degeneration and adrenal hemorrhage, whereas vascular thrombosis was seen in one patient.<sup>[11]</sup> The authors attributed these pathological lesions to COVID-19.<sup>[11]</sup> Interestingly, there was no biochemical evidence of AI before death as serum cortisol levels measured 24–48 h before death were appropriate for the levels of patients' stress.<sup>[11]</sup> In another smaller autopsy study of 5 patients who died from COVID-19, Iuga *et al.*<sup>[12]</sup> reported acute fibrinoid necrosis of small vessels of adrenal glands. No significant inflammation, infarcts, or thrombi were appreciated.<sup>[12]</sup> Interestingly, in the previous 2 autopsy studies, the causative virus of COVID-19, that is, the severe acute respiratory syndrome coronavirus 2, was not isolated from any autopsy specimen.<sup>[11,12]</sup>

### Effect of glucocorticoid therapy on adrenal function in COVID-19

In the RECOVERY trial conducted in the UK, the investigators randomized hospitalized patients with COVID-19 into two groups in a 2:1 ratio; the larger group ( $n = 4,321$ ) received usual care while the smaller group ( $n = 2,104$ ) received usual care plus low-dose dexamethasone 6 mg/d orally or intravenously for up to 10 days in an open-label fashion.<sup>[13]</sup> Significantly fewer patients assigned to dexamethasone reached the primary outcome of 28-day mortality compared with usual care, 21.6% and 24.8%, respectively; relative risk 0.83; 95% CI 0.74–0.92 ( $P < 0.001$ ).<sup>[13]</sup> The RECOVERY dexamethasone protocol is currently followed throughout the world and was supported by the World Health Organization.<sup>[14]</sup> It is unknown whether dexamethasone doses and duration in the RECOVERY trial can cause secondary (iatrogenic) AI by suppression of the hypothalamic-pituitary-adrenal axis.<sup>[1]</sup> To the authors' best knowledge, no cases of AI or adrenal crises were reported following the termination of this dexamethasone course in patients with COVID-19. The latter observation is likely due to the relatively small dose (6 mg/d) and short-duration (<10 days) of dexamethasone treatment in the RECOVERY trial. However, it is wise to be aware of the possibility of the development of AI or crisis in the weeks following the withdrawal of dexamethasone. Thus, if any symptoms or signs of AI occur during this time frame (e.g., unexplained hypotension, vomiting, abdominal pain, diarrhea, and new-onset hyponatremia), the authors suggest drawing serum cortisol or performing the cosyntropin (synthetic ACTH)

stimulation test and start empiric glucocorticoids (e.g., 100 mg hydrocortisone intravenously) pending the results of cortisol and cosyntropin stimulation test.

## CONCLUSIONS AND CURRENT NEEDS

No doubt, our knowledge about AI in COVID-19 is still in its stage of infancy. Available data suggest that AI is rarely documented in patients with COVID-19 admitted to the hospital and is likely underreported. Three of 4 cases of AI reported have underlying pathology that predisposes patients with COVID-19 to develop AI, namely APLS or a pituitary tumor.<sup>[4-6]</sup> However, imaging and autopsy investigations suggest that adrenal infarction and pathologic involvements of adrenals are not uncommon in patients with severe COVID-19.<sup>[8,11,12]</sup> A prospective study is underway to examine the impact of COVID-19 on adrenal function by measuring serum levels of cortisol and ACTH in patients with severe COVID-19.<sup>[15]</sup> The results of this study should clarify the prevalence of adrenal dysfunction in patients with severe COVID-19. In the meantime, physicians should be aware of the symptoms and signs of AI and adrenal crisis that may be obscured by those of COVID-19.

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