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RESEARCH LETTER

Is there a link between COVID-19 and adrenal insufficiency?

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Abbreviations

ACE2	Angiotensin-converting enzyme 2
ACTH	Adrenocorticotropic hormone
AI	Adrenal insufficiency
COVID-19	Coronavirus disease 2019
ICU	Intensive care unit
SARS-CoV-1	Severe acute respiratory syndrome coronavirus 1
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, which can result in coronavirus disease 2019 (COVID-19), has caused an unprecedented global pandemic. The epicenter of that pandemic in Latin America was Brazil, where more than 670,000 deaths have been attributed to COVID-19 [1]. The receptor-binding domain of the SARS-CoV-2 spike protein uses host angiotensin-converting enzyme 2 (ACE2) as the receptor for membrane fusion, thus potentially disrupting hypothalamic expression of ACE2. Anti-SARS-CoV-2 antibodies might interfere with circulating adrenocorticotropic hormone (ACTH), which could blunt the stress-induced cortisol response [2].

In this research letter, we describe 13 patients with COVID-19–associated renal failure who, despite undergoing dialysis in the intensive care unit (ICU), presented persistent hyperkalemia, hyponatremia, or both. We hypothesized that these patients, while in the ICU and on dialysis, could have had adrenal insufficiency in addition to acute kidney injury.

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The patients were admitted to a tertiary hospital in the Brazilian cities of São Paulo and Goiânia, respectively, between April 1 and August 16, 2020. Twelve of the patients were dialysis dependent and treated with continuous venovenous hemodiafiltration or continuous venovenous hemodialysis, at 35 mL/kg/h, and presented persistent hyperkalemia, hyponatremia, or both, despite > 48 h of hemodialysis and clinical measures. There was no rhabdomyolysis or severe acidosis to explain the hyperkalemia. Ten of the patients were male. The median age was 69 years (Q1-Q3: 65–73 years), and the median ICU stay was 26 days (Q1-Q3: 19–40 days). Six patients had diabetes, 10 had hypertension, 4 class III obesity, and one had a history of cancer. Eleven patients required mechanical ventilation and vasopressor support. Two patients were on chronic dialysis. Among the patients evaluated, the ICU mortality rate was 76.9%. Additional clinical and biochemical data are reported in Table 1. Unfortunately, we were not able to collect all of the hormonal results to make a clear diagnosis of AI. However, after the suspicion of AI had been raised, all of the patients received glucocorticoid therapy, which normalized serum electrolytes and bicarbonate, while the same dialysis dose was maintained.

Cortisol deficiency can be difficult to diagnose in ICU patients because the clinical indicators are frequently nonspecific [3]. In ICU patients with cortisol deficiency who are on dialysis, findings such as hyperkalemia and hyponatremia can be misleading [4]. However, the persistence of such disturbances after initiation of efficient dialysis treatment should raise the suspicion of cortisol deficiency [5], as in the cases reported here [5]. Our hypothesis that SARS-CoV-2 can induce adrenal insufficiency is supported by the findings of many other studies. In one recent systematic review [6], the authors summarized data on the occurrence of adrenal insufficiency in patients with COVID-19. Among the included studies, the reported prevalence of adrenal insufficiency ranged from 3.1% to 64.3%, suggesting that adrenal insufficiency is quite common in patients with COVID-19. In an autopsy study of adrenal pathology in COVID-19 [7],

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Table 1 Demographic, clinical, and serum biochemical characteristics of patients admitted to the intensive care unit with severe coronavirus disease 2019[a] and treated with glucocorticoids

Patient	Age	Sex	SAPS 2	Cr[b]	Urea[b]	Minimum Na	Maximum K	Pre-treatment			Post-treatment		
								DHEA	Cortisol	Ald	Average K	Average Na	Urea
	(years)			(mg/dL)	(mg/dL)	(mEq/L)	(mEq/L)	(ng/mL)	(μg/dL)	(ng/dL)	(mEq/L)	(mEq/L)	(mg/dL)
1	70	M	88	13.48	332	134	7.4	ND	ND	ND	3.4	155	98
2	69	M	89	11.12	228	133	7.0	ND	ND	ND	3.9	146	50
3	65	M	71	10.52	145	127	7.9	ND	25.8	21.4	3.4	136	38
4	60	F	82	6.5	298	130	7.3	ND	ND	ND	4.1	138	100
5	65	M	80	4.63	99	127	7.5	ND	ND	ND	3.5	143	83
6	73	M	75	5.16	131	131	6.0	151	28.4	7.9	3.3	150	48
7	68	M	80	3.29	229	133	7.8	ND	ND	ND	3.7	145	86
8	76	M	49	0.92	314	132	6.8	ND	ND	ND	3	145	48
9	59	M	82	10.92	158	130	7.6	365	33	40.5	4	147	92
10	66	F	ND	3.2	134	128	6.7	93	12.1	15.5	3.6	141	67
11	73	M	93	1.88	113	132	6.3	ND	ND	7.8	3.9	144	88
12	76	F	79	0.8	26	126	7.3	ND	30.5	41.5	3.3	148	20
13	78	M	59	2.5	78	130	7.1	ND	14.8	ND	4.2	140	30

SAPS 2 Simplified Acute Physiology Score 2, *Cr* creatinine, *DHEA* dehydroepiandrosterone, *Ald* aldosterone, *ND* no data

[a]All of the patients tested positive for infection with severe acute respiratory syndrome coronavirus 2, on high-throughput sequencing real-time reverse transcriptase–polymerase chain reaction assay of nasal-pharyngeal/tracheal swab specimens or on an antibody test

[b]At admission

seven cases showed necrosis, which was mostly ischemic. Four of those cases showed cortical lipid degeneration, whereas two showed hemorrhage and one nonspecific focal adrenalitis. Focal inflammation was observed in combination with other findings in three patients, whereas vascular thrombosis was seen in one. In that same study, plasma samples collected 1 or 2 days before death were sent for cortisol measurement and none were found to have a cortisol level < 10 μg/dL. In another autopsy study evaluating adrenal vascular changes in patients who died from COVID-19 [8], the authors demonstrated acute fibrinoid necrosis of small vessels, mainly arterioles, in the adrenal parenchyma, adrenal capsule, and immediately adjacent periadrenal adipose tissue. They also detected subendothelial vacuolization and apoptotic debris. The vascular involvement was disproportionately conspicuous in the adrenal gland (i.e., not as evident in the other organs examined). The authors stated that it was unclear whether the adrenal vascular involvement was attributable to hypoxia, abnormal vascular reaction/blood flow patterns, a direct viral cytopathic effect, immune-mediated injury, or a combination of such factors.

Furthermore, in a very elegant autopsy study, Paul et al. [9] demonstrated inflammation, accompanied by inflammatory cell death, in the adrenal glands of patients who died with severe COVID-19. Histopathologic analysis revealed widespread microthrombosis and severe adrenal injury. The authors suggested that SARS-CoV-2 infection favors the onset of adrenalitis. They called attention to the fact that, given the central role of the adrenal glands in immunoregulation and the significant adrenal injury observed, it is important to screen for adrenal insufficiency during acute SARS-CoV-2 infection and during recovery. One unique finding of their study was the detection of the SARS-CoV-2 spike protein by immunohistochemistry in the adrenal cortical cells of all 19 study patients. Viral tropism for adrenal cells was further validated by in situ hybridization. The authors were also able to identify SARS-CoV-2 spike protein RNA in the adrenal cortex.

In summary, our clinical series, within the limits of lack of in-depth studies, further stresses that adrenal insufficiency should be considered in all patients with COVID-19 who present hyponatremia or hyperkalemia of no known cause, and that this possibly overlooked complication should be kept in mind also in patients treated with hemodialysis.

Declarations

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Authors' contributions All of the authors were involved in the writing, preparation, critical revision, and final approval of the manuscript.

Ethics approval and consent to participate Written informed consent was obtained from the patient for publication of this case report. The study was approved by the Institutional Ethics Board of the University of São Paulo School of Medicine *Hospital das Clínicas* (Reference no. 4.129.320).

Conflict of interest The authors declare that they have no competing interests.

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