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LETTER

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Letter to the editor of clinical endocrinology: Assessment of adrenal function in patients who survive COVID-19

It is widely recognised that the effects of COVID-19 extend beyond the respiratory system. Moreover, there are an estimated 1.3 million people living with long COVID (symptoms persisting beyond 12 weeks after infection) in the United Kingdom alone,[1] with one study finding that 57% of patients with COVID-19 experienced at least one symptom of long COVID in the 6 months following infection.[2] Current endeavours are therefore focused on understanding the pathophysiology of persistent symptoms after acute COVID-19, with a view to informing the development of novel therapeutics.

A recent article by Kanczkowski and colleagues[3] sought to determine whether there was any histological evidence of adrenal damage present in patients with COVID-19. This is particularly pertinent given that both ACE2 receptors and transmembrane serine protease 2 (TMPRSS; the permissive protein for cellular entry) have been identified in the adrenal microvasculature and the adrenal cortex itself,[4] providing biological plausibility for the ability of SARS-CoV-2 to both gain cellular access and cause adrenocortical dysfunction.

Using autopsy samples from 40 patients who had died from COVID-19, the authors observed small vessel vasculitis and perivascular lymphoplasmacellular infiltration within the periadrenal fat tissue and adrenal parenchyma, but did not observe extensive degradation of adrenocortical cells. Additionally, using a monoclonal antibody, they identified the SARS-CoV-2 spike protein in adrenocortical cells of 45% of adrenal gland tissues, and using multiplex reverse-transcription quantitative polymerase chain reaction (RT-qPCR) confirmed SARS-CoV-2 expression in 15 out of 30 adrenal gland tissues of patients with COVID-19.

These data confirm the presence of SARS-CoV-2 within the adrenal glands and hence raise the question of hypoadrenalism in patients with COVID-19.

Indeed, several case reports exist of adrenal insufficiency in patients diagnosed with acute COVID-19. Typically, adrenal haemorrhage was observed in patients with no known underlying adrenal lesions.[5–7] Adrenal insufficiency secondary to adrenal infarct has also been reported, although this predominantly occurred in patients with underlying antiphospholipid syndrome, predisposing patients to thrombotic events.[8,9]

However, as the authors suggest, although these findings confirm histopathological evidence of the presence of the SARS-CoV-2 virus within the adrenal cortex in patients who died of COVID-19, the question remains regarding whether or not adrenocortical dysfunction contributes to the symptoms of long COVID in patients who survive the disease.

We have recently published data from 70 survivors of COVID-19, whereby adrenal function was comprehensively assessed using the gold-standard 'Short Synacthen test'.[10] Briefly, patients aged ≥18 years with a diagnosis of COVID-19, confirmed using either real-time RT-PCR testing of nasopharyngeal swab, confirmatory imaging (chest radiograph or computed tomography scan) or positive serum SARS-CoV-2 immunoglobulin G antibody test taken after symptom onset were eligible for inclusion. Participants were invited to attend for a research study visit at ≥3 months following initial presentation and underwent clinical assessment, including screening for persistent symptoms and a physical examination. A cannula was subsequently inserted, and serum samples were taken including for cortisol, renin, aldosterone and dihydroepiandrosterone (DHEAS). Following this, 250 μg tetracosactide (Synacthen) was administered intravenously, and further serum samples were taken at 30 and 60 min for measurement of cortisol.

Adequate response to Synacthen was determined by either reaching a peak cortisol value of ≥450 nmol/L and increment by ≥150 nmol/L from baseline, either at 30 or 60 min after Synacthen.[11,12]

Serum renin, aldosterone and DHEAS were measured using high-performance liquid chromatograph mass spectrometry (HPLC-MS/MS). Lower limits of quantification were as follows: renin 0.6 nmol/L, aldosterone 60 pmol/L, DHEAS 0.41 μmol/L. Interassay coefficients of variation were as follows: renin <10%, aldosterone <15%, DHEAS <10%.

Age-specific reference ranges for DHEAS were as follows: age 20–39 years 0.7–11.5 μmol/L, 40–59 years 0.8–6.9 μmol/L, over 60 years 0.4–4.7 μmol/L. Serum cortisol was measured using Abbott Alinity ci-series analyser, using chemiluminescent mircoparticle immunoassays. The lower limit of detection was 19.3 nmol/L, interassay coefficient of variation was ≤5.1%, intra-assay coefficient of variation was ≤4.3%.

Regardless of disease severity or treatment received, all participants had an appropriate response to 250 mcg Tetracosactide, consistent with adequate adrenal reserve. Furthermore, although 44 patients (62.8%) had persistent fatigue at ≥3 months' postpresentation, neither peak cortisol achieved following stimulation, nor baseline cortisol differed between survivors with fatigue compared to those without.[10] Additionally, unpublished data from this cohort of the 69 patients with measurement of postural blood pressure revealed that only two patients (2.9%) had an asymptomatic postural drop of ≥20 mmHg, with normal peak cortisol values of 593 and 608 nmol/L after Synacthen 250 mcg.

For those who had DHEAS measured ($n = 68$), 4.4% ($n = 3$) had values below the age-specific reference range. All patients had a

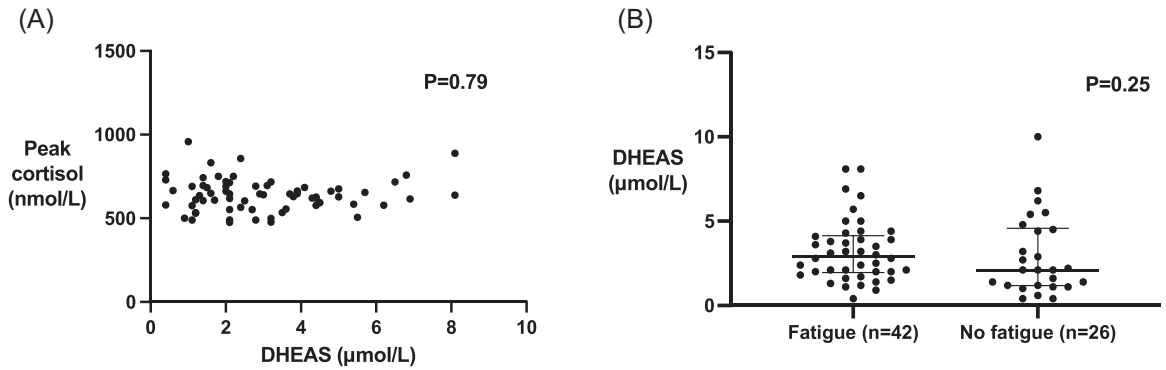

FIGURE 1 Dihydroepiandrosterone (DHEAS) and peak cortisol levels following administration of Synacthen (Tetracosactide) 250 µg in survivors of COVID-19 ≥3 months after initial presentation. (A) Individual peak cortisol (nmol/L) levels and baseline DHEAS values (µmol/L) following administration of Synacthen (tetracosactide) 250 µg are presented for patients for whom data is available ($n = 68$). (B) Individual DHEAS values are presented for those patients with persistent fatigue ≥3 months after initial presentation with COVID-19 ($n = 42$) and those without persistent fatigue ($n = 26$).

satisfactory cortisol response to Synacthen, with a mean baseline cortisol of 94, 288 and 304 nmol/L and a peak cortisol of 507, 572 and 608nmol/L. Peak cortisol response following Synacthen was not significantly different in those with DHEAS values within the age- and sex-specific reference range nor those with DHEAS values below the age- and sex-specific reference range ($p = .12$). Additionally, peak cortisol level was not related to basal DHEAS values ($p = .79$) (Figure 1A). DHEAS was not significantly different between those patients who were fully recovered, and those with persistent fatigue ($p = .25$) (Figure 1B). In our cohort, 13 (21.7%) of 60 patients who had aldosterone measured, had aldosterone levels below the lower limit of the reference range, albeit none had elevated renin values.

Our findings are similar to those from other groups. In data presented at the British Endocrine Society meeting in 2021, Eltayeb and colleagues observed that although 30% (18/60) of patients treated dexamethasone for acute Covid-19 had evidence of adrenal insufficiency after initially stopping dexamethasone, the majority of patients had recovered by 4 weeks, suggesting that any early adrenal insufficiency observed was likely related to steroid treatment, rather than COVID-19 per se.[13]

In summary, despite recent histopathological evidence of the presence of SARS-CoV-2 within the adrenal glands, there is no evidence to date that, in patients who survive COVID-19, adrenocortical or mineralocorticoid function is persistently affected, even in those patients with ongoing fatigue at ≥3 months after presentation. Given that long COVID is a complex, multi-system disorder, that remains little understood, larger long-term studies comparing patients diagnosed with COVID-19 and persistent symptoms, to those without, as well as healthy controls, might provide interesting insights into the prevalence of subtle perturbations in adrenal function.

KEYWORDS
adrenal cortex hormones, adrenal insufficiency, COVID-19, mineralocorticoids

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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