



Is there a role for the adrenal glands in long COVID?

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The symptoms of long COVID and chronic adrenal insufficiency have striking similarities. Therefore, we aim to raise awareness of assessing adrenal function in patients with long COVID.

After the acute phase of SARS-CoV-2 infection, roughly 20% of patients report one or more complications, which are particularly apparent during mental or physical stress. These complications include extreme chronic fatigue, shortness of breath, sleep abnormalities, headache, brain fog, joint pains, nausea, cough and abdominal pain. When symptoms persist for more than four weeks after initial infection and cannot be attributed to other known diseases, they are described as long COVID¹. When comparing the clinical presentation of long COVID and chronic adrenal insufficiency, overlap between the conditions can be seen, suggesting that long COVID might be related to some form of adrenal dysfunction². Here we discuss the role of the adrenal glands in long COVID.

Is SARS-CoV-2 targeting adrenal cells?

Bacterial and viral tropism to adrenal glands is quite common, and certain infections can cause adrenal damage². Adrenal insufficiency is frequently found in patients with meningococcal sepsis, tuberculous adrenalitis and opportunistic viral infections. These infections are associated with an increased risk of bilateral adrenal gland haemorrhages and inflammation orchestrated by infiltrating immune cells. In addition, several pathogen-derived toxins might directly affect adrenocortical cell function through binding to toll-like receptors expressed by those cells. Moreover, adrenocortical cells might undergo programmed apoptotic or necrotic cell death as a consequence of intracellular viral replication².

To be a target of SARS-CoV-2, cells must express angiotensin-converting enzyme 2, which enables direct binding of virus spike protein to the cell surface. Susceptible cells also need to express co-receptors required for virus internalization, such as transmembrane protease serine 2 or furins. Several reports, including our own, have confirmed the expression of these receptors in the adrenal gland^{3,4}. Moreover, these reports provided evidence that SARS-CoV-2 might not only target human adrenocortical cells^{3,4}, but might also actively replicate in these cells⁴. For example, SARS-CoV-2 RNA and protein were detected in 45% of adrenal glands

obtained from patients who died due to a critical course of COVID-19 infection³. Interestingly, SARS-CoV-2 was also detected in adrenal endothelial cells⁴. However, no proof of an active replication could be found, indicating that SARS-CoV-2 is passively transmitted through the adrenal vascular system⁴. In addition, SARS-CoV-2 infection was associated with increased inflammation and activation of programmed cell death pathways in human adrenocortical cells^{3,4}.

Histopathological analysis of adrenal glands revealed frequent (in 90% of patients) lymphocytic infiltration and pronounced inflammation of adrenal vessels (endotheliitis) in adrenal parenchyma and in the periadrenal adipose tissue³. However, histological studies did not find extensive degeneration of the adrenocortical cells that might have led to complete functional adrenal insufficiency. Therefore, there is no proof that the high vulnerability of adrenals to viral infection will necessarily lead to the manifestation of clinically relevant adrenal insufficiency.

COVID-19 and adrenal insufficiency

COVID-19 is widely recognized as a vascular disease; around 30% of patients with COVID-19 develop venous thromboembolic coagulopathy⁵. Although cellular damage due to SARS-CoV-2 infections might not lead to adrenal insufficiency, COVID-19 associated haemorrhages and infarctions might. Interestingly, histopathological studies analysing tissues obtained from autopsies of patients with COVID-19 found fibrin and microthrombi deposition in adrenal capillaries⁴. The ample vascularization and blood flow in the adrenals illustrate the susceptibility of the adrenal glands to vascular damage. In fact, the adrenal glands can receive nearly ten times the amount of blood flow as would be expected from their size². Accordingly, unilateral and bilateral acute adrenal gland infarctions are frequent findings during routine computer tomographic examinations of patients with COVID-19 and suspected severe pneumonia⁶.

There are at least 12 case studies and nine prospective case series in the literature describing adrenal insufficiency related to COVID-19. These studies reported

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that adrenal haemorrhages and infarctions might not only occur in severe cases of COVID-19, but also in mild ones⁷. Furthermore, pre-existing adrenal disease or Addison disease can be exacerbated by SARS-CoV-2 infection. In conclusion, adrenal vascular damage triggered by COVID-19 might develop as a complication, predisposing the patient to adrenal insufficiency, with potential life-threatening consequences.

COVID-19 might predispose patients to reversible dysfunction of the adrenal glands, known as critical illness-related corticosteroid insufficiency (CIRCI). In CIRCI, glucocorticoid actions are insufficient to control cellular inflammation. Multiple factors could contribute to the development of CIRCI in patients with COVID-19, including dysregulation of the hypothalamic–pituitary–adrenal axis, reduced cortisol metabolism or glucocorticoid receptor alpha tissue resistance. Based on morning cortisol levels (<10 µg/dl) or a cortisol increase in response to adrenocorticotrophic hormone (ACTH) stimulation (<9 µg/dl), the frequency of CIRCI among patients with mild or severe COVID-19 was found to be 4.4–32.0%⁸. Although the majority of studies reported adequate adrenal cortisol levels in patients with acute COVID-19, adrenal gland insufficiency cannot be excluded, particularly because the manifestation of adrenal insufficiency might be either delayed or masked by decreased cortisol metabolism.

Consequently, adrenal insufficiency might develop several weeks after an acute phase of COVID-19. Late-onset of adrenal gland insufficiency in patients who recovered from SARS-CoV-2 infection could be a direct consequence of persisting dysregulation of the hypothalamic–pituitary–adrenal axis, reactivation of latent viral infections, such as cytomegalovirus, or an autoimmune response against key factors involved in the regulation of adrenocortical cell function. In line with this hypothesis, it has been suggested that there is a high molecular similarity between SARS-CoV-2 peptides and human adrenocorticotrophic hormone. Although there is currently not enough clinical evidence supporting this claim, high titers of anti-ACTH antibodies were found in patients with long COVID, indicating a potential pathophysiological mechanism for an adrenocorticotrophic impairment related to infections with COVID-19 (REF.⁹). Furthermore, secondary adrenal gland insufficiency following treatment of COVID-19 with high doses of glucocorticoids (dexamethasone) should be considered.

Ruling out adrenal gland dysfunction

Initial reports did not suggest notable adrenal gland dysfunction in patients with long COVID. In fact, a normal adrenal gland response to the ACTH test was found in patients who recovered from COVID-19 and had been treated with moderate doses of dexamethasone (6 mg daily for ten days)¹⁰. However, mild adrenal gland insufficiency might have not been detected because high doses of an ACTH mimic (250 µg of

synacthen), which are commonly used for ACTH tests, cannot exclude subclinical forms of adrenal dysregulation. Moreover, from our own clinical experience with a large number of patients with COVID-19 (>2,000), up to 30% of patients who have recovered from COVID-19 might have received extended glucocorticoid treatment for 6 weeks or longer. This extensive use of steroids will result in secondary adrenal gland insufficiency in most patients. As the ACTH test is inferior to the corticotropin-releasing hormone test as a diagnostic tool for the detection of secondary adrenal insufficiency, these patients should receive stimulation with corticotropin-releasing hormone to rule out secondary adrenal insufficiency. Particularly in patients for whom glucocorticoid therapy was not properly tapered off after dismissal from tertiary and secondary clinics into primary care. In our clinic, we have seen many patients displaying symptoms resembling those of long COVID for whom the symptoms were temporary and were actually induced by abrupt termination of long-term use of glucocorticoids.

Taken together, adrenal gland insufficiency in patients with COVID-19 might be induced through different mechanisms, including vascular damage, viral replication, inflammatory factors and improper tapering off of long-term steroid replacement. Further studies are needed to define the role of the adrenal gland in long COVID and the potential benefit of low dose glucocorticoid replacement.

In conclusion, SARS-CoV-2 targets the adrenal gland and can cause adrenal insufficiency in some patients. Furthermore, numerous patients with COVID-19 have received glucocorticoid treatment over an extended period of time, therefore we believe that adrenal gland insufficiency needs to be considered and carefully ruled out in all patients with COVID-19 and long COVID.

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Competing interests

The authors declare no competing interests.