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LETTER TO THE EDITOR

COVID-19, hypothalamo-pituitary-adrenal axis and clinical implications

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A novel coronavirus disease (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has affected over 1,000,000 individuals, claiming more than 56,000 lives in over 200 countries worldwide ever since its mysterious outbreak in Wuhan, China in December 2019. The largest case series from China had shown that majority of the patients belonged to the age group of 30–79 years. Most of the cases were mild (81%), while 14% cases were severe and only 5% critical. The overall case-fatality rate was 2.3% [1]. SARS-CoV-2 primarily affects the lungs, resulting in viral pneumonia often complicated by acute respiratory distress syndrome and sepsis. The virus is able to evade the host immune system by avoiding detection of their dsRNA and by inhibiting the host interferon-I pathway [2]. The pathogen enters the pneumocyte using the host angiotensin-converting enzyme 2 (ACE2) as a receptor. In addition, the enzyme is expressed on the arterial and venous endothelial cells of many organs including the adrenal glands. Autopsy studies on patients who died from SARS (the original outbreak in 2003) had shown degeneration and necrosis of the adrenal cortical cells. The SARS-CoV (the 'cousin' of SARS-CoV-2) was in fact identified in the adrenal glands, hinting towards a direct cytopathic effect of the virus. Hence it is likely that cortisol dynamics may be altered in patients with SARS (and COVID-19). However, the literature is scarce is this regard.

One of the primary immunoinvasive strategy employed by the SARS-CoV, like influenza virus, is to knock down the host's cortisol stress response. To achieve the same, SARS-CoV expresses certain amino acid sequences that act as molecular mimics of the host adrenocorticotropic hormone (ACTH). The first 24 amino acids of ATCH ($ACTH_{1\text{-}24}$) are highly conserved between different mammalian species while $ACTH_{25\text{-}39}$ represents the less conserved region. Six amino acids at position 26, 29, 31, 33, 37, and 39 represent the antigenically important positions for mammalian ACTH. SARS (and influenza virus) contain many permutations of amino acid sequences with homology to these probable ACTH key residues. Antibodies produced by the host to counteract the virus, in turn, would unknowingly destroy the host ACTH, thereby blunting the cortisol rise. This would imply that all patients with SARS might have had underlying relative cortisol insufficiency [3]. However, data on serum cortisol levels in patients with SARS (or COVID-19) are unavailable till date.

SARS (and COVID-19) might affect the hypothalamic-pituitary-adrenal (HPA) axis as well. Biochemical evidence of HPA axis involvement in SARS was first reported by Leow *et al*. Sixty-one survivors of the SARS outbreak were evaluated at 3 months after recovery and periodically thereafter. Forty percent of patients had evidence of central hypocortisolism, majority of which resolved within a year. A small percentage of patients also had central hypothyroidism and low dehydroepiandrosterone sulfate. The authors had proposed the possibility of a reversible hypophysitis or a direct hypothalamic damage that could have led to a state of transient hypothalamo-pituitary dysfunction [4]. Infact, edema, and neuronal degeneration along with SARS-CoV genome have been identified in the hypothalamus on autopsy studies. Hypothalamic and pituitary tissues do express ACE2 and can therefore be viral targets. The portal of entry of the virus into the hypothalamus-pituitary could be either directly thorough the cribriform plate via hematogenous route. Nevertheless, frank hypocortisolism has never been documented in patients with active SARS (or COVID-19). A prospective study evaluating serum cortisol and ACTH

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in patients with severe COVID-19 is presently underway (ChiCTR20000301150).

Irrespective of serum cortisol levels, glucocorticoids have been used in patients with critical illnesses including SARS. Glucocorticoids are also being used in patients with COVID-19, although the current interim guidance from the WHO (released Jan 28, 2020) advises against its routine use. Its use in COVID-19 is based on the premise that the virus is able to elicit a *cytokine storm* in the host that can be averted by the use of glucocorticoids. Glucocorticoids have been used in the treatment of other viral infections, notably, respiratory syncytial virus, influenza, and Middle East Respiratory Coronavirus, however, no clinical data exist to indicate any net benefit [5]. Benefits of glucocorticoids have been documented in patients with septic shock; shock in patients with COVID-19, although seen in about 5% of the cases, is often a result of increased intrathoracic pressure (due to invasive ventilation) that impedes cardiac filling. Thus, in the absence of septic shock, use of glucocorticoids in COVID-19 is debatable. A clinical trial on efficacy and safety of corticosteroids in COVID-19 is currently underway (NCT04273321).

A report by Panesar et al. in patients with SARS had shown that lymphopenia, seen in about half of the patients, was related to prevailing serum cortisol levels. Patients with lymphopenia had higher serum cortisol and than those without lymphopenia. Similar data in patients with COVID-19 is lacking as of now. However, absence of lymphopenia in patients with COVID-19 could be used a marker of hypocortisolism (absolute or relative) and a low threshold could be kept for initiating glucocorticoid therapy in the presence of shock or acute respiratory distress syndrome. Nevertheless, people with known adrenal insufficiency should follow sick-day guidelines and in general, should double the dose of glucocorticoids in times of acute illness. In addition, individuals with adrenal insufficiency have an increased rate of respiratory infection-related deaths, possibly due to impaired immune function and hence need to take extra precautions amid the ongoing COVID-19 pandemic [6].

Compliance with ethical standards

Conflict of interest The author declare that he has no conflict of interest.

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