COVID-19 and Endocrine Disorders – Emerging Links in this Puzzle

The COVID-19 pandemic is well into its second year of existence and our knowledge about this novel infection has increased substantially in this period. The causative agent of COVID-19, the SARS CoV-2, has demonstrated that it is capable of involving multiple organ systems rather than being just a respiratory pathogen. The link with endocrine disorders was noticed quite early when it was found that patients with diabetes and uncontrolled hyperglycemia were at an increased risk of severe disease as well as mortality from COVID-19.[1] However, the other endocrine manifestations of COVID-19 probably were more subtle and information about them emerged more gradually over a period of time. In this issue, Kumar *et al*. have reported endocrine abnormalities in COVID-19 patients with a focus on thyroid and adrenal function.[2]

Thyroid diseases are common endocrine disorders; and accordingly, a lot of attention has gone into the study of how COVID-19 affects the thyroid. Although the majority of mild to moderate COVID-19 patients remain euthyroid, a significant proportion of those with severe disease manifest with abnormalities in thyroid function. These manifestations include low TSH and low T3 levels, whereas low T4 levels were observed less commonly.[3] Kumar *et al*. also found that nearly a quarter of their study population had low T3 syndrome, whereas low T4 was seen in 5%. This picture has been likened to the non-thyroidal illness pattern of thyroid dysfunction. The prognostic implications of these manifestations have also been investigated.[4] Apart from this, several reports of subacute thyroiditis following COVID-19 have also been published.[5] Although direct causality has not been proven, no other causative factor was identified in these reports. COVID-19 related thyroiditis has been proposed as a novel entity.[6] Similarly, Graves' disease has been reported to occur in patients who had recovered from COVID-19.[7]

In a large study, thyrotoxicosis occurred in 20% of COVID-19 patients suggesting the role of systemic immune activation.[8] Hypothyroidism, predominantly subclinical, has been found in few patients, a finding corroborated by the study published in this issue.[2,8] A possibility of central hypothyroidism, which improved after recovery from COVID-19, has been reported in a few cases in one study.[9]

Adrenal dysfunction in COVID-19 has now been reported in several studies. The receptors for the SARS-CoV-2, angiotensin-converting enzyme 2(ACE2), and transmembrane serine protease 2 (TMPRSS2) have been localized in adrenals providing a pathway for the virus to affect the gland.[10] Low basal serum cortisol and plasma adrenocorticotropic hormone (ACTH) have been documented in COVID-19 patients mimicking a picture of central adrenal insufficiency. The levels are found to be lower in patients with more severe disease, and critically ill COVID-19 patients have lower cortisol levels than those with critical illness without COVID-19.[11] In this respect, the present study by Kumar *et al*. differs – severe cases appeared to have higher basal and stimulated serum cortisol than mild cases; although, critical illness-related corticosteroid insufficiency (CIRCI) was reported by Kumar *et al*. also.[2] Interestingly, Kumar *et al*. found evidence of adrenal insufficiency mainly in asymptomatic and mild COVID-19 patients. This finding is not surprising as the adrenal crisis has been reported in asymptomatic COVID -19 patients.[12]

Vascular complications in the adrenals can also occur. Both unilateral and bilateral adrenal hemorrhage has been reported.[13,14] Furthermore, adrenal infarction has been known to occur.[15] Acute adrenal infarction has been reported as an incidental finding on CT scans in nearly a fourth of severe COVID-19 patients and may portend a poor prognosis.[16] A delayed onset central hypoadrenalism during recovery from COVID-19 has been reported.[17] Ischemic necrosis, lipid degeneration, hemorrhage, and adrenalitis have been found in autopsy studies of adrenals.[18]

The parathyroids appear to have been spared by the SARS CoV-2. A single case report of hypoparathyroidism due to COVID-19 has been published.[19] Additionally, serum calcium has been proposed as a biomarker of severity in COVID-19.[20]

Regarding pituitary dysfunction, data are again scanty. Apart from the involvement of the pituitary-thyroid and pituitary-adrenal axis by COVID-19, as discussed above, several case reports of pituitary apoplexy within pituitary adenomas in patients with COVID-19 have come to light.[21-23] In one case, apoplexy appeared to occur in the absence of a pituitary adenoma or other risk factors, raising the possibility of COVID-19 itself being the cause.[24,25] Hyperprolactinemia has been reported in COVID-19 patients.[26] Kumar *et al*. have also reported hyperprolactinemia in around 9% of their patients.[2]

Gonadal function in COVID-19 has received some attention. Serum testosterone levels were found to be lower in patients with severe COVID-19 as compared to mild or moderate cases, but this effect may be entirely attributable to critical illness rather than a COVID-19 manifestation.[27] A systematic review also found low testosterone and high luteinizing hormone (LH) levels in COVID-19 patients.[28] Furthermore, autopsy studies have shown evidence of damage to seminiferous tubules, a

reduction in Leydig cells, and infiltration by lymphocytes.[29] The male genital tract appears to express ACE2 and TMPRSS2 receptors at various sites, increasing its susceptibility to the SARS-CoV-2.[30] Overall, males seem to have a poor outcome from COVID-19, a phenomenon that may be linked to the different sex hormone milieu in males and females.[31] The female reproductive tract may not be rich in receptors like ACE 2 and TMPRSS2.[32] Accordingly, changes in female sexual function and hormone levels have been reported to be infrequent.[33]Although diabetes was the very first endocrine disorder to gain importance in the pandemic, the ability of the SARS-CoV-2 to affect pancreatic beta cells and cause diabetes is still a matter of debate. There were initial concerns regarding new-onset diabetes and ketoacidosis with COVID-19.[34] Some studies reported that the ACE 2 receptor was present on beta cells, whereas other studies found it to be absent.[35,36] The incidence of type 1 diabetes does not appear to have increased in the pandemic which also does not support a direct toxic effect of the SARS-CoV-2 on beta cells.[37,38] Factors such as undiagnosed pre-existing diabetes, stress hyperglycemia, and steroid-induced diabetes, make deciphering the impact of SARS-CoV-2 on diabetes a difficult task.[39]

The endocrine manifestations of COVID-19 can be likened to pieces of a puzzle – one which is slowly but surely coming together.

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