Coexistence of growth hormone, adrenocorticotropic hormone, and testosterone deficiency associated with coronavirus disease 2019: a case followed up for 15 months

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Abstract. Coronavirus disease 2019 (COVID-19) is associated with endocrine disorders, but their long-term clinical course remains unclear. We here report the 15-month clinical course for an individual with multiple endocrine disorders of the pituitary gland and testis likely triggered by COVID-19. A 65-year-old man with no history of endocrinopathy was admitted for acute COVID-19 pneumonia. Although his respiratory condition improved after administration of antiviral drugs, his blood pressure dropped suddenly to a preshock level and was refractory to vasopressors. The circulating adrenocorticotropic hormone (ACTH) and cortisol concentrations were low, and secondary adrenal insufficiency was suspected. Administration of hydrocortisone rapidly ameliorated the hypotension, and the patient was discharged taking 15 mg of hydrocortisone daily. An insulin tolerance test performed 3 months later revealed impaired ACTH, cortisol, and growth hormone (GH) responses, indicative of combined hypopituitarism. The patient also manifested symptoms of hypogonadism, and a hormonal workup suggested primary hypogonadism. At 12 months after discharge, GH and ACTH responses had recovered completely and partially, respectively. After another 3 months, basal ACTH and cortisol levels had been restored to the normal range and the patient discontinued hydrocortisone replacement without exacerbation of symptoms, although his hypogonadism persisted. The patient thus developed transient GH and ACTH deficiency that lasted for more than a year as well as persistent primary hypogonadism during intensive care for COVID-19. Certain prolonged symptoms of COVID-19 might be accounted for by such hormonal disturbance.

Key words: Coronavirus disease 2019 (COVID-19), Hypopituitarism, Hypogonadism, Adrenal insufficiency, Adult growth hormone deficiency

PITUITARY INSUFFICIENCY is associated with various conditions, including neoplasms, autoimmune disease, infectious disease, head injury, brain surgery, or irradiation [1]. Although cases of pituitary insufficiency triggered by virus infection are rare, viruses associated with this endocrinopathy include hantavirus [2-8], coxsackievirus [9], herpes simplex virus [10, 11], and human immunodeficiency virus [1, 12]. In addition, transient secondary adrenal insufficiency also developed in patients infected with SARS coronavirus 1 (SARS-CoV-1) during the recent pandemic of a severe acute respiratory syndrome (SARS) [13].

Coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 has been associated with various nonrespiratory manifestations [14], including those affecting cardiovascular, gastrointestinal, neural, coagulation, and locomotor systems, although endocrine disorders such as diabetes mellitus [15], thyroiditis [16-18], male infertility [19, 20], adrenal hemorrhage [21, 22], and adrenal insufficiency [23] have been described as complications of COVID-19, except for a few cases of pituitary apoplexy in patients with underlying pituitary tumors [24-26]. Although there have been several reports suggesting COVID-19-associated secondary adrenocortical

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insufficiency, they have been tentatively diagnosed with secondary cause based on low basal ACTH and cortisol levels in addition to a low cortisol response during cosyntropin tests instead of performing insulin tolerance test (ITT) or corticotropin-releasing hormone test [27-29].

Here, we report a 15-month follow-up for a case of combined pituitary hormone deficiency of ACTH and GH with primary hypogonadism that developed after recovery from respiratory failure in an individual with COVID-19.

Methods

Blood sample collection and secretory hormone tests were performed in the early morning, with the patient in a supine position after an overnight fast. An ITT was performed by intravenous injection of human regular insulin (0.10 U/kg) [30], with the patient not having taken hydrocortisone for 24 h. The plasma level of ACTH and serum levels of cortisol, GH (Tosoh, Tokyo, Japan), prolactin, luteinizing hormone (LH), and follicle-stimulating hormone (FSH) (Abbott Japan, Tokyo, Japan) were measured by chemiluminescence enzyme immunoassays. GH values were adjusted based on the World Health Organization (WHO) standards for human GH of pituitary origin [31]. The serum levels of free triiodothyronine (FT3), free thyroxine (FT4), and thyroid-stimulating hormone (TSH) were determined by electrochemiluminescence immunoassays (ECLusys; Roche Diagnostics, Mannheim, Germany). The serum concentration of insulin-like growth factor–I (IGF-I) was measured using an immunoradiometric assay kit (Daiichi Radioisotope Laboratories, Tokyo, Japan), and the reference range of IGF-I matched to age and sex for the Japanese population was determined by a previous study [32]. The serum level of free testosterone was measured by a radioimmunoassay (LSI Medience, Tokyo, Japan), with reference ranges shown in Table 1.

Case Report

A 65-year-old man without obesity (body mass index, 24.8 kg/m²) in good general health and with no history of endocrinopathy or steroid use was admitted to the Kakogawa Medical Center because of an 8-day history of dyspnea and fever associated with a positive reverse transcription-polymerase chain reaction (RT-PCR) test for COVID-19 (Fig. 1). After treatment for 2 days with ciclesonide (200 μg per day), mechanical ventilation was initiated as a result of rapidly progressing respiratory failure. As a result, ciclesonide was terminated, and favipiravir, ritonavir, and lopinavir, a standard regimen during the early phase of the COVID-19 pandemic, were initiated; however, high-dose corticosteroids therapy was not performed.

Table 1 Reference range for free testosterone in men by age

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Reference range (pg/mL)</th>
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<tbody>
<tr>
<td>20–29</td>
<td>7.6–23.8</td>
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<tr>
<td>30–39</td>
<td>6.5–17.7</td>
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<td>4.6–19.6</td>
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<tr>
<td>60–69</td>
<td>5.3–11.5</td>
</tr>
<tr>
<td>≥70</td>
<td>4.6–16.9</td>
</tr>
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Fig. 1 Clinical course of COVID-19. SBP, systolic blood pressure.
The patient gradually recovered from respiratory failure and was extubated on the 25th day of his hospital stay. He tested negative for COVID-19 by RT-PCR on day 31.

On the 36th day of hospitalization, the patient’s blood pressure dropped suddenly from 120/80 to 80/50 mmHg in association with a reduction in heart rate and was refractory to vasopressors. In addition, the levels of plasma ACTH and serum cortisol were 6.1 pg/mL and 8.17 μg/dL, respectively, suggestive of secondary adrenocortical insufficiency, and the results of coagulation tests were suggestive of disseminated intravascular coagulation (Table 2). Administration of hydrocortisone (100 mg) ameliorated the refractory hypotension for a few hours. Hydrocortisone was then tapered, and the patient was discharged on the 96th day, taking 15 mg of hydrocortisone daily (Fig. 1).

The patient underwent pituitary function tests 3 months after discharge, given that it is difficult to evaluate endocrine function during the acute phase of COVID-19. Whereas magnetic resonance imaging showed no obvious abnormality in the hypotalamic-pituitary region and conserved high-intensity signals in the posterior pituitary lobe on non-contrast T1-weighted imaging (Fig. 2), an insulin tolerance test (ITT) revealed that the responses of ACTH and cortisol to hypoglycemia were markedly blunted, suggestive of secondary adrenal insufficiency (Table 3). A cosyntropin test also exhibited insufficient cortisol response to ACTH, which was consistent with adrenal insufficiency (Table 3).

The GH response during the ITT was also impaired (peak value of 2.4 ng/mL at 90 min) and met the criteria for adult GH deficiency [30]. On the other hand, the GH response during the GH releasing peptide 2 (GHRP-2) test was conserved and could exclude the severe adult GH deficiency (peak value 33.2 ng/mL at 30 min). In addition, the circulating concentration of IGF-I was lower than that of the reference range matched to the age and sex for the Japanese population [32] (Table 4). Potential causes for the low level of IGF-I, including low dietary intake or leanness, diabetes mellitus, and chronic liver or kidney disease, were not apparent, suggesting that it was attributable to GH deficiency.

The basal levels of TSH, FT3, and FT4 were within the reference ranges, and the response of TSH during a thyrotropin-releasing hormone (TRH) stimulation test was preserved (Tables 3 and 4). The level of free testosterone was below the age-specific reference range, and LH and FSH were elevated. The patient reported a reduced libido since the development of COVID-19, and a urologist diagnosed dyspermatism with azoospermia but without obvious pubic hair loss or testicular atrophy. These observations collectively suggested that the patient had secondary adrenal insufficiency and moderate GH deficiency with preserved secretory capacity for TSH and gonadotropins, as well as primary hypogonadism. We did not perform the evaluation test for central diabetes insipidus because he lacked any symptoms such as polyuria and polydipsia.

Six months after the patient’s discharge, his serum concentration of IGF-I was at the low end of the reference range (77 ng/mL). However, the low level of free testosterone (3.0 pg/mL) and high levels of FSH (41.1 mIU/L) and LH (34.3 mIU/L) persisted, and the patient started testosterone supplementation because his

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Reference range</th>
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</thead>
<tbody>
<tr>
<td>PT-INR</td>
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<td>0.9–1.1</td>
</tr>
<tr>
<td>PT (%)</td>
<td>55</td>
<td>70–130</td>
</tr>
<tr>
<td>Fibrinogen (mg/dL)</td>
<td>486</td>
<td>150–400</td>
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<tr>
<td>D-dimer (μg/dL)</td>
<td>14.2</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Antithrombin III (%)</td>
<td>54.5</td>
<td>80–130</td>
</tr>
</tbody>
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PT-INR, prothrombin time–international normalized ratio.

Fig. 2 Magnetic resonance imaging of the hypothalamus and pituitary region at 3 months after discharge. Coronal (A) and sagittal (B) gadolinium-enhanced T1-weighted images of the patient are shown.
symptoms of hypogonadism, in particular, dysspermatism had worsened.

Twelve months after the patient’s discharge, he underwent a repeat ITT (Table 3). The basal level of ACTH was higher than that of the normal range, and the basal cortisol concentration remained low. Both ACTH and cortisol responses were insufficient but had improved since the last test, suggesting that the patient was recovering from the hypothalamic-pituitary-adrenal (HPA) axis disorder. Whereas the GH response had also improved (peak value of 4.6 ng/mL) and no longer met the criteria for adult GH deficiency, the serum level of IGF-I was still low (Tables 3 and 4). Under the condition of 3 weeks after intramuscular injection of testosterone, the levels of FSH, LH, and free testosterone had normalized (Table 4), and the symptoms of hypogonadism had ameliorated with testosterone supplementation.

Fifteen months after discharge, levels of early-morning ACTH (15.8 pg/mL) and cortisol (19.5 μg/dL) had recovered to the normal range (Table 4), and the patient was able to terminate glucocorticoid supplementation without the onset of symptoms of adrenal insufficiency. Although we attempted to discontinue testosterone replacement after improving a reduced libido and dysspermatism, the patient resumed testosterone replacement due to the re-exacerbation of those symptoms. Thus, we conclude that his hypogonadism remains.

**Discussion**

The present patient suddenly developed catecholamine-resistant, hydrocortisone-responsive hypotension during treatment for COVID-19, without any other apparent cause for this drop in blood pressure. ACTH and GH insufficiencies responses were revealed using an ITT, and the condition persisted for more than a year before recovery. These observations suggest that the hypopituitarism of the present case was induced by COVID-19. Impaired function of the HPA axis has been detected in
Multiple hormone deficiencies in COVID-19

individuals with SARS, a disease caused by SARS-CoV-1. A prospective study in Singapore revealed that 24 (39%) of 61 patients who survived SARS had apparent secondary adrenal insufficiency [13]. A recent study in Saudi Arabia showed that, among 28 patients with COVID-19 who underwent random measurement of circulating levels of ACTH and cortisol, 9 individuals (32%) were suspected of having adrenal insufficiency based on a serum cortisol concentration <300 nmol/L [23]. More recently, Turkish investigators reported that cortisol and GH responses in pituitary function tests were impaired in individuals who had recovered from acute COVID-19 [27]. Another Turkish group also reported that adrenal insufficiency was observed in 8.2% of patients with COVID-19 whose adrenal function has recovered in 6 months [33]. Additionally, several reported cases exhibited rather higher basal ACTH for the lower level of cortisol, suggesting that the study group might include patients with primary adrenal insufficiency [23, 27]. Indeed, the adrenal gland is known as the target of SARS-CoV2, which causes adrenalitis and primary adrenal insufficiency [34].

Individuals with serious illness sometimes manifest high levels of serum cortisol as a result of suppression of cortisol metabolism and a consequent decrease in the circulating ACTH concentration [35]. Moreover, long-term use of dexamethasone, sometimes adopted for virus-induced acute respiratory failure, may give rise to adrenocortical insufficiency as a result of steroid withdrawal syndrome. However, the present patient had received only 200 μg of ciclesonide through inhalation for 2 days, and treatment with this drug for 4 weeks has not been found to result in substantial cortisol suppression [36]. In addition, antiviral drugs such as ritonavir and lopinavir can increase steroid metabolism by inhibiting the enzyme cytochrome P450 3A4 (CYP3A4) [37], which may have exacerbated the adrenal insufficiency of the present patient. Whereas cases of adrenal insufficiency have been reported for individuals with SARS or COVID-19 [13, 23, 27], hormone tests that discriminate between primary and secondary adrenal insufficiency were not performed for these cases. Thus, the present case is the first of secondary adrenal insufficiency confirmed using an ITT after recovery from COVID-19.

A conserved GH response during the GHRP-2 test in our case suggested that the somatotroph function seemed to be at least conserved. However, since GHRP-2 stimulates somatotrophs and the hypothalamus, our case cannot be diagnosed whether pituitary or hypothalamic origin [38]. Furthermore, Giustina et al. reported that glucocorticoid supplementation recovers GH secretion in cases with GH deficiency combined with adrenal insufficiency, while the period for recovery of GH secretion varies from 8 months to 3 years [39]. Therefore, transient GHD in our case might be explicable by this mechanism.

Although the underlying mechanism by which COVID-19 might trigger pituitary insufficiency also remains unknown, it has been reported that viral infections such as influenza-A, herpes simplex, and puumala virus-induced meningoencephalitis are associated with transient hypopituitarism [40-43]. Therefore, the central nervous system is likely a target for SARS-CoV-2 infection and angiotensin-converting enzyme 2 (ACE2), an enzyme that plays an essential role in the regulation of the renin-angiotensin-aldosterone system. Moreover, transmembrane protease serine 2 (TMPRSS2) is an enzyme that belongs to the serine protease family. Both

| Table 4 Circulating hormone levels at 3, 6, 12, and 15 months after discharge |
|---------------------------|----------------|------------------|
| Hormone                  | Value          | Reference range  |
| 3 months                 |                |                  |
| IGF-I (ng/mL)            | 69             | 72.0–221.0*      |
| FT3 (pg/mL)              | 2.7            | 2.3–4.0          |
| FT4 (ng/dL)              | 1.0            | 0.90–1.70        |
| Free testosterone (pg/mL)| 3.1            | 5.3–11.5         |
| 6 months                 |                |                  |
| IGF-I (ng/mL)            | 77             | 72.0–221.0*      |
| TSH (mIU/mL)             | 3.31           | 0.610–4.230      |
| FT4 (ng/dL)              | 1.1            | 0.90–1.70        |
| Prolactin                | 7.3            | 3.58–12.78       |
| FSH (mIU/L)              | 41.1           | 2.0–8.3          |
| LH (mIU/L)               | 34.3           | 0.79–5.72        |
| Free testosterone (pg/mL)| 3.0            | 5.3–11.5         |
| 12 months                |                |                  |
| IGF-I (ng/mL)            | 61             | 72.0–221.0*      |
| FT4 (ng/dL)              | 1.0            | 0.90–1.70        |
| FSH (mIU/L)              | 3.4            | 2.0–8.3          |
| LH (mIU/L)               | 1.4            | 0.79–5.72        |
| Free testosterone (pg/mL)| 9.4            | 5.3–11.5         |
| 15 months                |                |                  |
| ACTH (pg/mL)             | 15.8           |                  |
| Cortisol (μg/dL)         | 19.5           |                  |
| IGF-I (ng/mL)            | 86             | 70.0–219.0*      |
| TSH (mIU/mL)             | 5.05           | 0.610–4.230      |
| FT4 (ng/dL)              | 1.17           | 0.90–1.70        |
| Prolactin                | 6.0            | 3.58–12.78       |
| FSH (mIU/L)              | 34.4           | 2.0–8.3          |
| LH (mIU/L)               | 31.1           | 0.79–5.72        |
| Free testosterone (pg/mL)| 6.2            | 5.3–11.5         |

* The reference range for IGF-I matched to age and sex for the Japanese population was determined by a previous study [32].
enzymes are required for cellular entry of the virus and are expressed in the hypothalamic-pituitary axis [44]. Intriguingly, the hypothalamus exhibited higher TMPRSS2 expression than that of the pituitary, while there was no difference in the expression level of ACE2 between the pituitary and hypothalamus, which indicates that SARS-CoV2 may target the hypothalamic as well as the pituitary [44].

Pituitary insufficiency in the present case might have been caused by direct infection of the axis by SARS-CoV-2. Laboratory data suggestive of a blood coagulation disorder were obtained at the time of onset of adrenal insufficiency. Given that thrombotic and hypercoagulability complications of COVID-19 have been described [45], hemodynamic changes such as ischemia-induced by such abnormalities in the hypothalamus-pituitary region might have contributed to the hormonal disorders of the proband.

In the present case, the symptoms of hypogonadism developed after the recovery from COVID-19 and have persisted to date. In addition, the testis expresses both ACE2 and TMPRSS2 and serves as a target of SARS-CoV-2 [44]. Furthermore, germ cell destruction associated with the infiltration of macrophages and lymphocytes was detected by pathological examination of the testis of patients with SARS [46]. Cases of acute orchitis have also been associated with COVID-19 [47]. Moreover, a quarter of sexually active men were found to manifest disorders of semen, such as azoospermia and oligospermia, after recovery from COVID-19 [48, 49].

The immunological response to the virus infection may also have contributed to the pathogenesis of the multiple endocrine disorders in the present case. Various autoantibodies against phospholipids and SSA/Ro autoantigen, which were originally identified in patients with Sjögren’s syndrome, have been identified during the clinical course of COVID-19 [50]. Autoimmune conditions, including systemic autoimmune rheumatic diseases, Guillain-Barré syndrome, immune thrombocytopenic purpura, and autoimmune hemolytic anemia, have also been newly diagnosed during the treatment of COVID-19 [50]. In addition, endocrinopathies such as autoimmune polyglandular syndrome, hypophysitis, autoimmune thyroid disease, type 1 diabetes mellitus, and Addison disease [51, 52] are triggered by autoimmunity. Turkish group reported that anti-hypothalamus and anti-pituitary antibodies were detected in the sera obtained from patients with COVID-19 with adrenal insufficiency [33]. Thus, an exaggerated immune response triggered by SARS-CoV-2 may have resulted in the dysfunction of multiple endocrine organs in the present patient.

Certain COVID-19-associated conditions develop after the onset of or the recovery from respiratory disorders, as was apparent in the present case. Prolonged symptoms of COVID-19 include fatigue, weakness, hair loss, diarrhea, arthralgia, and depression, with such symptoms also being associated with pituitary insufficiency, most frequently with secondary adrenocortical insufficiency [53, 54]. Dexamethasone administration for the treatment of COVID-19 might mask adrenocortical insufficiency if the endocrine condition occurs during the acute phase of the disease. The possibility of pituitary insufficiency should be considered in patients with prolonged symptoms of COVID-19, given that appropriate hormone supplementation in individuals with pituitary insufficiency markedly ameliorates their symptoms and improves their quality of life.

In conclusion, we present a case of multiple endocrine deficiencies affecting the HPA axis, GH–IGF-I axis, and testis that was likely triggered by COVID-19. However, the mechanisms linking hormonal disorders and infectious diseases remain to be elucidated. An important finding in the present case is the eventual recovery from hypopituitarism over time, but not from hypogonadism. Further study is required to determine whether other COVID-19-associated hormonal disorders share such a transient nature. Given that certain prolonged symptoms of COVID-19 may be accounted for by hormone deficiency, it might be worthwhile to screen for endocrine dysfunction in patients with such persistent symptoms after their recovery from the acute disease.

Declarations

Conflict of interest
The authors declare no conflict of interest.

Ethical approval
Not applicable.

Consent to participate
Not applicable.

Consent for publication
Informed consent for publication of the clinical data was obtained from the patient

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