Case Report

Pituitary insufficiency as a complication of COVID-19

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Abstract

Whereas coronavirus disease 2019 (COVID-19) triggers various nonrespiratory disorders including endocrinopathies, a confirmed case of pituitary insufficiency has not been described to date. We here describe the case of a 65-year-old man with no history of endocrinopathy who was hospitalized because of dyspnea and fever with a positive test for COVID-19. After treatment with ciclesonide, mechanical ventilation was initiated because of rapidly progressing respiratory failure and antiviral drugs were administered. His respiratory condition improved gradually, but 11 days after extubation his blood pressure dropped suddenly to a preshock level and was refractory to vasopressors. Circulating ACTH and cortisol concentrations were low, suggestive of secondary adrenal insufficiency. 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 GH responses, indicative of secondary adrenal insufficiency with GH deficiency. A hormonal workup at this time also suggested primary hypogonadism, consistent with hypogonadal symptoms that developed after discharge. Six months after discharge, ACTH and cortisol responses to CRH stimulation were blunted, confirming corticotroph dysfunction. Somatotroph insufficiency and primary hypogonadism remained evident. These findings thus suggest that the patient developed insufficiency of hormone secretion by corticotrophs and somatotrophs in the pituitary together with hormonal deficiency in the testis, all likely as a complication of COVID-19. Given that certain prolonged symptoms of COVID-19 might be accounted for by such hormonal disturbance, screening for endocrine dysfunction in patients with such symptoms who have recovered from acute disease may be warranted.

Introduction

Pituitary insufficiency is associated with various conditions including neoplasms, autoimmune disease, infectious disease, head injury, and 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), coxsackie virus (9), herpes simplex virus (10, 11), and human immunodeficiency virus (1, 12). Transient secondary adrenal insufficiency also developed in patients infected with SARS coronavirus 1 (SARS-CoV-1) during the recent pandemic of severe acute respiratory syndrome (SARS) (13).

Coronavirus disease 2019 (COVID-19) has been associated with various nonrespiratory manifestations—including those affecting cardiovascular, gastrointestinal, neural, coagulation, and locomotor systems—although the pathogenesis of these manifestations is not fully understood (14). Whereas several 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, with the exception of a few cases of pituitary apoplexy in patients with underlying pituitary tumors (24-26) there has been no report of COVID-19–associated pituitary insufficiency.

We here report a case of multiple endocrine disorders—hypopituitarism with multiple hormone insufficiency and primary hypogonadism—that developed after recovery from respiratory failure in an individual with COVID-19.

Methods

Blood sample collection and hormone secretory tests were performed in the early

morning, with the patient in a supine position after an overnight fast. An insulin tolerance test (ITT) was performed by intravenous injection of human regular insulin (0.10 U/kg) (27). The plasma level of ACTH as well as the serum levels of cortisol, GH (Tosoh, Tokyo, Japan), prolactin, LH, FSH, and total testosterone (Abbott Japan, Tokyo, Japan) were measured with chemiluminescence enzyme immunoassays. The serum levels of free triiodothyronine (FT3), free thyroxine (FT4), and TSH were determined with electrochemiluminescence immunoassays (ECLusys; Roche Diagnostics, Mannheim, Germany). The serum concentration of IGF-I was measured with an immunoradiometric assay kit (Daiichi Radioisotope Laboratories, Tokyo, Japan), with the reference range of IGF-I matched to age and sex for the Japanese population being determined by a previous study (28).

Case Report

A 65-year-old man who was generally in good health and with no history of endocrinopathy or steroid use was admitted to Kakogawa Medical Center because of an 8-day history of dyspnea and fever associated with a positive RT-PCR test for COVID-19 (Fig. 1). After treatment for 2 days with ciclesonide, mechanical ventilation was initiated as a result of rapidly progressing respiratory failure. Ciclesonide was terminated, and favipiravir, ritonavir, and lopinavir were initiated. 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 blood pressure of the patient dropped suddenly from ~120/80 to ~80/50 mmHg in association with a reduction in heart rate and was refractory to vasopressors. The levels of plasma ACTH and serum cortisol were

6.1 pg/mL and 8.17 µg/dL, respectively, suggestive of impaired adrenocortical function. Administration of hydrocortisone resulted in a rapid amelioration of the refractory hypotension. Hydrocortisone was then tapered, and the patient was discharged on day 96 taking 15 mg of hydrocortisone daily.

The patient underwent pituitary function tests at 3 months after discharge. Whereas magnetic resonance imaging showed no obvious abnormality in the hypothalamic-pituitary region, an ITT revealed that the responses of ACTH and cortisol to hypoglycemia were markedly blunted, suggestive of secondary adrenal insufficiency (Table 1). The GH response during the ITT was also impaired (peak value of 2.4 ng/mL) and met the criteria for adult GH deficiency (27). The circulating concentration of IGF-I was lower than the reference range matched to age and sex for the Japanese population (28) (Table 2), consistent with adult GH deficiency. The basal levels of TSH, FT3, and FT4 were within the reference ranges, and the response of TSH during a TRH stimulation test was preserved (Tables 1 and 2). Although the total testosterone level was within the reference range, the levels of LH and FSH were above the reference ranges. The patient had also noted dysspermatism and a reduced libido after his discharge from the hospital. These observations collectively indicated that the patient had apparent secondary adrenal insufficiency and moderate GH deficiency with preserved secretory capacity for TSH and gonadotropins, in addition to primary hypogonadism.

Six months after discharge of the patient, a CRH test was performed to further evaluate his pituitary insufficiency (Table 1). The responses of ACTH and cortisol to CRH were markedly blunted, indicative of corticotroph dysfunction. The serum concentration of IGF-I at this time was borderline low, suggesting that somatotroph

function had not been fully restored (Table 2). The increased levels of FSH and LH persisted, and the patient decided to receive testosterone supplementation therapy because his symptoms of hypogonadism had worsened.

Discussion

In this case, pituitary insufficiency and primary hypogonadism newly developed most likely as a complication of COVID-19, a disease caused by infection with SARS-CoV-2. Whereas a variety of conditions has been associated with this infectious disease, a confirmed case of pituitary insufficiency has not been described previously.

Impaired function of the hypothalamic-pituitary-adrenal axis has been detected in 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 ACTH and cortisol levels, 9 individuals (32%) were suspected of having adrenal insufficiency on the basis of a serum cortisol concentration of <300 nmol/L (23). Individuals with serious illness sometimes manifest high serum cortisol levels as a result of suppression of cortisol metabolism and a consequent decrease in the circulating ACTH concentration (29). 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. These previous studies of patients with SARS or COVID-19 (13, 23) did not report the results of hormone tests that allow differentiation between primary and secondary adrenal insufficiency. The present case is the first for which secondary adrenal insufficiency was confirmed in a

COVID-19 patient by performance of an ITT and CRH stimulation test.

The serum concentrations of IGF-I measured at 3 and 6 months after discharge of the present patient were low and borderline low, respectively. During serious illness, both the frequency and amplitude of GH pulses are often increased as a result of down-regulation of the GH receptor in the liver, while hepatic IGF-I production is suppressed (30). In addition, the circulating level of IGF-I is reduced in association with malnutrition, obesity, diabetes, hypothyroidism, or liver or renal failure (31). The present case was not associated with such conditions that influence the levels of GH or IGF-I, with the impaired GH response of the patient to hypoglycemia being indicative of somatotroph dysfunction. GH deficiency in this case was thus likely a complication of COVID-19.

A clinical study in Germany evaluated pituitary function with hormone stimulation tests including an ITT performed between 10 and 56 months after acute illness in 19 patients with central nervous system infection with coxsackie B5 virus, influenza A virus, herpes simplex virus, or other viruses (32). Whereas no patient manifested GH deficiency, four (21%) and two (11%) individuals showed corticotroph or gonadotroph insufficiency, respectively. The central nervous system is likely an infectious target of SARS-CoV-2, and both ACE2 and TMPRSS2, which are required for cellular entry of the virus, are expressed in the hypothalamus-pituitary axis (33). It is thus possible that pituitary insufficiency in the present case was caused by direct infection of this axis with SARS-CoV-2.

In the present case, the symptoms related to hypogonadism developed after the recovery from COVID-19 and have persisted to date, suggesting that the primary hypogonadism was triggered by COVID-19. The testis is also known to express both

ACE2 and TMPRSS2 and to serve as a target of SARS-CoV-2 (33). Germ cell destruction associated with the infiltration of macrophages and lymphocytes was also detected by pathological examination of the testis of patients with SARS (34).

The immunological response to the virus infection may also have contributed to pathogenesis of the multiple endocrine disorders in the present case. Various autoantibodies including those to phospholipids and to SSA/Ro have been identified during the clinical course of COVID-19 (35). Autoimmune conditions including systemic autoimmune rheumatic diseases, Guillain-Barré syndrome, immune thrombocytopenic purpura, and autoimmune hemolytic anemia have also been newly diagnosed during treatment of COVID-19 (35). Endocrinopathies such as autoimmune polyglandular syndrome, hypophysitis, autoimmune thyroid disease, type 1 diabetes mellitus, and Addison disease (36, 37) are triggered by autoimmunity. It is thus possible that 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, mostly frequently with secondary adrenocortical insufficiency (38, 39). Dexamethasone is sometimes administered for the treatment of COVID-19, and such treatment might mask adrenocortical insufficiency if the endocrine condition occurs during the acute phase of the disease. The possibility of pituitary insufficiency should thus be considered in patients with prolonged symptoms of COVID-19, given that appropriate hormone supplementation in individuals with pituitary insufficiency markedly ameliorates their

193 symptoms and improves their quality of life.

194 In conclusion, we experienced a case of multiple endocrine deficiency affecting
195 somatotrophs, corticotrophs, and the testis that was likely triggered by COVID-19,
196 although the mechanisms linking the hormonal disorders and the infectious disease
197 remain unclear. Given that certain prolonged symptoms of COVID-19 may be
198 accounted for by hormone deficiency, it might be worthwhile to screen for endocrine
199 dysfunction in patients with such persistent symptoms after their recovery from the
200 acute disease.

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208 ***Data Availability:*** Data sharing is not applicable to this article because no data sets were
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Table 1. Results of an insulin tolerance test, TRH test, and LHRH test at 3 months after discharge and of a CRH test at 6 months.

Parameter	Time (min)				
	0	30	60	90	120
<u>Insulin tolerance test</u>					
Blood glucose (mg/dL)	84	34	45	70	71
ACTH (pg/mL)	14.9	16.8	23.8	16.7	19
Cortisol (mg/dL)	7	5.5	6.7	7.9	6.8
GH (ng/mL)	0.2	0.37	0.9	2.4	0.7
<u>TRH test</u>					
TSH (mIU/mL)	3.98	12.8	10.9	9.08	7.75
prolactin (ng/mL)	10.7	56.6	42.2	32	27
<u>LHRH test</u>					
LH (mIU/L)	36.8	86.6	79.1	74.8	74.4
FSH (mIU/L)	42	26.6	52.3	52.1	50.9
<u>CRH test</u>					
ACTH (pg/mL)	5	7.8	6.9	7.2	6.3
Cortisol (mg/dL)	16.1	12.1	10.2	8.5	6.8

Table 2. Circulating hormone levels at 3 and 6 months after discharge

*: The reference range of IGF-I matched to age and sex for the Japanese population being determined by a previous study (28).

Hormone	Value	Reference range
<u>3 months</u>		
IGF-I (ng/mL)	69	72.0–221.0*
FT3 (pg/mL)	2.7	2.3–4.0
FT4 (ng/mL)	1.0	0.90–1.70
Total testosterone (ng/mL)	5.0	2.9–9.5
<u>6 months</u>		
IGF-I (ng/mL)	77	72.0–221.0*
TSH (mIU/mL)	3.31	0.610–4.230
FT4 (ng/mL)	1.1	0.90–1.70
Prolactin	7.3	3.58–12.78
FSH (mIU/L)	41.1	2–8.3
LH (mIU/L)	34.3	0.79–5.72
Total testosterone (ng/mL)	2.9	2.9–9.5

Figure 1. Clinical course of COVID-19.

SBP, systolic blood pressure.