Journal of Endocrinology, Metabolism and Diabetes of South Africa 2024; 29(3):77–86
https://doi.org/10.1080/16089677.2024.2411924

JEMDSA
ISSN 1608-9677 EISSN 2220-1009

CASE REPORT

Clinical characteristics of endocrine disturbances in post-COVID-19 condition, case report with review of literature

W. Ji, XM. Xie*, L. Zhang, HY. Zhou, GR. Bai, L. Li, YT. He, J. He, CY. Xia, H. Li, RD. Li, R. Ping and D. Qiang

The Second Clinical Medical College of Ningxia Medical University, Yinchuan, 75001, People's Republic of China
**Correspondence: xxm2324@126.com*

Post-COVID-19 condition (PCC) is frequently associated with multiple endocrine hormone disturbances, primarily involving the hypothalamic–pituitary–adrenal axis. However, the exact cause remains unclear, particularly concerning whether these symptoms result from hypothalamus damage. This study reports on the clinical characteristics and examination methods of five patients exhibiting multiple endocrine disorders during PCC following SARS-CoV-2 infections, as well as the corresponding treatment strategies. Insulin tolerance test (ITT), arginine stimulation test, rapid adrenocorticotropic hormone (ACTH) stimulation test, and supine–standing test were used to evaluate endocrine hormone disturbances. Magnetic resonance imaging of the pituitary and computed tomography of the adrenal gland on one patient were performed to reveal the pathology. All five patients had hypothalamic syndrome with secondary adrenal insufficiency, growth hormone (GH) deficiency, and secondary hyperaldosteronism. Treatment included ACTH injection, recombinant human GH injection, and/or oral administration of synthetic glucocorticoids (prednisone acetate or methylprednisolone) and mineralocorticoid receptor antagonist finerenone. Remarkable improvement was observed within one week for all patients. To assess disorders in the hypothalamic–pituitary–§adrenal axis, dynamic endocrine testing is recommended. Upon confirmation of a diagnosis, timely supplementation of ACTH, glucocorticoids, GH, and aldosterone antagonists can yield remarkable therapeutic outcomes.

Keywords: post-COVID-19 condition, long COVID, endocrine hormone disturbances, hypothalamic–pituitary–adrenal axis, insulin tolerance test

Introduction

Persistent, returning, or newly emerging symptoms following infection with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus responsible for Coronavirus Disease 2019 (COVID-19), are commonly known as post-COVID-19 condition (PCC).[1] PCC consists of multiple symptoms, including fatigue, dyspnoea, and cognitive dysfunction. Typically, these symptoms manifest within three months of the onset of symptomatic COVID-19, last for at least two months, and cannot be attributed to an alternative diagnosis.[1] A prospective study involving South African adults indicated a close association between the presence of acute COVID-19 symptoms, especially in critically ill patients, and the development of PCC, with a tendency for patients to be female.[2] In China, the prevalence of severe PCC was estimated at 31.0%, with the most common severe symptoms including fatigue (33.7%), cough (31.9%), sore throat (31%), difficulty in concentrating (30.5%), anxiety (30.2%), myalgia (29.9%), and arthralgia (29.9%).[3]

The acute phase of SARS-CoV-2 infection triggers a cytokine storm that damages multiple organs, including potential impact on the hypothalamic–pituitary–adrenal (HPA) axis.[4–7] This damage may lead to growth hormone (GH) deficiency, adrenal insufficiency, and reduced cortisol and adrenocorticotropic hormone (ACTH) levels.[8–12] In the convalescent period, some 40% of patients may experience mild secondary adrenal insufficiency, affecting GH, ACTH, and cortisol response to insulin tolerance tests (ITT).[13,14] The exact cause of hormonal imbalances in PCC remains unclear, particularly regarding damage to the hypothalamus. Current understanding is that SARS-CoV-2 infection contributes to the formation of stable angiotensin-converting enzyme 2 (ACE2)-viral spike protein complexes, which persist even after disease resolution.[15–20] Furthermore, infection can activate ACE2 receptors in the hypothalamus and pituitary, resulting in increased blood–brain barrier permeability, disruption of tight junctions, and impacting angiotensin II and aldosterone levels within the renin–angiotensin–aldosterone system (RAAS).[19,21–23] However, the association between PCC and persistently elevated aldosterone levels remains unclear.

To explore potential PCC aetiology, this study reported on five COVID-19 patients presenting diverse PCC symptoms. Multiple dynamic endocrine testing revealed that these symptoms were associated with the disruption of various endocrine hormone axes, attributed to damage to the hypothalamic neuroendocrine centre. Furthermore, the implemented comprehensive treatment strategies resulted in favourable outcomes for these patients. These findings may contribute valuable insights for diagnosing and treating PCC in clinical settings.

Methods

Subjects

From June 12, 2023 to July 7, 2023, five patients with confirmed SARS-CoV-2 infection for over three months were hospitalised in the Endocrinology Department of the Second Affiliated Hospital of Ningxia Medical University. The diagnoses of COVID-19 and PCC were in accordance with the World Health Organization (WHO) definition. According to the American Diabetes

Association, one had prediabetes, one had type 1 diabetes combined with cirrhosis, and two had type 2 diabetes.

Blood testing

Fasting peripheral venous blood samples were collected after an overnight fast (8–12 hours). Dynamic endocrine testing was performed according to the diagnostic process (Figure 1). Plasma levels of ACTH, GH, aldosterone, renin, and the aldosterone-to-renin ratio (ARR) were measured using an Autobio biochemistry analyser (Autobio Diagnostics Co, Zhengzou, China). Plasma cortisol was measured using a Cobas 6000 automated immunoassay analyser (Roche Diagnostics, Basel, Switzerland). Liquid chromatography tandem mass spectrometry (LC-MS/MS) was used to measure the free cortisol, urine aldosterone, and insulin-like growth factor 1 (IGF-1) in 24-hour urine samples.

Measurements

For ITT, blood samples were collected at 0, 30, 60, 90 and 120 minutes after insulin injection (0.10–0.15 U/kg), and the levels of blood glucose (GLU), cortisol, ACTH, and GH were measured. Additionally, fasting blood samples were collected at 8 am to serve as baseline measurements. For arginine stimulation test, arginine (0.5 g/kg, maximum 30 g) was administered intravenously through a 100 mL normal saline drip over 30 minutes. The levels of GLU, cortisol, ACTH, and GH were measured in blood samples at baseline (30 minutes before arginine infusion) and at 0 (end of arginine infusion), 30, 60, 90, and 120 minutes after infusion. Regarding the rapid ACTH stimulation test, ACTH (25 IU) was administrated intravenously. The levels of cortisol and ACTH were measured in blood samples at baseline and at 0, 30, and 60 minutes after infusion. In the supine–standing test, patients remained in an upright position (sitting, standing, or walking) for at least 2 hours after intramuscular administration of furosemide (40 mg). Subsequently, blood samples were collected in the standing position, and levels of aldosterone, renin, cortisol, and ACTH were measured.

Case presentation

Patient 1

A 59-year-old female was admitted to our hospital on June 12, 2023, presenting with a recurrent rash and generalised oedema on the face and body that had lasted for 4 months. The patient had received three doses of SARS-CoV-2 vaccine in 2022 and had a history of rash and allergic rhinitis. There was no history of drug or food allergies, and there were no other autoimmune diseases. Six months previously, she had contracted SARS-CoV-2 and experienced symptoms such as dyspnoea, chest tightness, cough, and sputum production. Haematological analysis indicated a relatively lower level of peripheral blood lymphocytes (PBL) (Table 1). After being diagnosed with severe COVID-19 and receiving comprehensive treatments (antiviral therapy, anticoagulation, and anti-infection treatment), these symptoms almost completely resolved.

On February 9, 2023, due to high-intensity stress and fatigue, the patient developed generalised rash, pruritus, non-pitting oedema, muscle pain, and insomnia, as well as brain fog.

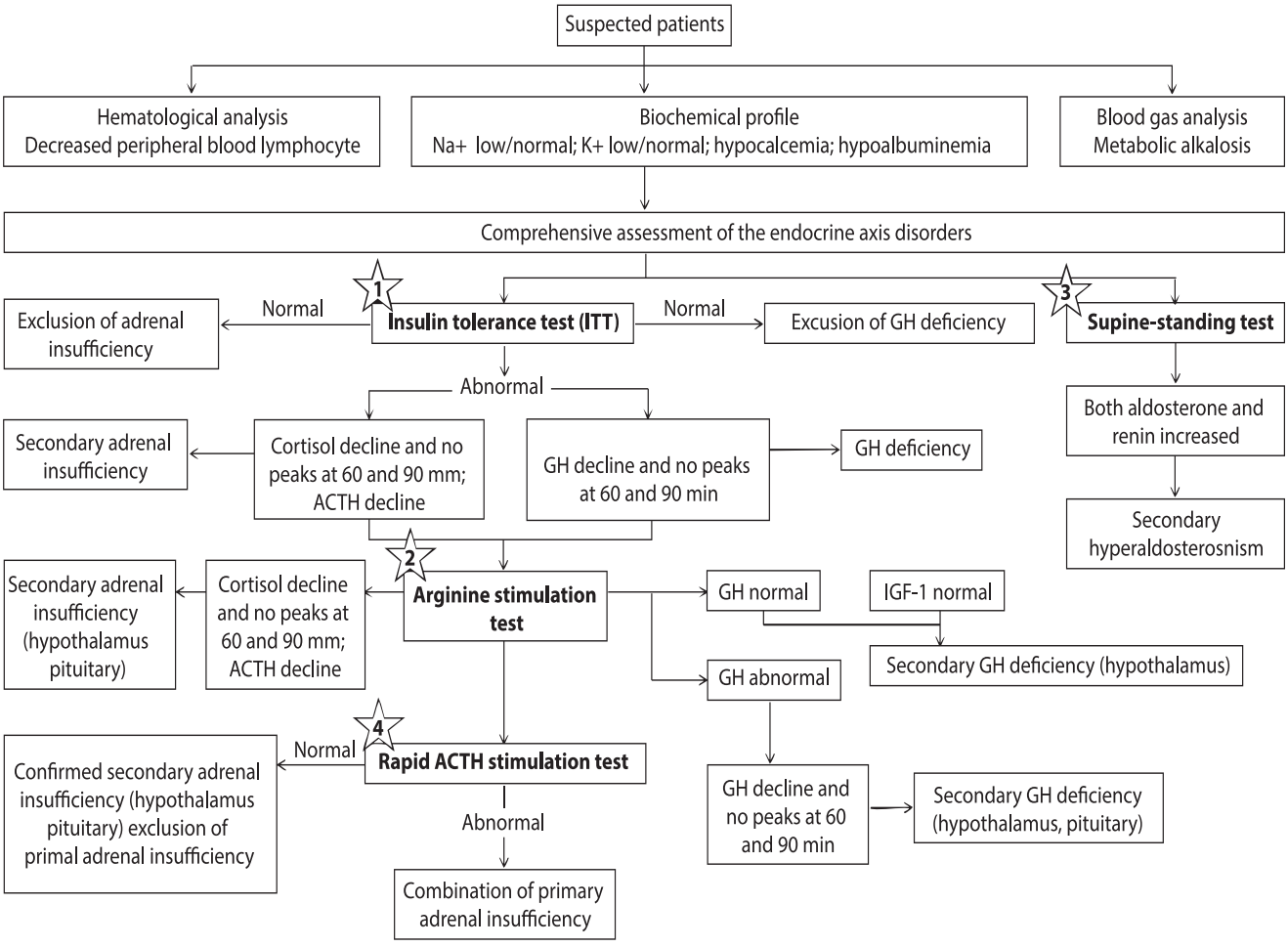

Figure 1: Flowchart of dynamic endocrine testing.

Table 1: Haematological analysis of the five patients

Factor			WBC (10^9/L)	Neutrophil (%)	Neutrophil (10^9/L)	LYMPH (%)	LYMPH (10^9/L)	FBG (mmol/L)	ALT (U/L)	AST (U/L)	Cr (μmol/L)
Normal reference range			**3.5–9.5**	**40–75%**	**1.8–6.3**	**20–50**	**1.1–3.2**	**3.9–6.1**	**7–40**	**13–35**	**41–73**
Patient 1	First SARS-CoV-2 infection	At confirmed diagnosis of pneumonia	2.50	56.90	1.44	27.00	0.69	6.00	33.00	32.00	65.60
		After treatment of pneumonia	7.50	77.50	5.77	13.10	0.98	4.99	43.7	17.70	60.40
		At confirmed diagnosis of immunodeficiency	12.60	84.60	10.63	8.10	1.02	5.99	42.1	15.40	64.60
		After treatment of immunodeficiency	4.40	73.70	3.24	17.00	0.75	5.00	81.20	53.20	76.70
	Second SARS-CoV-2 infection	At confirmed diagnosis of immunodeficiency	9.00	87.30	7.85	9.40	0.84	7.71	25.30	20.70	69.50
		Before confirmed diagnosis of endocrine imbalance	7.30	68.40	5.03	23.70	1.74	5.09	46.60	28.90	85.60
		After treatment of endocrine imbalance	5.10	63.60	3.42	26.50	1.42	5.27	36.80	21.00	80.60
	At 3-month follow-up after treatment		4.8	71.2	3.42	18.6	0.90	4.95	25.7	19.7	78.8
Patient 2			5.60	69.00	3.87	26.8	1.50	5.15	10.80	17.50	68.70
Patient 3			6.30	61.80	3.87	25.50	1.60	5.12	13.90	15.50	57.70
Patient 4			5.20	59.00	3.08	20.7	1.55	6.58	23.70	17.10	77.00
Patient 5			2.10	49.40	1.09	42.1	0.93	–	27.50	47.70	24.90

Factor			TP (g/L)	ALB (g/L)	K^+ (mmol/L)	Na^+ (mmol/L)	Cl^- (mmol/L)	Ca^{2+} (mmol/L)	Mg^{2+} (mmol/L)	Zn (μmol/L)
Normal reference range			**65–85**	**40–55**	**3.6–5.2**	**137–147**	**99–110**	**2.11–2.52**	**0.75–1.02**	**9–20.7**
Patient 1	First SARS-CoV-2 infection	At confirmed diagnosis of pneumonia	–	–	3.90	139.3	106.2	2.20	0.90	2.20
		After treatment of pneumonia	62.40	41.40	4.01	138.9	103.2	2.15	0.77	–
		At confirmed diagnosis of immunodeficiency	62.10	28.70	–	–	–	2.07	0.80	6.10
		After treatment of immunodeficiency	75.60	35.90	4.23	135.5	102.0	2.14	0.72	13.60
	Second SARS-CoV-2 infection	At confirmed diagnosis of immunodeficiency	78.70	38.50	4.10	138.6	102.2	2.16	0.78	8.50
		Before confirmed diagnosis of endocrine imbalance	69.10	28.80	3.68	142.5	103.3	–	0.76	10.40
		After treatment of endocrine imbalance	67.10	36.20	3.95	138.5	99.50	2.27	0.91	–
	At 3-month follow-up after treatment		54.05	38.05	4.02	142.6	102.8	2.08	0.89	6.90
Patient 2			71.70	45.00	3.89	145.0	105.9	2.20	0.81	–
Patient 3			63.40	38.30	3.64	140.7	105.6	2.00	0.80	–
Patient 4			69.20	44.80	3.44	143.5	105.4	2.10	–	–
Patient 5			50.10	21.50	3.87	137.4	104.9	1.80	0.54	4.70

WBC: white blood cell; LYMPH: lymphocytes; FBG: fasting blood glucose; ALT: alanine aminotransferase; AST: aspartate aminotransferase; Cr: creatinine; TP: total protein; ALB: albumin.

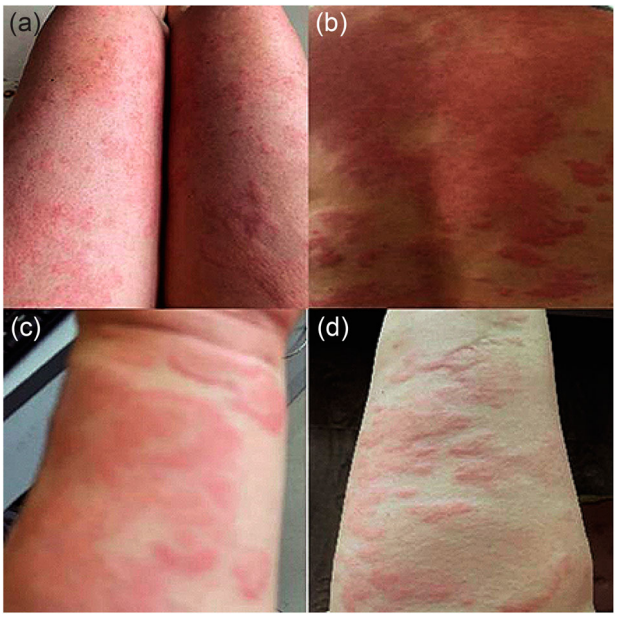

Figure 2: Generalised rash of patient 1.

Table 1 lists the patient's haematological and biochemical data. The patient was then diagnosed with secondary immunodeficiency and hypoalbuminaemia. Treatment includes oral and intravenous corticosteroids, high-dose intravenous immunoglobulin, a high-protein diet, and daily intravenous albumin infusions (10 g/day, for 4 days). Despite these treatments, plasma albumin levels continued to decline (see Table 1). To address this, recombinant human growth hormone (rhGH, 30 IU/3 mL; Jinsai Pharmaceutical Co., Changchun, China) was injected subcutaneously every night at doses of 1.0–1.5 IU. After five days of treatment, PBL and serum albumin levels returned to normal. Fourteen days before readmission, the patient contracted SARS-CoV-2 again. Seven days before readmission, she experienced intermittent fever (37.2–37.5°C), fatigue, and insomnia without respiratory symptoms. The day before readmission, the patient again developed a generalised rash (Figure 2).

As the oral antiviral medications did not produce a satisfactory effect, the patient was readmitted to the hospital for further treatment. The physical examination revealed scattered red rashes, slightly elevated skin temperature, and non-blanching rashes under pressure. No abnormalities were observed in the heart, lungs, or abdomen. Laboratory tests revealed PBL of 0.84×10^9/L and albumin of 38.5 g/L (see Table 1). Chest CT showed no abnormalities. Treatment with cortisol and high-dose intravenous immunoglobulin for one week resulted in complete regression of the rash, but non-pitting oedema, fatigue, insomnia, and brain fog persisted. Furthermore, the patient reported intermittent sensations of 'ant crawling' on the skin, along with muscle twitching, stiffness, and pain.

Further laboratory tests revealed abnormalities in high thyroid peroxidase and prolactin levels. ITT indicated insufficient GH, cortisol, and ACTH under hypoglycaemic stress, especially at 60, 90, and 120 minutes. Arginine stimulation test results showed that GH levels increased 7–8-fold at 0 and 30 minutes, but decreased significantly at 60, 90, and 120 minutes. Additionally, cortisol and ACTH levels were insufficient, with significant reduction at 60, 90, and 120 minutes. Rapid ACTH stimulation test showed an approximately 2.5-fold increase in plasma cortisol (Table 2). The patient exhibited abnormal levels of aldosterone and renin, with increased 24-hour urine aldosterone, decreased 24-hour urine free cortisol, and increased 24-hour urine creatinine (Table 2). Pituitary magnetic resonance imaging (MRI) revealed pituitary enlargement (Figure 3), while adrenal computed tomography (CT) indicated a suspicious nodule in the left adrenal gland (Figure 4), suggestive of an adenoma. The patient was diagnosed with hypothalamic syndrome, pituitary inflammation, secondary adrenal insufficiency, secondary GH deficiency, secondary hyperaldosteronism, secondary immunodeficiency, hypoalbuminaemia, hypocalcaemia, and hypomagnesaemia, as well as a pending confirmation of adrenalitis.

The treatment plan included: (1) weekly intramuscular injection of ACTH (25 IU); (2) morning and afternoon doses of methylprednisolone (4 and 2 mg, respectively, with an additional 4 mg during stressful situations) and tapering to 4 mg in the morning after one month; (3) nightly subcutaneous injection of rhGH (2.0 IU); (4) twice-daily oral finerenone (10 mg); and (5) supplementation with calcium, magnesium, and zinc elements. After one week of treatment, generalised oedema subsided, sleep improved, and symptoms such as brain fog disappeared. At three-month follow-up, cortisol, ACTH, and GH levels showed apparent improvement, and autoimmune thyroid antibodies returned to normal.

Patient 2

A 53-year-old female was admitted to our hospital on July 20, 2023. She had previously contracted SARS-CoV-2 in December 2022, experiencing symptoms such as fever, cough, and sputum production. After one week of treatment, these symptoms improved. However, three months before admission, she began experiencing symptoms such as excessive sweating, cold intolerance, fatigue, intermittent joint and muscle pain, and poor sleep. Additionally, there was oedema in her hands and lower extremities, with the oedema becoming more pronounced over time.

Physical examination upon admission revealed no abnormalities in the heart, lungs, or abdomen. Haematological analysis details are indicated in Table 1. The circadian rhythm of serum cortisol levels was 339.3 nmol/L at 8 am, 221.1 nmol/L at 4 pm, and 32.37 nmol/L at 0 am. The circadian rhythm of serum ACTH levels was 7.05 pmol/L at 8 am, 2.55 pmol/L at 4, and 0.86 pmol/L at 0 am. The results of ITT, arginine stimulation test, rapid ACTH stimulation test, and supine–standing test are detailed in Table 2. The diagnosis for the patient included hypothalamic syndrome with secondary adrenal insufficiency and secondary GH deficiency, secondary hyperaldosteronism, and primary hypothyroidism.

The treatment plan included (1) weekly intramuscular injection of ACTH (12.5 IU); (2) morning and afternoon dose of prednisone acetate (2.5 and 1.25 mg, respectively, with an additional 2.5 mg during stressful situations) and tapering to 2.5 mg in the morning after one month; (3) twice-daily oral finerenone at 5 mg, eventually reduced to 5 mg in the morning after one month. Remarkable improvement in symptoms was observed after one week of treatment.

Patient 3

A 38-year-old female patient was admitted to our hospital on July 5, 2023. Four years earlier, she was diagnosed with type 2 diabetes, took oral medication for one year, and discontinued this herself. In December 2022, she contracted SARS-CoV-2, with symptoms of cough, sputum production, and fatigue.

Table 2: Endocrine hormones analysis of the five patients

Factor			Insulin tolerance test (ITT)				Arginine stimulation test				Rapid ACTH test	
			GLU (mmol/L)	GH (mIU/L)	Cortisol (nmol/L)	ACTH (pmol/L)	GLU (mmol/L)	GH (mIU/L)	Cortisol (nmol/L)	ACTH (pmol/L)	Cortisol (nmol/L)	ACTH (pmol/L)
			3.90–6.10	0.09–11.50	133.0–537.0 (6–10 am) 68.20–327.0 (4–8 pm)	1.59–13.96	3.90–6.10	0.09–11.50	133.0–537.0 (6–10 am) 68.20–327.0 (4–8 pm)	1.59–13.96	133.0–537.0 (6–10 am) 68.20–327.0 (4–8 pm)	1.59–13.96
Patient 1	Before treatment	Baseline	5.27	6.06	274.8	2.45	5.91	< 0.06	49.03	0.58	206.4	2.53
		0 min	1.05	4.32	229.0	0.27	8.46	7.59	42.50	0.75	208.8	> 440.4
		30 min	4.67	3.69	372.6	0.38	7.32	8.78	43.99	0.85	469.7	> 440.4
		60 min	4.99	3.69	382.2	0.25	5.80	3.34	51.50	1.02	532.8	> 440.4
		90 min	6.95	2.52	230.0	0.25	5.68	1.35	50.63	0.91	–	–
		120 min	5.75	2.73	302.8	<0.22	6.12	0.91	50.24	0.94	–	–
	After treatment	Baseline	4.99	3.99	350.5	3.01	5.14	41.31	362.4	1.90	261.0	1.89
		0 min	1.21	15.38	275.7	2.09	7.25	57.84	308.7	1.59	287.9	> 440.4
		30 min	2.04	27.92	458.6	5.65	5.36	44.68	272.4	1.57	624.3	> 440.4
		60 min	3.61	14.56	508.6	9.64	5.43	30.78	220.1	1.40	687.7	> 440.4
		90 min	5.32	5.63	420.6	3.03	5.56	16.33	176.6	1.13	–	–
		120 min	5.21	3.52	328.9	1.43	5.05	9.17	148.6	0.98	–	–
Patient 2		Baseline	5.15	0.72	224.7	2.47	7.28	8.63	256.2	2.73	275.0	5.78
		0 min	1.52	0.22	191.7	1.86	4.84	4.15	254.8	4.36	345.3	> 440.4
		30 min	2.32	8.73	156.2	2.19	5.35	2.41	232.2	3.03	517.8	> 440.4
		60 min	5.51	3.91	190.6	2.34	4.99	7.32	174.9	2.37	570.5	> 440.4
		90 min	3.02	0.80	137.6	1.82	5.21	2.35	138.9	2.12	–	–
		120 min	5.01	0.33	185.9	3.28	5.37	1.01	134.9	2.00	–	–
Patient 3		Baseline	5.63	0.34	179.9	3.37	5.38	2.93	242.6	4.76	–	–
		0 min	2.53	0.06	148.9	3.56	7.67	11.06	185.5	5.90	–	–
		30 min	5.42	0.17	208.6	6.55	6.12	6.24	200.1	6.24	–	–
		60 min	5.86	< 0.06	268.7	6.58	4.95	1.92	161.2	5.69	–	–
		90 min	4.51	< 0.06	233.8	6.61	5.44	0.44	166.7	7.01	–	–
		120 min	4.97	0.56	244.0	7.70	5.51	0.11	144.2	5.96	–	–
Patient 4		Baseline	7.41	0.07	435.2	9.53	7.06	0.10	323.6	3.49	269.80	3.43
		0 min	3.04	4.12	402.7	5.63	9.25	4.00	222.4	2.29	312.30	> 440.4
		30 min	6.53	4.69	460.4	6.06	8.89	2.21	195.8	2.43	660.9	> 440.4
		60 min	6.07	0.83	360.2	3.93	7.27	1.77	187.2	2.65	668.6	> 440.4
		90 min	6.47	0.25	276.1	1.98	6.55	0.45	184.6	2.99	–	–
		120 min	5.10	0.06	226.0	2.46	6.23	0.11	225.7	3.51	–	–

(*Continued*)

Table 2: Continued.

Factor			Insulin tolerance test (ITT)				Arginine stimulation test				Rapid ACTH test	
			GLU (mmol/L)	GH (mIU/L)	Cortisol (nmol/L)	ACTH (pmol/L)	GLU (mmol/L)	GH (mIU/L)	Cortisol (nmol/L)	ACTH (pmol/L)	Cortisol (nmol/L)	ACTH (pmol/L)
Patient 5		Baseline	11.89	13.67	332.4	6.58	10.84	12.93	480.9	17.69	175.0	2.63
		0 min	2.97	50.43	433.3	32.62	10.11	14.58	365.7	11.96	162.8	> 440.4
		30 min	7.76	33.02	443.3	15.49	10.51	32.70	339.5	8.86	564.3	> 440.4
		60 min	9.65	20.89	370.6	7.54	9.83	19.44	278.0	6.83	620.4	> 440.4
		90 min	6.21	20.54	344.8	7.11	9.20	17.85	253.2	6.27	–	–
		120 min	6.97	11.56	249.5	3.77	8.88	13.03	197.1	5.46	–	–

			Supine–standing test								
			ALD (pg/mL)	REN (pg/mL)	ARR	Cortisol (nmol/L)	ACTH (pmol/L)	24 h urine free cortisol (μg/24 h)	24 h urine ALD (nmol/24 h)	IGF-1 (ng/mL)	Prolactin (μIU/mL)
			10–160 (supine) 40–310 (standing)	2.4–32.8 (supine) 3.8–38.8 (standing)	< 30	133–537 (6–10 am) 68.2–327 (4–8 pm)	1.59–13.96	3.5–45 (for adults)	< 16.5	50.0–317.0	102–496
Patient 1	Before treatment	Supine	183.7	24.50	7.02	33.07	0.67	< 3.90	49.00	278.9	505.7
		Standing	493.4	76.78	6.43	140.7	2.96				616.5
	After treatment	Supine	133.4	18.22	7.32	–	–	18.00	36.70	–	529.1
		Standing	388.6	43.58	8.92	–	–				
Patient 2		Supine	82.29	0.50	164.6	363.1	8.30	26.00	6.80	133.6	17.8
		Standing	98.66	2.15	45.89	318.1	8.93				
Patient 3		Supine	119.1	3.87	30.78	302.3	8.86	14.20	17.00	154.2	–
		Standing	225.5	10.69	21.10	223.5	3.46				
Patient 4		Supine	–	–	–	–	–	23.20	13.20	133.4	269.9
		Standing	–	–	–	–	–				
Patient 5		Supine	83.57	1.46	57.24	172.30	9.25	33.60	6.70	21.70	109.9
		Standing	115.15	5.70	20.20	406.10	16.58				

GLU: blood glucose; GH: growth hormone; ACTH: adrenocorticotropic hormone; ALD: aldosterone; REN: renin; ARR: aldosterone/renin ratio; IGF-1: insulin-like growth factor 1.

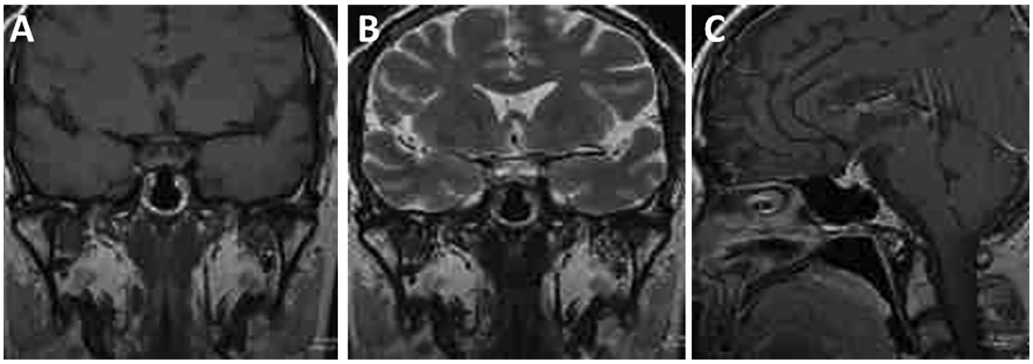

Figure 3. Magnetic resonance imaging of the pituitary in patient 1 upon hospital admission. (A) Coronal T1-weighted image. (B) Coronal T2-weighted image. (C) sagittal image.

The patient self-administered unspecified oral antiviral medications and showed improvement within a week. Two months before admission, she began experiencing intermittent fatigue, plus non-pitting oedema of the face and extremities, along with numbness and pain in the back. Occasional blurred vision, chest tightness, and dyspnoea occurred after light physical labour.

Physical examination revealed non-pitting oedema of the face and lower limbs (Figure 5). No abnormal findings were observed in the heart, lungs, and abdomen. Table 1 lists the patient's haematological and biochemical data. Thyroid function was normal. The circadian rhythm of serum cortisol levels was 176.5 nmol/L at 8 am, 129.9 nmol/L at 4 pm, and 37.26 nmol/L at 0 am. The circadian rhythm of serum ACTH levels was 6.31 pmol/L at 8 am, 2.26 pmol/L at 4, and 1.20 pmol/L at 0 am. The results of ITT, arginine stimulation test, and supine–standing test are detailed in Table 2. The diagnosis for this patient included hypothalamic syndrome with secondary adrenal insufficiency and secondary GH deficiency, secondary hyperaldosteronism, hypoalbuminaemia, hypocalcaemia, hypomagnesaemia, and type 2 diabetes.

The treatment plan included (1) prednisone acetate 5.0 mg in the morning, 2.5 mg in the afternoon, and an additional 2.5 mg during stressful situations; (2) rhGH at a nightly dosage of 2.0 IU; and (3) finerenone 10 mg twice daily. Following one week of treatment, notable improvements were observed, with fatigue alleviating and oedema diminishing remarkably.

Patient 4

A 59-year-old male patient was admitted to our hospital on July 18, 2023, reporting intermittent fatigue and skin itching within the last 6 months, with a recent worsening of symptoms over the last month. The patient had a 15-year history of type 2 diabetes and hypertension. In December 2022, the patient contracted SARS-CoV-2, presenting symptoms of cough, limited sputum production, fever (peaking at 38.5°C), and generalised muscle pain. Despite self-administration of oral acetaminophen and traditional Chinese medicine, and a subsequent negative result in the SARS-CoV-2 examination, there was no improvement. The persistent cough continued for over four months, accompanied by intermittent itching of the neck and back. In the past month, skin itching had worsened, extended to the lower back and ankles, and was accompanied by nasal congestion and rhinorrhoea.

No abnormality was found on physical examination. Table 1 lists the patient's haematological and biochemical data. The circadian rhythm of serum cortisol levels was 295.4 nmol/L at 8 am, 178.7 nmol/L at 4 pm, and 81.34 nmol/L at 0 am. The circadian rhythm of serum ACTH levels was 4.61 pmol/L at 8 am, 2.21 pmol/L at 4, and 1.31 pmol/L at 0 am. The results of ITT, arginine stimulation test, and rapid ACTH stimulation test are detailed in Table 2. The diagnosis for this patient included hypothalamic syndrome with secondary adrenal insufficiency and secondary GH deficiency, secondary hyperaldosteronism, hypothyroidism, type 2 diabetes, and hypertension.

Treatment involved oral finerenone (10 mg, twice daily). One week after discharge, the patient was reinfected with SARS-CoV-2, presenting with fever (38–38.9°C), cough, minimal sputum production, chest tightness, dyspnoea, scattered skin rashes, and itching. The physical examination indicated a pulmonary infection, manifested by moist rales in both lungs and a lymphocyte count of 0.64×10^9/L. The patient was given antiviral treatment with nirmatrelvir/ritonavir and methylprednisolone sodium succinate (40 mg twice

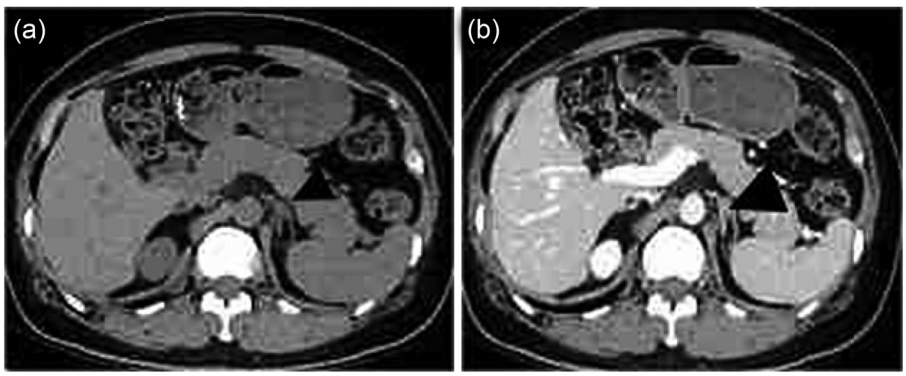

Figure 4: Computed tomography images of the left adrenal gland in patient 1. (A) Plain scan. (B) Contrast-enhanced scan.

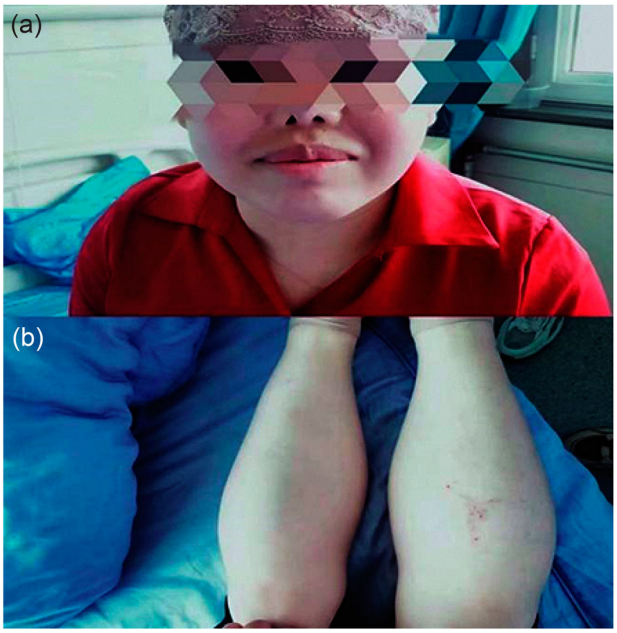

Figure 5: Non-pitting oedema of the face and bilateral lower limbs in patient 3.

daily), along with appropriate symptomatic treatments of infection, resulting in significant improvement after 24 hours. After discharge, the patient received: (1) weekly intramuscular injection of ACTH (25 IU); (2) hydrocortisone (4 mg) in the morning; (3) rhGH at a nightly dosage of 2.0 IU; and (4) finerenone (10 mg twice daily). At one-month follow-up, significant improvement was noted, with stabilised blood sugar reaching normal standard.

Patient 5

A 33-year-old female was admitted to our hospital on July 17, 2023, reporting fatigue and weight loss for 3 months, and oedema for the last 2 days. Medical history included tuberculous peritonitis, cirrhosis, hypersplenism, and upper gastrointestinal bleeding. In November 2022 she had contracted SARS-CoV-2, experiencing symptoms of fever, cough, and muscle pain. Self-administered medication led to recovery within 10 days (the specific medication was unknown). Three months ago, she once again experienced symptoms of low-grade fever, sore throat, and muscle pain, which were relieved within 10 days through self-medication (the specific medication was unknown). Despite this, symptoms of fatigue and weight loss persisted. Furthermore, she noted intermittent foamy urine, with no changes in urine colour or volume. Over the past six months, she gradually lost approximately 10 kg in weight. Two days before admission, she developed bilateral lower limb oedema, worsening with physical activity.

The physical examinations indicated normal findings in the heart and lungs. However, abdominal examination showed positive shifting dullness, while oedema was noted bilaterally in the lower limbs during assessment of the extremities. Abdominal CT revealed cirrhosis, splenomegaly, and a large amount of ascites. Table 1 lists the patient's haematological and biochemical data. The circadian rhythm of serum cortisol levels was 392.4 nmol/L at 8 am, 248.6 nmol/L at 4 pm, and 45.03 nmol/L at 0 am. The circadian rhythm of serum ACTH levels was 8.43 pmol/L at 8 am, 6.17 pmol/L at 4, and 0.54 pmol/L at 0 am. The results of ITT, arginine stimulation test, and rapid ACTH stimulation test are detailed in Table 2. The patient was diagnosed with hypothalamic syndrome with secondary adrenal insufficiency and secondary GH deficiency, secondary hyperaldosteronism, type 1 diabetes, and decompensated cirrhosis (ascites, hypoalbuminaemia, portal hypertension, splenic hyperfunction, leukopaenia, and thrombocytopaenia).

The treatment plan included: (1) weekly intramuscular injection of ACTH (12.5 IU); (2) prednisone acetate 5.0 mg in the morning, 2.5 mg in the afternoon, and an additional 2.5 mg during stressful situations; (3) rhGH at a nightly dosage of 2.0 IU; and (4) finerenone 2 mg twice daily. Following one week of treatment, fatigue and oedema remarkably improved, her spirits became better, and weight increased. One month later, the patient self-discontinued ACTH and rhGH and reported regaining the ability to perform daily work.

Discussion

Infection with SARS-CoV-2 has been implicated in hypothalamic damage through the activation of ACE2 receptors. leading to dysfunction of multiple endocrine hormone axes.[24,25] The impairment of the hypothalamic median eminence can lead to abnormalities in the secretion of ACTH, GH, prolactin, and thyrotropin-releasing hormone (TRH). However, discerning whether abnormalities in ACTH, cortisol, and GH secretion are attributable to hypothalamic damage is challenging in clinical practice. Patient 1, the first in this series, showed unexplained hypoalbuminaemia and elevated creatinine six months before hospitalisation. She developed secondary immunodeficiency within 50 days of diagnosis of SARS-CoV-2 infection (first infection). After second infection, recurrence of secondary immunodeficiency happened in 15 days. Despite treatments, hypoalbuminaemia persisted, with noticeable potassium and sodium fluctuations. To elucidate the cause and pathogenesis of the patient's condition, a dynamic evaluation of multiple endocrine hormone axes was conducted. This evaluation was subsequently validated in four other patients with a history of SARS-CoV-2 infection, all of whom were hospitalised for PCC-related symptoms during the same period.

The hypothalamus plays a dual role in regulating GH secretion from pituitary cells through two mechanisms: (1) via growth hormone-releasing hormone (GHRH) and (2) via somatostatin (growth hormone-inhibiting peptide, GHIP). IGF-1, produced in the liver and peripheral tissues, functionally participates in the negative feedback regulation of GH through IGF-binding proteins (IGF-BP). Therefore, the multiple activities of the GH-IGF-1 axis are primarily regulated through the synergy of GH and IGF-I.[26] While several studies indicated GH deficiency during the acute phase of SARS-CoV-2 infection, and ITT revealed impaired GH response during the convalescent period, the mechanism underlying the impaired GH response in PCC patients remains unclear.[6,14] In normal circumstances, insulin injection triggers a robust increase in GH and cortisol in response to hypoglycaemia. However, in the present study, all five patients exhibited decreased GH secretion, with no peak values observed at 60, 90, and 120 minutes. Arginine stimulation test further showed a two-fold increase in GH levels after arginine stimulation. However, no distinct peaks were observed at 60 and 90 minutes, with values below the lower limit of measurability. Despite normal IGF-1 levels, reduced GH secretion may be attributed to impaired hypothalamic median eminence, coupled with varying degrees of pituitary damage. Notably, damage to the hypothalamic median eminence was also reported to be associated with elevated PRL levels.[27] In the present study,

patients 1–4 exhibited noticeable high PRL levels, further supporting the notion that the hypothalamic median eminence is the damaged site following SARS-CoV-2 infection.[28,29] In clinical practice, if patients with a history of the SARS-CoV-2 infection develop unexplained hypoalbuminaemia during PCC period, it is recommended to explore the possibility of secondary GH deficiency due to hypothalamic and pituitary damage.

The cytokine storm induced by SARS-CoV-2 infection may damage the HPA axis, resulting in adrenal insufficiency and GH deficiency. In the present study, all five patients underwent a comprehensive evaluation, including ITT, arginine stimulation test, rapid ACTH stimulation test, and supine–standing test. The results revealed insufficient cortisol secretion, absence of normal ACTH rhythm, and noticeable reduction in cortisol and ACTH production, particularly in the arginine stimulation test as compared with ITT. Secondary adrenal insufficiency can be attributed to factors such as pituitary inflammation, pituitary infection, pituitary tumours, and prolonged high-dose use of glucocorticoids, which suppress the secretion of corticotropin-releasing hormone (CRH) and ACTH by the hypothalamus and pituitary.[30] In a recent case report involving a women with mild COVID-19, it was concluded that the development of secondary adrenal insufficiency was not attributed to prolonged steroid treatment.[6] Consistent with our study, patients 2–4, who did not receive steroid treatment, exhibited normal levels in 24-hour urinary free cortisol, 24-hour blood cortisol, and ACTH rhythm. These findings suggest that conventional diagnostic procedures for adrenal insufficiency may face challenges in identifying the aetiology for COVID-19 patients with PCC condition exhibiting normal cortisol and ACTH rhythm, 24-hour urinary free cortisol, and rapid ACTH test. Therefore, it is recommended to adopt a timely and scientifically rational diagnostic procedure, as depicted in Figure 1.

While the acute-phase of SARS-CoV-2 infection can potentially lead to an overstimulation of the immune response, the question remains unanswered regarding the presence of autoimmune disease in patients with PCC.[31] In a case report by Suryadevara et al., a patient with type 2 autoimmune polyendocrine syndrome developed adrenal crises due to SARS-CoV-2 infection.[32] In this study, the first patient developed a secondary immunodeficiency with thyroid peroxidase antibody titres that began to rise after the first infection with SARS-CoV-2. Concurrently, she gradually experienced intermittent sensations of skin crawling that worsened after exertion. Symptoms of adrenal insufficiency and the activation of autoimmune thyroiditis became apparent during this period. Subsequent to the second SARS-CoV-2 infection, the patient experienced a recurrent episode of secondary immunodeficiency, characterised by a quick onset, more severe symptoms, and a substantial increase in medication dosage. Furthermore, there was a rise in thyroglobulin antibody titres, a further increase in thyroid peroxidase antibody titres, overall enlargement of the pituitary, and the presence of adrenal masses. These collective observations suggest the possibility that this patient might have been infected with SARS-CoV-2 at an early stage without a diagnosis. Successive triple SARS-CoV-2 vaccinations and two later subsequent SARS-CoV-2 infections may have led to repeated viral attack to the hypothalamus, pituitary, and adrenal glands, resulting in prolonged reduction of adrenocortical hormone and the development of closely related autoimmune diseases.[6,24,25,33]

On the other hand, SARS-CoV-2 infection may affect the renin–angiotensin–aldosterone axis, leading to alterations in angiotensin II and aldosterone levels.[19,22,23] In this study, all patients exhibited secondary hyperaldosteronism. We propose that this condition may be a consequence of glucocorticoid deficiency, as demonstrated in Pomc (−/−) mice lacking endogenous ACTH.[34] The potential mechanism of secondary hyperaldosteronism involves damage to the hypothalamus and/or pituitary, resulting in reduced ACTH levels. This, in turn, causes adrenocortical hormone deficiency and hyponatraemia.[34] Long-term adrenocortical hormone deficiency is characterised by manifestations such as hyponatraemia, elevated plasma potassium, and increased free water, potentially leading to water intoxication. In contrast, secondary hyperaldosteronism is associated with hypokalaemia, elevated plasma sodium, fluid retention, and metabolic alkalosis.[18] Coexistence of both adrenocortical hormone deficiency and hyperaldosteronism in a patient can pose challenges in observing typical changes in plasma sodium and potassium levels. This complexity arises because hyperaldosteronism causes thirst by stimulating the hypothalamus, which in turn accelerates the secretion of antidiuretic hormones. This cascade of effects contributes to potassium excretion, sodium retention, and water conservation.[35–37] In this study, Patient 1 experienced persistent hypotension after two SARS-CoV-2 infections. Following the diagnosis of secondary adrenal insufficiency and secondary hyperaldosteronism, adrenocortical hormones and aldosterone antagonists were administered, resulting in the resolution of generalised oedema.

In these patients with PCC, simultaneous dysfunction in the HPA axis, GH-IGF-1 axis, and renin–angiotensin–aldosterone axis may result in a variety of clinical symptoms, including hyponatraemia, increased free water, formication, rashes, oedema, weakness, fatigue, hypotension, or neuromuscular pain. While ACTH supplementation is thought to alleviate pressure on the hypothalamic–pituitary axis caused by low cortisol levels by stimulating adrenal glands to secrete cortisol, this notion remains controversial.[6] Nonetheless, our study revealed promising outcomes, with all patients showing remarkable improvement after just one to four weeks of multi-hormone combination therapy. For patients with mild symptoms, judicious use of adrenocortical hormones and GH is recommended based on disease condition. Nevertheless, there is a need for careful consideration regarding whether adrenocortical hormones should be used/promptly administered for diabetic patients with the complication of multiple endocrine hormone axes disorders.

Conclusion

Patients after SARS-CoV-2 infections, irrespective of the duration of their PCC, may suffer damage to the hypothalamic median eminence, resulting in dysfunction in the HPA axis, GH-IGF-1 axis, and renin–angiotensin–aldosterone axis. If a patient presents with symptoms as described in this study, a thorough evaluation of hypothalamic and pituitary endocrine function is warranted. Recommended diagnostic tests include the ITT and the supine-–standing test. Once a diagnosis is confirmed, timely supplementation of ACTH, glucocorticoids, GH, and oral aldosterone antagonists can yield remarkable therapeutic outcomes.

Consent to publish

Informed consent from the patient has been obtained.

Disclosure statement – No potential conflict of interest was reported by the authors.

Funding – This project was supported by the 2024 Key Research and Development Project of the Autonomous Region (grant number: 2024BEG02015).

Supplementary data – Supplementary data for this article can be accessed online at https://doi.org/10.1080/16089677.2024.2411924.

References

1. Soriano JB, Murthy S, Marshall JC, et al. A clinical case definition of post-COVID-19 condition by a Delphi consensus. *Lancet Infect Dis*. 2022;22:e102–e107. doi:10.1016/S1473-3099(21)00703-9
2. Dryden M, Mudara C, Vika C, et al. Post-COVID-19 condition 3 months after hospitalisation with SARS-CoV-2 in South Africa: a prospective cohort study. *Lancet Glob Health*. 2022;10:e1247–e1256. doi:10.1016/S2214-109X(22)00286-8
3. Wong MC, Huang J, Wong YY, et al. Epidemiology, symptomatology, and risk factors for long COVID symptoms: Population-based, multicenter study. *JMIR Public Health Surveill*. 2023;9:e42315. doi:10.2196/42315
4. Zimecki M, Actor JK, Kruzel ML. The potential for Lactoferrin to reduce SARS-CoV-2 induced cytokine storm. *Int Immunopharmacol*. 2021;95:107571. doi:10.1016/j.intimp.2021.107571
5. Celardo I, Pace L, Cifaldi L, Gaudio C, Barnaba V. The immune system view of the coronavirus SARS-CoV-2. *Biol Direct*. 2020;15:30. doi:10.1186/s13062-020-00283-2
6. Van A, Kim A, Dolan J. SARS-CoV-2-induced secondary adrenal insufficiency. *Chest*. 2021;160:A959. doi:10.1016/j.chest.2021.07.893
7. Bateman A, Singh A, Kral T, Solomon S. The immune-hypothalamic-pituitary-adrenal axis. *Endocr Rev*. 1989;10:92–112. doi:10.1210/edrv-10-1-92
8. Sanchez J, Cohen M, Zapater JL, Eisenberg Y. Primary adrenal insufficiency after COVID-19 infection. *AACE Clin Case Rep*. 2022;8:51–53. doi:10.1016/j.aace.2021.11.001
9. Profka E, Rodari G, Giacchetti F, Giavoli C. GH deficiency and replacement therapy in hypopituitarism: Insight into the relationships with other hypothalamic-pituitary axes. *Front Endocrinol (Lausanne)*. 2021;12:678778. doi:10.3389/fendo.2021.678778
10. Alvarez-Troncoso J, Zapatero Larrauri M, Montero Vega MD, et al. Case report: COVID-19 with bilateral adrenal hemorrhage. *Am J Trop Med Hyg*. 2020;103:1156–1157. doi:10.4269/ajtmh.20-0722
11. Frankel M, Feldman I, Levine M, et al. Bilateral adrenal hemorrhage in Coronavirus disease 2019 patient: A case report. *J Clin Endocrinol Metab*. 2020;105(12):3745–3749. doi:10.1210/clinem/dgaa487
12. Alzahrani AS, Mukhtar N, Aljomaiah A, et al. The impact of COVID-19 viral infection on the hypothalamic-pituitary-adrenal axis. *Endocr Pract*. 2021;27:83–89. doi:10.1016/j.eprac.2020.10.014
13. Kazakou P, Paschou SA, Psaltopoulou T, et al. Early and late endocrine complications of COVID-19. *Endocr Connect*. 2021;10:R229–R239. doi:10.1530/EC-21-0184
14. Yoshimura K, Yamamoto M, Inoue T, et al. Coexistence of growth hormone, adrenocorticotropic hormone, and testosterone deficiency associated with coronavirus disease 2019: a case followed up for 15 months. *Endocr J*. 2022;69:1335–1342. doi:10.1507/endocrj.EJ22-0108
15. Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell*. 2020;181:271–280.e8. doi:10.1016/j.cell.2020.02.052
16. Wan Y, Shang J, Graham R, Baric RS, Li F. Receptor recognition by the novel Coronavirus from Wuhan: an analysis based on decade-long structural studies of SARS Coronavirus. *J Virol*. 2020;94(7). doi:10.1128/JVI.00127-20
17. Wrapp D, Wang N, Corbett KS, et al. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. *Science*. 2020;367:1260–1263. doi:10.1126/science.abb2507
18. Reindl-Schwaighofer R, Hodlmoser S, Eskandary F, et al. ACE2 elevation in severe COVID-19. *Am J Respir Crit Care Med*. 2021;203:1191–1196. doi:10.1164/rccm.202101-0142LE
19. Nagy B Jr, Fejes Z, Szentkereszty Z, et al. A dramatic rise in serum ACE2 activity in a critically ill COVID-19 patient. *Int J Infect Dis*. 2021;103:412–414. doi:10.1016/j.ijid.2020.11.184
20. Kragstrup TW, Singh HS, Grundberg I, et al. Plasma ACE2 predicts outcome of COVID-19 in hospitalized patients. *PLoS One*. 2021;16:e0252799. doi:10.1371/journal.pone.0252799
21. Wang P, Jin L, Zhang M, et al. Author Correction: Blood–brain barrier injury and neuroinflammation induced by SARS-CoV-2 in a lung–brain microphysiological system. *Nat Biomed Eng*. 2023. doi:10.1038/s41551-023-01141-y
22. Briquez PS, Rouhani SJ, Yu J, et al. Severe COVID-19 induces autoantibodies against angiotensin II that correlate with blood pressure dysregulation and disease severity. *Sci Adv*. 2022;8:eabn3777. doi:10.1126/sciadv.abn3777
23. Campana P, Palaia ME, Conte M, et al. The elderly at risk: aldosterone as modulator of the immune response to SARS-CoV-2 infection. *Geroscience*. 2022;44:567–572. doi:10.1007/s11357-021-00481-4
24. Mortimer CH, Besser GM, McNeilly AS, et al. Luteinizing hormone and follicle stimulating hormone-releasing hormone test in patients with hypothalamic-pituitary-gonadal dysfunction. *Br Med J*. 1973;4:73–77. doi:10.1136/bmj.4.5884.73
25. Gu WT, Zhou F, Xie WQ, et al. A potential impact of SARS-CoV-2 on pituitary glands and pituitary neuroendocrine tumors. *Endocrine*. 2021;72:340–348. doi:10.1007/s12020-021-02697-y
26. Mancini A, Arosio M, Kreitschmann-Andermahr I, Persani L. Editorial: New insights and controversies in diagnosis and treatment of adult growth hormone deficiency. *Front Endocrinol (Lausanne)*. 2022;12:819527. doi:10.3389/fendo.2021.819527
27. Facondo P, Maltese V, Delbarba A, et al. Case report: Hypothalamic amenorrhea following COVID-19 infection and review of literatures. *Front Endocrinol (Lausanne)*. 2022;13:840749. doi:10.3389/fendo.2022.840749
28. Levy S, Arguello M, Macki M, Rao SD. Pituitary dysfunction among men presenting with hypogonadism. *Curr Urol Rep*. 2019;20:78. doi:10.1007/s11934-019-0935-z
29. Buchanan GC, Tredway DR, Pittard JC, et al. Gonadotropin secretion and hypothyroidism. *Obstet Gynecol*. 1977;50:392–396.
30. Guaraldi F, Karamouzis I, Berardelli R, et al. Secondary adrenal insufficiency: Where is it hidden and what does it look like? *Front Horm Res*. 2016;46:159–170. doi:10.1159/000443915
31. Vakhshoori M, Heidarpour M, Bondariyan N, Sadeghpour N, Mousavi Z. Adrenal insufficiency in Coronavirus disease 2019 (COVID-19)-infected patients without preexisting adrenal diseases: A systematic literature review. *Int J Endocrinol*. 2021:2271514. doi:10.1155/2021/2271514
32. Suryadevara V, Merugu C, Perumal NL, et al. Adrenal crisis in a patient with APS2 due to COVID-19: A case report. *J Family Med Prim Care*. 2022;11:2228–2230. doi:10.4103/jfmpc.jfmpc_1405_21
33. Pezzaioli LC, Gatta E, Bambini F, et al. Endocrine system after 2 years of COVID-19 vaccines: A narrative review of the literature. *Front Endocrinol (Lausanne)*. 2022;13:1027047. doi:10.3389/fendo.2022.1027047
34. Linhart KB, Majzoub JA. Pomc knockout mice have secondary hyperaldosteronism despite an absence of adrenocorticotropin. *Endocrinology*. 2008;149:681–686. doi:10.1210/en.2006-1136
35. Patel S, Rauf A, Khan H, Abu-Izneid T. Renin-angiotensin-aldosterone (RAAS): The ubiquitous system for homeostasis and pathologies. *Biomed Pharmacother*. 2017;94:317–325. doi:10.1016/j.biopha.2017.07.091
36. Aung AK, Aitken T, Teh BM, et al. Angiotensin converting enzyme genotypes and mortality from COVID-19: An ecological study. *J Infect*. 2020;81:961–965. doi:10.1016/j.jinf.2020.11.012
37. Hunyady L, Catt KJ. Pleiotropic AT1 receptor signaling pathways mediating physiological and pathogenic actions of angiotensin II. *Mol Endocrinol*. 2006;20:953–970. doi:10.1210/me.2004-0536

Received: 18-03-2024 Accepted: 30-09-2024