AACE Clinical Case Rep. 7 (2021) 2–5

Contents lists available at ScienceDirect

AACE Clinical Case Reports

journal homepage: www.aaceclinicalcasereports.com

Case Report

Delayed Onset of Central Hypocortisolism in a Patient Recovering From COVID-19

Marvin Wei Jie Chua, MBBS (Singapore), MRCP (UK) *,
Melvin Peng Wei Chua, MBChB, MRCP (UK)

Department of General Medicine, Sengkang General Hospital, Singapore

ARTICLE INFO

Article history:
Available online 28 November 2020

Key words:
central hypocortisolism
COVID-19
hypocortisolism

ABSTRACT

Objective: The objective of this report is to highlight the possible but little-known association between coronavirus disease 2019 (COVID-19) and delayed onset of central hypocortisolism, which may be of significant clinical importance.
Methods: We describe a patient who developed new-onset central hypocortisolism in the convalescent phase of mild COVID-19, which has not been previously reported.
Results: A 47-year-old man with recent COVID-19 upper respiratory tract infection developed new-onset persistent dyspepsia and eosinophilia for which multiple investigations were normal. He was eventually diagnosed with central hypocortisolism, as evidenced by 8 AM cortisol level of 19 nmol/L (normal, 133-537 nmol/L) and adrenocorticotropic hormone of 7.1 ng/mL (normal, 10.0-60.0 ng/mL). He was started on hydrocortisone, which led to resolution of both dyspepsia and eosinophilia. At the same time, an interesting thyroid function trend was observed—an initial increase in both free thyroxine and thyroid stimulating hormone was followed by temporary central hypothyroidism before subsequent spontaneous recovery. On follow-up 3 weeks later, the patient remained hypocortisolemic.
Conclusion: COVID-19 may be associated with the delayed onset of central hypocortisolism in its convalescent phase. Although various mechanisms are possible, hypothalamic-pituitary activation during systemic illness, followed by a rebound decrease in activity after recovery, is consistent with the clinical course and thyroid function trend in this patient. It is essential that physicians consider endocrinopathies in the differential diagnosis of such cases, given the risk of life-threatening adrenal crises and their possible contribution to persistent symptoms following recovery from COVID-19.
© 2020 AACE. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Introduction

Hypocortisolism has been reported as a delayed complication of severe acute respiratory syndrome (SARS), a previous coronavirus pandemic. However, a similar occurrence of hypocortisolism in coronavirus disease 2019 (COVID-19) is relatively unknown. We report the case of a patient who developed new-onset central hypocortisolism in the convalescent phase of COVID-19 upper respiratory tract infection (URTI). As far as we are aware, this has not been previously reported.

Case Report

A 47-year-old man with a known history of type 2 diabetes mellitus (HbA1c 6.4% [46 mmol/mol] in July 2020) was admitted for a right tibial wound that had been treated conservatively. In view of his low-grade fever and anosmia, an oropharyngeal swab was done, which tested positive for SARS coronavirus 2 by real-time polymerase chain reaction. The diagnosis was COVID-19 URTI; however, no treatment was given; in particular, the patient did not receive any corticosteroids, including dexamethasone. He was discharged to an isolation facility, but he was readmitted 1 week later due to a new-onset seizure.

Abbreviations: ACTH, Adrenocorticotropic hormone; COVID-19, coronavirus disease 2019; fT4, Free thyroxine; SARS, severe acute respiratory syndrome; TFT, thyroid function test; TSH, thyroid stimulating hormone; URTI, upper respiratory tract infection.

* Address correspondence and reprint requests to Dr Marvin Wei Jie Chua, Department of General Medicine, Sengkang General Hospital, 110 Sengkang East Way, Singapore 544886.
E-mail address: marvin.chua.w.j@singhealth.com.sg (M.W.J. Chua).

https://doi.org/10.1016/j.aace.2020.11.001
2376-0605/© 2020 AACE. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Table 1
Initial Investigations

Investigation	Results	Reference Range	Remarks
Full blood count			
Hemoglobin (g/dL)	14.6	14.0-18.0	Normal
White blood cells (10^9/L)	8.33	4.00-10.00	Normal
Absolute neutrophil count (10^9/L)	2.98	2.00-7.50	Normal
Absolute lymphocyte count (10^9/L)	2.66	1.00-3.00	Normal
Absolute eosinophil count (10^9/L)	**1.54**	0.04-0.44	**Increased**
Platelets (10^9/L)	294	140-440	Normal
Biochemistry profile			
Sodium (mmol/L)	136	136-146	Normal
Potassium (mmol/L)	3.8	3.5-5.1	Normal
Urea (mmol/L)	0.9	2.0-6.9	Normal
Creatinine (μmol/L)	75	59-104	Normal
Glucose (mmol/L)	7.0	3.9-11.0	Normal
Inflammatory Markers			
C-reactive protein (mg/L)	1.1	0.2-9.1	Normal
Procalcitonin (μg/L)	<0.06	≤0.49	Normal
Chest x-ray			
There is no consolidation or effusion.			
Computed tomography of the brain			
There is no infarct, acute intracranial hemorrhage, space-occupying lesion, or mass effect.			
Cerebrospinal fluid			
White blood cells (/μL)	0	N/A	Normal
Red blood cells (/μL)	**50**	N/A	Suggests mild trauma from lumbar puncture
Glucose (mmol/L)	3.80	2.22-3.89	Normal
Total protein (mmol/L)	0.32	0.15-0.45	
Gram stain and culture	Clear. Nil leukocytes or organisms seen. No bacterial growth.		
Acid-fast bacilli smear	No acid-fast bacilli seen		
Mycobacterium tuberculosis DNA amplification	Not detected		
Severe acute respiratory syndrome coronavirus 2 polymerase chain reaction	Not detected		
Cytomegalovirus, Herpes Simplex, *Varicella Zoster*, *Toxoplasma Gondii* polymerase chain reaction	Not detected		
Endocrine			
Cortisol (nmol/L)	**19**	133-537	**Decreased** Done at 8 AM
Adrenocorticotropic hormone (ng/L)	**7.1**	10.0-60.0	**Decreased**
Free thyroxine (pmol/L)	**10.6**	12.7-20.3	**Decreased**
Thyroid stimulating hormone (mIU/L)	2.99	0.701-4.28	Normal
Thyroid peroxidase antibodies (IU/mL)	1.1	<9.0	Normal
Follicle-stimulating hormone (U/L)	5.0	Male: 1.5-12.4	Normal
Luteinizing hormone (U/L)	6.5	Male: 1.7-8.6	Normal
Total testosterone (nmol/L)	20.4	7.3-27.4	Normal
Cosyntropin (250 μg) stimulation test (done at 8 AM)			
0-min cortisol (nmol/L)	**36**	Peak cortisol levels of >550 nmol/L suggests intact hypothalamo-pituitary-adrenal axis	**Decreased**
30-min cortisol (nmol/L)	**100**		
60-min cortisol (nmol/L)	**115**		
Magnetic resonance imaging of the brain			
There is no acute infarct or hemorrhage. No pituitary lesion or mass appreciated.			

On initial assessment, the patient was afebrile (36.5 °C) with normal blood pressure (118/77 mm Hg), heart rate (96 beats/min), and oxygen saturation (96% on room air). The patient was oriented with a Glasgow Coma Scale score of 15, and there were no signs of meningism or neurologic deficits. The rest of the physical examination was unremarkable. Apart from eosinophilia, blood and cerebrospinal fluid investigations were unremarkable (Table 1).

The patient developed new-onset persistent dyspepsia but computed tomography of the abdomen and esophago-gastroduodenoscopy were normal. Persistent eosinophilia raised the suspicion of hypocortisolism, which was promptly confirmed. Adrenocorticotropic hormone (ACTH) level was low, consistent with central hypocortisolism (Table 1). The patient remained hemodynamically stable and was started on hydrocortisone 10 mg in the morning and 5 mg in the evening, which led to resolution of both the dyspepsia and eosinophilia.

An initial thyroid function test (TFT) done during the first admission for COVID-19 URTI showed elevation in both free thyroxine (fT4) and thyroid stimulating hormone (TSH) levels (Table 2). Subsequently, there was a progressive decrease in both TSH and fT4; at the time of diagnosis of hypocortisolism, fT4 was decreased but TSH was normal, which was suggestive of central hypothyroidism. However, thyroid function spontaneously normalized at 6 weeks after the initial TFT (Table 2). There were no other anterior pituitary hormone deficiencies, and magnetic resonance imaging of the brain did not reveal any pituitary lesions. Cortisol and ACTH remained low 3 weeks after the initiation of hydrocortisone replacement (Table 2).

Table 2
Trend of Cortisol, Adrenocorticotropic hormone, and Thyroid Function

Investigation	D − 20	Reference Range	Remarks	D − 2	D + 0	Remarks	D + 23	Reference Range	Remarks
Cortisol (nmol/L)	N/A	N/A	N/A	N/A	**19**	**Decreased;**	**20**	133-537	**Decreased**
Adrenocorticotropic hormone	N/A	N/A	N/A	N/A	**7.1**	Done at 8 AM. Hydrocortisone initiated on D + 0.	**7.9**	10.0-60.0	Done at 8 AM. Hydrocortisone was withheld for 24 h prior to tests.
Free thyroxine (pmol/L)	**15.9**	8.8-14.4	Initial thyroid function test was done during the first admission for coronavirus disease 2019 upper respiratory tract infection	**11.2**	**10.6**	Not applicable	12.7	12.7-20.3	The change in the reference range for thyroid function test done from D − 2 onwards was due to different thyroid assay used (logistic reasons).
Thyroid stimulating hormone (mIU/L)	**5.54**	0.65-3.70		**4.51**	2.99		3.7	0.701-4.28	

Discussion

There is some published literature on the impact of COVID-19 on established endocrinopathies and vice versa. New-onset hypocortisolism has been reported in a patient with severe COVID-19 who presented with vasopressor-refractory hypotension; however, its etiology was unclear as data on ACTH levels was not available.[1] In a retrospective study of 219 patients with severe COVID-19, radiological evidence of acute adrenal infarction was noted in 23% of the patients; among these, 8% had biochemical hypocortisolism[2]. Several mechanisms have been proposed, including a cytokine storm with increased production of pro-inflammatory cytokines such as tumor necrosis factor-α, which leads to decreased ACTH release and impaired function of ACTH and angiotensin-2 on adrenal cells.[1,3] A prothrombotic state culminating in disseminated intravascular coagulation has been described, which might be contributed to by direct viral endothelial cell invasion.[1,3,4] Other possible mechanisms of hypocortisolism in severe COVID-19 include decreased availability of high-density lipoprotein cholesterol—an essential substrate for cortisol production, decreased cortisol-binding globulin, and increased activity of the 11-β-hydroxysteroid dehydrogenase type 2 enzyme responsible for cortisol inactivation.[1] However, the development of central hypocortisolism in the convalescent phase of mild COVID-19 has not been reported previously.

Proposed mechanisms of the central hypocortisolism seen in our patient include both direct and indirect effects of COVID-19. Direct hypophysitis could occur due to viral neuro-invasion from hematogenous spread, retrograde axonal transport, or entry via the angiotensin converting enzyme receptor.[5] Strengthening this hypothesis was our patient's presentation with seizures, which is believed to be due to similar mechanisms.[5] This notwithstanding, indirect effects are equally worthy of consideration. An interesting possibility is hypothalamic-pituitary activation with chronic cortisol hypersecretion during systemic illness, followed by a rebound decrease in hypothalamic-pituitary activity after recovery.[6] In our patient, the occurrence of this mechanism was supported by his thyroid function trend. In addition, SARS coronavirus infection has been postulated to lead to antibody-mediated destruction of the ACTH through molecular mimicry. As the proteins of SARS coronavirus 2 share 95% to 100% homology with those of SARS coronavirus, similar mechanisms could also be responsible in COVID-19.[7]

We can draw invaluable lessons from a previous coronavirus pandemic, i.e., SARS caused by the SARS coronavirus. In a study of 61 SARS survivors, 39.3% had hypocortisolism, and of these, 83.3% had central hypocortisolism. The onset of hypocortisolism occurred at several weeks post-infection, with 62.5% resolving within one year[8]. This illustrates 3 important points pertinent to COVID-19. First, there is a significant incidence of hypocortisolism, and thereby, risk of life-threatening adrenal crises. Second, onset is usually in the convalescent phase, as seen in our patient. Third, it is likely that most cases would be transient and would spontaneously resolve; even though this was not observed in our patient, clarification from further studies is awaited.

Our patient's TFT trend was intriguing. His initial hyperthyroxinemia (elevation in fT4) and hyperthyrotropinemia (elevation in TSH) could be attributed to hypothalamic-pituitary activation during acute illness.[6] With recovery, decrease in hypothalamic-pituitary activity led to a progressive decrease in TSH and, therefore fT4, with temporary central hypothyroidism before subsequent recovery. Indeed, we propose that this is the most likely mechanism that accounts for both central hypocortisolism and thyroid dysfunction in our patient. In the aforementioned study by Leow et al[8], 3 patients with SARS developed central hypothyroidism, 2 of whom had concomitant central hypocortisolism; nonetheless, thyroid function spontaneously normalized between 3 to 9 months in all. In both coronavirus infections, a consistent reduction in TSH and T3 has been observed which was correlated with disease severity.[9,10] This further strengthens our theory that both viruses act through similar pathophysiologic mechanisms.

Another possible etiology of thyroid function abnormalities is hypocortisolism itself. As cortisol exerts an inhibitory effect on TSH secretion, hyperthyrotropinemia might be encountered in hypocortisolism, which often normalizes following corticosteroid replacement.[11-13] Hyperthyroxinemia has also been described in hypocortisolism, which is believed to be due to loss of the inhibitory effect of thyroxine on TSH, leading to a state of acquired thyroid hormone resistance.[11] However, as both hyperthyroxinemia and hyperthyrotropinemia spontaneously resolved in our patient prior to corticosteroid replacement (Table 2), this explanation is less likely.

A specific point to highlight is the possible contribution of hypocortisolism and thyroid dysfunction to persistent symptoms following recovery from COVID-19. The latter is a clinical problem of significant magnitude, yet little is known at present.[14,15] In an Italian study published in the Journal of the American Medical Association, at 60 days post COVID-19 onset, 87.4% of patients reported persistence of at least 1 symptom, the most common being fatigue, dyspnea, or joint pain.[14] Although the etiology of this "post COVID syndrome" is currently unclear, a contributory cause could be underlying endocrinopathy. Indeed, hypocortisolism was proposed to be the cause of similar symptoms in patients recovering from SARS.[6,8]

Conclusion

This report illustrates an important complication of COVID-19: central hypocortisolism, which may have a delayed onset during the convalescent phase of the illness, i.e., at a time when most patients would be expecting to get better. However, little is known about its incidence, natural history, or prognosis. Based on our

observations in this case and previous experience with SARS patients, central hypocortisolism post COVID-19 may be transient, although this remains to be determined. In patients recovering from COVID-19, who should be screened, and at what time points? Due to the huge global burden of COVID-19, risk of life-threatening adrenal crises, and contribution to persistent symptoms post-recovery, these are important questions that need to be answered.

Disclosure

The authors have no multiplicity of interest to disclose.

References

1. Heidarpour M, Vakhshoori M, Abbasi S, Shafie D, Rezaei N. Adrenal insufficiency in coronavirus disease 2019: a case report. *J Med Case Rep*. 2020;14(1):134. https://doi.org/10.1186/s13256-020-02461-2.
2. Leyendecker P, Ritter S, Riou M, et al. Acute adrenal infarction as an incidental CT finding and a potential prognosis factor in severe SARS-CoV-2 infection: a retrospective cohort analysis on 219 patients. *Eur Radiol*. 2020:1–6. https://doi.org/10.1007/s00330-020-07226-5.
3. Li H, Liu L, Zhang D, et al. SARS-CoV-2 and viral sepsis: observations and hypotheses. *Lancet*. 2020;395(10235):1517–1520. https://doi.org/10.1016/S0140-6736(20)30920-X.
4. Varga Z, Flammer AJ, Steiger P, et al. Endothelial cell infection and endotheliitis in COVID-19. *Lancet*. 2020;395(10234):1417–1418. https://doi.org/10.1016/S0140-6736(20)30937-5.
5. Lahiri D, Ardila A. COVID-19 pandemic: a neurological perspective. *Cureus*. 2020;12(4):e7889. https://doi.org/10.7759/cureus.7889.
6. Chrousos GP, Kaltsas G. Post-SARS sickness syndrome manifestations and endocrinopathy: how, why, and so what? *Clin Endocrinol*. 2005;63(4):363–365. https://doi.org/10.1111/j.1365-2265.2005.02361.x.
7. Pal R. COVID-19, hypothalamo-pituitary-adrenal axis and clinical implications. *Endocrine*. 2020;68(2):251–252. https://doi.org/10.1007/s12020-020-02325-1.
8. Leow MK, Kwek DS, Ng AW, Ong KC, Kaw GJ, Lee LS. Hypocortisolism in survivors of severe acute respiratory syndrome (SARS). *Clin Endocrinol*. 2005;63(2):197–202. https://doi.org/10.1111/j.1365-2265.2005.02325.x.
9. Chen M, Zhou W, Xu W. Thyroid function analysis in 50 patients with COVID-19: a retrospective study. *Thyroid*. 2020. https://doi.org/10.1089/thy.2020.0363.
10. Wei L, Sun S, Xu C-H, et al. Pathology of the thyroid in severe acute respiratory syndrome. *Hum Pathol*. 2007;38(1):95–102. https://doi.org/10.1016/j.humpath.2006.06.011.
11. Stryker TD, Molitch ME. Reversible hyperthyrotropinemia, hyperthyroxinemia, and hyperprolactinemia due to adrenal insufficiency. *Am J Med*. 1985;79(2):271–276. https://doi.org/10.1016/0002-9343(85)90022-1.
12. Samuels MH. Effects of variations in physiological cortisol levels on thyrotropin secretion in subjects with adrenal insufficiency: a clinical research center study. *J Clin Endocrinol Metab*. 2000;85(4):1388–1393. https://doi.org/10.1210/jcem.85.4.6540.
13. Bancos I, Hahner S, Tomlinson J, Arlt W. Diagnosis and management of adrenal insufficiency. *Lancet Diabetes Endocrinol*. 2015;3(3):216–226. https://doi.org/10.1016/S2213-8587(14)70142-1.
14. Carfì A, Bernabei R, Landi F. Gemelli Against COVID-19 Post-Acute Care Study Group. Persistent symptoms in patients after acute COVID-19. *JAMA*. 2020;324(6):603–605. Aug. 2020, doi: 10.1001/jama.2020.12603.
15. Halpin SJ, McIvor C, Whyatt G, et al. Postdischarge symptoms and rehabilitation needs in survivors of COVID-19 infection: a cross-sectional evaluation. *J Med Virol*. 2020. https://doi.org/10.1002/jmv.26368.