ESPE Physician Information on COVID-19 and Pediatric Endocrine Diseases

Disease specific information and advice: ADRENAL INSUFFICIENCY

Introduction

A novel coronavirus disease (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has affected (as of October 10, 2020) almost 37,350,000 individuals, claiming more than 1,000,000 lives in over 200 countries worldwide ever since its outbreak in Wuhan, China in December 2019. The disease then rapidly spread from Wuhan to other areas of China and throughout the world. On January 3, 2020, a novel coronavirus—severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2 or 2019-nCoV)—with phylogenetic similarity to the SARS coronavirus (SARS-CoV), the cause of the 2003 SARS outbreak, was isolated in samples of bronchoalveolar lavage fluid from patients in Wuhan and was confirmed as the cause of the novel atypical form of pneumonia (**1**). On March 11, 2020, the World Health Organization (WHO) declared COVID-19 a public health emer- gency of international concern (**2**). As of July 4 2020, 10,922,324 people have been infected and 523,011 people have died from COVID-19 globally. The virus spreads like any other respiratory infectious disease, through contaminated air-droplets of infected persons when talking, coughing, or sneezing. It can survive in the environment from a few hours to a few days, depending on surfaces and environmental conditions. The mouth, nose, and ocular mucosa appears to be the major way of transmission.

In this review, we present a brief overview of the current knowledge on COVID-19 and its relationship with endocrine diseases, and we make recommendations as Pediatric Endocrinologists managing patients with increased susceptibility to Covid-19.

Primary adrenal insufficiency

Currently, there is no evidence indicating that patients with adrenal insufficiency (AI) are at an increased risk for COVID-19 infection. However, several studies have demonstrated that AI patients have a 2-fold to 8-fold higher risk for infection, which inherently increases the risk of death from COVID-19 (**3-8**). In patients with AI, the innate immune response (e.g., natural killer cell cytotoxicity) is impaired, thereby potentially compromising antiviral immune defense mechanisms and increasing patients' susceptibility to respiratory viral infections (**9, 10**). Moreover, the life-long requirement for

supraphysiologic glucocorticoid replacement using currently available preparations may place patients with AI at an increased risk for infectious diseases.

Central (secondary/tertiary) adrenal insufficiency

One of the primary immunoinvasive strategy employed by the SARS-CoV, like influenza virus, is to knock down the host's cortisol stress response. To achieve the same, SARS-CoV expresses certain amino acid sequences that act as molecular mimics of the host adrenocorticotropic hormone (ACTH). The first 24 amino acids of ATCH ($ACTH_{1-24}$) are highly conserved between different mammalian species, while $ACTH_{25-39}$ represents the less conserved region. Six amino acids at positions 26, 29, 31, 33, 37, and 39 represent the antigenically important positions for mammalian ACTH. SARS (and influenza virus) contain many permutations of amino acid sequences with homology to these probable ACTH key residues. Antibodies produced by the host to counteract the virus, in turn, would destroy the host ACTH, thereby preventing the rise in cortisol concentrations. This would imply that all patients with SARS might have underlying relative cortisol insufficiency (**11**). However, data on serum cortisol concentrations in patients with SARS (or COVID-19) are still not available to date.

SARS (and COVID-19) might also affect the hypothalamic-pituitary-adrenal (HPA) axis. HPA axis involvement in SARS was first reported by Leow et al., who evaluated prospectively 61 survivors of the SARS outbreak 3 months after recovery and periodically thereafter. Forty percent of patients had evidence of central hypocortisolism, however, the majority recovered fully within one year. A small percentage of patients also had central hypothyroidism and low dehydroepiandrosterone sulfate concentrations. The authors had proposed the possibility of a reversible hypophysitis or a direct hypothalamic damage that could have led to a state of transient impaired HPA axis function (**12**). Indeed, edema and neuronal degeneration along with SARS-CoV genome had been identified in the hypothalamus on autopsy studies. It is worth noting that frank hypocortisolism has never been documented in patients with active SARS (or COVID-19). A prospective study evaluating serum cortisol and plasma ACTH concentrations in patients with severe COVID-19 is currently ongoing underway (ChiCTR20000301150).

Tertiary adrenal insufficiency owing to exogenous glucocorticoid administration

Chronic exogenous glucocorticoid administration, including topical, inhaled, oral, intra-articular or parenteral administration, is widely used to treat various disorders. Excessive glucocorticoid use itself is associated with severe and intractable courses of viral infections due to the

immunosuppressive actions of glucocorticoids (**13-15**). On the other hand, the anti-inflammatory action of glucocorticoids may mask fever and other indicators of active infection. Therefore, patients taking supraphysiological doses of glucocorticoids may be more susceptible to COVID-19, although there is still limited concrete evidence to support this concept. Furthermore, suppression of the HPA axis in long-term steroid users may cause symptoms of AI. The dose and duration of glucocorticoids that suppress the HPA axis have not been well established and vary considerably depending on the subject's sensitivity to glucocorticoids (**16**). Therefore, these patients should be monitored closely to detect symptoms of AI at an early stage and should be prompted to modify their glucocorticoid replacement dose in order to prevent adrenal crisis and mortality.

Management

Infection is a condition of acute stress that triggers a cytokine-mediated inflammatory response, which requires an increased dose of glucocorticoids. Since adrenal crises precipitated by infections are the major cause of death in AI patients (**17, 18**), an immediate modification of the glucocorticoid regimen, as indicated in so-called "sick day rules," should be conducted at the beginning of an infection. Whenever patients with AI present with cough, sputum, or fever (≥37.5°C), which are symptoms suspicious for COVID-19, they need to immediately double or triple their daily oral glucocorticoid dose and continue with the increased dose until the symptoms resolve in order to avoid adrenal crisis. In addition, patients need to consume more electrolyte-containing fluids. If their condition deteriorates, or they cannot eat due to vomiting or diarrhea, they should be admitted to the hospital to receive intravenous hydrocortisone (**19, 20**). Furthermore, patients are advised to obtain sufficient hydrocortisone and fludrocortisone supplementation to prepare for "sick day rules" and "social distancing" during the COVID-19 outbreak in order to maintain the social confinement when required for impeding the COVID-19 outbreak spread.

References:

1. Lu R, Zhao X, Li J, Niu P, Yang B, Wu H, et al.Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet 2020; 395: 565-74.
2. World Health Organization. WHO Director-General's open- ing remarks at the media briefing on COVID-19—11 March 2020 [Internet]. Geneva: World Health Organization; 2020 [cited 2020 Apr 20]. Available from: https://www.who.int/ dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020.

3. Bergthorsdottir R, Leonsson-Zachrisson M, Oden A, Johannsson G. Premature mortality in patients with Addison's disease: a population-based study. J Clin Endocrinol Metab 2006; 91: 4849-53.
4. Erichsen MM, Lovas K, Fougner KJ, Svartberg J, Hauge ER, Bollerslev J, et al. Normal overall mortality rate in Addison's disease, but young patients are at risk of premature death. Eur J Endocrinol 2009; 160: 233-7.
5. Burman P, Mattsson AF, Johannsson G, Hoybye C, Holmer H, Dahlqvist P, et al. Deaths among adult patients with hy- popituitarism: hypocortisolism during acute stress, and de novo malignant brain tumors contribute to an increased mortality. J Clin Endocrinol Metab 2013; 98: 1466-75.
6. Lee YY, Cho NH, Lee JW, Kim NK, Kim HS, Kim MK. Clinical characteristics of patients with adrenal insufficiency in a general hospital. Endocrinol Metab (Seoul) 2017; 32: 83-9.
7. Hong AR, Ryu OH, Kim SY, Kim SW; Korean Adrenal Gland and Endocrine Hypertension Study Group, Korean Endocrine Society. Characteristics of Korean patients with primary adrenal insufficiency: a registry-based nationwide survey in Korea. Endocrinol Metab (Seoul) 2017; 32: 466-74.
8. Tresoldi AS, Sumilo D, Perrins M, Toulis KA, Prete A, Red- dy N, et al. Increased infection risk in addison's disease and congenital adrenal hyperplasia. J Clin Endocrinol Metab 2020; 105: 418-29.
9. Bancos I, Hazeldine J, Chortis V, Hampson P, Taylor AE, Lord JM, et al. Primary adrenal insufficiency is associated with impaired natural killer cell function: a potential link to increased mortality. Eur J Endocrinol 2017; 176: 471-80.
10. Edvardsen K, Bjanesoy T, Hellesen A, Breivik L, Bakke M, Husebye ES, et al. Peripheral blood cells from patients with autoimmune addison's disease poorly respond to interferons in vitro, despite elevated serum levels of interferon-induc- ible chemokines. J Interferon Cytokine Res 2015; 35: 759-70.
11. Wheatland R. Molecular mimicry of ACTH in SARS—implications for corticosteroid treatment and prophylaxis. Med. Hypoth. 2004; 63, 855–862.
12. Leow MK, Kwek DS, Ng AW, Ong KC, Kaw GJ, Lee LS. Hypocortisolism in survivors of severe acute respiratory syndrome (SARS). Clin. Endocrinol. (Oxf.) 2005; 63, 197–202.
13. Fareau GG, Vassilopoulou-Sellin R. Hypercortisolemia and infection. Infect Dis Clin North Am 2007; 21: 639-57.
14. Dekkers OM, Horvath-Puho E, Jorgensen JO, Cannegieter SC, Ehrenstein V, Vandenbroucke JP, et al. Multisystem morbidity and mortality in Cushing's syndrome: a cohort study. J Clin Endocrinol Metab 2013; 98: 2277-84.
15. Pivonello R, Isidori AM, De Martino MC, Newell-Price J, Biller BM, Colao A. Complications of Cushing's syndrome: state of the art. Lancet Diabetes Endocrinol 2016; 4: 611-29.

16. Melmed S, Polonsky K, Larsen PR, Kronenberg H. Williams textbook of endocrinology. 13th ed. Philadelphia: Saunders Elsevier; 2016. Chapter 16, The adrenal cortex; p. 489-555.
17. Hahner S, Loeffler M, Bleicken B, Drechsler C, Milova- novic D, Fassnacht M, et al. Epidemiology of adrenal crisis in chronic adrenal insufficiency: the need for new preven- tion strategies. Eur J Endocrinol 2010; 162: 597-602.
18. Hahner S, Spinnler C, Fassnacht M, Burger-Stritt S, Lang K, Milovanovic D, et al. High incidence of adrenal crisis in ed- ucated patients with chronic adrenal insufficiency: a prospective study. J Clin Endocrinol Metab 2015; 100: 407-16.
19. Charmandari E, Nicolaides NC, Chrousos GP. Adrenal insufficiency. Lancet. 2014; 383(9935): 2152-67.
20. Bornstein SR, Allolio B, Arlt W, Barthel A, Don-Wauchope A, Hammer GD, et al. Diagnosis and treatment of primary adrenal insufficiency: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2016; 101: 364-89.