



HYPERKALEMIA IN COVID-19 PATIENTS

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ABSTRACT

The coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2, affects various organ systems besides lungs. Dyselectrolytemia have been described with this illness, as hypo or hypernatremia and hypokalemia. Hyperkalemia is rare, and described in the present case series with possible cause and treatment with fludrocortisone.

KEYWORDS: COVID-19, dyselectrolytemia, hyperkalemia, fludrocortisone, severe acute respiratory syndrome coronavirus 2.

INTRODUCTION

The coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), as a pandemic in the year 2020 had a major impact over health facilities all over the world. Majority of the patients have lung affection, with kidneys and heart affection being next two commonly involved organs. Studies investigating whether SARS-CoV-2 may directly attack the endocrine glands (thyroid and adrenals), causing disorders that make the prognosis of affected patients worse are lacking.^[1] Data published so far have not considered the possibility of direct aggression towards the adrenal gland by this virus in previously healthy subjects^[2, 3] Besides inflammation, patients with COVID-19 are susceptible to the development of microthrombosis and disseminated intravascular coagulation. Glucocorticoids (GC) in supraphysiological doses have been used commonly in COVID-19 treatment, as anti-inflammatory agent.^[4] COVID-19 can lead to hyperkalemia is described in this paper as observed in 5 patients, with probable mechanism.

MATERIAL AND METHOD

We had 2870 COVID-19 patients from March 2020 to January 2021 admitted to our hospital, a tertiary care center, out of whom 539 patients were referred to nephrology service for various renal issues like electrolytes abnormalities (120), oliguria (108), acute kidney injury (151), acute on chronic kidney disease (110), end stage disease patients requiring maintenance hemodialysis (50). Among those with dyselectrolytemia, sodium levels were abnormal (low or high) in 70 patients, suggestive of disorder of water homeostasis. 50 patients had potassium abnormalities, out of which 45

patients had abnormal potassium levels (low or high) associated with renal dysfunction. There were 5 patients who had normal renal function and unexplained hyperkalemia, serum potassium levels between 6-7 mEq/L and no prior co-morbidity. They had no hypertension or diabetes mellitus. Their dietary potassium intake was not high (all of them had limited access to food inside the COVID-19 positive area), were not receiving any medicines like renin-angiotensin-aldosterone inhibitors (RAAS-i) (angiotensin-converting enzyme inhibitors, ACEIs; angiotensin-II receptor blockers ARBs; or mineralocorticoid receptor blockers, MRA), non-steroidal anti-inflammatory agents (NSAIDs) or oral or IV potassium supplements, and had normal renal function with normal urinalysis. Their acid-base status was also normal.

Spot urinary potassium to creatinine ratio and transtubular potassium gradient (TTKG) was calculated to assess the cause of hyperkalemia. Spot urine sodium was also calculated. The TTKG was calculated with following formula: (which is the measure of potassium exchange between the tubular fluid at the end of the cortical collecting tubule and the plasma).

$TTKG = (\text{Urine K} \div [\text{Urine osmolality} / \text{Plasma osmolality}]) \div \text{Plasma K}.$

RESULTS

A spot urine potassium-to-creatinine ratio was less than 13 mEq/g creatinine (1.5 mEq/mmol), which indicated that there was no inappropriate renal potassium loss, in all patients. The TTKG values were < 3 in all patients. The urine sodium level was > 25 in all patients, and urinary osmolality was >300 mosm/l in all patients (which was more than serum osmolality, required to

validate TTKG results). The usual measures of dietary potassium restriction, IV calcium gluconate, glucose insulin drip and oral potassium binder with polystyrene sulfonate failed to control serum potassium levels. They were all treated with fludrocortisone and potassium levels were controlled during their hospitalization. Serum potassium levels normalized within a week of discharge and fludrocortisone was omitted.

DISCUSSION

Adrenal insufficiency (AI)^[5]

AI is attributed to a failure of cortisol production by the zona fasciculata of the adrenal cortex (primary AI or Addison disease) or by a deficiency of adrenocorticotropin hormone (ACTH, secondary AI) and/or corticotropin-releasing hormone (CRH, tertiary AI). Primary AI is mainly caused by autoimmune adrenalitis or infectious diseases (tuberculosis, paracoccidioidomycosis, HIV).^[6, 7] Hemorrhage or thrombosis are rare causes of primary AI, including thrombocytopenia, Waterhouse-Friderichsen syndrome due to meningococcemia, trauma, lupus erythematosus, antiphospholipid syndrome, panarteritis nodosa, and anticoagulant therapy. Although microthrombosis and hypercoagulability have been identified in COVID-19, an association with AI is yet to be established.

Similarly, presence of anti-phospholipid antibody (APLA) has also been reported in COVID-19. It is known that APLA can arise transiently in patients with critical illnesses and various infections, case series have detected APLA in COVID-19 patients.^[8] However, whether it causes AI and account for hyperkalemia is not known.

Investigating for hyperkalemia

Spot urine potassium to urine creatinine ratio (UK/UCreatinine): Because creatinine is excreted at a near-constant rate throughout the day, one can use the UK/UCreatinine to assess the rate of K⁺ excretion. Hyperkalemia due a shift of K⁺ out of cells is usually recognized by its acute onset and the clinical setting. The UK/UCreatinine is less useful in patient with chronic hyperkalemia.

In patients with hypokalemia and hyperkalemia, the degree of renal potassium excretion in the distal nephron can be estimated by calculating the TTKG, which is utilized to determine whether the renal response to hyperkalemia or hypokalemia is appropriate.^[9] In other words, one needs to know whether the focus should be on kidney or outside kidney to determine cause of hyperkalemia.

During hyperkalemia, the TTKG should be greater than 7; lower values suggest hypoaldosteronism. During hypokalemia, the TTKG should be less than 3; greater values suggest renal potassium wasting. In this model, we assume that the urine and plasma osmolality are similar at the end of the cortical

collecting tubule and that potassium is neither excreted nor reabsorbed in the medullary collecting tubule.

When one measures the potassium concentration in urine, we know this is somewhat higher than the original concentration in the cortical collecting tubule since water is reabsorbed in the distal nephron (and the urine concentration of potassium rises). This reabsorption of water is adjusted for by dividing the urine potassium concentration by the ratio of the urine to plasma osmolality.

For this formula to be accurate, urine osmolality must exceed plasma osmolality and urine sodium should be greater than 25 mEq/L.^[10]

In all these 5 patients, Uk/UCreatinine and TTKG values were on lower side, suggestive of inappropriate potassium excretion and hypoaldosteronism respectively. To prove this, one has to measure serum aldosterone level or do a stimulatory test by administering aldosterone agonist, commonest being fludrocortisone, and recalculating TTKG after 4 hours; if TTKG goes >6, it proves aldosterone deficiency. If TTKG remains <6, it means either aldosterone resistance or some other problem in DCT which does not allow potassium to be secreted. We did not measure aldosterone level in these patients, however, serum potassium levels were controlled after adding fludrocortisone was suggestive of transient aldosterone deficiency, probably in the setting of COVID-19 infection. The problem was transient, as the serum potassium levels became normal without any medication by the time COVID-19 infection came under control.

Why would hyperkalemia occur in COVID-19?

Considering the inflammation and cytokine storm in severe COVID-19, GC treatment for ARDS and septic shock associated with SARS-CoV-2 infection has been debated. However, all the 5 patients were treated with GC, which would generally cause hypokalemia. All individuals receiving a GC dose comparable with ≥ 20 mg/day of prednisone for more than 2 weeks, or ≥ 5 mg of prednisone for more than 3-4 weeks, can present with suppression of ACTH/CRH release. However, a study of 41 patients did not report any hyperkalemia.^[11]

The angiotensin converting enzyme 2 (ACE2) is the enzyme that physiologically counters RAAS activation, which is the functional receptor to SARS-CoV-2, the virus responsible for COVID-19 pandemic. This is the mechanism for hypokalemia, as reported in 54% of patients in a series, and the authors concluded that the high prevalence of hypokalemia among patients with COVID-19 suggests the presence of disordered rennin-angiotensin system activity, which

increases as a result of reduced counter-activity of ACE2, which is bound by SARS-CoV-2.^[12]

None of the reported cases in our series were on ACEi or ARB. Hence hyperkalemia is otherwise unexplainable. We have tried to conclude that this could be due to aldosterone deficiency. We could not prove with further tests, but we had appropriate therapeutic response to the intervention carried out.

CONCLUSION

Though hypokalemia is common among patients with COVID-19 infection, we have encountered 5 cases with otherwise unexplained hyperkalemia. These were presumed to be due to transient aldosterone deficiency due to COVID-19 infection, and responded to treatment with fludrocortisone. If hyperkalemia is encountered in COVID-19 cases without obvious cause, keep aldosterone deficiency in mind and treat accordingly.

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