An Unusual Presentation of Autoimmune Primary Adrenal Insufficiency
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CASE DESCRIPTION

An 8-year-old boy presented to the emergency department with Kussmaul breathing, fever, and vomiting. He was confirmed positive for SARS-CoV-2 by polymerase chain reaction testing, having been a close contact of a known case. Further history, however, revealed a 1-week history of polyuria, polydipsia, and recent unintentional weight loss. There was no history of diarrhea.

His past medical history was unremarkable. His mother had type 1 diabetes mellitus (T1D) but there was no other history of autoimmune disorders in his family.

On examination, he was tachycardic (heart rate 148 bpm), tachypnoeic (respiratory rate 40 breaths per minute), and hypertensive (blood pressure 151/94 mmHg). He was given a 10 mL/kg bolus of 0.9% saline by first responders. He otherwise had an unremarkable cardiovascular, respiratory, and abdominal examination with no evidence of hyperpigmentation.

His initial venous blood analysis revealed hyperglycemia (glucose 438 mg/dL; reference interval [RI]: 55–140) and a high anion gap metabolic acidosis with pH 7.02 (RI: 7.35–7.45), sodium 119 mmol/L (RI: 135–145), potassium 5.7 mmol/L (RI: 3.6–5.3), chloride 99 mmol/L (RI: 97–110), and bicarbonate 9 mmol/L (RI: 17–30). The plasma lactate and capillary β-hydroxybutyrate concentrations, measured using point-of-care devices, were 2.0 mmol/L (RI: <0.5–2.2) and 5.6 mmol/L (RI: <0.5), respectively. He was diagnosed with new-onset T1D with severe diabetic ketoacidosis (DKA). There were initial concerns regarding altered levels of consciousness since his actual and predicted PCO2 (using Winter’s formula) were 22 mmHg and 17 mmHg, respectively. Clinically, however, he was appropriately interactive and responsive. Formal laboratory investigations suggested renal impairment (pre-renal) with increased serum urea (22 mg/dL [RI: 7–17]) and creatinine (0.93 mg/dL [RI: <0.66]). It was noted that his sodium concentration, corrected for glucose, was decreased (127 mmol/L [RI: 135–140]).

MANAGEMENT AND CLINICAL COURSE

Initial insulin, intravenous fluid (IVF), and electrolyte management as well as associated biochemistry are outlined in Fig. 1A. Following an additional 10 mL/kg bolus of 0.9% saline, an intravenous insulin infusion (50 U of human neutral insulin [Actrapid®] in 50 mL 0.9% saline) was commenced at 0.05 unit/kg/h. He was initially started on 150 mL/h (calculated as maintenance and 7.5% dehydration replacement over 48 h) of IVF with 40 mmol/L of potassium chloride. Dextrose was added to the IVF to maintain glucose concentrations as required per protocol. His IVF rate was reduced to 90 mL/h in the first 24 h due to a decrease in his Glasgow Coma Scale and concern regarding potential cerebral edema in the context of hyponatremia.

Over the following 36 h, his hyperglycemia and ketosis slowly corrected, with serum bicarbonate improving to 15 mmol/L. He was transitioned to subcutaneous insulin injections and his IVF replacement was ceased. Despite correction of the acidosis and achieving euglycemia, hyponatremia persisted with sodium concentrations ranging between 128 to 130 mmol/L.

QUESTIONS TO CONSIDER

1. What are the possible etiologies of hyponatremia in DKA?
2. What is the best tool for monitoring progression in AAI?
3. What other autoimmune conditions should be considered in this patient with regard to his APS 2?
Urinary sodium concentrations were high during the periods of hyponatremia, and even accounting for the intravenous sodium replacement, suggestive of inappropriate renal sodium loss. He was started on oral sodium chloride replacement (2.0 mmol/kg/d) and, following normalization of his serum sodium concentration, sodium supplementation was ceased. However, over the next 48 h, there was a progressive decrease in his serum sodium concentration and increase in potassium concentration.

Investigations were undertaken to exclude adrenal insufficiency (AI), including analysis of retrospective samples (Table 1). The cortisol concentrations at the time of presentation (during critical illness) and on an early morning sample 18 h later were 41.0 µg/dL and 26.4 µg/dL, respectively, which indicated that the patient did not have glucocorticoid deficiency. Repeat measurement of urinary sodium continued to demonstrate inappropriate sodium loss. On sodium supplementation, with borderline normal sodium concentrations, plasma aldosterone concentration measured using LC-MS/MS was decreased and plasma renin mass was increased. Following cessation of sodium supplementation, with resulting hyponatremia, the aldosterone concentration was inappropriately normal with markedly increased renin mass. The patient was therefore commenced on fludrocortisone and subsequent serum sodium concentrations were maintained between 135 and 140 mmol/L.

Investigations for the underlying cause of the mineralocorticoid deficiency revealed anti-adrenal antibody titers of 640 (RI: <40), consistent with an autoimmune etiology. Further screening for autoimmune conditions associated with T1D included normal thyroid function tests with negative thyroid peroxidase, anti-thyroglobulin antibodies, and tissue transglutaminase antibodies. He was followed up routinely in the

Fig. 1. (A), Clinical course during the acute management of DKA with corresponding glucose, bicarbonate, sodium, potassium concentrations performed via venous blood gas, and measured urinary sodium concentrations; (B), the pathogenesis of autoimmune adrenal insufficiency, including clinical and biochemical features of the 5 stages. Modified from (1).
<table>
<thead>
<tr>
<th>Reference Interval</th>
<th>At presentation</th>
<th>+18 h</th>
<th>+50 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>7.35–7.45</td>
<td>+18 h^a</td>
<td>7.29</td>
</tr>
<tr>
<td>Bicarbonate, mmol/L</td>
<td>17–30</td>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td>PCO2, mmHg</td>
<td>35–45</td>
<td>22</td>
<td>21</td>
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<tr>
<td>Sodium, mmol/L</td>
<td>133–144</td>
<td>119</td>
<td>128</td>
</tr>
<tr>
<td>Corrected sodium, mmol/L</td>
<td>131–144</td>
<td>127</td>
<td>131</td>
</tr>
<tr>
<td>Potassium, mmol/L</td>
<td>3.6–5.3</td>
<td>5.7</td>
<td>4.0</td>
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<tr>
<td>Chloride, mmol/L</td>
<td>97–110</td>
<td>99</td>
<td>99</td>
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<tr>
<td>Glucose, mg/dL</td>
<td>55–140</td>
<td>438</td>
<td>214</td>
</tr>
<tr>
<td>Anion gap, mmol/L</td>
<td>4–13</td>
<td>14</td>
<td>10</td>
</tr>
<tr>
<td>Cortisol, µg/dL</td>
<td>2.2–20.7</td>
<td>41.0</td>
<td>26.4</td>
</tr>
<tr>
<td>Urinary sodium concentration, mmol/L</td>
<td>45–230</td>
<td>295</td>
<td>111</td>
</tr>
</tbody>
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**Comment**
- Hypovolemic, critically unwell
- Early morning samples
- Transitioned to subcutaneous insulin and 0.9% saline injections, and oral salt supplementation following cessation of sodium supplementation for 24 h

**Abbreviation:** ACTH, adrenocorticotropic hormone.

^a Plasma electrolytes measured by venous blood gas analysis. Serum electrolytes measured by formal laboratory analysis. Cortisol and ACTH measured by formal laboratory analysis.

^b Hypovolemic, critically unwell
diabetes clinic with 3-monthly early morning cortisol and adrenocorticotropic hormone (ACTH) measurements to monitor adrenal function.

**DISCUSSION**

This patient’s presentation with severe DKA and a new-onset T1D in the context of COVID-19 infection was classical except for his clinically significant and persistent hyponatremia, raising the suspicion of partial or complete AI. The subsequent finding of mineralocorticoid deficiency with positive anti-adrenal antibody titers demonstrated an early diagnosis of autoimmune adrenal insufficiency (AAI) without glucocorticoid deficiency.

Primary adrenocortical insufficiency (PAI) (3) can result from a broad range of etiologies (4). AAI, a rare cause of PAI, is characterized by the development of anti-adrenal or 21-hydroxylase antibodies directed against the adrenal cortex, leading to progressive decline in function. Like other causes of PAI, patients with AAI require lifelong mineralocorticoid and glucocorticoid replacement and are at risk of life-threatening adrenal crises. AAI has been associated with both autoimmune polyglandular syndrome (APS) 1, characterized by mucocutaneous candidiasis and hypoparathyroidism, as well as APS 2 with co-existing T1D and autoimmune thyroid disease (5). Given our patient’s presentation, a diagnosis of A2 was made, with no current thyroid dysfunction. The temporal progression though the various stages of AAI often occurs over years, and in some cases, decades.

Despite the association of AAI and T1D, 21-hydroxylase or anti-adrenal antibodies are not routinely measured at diagnosis of T1D. AAI is suspected clinically in patients with T1D when typical signs and symptoms of AI develop, but also if there is substantially decreased insulin requirement or increased frequency and severity of hypoglycemia.

The global rates of T1D, and initial presentation with severe DKA, have increased significantly during the COVID-19 pandemic (6). PAI has been described following infection with SARS-CoV-2, and has been attributed to both cytokine-induced adrenitis and bilateral adrenal hemorrhage. A case of AAI and autoimmune hypothyroidism following COVID-19 infection, as part of APS 2, has been reported (7) but ours was a case of new-onset T1D and AAI.

The presence of concomitant autoimmune diseases in APS 2 are more common in individuals with AAI (5), with the reported rates of co-existing autoimmune diseases in large Swedish and Norwegian cohorts of 39.9% to 41% for autoimmune hypothyroidism, 15% for celiac disease, 11% to 12% for T1D, 6.1% to 11% for vitiligo, and 1.15% to 3.8% for alopecia, and 5.4% to 6.6% in females and 0.7% in males for gonadal failure.

AAI is known to follow a similar course to T1D, with multiple stages prior to presentation with clinical symptoms (8). The classical natural history moves through 5 stages (0 through 4) of progressive adrenal dysfunction (1), the pathogenesis, clinical, and biochemical features of which are described in Fig. 1B. This patient is currently in stage 1 with isolated mineralocorticoid deficiency, and robust cortisol response during critical illness.

In our patient, persistent hyponatremia was the main clue to his diagnosis. The homeostatic mechanisms maintaining normal sodium concentrations are complex (9). Based on serum sodium concentration, hyponatremia may be categorized as mild (130 to 134 mEq/L), moderate (120 to 129 mEq/L), or severe (<120 mEq/L). In DKA, patients will often have a total body sodium deficit ranging from 5 to 13 mmol/kg. Despite this deficit, the measured sodium in DKA can vary from mild hyponatremia to mild hypernatremia.

Hyperglycemia drives a dilutional hyponatremia through the movement of water from the intracellular to extracellular space in response to increased plasma osmolality. In this scenario, it is important to correct the measured sodium concentration, given there is not established hyponatremia (8). This correction was originally performed by the equation developed by Katz (10):

\[
\text{Measured sodium in mEq/L + 0.016 (serum glucose in mg/dL—100)}.
\]

This approach was more recently updated by Hillier et al. (2):

\[
\text{Measured sodium in mEq/L + 0.024 x (serum glucose in mg/dL—100)}.
\]

The correction factor proposed by Hillier et al. is more reliable in the presence of hyperglycemia and a hyposmolar state because it adjusts the corrected sodium concentration closer to the estimated effective osmolarity or tonicity (2).

Hyperglycemia can also cause hypernatremia due to osmotic diuresis; with glycosuria, there is both sodium and water loss, with the latter usually in excess of the former. These 2 mechanisms allow for the wide range of presentations with regards to measured sodium (8).

In DKA, sodium correction is usually observed with intravenous resuscitation as water moves out of the vasculature with correction of hyperglycemia. In our case, an additional component to the hyponatremia was considered when sodium did not normalize as expected. While his sodium did improve with resuscitation, he remained hyponatremic despite normoglycemia, caused by AI.

This case demonstrates an unusual presentation of early AAI, with isolated mineralocorticoid deficiency driving hyponatremia from continued renal sodium loss. It also highlights the need to consider other causes
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of electrolyte disturbances in patients with DKA, and the importance of investigating hyponatremia with high anion gap metabolic acidosis.

**POINTS TO REMEMBER**

- Serum sodium concentrations in DKA are influenced by many factors and should be “correct” for glucose to assist in fluid management decisions.
- Mineralocorticoid deficiency may be the first detectable sign of adrenal insufficiency and early detection can prevent life-threatening adrenal crises.
- In patients with one autoimmune condition, surveillance for additional autoimmune conditions should be undertaken in order to identify those who may potentially have APS.

**Nonstandard Abbreviations:** T1D, type 1 diabetes; DKA, diabetic ketoacidosis; IVF, intravenous fluid; AAI, autoimmune adrenocortical insufficiency; PAI, primary adrenocortical insufficiency; APS, autoimmune polyglandular syndrome.

**Author Contributions:** All authors confirmed they have contributed to the intellectual content of this paper and have met the following 4 requirements: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; (c) final approval of the published article; and (d) agreement to be accountable for all aspects of the article thus ensuring that questions related to the accuracy or integrity of any part of the article are appropriately investigated and resolved.

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**References**