CASE REPORT

Severe hyponatraemia with absence of hyperkalaemia in rapidly progressive Addison's disease

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SUMMARY

We present a case of rapidly progressing Addison's disease in adrenal crisis with severe hyponatraemia and absence of hyperkalaemia in a 10-year-old girl. She presented with 2 weeks of vomiting, fatigue and weight loss. Her serum electrolytes obtained 1 week prior to presentation were normal, except for mild hyponatraemia at 131 mmol/L, which dropped to 112 mmol/L on admission. She had normal serum potassium, low-serum osmolality, with elevated urine sodium and osmolality, indistinguishable from syndrome of inappropriate antidiuretic hormone (SIADH). Subsequently, Addison's disease was diagnosed on the basis of gingival hyperpigmentation and undetectable cortisol on adrenocorticotrophic hormone stimulation test. She rapidly responded to stress dose hydrocortisone, followed by hydrocortisone and fludrocortisone replacement therapy. The absence of hyperkalaemia in the presence of severe hyponatraemia cannot rule out Addison's disease in children. The mechanism of hypo-osmolar hyponatraemia in primary adrenal insufficiency and clinical clues to differentiate it from SIADH are discussed.

BACKGROUND

Primary adrenal insufficiency is defined by impaired synthesis and release of adrenocortical hormones resulting from intrinsic disease of the adrenal cortex. Some of the causes of primary adrenal insufficiency in children include congenital adrenal hyperplasia (CAH), adrenoleucodystrophy, infection, trauma resulting in adrenal haemorrhage and autoimmune destruction. Autoimmunity of the adrenal gland, also known as Addison's disease, is characterised by cell-mediated immune destruction of the adrenal cortex. While a majority of cases of primary adrenal insufficiency in adults are due to Addison's disease, in children, CAH is the most frequent (70%) aetiology and Addison's disease accounts for only 15% of primary adrenal insufficiency in children.¹ Thomas Addison first reported on the clinical features of 11 patients in 1855.² However, a treatment, cortisone, was not developed until 1949 and the role of autoimmunity in the disease was shown in 1957.^{3 4}

The initial clinical findings in children with primary adrenal insufficiency tend to be vague; they include fatigue, weight loss, nausea and vomiting, all of which may be of insidious onset. Owing to these non-specific symptoms, diagnosis in children is often delayed or missed. In fact, one study showed a median of 2 years between the onset of

symptoms and diagnosis.⁵ If initially unrecognised, adrenal crisis can occur, and is characterised by orthostatic hypotension, frank hypotension or shock, hyponatraemia, hyperkalaemia and hypoglycaemia. Adrenal crisis is a life-threatening condition and an absolute medical emergency, requiring prompt diagnosis and treatment to prevent significant morbidity or mortality. We present a case of rapidly progressing Addison's disease in a child who progressed to severe hyponatraemia over a relatively short period of time, with absence of hyperkalaemia, which led to an inappropriately low index of suspicion initially at presentation.

CASE PRESENTATION

A previously healthy 10-year-old girl presented to the emergency department with 2 weeks of vomiting, choking, gagging on food, decreased appetite, 13 lb weight loss and fatigue, which developed soon after having flu 3 weeks earlier. She was evaluated 7 days prior by her primary care paediatrician who ordered a brain CT scan due to persistent vomiting. The brain CT scan was read as normal. Laboratory tests obtained at that time showed normal blood counts, hepatic function panel, amylase, lipase and thyroid function tests. Biochemistry results revealed mild hyponatraemia with sodium of 131 mmol/L, normal potassium and mildly low glucose at 62 mg/dL. The girl appeared to have anxiety about eating, which was felt to be related to fear of vomiting. There was also concern of food aversion due to her lack of interest in food. Because of this, her parents sought help from a psychologist; she was taught several relaxation techniques including diaphragmatic breathing and imagery to reduce her anxiety. Her symptoms got worse on the day of presentation and she felt so weak that she was unable to get up and walk. Her medical history and family history were unremarkable.

On examination, her weight was at the 57th centile, height at the 90th centile and with BMI at the 40th centile. Her supine blood pressure was 109/56 mm Hg, with an elevated heart rate at 120 bpm. She was generally appearing ill, with normal physical examination including neurological status. She had generalised tanned skin, which was not deemed unusual due to the season being the end of summer. Her blood chemistry was significant for severe hyponatraemia with sodium of 112 mmol/L, hypochloremia with chloride of 77 mmol/L and normal potassium (table 1). Her

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Table 1 Laboratory investigations during course of acute illness

Laboratory tests (normal range)	7 Days before admission	On admission	Day 2	Day 3 (before discharge)
Sodium (135–145 mmol/L)	131	112	111–122	132–137
Potassium (3.7–5.6 mmol/L)	4.1	4.8	4.1	3.7
Chloride (95–106 mmol/L)	94	77	90	103
Carbon dioxide (18–27 mmol/L)	23	23	22	25
Blood urea nitrogen (5–18 mg/dL)	27	15	5	7
Creatinine (0.20–0.70 mg/dL)	0.62	0.54	0.45	0.51
Glucose (3.3–6.3 mmol/L or 60–115 mg/dL)	3.38 (61 mg/dL)	3.6 (66 mg/dL)	4.1 (74 mg/dL)	6.2 (112 mg/dL)
Baseline cortisol (0.08–0.58 µmol/L or 3–21 µg/dL)			<0.02 (<1.0 µg/dL)	
Cortisol at 20, 40 min after cosyntropin (0.55 µmol/L or >20 µg/dL)			<0.02 (<1.0 µg/dL)	
Adrenocorticotrophic hormone (1.3–10.5 pmol/L or 6–48 pg/mL)			734.8 (3340 pg/mL)	
Renin (50–330 ng/dL/h)			8326	
Aldosterone (2–22 ng/dL)			<1.0	

urine specific gravity was 1.025 with large ketonuria. She was subsequently admitted to the paediatric intensive care unit for further evaluation and treatment. Her blood pressure was intermittently low at 81–86/38–44 mm Hg on repeat measurements.

INVESTIGATIONS AND TREATMENT

The differential diagnosis for hyponatraemia in children is broad and can be broken down into three groups relating to fluid status: hypovolaemia, normovolaemia and hypervolaemia. Hypovolaemic hyponatraemia can be caused by gastrointestinal losses as seen in gastroenteritis, renal salt wasting and intense exercise. Conditions associated with renal salt wasting include cerebral salt wasting, primary renal tubular disorders and adrenal insufficiency, including Addison's disease, CAH and hypoadosteronism. Normovolaemic causes include syndrome of inappropriate antidiuretic hormone (SIADH) and primary polydipsia. Hypervolaemic causes include nephrotic syndrome, heart failure and renal failure.

In this case, hypervolaemic cause is unlikely. Addison's disease was in consideration, but because of the lack of hyperkalaemia, with normal blood urea nitrogen (BUN) and creatinine, SIADH was initially entertained. Additional tests were obtained including urine osmolality, which was elevated at 631 mOsmol/kg, serum osmolality being low at 246 mOsmol/kg (normal, 270–310). Urine sodium was elevated at 135 mmol/L. The patient received a 20 mL/kg bolus of 0.9% saline and was placed on continuous 0.9% saline at maintenance rate. Her serum sodium remained low at 111–114 mmol/L after 12 h of initial treatment with isotonic saline solution. At that time, endocrinology consultation was made. It was noted that she had some slight hyperpigmentation of her skin creases and her gums were noted to be hyperpigmented (figure 1). Further laboratory testing was obtained with concern for primary adrenal insufficiency, which included a stat cortisol, followed by an adrenocorticotrophic hormone (ACTH) stimulation test (using cosyntropin 250 mg). The baseline cortisol and stimulated cortisol levels were all undetectable (<0.02 µmol/L (<1.0 µg/dL); with normal stimulated cortisol, >0.55 µmol/L (>20 µg/dL)), confirming severe adrenal insufficiency. The patient was immediately given a stress dose of hydrocortisone (100 mg/M²/day) intravenously, followed by replacement therapy

of oral hydrocortisone (12.5 mg/M²/day, three times per day) and daily oral fludrocortisone at 0.1 mg/day.

Her baseline ACTH level was markedly elevated at 734.8 pmol/L (3340 pg/mL; normal 1.3–10.5 pmol/L (6–48 pg/mL)), confirming primary adrenal insufficiency. Her baseline renin level was markedly elevated, while serum aldosterone level was undetectable, documenting mineralocorticoid deficiency. Further laboratory testing was performed to evaluate the cause of her primary adrenal insufficiency and any other potential associated autoimmune endocrine disorders. Antithyroglobulin, antithyroid peroxidase, anti-islet cell, antiglutamic acid decarboxylase 65, anti-insulin and antiovarian antibodies were all negative. However, antiadrenal antibodies were significantly elevated at 374.6 U/mL (normal 0–1), confirming the diagnosis of isolated autoimmune primary adrenal insufficiency.

OUTCOME AND FOLLOW-UP

After two doses of intravenous stress doses of hydrocortisone, along with intravenous 0.9% saline and fludrocortisone, the patient's hyponatraemia improved by ~10 mEq/day and had resolved by 36 h of treatment (table 1). She was feeling well, and was able to tolerate a regular meal without emesis. Education on adrenal insufficiency and stress dose hydrocortisone were provided to the parents and they were also taught how to administer hydrocortisone intramuscularly for those episodes of stress when

Figure 1 Photograph of the patient at diagnosis showing pigmentation of maxillary gingiva (courtesy of John Kalmar, DMD, PhD).

their daughter was unable to take oral hydrocortisone. Over the past 4 years, she has had normal growth and normal onset of menarche with no further hospitalisations for any illnesses. Her gingival hyperpigmentation showed improvement with hormonal therapy. Her hydrocortisone dose was adjusted periodically for growth and based on clinical symptoms, while fludrocortisone has been maintained at 0.1 mg daily.

DISCUSSION

Primary adrenal insufficiency in children is typically a slowly developing condition with non-specific symptoms developing over months to years.⁵ We herein report a case of a child with Addison's disease who rapidly progressed to adrenal crisis within 2 weeks of developing symptoms, with serum sodium level dropping from 131 to 112 over the course of 7 days. The case highlights an interesting presentation of Addison's disease that can be very rapid in progression. Another case of rapidly progressive Addison's disease previously reported was of a child who became significantly hyponatraemic within 1 week of symptoms.⁶ Although, in that case, the most recent sodium level was 2 years prior so it is unknown if the patient's sodium level had been dropping slowly over a longer time period. It was also later determined that the child had been showing some issues with school performance much earlier, thus suggesting that hyponatraemia-induced encephalopathy might have been the initial presenting sign.

The classic biochemical signs of primary adrenal insufficiency include hyponatraemia, hyperkalaemia and mild hypoglycaemia. The absence of hyperkalaemia in our patient is likely due to protracted vomiting and may have misled the treating clinicians to consider SIADH initially. In fact, elevated urine osmolality greater than serum osmolality together with urine sodium excretion >20 mmol/L—as seen in our patient—is suggestive of SIADH. The normal BUN and creatinine in our patient gave the impression of normovolaemic hyponatraemia. In Addison's disease, sodium wasting secondary to mineralocorticoid deficiency results in hyponatraemia; although another significant contributing factor is vasopressin hypersecretion with resultant renal water retention.⁷ The latter mechanism is the physiological response to nausea, hypovolaemia and hypotension, as well as the direct effect of glucocorticoid deficiency causing a loss of hypotonic suppression of the osmostat for vasopressin release, leading to inappropriately high vasopressin levels.⁷ Therefore, it may be difficult to distinguish patients with hyponatraemia secondary to adrenal insufficiency from SIADH by serum and urine electrolytes, and osmolality measurements, as demonstrated by our case. However, our patient's clinical history, including weight loss and especially clinical sign of the gingival hyperpigmentation, provided the clues to the diagnosis of primary adrenal insufficiency. Large ketonuria found in this patient also points towards adrenal insufficiency. Deficiency of cortisol, a counter-regulatory hormone, causes decreased gluconeogenesis, resulting in hypoglycaemia. This leads to increased use of fat as an energy source, leading to fatty acid oxidation and production of ketones.

While cutaneous hyperpigmentation typically localises to sun-exposed surfaces, hyperpigmentation of the oral mucosa is less common but considered to be pathognomonic for the disease.⁸ One review of 86 cases found increased buccal mucosa pigmentation in 71% of patients, compared with 93% showing increased pigmentation in sun-exposed areas.⁹ Adequate hormonal replacement therapy typically results in the resolution of cutaneous pigmentation, though oral pigmentation may persist indefinitely.⁸ Hyperpigmentation was observed in 67% of

children with Addison's disease,¹⁰ though there are no studies reporting specifically on the frequency of oral pigmentation.

A recent study by Hsieh and White¹⁰ found that hyperkalaemia was present in only 50% of children with primary adrenal insufficiency (excluding CAH). Authors also noted that hyperkalaemia was usually mild even with markedly elevated renin levels.¹⁰ This contrasts with salt wasting CAH presenting in infancy, in which hyperkalaemia is almost invariably present along with hyponatraemia, and is often severe.¹¹ Our case serves as a reminder to clinicians to have a high index of suspicion of primary adrenal insufficiency in patients with hypo-osmolar hyponatraemia even in the absence of hyperkalaemia, and not to be confused with SIADH, in which similar electrolytes findings can be seen.

Patient's perspective

- The onset of disease was apparently quick with no obvious symptoms preceding an episode of flu symptoms. Three days after recovering from the flu, my daughter developed nausea and vomiting that became more frequent until it immediately followed any oral consumption including just water. Her increasing fatigue, headaches and persistent vomiting precluded any school attendance. Her paediatrician ordered blood work and a head CT scan that showed no abnormalities. She was referred to a psychologist, suspecting either a possible aversion to food or psychological trauma from having vomited in front of peers, causing significant anxiety. We had numerous discussions with the psychologist and paediatrician but no direction or suggestion was offered. This period of about 2 weeks without direction was very frustrating and anxiety provoking. Weakness continued to the point where she was unable to wash or dress herself, lacking the strength and ability to even stand. After ER visit, then admission to the paediatric ICU, Addison's disease was diagnosed on the second day. Upon treatment with IV hydrocortisone she immediately felt comfortable enough to sleep restfully. After only a few hours of sleep she awoke with energy and had an appetite for the first time in 15 days. She experienced no vomiting or nausea once treatment began and was released from the hospital in 3 days.
- It took her nearly 10 days to regain enough physical strength to return to a full day of school. Upon returning to school two things became very apparent: her classmates had been very worried and they were very concerned about what kind of illness could have done this to someone their age. She was so excited to share her experience and tell her classmates about her disease that she created a power point presentation to share with her class. This prompted a classmate with juvenile diabetes to also share with the class information about his disease. These two classmates became 'clinic buddies', each having to make lunchtime visits to the nurses' clinic daily. They began to watch out for each other. When one was not feeling well they could easily turn to the other to help them to the clinic or even just help them communicate with the teacher that they weren't feeling well. This peer support has remained consistent. Now into high school it has become quite a reassurance not only during daily activities but also during field trips and during summer camp activities when they were both involved. The peer support and friendship that has developed remains important even today.

Learning points

- ▶ It is important to include primary adrenal insufficiency in the differential diagnosis for significant hyponatraemia even with the absence of hyperkalaemia.
- ▶ Hypo-osmolar hyponatraemia with urine osmolality greater than serum osmolality and urinary sodium excretion >20 mmol/L, typically seen in syndrome of inappropriate antidiuretic hormone (SIADH), can also be seen in adrenal insufficiency, due to increased vasopressin secretion.
- ▶ Ketonuria is seen in patients with hyponatraemia secondary to adrenal insufficiency, not SIADH. The urine ketone test is an easy point-of-care test to differentiate between these two causes of hyponatraemia.
- ▶ Gingival hyperpigmentation is an important physical finding to look for in Addison's disease, even in the absence of obvious hyperpigmentation of sun-exposed skin.

Contributors MDT carried out the literature review and drafted the manuscript. EK collected clinical data and contributed to the writing. SAB diagnosed and treated the patient, wrote the manuscript and critically revised the manuscript for important intellectual content.

Competing interests None declared.

Patient consent Obtained.

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