INDEX OF SUSPICION

Recurrent Vomiting in a 6-year-old Boy

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PRESENTATION

A 6-year-old boy presents to the emergency department (ED) with a 1-day history of nonbilious, nonbloody vomiting occurring every 1 to 2 hours. He was not tolerating oral fluids and had decreased urination for 24 hours before presentation. He has nasal congestion and discharge but no fever, abdominal pain, or diarrhea. The parent denies sick contacts and the possibility of ingestions. Vital signs are notable for tachycardia (heart rate, 114 beats/min) and mild hypotension (blood pressure, 88/65 mm Hg). Physical examination reveals a lean boy with dry mucous membranes and normal mental status. Shotty cervical lymph nodes are palpated. Tonsils are mildly enlarged without exudates. Abdomen is soft, without localized tenderness. The remainder of the examination findings are normal.

The initial laboratory evaluation in the ED demonstrates a normal white blood cell count of 12,200/μL (12.2×10^9/L), a normal sodium level of 139 mEq/L (139 mmol/L), a potassium level of 4.6 mEq/L (4.6 mmol/L), normal liver and kidney function, mild acidosis with a bicarbonate level of 14 mEq/L (14 mmol/L), and hypoglycemia (serum glucose level, 48 mg/dL [2.66 mmol/L]). Urine analysis shows 3+ ketones. He receives a 5-mL/kg dextrose 10% (D10) bolus, a 10-mL/kg normal saline (NS) bolus, and intravenous (IV) ondansetron in the ED. Hypoglycemia improves initially, but the glucose level drops again to 46 mg/dL (2.55 mmol/L), requiring a second 5-mL/kg D10 bolus. A cortisol level at the time of hypoglycemia is 12.1 μg/dL (333.81 nmol/L) (reference range, 4.5–23 μg/dL [124.15–634.52 nmol/L]). D10 NS IV fluids at a maintenance rate are started, and the patient is admitted to the hospital.

Further review of the patient's medical records reveals recurrent episodes of vomiting and dehydration resulting in a PICU admission and 3 ED visits in the 2 years before presentation. His PICU admission was due to hypovolemic shock requiring multiple fluid boluses (total of 60 mL/kg), when he presented with fever, vomiting, and hypotension. Blood cultures were negative and rhinovirus/enterovirus polymerase chain reaction was positive. He had mild hyponatremia (sodium level, 131 mEq/L [131 mmol/L]), with acidosis (pH 7.18; bicarbonate, 10 mEq/L [10 mmol/L]), an elevated C-reactive protein level of 7.1 mg/dL (71 mg/L) (reference range, ≤0.8 mg/dL [≤8 mg/L]), and a normal glucose level of 99 mg/dL (5.49 mmol/L). Subsequently, he presented to the ED on 3 different occasions with vomiting and dehydration. At the first visit he had hypoglycemia (glucose level, 44 mg/dL [2.44 mmol/L]) with normal electrolyte levels and was discharged after receiving a

AUTHOR DISCLOSURE Drs Verma and Merjaneh have no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device. Dr Verma's current affiliation is Department of Pediatrics, University of Nevada Reno School of Medicine, Reno, NV.

5-mL/kg D10 bolus, two 20-mL/kg NS fluid boluses, and antiemetics. At the second visit he was diagnosed as having streptococcal pharyngitis; his glucose level was 61 mg/dL (3.39 mmol/L), which improved after a 5-mL/kg D10 bolus, and he was discharged after two 10-mL/kg NS fluid boluses. At the third visit he had mild hyponatremia (sodium level, 134 mEq/L [134 mmol/L]), a normal potassium level (4.4 mEq/L [4.4 mmol/L]), mild acidosis (bicarbonate level, 14 mEq/L [14 mmol/L]), and a normal glucose level (72 mg/dL [4.0 mmol/L]). He was discharged after receiving two 20-mL/kg NS fluid boluses and antiemetics.

During the 2 years before presentation his weight declined from the 90th to the 40th percentile, and his BMI declined from the 50th percentile to less than the 3rd percentile (Fig 1A and C), whereas his height was following close to the 95th percentile (Fig 1B). Further laboratory evaluation reveals the diagnosis.

DISCUSSION

Differential Diagnosis

An acute viral gastroenteritis with idiopathic ketotic hypoglycemia seems likely. Idiopathic ketotic hypoglycemia occurs most commonly in young children and is characterized by decreased fasting tolerance with episodes of symptomatic hypoglycemia and ketosis, in the absence of endocrine or metabolic causes. Given the recurrent presentation and poor weight gain, other causes of ketotic hypoglycemia should be considered, including glycogen storage disorders (usually associated with elevated transaminase levels and hepatomegaly), growth hormone deficiency (unlikely because height is at the 95th percentile), adrenal insufficiency (AI), and ketone utilization disorders (rare disorders characterized by recurrent episodes of ketoacidosis). Cyclic vomiting syndrome would be considered if laboratory findings were normal.

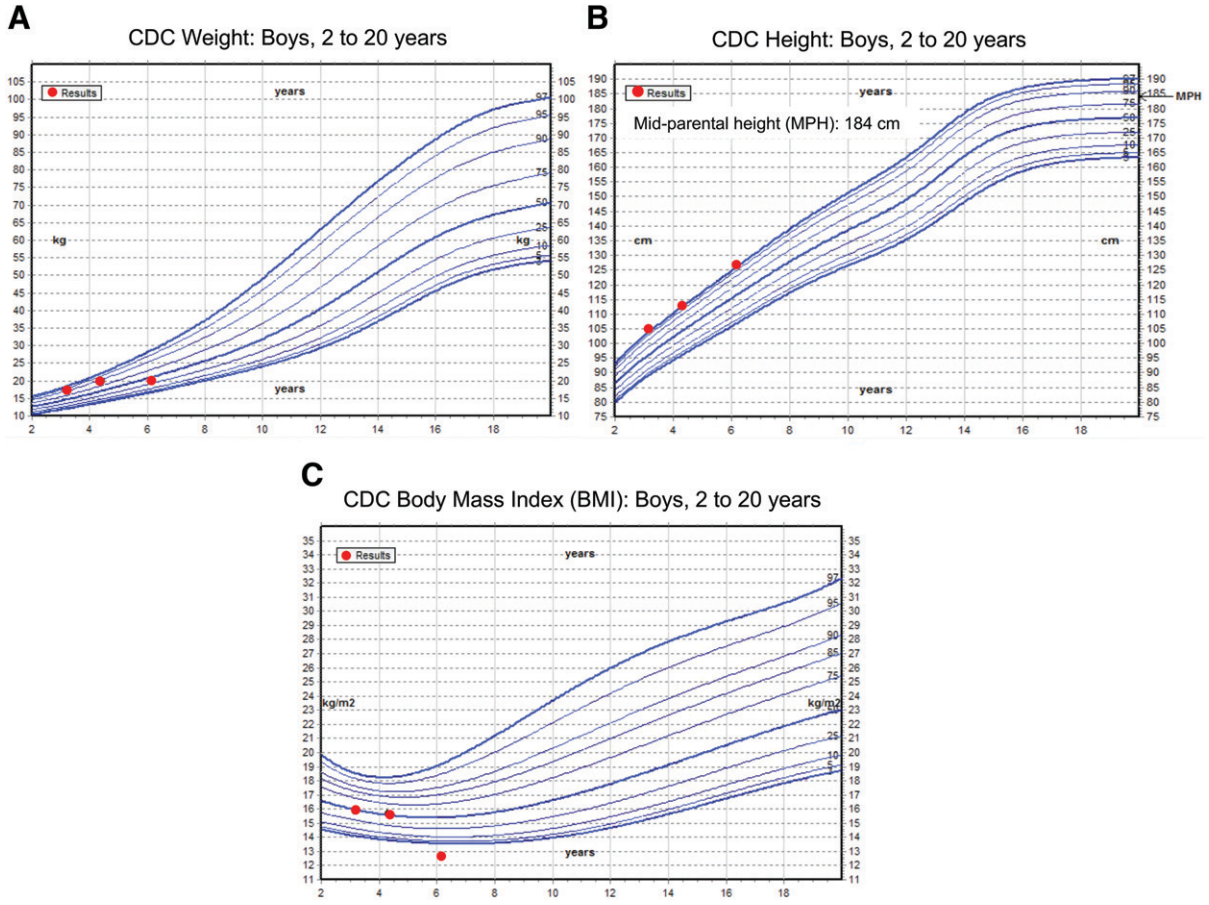

Figure 1. The patient's growth charts demonstrate no weight gain (A), normal linear growth (B), and a declining BMI (C) from ages 4 to 6 years. CDC indicates Centers for Disease Control and Prevention.

Actual Diagnosis

The history of recurrent emesis, poor weight gain, low blood pressure, and acidosis in the setting of hypoglycemia and hyponatremia, in addition to the unusually severe courses of viral illnesses leading to multiple ED visits and an ICU admission, should raise suspicion for AI. Cortisol levels must be interpreted based on the clinical setting in which they are tested, and a level of 18 μg/dL or greater (≥496.58 nmol/L) is expected during illness or hypoglycemia if adrenal function is normal. (1) A cortisol level of 12.1 μg/dL (333.81 nmol/L) during hypoglycemia in our patient, although within the reference range, is not robust enough during hypoglycemia and warrants additional investigation. Definitive testing with a 250-μg dose of cosyntropin (synthetic corticotropin), known as a corticotropin stimulation test, was performed. Baseline cortisol level was 11.7 μg/dL (322.78 nmol/L), and a poststimulation 60-minute cortisol level remained unchanged at 11.7 μg/dL (322.78 nmol/L), confirming AI (a normal response to stimulation is a cortisol level ≥18 μg/dL [≥496.58 nmol/L]). A corticotropin level determined before definitive testing was elevated at 400 pg/mL (88.0 pmol/L) (reference range, 7.2–63.0 pg/mL [1.58–13.86 pmol/L]), indicating primary AI (PAI).

Further testing to investigate the etiology of the AI revealed a normal 17-hydroxyprogesterone level (25 ng/dL), ruling out congenital adrenal hyperplasia, negative 21-hydroxylase antibodies less than 1 U/mL (making autoimmune AI less likely), and elevated very long-chain fatty acid (VLCFA) levels. Elevated VLCFA levels in a boy with AI are indicative of X-linked adrenoleukodystrophy (ALD). Genetic testing confirmed a hemizygous pathogenic variant in the *ABCD1* gene.

The Condition

AI occurs due to impairment of glucocorticoid and/or mineralocorticoid secretion from the adrenal cortex. It is relatively uncommon, but if unrecognized it can become life-threatening. (1) Symptoms are nonspecific, and diagnosis is commonly missed. (1) A high clinical suspicion is required. Fatigue, headache, upper gastrointestinal symptoms, poor growth, and loss of appetite are frequent. Ketotic hypoglycemia is common. Hypotension may be present. Symptoms can be exacerbated by infection, trauma, or physical stress. Hyperpigmentation may be present if corticotropin levels are high. Mineralocorticoid deficiency results in hyponatremia, hyperkalemia, hyperreninemia, and mild acidosis. (2)

PAI is caused by destruction of the adrenal cortex, impaired adrenal steroidogenesis, or adrenal dysgenesis. (2)(3) In PAI, cortisol deficiency results in lack of feedback to the hypothalamic-pituitary axis, leading to elevated plasma corticotropin levels, and disruption of mineralocorticoid production leads to elevated renin levels. This differentiates PAI from secondary (also known as central) AI, where there is insufficient production of corticotropin and no effect on the renin-aldosterone system.

A morning cortisol level less than 5 μg/dL (<137.94 nmol/L) with plasma corticotropin more than 2-fold the upper limit of the reference range makes PAI highly likely. (4) However, a high-dose cosyntropin stimulation test is the gold standard for diagnosis. (4) A cortisol level before and 60 minutes after an IV or intramuscular corticotropin dose of 125 μg (age <2 years) or 250 μg (age >2 years) is checked. Peak cortisol level less than 18 μg/dL (<496.58 nmol/L) after corticotropin stimulation indicates AI. (4) A critical sample with a cortisol level less than 18 μg/dL (<496.58 nmol/L) at the time of hypoglycemia is also supportive of AI. (2) Measurement of renin and aldosterone levels before glucocorticoid and mineralocorticoid replacement are also helpful in the diagnosis of PAI. (4)

Our patient presented multiple times for medical care with similar symptoms, and his diagnosis was repeatedly missed. Note that hyponatremia and hyperkalemia (mineralocorticoid deficiency) and hypoglycemia (glucocorticoid deficiency) may not be present simultaneously or consistently because AI can be an evolving process.

Congenital adrenal hyperplasia is the most common cause of PAI in infancy, and autoimmunity is most common beyond infancy. (5) However, X-linked ALD is the cause in up to 20% of boys with idiopathic PAI. (6) Thus, if the 17-hydroxyprogesterone level is normal, adrenal autoantibodies and VLCFAs are tested before considering other rare causes of PAI. (4)

ALD is an X-linked disorder caused by mutations in the *ABCD1* gene, which normally encodes the ATP binding cassette transport protein that helps VLCFAs move from the cytoplasm into the peroxisome. This mutation leads to accumulation of VLCFAs (particularly C26 and C24) in the adrenal cortex and nervous system, causing adrenocortical failure and degenerative neurologic disease. (7) Girls are generally asymptomatic, but neurodegenerative changes can occur in late adulthood. In boys it presents as 3 phenotypes: cerebral ALD, adrenomyeloneuropathy, or Addison disease only. Phenotype cannot be predicted through VLCFA levels, family history, or the type of mutation in the *ABCD1* gene. (8) Addison disease only presents

most commonly by age 7 1/2 years without evidence of neurologic abnormality initially, but some degree of neurologic disability usually develops by middle age. (8)

Treatment/Management

AI requires lifelong hydrocortisone and fludrocortisone replacement. Daily hydrocortisone, 8 to 12 mg/m^2 per day divided every 8 to 12 hours, is the maintenance dose; 30 to 40 mg/m^2 per day divided every 6 to 8 hours is the stress dose used during periods of trauma or illness. Overtreatment is avoided to prevent growth retardation and Cushing syndrome. Fludrocortisone, 0.05 to 0.2 mg per day, is started and is titrated based on blood pressure, electrolyte levels, and renin levels.

Once the diagnosis of ALD is made, obtaining baseline and periodic brain magnetic resonance images (MRIs) for surveillance is crucial because MRI changes occur before the onset of clinical cerebral disease. (9) Neurologic and neuropsychological evaluations are performed to determine the degree of central nervous system involvement. (8) Hematopoietic stem cell transplantation is the treatment for boys with MRI changes even before symptoms occur. It offers the best outcome because it can halt or even reverse demyelination at a very early stage. (10)

Patient Course

Stress-dose IV hydrocortisone was initiated until emesis resolved, followed by maintenance hydrocortisone, 8 mg/m^2 per day, and fludrocortisone, 0.1 mg once daily. Referral to biochemical genetics and neurology was made. Outpatient endocrinology follow-up continued. Brain MRIs at diagnosis and follow-up were normal.

Lessons for the Clinician

- Symptoms of adrenal insufficiency are nonspecific and can be life-threatening if unrecognized.
- Idiopathic ketotic hypoglycemia is a diagnosis of exclusion. Other endocrine and metabolic causes of hypoglycemia should be ruled out based on the clinical scenario.
- The corticotropin stimulation test is the gold standard to diagnose adrenal insufficiency and should be pursued if clinical suspicion is high.
- X-linked adrenoleukodystrophy should be ruled out in all boys with adrenal insufficiency.
- In all boys with adrenoleukodystrophy, neurologic evaluation and periodic surveillance with brain magnetic resonance imaging (MRI) every 6 months to yearly should be performed to screen for white matter changes before symptoms occur.
- Hematopoietic stem cell transplantation is the treatment for boys with brain involvement on MRI because it can halt or reverse demyelination at an early stage. (10)

References for this article can be found at http://pedsinreview.aappublications.org/content/42/No. 8/453.