



# **Council for the Advancement of Diabetes Research and Education**

## **MISSION STATEMENT**

CADRE is a nonprofit organization committed to reducing the burden of diabetes by providing health care professionals with scientific information and educational initiatives designed to translate research into effective clinical practice.

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## CADRE'S "DIABETES TACTICS"

CADRE's "Diabetes Tactics" are case studies presenting challenging diabetes treatment scenarios that practitioners are likely to encounter. These brief case studies explore controversies or dilemmas in diabetes management and offer practical suggestions for dealing with management challenges. CADRE is pleased to partner with *Insulin* to provide these educational cases to readers of this journal.

This issue's "Diabetes Tactics" discussion is provided by Anisha D. Patel, DO, and William V. Tamborlane, MD, Department of Pediatrics, Center for Clinical Investigation, Yale University School of Medicine, New Haven, Connecticut.

## HIGH INDEX OF SUSPICION FOR ADDISON'S DISEASE IN PATIENTS WITH TYPE 1 DIABETES MELLITUS (DM)

### CASE PRESENTATION

A 3-year-old white twin boy was brought to the emergency department (ED) because of lethargy, nausea, and vomiting for 3 days. He had a 2-week history of polyuria, polydipsia, and weight loss (11 lb). He had no symptoms of upper respiratory infection, fever, or sick contacts. He had experienced a similar episode requiring 1-day hospitalization 2 months previously, which was attributed to acute gastritis and dehydration. At that time, his blood glucose level was 213 mg/dL and his sodium level decreased from 132 mmol/L to 125 mmol/L after receiving intravenous dextrose 5% in 1/4 normal saline (NS). These abnormalities were thought to be iatrogenic due to stress and infusion of exogenous glucose and hypotonic fluids. He improved clinically, his vomiting resolved, and he was discharged.

The patient's medical history is significant for prematurity (27 weeks estimated gestational age), apnea of prematurity, gastroesophageal reflux, constipation, and excessive salt craving "all his life." His family history is positive for type 1 DM in a maternal cousin.

On arrival at the ED, he was lethargic and moderately dehydrated; his pulse was 134 beats/min, blood pressure was 80/48 mm Hg, and respiratory rate was 30 breaths/min. Aside from a slightly tan skin color, the physical examination was normal. Laboratory test results showed the following: blood glucose, 323 mg/dL; sodium, 114 mmol/L; bicarbonate, 12 mmol/L; potassium, 6.7 mmol/L. Urinalysis showed ketosis and glucosuria. Venous blood gas determination showed: pH, 7.34; carbon dioxide, 25 mm Hg. He was given aggressive fluid resuscitation with NS and started on intravenous regular insulin drip at a rate of 0.1 U/kg per hour. He continued to receive NS at 1.5 times the maintenance level without potassium supplementation. He was transitioned from insulin drip to subcutaneous insulin after resolution of acidosis. His serum sodium level remained between 125 and 129 mmol/L despite intravenous NS and decreased to 124 mmol/L after discontinuing NS. Because his blood glucose levels were <323 mg/dL, his corrected serum sodium was similar to the measured serum sodium. His potassium level decreased to 4.1 mmol/L during the insulin drip but remained between 5.2 and 5.4 mmol/L during hospitalization. Urine sodium was 79 mmol/L, and urine potassium was 14.8 mmol/L; urine and serum osmolality were 356 and 279 mOsm/kg, respectively.

Additional workup was done because of the patient's persistent hyponatremia after resolution of acidosis. A renal consult suggested syndrome of inappropriate antidiuretic hormone (SIADH) resulting from the high urine osmolality in a setting of low serum osmolality. The potential for mild cerebral edema associated with diabetic ketoacidosis (DKA) was considered the etiology for SIADH, which was exacerbated by aggressive fluid resuscitation. While the results of laboratory studies for workup of adrenal insufficiency were pending, fluids were restricted to two thirds of maintenance levels; serum sodium remained 124 mmol/L. Baseline plasma cortisol at 8:00 AM was inappropriately "normal" at 15 µg/dL and failed to increase following administration of cosyntropin 0.25 mg. Serum adrenocorticotropic hormone (ACTH) was 280 pg/mL (reference: 6–48 pg/mL); plasma renin, 42.9 ng/mL per hour (reference: <10 ng/mL per hour); serum aldosterone, 1 ng/dL (reference: 2–37 ng/dL); antiadrenal antibodies – positive; islet cell antigen 512 antibody, 18 U/mL (reference: <1.0 U/mL); anti-insulin antibody, 32 µU/mL (reference: 0–5 µU/mL); and antiglutamic acid decarboxylase 65 antibodies, <0.5 U/mL. In addition to insulin, he was started on hydrocortisone 12 mg/m<sup>2</sup> daily in 3 divided doses and fludrocortisone 0.1 mg daily. The child's parents underwent rigorous education for maintenance of diabetes and adrenal disease, including management of adrenal crisis, hypoglycemia, and hyperglycemia/DKA, at the time of diagnosis.

### Analysis

Although electrolyte abnormalities associated with gastroenteritis, intravenous fluid administration, and new-onset type 1 DM are common, persistence of hyponatremia requires further investigation. During the treatment of DKA in children, falling serum sodium concentrations can be an ominous early sign of cerebral edema and SIADH, as suggested by our renal consultants. However, with persistent hyponatremia after resolution of DKA, a high index of suspicion for comorbid Addison's disease (AD) should be raised.<sup>1,2</sup> Association of AD with type 1 DM is seen in autoimmune polyglandular syn-

dromes (APSs): APSs involve 2 or more organ-specific autoimmune dysfunctions and are classified into 4 types, based on the organs involved.<sup>2</sup> APS type I is an autosomal recessive disorder caused by a defect in the autoimmune regulator gene on chromosome 21q22.3.<sup>3</sup> It presents with a history of chronic mucocutaneous candidiasis in infancy and eventual hypocalcemia due to autoimmune hypoparathyroidism and AD later in life.<sup>4</sup> APS type II is more common than APS type I and includes type 1 DM, AD, and thyroid autoimmune disease; the combination of hypothyroidism and AD is called Schmidt's syndrome, and the addition of type 1 DM is known as Carpenter's syndrome.<sup>3,4</sup> APS type II is associated with many human leukocyte antigen (HLA) alleles.<sup>5</sup> APS type III includes thyroid autoimmune disease with other autoimmune diseases, excluding AD and/or hypoparathyroidism.<sup>3</sup> Finally, APS type IV is a combination of organ-specific diseases not included in the previous groups.<sup>3</sup>

## Recommendations

Patients with type 1 DM are at increased risk of developing other autoimmune diseases; therefore, it is important to monitor and screen for the frequently associated autoimmune abnormalities.<sup>6</sup> The American Diabetes Association and the International Society of Pediatric and Adolescent Diabetes have guidelines that recommend screening for thyroid and celiac disease.<sup>7,8</sup> Approximately 3% to 18% of patients with type 1 DM have been reported to develop autoimmune hypothyroidism; ~25% to 30% develop thyroid antibodies.<sup>6-8</sup> The current recommendation is to obtain thyroid-stimulating hormone (TSH) and thyroid antibodies at the time of diagnosis of type 1 DM and TSH every 2 years thereafter if the patient is asymptomatic (more frequently if the patient is symptomatic).<sup>7,8</sup>

Celiac disease is reported to occur in 1% to 10% of patients with type 1 DM, and the current recommendation is to obtain immunoglobulin A (IgA) antitissue transglutaminase (TTG) antibodies at the time of diagnosis of type 1 DM and every 2 years thereafter if the patient is asymptomatic (sooner if the patient is symptomatic).<sup>7,8</sup> TTG autoantibodies are a sensitive and specific marker, recognizing 95% of patients with celiac disease. If TTG antibody testing is not available, IgA antiendomysial antibodies can be used. If the screening results are positive, referral to a gastroenterologist for confirmatory small-bowel biopsy is indicated.<sup>7,8</sup>

AD is also seen in higher frequency in patients with type 1 DM than in the general population, occurring in ~2% of patients with type 1 DM, and is more common in adults than in children.<sup>8</sup> Currently, routine screening for AD is not recommended in youths with type 1 DM because its low prevalence makes screening not cost-effective. However, screening should be targeted to patients at high risk for the disease, which includes having a first-degree relative with AD and having clinical signs of AD.<sup>9</sup> In general, a strong family history of autoimmune disease in a first-degree relative increases the risk of developing organ-specific autoimmune disease. The signs and symptoms of AD in patients with type 1 DM include fatigue, weakness, hypotension, hyperpigmentation, salt craving, unexplained hypoglycemia, and decreasing insulin requirements. Some of these symptoms are nonspecific, and AD can be misdiagnosed. This is a life-threatening condition that requires a high degree of suspicion as well as prompt evaluation and treatment. Evaluation in an asymptomatic patient includes measurement of adrenal cortex autoantibodies (by immunofluorescence) and/or 21-hydroxylase antibodies (by radioimmunoassay). Additional tests include plasma renin, aldosterone, ACTH, basal AM plasma cortisol, and post- $\text{ACTH}$ -stimulation plasma cortisol levels.

## Rationale

The natural history of AD is divided into 3 phases (potential, subclinical, and clinical) and 5 stages (**Table**).<sup>10</sup> Currently, we do not have a complete understanding of the factors that influence the speed of progression of the disease. However, certain HLA alleles are associated with more rapid development of clinical AD. Specifically, patients with DRB1\*0404 and 21-hydroxylase antibodies are at high risk for the disease, whereas those with DRB1\*0401 and DRB1\*0402 and 21-hydroxylase antibodies have a limited risk of disease progression.<sup>11,12</sup> Many other variables may contribute to the progression of AD and, because HLA typing usually is not available, clinical suspicion is important in prompting further evaluation.

**Table.** Natural history of Addison's disease (AD).<sup>10</sup>

Adrenal Function	Stage	ACA	PRA	Aldosterone	ACTH	Cortisol	Cortisol After 60 Minutes	Clinical Manifestations
Potential	0	+	Normal	Normal	Normal	Normal	Normal	Absent
Subclinical	1	+	High	Normal/low	Normal	Normal	Normal	Absent
Subclinical	2	+	High	Low	Normal	Normal/low	Low response	Absent
Subclinical	3	+	High	Low	High	Low	No response	Absent
Clinical AD	4	+	High	Low	Very high	Very low	No response	Present

ACA = adrenal cortex autoantibodies; PRA = plasma renin activity; ACTH = adrenocorticotrophic hormone; + = positive.

## Outcome

This patient has done very well with insulin, hydrocortisone, and fludrocortisone replacement with ad lib salt intake. His glycosylated hemoglobin level after 6 months of treatment improved from 9.7% to 6.6%, and he has had no severe hypoglycemic events that required assistance. His parents called in daily blood glucose readings for insulin dose adjustments for 3 weeks and continue to call as needed for further adjustments. The patient underwent a honeymoon period, during which his insulin requirement was <0.5 U/kg per day. The parents were instructed to call the clinic and give stress-dose (triple-dose) steroids for fever >101°F or nausea/vomiting. They were also given hydrocortisone sodium succinate for injection for adrenal crisis and glucagon for severe hypoglycemia. The patient's blood pressure is normal; his sodium and potassium levels have remained in the normal range, and he has had no episodes of adrenal crisis. The patient's twin sibling is clinically well and has a normal ACTH level.

### Key Messages

- Patients with type 1 DM are at increased risk of developing other associated autoimmune diseases. The presence of autoantibodies to 2 or more organs is known as APS.
- The combination of type 1 DM, AD, and thyroid autoimmune disease is classified as APS type II.
- Patients with new-onset type 1 DM and persistent hyponatremia after resolution of DKA/dehydration should raise a high index of suspicion for AD.
- In patients with type 1 DM, nonspecific symptoms such as fatigue, weight loss, unexplained hypoglycemia, and decreased insulin requirements should raise a high index of suspicion for AD.
- Risk for autoimmune AD includes having a first-degree relative with AD or being affected by another autoimmune disease (eg, type 1 DM, hypoparathyroidism, hypothyroidism, chronic candidiasis).
- AD is seen in ~2% of patients with type 1 DM and can be screened with adrenal cortex autoantibodies by immunofluorescence and/or 21-hydroxylase antibodies by radioimmunoassay.
- Plasma renin, aldosterone, ACTH, basal AM plasma cortisol, and post-ACTH-stimulation plasma cortisol levels are needed for diagnosis of AD.

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