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Up Schmidt's creek: When the right treatment goes wrong

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CASE PRESENTATION

A 15-year-old girl, previously well, presented to her family physician with a 2-month history of fatigue and exercise intolerance. There was no history of fever, syncope, palpitations, wheezing, polyuria, polydipsia, constipation or cold intolerance. She had no sick contacts. Breast development began at 12 years but she had not experienced menarche. There were no medications or recreational drug use. Her father has type 1 diabetes mellitus and her maternal grandfather had acquired anemia. Investigations included elevated thyroid stimulating hormone (TSH) and low free T4. She was diagnosed with hypothyroidism. Levothyroxine was initiated at 50 μg (1.3 μg/kg) daily, thyroid function tests were repeated 6 weeks later without dose change. Over the ensuing 3 months, there was no symptomatic relief. Rather, she reported progressive fatigue, abdominal pain and 5 lbs weight loss. Three months later, she presented to our emergency department. Blood pressure was 92/60, heart rate was 90 bpm without orthostatic changes. Cardiovascular, respiratory, abdominal and neurologic exams were normal. TSH was 14 mIU/L (0.5 to 5.0); free T4 was 11.3 pmol/L (10.0 to 23.0). Complete blood count (CBC), C-reactive protein (CRP), glucose, electrolytes and urinalysis were normal. Levothyroxine was increased to 75 μg daily. Ten days later, she returned to the emergency department with hypotension and worsening fatigue. She was afebrile. Blood pressure was 72/44 without orthostatic change. Supine heart rate was 118 bpm and standing was 140 bpm. Thyroid examination was normal. Examination and further bloodwork confirmed the diagnosis.

DISCUSSION

Examination was notable for peri-orbital and mucosal hyperpigmentation. Investigations demonstrated low sodium of 130 mmol/L and undetectable cortisol level despite hypotension, consistent with adrenal crisis. In primary adrenal insufficiency both cortisol and aldosterone production are impaired due to destruction of the adrenal cortex. Our patient's cortisol level remained undetectable despite cosyntropin stimulation, confirming adrenal insufficiency. She was also found to have an elevated adrenocorticotropic hormone (ACTH) level, indicative of *primary* adrenal insufficiency.

Table 1. Comparison of autoimmune polyglandular syndromes type I and type II

	Autoimmune polyglandular syndromes	
	Type I (APECED)	Type II
Genetics	AIRE gene mutation; autosomal recessive	Polygenic, autosomal dominant with low penetrance, association with HLA-DR3/DQ2 and DR4/DQ8
Age of onset	Infancy or childhood	Childhood to late adult
Prevalence	1:100,000 although in select populations, as high as 1:9000–1:25,000	1:20,000
Female:male ratio	0.1:1 to 2.4:1	3:1
Clinical manifestations	Hypoparathyroidism*	Primary adrenal insufficiency
	Chronic mucocutaneous candidiasis*	Autoimmune thyroid disease
	Primary adrenal insufficiency*	Type 1 diabetes mellitus
	Primary hypogonadism	Pernicious anemia
	Malabsorption or gastrointestinal disorders	Hypogonadism
	Chronic active hepatitis	Vitiligo
	Type 1 diabetes mellitus	Autoimmune hypophysitis
	Autoimmune thyroid disease	
	Pernicious anemia	
	Vitiligo	
	Alopecia	

APECED Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy

*Hypoparathyroidism, mucocutaneous candidiasis and adrenal insufficency constitute the 'classic triad' of Type I APS

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Hyperpigmentation in primary adrenal insufficiency results from cosecretion of ACTH and melanocyte-stimulating hormone (MSH) which are derived from a common precursor protein, pro-opiomelanocortin. When cortisol declines in primary adrenal insufficiency ACTH and MSH both rise in response, contributing to hyperpigmentation. Salt cravings occur with primary adrenal insufficiency due to mineralocorticoid deficiency. The differential diagnosis of acquired primary adrenal insufficiency includes autoimmune adrenalitis, infectious adrenalitis, bilateral adrenal infarction, drugs and infiltration. Autoimmune adrenalitis (Addison's disease) is the most common cause of acquired adrenalitis in Western countries, while tuberculosis remains a common cause worldwide.

Given this patient's family history of autoimmune disease and her age, autoimmune adrenalitis was considered most likely. Therapy was initiated with hydrocortisone and fludrocortisone to replace deficient glucocorticoid (cortisol) and mineralocorticoid (aldosterone), respectively. Following replacement there was rapid resolution of hypotension, fatigue and abdominal pain.

Multiple case reports describe precipitation of adrenal crisis in individuals with undiagnosed primary adrenal insufficiency upon initiation of levothyroxine (1,2). The postulated mechanism invokes diminished cortisol requirements in the hypometabolic state of hypothyroidism. Once euthyroidism is re-established, glucocorticoid requirements increase. Our patient's deterioration was likely triggered by the introduction and increase of levothyroxine.

TSH levels may be elevated in the setting of adrenal insufficiency in the absence of intrinsic thyroid disease. This may reflect a tonic suppression of TSH by physiologic levels of glucocorticoids (3). In this circumstance, TSH normalizes following initiation of steroid therapy. Alternatively, autoimmune adrenal disease may be associated with other autoimmune endocrinopathies. Autoimmune polyglandular syndrome type 1 (APS I), also known as autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED), is an autosomal recessive disease characterized by hypoparathyroidism, mucocutaneous candidiasis and primary adrenal insufficiency. Autoimmune polyglandular syndrome Type II (APS II) is more common (see Table 1 for comparisons). The diagnosis is made by a history of adrenal insufficiency and one of: type 1 diabetes mellitus or autoimmune thyroid disease. Other associations with APS II include pernicious anemia, primary gonadal failure, vitiligo and autoimmune hypophysitis. The coexistence of autoimmune thyroiditis and adrenalitis is also known as Schmidt syndrome (4,5).

Thyroid function was reassessed following initiation and titration of hydrocortisone and fludrocortisone. While there was a reduction in her levothyroxine dose, there was a persistent requirement for thyroid replacement. Anti-thyroid perioxidase antibodies and antithyroglobulin antibodies were also present, consistent with a concurrent diagnosis of autoimmune hypothyroidism. Given autoimmune hypothyroidism and primary adrenal insufficiency, she was diagnosed with APS II.

CLINICAL PEARLS

- Primary adrenal insufficiency is rare and the presentation can be nonspecific and indolent. Index of suspicion must be high to avoid missed diagnoses. Hyperpigmentation of sun-unexposed areas is a fairly specific sign of primary adrenal insufficiency and can be identified around the areolae, genitals, oral mucosa and palmar creases.
- Primary hypothyroidism and primary adrenal insufficiency can present concurrently in Autoimmune Polyglandular Syndrome Type II (APS II). APS II is characterized by primary adrenal insufficiency and one of type 1 diabetes mellitus or autoimmune thyroid disease.
- Administration of levothyroxine in the setting of untreated adrenal insufficiency may precipitate an adrenal crisis. If there is salt craving or hyperpigmentation, rule out adrenal insufficiency prior to initiating levothyroxine. If levothyroxine is initiated and the patient deteriorates, reassess for concurrent adrenal insufficiency and treat accordingly. Routine clinical follow-up is always indicated following initiation of treatment. Primary adrenal insufficiency may be confirmed with elevated ACTH>22 pmol/L (100 pg/mL) and low serum cortisol < 275 nmol/L (10 μg/dL). If further confirmation is required, stimulation with cosyntropin 250 mcg (or 35 mcg/kg for infants < 7 kg) should result in elevation of serum cortisol > 500 nmol/L (18 μg/dL) 60 min after administration, in patients with adequate adrenal response (1).

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Conflict of Interest

The authors have no competing interests to declare.

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