Polyglandular Dysfunction in Patients With Type 1 Diabetes: Recurrent Hypoglycemia Is an Alarming Symptom

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Presentation

A 35-year-old man known to have type 1 diabetes for 8 years presented to the emergency department with disturbed conscious level. He gave a history of recurrent similar attacks during the previous 8 months. All of these attacks were proved to be due to hypoglycemia. Some of the episodes were mild and treated by oral glucose only, whereas others were severe, requiring hospital admission and treatment with an intravenous glucose infusion.

The patient had been taking human mixed insulin for the past 2 years. His insulin doses were reviewed by his primary care providers and decreased after each episode of hypoglycemia. His total daily insulin dose had been decreased from 70 to 10 units during the previous 8 months.

The patient gave a history of darkening of the skin of his face and extremities associated with significant weight loss throughout the previous year. He had no family history of type 1 diabetes or thyroid or adrenal diseases.

On admission to the emergency department, the patient had disturbed conscious level with no signs of lateralization. His blood pressure was 70/40 mmHg, pulse was 72 bpm and regular, weight was 60 kg, and BMI was 20.7 kg/m². Hyperpigmentation of the face, oral mucosa, and exposed areas of upper and lower limbs was evident, especially when compared to old photographs of the patient. No other significant clinical findings

were noticed. His random blood glucose was 32 mg/dL.

The patient was admitted to the intensive care unit. After receiving dextrose 25% intravenously, his conscious level improved significantly and was back to normal within 2 hours. Serum cortisol and free thyroxine (FT4) were very low. Thyroid-stimulating hormone (TSH) and adrenocorticotrophic hormone (ACTH) were very high—150 mIU/mL (normal 0.35–5.5 mIU/mL) and 972 pg/mL (normal 10–46 pg/mL), respectively (Table 1). Renal function was normal. Thyroid peroxidase (TPO) antibodies were highly positive.

The patient was diagnosed to have polyglandular autoimmune syndrome type II (PAS II). He was started on hormonal replacement therapy (hydrocortisone before levothyroxine to avoid precipitating an adrenal crisis), with dose adjustments made during the following weeks. His general condition, blood pressure, and blood glucose showed significant improvement within 3 weeks. His insulin doses were gradually increased to achieve optimum blood glucose control.

Questions

1. In type 1 diabetes, could recurrent hypoglycemia be the result of endocrine dysfunction?
2. What signs should prompt providers to suspect PAS II, and how is the condition diagnosed?

Commentary

Polyglandular autoimmune syndromes are rare endocrinopathies

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characterized by clinical diversity. PAS II refers to Addison's disease plus thyroid autoimmunity or type 1 diabetes (1). The prevalence of PAS II is 1/20,000 (2). It is more frequently encountered in women, and the male-to-female ratio is 1:3 (3). PAS II mostly occurs in adulthood during the third and fourth decades of life. Although there is some correlation between the ages of onset of one PAS illness with another, there is often a long interval between the manifestation of the first and second component diseases of PAS II, which can span years to decades (3,4). The peak incidence of PAS II is between the ages of 20 and 60 years, and it is common for multiple generations to be affected by one or more component of the syndrome (5).

Type 1 diabetes is a very frequent component of PAS II and is often its first symptom. The simultaneous occurrence of type 1 diabetes and autoimmune hypothyroidism can lead to hypoglycemia. Reduced insulin clearance, slow gastric emptying, and decreased intestinal absorption of glucose are contributing factors. Reduction of gluconeogenesis and impairment of glycogenolysis and glucagon secretion prevent recovery from the hypoglycemia (6,7). Deficiency in cortisol, a counterregulatory hormone, can also cause hypoglycemia because of associated decreased gluconeogenesis and increased insulin sensitivity (4).

The patient in this case was given no explanation for his recurrent episodes of hypoglycemia. No further investigations were done to explore the cause of those attacks during an 8-month period. The persistence of

the problem after reducing his insulin doses should have alerted the primary care providers to the presence of an underlying cause.

His low blood pressure on admission and history of skin hyperpigmentation pointed to Addison's disease. The presence of a low cortisol level along with very high ACTH confirmed the diagnosis. High TSH and low FT4 with highly positive TPO antibodies secured the diagnosis of autoimmune primary hypothyroidism. Thus, this patient had the three main components of PAS II.

In patients with concomitant Addison's disease and hypothyroidism, thyroid hormone therapy should not precede glucocorticoid replacement. Thyroxine increases hepatic corticosteroid metabolism and may cause hypotension and acute adrenal insufficiency (1). This patient was therefore started on hydrocortisone before levothyroxine to avoid precipitating an adrenal crisis. His blood pressure and blood glucose showed significant improvement. As his insulin requirements gradually increased, dose adjustments were needed to optimize blood glucose control.

Clinical Pearls

- Recurrent hypoglycemia in type 1 diabetes, especially after insulin dose adjustment, should alert

the primary care provider to the presence of an underlying cause or causes.

- Associated autoimmune endocrine diseases (Addison's disease or hypothyroidism) are among the possible causes.
- Early diagnosis and treatment of the multiple endocrine deficiencies could prevent life-threatening complications.

TABLE 1. Hormonal Analysis Results

Hormone	Result	Normal Range
TSH (mIU/mL)	150	0.35–5.5
Morning ACTH (pg/mL)	972	10–46
FT4 (ng/dL)	0.5	0.8–2
Morning cortisol (μg/dL)	0.33	5–25

Duality of Interest

No potential conflicts of interest relevant to this article were reported.

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