



# Hypoglycemia-Associated Autonomic Failure in Type 1 Diabetes: Beyond Hypoglycemia Unawareness

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## Case Presentation

A 14-year-old girl with a 4-year history of type 1 diabetes was admitted to our hospital after a severe hypoglycemic episode. After a usual morning awakening and before the mealtime insulin injection for breakfast, while sitting in bed and reading a magazine, she suddenly lost consciousness and started having generalized seizures, progressing into coma. The blood glucose reading on her glucose meter showed “low,” and her mother immediately administered 1 mg of glucagon intramuscularly, after which she recovered.

At admission, her orthostatic vital signs were normal (heart rate 84 bpm and blood pressure 111/66 mmHg when supine and heart rate 85 bpm and blood pressure 110/68 mmHg in a standing position), and her oxygen saturation was 98%. Her neurologic examination was normal, with no fever or other clinical signs of infection. She did not recall having any adrenergic symptoms such as tremor, sweating, or headache before losing consciousness. Blood analysis showed normal complete blood count (hemoglobin 14.5 g/dL and white blood count 6.910), glucose (72 mg/dL [4 mmol/L]), and normal electrolytes (potassium 4.2 mmol/L, sodium 138 mmol/L, and calcium 9.78 mg/dL [2.44 mmol/L]).

In the recent past, she had reported a similar episode in the morning, which had been reverted by an

intramuscular glucagon injection by her mother, but at that time she was not hospitalized.

The patient was also taking levothyroxine for autoimmune thyroiditis and had a normal menstrual cycle. Her diabetes treatment plan included a multiple daily injection insulin regimen with glargine and lispro analogs, with an average total insulin dose of 1.2 units/kg. Her basal insulin was 38 units administered every night at 10:00 p.m., and her bolus mealtime insulin was calculated using 1 unit for 10 g carbohydrate. Her latest A1C was 7.8%.

Her apparent abnormal counterregulatory response to the hypoglycemic episode, with the emergence of sudden severe neuroglycopenic symptoms without any preceding adrenergic symptoms led us to perform an adrenal workup, which revealed a normal early morning cortisol of 1,037  $\mu\text{g/dL}$  (286 nmol/L) but inappropriately high ACTH of  $>2,000$  pg/mL (440 pmol/L). In addition, her renin was increased to 44.9 pg/mL (1.06 pmol/L) (normal range 1.3–13.8 pg/mL), but the aldosterone level was normal at 152 pg/mL (0.42 nmol/L) (normal range 50–175 pg/mL). A short Synacthen test (250  $\mu\text{g}$ ) showed an abolished adrenal response to ACTH with cortisol of 1,006  $\mu\text{g/dL}$  (277.5 nmol/L) at 0 minutes and 1,039  $\mu\text{g/dL}$  (286.6 nmol/L) at 60 minutes. Antibodies against adrenal 21-hydroxylase were positive. Interestingly, our patient had not complained of any weakness, fatigue, or gastrointestinal symptoms in the past and had no clinical signs of hyperpigmentation of skin or mucosae.

She was started on hydrocortisone replacement therapy at a dose of 12  $\mu\text{g/m}^2$  and was discharged with instructions for hydrocortisone supplemental doses in cases of stress and frequent follow-up.

## Questions

1. What comorbidities can adversely affect the counterregulatory response to a hypoglycemic episode?
2. What factors from medical history and/or analysis of the hypoglycemic episode may point to an etiology of autonomic failure other than hypoglycemia unawareness?

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## Commentary

Hypoglycemic episodes are a frequent complication in type 1 diabetes, as a result of the long-term effort to maintain glucose levels within the euglycemic range (1). Frequent hypoglycemic events may lead to the development of hypoglycemia unawareness, a gradually developing phenomenon defined as a patient's inability to detect an impending hypoglycemia event (2). It is also known as hypoglycemia-associated autonomic failure (HAAF) (3), is enhanced by antecedent hypoglycemia (4), and affects as many as 29% of children and adolescents with type 1 diabetes (1).

The first step in the physiological chain of reactions to hypoglycemia is the suppression of endogenous insulin production to untraceable levels, which is unattainable in people with type 1 diabetes because of the presence of exogenous insulin in the bloodstream (5). The second step is the increase of glucagon secretion, which may also be impaired in patients with diabetes because of the existent insulin (6), an inherent dysfunction of the neighboring  $\beta$ -cells, or other unidentified factors (7). At even lower blood glucose levels, adrenaline, growth hormone, and cortisol are also increased to protect the brain from hypoglycemia. Activation of the autonomic nervous system is clinically manifested by the adrenergic symptoms of sweating, tremor, and tachycardia. Although the glycemic thresholds for the above reactions in normal individuals follow a strict order and are reproducible, this is not the case in people with type 1 diabetes (5). Recurrent episodes of hypoglycemia lower the threshold of sympathoadrenal responses, resulting in HAAF, a major component of hypoglycemia unawareness (2).

Adrenaline production during the counterregulatory response is linked to cortisol secretion in the adrenals, demonstrated initially in hypophysectomized rats that showed a marked reduction in epinephrine secretion, which was restored by ACTH. Glucocorticoids from the adrenal cortex activate the phenyl-ethanolamine N-methyltransferase, an enzyme found primarily in the adrenal medulla that converts norepinephrine to epinephrine (8). The adrenal medulla receives portal venous blood with a cortisol concentration 100-fold higher than peripheral blood. Impaired cortisol secretion in adrenal insufficiency reduces the rate at which epinephrine is secreted in response to hypoglycemia (9).

The above pathophysiological consequences may occur during the autoimmune destruction of adrenals, which

is reported in only 0.5% of patients with type 1 diabetes (10), a frequency that is still 10 times higher than in the general population (11). The constellation of type 1 diabetes, autoimmune adrenalitis, and Hashimoto's thyroiditis constitutes the autoimmune polyglandular syndrome type 2 (APS 2) syndrome. APS 2 occurs mostly during the third or fourth decade of life, with a prevalence of 1 in 20,000, with occurrence more frequently in females (12). It is rare in childhood and adolescence, with only a few cases reported (13). Characteristically, for each of the component diseases of APS 2, organ-specific autoantibodies are detected (12).

In this case, the development of autoimmune adrenalitis was indolent and, at that time, restricted to glucocorticoid insufficiency. Mineralocorticoids in serum were within the normal range, as were electrolytes. Furthermore, our patient did not complain of any weakness, fatigue, or skin hyperpigmentation. However, these endocrinopathies evolve over time, and frequent surveillance is needed.

The characteristics of the hypoglycemic episode in the context of the patient's glycemic profile may give some clues for suspecting an abnormal adrenal function. Our patient's inadequate glycemic regulation without frequently reported hypoglycemic events was unlikely to have primed the development of hypoglycemia unawareness. Thus, the complete absence of adrenergic symptoms in response to the low levels of glucose pointed to low adrenaline or noradrenaline production, apparently caused by the insufficient intra-adrenal cortisol.

The importance of establishing early the diagnosis of adrenal insufficiency is crucial in these cases because a severe hypoglycemic episode may easily evolve into a life-threatening situation.

It is important to realize that, in the context of type 1 diabetes, the absence of an adrenergic component in a hypoglycemia response is not always because of hypoglycemia unawareness but may represent adrenal failure as part of an autoimmune polyglandular syndrome.

## Clinical Pearls

- The dissection of a severe hypoglycemic episode may reveal an abnormal counterregulatory response in a patient with type 1 diabetes.
- HAAF in the context of non-tight glycemic regulation may point to a different etiology than hypoglycemia unawareness.

## CASE STUDY

- Coexistent adrenal insufficiency must be suspected when severe hypoglycemic episodes are followed by impaired autonomic response and predominant neuroglycopenic symptoms.
- The combination of type 1 diabetes and other autoimmune endocrinopathies is part of an autoimmune polyglandular syndrome.

### DUALITY OF INTEREST

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

### AUTHOR CONTRIBUTIONS

A.G. conceptualized and wrote the manuscript A.E., A.C., and D.C. contributed to discussion and reviewed/edited the manuscript. D.C. is the guarantor of this work and, as such, had full access to all the data in the case and takes responsibility for the integrity of the data and the accuracy of the case presentation.

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