Unusual association of diseases/symptoms

Ketosis-prone type 2 diabetes mellitus in a patient with Sheehan's syndrome: a rare convergence of two distinct endocrine entities

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Summary

A 36-year-old housewife, previously diagnosed with Sheehan's syndrome on glucocorticoid and thyroxine replacement therapy, presented with unprovoked diabetic ketoacidosis. Ketoacidosis was corrected with intravenous fluids and insulin therapy. Further evaluation was suggestive of type 2 diabetes mellitus. On follow-up, she experienced repeated episodes of hypoglycaemia and insulin was tapered and stopped. Adequate glycaemic control was maintained with metformin monotherapy.

BACKGROUND

Ketosis-prone type 2 diabetes is a variant of type 2 diabetes characterised by ketoacidosis at presentation.¹ Typically these patients have well-preserved β -cell function, achieving near normoglycaemia within 10 weeks of the episode of ketoacidosis.² Furthermore, up to 40% of these patients remain insulin free 10 years after the episode. Sheehan's syndrome is a form of hypopituitarism secondary to pituitary infarction in the peripartal period, most often due to severe haemorrhage.

This case represents a rare convergence of these two distinct endocrine disorders. While there are other case reports^{3–5} linking diabetes mellitus and Sheehan's syndrome, they describe the development of Sheehan's syndrome on a background of diabetes, while we describe the opposite. Indeed, the very course of this case goes against the Houssay phenomenon, as will be elaborated later. Finally, to the best of our knowledge, no similar cases have been reported in medical literature, linking ketosis-prone type 2 diabetes and Sheehan's syndrome.

CASE PRESENTATION

A 36-year-old housewife presented with symptoms of four episodes of vomiting and drowsiness since the past 2 days. She had been diagnosed with Sheehan's syndrome nearly 17 years ago, since when she had been kept on glucocorticoid and thyroxine replacement therapy. At that time, she had developed severe antepartal haemorrhage, resulting in intrauterine foetal death; it was followed shortly by persistent amenorrhea.

Her history was otherwise unremarkable. At the time of the current admission, she claimed to have been compliant on therapy. She denied any form of substance abuse. She had one living issue; her second pregnancy having terminated in the aforementioned manner. Review of family history revealed that her father was a type 2 diabetic on therapy with oral antidiabetic drugs.

On examination, she was in shock. Signs of dehydration were evident in the form of loss of skin turgor and a coated tongue. Her breathing was acidotic. Centripetal obesity, moon facies and breast atrophy were notable. Focal deficits were ruled out by neurological examination. Her body mass index was 29.09 kg/m².

INVESTIGATIONS

Routine laboratory parameters at presentation showed hyperglycaemia (random blood glucose: 329 mg/dl), mild renal failure (creatinine: 1.7 mg/dl) and neutrophilic leucocytosis (total leucocytes: 17 900/mm³; 39% bands). Thyroid function tests were suggestive of secondary hypothyroidism (T_3 <0.2 ng/ml, T_4 4.1 mcg/dl, thyroid stimulating hormone 0.015 mIU/ml). Serum cortisol level was high (>63.4 mcg/dl); serum estradiol levels were persistently low (5 pg/ml). Transvaginal ultrasonography revealed an atrophic uterus; her ovaries could not be visualised. Urinalysis confirmed the presence of ketosis (40 mg/dl); arterial blood gas analysis showed metabolic acidosis (pH: 7.28, HCO_3^- : 15). Evaluation for the underlying cause of ketoacidosis was negative. Blood and urine cultures performed prior to initiation of antibiotic therapy were sterile. Electrocardiography was normal. Evaluation of hyperglycaemia revealed elevated HbA_{1c} levels (9.8%), ruling out stress hyperglycaemia. Auto-immune markers were not performed as the patient had a preserved β -cell function (see below).

DIFFERENTIAL DIAGNOSIS

- Unprovoked diabetic ketoacidosis on a background of Sheehan's syndrome.
- Hyperglycaemia secondary to over-supplementation of replacement steroid therapy, resulting in ketoacidosis.

TREATMENT

A diagnosis of diabetic ketoacidosis on a background of Sheehan's syndrome was made and the patient was

treated with intravenous rehydration and insulin infusion. Empirical therapy with broad-spectrum parenteral antibiotics was also initiated.

OUTCOME AND FOLLOW-UP

She made a steady recovery with complete resolution of the ketoacidosis. C-peptide levels estimated 4 weeks after recovery from the acute event were normal (1.62 ng/ml), confirming preservation of β -cell function. She was therefore discharged on premixed insulin and oral metformin. Thyroxine supplementation was increased from 150 to 200 mcg/day, while glucocorticoid supplementation was continued with oral prednisolone at 7.5 mg/day. Oral conjugated estrogen supplementation (0.625 mg/day) was also started in consultation with gynecologists.

On follow-up, she developed recurrent episodes of hypoglycaemia. Insulin therapy was therefore tapered and ultimately stopped 4 months after the initial episode. Glycaemic control was maintained with metformin monotherapy. A secondary diagnosis of ketosis-prone type 2 diabetes mellitus was made.

DISCUSSION

Hypopituitarism and diabetic ketoacidosis have been linked in various ways. Dunlop *et al* described a case of hypopituitarism following diabetic ketoacidosis complicated by cerebral oedema in a type 1 diabetic. In that case, hypothalamo-pituitary axis damage from the episode of cerebral oedema, manifested as hypopituitarism 2 years after the index event.

The Houssay phenomenon was first described by Houssay and Biasotti in animal studies and by Balo and Calder in humans. It refers to the amelioration of diabetes following the development of hypopituitarism, possibly due to the deficiency of counterregulatory hyperglycemic hormones.

While both the case report by Dunlop *et al*³, and the Houssay phenomenon describe the impact of hypopituitarism on a background diabetic state, we report the development of diabetes in a patient with a long-standing Sheehan's syndrome. Our case is therefore unique insofar as it goes against the Houssay phenomenon. Although the case described by Irvine *et al* also described hyperglycaemia in a patient with Sheehan's syndrome, the cause was most likely thyrotoxicosis and not diabetes mellitus *per se*. Furthermore, the case in question did not develop ketoacidosis.

Moreover, our patient displayed several characteristic features of ketosis-prone type 2 diabetes, including a positive family history of diabetes and an overweight body habitus, in addition to the typical natural history of her illness.

Interestingly, our patient had physical attributes suggestive of a Cushingoid habitus, and her serum cortisol levels were high at presentation. Considering these findings, a possibility of ketoacidosis secondary to possible over-

supplementation of glucocorticoids was considered. While this possibility could not be ruled out, the patient's claim that she was compliant to glucocorticoid therapy at conventional replacement doses, played against this hypothesis. The situation was also complicated by the fact that the patient was under severe stress at the time, making it difficult to judge whether her apparent hypercortisolaemia was iatrogenic or an indicator of physiologic endogenous cortisol secretion in response to stress. Moreover, panhypopituitarism itself is known to produce centripetal obesity, mimicking features of a Cushingoid habitus.

We also reviewed the role of glucocorticoids supplementation in patients with pituitary disease and partial adrenocorticotrophic hormone (ACTH) deficiency. A study by Agha *et al*⁶ showed that even conventional dosing can produce hypercortisolaemia in such patients, especially under unstressed physiological conditions. This finding probably reflects the preserved adrenal gland function in these patients.

If this were indeed the situation in our patient, it suggests that externally administered counterregulatory hormones can trigger diabetic ketoacidosis in susceptible individuals, even in the presence of Sheehan's syndrome.

Learning points

- ▶ Externally administered counterregulatory hormones can trigger diabetic ketoacidosis in susceptible individuals, even in the presence of Sheehan's syndrome.
- ▶ Conventional replacement dosing of glucocorticoids can produce hypercortisolaemia with resulting complications in patients with pituitary disease and partial ACTH deficiency.
- ▶ The Houssay phenomenon can under certain circumstances be reversed.

Competing interests None.

Patient consent Obtained.

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