

Severe hypoglycemia and hyponatremia caused by hypopituitarism in a female patient with type 1 diabetes

A case report

Fangqiu Zheng, PhD*, Mingcai Qiu, MD, Hongyan Wei, MD

Abstract

Rationale: The misdiagnosis of hypopituitarism is common due to its rarity and its nonspecific clinical manifestations. Our case report highlights the importance of critical evaluation regarding hypopituitarism as a cause of recurrent hypoglycemia, hyponatremia, and gastrointestinal symptoms in patients with T1DM, as misdiagnosis might be fatal to the patient.

Patient concerns: We herein report the case of 35-year-old female patient who presented with 18 years of history of well-controlled type 1 diabetes mellitus and a 6-month history of recurrent nausea and vomiting, generalized weakness, hyponatremia, and severe hypoglycemia, despite a reduction in the dose of insulin. She was considered as having “type 1 diabetes and gastroparesis.” Four months later, she was diagnosed with hypothyroidism, and 25 µg/d of levothyroxine was prescribed. However, the levothyroxine had to be discontinued 1 week later because of frequent vomiting by the patient.

Diagnosis: Further evaluation in our hospital revealed low-normal adrenocorticotropic hormone, low-normal serum cortisol, and low 24-hours urinary cortisol excretion. Secondary hypothyroidism and hypogonadotropic hypogonadism were also demonstrated. Based on the endocrinological findings, she was diagnosed with hypopituitarism possibly due to lymphocytic hypophysitis. Diabetic nephropathy was another diagnosis made after kidney biopsy.

Interventions: The patient was treated with 100 mg/d of hydrocortisone intravenously for 2 weeks. After that, she continued on 15 mg/d of prednisone, and then 25 µg/d of levothyroxine was administered.

Outcomes: The patient’s insulin requirement increased to a pre-morbid level, the severe hypoglycemia resolved, the physical discomforts were alleviated, and blood electrolytes returned to normal.

Lessons: This uncommon case reinforced the significance of a timely diagnosis and appropriate treatment of hypopituitarism. We recommend that physicians focus their awareness on this potentially life-threatening disease, as it is a condition potentially fatal to the patient if not recognized and treated.

Abbreviations: APS = autoimmune polyendocrine syndrome, FPG = fasting plasma glucose, HbA1c = glycosylated hemoglobin, TIN = tubulointerstitial nephritis.

Keywords: diabetic kidney disease, hypoglycemia, hypopituitarism, type 1 diabetes

1. Introduction

Hypopituitarism is a rare condition that may present as recurrent severe hypoglycemia and can influence the glycemic profile of

patients with type 1 diabetes.^[1,2] However, hypopituitarism often develops insidiously,^[1] the diagnosis of hypopituitarism still remained challenging and often delayed by several months. In the present case report, we aimed to demonstrate the uncommon association of hypoglycemia, hyponatremia, and gastrointestinal symptoms with hypopituitarism in a female patient with type 1 diabetes. This is a potentially fatal condition to the patient if not recognized and treated.

Editor: Tuck Yean Yong.

Informed written consent was obtained from the patient for publication of this case report and accompanying images.

The authors have no funding and conflicts of interest to disclose.

Department of Endocrinology, Tianjin Medical University General Hospital, Tianjin, China.

* Correspondence: Fangqiu Zheng, Tianjin Medical University General Hospital, He Ping District, Tianjin, China (e-mail: fqzheng@163.com).

Copyright © 2019 the Author(s). Published by Wolters Kluwer Health, Inc. This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

Medicine (2019) 98:28(e16407)

Received: 2 January 2019 / Received in final form: 10 May 2019 / Accepted: 13 June 2019

<http://dx.doi.org/10.1097/MD.00000000000016407>

2. Case presentation

2.1. Patient

A 35-year-old female patient with previously well-controlled type 1 diabetes mellitus for 18 years presented with a 6-month history of recurrent nausea and vomiting, generalized weakness, hyponatremia, and recurrent hypoglycemia.

The patient’s type 1 diabetes mellitus was complicated only by diabetic nephropathy. On a basal-bolus insulin regime (16 units of insulin glargine before bed) and insulin aspart (10 units in the morning, 10 units midday, and 10 units in the evening). Glycosylated hemoglobin (HbA1c) was 6.5%. However, during

the preceding 6 months, the woman developed recurrent nausea, vomiting, and multiple episodes of unexplained hypoglycemia – all requiring intervention by hospital staff. As a result, the patient's insulin dose was reduced. She was then sent to a local hospital, where she was considered to have “type 1 diabetes mellitus, gastroparesis and hyponatremia,” and was treated with antacid and motility agents. However, the symptoms were not relieved. Four months later, she was diagnosed with hypothyroidism, with free triiodothyronine and free thyroxine lower than normal and TSH not known in detail; and 25 µg/d of levothyroxine was prescribed. However, the levothyroxine had to be discontinued 1 week later because of frequent vomiting by the patient. Over the next 2 months, she was readmitted with recurrent hypoglycemic attacks despite reducing her insulin dosage to 6 units of insulin glargine before bed and insulin aspart – 6 units in the morning, 4 units at midday, and 4 units in the evening. The woman became anorectic, tired, complained of feeling “exhausted, miserable, and low,” and lost weight. Additionally, she developed amenorrhea, and was therefore referred to our hospital. The patient had a daughter 9 years of age and she had no history of postpartum hemorrhage.

Initial investigations by routine urinalysis revealed that urinary ketobodies were positive, and her blood glucose level was 15.97 mmol/L, blood potassium was 2.36 mmol/L, and blood sodium was 115 mmol/L. The patient was treated with intravenous rehydration and low-dose insulin infusion, and the urine ketobodies disappeared; however, the symptoms of nausea and vomiting were not ameliorated.

2.2. Physical examination

The core body temperature was 36.3°C, pulse rate was 90 bpm, respiratory rate was 19/min, blood pressure was 115/70 mm Hg, and body mass index was 19.6 kg/m².

eyebrow and armpit hair were sparse, and the patient showed facial edema. The remainder of the examination was normal.

2.3. Laboratory testing

Laboratory investigations revealed moderate anemia, with a hemoglobin of 99 g/L, a HbA1c of 6.4%, and a fasting plasma glucose (FPG) of 14.1 mmol/L. Biochemical testing also revealed reduced serum levels of sodium and potassium, and normal liver enzymes, with a mild elevation in serum creatinine. Serum calcium, phosphorus were all within normal limits. Twenty-four-hour urinary calcium was low, while 24-hour urinary microalbumin excretion was elevated. We observed very low 24-hour urinary cortisol and low-normal adrenocorticotropic hormone and low-normal morning serum cortisol, which was consistent with secondary adrenal insufficiency (Table 1); magnetic resonance imaging (MRI) of the pituitary was normal (Fig. 1). Thyroid function tests were positive for anti-thyroglobulin and anti-thyroperoxidase antibodies; with normal thyroid-stimulating hormone, low free triiodothyronine, and low free thyroxine, which demonstrated secondary hypothyroidism. B-Ultrasonography of the thyroid showed multiple low-level echogenic areas in fragments, and chronic thyroiditis was also suspected. Gonadal hormone determinations were suggestive of hypogonadotropic hypogonadism, and hypopituitarism was confirmed upon testing of pituitary hormone concentrations. Antinuclear antibodies, islet-specific autoantibodies against glutamic acid decarboxylase, islet cell antibodies, and insulin autoantibody were all negative

Table 1

Laboratory values during inpatient evaluation.

	Value	Unit	Normal range
Cortisol (8:AM)	7.2	µg/dL	5–25
ACTH (8:AM)	8.3	pg/mL	0–46
Free T ₃	2.09	pmol/L	3.5–6.5
Free T ₄	10.44	pmol/L	11.5–23.5
TSH	1.735	µIU/mL	0.3–5.0
Anti-TPO	185.4	IU/mL	0–12
Anti-Tg	93	IU/mL	0–40
FSH	3.4	IU/L	2.5–10.2
LH	2.68	IU/L	1.9–12.5
E2	<11.8	pg/mL	19–144
T	<10	ng/dL	14–76
PRL	11.97	ng/mL	2.8–29.2
P	<0.21	ng/mL	0.15–1.4
25 (OH)VD ₃	21.31	nmol/L	47.7–144
1,25 (OH) ₂ VD ₃	36.37	pmol/L	39–193
Sodium	130	mmol/L	135–155
Potassium	2.36	mmol/L	3.5–5.5
Calcium	2.30	mmol/L	2.15–2.55
Phosphorus	1.2	mmol/L	0.8–1.6
Urea nitrogen	7.8	mmol/L	3.2–7.1
Creatinine	132	µmol/L	44–115
Hemoglobin	99	g/L	110–150
HbA1c	6.4%		4.4–6.0%
ICA	–		
GADA	–		
IAA	–		
ANA	–		
ESR	18	mm/h	
24-h urinary calcium	64	mg/24 h	150–300
24-h urinary MALB	142	mg/24 h	<30
24-h urinary cortisol	<30	µg/24 h	30–110

1,25 (OH)₂VD₃=1,25 dihydroxyvitamin D₃, 25 (OH)VD₃=25-hydroxyvitamin D₃, ACTH=adrenocorticotropic hormone, ANA=antinuclear antibody, E2=estradiol, ESR=erythrocyte sedimentation rate, FSH=follicle-stimulating hormone, FT₃=free triiodothyronine, FT₄=free thyroxine, GADA=glutamic acid decarboxylase antibody, HbA1c=glycosylated hemoglobin, IAA=insulin autoantibody, ICA=islet cell antibody, LH=luteinizing hormone, MALB=microalbumin, P=progesterone, PRL=prolactin, T=testosterone, Tg=thyroglobulin, TPO=thyroid peroxidase, TSH=thyroid-stimulating hormone.

(Table 1). Both serum 25-hydroxyvitamin D and 1,25 dihydroxyvitamin D levels were also low, suggesting an insufficiency of vitamin D. Gastroscopic examination revealed chronic gastritis and gastric retention. Contrast-enhanced computed tomography scans of the abdomen also demonstrated gastric retention. Kidney biopsy was done to the patient after written informed consent had been obtained. The Ethical Committee of Tianjin Medical University General Hospital approved the study. Renal pathological examination showed slight or moderate glomerular mesangial cell and matrix hyperplasia diffusion, and local K-W nodule formation. The capillary basement membrane also manifested vacuole-like changes that could alter diffusion. We additionally noted granular degeneration of the renal tubular epithelium and scattered foci of tubular atrophy. Part of the brush border showed desquamation, and epithelia became thin and flattened, with luminal extensions. Red blood cells, protein, and cellular debris casts were found in parts of the lumen. We observed scattered foci of lymphocyte and monocyte infiltration in the interstitium, scattered foci of interstitial fibrosis, and changes in vessel wall thickness of the small renal arteries. Deposits of the immunoglobulin G, immunoglobulin M,

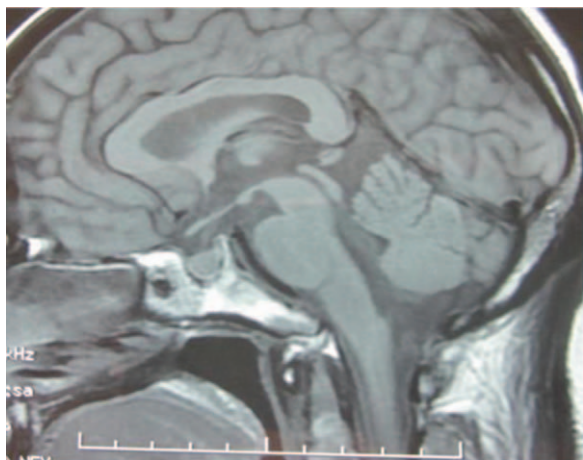


Figure 1. MRI of the pituitary was normal. MRI = magnetic resonance imaging.

complement 3, complement 1q, and fibrin-related antigen were observed in the glomerulus. Diabetic glomerular sclerosis and subacute tubulointerstitial nephropathy constituted the pathologic diagnosis (Fig. 2). There were no obvious abnormalities found upon ophthalmologic examination, with no visual field defects.

2.4. Interventions

The patient was treated with 100 mg/d of hydrocortisone intravenously for 2 weeks, which produced an improvement in her symptoms, and serum sodium returned to normal (138 mmol/L). Two weeks later, she continued on 15 mg/d of prednisone, and then 25 µg/d of levothyroxine was administered. Three weeks later, the patient's insulin requirement increased, and 20U of premixed insulin was injected subcutaneously twice a day, as the frequency of hypoglycemia decreased. Providing continuous follow-up of renal disease is important, as these conditions can affect the blood glucose and sodium concentrations. Four weeks later, her serum creatinine was normal at 106 µmol/L, FPG was

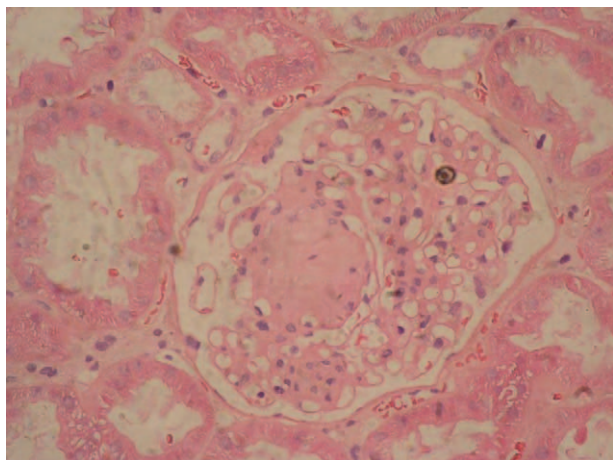


Figure 2. Light microscopic changes in kidney: glomerular mesangial cells and matrix hyperplasia diffusion (slightly or moderately), and local K-W nodule formation. Scattered foci of inflammatory cell infiltration in the interstitium. Wall thickness of renal small arterial vessels (H&E, ×400).

8 mmol/L, and postprandial blood glucose was 7 to 11 mmol/L. At 2 months of follow-up, the patient was found to be doing well, with no severe episodes of hypoglycemia.

3. Discussion

We herein describe the case of a type 1 diabetic female patient who developed recurrent severe hypoglycemic episodes, electrolyte abnormalities, and gastrointestinal symptoms. She was diagnosed with hypopituitarism based on her endocrinologic findings. The presence of low-normal adrenocorticotropic hormone and blood cortisol; a low level of urinary cortisol excretion; low-level estradiol, testosterone, and progesterone; low-normal follicle-stimulating hormone and luteinizing hormone, and secondary hypothyroidism indicated that hypopituitarism was the most likely diagnosis. Twenty-four-hour urinary cortisol excretion is often used to measure hypothalamic-pituitary-adrenal axis activity. It has the advantage of being unaffected by the circadian rhythm of cortisol and by varying plasma protein-binding capacities. Hypopituitarism often develops insidiously, and undiagnosed hypopituitarism can influence the glycemic profile of patients with type 1 diabetes. Replacement therapy with glucocorticoid restored the patient's normal total insulin requirement.

There are many causes of hypoglycemia in diabetic patients, including improper insulin treatment, reduced dietary intake, increased physical exercise, concurrent medications, or deteriorating renal function. Hypopituitarism could lead to recurrent hypoglycemia in diabetic patients and to a reduction in their insulin requirements as a result of adrenocorticotropic hormone deficiency (the Houssay phenomenon).^[3,4] Obscure recurrent hypoglycemia requires endocrinologic tests to clarify possible underlying hypocortisolism.^[5]

The differential diagnosis of hypopituitarism includes head trauma, pituitary adenoma, tumors, pituitary infarctions, granulomas, Langerhans' cell histiocytosis, and lymphocytic hypophysitis. Panhypopituitarism following radiotherapy for nasopharyngeal carcinoma was also reported.^[5] Our patient had no history of head injury, radiotherapy, or surgical intervention, and MRI showed no evidence of tumors. This patient did not experience acute headaches followed by a sudden reduction in insulin requirements, which would reflect pituitary necrosis^[3]; thus, pituitary necrosis is unlikely to be the etiologic factor in our patient. We also speculated that Sheehan syndrome due to postpartum pituitary infarction following adenohypophyseal vasospasm during postpartum hemorrhaging was unlikely because our patient had no history of postpartum hemorrhage. After excluding the possibility of hypopituitarism secondary to a tumor, granulomatous disease, or infection, we hypothesized that a diagnosis of lymphocytic hypophysitis was the most probable cause of the patient's pituitary disorder. However, MRI showed no evidence of enlargement of the pituitary gland or stalk, which are findings specific to lymphocytic hypophysitis. Hence, our patient's findings corresponded to a suspected case of lymphocytic hypophysitis according to the relevant diagnostic criteria.^[1]

Lymphocytic hypophysitis has been recognized to be a cause of hypopituitarism with the disorder first documented by Goudie and Pinkerton in 1962,^[6] and it is reported frequently in women during the antepartum or postpartum period, with the infiltration of lymphocytes into the pituitary gland a key histologic feature. Insufficient secretion of adrenocorticotropic hormone is usually the earliest and most frequent feature in patients with

lymphocytic hypophysitis, presenting in approximately 65% of cases. Pituitary MRI usually shows a pituitary mass, pituitary enlargement with homogeneous contrast enhancement, and a thickened pituitary stalk.^[7] In our patient, the absence of pituitary enlargement upon MRI made the diagnosis of lymphocytic hypophysitis more difficult. However, there are many variations of MRI features with respect to lymphocytic hypophysitis. For example, a cystic appearance of the pituitary by MRI has been reported.^[8,9] Lymphocytic hypophysitis with a normal-sized pituitary by MRI was also documented in several case reports. Akahori reported a patient with lymphocytic hypophysitis who experienced regression of the pituitary mass 3 years after the onset of central diabetes insipidus. Therefore, a diagnosis of lymphocytic hypophysitis was suggested based on the clinical course.^[10] In the current case, it is possible that we detected the lymphocytic hypophysitis at an advanced stage.

While the pathogenesis of lymphocytic hypophysitis is unclear, an autoimmune etiology has been suggested. It is well recognized that type 1 diabetic patients have an increased risk of other autoimmune diseases, including autoimmune thyroid disease, Addison's disease, or celiac disease. In our study, antibodies to thyroglobulin and thyroid peroxidase were present, and B-ultrasonography of the thyroid showed chronic thyroiditis. Autoimmune thyroiditis was demonstrated in the present case although the hypothyroidism was secondary to hypopituitarism. The coexistence of type 1 diabetes, autoimmune thyroiditis, and lymphocytic hypophysitis in the patient were in accordance with the diagnosis of autoimmune polyendocrine syndrome-2 (APS-2). APS – also called polyglandular autoimmune syndromes – constitutes a group of rare diseases characterized by autoimmune activity against more than 1 endocrine organ, although non-endocrine organs can also be affected.^[11]

In addition, gastric retention was demonstrated in the present case, which we believe is due to a delay in gastric emptying, and we, therefore, considered diabetic gastroparesis. Gastroparesis is a complication of long-standing type 1 and type 2 diabetes mellitus. Clinical symptoms include early satiety, prolonged postprandial fullness, bloating, nausea and vomiting, and abdominal pain. Current treatment approaches include improving glucose control with insulin and prescribing anti-nauseant drugs, prokinetic agents, and gastric electric stimulation.^[12] For patients with type 1 diabetes, the presence of gastrointestinal symptoms should arouse suspicion of glucocorticoid insufficiency apart from gastroparesis.

Our patient's 24 hours urinary microalbumin excretion was elevated and serum creatinine was mildly elevated, which indicated diabetic nephropathy and renal insufficiency. However, the 24 hours urinary microalbumin excretion did not keep pace with the level of blood creatinine, and thus, we performed a kidney biopsy. Diabetic glomerular sclerosis and subacute tubulointerstitial nephropathy were then found by pathological diagnosis by kidney biopsy. The Immunocomplexes deposited in the glomeruli suggested that immunity lesions were involved in the development of diabetic kidney disease, and we observed an increased incidence of tubulointerstitial nephritis (TIN).^[13] TIN is characterized by histologic interstitial abnormalities that reflect infiltration by various inflammatory cells, including lymphocytes, plasma cells, and macrophage, and it is often accompanied by tubulitis. The common clinical presentations are rash, fever, eosinophilia, and elevated immunoglobulin E levels; but patients often present with nonspecific symptoms that can lead to delayed

diagnosis and treatment of the disease, resulting in renal dysfunction. The causes of TIN include drug reactions, infections, and autoimmune diseases such as Sjögren syndrome or IgG4-related disease. In our case, an autoimmune lesion may have been the pathogenic factor, but, fortunately, renal function improved. Immunologic evidence of renal damage thus supported the diagnosis of APS-2 in our patient. Moderate anemia in the patient is another pathological condition associated with APS-2. The low level of 1,25 dihydroxyvitamin D and low levels of urinary calcium excretion suggested 1-alpha hydroxylase deficiency caused by tubulointerstitial nephropathy.

In summary, we herein described a case of type 1 diabetes complicated by hypopituitarism that was possibly due to lymphocytic hypophysitis. The development of recurrent hypoglycemia, electrolyte abnormalities, and gastrointestinal symptoms; however, should arouse suspicion of glucocorticoid insufficiency. Our case report highlights the importance of evaluating hypopituitarism as a cause of recurrent hypoglycemia, hyponatremia, and gastrointestinal symptoms in patients with type 1 diabetes mellitus.

Author contributions

Investigation: Fangqiu Zheng, Hongyan Wei.

Methodology: Fangqiu Zheng, Mingcai Qiu.

Supervision: Mingcai Qiu.

Writing – original draft: Fangqiu Zheng.

Writing – review and editing: Fangqiu Zheng.

References

- [1] Matoba K1, Mitsuishi S, Hayashida S, et al. Hypopituitarism possibly due to lymphocytic hypophysitis in a patient with type 1 diabetes. *Intern Med* 2014;53:1961–4.
- [2] Hardy KJ, Burge MR, Boyle PJ, et al. A treatable cause of recurrent severe hypoglycemia. *Diabetes Care* 1994;17:722–4.
- [3] Tahrani AA, West TE, Macleod AF. An unusual cause of severe hypoglycaemia in type 1 diabetes mellitus. Antepartum pituitary failure: a case report and literature review. *Exp Clin Endocrinol Diabetes* 2007;115:136–8.
- [4] Pramanik S, Bhattacharjee R, Mukhopadhyay P, et al. Lesson of the month 2: Houssay phenomenon - hypopituitarism leading to remission of diabetes. *Clin Med (Lond)* 2016;16:294–6.
- [5] Schwarz F, Roden M, Fritsche A, et al. Rare cause of recurrent hypoglycaemia in type 1 diabetes mellitus – case 6/2013. *Dtsch Med Wochenschr* 2013;138:1470.
- [6] Goudie RB, Pinkerton PH. Anterior hypophysitis and Hashimoto's disease in a young woman. *J Pathol Bacteriol* 1962;83:584–5.
- [7] Lee P, Chrysostomou A, Tress B, et al. Lymphocytic hypophysitis: a rare cause of hypoglycaemia in a man with type 2 diabetes mellitus. *Intern Med J* 2005;35:254–7.
- [8] Tamiya A, Saeki N, Kubota M, et al. Unusual MRI findings in lymphocytic hypophysitis with central diabetes insipidus. *Neuroradiology* 1999;41:899–900.
- [9] Farah JO, Rossi M, Foy PM, et al. Cystic lymphocytic hypophysitis, visual field defects and hypopituitarism. *Int J Clin Pract* 1999;53:643–4.
- [10] Akahori H. Reversible impairment of the processing of proopiomelanocortin into ACTH in pituitary enlargement suspected of lymphocytic hypophysitis. *Endocr J* 2012;59:1121–9.
- [11] Cutolo M. Autoimmune polyendocrine syndromes. *Autoimmun Rev* 2014;13:85–9.
- [12] Koch KL, Calles-Escandón J. Diabetic gastroparesis. *Gastroenterol Clin North Am* 2015;44:39–57.
- [13] Oyama S, Hosohata K, Inada A, et al. Drug-induced tubulointerstitial nephritis in a retrospective study using spontaneous reporting system database. *Ther Clin Risk Manag* 2018;14:1599–604.