

Hypopituitarism Possibly due to Lymphocytic Hypophysitis in a Patient with Type 1 Diabetes

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Abstract

Hypopituitarism often develops insidiously, and undiagnosed hypopituitarism can influence the glycemic profile of patients with type 1 diabetes. We herein report the case of a 49-year-old man with type 1 diabetes and Hashimoto's thyroiditis who experienced an unexplained improvement in his glycemic level and recurrent severe hypoglycemia, despite a reduction in the dose of insulin. Based on the patient's endocrinological findings, he was diagnosed with hypopituitarism possibly due to lymphocytic hypophysitis, as supported by positive results for human leukocyte antigen A24 and Cw3. Following the administration of hydrocortisone replacement therapy, his insulin requirement increased to a premonitory level, and the severe hypoglycemia resolved.

Key words: type 1 diabetes, hypopituitarism, lymphocytic hypophysitis, Hashimoto's thyroiditis, hypoglycemia

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Introduction

Hypopituitarism is an uncommon condition that may present as recurrent hypoglycemia and/or an unexplained improvement in the glycemic profile among patients with type 1 diabetes (1). Adreno-corticotrophic hormone (ACTH) insufficiency increases insulin sensitivity, resulting in an increased peripheral glucose uptake, impaired gluconeogenesis and decreased hepatic glucose output. We herein report a case of type 1 diabetes complicated with hypopituitarism that may have been caused by lymphocytic hypophysitis.

Case Report

A 49-year-old man was admitted to our hospital complaining of severe instability of his blood glucose level. He had developed type 1 diabetes at 39 years of age and thereafter required 26 units of insulin daily. His insulin requirement gradually decreased over the seven months preceding admission. However, he also reported recurrent severe hypoglycemic events, including a disturbance of consciousness, seizures and the need for intravenous glucose, despite taking

as little as 10 units of insulin daily. During this period, his glycated hemoglobin level varied from 14.6% to 8.3% (normal range, 4.6-6.2) without any changes in his diet or exercise habits. There was no family history of autoimmune disease. The patient's weight was 48 kg and his height was 161 cm (body mass index, 18.5 kg/m²). The results of a visual field analysis were normal. The urinary C-peptide level was less than 1.8 µg/day, indicating an insulin secretion deficiency. Proliferative diabetic retinopathy was observed in the ocular fundus. The level of creatinine clearance was decreased to 20.7 mL/min, and a urinalysis showed proteinuria. Meanwhile, neurological tests revealed sensory and motor nerve disorders. The patient had a history of Hashimoto's thyroiditis and congestive heart failure. Levothyroxine was used at a dose of 100 µg/day, and the laboratory data on admission showed a mild increase in serum thyroid-stimulating hormone (TSH) with a decrease in serum free T₃ (Table 1).

Glucocorticoid insufficiency was suspected based on the patient's hyponatremia and eosinophilia. Importantly, as shown in Fig. 1, the decrease in the HbA1c level correlated with the magnitude of hyponatremia and eosinophilia. The serum cortisol level responded well to the intravenous ad-

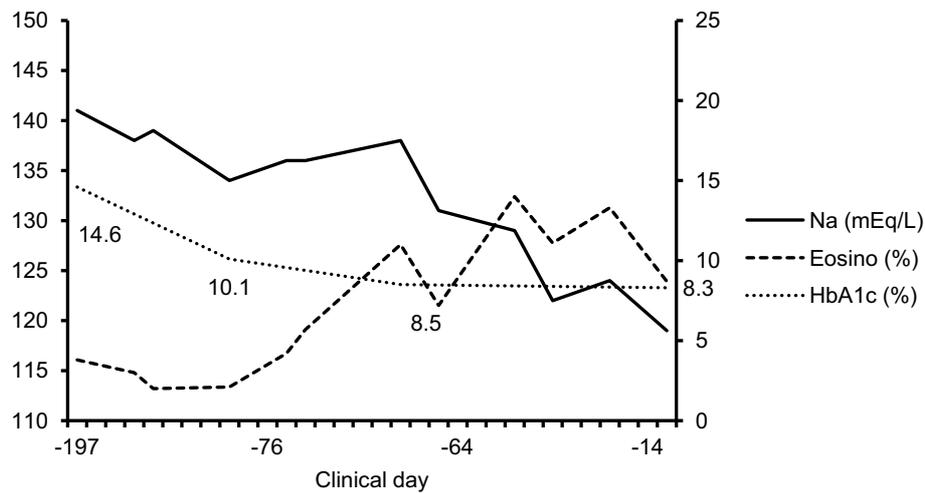


Figure 1. Clinical course before admission

Table 1. Laboratory Data on Admission

Urinalysis	Blood chemistry				
Protein (1+)	AST	24 IU/L	TSH	5.78 μ IU/mL	
Glucose (-)	ALT	34 IU/L	Free T ₄	1.40 ng/dL	
RBC	1-4/HPF	T-Bil	0.34 mg/dL	Free T ₃	1.1 pg/mL
WBC	100/HPF	CK	66 IU/L	HbA1c	8.3%
Peripheral blood	BUN	27.1 mg/dL	CRP	1.75 mg/dL	
WBC	7,100/ μ L	Cr	1.39 mg/dL	ACTH	17.1 pg/mL
Neutro	61.9%	UA	5.6 mg/dL	Cortisol	10.3 μ g/dL
Lymph	18.9%	Na	119 mEq/L		
Mono	9.5%	K	4.3 mEq/L		
Eosino	8.7%	Cl	82 mEq/L		
Baso	1.0%	Ca	8.6 mg/dL		
RBC	$382 \times 10^4/\mu$ L	P	2.6 mg/dL		
Hb	11.0 g/dL	TG	144 mg/dL		
Ht	31.4%	HDL-C	37 mg/dL		
Plt	$41.2 \times 10^4/\mu$ L	LDL-C	148 mg/dL		

ministration of 250 μ g of ACTH (Table 2). In addition, anti-adrenal antibodies were negative. Therefore, considering the possibility of a pituitary disorder, we investigated the patient's anterior pituitary function (Table 3). Provocative tests were performed using 100 μ g of growth hormone-releasing hormone (GRH), 100 μ g of gonadotropin-releasing hormone (GnRH), 500 μ g of thyrotropin-releasing hormone (TRH) and 100 μ g of corticotropin-releasing hormone (CRH). The peak ACTH level induced by the CRH tests was 45.6 pg/mL, indicating a partial deficiency of ACTH. The low luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels observed on the GnRH test suggested partial gonadotropin insufficiency. A TRH test showed an exaggerated response of TSH, compatible with a diagnosis of primary hypothyroidism. The patient's growth hormone (GH) and prolactin (PRL) responses were normal. Importantly, he displayed symptoms of adrenal insufficiency despite having normal basal ACTH and cortisol concentrations. We speculated that the relative lack of ACTH secretion under inflammatory conditions (diabetic gangrene and a chronic urinary tract infection) led to the hypoglycemia and electrolyte imbalance. While multiple factors, including renal dysfunction and heart failure, may have caused the decrease in the blood glucose level and hyponatremia, echocardiography revealed

a preserved left ventricular systolic function with no pericardial effusion at that time. Moreover, the patient's renal function, as assessed according to the estimated glomerular filtration rate, exhibited no correlation with the HbA1c level or serum sodium concentration throughout his clinical course. Therefore, we postulated that the effects of cardiovascular and renal disease on these parameters were limited.

In addition to anterior pituitary insufficiency, diabetes insipidus was suspected due to the patient's increased urine volume. His urinary output was 3.0-4.0 L/day, with a specific gravity of 1.004-1.007. The plasma osmolality was 292 mOsm/kg (data obtained after the start of hydrocortisone replacement therapy), whereas the urinary osmolality was 146 mOsm/kg. The plasma antidiuretic hormone (ADH) level was less than 1.2 pg/mL (normal range, <3.6). An increase in urine osmolality from 261 mOsm/kg to 340 mOsm/kg following the subcutaneous administration of 5 units of vasopressin indicated insufficient secretion of ADH (Table 4). Magnetic resonance imaging (MRI) demonstrated the lack of a normal hyperintense signal in the posterior pituitary lobe (Fig. 2). Furthermore, a number of clinical conditions that impair the ability to concentrate urine, including hypercalcemia, hypokalemia, sickle cell disease or trait, autosomal dominant polycystic kidney disease and medullary cystic kidney disease, were not observed. In addition, although the patient had mild psychiatric illnesses, polydipsia was absent, and he had no history of receiving lithium. Hypertonic saline and water deprivation tests were not performed due to the patient's history of severe congestive heart failure and a depressive state; however, the data observed in this case indicated the possibility of central diabetes insipidus. After excluding the possibility of hypopituitarism secondary to a tumor, granulomatous disease or infection, a diagnosis of lymphocytic hypophysitis was thought to be 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 specific findings of lymphocytic hypophysitis. Hence, our patient's findings corresponded to a suspected case of lymphocytic hypophysitis according to the

Table 2. ACTH Stimulation Test. Responses of Serum Cortisol to Intravenous Injection of Tetracosactide Acetate (250 µg)

Time (min)	0	30	60	normal range
Cortisol (µg/dL)	18.8	33.9	38.3	(4.0-18.3)

Table 4. Vasopressin Test. Responses of Urine Osmolality to Subcutaneous Injection of Vasopressin (5 Units)

Time (min)	0	30	60	90	120
Urine osmolality (mOsm/kg)	261	284	326	340	338

relevant diagnostic criteria (guidelines for the diagnosis and treatment of autoimmune hypophysitis issued by the research committee of the Ministry of Health, Labour and Welfare of Japan). Human leukocyte antigen (HLA) typing was positive for A24 and Cw3, both of which are associated with lymphocytic hypophysitis, and DR9, which is associated with type 1 diabetes.

Replacement therapy with hydrocortisone (15 mg/day) and 1-deamino-8-D-arginine vasopressin (dDAVP, 5 µg/day) was subsequently initiated. Due to the patient's prolonged low blood glucose level and polyuria, the doses of hydrocortisone and dDAVP were titrated to 20 mg/day and 20 µg/day, respectively. One month later, his insulin requirement increased, while the frequency of hypoglycemia decreased with treatment of 15 mg of hydrocortisone. We believe that appropriate treatment of the chronic urinary tract infection and diabetic gangrene allowed for a decrease in the dose of hydrocortisone. Therefore, appropriate intervention to improve the patient's management of his diabetes, the administration of antibiotic therapy based on susceptibility data and the provision of optimal care of neurogenic bladder are needed hereafter in this case. Providing continuous follow-up of cardiovascular and renal disease is also important, as these conditions can affect the blood glucose level and sodium concentration.

At three months of follow-up, the patient was found to be doing well, with no severe hypoglycemia or changes in MRI findings.

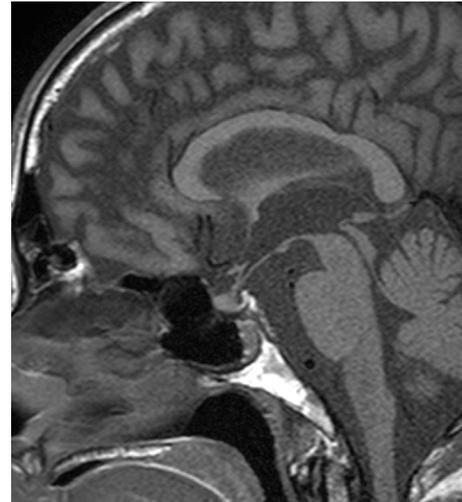
Discussion

We herein describe the case of a type 1 diabetic patient who developed recurrent hypoglycemic episodes in association with an unexplained improvement in his glycemic level. His condition appeared to be unrelated to his insulin treatment, meal planning, exercise pattern, alcohol consumption or concurrent medications. Based on his endocrinological findings, he was diagnosed with hypopituitarism. The administration of glucocorticoid replacement therapy restored the patient's normal total insulin requirement and eliminated his severe hypoglycemic events.

The differential diagnosis of hypopituitarism includes head trauma, pituitary adenoma, tumors, infections, granulomas and other conditions, including Langerhans' cell histiocytosis and lymphocytic hypophysitis. Our patient had no

Table 3. GRH, GnRH, TRH, CRH Stimulation Test. Responses of Pituitary and Adrenal Hormones to Intravenous Injection of GRH (100 µg), GnRH (100 µg), TRH (500 µg) and CRH (100 µg)

Time (min)	0	30	60	90	120	normal range
GH (ng/mL)	0.80	10.8	6.72	3.45	2.31	(< 2.47)
LH (mIU/mL)	4.88	13.91	17.25	15.48	16.39	(0.79-5.72)
FSH (mIU/mL)	6.81	7.90	8.54	9.07	9.34	(2.00-8.30)
TSH (µIU/mL)	4.28	25.8	23.4	19.0	16.6	(0.50-5.00)
PRL (ng/mL)	8.90	50.41	42.13	33.63	28.12	(4.29-13.69)
ACTH (pg/mL)	35.6	45.6	42.2	37.1	40.7	(7.2-63.3)
Cortisol (µg/dL)	12.3	12.3	13.2	11.5	11.7	(4.0-18.3)

**Figure 2. Pituitary MRI. T1-weighted sagittal MRI demonstrating the disappearance of a high-intensity signal in the posterior pituitary lobe.**

history of head injury or surgical intervention. Although examinations with gadolinium enhancement were avoided due to the patient's renal dysfunction, MRI showed no evidence of tumors. In addition, the levels of human chorionic gonadotropin β and α -fetoprotein were not elevated, and assays for interferon- γ release and serum β -d-glucan were negative. Furthermore, the cerebrospinal fluid obtained via lumbar puncture failed to reveal any increases in the number of cells, and a cerebrospinal fluid culture was negative. The serum concentrations of proteinase 3 anti-neutrophil cytoplasmic antibodies, myeloperoxidase anti-neutrophil cytoplasmic antibodies, angiotensin-converting enzyme and soluble interleukin-2 receptor were not elevated. Moreover, no inflammatory lesions were detected on gallium scintigraphy. A diagnosis of IgG4-related systemic disease was thought to be unlikely due to the absence of increased IgG and IgG4 levels. Based on these clinical findings, lymphocytic hypophysitis, including disorders of both the anterior pituitary (lymphocytic adenohypophysitis) and the posterior pituitary (lymphocytic infundibuloneurohypophysitis), was considered to be the most appropriate diagnosis in this case.

Although the incidence of lymphocytic hypophysitis remains unclear, this condition has been recognized to be a cause of hypopituitarism. The disorder was first documented by Goudie et al. in 1962 (2) and occurs most often in

women during the antepartum or postpartum period (3). Histologically, it is characterized by the infiltration of lymphocytes and plasma cells in the pituitary gland. As observed in the present case, insufficient secretion of ACTH is usually the earliest and most frequent feature in patients with lymphocytic hypophysitis, presenting in approximately 65% of cases (4). Gonadotropin insufficiency is also induced by lymphocytic hypophysitis, whereas the effects of this disease on GH secretion are infrequent (5). GH deficiency most commonly results from either damage to the pituitary gland during surgical intervention or a tumor or traumatic injury involving the pituitary (6).

One unique aspect of our case is the lack of pituitary enlargement. As noted above, there were no abnormal MRI findings in the anterior pituitary or pituitary stalk. MRI imaging of the pituitary in patients with histologically-confirmed lymphocytic hypophysitis usually shows a uniformly enlarged and homogeneously enhanced gland, often in association with enlargement of the infundibulum (3). Therefore, this case meets the diagnostic criteria for a suspected case of lymphocytic hypophysitis. However, there have been several case reports of lymphocytic hypophysitis with a long period of latency between the onset of hypopituitarism and enlargement of the pituitary gland (7, 8). For example, Akahori et al. reported a patient with lymphocytic hypophysitis who developed pituitary enlargement and thickening of the pituitary stalk two years after the onset of central diabetes insipidus (8). In the current case, it is possible that the lymphocytic hypophysitis was detected at an early stage or constituted the first manifestation of another systemic disease. Follow-up clinical, imaging and hormonal examinations are therefore in order, and the patient agreed to undergo a pituitary biopsy if the pituitary gland exhibited future expansion.

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 and celiac disease. In the present case, while antibodies to glutamic acid decarboxylase (743 U/mL), thyroglobulin (653 IU/mL) and thyroid peroxidase (251 IU/mL) were present, tests for anti-nuclear, anti-adrenal and anti-pituitary antibodies were negative. After reviewing the pertinent literature, we found case reports of type 1 diabetes, Hashimoto's thyroiditis and hypopituitarism occurring in a single individual (9, 10), indicating the presence of common immunological factors in the pathogenesis of these diseases. Many autoimmune disorders, including type 1 diabetes and Hashimoto's thyroiditis, are associated with HLA. In the present case, HLA typing detected DR9, which has been reported to be associated with increased susceptibility to both type 1 diabetes and Hashimoto's thyroiditis in Japanese autoimmune polyglandular

syndrome patients (11). Moreover, we also identified HLA A24 and Cw3, which are frequently detected in individuals with lymphocytic hypophysitis (12, 13). The clinical features, endocrine abnormalities and HLA status in the current patient may also be in accordance with the diagnosis of lymphocytic hypophysitis.

In summary, we herein described a case of type 1 diabetes complicated with hypopituitarism, possibly due to lymphocytic hypophysitis. A reduced insulin requirement leading to hypoglycemia in type 1 diabetic patients can arise from several causes, including changes in diet and exercise, as well as reduced insulin clearance as a result of renal dysfunction. The development of recurrent hypoglycemia with an unexplained impairment in the glycemic level and a reduction in the total insulin requirement, however, should arouse suspicion of glucocorticoid insufficiency. This report highlights the importance of considering hypopituitarism and secondary adrenal insufficiency as causes of such conditions.

The authors state that they have no Conflict of Interest (COI).

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