Type 1 Diabetes Mellitus and Isolated Adrenocorticotropin Deficiency Manifested by Parkinsonism: A Case Report and Literature Review

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Abstract

A 67-year-old woman developed isolated adrenocorticotropin deficiency (IAD), which manifested as lethargy, a 20-kg body weight loss, hypoglycemia, and parkinsonism, and began corticosteroid replacement. Her symptoms resolved rapidly, and her weight returned to normal within six months. However, she then developed slowly progressive type 1 diabetes mellitus (T1D) with co-existing Hashimoto thyroiditis, and commenced insulin therapy. To our knowledge, this is the first reported case of parkinsonism associated with IAD. In addition, because diabetes mellitus, including T1D, could be latent in patients with untreated IAD, careful assessment of glucose metabolism is needed after commencing corticosteroid replacement until weight regain is achieved.

Key words: isolated adrenocorticotropin deficiency, type 1 diabetes mellitus, Hashimoto thyroiditis, polyglandular autoimmune syndrome, parkinsonism, orthopedic surgery

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Introduction

Isolated adrenocorticotropin deficiency (IAD) is a rare endocrine disease characterized by secondary adrenal insufficiency with a low or absent cortisol production and normal secretion of pituitary hormones other than adrenocorticotrophic hormone (ACTH) (1). In addition to hypoglycemia, patients usually present with nonspecific symptoms such as anorexia, weight loss, or lethargy and may be misdiagnosed with neurological or psychiatric disorders (2, 3). Although the cause of most adult IAD is unknown, an autoimmune etiology is usually hypothesized. IAD is often associated with autoimmune thyroid diseases and occasionally with type 1 diabetes mellitus (T1D) (1).

T1D is a metabolic disease characterized by destruction of pancreatic beta cells, usually leading to insulin-deficient

hyperglycemia. Slowly progressive T1D is a subtype of T1D characterized by the presence of autoantibodies against islet antigens, a gradual decrease in insulin secretion, and the absence of diabetic ketoacidosis at diagnosis (clinical onset) (4).

Cases of IAD occurring in patients with insulin-treated T1D have been reported (5-12), but there are few reports on the development of T1D after IAD in the same patient. We herein report a patient who developed slowly progressive T1D following corticosteroid replacement therapy for IAD that was manifested by parkinsonism. In addition, previously reported cases of concomitant IAD and T1D are reviewed.

Case Report

A 67-year-old woman visited a local general hospital because of bilateral knee pain in September 2009. Her height

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Table 1. Laboratory Findings on Admission in May 2010.

Hematology		
Red blood cells	313 × 10 ⁴ /μL	(380–480)
Hemoglobin	9.1 g/dL	(11.3–15.2)
Hematocrit	27.1 %	(34.0–43.0)
White blood cells	3,060 /μL	(3,500–9,100)
Neutrophils	29.1 %	(36–71)
Lymphocytes	57.1 %	(20–50)
Monocytes	6.5 %	(< 12)
Eosinophils	6.2 %	(< 10)
Basophils	1.0 %	(< 3)
Platelets	26.2 × 10 ⁴ /μL	(13.0–36.9)
Chemistry		
Fasting plasma glucose	3.8 mmol/L	(3.9–6.1)
HbA1c (NGSP)	4.8 %	(4.6–6.2)
Total protein	6.2 g/dL	(6.7–8.3)
Albumin	3.4 g/dL	(4.0–5.0)
Aspartate aminotransferase	27 IU/L	(13–33)
Alanine aminotransferase	16 IU/L	(6–27)
Blood urea nitrogen	6.4 mg/dL	(8.0–22.0)
Creatinine	0.38 mg/dL	(0.40–0.70)
Sodium	133 mmol/L	(138–146)
Potassium	3.6 mmol/L	(3.6–4.9)
Chloride	100 mmol/L	(98–109)
C-reactive protein	1.60 mg/dL	(< 0.20)
Serum iron	53 μg/dL	(50–160)
Serum ferritin	824 ng/mL	(5–80)
Unsaturated iron binding capacity	119 μg/dL	(137–325)
Plasma arginine vasopressin	6.2 pg/mL	(0.3–4.2)
Plasma ACTH	9.0 pg/mL	(7.2–63.3)
Thyroid-stimulating hormone	9.36 μU/mL	(0.35–4.94)
Free triiodothyronine	2.61 pg/mL	(1.71–3.71)
Free thyroxine	0.97 ng/dL	(0.70–1.48)
Plasma renin activity	3.0 ng/mL/h	(0.1–2.0)
Serum cortisol	2.0 μg/dL	(4.5–21.1)
Serum DHEA-S	37 ng/dL	(120–1,330)
Serum aldosterone	12.2 ng/dL	(3.6–24.0)

Blood samples were taken in the morning with the patient in the supine position.

ACTH: adrenocorticotropic hormone, DHEA-S: dehydroepiandrosterone sulfate, NGSP: National Glycohemoglobin Standardization Program

and weight were 155 cm and 57 kg, respectively. Her medical history was unremarkable, and one of her brothers had type 2 diabetes mellitus and was on dietary therapy. She was diagnosed with knee osteoarthritis by an orthopedic surgeon and underwent successful right total knee arthroplasty (TKA) in December 2009. Immediately after surgery, she unexpectedly developed appetite loss, lethargy, bradykinesia, rigidity and upper extremity contracture. After a detailed examination at the neurology department of the same hospital, she was diagnosed to have parkinsonism. The patient underwent left TKA in March 2010, but her postoperative rehabilitation was incomplete because of lethargy and bradykinesia. Her knee contracture progressed to abasia. Despite receiving an oral carbidopa/levodopa combination at 300 mg/day, her symptoms persisted. She was transferred to the neurology department of our hospital to continue rehabilitation in May 2010.

On admission, the patient's body weight was 38 kg, and her body temperature, blood pressure, and pulse rate were 36.7°C, 98/62 mmHg and 72 beats per minute, respectively. No skin pigmentation, heart murmurs or chest rales were detected. Her consciousness was clear, but she presented with a mask-like face, microphonia, Myerson's sign, bradykinesia

and rigidity in the neck and upper extremities. She had limb contracture and gait inability due to fixed flexion contracture in both knee joints. Brain magnetic resonance imaging detected no abnormalities in the cerebrum, cerebellum or brainstem, and brain magnetic resonance angiography showed a normal blood flow. Iodine-123-metaiodobenzyl-guanidine myocardial scintigraphy showed a normal uptake [early phase heart-to-mediastinum ratio (HMR), 2.46; delay phase HMR, 2.28]. Laboratory findings revealed anemia, hyponatremia, mild hypoglycemia, high thyroid-stimulating hormone (TSH) and arginine vasopressin (AVP) levels, and low serum cortisol and plasma ACTH levels (Table 1). The patient was considered to have secondary adrenal insufficiency and began oral hydrocortisone at 20 mg/day in addition to the carbidopa/levodopa in June 2010.

A few days later, the patient regained her appetite and vitality, and upper extremity contracture and parkinsonism (bradykinesia, rigidity, a mask-like face, and microphonia) also resolved without the need for carbidopa/levodopa (Fig. 1). Her complete blood cell count, electrolytes, and serum TSH and plasma AVP levels normalized, and her body weight returned to 57 kg until December 2010.

Because her bilateral postoperative knee contracture persisted, the patient underwent left TKA revision surgery in early February 2011. The next morning, she developed hypotension and thus was referred to our department. On physical examination, the patient's consciousness was clear, and her body temperature, weight, blood pressure, and pulse rate were 35.8°C, 57 kg, 72/40 mmHg and 80 beats per minute, respectively. Because acute adrenal insufficiency was considered, 200 mg of hydrocortisone sodium succinate was administered intravenously, and her blood pressure recovered. Laboratory testing performed that afternoon showed casual plasma glucose levels of 8.6 mmol/L, an HbA1c (National Glycohemoglobin Standardization Program, NGSP) (13) of 6.7% and negativity for urinary ketone bodies. The patient tested negative for organ-specific autoantibodies, such as insulinoma-associated antigen-2 antibodies (<0.4 U/mL), insulin antibodies (<125.0 nU/mL), TSH receptor antibodies (<1.0 IU/L), gastric parietal cell antibodies (titer <1:10), intrinsic factor antibodies, anti-nuclear antibodies (titer <1:40) and rheumatoid factor (<5 IU/mL), and she tested positive for thyroglobulin autoantibodies (178.6 IU/mL, reference range: <28.0 IU/mL), thyroid peroxidase antibodies (250.8 IU/mL, reference range: <16.0 IU/mL) and glutamic acid decarboxylase 65 (GAD65) autoantibodies (41,000 U/mL, reference range: <1.5 U/mL) (Cosmic Corporation, Tokyo, Japan). Two weeks later, the presence of diabetes mellitus with relatively preserved endogenous insulin secretion was confirmed (Table 2A, B), and the patient then started injection therapy with 13 units/day biphasic insulin aspart 30 and continued oral hydrocortisone at a dose of 15 mg/day (Fig. 1). Although the patient was in a euthyroid state (Fig. 1), ultrasonography revealed rough and inhomogeneous echogenicity in the slightly enlarged thyroid gland with border irregularity, indicating Hashimoto thy-

Figure 1. Clinical course. The reference ranges for body weight, fasting plasma glucose (FPG), HbA1c (NGSP), thyroid-stimulating hormone (TSH), free triiodothyronine (FT₃), and free thyroxine (FT₄) are shown in parentheses. The reference range for body weight (kg) was calculated as those values between [body height (m)²×18.5] and [body height (m)²×25]. TKA: total knee arthroplasty

roiditis. Human leukocyte antigen (HLA) typing showed the presence of A*02:06/24:02, B*40:02/54:01 and C*01:02/03:03 class I genes and DRB1*04:05/14:05, DQB1*04:01/05:03, DQA1*01:04/03:03 and DPB1*02:01/05:01 class II genes.

Dynamic tests for secretion of pituitary and adrenal hormones performed in March 2011 showed normal release of growth hormone, TSH, prolactin, luteinizing hormone and follicle-stimulating hormone, but ACTH was absent as was the cortisol response to a corticotropin-releasing hormone (CRH) load (Table 2C). Also, ACTH and cortisol responses to growth hormone-releasing peptide (GHRP)-2 were reduced (Table 2D). Adequate cortisol secretion was observed within 4 days of a synthetic ACTH load (Table 2E). These findings indicated a diagnosis of IAD. Magnetic resonance imaging revealed no abnormalities in the pituitary gland (Fig. 2). Tests for anti-CRH antibodies, anti-pituitary cell antibodies and anti-adrenocortical antibodies (titer <1:10) were all negative.

The revision of right TKA was performed in May 2011. The patient became ambulatory and was discharged in July 2011.

In November 2014, the patient's weight and blood pressure were 54 kg and 124/82 mmHg, respectively, upon treatment with oral hydrocortisone at a dose of 15 mg/day and injections of 6 units/day biphasic insulin aspart 30 at the outpatient clinic. Laboratory findings showed casual plasma

glucose levels of 5.6 mmol/L, serum C-peptide of 1.0 ng/mL, an HbA1c (NGSP) of 6.3%, serum GAD65 autoantibodies of 71,000 U/mL, and normal serum TSH and thyroid hormones levels despite persistence of positive thyroid autoantibodies. Her subsequent clinical course has been uneventful without any additional complications.

Discussion

An elderly Japanese woman developed IAD that manifested as appetite loss, lethargy, hyponatremia, and mild hypoglycemia, as well as bradykinesia, rigidity, and a mask-like face shortly after undergoing orthopedic surgery. She was initially diagnosed to have parkinsonism (14). Her symptoms persisted during antiparkinsonism treatment but improved rapidly after treatment of IAD by corticosteroid replacement. Previous studies have reported cases of parkinsonism following extrapontine demyelolysis that were usually associated with the rapid correction of hyponatremia in patients with Addison's disease or adrenal insufficiency secondary to hypopituitarism (15–20). A case of parkinsonism that was associated with Addison's disease in the absence of demyelolysis and disappeared following corticosteroid replacement, without the use of antiparkinsonian drugs, has also been reported (21). The current patient did not exhibit pontine or extrapontine demyelolysis before or after corticosteroid replacement for IAD. Possible explanations for

Table 2. Endocrinological Investigation.**A. Plasma glucose levels throughout a day in mid-February 2011**

	Before breakfast	After 2 h	Before lunch	After 2 h	Before dinner	After 2 h
Plasma glucose (mmol/L)	8.1	13.8	14.2	20.3	12.1	16.4

B. Fasting serum C-peptide levels before and after intravenous administration of glucagon (1 mg) in mid-February 2011

	Before	5 min
Serum C-peptide (ng/mL)	1.1	3.1

C. CRH/GRF/TRH/LHRH stimulation test in March 2011

	Time (min)					
	0	15	30	60	90	120
Plasma ACTH (pg/mL)	20.7	13.4	19.6	24.1	17.9	20.5
Serum cortisol (μg/dL)	3.7	3.7	4.1	4.2	3.5	3.5
Thyroid-stimulating hormone (μU/mL)	2.44	19.74	27.94	21.64	13.17	10.99
Growth hormone (ng/mL)	0.19	8.70	4.63	3.79	2.00	0.96
Prolactin (ng/mL)	6.0	96.4	98.8	63.0	34.9	25.0
Luteinizing hormone (mIU/mL)	8.8	17.8	26.5	30.6	28.5	26.6
Follicle-stimulating hormone (mIU/mL)	25.6	29.0	32.0	34.0	34.7	35.5

The following were administered intravenously: human corticotropin-releasing hormone (CRH), 100 μg; growth hormone-releasing factor (GRF), 100 μg; thyrotropin-releasing hormone (TRH), 500 μg; and gonadotropin-releasing hormone (LHRH), 100 μg. Tests were conducted after cessation of hydrocortisone for half a day.

D. GHRP-2 stimulation test in March 2011

	Time (min)				
	0	15	30	45	60
Plasma ACTH (pg/mL)	20.6	36.2	39.2	21.6	25.0
Plasma arginine vasopressin (pg/mL)	3.6	6.1	3.2	2.0	2.0
Serum cortisol (μg/dL)	3.6	6.1	6.4	5.5	5.2
Growth hormone (ng/mL)	0.28	50.45	50.91	51.00	39.02
Prolactin (ng/mL)	7.8	50.5	58.7	45.9	56.9
Plasma osmolality (mOsm/kg)	289	283	284	285	283

Growth hormone-releasing peptide (GHRP)-2 (100 μg) was administered intravenously. Test was conducted after cessation of hydrocortisone for half a day.

E. Prolonged ACTH stimulation test in March 2011

	Before	4 days
Serum cortisol (μg/dL)	3.7	30.1
Serum DHEA-S (ng/mL)	27	58
Serum aldosterone (ng/dL)	14.1	7.4
Plasma renin activity (ng/mL/h)	2.9	0.5
Plasma ACTH (pg/mL)	20.7	< 1.0

Synthetic ACTH (cosyntropin zinc hydroxide 1.0 mg/day) was intramuscularly administered for 4 days. Hydrocortisone replacement was briefly discontinued the day before and during the period of test.

ACTH: adrenocorticotropic hormone, DHEA-S: dehydroepiandrosterone sulfate

Figure 2. Magnetic resonance imaging of the pituitary gland. Gadolinium-enhanced T1-weighted magnetic resonance imaging of the brain (A: coronal plane, B: sagittal plane) showed no abnormalities in the hypothalamus, hypophyseal stalk or pituitary gland.

Table 3. Summary of Reported Patients who Presented with Concomitant Isolated Adrenocorticotropin Deficiency and Type 1 Diabetes Mellitus.

Case	Sex	HLA-DR	HLA-DQ	Type 1 diabetes mellitus			Isolated adrenocorticotropin deficiency			Complicating disorders	Reference
				Age at onset (years)	*Islet-related autoantibodies	**Subtype	Age at diagnosis (years)	Autoantibodies against pituitary gland	Image findings of pituitary gland		
1	Female	N/A	N/A	10	N/A	Undetermined	29 (soon after cesarean delivery)	N/A	No abnormalities	Antepartum pituitary infarction	5
2	Female	N/A	N/A	41	N/A	Undetermined	63	N/A	No abnormalities	Hashimoto thyroiditis	6
3	Male	3, 4	N/A	20	Negative	Undetermined	45	Negative	No abnormalities	(-)	7
4	Female	4, 13	N/A	33	Negative	Undetermined	40	Positive	No abnormalities	Hashimoto thyroiditis Polychondritis	8
5	Male	N/A	N/A	20	N/A	Undetermined	43	N/A	No abnormalities	(-)	9
6	Female	N/A	N/A	37	Negative	Undetermined	51	Negative	Empty sella	(-)	10
7	Female	8, 9	N/A	37	N/A	Acute-onset	37 (9 months after diabetes onset)	Negative	N/A	(-)	11
8	Female	4, 15	3, 4	65	Negative	Fulminant	65 (2 months after diabetes onset)	Negative	No abnormalities	Hashimoto thyroiditis	12
9	Female	4, 14	4, 5	67 (8 months after IAD treatment)	Positive	Slowly progressive	67	Negative	No abnormalities	Hashimoto thyroiditis	Present case

*Positive islet-related autoantibodies were defined as a positive test for one or more antibodies against glutamic acid decarboxylase, islet cells, and insulinoma-associated antigen-2 at any time during the course of diabetes, and/or a positive insulin antibody test at onset.

**Type 1 diabetes mellitus was divided into fulminant, acute-onset, or slowly progressive based on published criteria (4, 27, 28). The subtypes of cases 1–6 were undetermined because of a lack of information regarding the duration of hyperglycemic symptoms before onset and the presence or absence of diabetic ketoacidosis, HbA1c values, and C-peptide levels at the onset of type 1 diabetes mellitus.

HLA: human leukocyte antigen, N/A: not available, IAD: isolated adrenocorticotropin deficiency

parkinsonism secondary to IAD include harmful effects of either glucocorticoid deficiency or raised CRH on dopaminergic neurons (22, 23). Although the precise mechanisms were unknown, this is the first reported case of parkinsonism associated with IAD.

During corticosteroid replacement for IAD, the patient developed diabetes mellitus without ketoacidosis in the presence of high serum GAD65 autoantibody titers. GAD65, a neuronal enzyme involved in the synthesis of the neurotransmitter gamma-aminobutyric acid, is localized mainly in the central nervous system and in pancreatic beta cells (24, 25). Although high serum GAD65 autoantibody titers are observed frequently in T1D patients, they are also found in patients with rare autoimmune neurological diseases such as stiff-person syndrome, which is characterized by progressive rigidity and muscle spasms (26). The current patient exhibited reversible parkinsonism but did not present with a characteristic clinical course or image findings of stiff-person syndrome or other GAD-related neurological disorders; therefore, her high GAD65 autoantibody titer likely reflected beta-cell destruction caused by slowly progressive T1D.

Table 3 shows a summary of previously reported patients who exhibited concurrent IAD and T1D. The cases included patients of all ages, with a female predominance. The patients were diagnosed with IAD characterized by frequent hypoglycemic attacks and a sudden decrease in insulin re-

quirement during insulin therapy for T1D. The current patient is the first reported case of T1D to occur after IAD.

As with two specific cases previously reported in the literature (cases 7 and 8 in Table 3), our patient developed both IAD and T1D at approximately the same time (the time lag was less than one year). Slowly progressive T1D, in contrast to acute-onset or fulminant T1D, is characterized by a slow progression of beta-cell failure, and the time to the clinical onset of diabetes mellitus may be long (4, 27, 28). Therefore, although the time point at which autoimmune destruction of pancreatic beta cells began is unknown in this case, the slowly progressive subtype of her T1D might have contributed to the interval between the development of IAD and subsequent T1D.

The patient developed slowly progressive T1D shortly after regaining 20 kg of body weight during the six month corticosteroid replacement for IAD. Glucocorticoid deficiency creates a tendency toward hypoglycemia, and weight loss might decrease the amount of insulin required to maintain an appropriate glucose metabolism (29). Therefore, the presence of IAD likely masked hyperglycemia by causing both glucocorticoid deficiency and weight loss prior to the clinical onset of T1D in our case. The possibility of latent diabetes mellitus, including T1D, should be considered in patients with untreated IAD, and a regular evaluation of glucose metabolism is needed after the commencement of corti-

costeroid replacement therapy until weight regain is achieved.

Polyglandular autoimmune syndrome (PGAS) is a group of endocrine or nonendocrine organ-specific autoimmune disorders (30). Our patient had autoantibodies against pancreatic islets and the thyroid gland and was considered to exhibit T1D and Hashimoto thyroiditis affected by PGAS type 3. The presence of the HLA-DRB1*04:05-DQA1*03:03-DQB1*04:01 haplotype supported the diagnoses of both T1D and PGAS type 3 (31). In addition, although the patient was negative for anti-pituitary cell antibodies, the absence of both structural pituitary defects and previous head trauma suggests an autoimmune etiology of her idiopathic IAD.

The patient had basal plasma ACTH levels of approximately 20 pg/mL and showed no ACTH response to an exogenous CRH load. However, a slight release of ACTH and cortisol was observed with secretion of AVP following a GHRP-2 load (Table 2). GHRP-2 is a potent growth hormone secretagogue and has been shown to stimulate the secretion of ACTH and cortisol in humans (32). In addition, the stimulating effects of GHRP-2 on ACTH release have been suggested to be mediated via CRH and/or AVP, or may occur independently of both peptides (33, 34). These findings suggest that, in the present case, administration of GHRP-2 may have stimulated corticotroph cells via pathways other than the CRH receptor under conditions of full endogenous CRH stimulation.

In summary, the present case of IAD provides a novel and unusual cause of secondary parkinsonism. In addition, our patient developed slowly progressive T1D in association with PGAS after the treatment of IAD with corticosteroid replacement. This suggests that diabetes mellitus, including T1D, might be latent in patients with untreated IAD. A careful assessment of the glucose metabolism is therefore needed until weight regain is achieved in patients with IAD starting corticosteroid replacement therapy.

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

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