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

Nobumasa Ohara1,2, Naoyuki Kojima3, Takashi Sato4, Tomoo Ikarashi1, Hirohito Sone2, Yutaka Oki5, Kyuzi Kamoi6, Masao Hara1 and Hideo Sasaki1

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

(Intern Med 54: 2629-2635, 2015)
(DOI: 10.2169/internalmedicine.54.5022)

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 adrenocorticotropic 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...
Table 1. Laboratory Findings on Admission in May 2010.

| Test                          | Value                     |
|-------------------------------|---------------------------|
| Red blood cells               | 313 × 10^6/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 μIU/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, rigidity 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: <1.5 IU/mL), and glutamic acid decarboxylase 65 (GAD65) autoantibodies (41,000 U/mL, reference range: <28.0 IU/mL), thyroid peroxidase antibodies (250.8 IU/mL, reference range: <1.60 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-
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 demyelinolysis 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 demyelinolysis 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 demyelinolysis before or after corticosteroid replacement for IAD. Possible explanations for

**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 demyelinolysis 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 demyelinolysis 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 demyelinolysis 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

| Time            | Before breakfast | After 2 h | Before lunch | After 2 h | Before dinner | After 2 h |
|-----------------|------------------|-----------|--------------|-----------|---------------|-----------|
| Plasma glucose  | 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

| Time (min) | 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   | 36.9   |
| Plasma osmolarity (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

| Time (4 days) | Before |
|---------------|--------|
| Serum cortisol (μg/dL) | 3.7   |
| Serum DHEA-S (ng/mL) | 27    |
| Serum aldosterone (ng/dL) | 14.1  |
| Plasma renin activity (ng/mL/h) | 2.9   |
| Plasma ACTH (pg/mL) | 20.7  |

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.
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 requirement 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).

Acknowledgement
We thank the clinical laboratory technicians of Niigata Medical Center for their helpful technical support. We also thank Dr. Kenzo Kaneko (Nagaoka Red Cross Hospital, Japan) for his helpful advice.

References
1. Andrioli M, Pecori Giraldi F, Cavagnini F. Isolated corticotrophin deficiency. Pituitary 9: 289-295, 2006.
2. Nemoto K, Kawanishi Y, Suzuki H, Mizukami K, Asada T. Isolated adrenocorticotrophic hormone deficiency presenting with delirium. Ann J Psychiatry 164: 1440, 2007.
3. Tatsuzawa Y, Ono Y, Takahashi T, Yoshino A, Nomura S. Case of isolated adrenocorticotrophic hormone deficiency mimicking major depressive disorder. Psychiatry Clin Neurosci 65: 302, 2011.
4. Committee of the Japan Diabetes Society on type 1 diabetes. Diagnostic criteria for slowly progressive insulin-dependent (type 1) diabetes mellitus (SPDDIM) (2012); Report by the Committee on Slowly Progressive Insulin-dependent (Type 1) Diabetes Mellitus of the Japan Diabetes Society. Tonyobyo (J Japan Diab Soc) 56: 590-597, 2013 (in Japanese, Abstract in English).
5. Wieland RG, Wieland JM. Isolated adrenocorticotropic hormone deficiency with antepartum pituitary infarction in a type 1 diabetic. Obstet Gynecol 65 (3 Suppl): 585-59S, 1985.
6. Sandler R, Proudfoot GR. Isolated ACTH deficiency contributing to frequent hypoglycemia in type 1 diabetes. Diabetes Care 8: 302-304, 1985.
7. Giustina A, Candrina R, Cimino A, Romanelli G. Development of isolated ACTH deficiency in a man with type 1 diabetes mellitus. J Endocrinol Invest 11: 375-377, 1988.
8. Takamatsu K, Nishiyama T, Nakauchi Y, Yamano T, Ohno F. A case of insulin dependent diabetes mellitus associated with relapsing polychondritis, Hashimoto’s thyroiditis and pituitary adrenocortical insufficiency in succession. Jpn J Med 28: 232-236, 1989.
9. Sakane N, Yoshida T, Yoshikawa K, Umekawa T, Kondo M. Severe hypoglycemia and type 1 diabetes with isolated ACTH deficiency. J Endocrinol Investig 18: 1621-1622, 1995.
10. Oishi H, Souda Y, Ito T, Morita H, Oki Y, Nakamura H. A case of insulin-dependent diabetes mellitus with ACTH deficiency contributing frequent hypoglycemia. Tonyobyo To Taisha (Diabetes J) 27: 59-63, 1999 (in Japanese).
11. Muro S, Tanaka T, Hanaoka I, Oki S. Ten cases of isolated adrenocorticotropic hormone deficiency. Horumon To Rinsho (Clinical Endocrinology) 49 (Suppl): 57-65, 2001 (in Japanese).
12. Kita Y, Matushita Y, Kato K, et al. Fulminant type 1 diabetes and isolated adrenocorticotropic hormone deficiency in a patient with autoimmune polyglandular endocrine syndrome. Nihon Naibunpitsu Gakkai Zasshi (Folia Endocrinologica Japonica) 87 (Suppl): 32-34, 2011 (in Japanese).
13. Committee on the Standardization of Diabetes Mellitus-Related Laboratory Testing of Japan Diabetes Society. International clinical harmonization of glycated hemoglobin in Japan: From Japan Diabetes Society to National Glycohemoglobin Standardization Program values. J Diabetes Invest 3: 39-40, 2012.
14. Weiner WJ. A differential diagnosis of Parkinsonism. Rev Neurol Dis 2: 124-131, 2005.
15. Lasheen I, Doi SA, Al-Shoumer KA. Glucocorticoid replacement in panhypopituitarism complicated by myelinolysis. Med Princ Pract 14: 115-117, 2005.
16. Okada K, Nomura M, Furusyo N, Otaguro S, Nabeshima S, Hayashi J. Amelioration of extrapontine myelinolysis and reversibility of parkinsonism in a patient with asymptomatic hypopituitarism. Intern Med 44: 739-742, 2005.
17. Sajith J, Dickfield A, Katiﬁ HA. Extrapontine myelinolysis presenting as acute parkinsonism. BMC Neurol 6: 33, 2006.
18. Srimanee D, Bhidayasiri R, Phanthumchinda K. Extrapontine myelinolysis in preoperative sellar region tumor: report of two cases. J Med Assoc Thai 81: 124-131, 2008.
19. Gujjar A, Al-Mamari A, Jacob PC, Jain R, Balkhair A, Al-Asmi A. Extrapontine myelinolysis as presenting manifestation of adrenal failure: a case report. J Neurol Sci 290: 169-171, 2010.
20. Imam YZ, Saqqur M, Alhaii H, Deleu D. Extrapontine myelinolysis-induced parkinsonism in a patient with adrenal crisis. Case Rep Neurol Med 2012: 327058, 2012.
21. Walji GM. Parkinsonism associated with Addison’s disease. Mov Disord 18: 340-342, 2003.
22. Stern RA, Prange AJ. Neuropsychiatric aspects of endocrine disorder. In: Comprehensive Textbook of Psychiatry. Kaplan HI, Sadock BJ, Eds. Milamills and Wilkins, Baltimore, 1995: 241-251.
23. Ros-Bernal F, Hunot S, Herrero MT, et al. Microglial glucocorticoid receptors play a pivotal role in regulating dopaminergic neurodegeneration in parkinsonism. Proc Natl Acad Sci U S A 108: 6632-6637, 2011.
24. Pihoker C, Gilliam LK, Hampe CS, Lernmark A. Autoantibodies in diabetes. Diabetes 54 (Suppl 2): S52-S61, 2005.
25. Ali F, Rowley M, Jayakrishnan B, Teuber S, Gershwin ME, Mackay IR. Stiff-person syndrome (SPS) and anti-GAD-related CNS degenerations: protein additions to the autoimmune central neuropathies. J Autoimmun 37: 79-87, 2011.
26. Alexopoulou H, Dalakas MC. Immunology of stiff person syndrome and other GAD-associated neurological disorders. Expert Rev Clin Immunol 9: 1043-1053, 2013.
27. Imagawa A, Hanafusa T, Awata T, et al. Report of the committee of the Japan Diabetes Society on the research of fulminant and acute-onset type 1 diabetes mellitus: New diagnostic criteria for fulminant type 1 diabetes mellitus (2012). J Diabetes Investig 3: 536-539, 2012.
28. Kawasaki E, Maruyama T, Imagawa A, et al. Diagnostic criteria for acute-onset type 1 diabetes mellitus (2012): Report of the Committee of Japan Diabetes Society on the Research of Fulminant and Acute-onset Type 1 Diabetes Mellitus. J Diabetes Investig 5: 115-118, 2014.
29. Gumbiner B, Polonsky KS, Beltz WF, et al. Effects of weight loss and reduced hyperglycemia on the kinetics of insulin secretion in obese non-insulin dependent diabetes mellitus. J Clin Endocrinol Metab 70: 1594-1602, 1990.
30. Cutolo M. Autoimmune polyendocrine syndromes. Autoimmun Rev 13: 85-89, 2014.
31. Hashimoto K, Maruyama H, Nishiyama M, et al. Susceptibility alleles and haplotypes of human leukocyte antigen DRB1, DQA1, and DQB1 in autoimmune polyglandular syndrome type III in Japanese population. Horm Res 64: 253-260, 2005.
32. Arvat E, di Vito L, Maccagno B, et al. Effects of GHRP-2 and hexarelin, two synthetic GH-releasing peptides, on GH, prolactin, ACTH and cortisol levels in man. Comparison with the effects of GHRH, TRH and hCRH. Peptides 18: 885-891, 1997.
33. Kimura T, Shimatsu A, Arimura H, et al. Concordant and discordant adrenocorticotropic (ACTH) responses induced by growth hormone-releasing peptide-2 (GHRP-2), corticotropic-releasing hormone (CRH) and insulin-induced hypoglycemia in patients with hypothalamopituitary disorders: evidence for direct ACTH releasing activity of GHRP-2. Endocr J 57: 639-644, 2010.
34. de Sá LB, Nascimento SO, Correa-Silva SR, et al. Effects of ghrelin, growth hormone-releasing peptide-6, and growth hormone-releasing hormone on growth hormone, adrenocorticotropic hormone, and cortisol release in type 1 diabetes mellitus. Metabolism 59: 1536-1542, 2010.

© 2015 The Japanese Society of Internal Medicine
http://www.naika.or.jp/imonline/index.html