Non-Insulin-Dependent Diabetes Mellitus Complicated with Idiopathic Hypoparathyroidism

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We report a case of non-insulin-dependent diabetes mellitus (NIDDM) complicated with idiopathic hypoparathyroidism. A 74-year-old male was hospitalized because of diplopia. He was revealed to have NIDDM. The levels of serum Ca and intact-PTH were 6.3 mg/dl and <5 pg/ml, respectively. Brain computed tomography revealed abnormal calcification in the cerebral basal ganglia and the cerebellum. After recovery from hypocalcemia, the endogenous insulin secretion was normalized. It is suggested that the pathogenesis of NIDDM in this patient may have been related to an insulin secretory defect as a result of hypocalcemia in addition to the hereditary risk. (Internal Medicine 34: 904-907, 1995)

Key words: hypocalcemia, insulin secretion, oculomotor nerve palsy

Introduction

Idiopathic hypoparathyroidism (IHP) is a rare disease characterized by hypocalcemia. We report a case of non-insulin-dependent diabetes mellitus (NIDDM) with right oculomotor nerve palsy in the natural course of IHP. The combination of IHP with insulin-dependent diabetes mellitus (IDDM) has been described to be a polyglandular autoimmune syndrome (1), but its genesis may differ from that of the combination of IHP and NIDDM. Only 4 cases of IHP and NIDDM have been reported however, no discussion of the pathogenesis was included (2-4).

In this patient, we examined the pancreatic endogenous insulin secretion using the glucagon stimulating test before and after the correction of hypocalcemia to evaluate the relationship between the pathogenesis of NIDDM and hypocalcemia due to hypoparathyroidism.

Case Report

A 74-year-old male was hospitalized in April 1993 because of diplopia and right blepharoptosis. He had a history of cataract and ophthalmological treatment. His mother and daughter had NIDDM.

On admission, his body temperature was 36.7°C, height 162 cm, weight 58 kg, and body mass index 22.1 kg/m². The blood pressure was 142/64 mmHg, and the heart rate was regular and

72/min. Consciousness was clear. No abnormal findings for the skin, nails or hair were noted.

Neurological examinations revealed right blepharoptosis. The right eyeball deviated to the lateral side and did not readily move to the medial side. Both pupils were of normal size, but the right pupillary light reflexes were depressed. No involvement of the other cranial nerves was evident, nor was hemiparesis or pathological reflex present. The deep tendon reflexes were slightly diminished. Glove and stocking type disturbance of vibratory sensation was present in the peripheral extremities. He showed the cerebellar sign of wide-based ataxic gait and dysmetria on the finger-nose-finger test. Extrapyramidal signs were not evident. Chvostek's sign and Trousseau's sign were negative.

Urinalysis revealed glucosuria, 2.6 g/24 h. Electrolysis indicated hypocalcemia and hyperphosphatemia, as follows: serum Ca, 6.3 mg/dl; Ca²⁺, 2.92 mg/dl; corrected Ca by Payne's method, 5.9 mg/dl; and P, 5.7 mg/dl. The levels of urine Ca and P were 17 mg/24 h and 302 mg/24 h, respectively. The level of intact parathyroid hormone (intact-PTH) was markedly low, <5 pg/ml. On the Ellsworth-Howard test, the excretion of phosphate into the urine was increased by 36.6 mg/2 h and that of cAMP was increased by 6.8 µmol/h following the intravenous administration of hPTH. The daily profile of blood glucose levels was as follows: before breakfast, 144 mg/dl; after breakfast, 265 mg/dl; and before dinner, 176 mg/dl. The level

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Received for publication January 26, 1995; Accepted for publication June 5, 1995

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of HbA_{1C} was 8.7%. The oral glucose tolerance test (OGTT) disclosed a blood glucose level of 137 mg/dl at the baseline, 175 mg/dl at 30 minutes, 263 mg/dl at one hour, and 323 mg/dl at two hours. The response of IRI to the OGTT was hypoactive;

Figure 1. The patient showed hypoglycemia after intravenous administration of regular insulin.

4.5 μ U/ml at the baseline, 7.6 μ U/ml at 30 minutes, 12.8 μ U/ml at one hour, and 18.8 μ U/ml at two hours. He showed no diabetic retinopathy on the ophthalmologic examination, but microalbuminuria (79.6 mg/g/creatinine) and mild neuropathy were noted. After the intravenous administration of regular insulin, the blood glucose level was 44 mg/dl at 30 minutes and 54 mg/dl at 45 minutes (Fig. 1); he then complained of hypoglycemic symptoms. Electrocardiography revealed a normal QT time. X-ray of the skull and computed tomography scan of the brain revealed broad and abnormal calcification in the cerebral basal ganglia and the cerebellum (Fig. 2). No ischemia of the brain was demonstrated by magnetic resonance imaging nor cerebral aneurysm by magnetic resonance angiography.

According to these findings, NIDDM with right oculomotor nerve palsy complicated with IHP was diagnosed. After 1,600-kilocalorie daily diet therapy for NIDDM was initiated, the levels of blood glucose became normalized. Diplopia and blepharoptosis due to right oculomotor nerve palsy disappeared two months later. Then, administration of alfacalcidol (activated vitamin D₃) for hypocalcemia was started, and the levels of serum Ca were elevated to 7.8 mg/dl. The glucagon stimulating test was performed before and after administration of activated vitamin D₃ (Fig. 3). The levels of serum C-peptide (CPR) and IRI after the administration of glucagon were significantly elevated after vitamin D₃ therapy compared with those before therapy. The peak level of CPR before the correction of hypocalcemia was 5.2 ng/ml at six minutes; after the correction this CPR value increased to 7.8 ng/ml (Fig. 4).

Discussion

The time of IHP onset in this patient is unknown, but he was considered to have long-standing hypocalcemia before the onset of NIDDM due to the presence of the abnormal intracranial calcification. The combination of IHP and IDDM was described in 1980 by Neufeld et al as polyglandular autoimmune

Figure 2. Brain computed tomography scan revealed abnormal calcification in the cerebral basal ganglia and the cerebellum.

Figure 3. Clinical course of the patient.

Figure 4. The glucagon stimulating test demonstrated improvement of insulin secretion after recovery from hypocalcemia (open circles) compared to that before the administration of activated vitamin D₃ (closed circles). The levels of blood glucose had no changes before and after.

syndrome type 1 (1). This syndrome is frequently characterized by systemic endocrinopathy related to autoimmune antibodies. However, the genesis of the combination of IHP and NIDDM may differ from that of polyglandular autoimmune syndrome, but only 4 cases have been reported previously (2–4).

Here, the results of the glucagon stimulating test prior to vitamin D₃ therapy, which may reflect endogenous insulin secretion from pancreatic β -cells, suggested that the hyperglycemia in this patient was at least partially due to an insulin secretory defect. Peripheral insulin resistance was not likely because of the occurrence of a hypoglycemic episode after the intravenous administration of regular insulin, though we did not examine the insulin sensitivity quantitatively by the glucose clamp or the steady state plasma glucose level method.

It has been confirmed that the insulin secretion from the pancreas is disturbed in the absence of extracellular Ca²⁺ in vitro (5, 6). The mechanism of the insulin secretion from pancreatic β -cells has been described, and it was confirmed that the entry of extracellular Ca²⁺ into the intracellular space via the voltage-dependent Ca²⁺ channel is an important step in the process of insulin release (7, 8). Yasuda et al (5) and Ikeda et al (9) reported that insulin response during the OGTT was reduced significantly in patients with IHP without diabetes mellitus compared to those of normal subjects and the response improved after recovery from hypocalcemia.

In the present patient the insulin secretion during the glucagon stimulating test was normalized in parallel with the correction of hypocalcemia following the administration of activated vitamin D₃, although we did not evaluate follow-up OGTT or urine CPR. Improvement of insulin secretion due to blood glucose control was not considered likely because the glucagon stimulating test was performed after the levels of blood glucose became stable by diet therapy. Thus, we suggest that the pathogenesis of NIDDM was related to an insulin secretory defect as a result of hypocalcemia due to hypoparathyroidism, in addition to hereditary risk of NIDDM. One case of other four patients with IHP and NIDDM had a strong hereditary risk for NIDDM as well (4).

However, it was reported that the vitamin D₃ receptor is localized in pancreatic β -cells and vitamin D₃ might affect insulin secretion (10). Thus, the levels of 1,25-(OH)₂D concentration should have been measured before and after administration of alfalcidol.

It is obvious that NIDDM is not a single disorder but rather a syndrome with wide heterogeneity. This patient was not obese and was elderly at onset. In the elderly, the level of serum calcium tends to be depressed. It is also reported that most non-obese and elderly diabetic patients show an insulin secretory defect (11). Therefore, we propose the recognition of

hypocalcemia to be one of the pathogenetic mechanisms of NIDDM.

It was reported that palsies of the extraocular muscle nerves are seen in 0.7–2% of diabetic patients and that the oculomotor nerve is most frequently involved (12, 13). Satisfactory recovery of nerve function is generally observed within several months after the control of blood glucose. In the present patient, diplopia and blepharoptosis disappeared and the mobility of the right eyeball was normalized within two months after admission. There has been no report to our knowledge of oculomotor nerve palsy complicated with IHP. Thus, the right oculomotor nerve palsy in the present patient was thought to be a mononeuropathy caused by diabetes.

References

- 1) Neufeld M, Maclaren N, Blizzard R. Autoimmune polyglandular syndrome. *Pediatr Ann* **9**: 154, 1980.
- 2) Shigemasa C, Tanaka T, Yoshida A, Okamura Y, Mashiba H, Abe K. A case of idiopathic hypoparathyroidism showed improvement of hypocalcemia and insulin secretion with administration of 1 α -hydroxycalciferol. *Naika* **47**: 327, 1981 (in Japanese).
- 3) Akasu F, Haraguchi K, Tsunoda S, Shiozawa Z, Onaya T. Hypoparathyroidism associated with ossification of posterior longitudinal ligament of the spine (OPLL) and glucose intolerance – report of two cases. *Naika* **57**: 383, 1986 (in Japanese).
- 4) Takeda H, Miyano R, Machimura H, et al. An autopsy case of idiopathic hypoparathyroidism with diabetes mellitus. *Hormone To Rinsho* **39**: 617, 1991 (in Japanese).
- 5) Yasuda K, Hurukawa Y, Okuyama M, Kikuchi M, Yoshinaga K. Glucose tolerance and insulin secretion in patients with parathyroid disorders. *N Engl J Med* **292**: 501, 1975.
- 6) Hellman B. The significance of calcium for glucose stimulation of insulin release. *Endocrinology* **97**: 392, 1975.
- 7) Bergsten P, Hellman B. Glucose inhibits insulin release when not promoting the entry of calcium into the β -cells. *Biochem Biophys Res Commun* **125**: 875, 1984.
- 8) Bergsten P, Grapengiesser E, Gylfe E, Tengholm A, Hellman B. Synchronous oscillations of cytoplasmic Ca²⁺ and insulin release in glucose-stimulated pancreatic islets. *J Biol Chem* **269**: 8749, 1994.
- 9) Ikeda T, Kurahashi A, Shigemasa C, et al. Insulin and glucagon secretion in a case of idiopathic hypoparathyroidism. *J Jpn Diabetes Soc* **24**: 581, 1981 (Abstract in English).
- 10) Johnson JA, Grandle JP, Roche PC, Kumar R. Immunohistochemical localization of the 1,25(OH)₂D₃ receptor and calbindin D28k in human and rat pancreas. *Am J Physiol* **267**: E356, 1994.
- 11) Arner P, Pollare T, Lithell H. Different aetiologies of type 2 (non-insulin-dependent) diabetes mellitus in obese and non-obese subjects. *Diabetologia* **34**: 483, 1991.
- 12) Katsui Y, Takahashi A, Takezawa H. Diabetic ophthalmoplegia. An analysis of 151 clinical cases in Japan and reevaluation of the foreign three postmortem studies. *Sinkei Naika* **23**: 122, 1985 (in Japanese).
- 13) Amenomori M, Yasuda H, Kikkawa R, Shigeta Y. Clinical features of diabetic mononeuropathy after rapid glycemic control. *J Jpn Diabetes Soc* **36**: 293, 1993 (Abstract in English).