Sheehan's Syndrome with Subsequently Developed Diabetes Mellitus: Endocrinological Studies

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A patient with Sheehan's syndrome who later developed diabetes mellitus is described. Endocrinological examinations revealed panhypopituitarism and impaired insulin and excessive glucagon secretion which was compatible with the findings of primary diabetes mellitus. Daily maintenance therapy was adequately provided with hydrocortisone, thyroxine and only 4 U of insulin.

Key Words: Diabetes mellitus, Sheehan's syndrome, Hypopituitarism, Insulin, Glucagon

The association of hypopituitarism during the course of diabetes mellitus is rare and only several well-documented cases have been reported with special emphasis on the clinical improvement of diabetes. On the other hand, the occurrence of diabetes mellitus in patients with preceding hypopituitarism is very uncommon and, to the best of our knowledge, only one case of Sheehan's syndrome complicated with diabetes has hitherto been described. We have recently observed a patient with Sheehan's syndrome who later developed diabetes mellitus. The following report describes this interesting case with special reference to the results of endocrinological examinations and characteristic features of diabetes mellitus associated with hypopituitarism.

CASF REPORT

History

The patient, a 45-year-old Japanese female, was admitted to the hospital with chief complaints of polydipsia and weight loss. Family history was negative for diabetes mellitus. She was well until her first delivery of a stillborn infant in 1956, complicated with copious hemorrhage. After the delivery, she had complained of easy fatigue and mental inactivity, although her menses were resumed one year later. In 1958, she had the second, uncomplicated delivery, which was followed by poor lactation and amenorrhea. After the delivery, she had complained of easy fatigue and mental inactivity, although her menses were resumed one year later. In 1958, she had the second, uncomplicated delivery, which was followed by poor lactation and amenorrhea. Without reapparance of menstruation, she became pregnant in 1960 and the delivery was complicated with severe genital bleeding and shock, for which hysterectomy was performed. After the delivery, there were failure of lactation and general weakness. Since 1967, she had episodes of fever, nausea, vomiting and mental confusion once a month. In 1969,
the diagnosis of Sheehan’s syndrome was made based on laboratory examinations and the treatment with prednisolone and desiccated thyroid powder was instituted. Since then, the patient had been in relatively good condition until 1975, when she first noted progressive general weakness and weight loss with polyuria. Glucosuria and hyperglycemia were evident and she was hospitalized to the Kobe University Hospital in June, 1975.

Physical Examination
The patient was a mentally alert, cooperative, middle-sized and relatively well-nourished female with dry and pale skin. The height was 159 cm, weight 55 Kg, and blood pressure 130/74. Scalp hair was slightly sparse and pubic and axillary hairs were very scanty. Pulse rate was 68/min, with regular rhythm. Findings from visual field and neurological examinations were normal. No abnormalities were found on percussion and auscultation of chest. Liver, spleen and kidneys were not palpable.

Laboratory and X-ray data
Urinalysis gave a 3+ test for glucose and negative test for albumin or ketone bodies. Twenty-four hour specimens of urine contained 60 to 120 g of glucose. Stool examination revealed no abnormality. RBC was 4.6 million, hemoglobin concentration 14.3 g/dl, hematocrit 42.6 %, platelet count 171,000 and WBC 6,260 with normal differential count. Blood urea nitrogen was 21 mg/dl, serum creatinine 0.9 mg/dl, Na 132 mEq/L, K 4.5 mEq/L, Cl 95 mEq/L, CPK 21 mU/ml and amylase 46 S.U. Liver function tests including serum bilirubin, GOT, GPT and alkaline phosphatase were all within normal limits. Serum triglyceride was 296 mg/dl, \( \beta \)-lipoprotein more than 1400 mg/dl, cholesterol 333 mg/dl and blood free fatty acids level 539 \( \mu \)Eq/L. Serum protein electrophoresis disclosed no abnormality. Serological examinations gave negative tests for rheumatoid factor, ASLO, antithyroid antibody and for syphilis. Skull and chest X-rays showed no abnormalities. Fundoscopic examination revealed hypertensive retinal change (H₂S₂) without signs of diabetic retinopathy.

Pituitary function
Plasma cortisol, examined 2 weeks after the cessation of replacement therapy, was not detectable throughout the day (<0.5 \( \mu \)g/dl). Urinary 17-OHCS and 17-KS excretions were 2.8 and 0.2 mg/day, respectively. An intravenous bolus injection of 0.25 mg of synthetic 1-24 ACTH caused a slight increase in plasma cortisol. However, intravenous drip infusion of 0.25 mg of 1-24 ACTH over a period of 8 hrs for 2 successive days caused a delayed but significant response of cortisol, suggesting that the adrenocortical insufficiency in this patient is a secondary one (Fig. 1). Oral administration of 1 g of metyrapone did not cause an increase of plasma 11-deoxycortisol.

Triosorb resin spong uptake was 29.6%, PBI 4.0 \( \mu \)g/dl, thyrroxine 3.7 \( \mu \)g/dl, and BMR +3%. Basal plasma TSH was within normal limit but its response to the intravenous injection of 500 \( \mu \)g of TRH was very limited as shown in Fig. 2. The results suggest the presence of mild secondary hypothyroidism. Plasma prolactin response to TRH was absent as shown in Fig. 2.

Plasma LH and FSH levels were within normal ranges but their responses to the intravenous injection of 100 \( \mu \)g of LH-RH were completely absent as shown in Fig. 3. Intravenous infusion of 30 g of arginine or

![Fig. 1. Plasma cortisol levels during the infusion of 0.25 mg of synthetic 1-24 ACTH over a period of 8 hours given on 2 successive days.](image-url)
intravenous injection of 0.05 U/Kg body weight of insulin did not elicit any significant increase in plasma growth hormone as shown in Fig. 4 and 5.

For comparison, endocrine function

Fig. 2. Plasma TSH and prolactin responses to the intravenous injection of 500 μg of TRH.

Fig. 3. Plasma LH and FSH responses to the intravenous injection of 100 μg of LH-RH.

Fig. 4. Responses of plasma growth hormone, insulin, glucagon and blood glucose to the intravenous infusion of 30 g of L-arginine over a period of 45 min.

Fig. 5. Effect of intravenous injection of 0.05 U/kg b.w. of pork insulin (dotted line) or beef insulin (solid line) on blood glucose and plasma growth hormone levels.

studies performed in 1969 were listed in Table 1. Presence of hypothyroidism and secondary hypoadrenocorticism was evident from these results.

**Pancreatic endocrine function**

Fasting blood glucose levels ranged from 249 to 334 mg/dl. As shown in Fig. 6, oral administration of 50 g of glucose produced a high and sustained increase of blood glucose, showing severe glucose intolerance. This is a great contrast to the normal glucose tolerance curve studied in 1969 (Table 1). Plasma insulin showed a markedly delayed response to glucose, with a peak at 120 min (Fig. 6). Different from results in normal subject, oral glucose loading did not cause a significant decline in plasma glucagon.

Intravenous infusion of 30 g of arginine caused almost normal response of plasma insulin as shown in Fig. 4. Basal plasma glucagon levels were elevated and arginine infusion elicited exaggerated response of plasma glucagon.

These results, especially low initial response of plasma insulin to glucose and exaggerated response of plasma glucagon to arginine, are compatible with data in primary diabetes mellitus. In contrast with usual diabetics, this patient was very sensitive to insulin, because only 0.05 U/Kg body weight of pork or beef insulin significantly lowered blood glucose, as shown in Fig. 5.

![Fig. 6. Responses of blood glucose, plasma insulin, glucagon, gastrin and growth hormone to the oral administration of 50 g of glucose.](image)

**Clinical course**

Replacement therapy with 20 mg hydrocortisone and 25 μg thyroxine was instituted which improved subjective complaints, and hypotension. During the course of hospitalization, the patient sometimes showed high blood pressure, 180/120, but pheochromocytoma was ruled out by glucagon test, retroperitoneal air insufflation study and normal urinary catecholamine excretion.

Restriction of caloric intake to 1800 Cal. only slightly lowered fasting blood glucose levels and, therefore, 4 U of Rapitard insulin was given once a day which significantly ameliorated both blood glucose and glucosuria without episodes of hypoglycemia.

**DISCUSSION**

This patient presented classical clinical findings of hypopituitarism and the diagnosis was established by endocrine examinations, though incomplete, in 1969. In the present study, thorough endocrine studies
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confirmed the diagnosis of panhypopituitarism: various stimulation tests revealed impaired secretion of ACTH, TSH, prolactin, LH, FSH and growth hormone. Her first delivery in 1956 was complicated with copious hemorrhage and followed by symptoms of mild hypopituitarism, although she had 2 deliveries thereafter. The third delivery was again accompanied with severe hemorrhage which required hysterectomy. Since then, she had classical symptoms of severe hypopituitarism, with episodes of possible adrenal insufficiency which disappeared by prednisolone therapy. The patient showed no neurological abnormalities, normal visual field and normal skull X-ray findings. There is little doubt, therefore, concerning the diagnosis of Sheehan's syndrome.

When the patient was examined in 1969, she showed no glucosuria and normal glucose tolerance curve. The symptoms of diabetes mellitus appeared since 1975 and the diagnosis of diabetes mellitus was established by laboratory examinations in 1976. Therefore, the diabetes became manifest at least 15 years, possibly 19 years, after the onset of hypopituitarism. Glucose intolerance is caused by a variety of diseases, such as endocrine, hepatic and pancreatic diseases. However, physical examination, laboratory data and X-ray studies in this patient could exclude Cushing's syndrome, acromegaly, pheochromocytoma, hyperthyroidism, liver and pancreatic diseases. Moreover, impaired initial response of plasma insulin to glucose along with almost normal plasma insulin response to arginine is a characteristic feature of mild to moderate diabetes of idio-pathic origin. Although family history of diabetes mellitus was not found in this patient, it is likely that she developed primary diabetes even though she was suffering from severe hypopituitarism. Mild obesity and steroid replacement therapy might be predisposing factors in this case for the development of diabetes mellitus.

The importance of the pituitary gland in the development of glucose intolerance was first demonstrated in dogs by Houssay. Some 20 years later, Poulsen reported the amelioration of preceding diabetes mellitus by the occurrence of Sheehan's syndrome in a female patient, the Houssay's phenomenon in man. More than 30 patients with diabetes mellitus who later developed hypopituitarism with reduced insulin requirement and improved glucose tolerance have been documented thereafter.

On the other hand, patients with preceding hypopituitarism seldom develop diabetes mellitus and we have collected only 10 cases from literature. Irie, Ewing et al and DiRaimondo and Earl reported patients who developed diabetes mellitus during the course of hypopituitarism caused by pituitary adenoma or craniophanryngioma. Only Pl-Sunyer and Cushman described a patient with Sheehan's syndrome in whom the diabetes became manifest 8 years later. In these patients, insulin requirement is usually very small. In a patient reported by DiRaimondo and Earl only 2 U of insulin resulted in good control and 8 U was sufficient to treat the ketoacidosis. Pl-Sunyer and Cushman reported that their ketosis-prone diabetic patient could be easily treated by 3 to 5 U insulin. Our patient was also treated by 4 U of insulin with good effect, even though she was on steroid and thyroid treatment. Therefore, marked insulin sensitivity in this patient might be resulted mainly from the lack of growth hormone. This patient had never been ketotic during the period of observation, even when she had high fasting blood sugar levels and marked glucosuria. This might be ascribed also to the lack of growth hormone and excessive cortisol secretion.

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REFERENCES

