NOTE

A Case of Acromegaly Improved by Pituitary Apoplexy

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Synopsis

This report deals with a detailed course of one patient with acromegaly who had a pituitary apoplexy. The pituitary apoplexy occurred suddenly 5 days after administration of an oral hypoglycemic agent, buformin, during hospitalization. Immediately after the attack changes of the concentrations of several hormones such as serum growth-hormone, serum thyroid hormone and urinary 17-hydroxycorticoids were followed until the development to hypopituitary state. Simultaneously with the decrease of the concentrations of the above-mentioned hormones, a regression of the physical manifestations of acromegaly and a complete amelioration of diabetes mellitus were observed.

Although pituitary apoplexy is a well-known accident in patients with acromegaly, detailed case reports dealing with it have been scarcely published, in which full courses of symptoms and of changes of functions of pituitary, adrenal and endocrine pancreas following pituitary apoplexy were described. Taylor et al. (Taylor et al., 1968) observed a course of pituitary apoplexy in one patient with acromegaly and diabetes mellitus, and reported the reductions in plasma growth-hormone, plasma cortisol and serum thyroxine concentrations following pituitary apoplexy. Their report seems to be only one detailed paper describing in English a full course of the attack. In Japan, up to the present there has been no such paper dealing with changes of pituitary, thyroid and adrenal functions during and after pituitary apoplexy in acromegaly. We recently had a chance to observe a full course of pituitary apoplexy in one patient which occurred during his hospitalization in our clinic. After the attack his symptoms of acromegaly, i.e., glucosuria, hyperglycemia and enlargement of hands, feet and face, disappeared or decreased significantly, and levels of hormones in the serum and in the urine were determined repeatedly before and after the accident of pituitary apoplexy in this patient.

Methods

To measure the hormone levels in the serum in the fasting state, the morning blood samples were obtained periodically from the patient before and after pituitary apoplexy. Also, to determine the functions of some endocrine organs various stimulation tests were carried out before and after the attack. Sera were frozen and kept at −20°C until the determination of hormones. Plasma glucose concentration was determined by an autoanalyser procedure using Momose’s method (Momose et al., 1960). Growth-hormone (HGH) and thyroid stimulating hormone (TSH) in the serum were measured by radioimmunoassay using commercial kits; the kit for HGH was supplied from Dainabot Radioisotope
Laboratory (Tokyo) and the kit for TSH from Daiichi Radioisotope Laboratory (Tokyo). Serum insulin (IRI) was determined by radioimmunoassay using ethanol-precipitation method (Nakamura et al., 1972). Plasma adrenocorticotropic hormone (ACTH) was measured with radioimmunoassay by the method of Matsukura (Matsukura et al., 1971).

Serum thyroxine (T4) was measured by competitive protein binding analysis using commercial kit supplied from Daiichi Radioisotope Laboratory (Tokyo) and serum triiodothyronine (T3) by radioimmunoassay using commercial kit supplied from Dainabot Radioisotope Laboratory (Tokyo). Determination of triiodothyronine resin sponge uptake (T3RSU) was performed by the Dainabot Triosorb kit method.

Urinary 17-hydroxycorticoids (17-OHCS) was determined by Sunderman Junior's method (Sunderman and Sunderman Junior, 1960).

For the stimulating test to release TSH, 500 µg of synthetic thyrotropin releasing hormone (TRH) supplied from Tanabe Pharmaceutical Co. Ltd., (Osaka), was given intravenously at 9:00 a.m., and blood samples were collected from the cubital vein at 15, 30, 60, 120 and 180 minutes after the administration. To stimulate ACTH release, 750 mg of metyrapone was administered orally 4-times with a 6-hr interval during 24 hours. Plasma ACTH levels were measured before the administration of metyrapone and 24 hours after the start of the test.

Case Report

A patient, Y. S., a 54-year-old man was admitted to the hospital of Tottori University School of Medicine. At age 26 in 1945 he noticed the enlargement of the hands and feet, because his old gloves and shoes became tight. When he was 44-year-old, 10 years before admission, symptoms of thirst, polyuria and polyphagia occurred. Since that time he suffered frequently from furuncles. Although these troubles suggested strongly an existence of acromegaly with diabetes mellitus, he had never been treated before the admission on July 23, 1973. The family history was unremarkable except that his younger brother was diabetic.

Clinical and laboratory findings at the admission

The patient showed a typical appearance of acromegaly (Figs. 1–1, 1–2, 1–3). His height was 162.8 cm, weight 63.5 kg, pulse rate 70/min and blood pressure 134/80 mmHg. Examinations of heart, lungs and
abdomen were unremarkable. Neurologic examination showed no evidence of involvement and his visual fields were intact.

The urinalysis revealed a slightly positive reaction for protein and a strongly positive for glucose. The urine sediment was unremarkable. Serum sodium was 140 mEq/l, potassium 3.8 mEq/l, chloride 97 mEq/l and phosphorus 3.8 mg/dl. Liver functions were within normal limits.

The fasting serum HGH level was 61 ng/ml which was much higher than normal upper limit (7 ng/ml). An oral glucose tolerance test (50 g) revealed a diabetic pattern; fasting plasma glucose 205 mg/dl, 60 minutes 300 mg/dl, 120 minutes 305 mg/dl and 180 minutes 265 mg/dl. During the oral glucose tolerance test the elevated level of HGH did not decreased and there was no increase of serum IRI as shown in Table 1. The PBI was 4.8 µg/dl. The serum T₄ and T₃ concentrations were 6.0 µg/dl and 102 ng/dl, respectively. Urinary 17-OHCS was 10.4 mg/day.

Roentgenograms revealed an enlargement of sella turcica and an increase in soft tissue thickness expressed by the heel pad of 35 mm which is larger than normal value (20 mm) (Fig. 2-1).

Clinical course during the admission.

Since August 5, the patient was treated with 150 mg of buformin, one of hypoglycemic biguanide agents, because of continuing high level of plasma glucose. On August 9, when his thirst subsided and a slight amelioration of plasma glucose was observed, he felt presbyopia and he went to a optician's shop in the burning sun under condition of severe diarrhea which might be caused by buformin. In the shop he suddenly complained of an attack of retrobulbar headache and fell into shock. Af-

| Table 1. Plasma glucose (BS), serum insulin (IRI) and serum growth-hormone (HGH) responses to oral 50g glucose before and after pituitary apoplexy |
|----------------------------------|---|---|---|---|---|---|---|
|                                | 0' | 30' | 60' | 90' | 120' | 180' |
| Before apoplexy (July 30, 1973) | BS (mg/dl) | 205 | 275 | 300 | 305 | 265 |
|                                 | IRI (µU/ml) | 10  | 8   | 8   | 11  | 7   |
|                                 | HGH (ng/ml) | 61  | 58  | 50  | 58  | 68  |
| On the 40th day after apoplexy (August 17, 1973) | BS (mg/dl) | 90  | 125 | 135 | 120 | 90  | 75  |
|                                 | IRI (µU/ml) | 13  | 22  | 23  | 26  | 16  | 15  |
|                                 | HGH (ng/ml) | 1.3 | 1.2 | 1.0 | 0.6 | 1.0 | 1.1 |

Figs. 2-1, 2-2. The heel pad before and after pituitary apoplexy. 2-1: The heel pad of 35 mm at the time of admission, 2-2: The heel pad of 20 mm on the 73th day after pituitary apoplexy.
After going back to the hospital by an ambulance, he was immediately treated with bed rest, transfusion of physiologic saline solution, analgesics and antibiotics. A temperature of 38°C and leucocytosis lasted for 3 days after the attack.

The clinical course following this attack progressed favourably and the retrobulbar headache disappeared completely 3 days after the attack. During the entire course, the patient had not complained of lethargy, nausea, vomiting and visual impairment, but an oculomotor paresis and Horner's syndrome in the right side were developed immediately after the attack and lasted for 63 days. Spinal fluid obtained on 10th day after the attack was xanthochromic.

Changes in the concentrations of various hormones in the serum and in the urine and plasma glucose are depicted in Figure 3. The fasting serum HGH level of 61 ng/ml at the time of admission decreased to 47.3 ng/ml 30 minutes after the attack, 5.5 ng/ml on the 5th day, 2.7 ng/ml on the 11th day and 1.8 ng/ml on the 15th day after the attack. The elevated fasting plasma glucose level of 234 mg/dl 2 days before the attack was improved into 215 mg/dl on the next day, 150 mg/dl on the third day, and 100 mg/dl 10 days after the attack. The serum PBI, T₄ and T₃ concentrations were depressed to 4.4 µg/dl, 5.5 µg/dl and 90.5 ng/dl, respectively, on the 11th day, and decreased gradually into the range of hypothyroidism such as the serum PBI of 3.7 µg/dl, T₄ 4.5 µg/dl and T₃ 65.0 ng/dl on the 30th day after the attack. At the time of developing overt hypothyroidism, urinary 17-OHCS was also depressed to less than normal range such as 2.0 mg/day.

On the 37th day after the attack, response of ACTH level to oral metyrapone admin-

![Fig. 3. The changes of fasting serum growth-hormone (HGH), fasting plasma glucose (FBS), serum thyroid hormone and urinary 17-OHCS concentrations in patient YS before and following pituitary apoplexy.](image-url)
Table 2. ACTH and TSH secretion tests after pituitary apoplexy

<table>
<thead>
<tr>
<th></th>
<th>Plasma ACTH (pg/ml)</th>
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<tbody>
<tr>
<td>Before metyrapone administration (September 14, 1973, 9:00 a.m.)</td>
<td>46</td>
</tr>
<tr>
<td>After 3 g metyrapone administration within 24-hr (September 15, 1973, 9:00 a.m.)</td>
<td>33</td>
</tr>
</tbody>
</table>

ACTH response to oral metyrapone on the 37th day after pituitary apoplexy.

<table>
<thead>
<tr>
<th></th>
<th>Serum TSH</th>
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<tbody>
<tr>
<td>Before TRH administration</td>
<td>n.d.</td>
</tr>
<tr>
<td>After 500 µg TRH administration</td>
<td>n.d.</td>
</tr>
<tr>
<td>15’</td>
<td>n.d.</td>
</tr>
<tr>
<td>30’</td>
<td>n.d.</td>
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<tr>
<td>60’</td>
<td>n.d.</td>
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<tr>
<td>120’</td>
<td>n.d.</td>
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<tr>
<td>180’</td>
<td>n.d.</td>
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</table>

TSH response to intravenous TRH on the 50th day after pituitary apoplexy.

According to literatures (Brougham et al., 1950; Rigolosi et al., 1968; Taylor et al., 1968), clinical findings of pituitary apoplexy in acromegaly were characterized by attacks of a severe headache, especially in retrobulbar region, lethargy, vomiting, fever and visual disturbances. In our patient, the symptoms in the attack were relatively mild except a typical headache. In the previous patients a definite diagnosis of pituitary apoplexy was made by surgical observation or by post-mortem examination. The predominant pathological change was ischemic pituitary necrosis (Gurling, 1955; Murakami, 1962), and intra- or perihypophyseal hemorrhage (Brougham, 1950; Argires and Nelson, 1966; Adriano and Al-Mondhiry, 1967). In our patient, intracranial hemorrhage was suspected because of xanthochromia of the spinal fluid. As one of causes of pituitary apoplexy, X-ray therapy on the pituitary tumor of patients with acromegaly had been noted in literatures (Uihlein et al., 1957; Locke and Tyler, 1961). Also two cases caused by diabetic acidosis were reported (Brougham, 1950; Gurling, 1955).

Up to the present paper, there has been no report that the pituitary apoplexy in acromegaly was brought about by an administration of oral hypoglycemic agents. However, in our patient, from the fact of occurring pituitary apoplexy simultaneously with diarrhea considered as one of the side-effects of buformin, it seemed reasonable to assume that the administration of buformin was one of the factors for the development of pituitary apoplexy.

With the observations of the reduction in hypophyseal functions following pituitary apoplexy in our case, we could observed hypopituitary state about one month after the apoplexy. With the examinations of the changes of the serum HGH and other...
hormones, it was proved that serum HGH level fell rapidly immediately after pituitary apoplexy and serum thyroid hormone and urinary 17-OHCS levels decreased gradually.

In some cases of acromegaly with only moderate or no glucose intolerance, an exaggerated plasma insulin response to glucose has been found (Cerasi and Luft, 1964; Sonksen et al., 1967). The cause of hypersecretion of insulin in such acromegalic patients is speculated to be due in part to potentiated beta cell response and increased beta cell mass (Ogilvie, 1964), or insulin resistance in peripheral cells (Galbraith et al., 1960; Beck et al., 1965).

In the patient of the present report, existence of hyperglycemia, glucose intolerance and the absence of an insulin response to glucose were shown before pituitary apoplexy. Although significant decrease of serum HGH, an amelioration of glucose tolerance and normalization of plasma glucose level were developed after the apoplexy, IRI response to glucose loading was restored incompletely. This suppression of IRI response might be caused by exhaustion of the beta cells or by his disposition to diabetes, nevertheless in the patient in the present report a heredity of diabetes seems to be more plausible explanation for the depression of insulin levels, because his brother has been suffering from diabetes without acromegaly.

Acknowledgements

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References
