A Case of Posttraumatic Hypopituitarism

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Synopsis

A case of posttraumatic hypopituitarism was studied. A 46-years-old man suffered from adrenal crisis after he showed symptoms of hypopituitarism which was caused by the head injury of 26 years ago. Hyponatremia was prominent at the time of admission. Clinical and laboratory studies revealed hypothyroidism, hypofunction of adrenal gland and hypogonadism. Blood pituitary hormones-ACTH, GH, TSH and LH were determined by radioimmunoassay. Plasma ACTH levels were not detectable (below 10 pg/ml) even after metyrapone administration. Base-line serum GH level was low and did not respond to the administration of insulin or L-arginine. Although the response was subnormal, serum TSH levels were increased in response to synthetic thyrotropin releasing hormone (TRH). Serum LH levels were low. Mechanism about the hyponatremia at the time of adrenal crisis in this case was discussed.

Posttraumatic hypopituitarism is a rare disease and no case of posttraumatic hypopituitarism has been reported in Japan. Conceivably, the rarity is due to the fact that the trauma severe enough to cause extensive damage to the pituitary gland or stalk is usually fatal (Klachko *et al.*, 1968).

We have performed radioimmunoassay study of blood pituitary hormones such as ACTH, GH, TSH, and LH in a case of hypopituitarism following head injury. Serum TSH was assayed after the administration of synthetic thyrotropin releasing hormone (TRH) to assess the reserve of pituitary gland to secrete TSH. The mechanism of hyponatremia at the time of adrenal crisis in this case was also discussed.

Case Report

A 46 years old man was admitted to Aizenbashi Hospital in Osaka on September 4, 1970, because of coma. Physical examination at Aizenbashi Hospital revealed that his body weight was 52 kg and height was 162 cm. Blood pressure was 110/90 mmHg. Pulse rate was 100/min and regular. Body temperature was 37.1°C. The skin was pale and dry. The fine wrinklins of skin were noted on the face and hands. There was no axillary hair. The scanty and fine hairs were seen only in the lower portion of the pubic area. There was thinning of outer half part of eyebrows. The penis size was normal, but testicles were soft and atrophic. The thyroid tissue was not palpable. The heart and lungs were within normal limits. No edema of lower extremities was noted. Blood sugar determined by Dextrostix (Ames) was 0 to 45 mg/100 ml. The

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administration of 20 ml of 50% glucose solution did not result in any improvement. Since it was considered from his past history that he might have posttraumatic hypopituitarism, 100 mg of hydrocortisone sodium succinate (Solu-Cortef) was administered intravenously. Fifteen minutes later he began to respond to physician's call.

Twenty-six years previously, his head was jammed between lathe and drill machine accidentally. There was massive bleeding from ears, nose and mouth and he remained unconscious for 33 days. Subsequently, he noticed complete lack of energy, loss of libido and impotency. He had been complaining of marked weakness since then. Diplopia also occurred but disappeared two months later. His beard, breast hair, axillary hair and pubic hair fell out within six months. Spells of hyperpyrexia (above 40°C), nausea, vomiting and diarrhea occurred with intervals of about a month. The hyperpyrexia subsided ten years later but nausea, vomiting and diarrhea occurred occasionally. Two or three years later, cold intolerance and constipation developed. His family perceived his personality changes such as mental dullness and depressive mood. There was no polydipsia or polyuria.

Five years after the accident, he was admitted to Kyoto Prefectural University Hospital and diagnosed as hypopituitarism. A bovine pituitary gland was embedded in his abdominal wall. He felt some improvement, but its effect lasted only three to six months. The second bovine pituitary embedding was performed three years later, but it was not contributory. Then, he had been seen by a general practitioner for more than ten years. Some preparations of sex hormones were administered once a month, but these were also not helpful. Although he used to stay at home, he began to go to concert every third day from two weeks before admission. Five days prior to admission, he could not go to the concert because of marked weakness, nausea and epigastric pain. Because of nausea and

epigastric pain, he could not eat and drink anything from two days before admission. A dose of 400 ml of plasmanate was given daily by the general practitioner in these two days. Two days prior to admission he vomitted once, but there was no diarrhea. While the frequency of urination was usually two times daily and urinary volume was low, there was no urinary voidance in these two days. His condition getting worse and on the morning of admission, he seemed stuporous and could not make any reply to his families.

He was referred to Osaka City University Hospital on September 12, 1970. Hypopituitarism was confirmed and he was well controlled with the maintenance dose of cortisone acetate 18.5 mg/day and dessicated thyroid 40 mg/day. Therapy using sexual hormone was not instituted because of his family's opposition. He was discharged on November 11, 1970 and was readmitted for further endocrinological studies in June, 1971.

Electrocardiogram showed low voltage. No abnormalities of skull and sella turtica were found on skull X-ray. Pneumoencephalography and internal carotid artery angiography showed no abnormalities either. Liver function test was within normal range, and the creatinine clearance was 50.7 ml/min.

Laboratory Data

On admission the laboratory data revealed that, hemoglobin concentration was 10.6 g/100 ml, red blood cells were 3.16 million/mm³, white blood cells were 3,700/mm³, blood urea nitrogen was 15 mg/100 ml, total protein was 7.0 g/100 ml and total cholesterol was 144 mg/100 ml.

As cited in Table 1, there was prominent hyponatremia on admission. 400 ml of fresh blood was administered in the emergency room. A dose of 1,500 ml of low sodium electrolytes solution was administered daily with hydrocortisone succinate 200 mg on the first hospital day and 150 mg on the second

Table 1. Serum electrolytes and urinary volume changes

Date	Serum Na mEq/L	Serum K mEq/L	Serum Cl mEq/L	Urinary Volume ml	Volume and Na mEq/L	Volume and K mEq/L	Volume and Cl mEq/L	Treatment
Sept. 4, 1970. (on admission)	115	4.1	*	*	*	*	*	400 ml of fresh blood 1500 ml of electrolytes solution** 200 mg of hydrocortisone
Sept. 5.	110.5	4.0	85.9	900	*	*	*	1500 ml of electrolytes solution** 150 mg of hydrocortisone
Sept. 6.	*	*	*	1300	*	*	*	500 ml of electrolytes solution*** 1000 ml of Ringer's solution 40 mg of hydrocortisone
Sept. 7.	108	4.0	97.5	2250	20	39	70	500 ml of electrolytes solution** 500 ml of Ringer's solution 40 mg of hydrocortisone 5 mg of desoxycorticosterone [#]
Sept. 8.	128	3.5	110	1750	20	17	70	500 ml of Ringer's solution 40 mg of hydrocortisone 5 mg of desoxycorticosterone
Sept. 9.	135	3.9	110	500	47	40	126	500 ml of Ringer's solution 40 mg of hydrocortisone 5 mg of desoxycorticosterone

* not available.

** Electrolytes solution contains 35 mEq/L of sodium, 35 mEq/L of chloride, 20 mEq/L of potassium and 7.5% of glucose.

*** Electrolytes solution contains 90 mEq/L of sodium, 70 mEq/L of chloride and 2.6% of glucose.

[#] The administration of deoxycorticosterone was started in this evening.

hospital day. Serum sodium level was 110.5 mEq/L, potassium 4.0 mEq/L and chloride 85.9 mEq/L on the second hospital day. The urinary output on the second day was 900 ml. On the third day 500 ml of electrolytes solution (sodium 90 mEq/L, chloride 70 mEq/L) and Ringer's solution was administered with 40 mg of hydrocortisone. Urinary output of the third day was 1,300 ml. On the fourth morning marked hyponatremia persisted. On the fourth day 500 ml of electrolytes solution and 500 ml of Ringer's solution was infused with 40 mg of hydrocortisone. The urinary output of the fourth day increased to 2,250 ml. Urinary sodium concentration was 20 mEq/L, chloride 70 mEq/L and potassium 39 mEq/L. A dose of 5 mg of deoxycorticosterone (DOCA) was administered in this evening. The serum electrolytes levels were improved in the next morning (Table 1). On the fifth day he was given 500 ml of Ringer's solution with 40 mg of hydrocortisone and

5 mg of DOCA. Urinary output of the fifth day was 1,750 ml and there was decrease of urinary potassium excretion rather than increase compared with the urine of fourth day. Serum electrolytes levels returned to normal levels on the next day (Table 1). A dose of 5 mg of DOCA was administered daily for five successive days. No serum electrolytes abnormalities were appeared.

Pituitary Function Studies

Blood pituitary hormones-ACTH, GH, TSH and LH were determined by radioimmunoassay. These assay methods were as follows; ACTH by the method of Matsukura *et al.* (1971), GH by the method of Utiger *et al.* (1962), TSH by the method of Odell *et al.* (1965) and LH by the method of Odell *et al.* (1967).

Twenty-four hours prior to plasma ACTH

Table 2. GH levels in response to insulin and arginine administration

Min	Insulin 0.1 U/kg I.V.		Insulin 0.05 U/kg I.V.		*Arginine (10%) 250ml I.V.	
	Blood Sugar mg/100ml	[HGH] m μ g/ml	Blood Sugar mg/100ml	HGH m μ g/ml	Blood Sugar mg/100ml	HGH m μ g/ml
0	80	0.8	65	1.9	70	1.0
30	15	0.8	43	1.0	95	0.8
60	*	*	53	0.9	67	1.9
120			85	1.0	80	1.2

* The test was discontinued because of hypoglycemic shock.

* The infusion was performed during the period of 30 min.

measurement, maintenance dose of 18.5 mg of cortisone acetate was withdrawn. Blood samples for plasma ACTH were taken at 8 AM and 10 AM the morning following the midnight metyrapone administration with a dose of 30 mg/kg. Control blood sample was drawn at 8 AM on the previous day.

Plasma ACTH levels were not detectable in all these samples (below 10 pg/ml). Plasma cortisol levels of the same samples, determined by competitive protein binding assay (Murphy, 1967), were not detectable. Base-line serum GH level was low and failed to increase in response of L-arginine administration and

in euthyroid state (Table 2). Blood samples for serum TSH determination were drawn before and 30 min and 60 min after the intravenous administration of 0.5 mg of synthetic thyrotropin releasing hormone (TRH). Serum TSH levels increased in response to TRH administration, but these increments were significantly reduced compared with those of normal subjects (Fig. 1, Table 3). Serum LH levels obtained from the same blood samples were low (Table 3).

Adrenal Function Studies

Rapid ACTH Test: At 11 PM dexamethasone, 1 mg, was administered to suppress endogenous ACTH secretion and at 9 AM in the next morning control blood sample was drawn. Immediately after control blood was drawn, 0.25 mg of synthetic ACTH (Cortrosin) was administered intravenously. One hour after synthetic ACTH administration the second blood sample was obtained. The plasma cortisol for control was 4.8 μ g/100 ml and 6.0 μ g/100 ml after ACTH administration.

Oleesky water excretion test (Oleesky, 1953) showed marked impairment of water diuresis. The maximum rate of urine flow was below 2 ml/min. With the administration of 1.5 mg of dexamethasone four hours prior to Oleesky test the maximum rate of urine flow increased to 7.1 ml/min. Serum sodium was 145.5 mEq/L, potassium 4.6 mEq/L and

Fig. 1. Serum TSH response to synthetic TRH administration.

Table 3. TSH and LH response to synthetic TRH* administration

		TSH $\mu\text{U/ml}$	LH mIU/ml
Min	patient	normal subjects (n = 9) Mean $\pm$ SEM	patient normal range (5-15 mIU/ml)
0	3.1	1.72 $\pm$ 0.9	1.9
30	7.9	20.5 $\pm$ 2.5	0.3
60	7.1	13.1 $\pm$ 2.3	3.6

* 0.5 mg of synthetic thyrotropin releasing hormone was administered intravenously.

chloride 97 mEq/L in Oleesky test. Urine osmolarity was 584 mOsm/L before water loading and it was 96 mOsm/L in the period of maximum rate of urine flow with dexamethasone administration.

The 100 g oral glucose tolerance test revealed low flat curve even a month after he was treated with cortisone acetate: fasting blood sugar 75 mg/100 ml, 63 mg/100 ml at 30 min, 68 mg/100 ml at 60 min, 62 mg/100 ml at 90 min, 66 mg/100 ml at 120 min and 52 mg/100 ml at 180 min.

Thyroid Function Studies

Basal metabolic rate was -30.5% , T_3 -resin sponge uptake was 24.5% and T_4 (Tetrasorb) was $2.7 \mu\text{g}/100 \text{ ml}$. The 24 hr thyroid radioiodine uptake was 2.6% . After the administration of bovine thyrotropin (Thytropar) in a dose of 5 units daily for three days, the 24 hr thyroid radioiodine uptake increased to 12% .

Discussion

The reports of posttraumatic hypopituitarism are rare. To our present knowledge, only twenty-four cases have been reported in the literature. Altman & Pruzanski (1961) reviewed fifteen cases of posttraumatic hypopituitarism including his own case. Addi-

tional nine cases have been reported to date (Goldman and Jacobs, 1960; Werner, 1960; Gennes *et al.*, 1963; Kupperman, 1963; Linquette *et al.*, 1968; Mäkelä and Oka, 1968; Fontaine *et al.*, 1969; Kubachi and Krzyżowski, 1970; Pittman *et al.*, 1971). In most cases of these patients reported in their literature, the severity of the trauma and the damage to the gland and the pituitary stalk were not sufficient to cause death. Our patient also survived after coma of 33 days duration.

Recent advances of radioimmunoassay methods enable us to perform direct determination of blood pituitary hormones such as ACTH, GH, TSH and LH. In this case the deficiency of ACTH, GH and TSH was proved by radioimmunoassay. LH deficiency was also very probable from the clinical symptoms and low resting level of LH as was elicited by radioimmunoassay. There was no GH release by the administration of L-arginine or insulin induced hypoglycemia. Because of severe hypoglycemic symptoms in the initial insulin administration, the dose of regular insulin to elicit hypoglycemia was reduced to 0.05 U/kg in the second GH releasing test. The hypoglycemia with this dose was mild, but it seemed probably sufficient to release GH (Glick, 1970). Although the response was subnormal, serum TSH levels were increased in response to synthetic TRH administration. This suggests that the traumatic lesion may be located at the level of hypothalamus or upper hypothalamo-pituitary tract. Pittman *et al.* (1971) supposed their patient as hypothalamic hypothyroidism, who had hypothyroidism and undetectable serum TSH levels, with a normal response to TRH. Daniel *et al.* (1959) proposed that if the section level of pituitary stalk by trauma was above the site of entry of the hypophyseal arteries into the stalk, there was no pituitary necrosis. They also found that the section at a lower level of pituitary stalk caused necrosis of the central portion of the anterior lobe, while a small area adjacent to the posterior lobe, supplied by short hypophyseal portal vessels, usually survived. So

the possibility that the synthetic TRH fully stimulated the reservoir of remnant anterior pituitary gland should also be taken into consideration.

Although hyponatremia in hypopituitary patients is by no means uncommon, the mechanism of its development remains incompletely clarified and these patients have usually associated stressful situations (Bethune and Nelson, 1965). In this case no remarkable stress was found such as trauma or infection, but it was stressful enough for him to go out so often in summer.

Although available clinical data is insufficient to discuss the mechanism of hyponatremia, it is supposed that the effective plasma flow has been decreased at the time of adrenal crisis, probably due to dehydration. Share and Travis (1970) demonstrated that the plasma ADH concentration can rise in adrenal insufficiency and this effect appears to be the consequence of a reduction in blood volume, rather than the lack of a direct inhibitory action of the glucocorticoids on the secretion of ADH. Bethune and Nelson (1965) concluded that in three of the five patients of hypopituitarism the mechanism of hyponatremia seemed due entirely to water retention and the other two patients this mechanism was mainly responsible for the decreased serum sodium, but an abnormal urinary sodium loss also contributed. In this patient, it was uncertain whether there was abnormal urinary sodium loss or not. There was no urinary output from two days before admission. It may have been merely due to dehydration, but there was also such a possibility that increased secretion of ADH may have induced this condition. Since the administration of hypotonic solution in the first two hospital days may have been not only improper to correct the low plasma osmolarity but insufficient to increase the effective plasma flow, hyponatremia deteriorated and diuresis did not occur during this period. The ineffectiveness of glucocorticoids administration to correct hyponatremia in this case may be

partly explained as Share and Travis (1970) claimed in their experiments that glucocorticoids had no effect to reduce the elevated ADH level when the effective blood volume was reduced in adrenal insufficiency. Though the changes of urinary electrolytes excretion were equivocal, serum electrolytes levels were corrected after the administration of DOCA. The administration of DOCA may have played a role in correcting the hyponatremia. Williams *et al.* (1971) reported the abnormal aldosterone response to sodium restriction and ACTH stimulation in hypopituitarism. They pointed out an important role of the pituitary gland in the normal control of aldosterone and suggested a possible mechanism for the hyponatremia found in some hypopituitary patients. Unfortunately, aldosterone assays were not performed so that it is not possible to discuss whether aldosterone was related to the hyponatremia of this patient.

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