Secondary Adrenal Insufficiency Caused by Adult Development of Pituitary Stalk Transection

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Abstract

We report the case of a 38-year-old man with secondary adrenal insufficiency due to pituitary stalk transection that may have been caused by birth injury. He was admitted to our hospital with epigastralgia and severe hyponatremia (120 mEq/L). His past history showed fetal distress due to an abnormal delivery, and he received growth hormone replacement therapy for growth hormone-deficient short stature. Magnetic resonance imaging of the brain revealed an atrophic anterior lobe, a pseudo-posterior lobe of the pituitary gland, and a transection of the pituitary stalk. Endocrinological examination revealed secondary adrenal insufficiency due to a suprapituitary lesion, with concomitant impaired secretion of growth hormone, gonadotropins, and thyroid-stimulating hormone. Hyponatremia was improved immediately after administration of hydrocortisone. This is a case of adult development of pituitary stalk transection syndrome, involving the sequential impairment of the secretion of several pituitary hormones, and finally presenting severe hyponatremia caused by secondary adrenal insufficiency.

Key words: pituitary stalk transection syndrome, hyponatremia, adrenal insufficiency, hypopituitarism

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Introduction

Patients with growth hormone deficient short stature who have a past history of abnormal delivery at birth rarely show an atrophic anterior lobe of the pituitary gland, formation of a pseudo-posterior lobe instead of the posterior lobe, and transection of the pituitary stalk on brain magnetic resonance imaging (MRI) (1). Such patients are sometimes affected by insufficiencies of not only GH, but also several other pituitary hormones in later life, a situation collectively referred to as “pituitary stalk transection syndrome” (2). Patients with this syndrome have been reported to present sequential impairment of multiple pituitary hormones, and may suffer from adrenal insufficiency as adults, because ACTH deficiency is the last to develop.

Here, we report an adult patient presenting with severe hyponatremia due to secondary adrenal insufficiency, which was highly suspected to be due to pituitary stalk transection syndrome.

Case Report

A 38-year-old man with persistent epigastric pain and diarrhea was admitted to our hospital because of severe hyponatremia (120 mEq/L). On physical examination, the patient appeared pale. His blood pressure was 102/66 mmHg, the pulse 64 beats per minute, and the body temperature was 36.4°C. There was mild epigastric tenderness, but the abdomen was soft and nondistended with normal active bowel sounds. No pigmentation was evident in the skin and oral cavity. He had normal pubic, axial, and facial hair, but small testes, and complained of decreased libido. Laboratory examination showed mild anemia, extremely low levels of serum sodium (117 mEq/L) and osmolarity (242.37 mOsm/kgH2O), and elevation of creatine kinase (2330 U/L) with a predominant component of the CK-MM isozyme (Table 1). Electrocardiography revealed a negative T wave in chest leads (V1-V3).

His past history revealed fetal distress and torticollis due to breech presentation at birth. At the age of 9 years, he showed growth retardation (height 118 cm, -3.6 SD), and
was diagnosed as having growth hormone deficient short stature. He received growth hormone replacement therapy until the age of 18 years, and attained a final height of 171.8 cm. At 16 years of age, he was also found to have hypothyroidism and hypogonadism due to an insufficiency of TSH and gonadotropin responses, and was started on L-thyroxine and testosterone replacement therapy. The basal values of ACTH and cortisol were normal at that time. Hydrocortisone replacement therapy was not started, because his ACTH and cortisol values were recognized as within the normal level. He had been followed at a nearby clinic for the past several years, but his adherence to drug treatment was not good.

On suspicion of adrenal insufficiency, hydrocortisone (100 mg) was immediately administered intravenously after admission, followed by continuous infusion of saline (1.5 L). In response, the serum sodium level rapidly increased (132 mEq/L) and the abdominal symptoms disappeared on the following day. On the third day, transient delirium developed, but disappeared within a few days.

Endocrinological examination showed very low levels of GH, LH, and FSH. The levels of thyroid hormones, testosterone, and cortisol, as well as urinary excretion of free cortisol, 17-OHCS and 17-KS, were also low. Plasma ADH concentration was inappropriately high in contrast to serum osmolarity (Table 2). Evaluation of the function of the hypothalamic-pituitary-adrenal (HPA) axis (Fig. 1) showed a normal response of ACTH and low response of cortisol to exogenous CRH (100 μg). The rapid ACTH test showed a cortisol response from 0.52 μg/dl to 6.70 μg/dl, compatible with secondary adrenal insufficiency. The insulin tolerance test (regular insulin 0.05 U/kg body weight) produced no response by ACTH and cortisol. Plasma ACTH was measured by an immunoradiometric assay (ACTH IRMA Mitsubishi, Mitsubishi, 1986).
Figure 1. Endocrine examination of hypothalamic-pituitary-adrenal axis. a) CRH loading test (100 μg), b) Insulin tolerance test (0.05 U/kg weight), c) Rapid ACTH test (250 μg): plasma ACTH (●), cortisol (○), GH (□), plasma glucose (■).

Figure 2. Stimulation with a) GRH (100 μg); b) LHRH (100 μg); c) TRH (100 μg): b) LH (●), FSH (○), c) TSH (●), PRL (○).

Mitsubishi Chemical, Tokyo, Japan). Plasma and urinary cortisol were measured by a radioimmunometric assay (cortisol kit, TFB, Tokyo, Japan). After stimulation with GRH (100 μg), TRH (100 μg), and LHRH (100 μg), GH, LH, and FSH showed low and delayed responses, and TSH as well as prolactin showed mostly normal but slightly delayed responses (Fig. 2). Brain MRI showed the presence of an atrophic anterior lobe, and pseudo-posterior lobe in the infundibulum, and transection of the pituitary stalk (Fig. 3). Testicular biopsy showed irreversible aspermatogenesis.

As the result of the evaluation of these endocrinological and characteristic MRI findings, we diagnosed the patient as having secondary adrenal insufficiency due to pituitary stalk transection syndrome caused by the abnormal delivery at birth. He was placed on a maintenance regimen of replacement therapy (20 mg hydrocortisone, 100 μg L-thyroxine daily, and testosterone enantate 250 mg twice per month) and discharged from hospital.

Discussion

Pituitary stalk transection syndrome is defined as a hypopituitarism with some grade of insufficiency of several pituitary hormones caused by the transection (or disappearance) of the pituitary stalk, accompanied by atrophy of the anterior lobe and formation of a pseudo-posterior lobe of the pituitary gland. Transection of the pituitary stalk occurs mainly during an abnormal delivery, namely the fixed head of the fetus and breech presentation due to small maternal pelvis induces traction and transection of the pituitary stalk, but rarely the brain trauma such as that which would result, for example, from a traffic accident (3).
Hypothalamic hypopituitarism may develop because transection of the pituitary stalk leads to an impaired transport of hypothalamic hormones and nutrients through the hypothalamic portal system. In the present case, diabetes insipidus had not developed in the presence of a pseudo-posterior lobe, because vasopressin secretion is preserved from the transected part of the stalk. On the other hand, patients without a pseudo-posterior lobe often develop diabetes insipidus due to autolysis of vasopressin-producing cells (4).

The present case showed ACTH secretion in response to the CRH test, while there was no response to the insulin tolerance test, leading to the diagnosis of hypothalamic adrenal insufficiency complicated by other pituitary hormone insufficiencies. Hyponatremia and the abdominal symptoms improved quickly after the administration of hydrocortisone, but transient delirium appeared, presumably due to rapid improvement of hyponatremia, while central pontine myelolysis was denied by brain MRI.

The present case demonstrates the sequential impairment of the secretion of multiple pituitary hormones. Initially, the patient suffered GH insufficiency that developed slowly during infancy, followed by insufficiencies of gonadotropins and TSH during childhood, and finally ACTH insufficiency in later adulthood, while prolactin secretion was reserved. Although the sequential insufficiency of the secretion of multiple pituitary hormones as observed in this case could represent the typical clinical course of pituitary stalk transection syndrome, the severity and the age of development may differ from case by case.

The exact mechanism by which a hypopituitarism develops slowly despite stalk transection remains controversial. In most cases, GH insufficiency develops first, probably because GRH-containing neurons in the arcuate nuclei are the most likely to be affected by stalk transection, whereas the prolactin level is elevated due to the lack of hypothalamic tonic inhibitor. On the other hand, TSH secretion is generally maintained during infancy, presumably due to the vascularized anterior lobe to some extent by the arterial system, but it gradually decreases during childhood and puberty. Indeed, on brain MRI obtained by the turbo-FLASH method using Gd-DTPA, the anterior lobes of such patients are enhanced during the arterial phase (5). In general, hypogonadism also appears until puberty.

Compared with other pituitary hormones, ACTH deficiency may develop last. Miyamoto et al (6) reported that 24% of patients under the age of 10 years old and 56% under 25 years old with this syndrome show a maximal cortisol level below 15 μg/dl in response to the insulin tolerance tests. Furthermore, Martin et al reported (7) that 44% of adult patients diagnosed with idiopathic GH insufficiency during childhood show decreased cortisol responses to the insulin tolerance tests. These results suggest that pituitary stalk transection syndrome exists latently in patients diagnosed with idiopathic GH insufficiency, and that they have the potential risk of secondary adrenal insufficiency in adulthood, such as in the present case.

In conclusion, the present case of pituitary stalk transection syndrome, initially diagnosed as growth hormone-deficient short stature, later developed sequential insufficiency of several other pituitary hormones, and finally, ACTH deficiency in adulthood. Thus, patients with this syndrome require life-long follow-up due to the possible risk of developing secondary adrenal insufficiency even in adulthood.

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