INTERNAL MEDICINE

□ CASE REPORT □

Isolated Adrenocorticotropic Hormone Deficiency Following Chronic Subdural Hematoma in an Elderly Man: Is There a Connection?

Satoshi Suzuki and Keiko Suzuki

Abstract

The delayed diagnosis of adrenal insufficiency is relatively common because its symptoms are non-specific. One of the causes of adrenal insufficiency is isolated adrenocorticotropic hormone deficiency (IAD), which is sometimes caused by traumatic brain injury. Indeed, severe head trauma is considered to contribute to the incidence of this disease. However, the relationship between milder head trauma—such as chronic subdural hematoma — and the occurrence of hormonal deficiency is uncertain. We herein report the case of a 79-year-old man with IAD who presented with leg edema and pain in his extremities following a recent history of chronic subdural hematoma.

Key words: isolated adrenocorticotropic hormone deficiency, hypopituitarism, chronic subdural hematoma, traumatic brain injury

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Introduction

Adult-onset adrenal insufficiency is difficult to diagnose due to its non-specific symptoms; thus, the diagnosis is often delayed (1). Recently, an increasing number of studies have focused on isolated adrenocorticotropic hormone deficiency (IAD), which is assumed to be a sequela of the autoimmune process and brain injury (2-5). Moreover, several investigators have noted that hypopituitarism often occurs following traumatic brain injury (TBI) (5). Specifically, several studies on this subject have shown that the prevalence of hypopituitarism in severely injured patients was greater than that in patients with mild or moderate injury, and that most types of hormonal deficiency were isolated forms (4). On the contrary, other studies have reported that the occurrence of hypopituitarism does not depend on severity of TBI (6).

To our knowledge, no cohort studies or case reports have described chronic subdural hematoma-associated hypopituitarism. We herein report the case of an IAD patient with a history of surgical evacuation for chronic subdural hematoma who presented with non-specific symptoms beginning with leg edema and myalgia in his extremities.

Case Report

A 79-year-old man was admitted to the Department of General Internal Medicine of our hospital with leg edema and painful extremities. He had received percutaneous coronary intervention for angina pectoris 10 years prior to this presentation and had since attended regular follow-up appointments at our hospital's Cardiovascular Department. He regularly took aspirin, pravastatin, nifedipine, ambroxol hydrochloride, and isosorbide dinitrate via a transdermal patch. He suffered a laceration of the occipital scalp due to fall in a house 11 months prior to his presentation. At the time of the injury, he had no consciousness disturbance; however, there was a significant amount of bleeding from the scalp surface. He was transferred to a hospital and underwent a hemostatic procedure. A brain CT scan showed no signs of skull fracture or brain contusion at that time. One month later, when he visited the hospital for a follow-up CT scan, he experienced a slight difficulty in walking and a chronic

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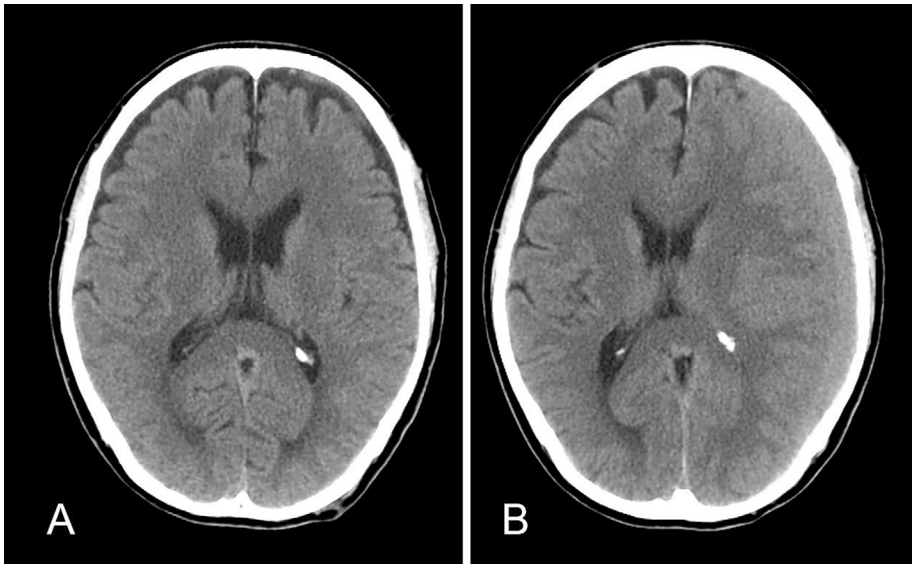

Figure 1. Brain CT scan. A: A CT image at the time of initial head trauma showed neither skull fracture nor brain contusion. B: An image 1 month after the initial head trauma showed isodense crescent-shaped hematoma on the surface of the left brain cortex, accompanied by slight midline shift to the opposite side.

subdural hematoma was found in the left hemisphere (Fig. 1). Surgical hematoma evacuation was performed twice within 2 months due to recurrence. He had no symptoms after the second surgery. One month prior to his presentation, he took a 3-day trip to play golf, which involved taking domestic flights; after the trip, he noticed edema in his lower extremities. Additionally, he gradually began to feel pain in his shoulders, elbows, and thighs and numbness in the third and fourth fingers of his right hand. Two weeks prior to his presentation, he visited an orthopedist who prescribed an herbal medicine; however, his symptoms did not improve. On the day of presentation, he found that his blood pressure was lower than usual using a home blood pressure device and visited the attending cardiologist. The doctor believed that his existing heart disease did not explain his hypotension and referred him to the Department of General Internal Medicine.

On examination, his blood pressure was 78/37 mmHg, his pulse rate was 67 beats/min and regular, and his body temperature was 36.6℃. A physical examination, revealed proximal gripping myalgia in all extremities as well as in the plantars, muscular tenderness near the lower edge of the right scapula, and bilateral pitting edema on both legs. Auscultation revealed a systolic ejection murmur at the apex of the heart. Arthralgia was not detected. The remainder of the examination was normal.

The results of the laboratory tests (Table 1) were as follows: WBC count, 5,600/μL with 7.7% eosinophils (reference range 0.2-6.8%), Hb 12.5 g/dL; platelet count, 16.0×10^4/μL; sodium, 139 mEq/L; potassium, 3.7 mEq/L (no other electrolyte abnormalities were observed); blood urea nitrogen, 14.6 mg/dL, creatinine, 1.00 mg/dL; fasting plasma glucose (FPG), 79 mg/dL; erythrocyte sedimentation rate (ESR), 22 mm/h; C-reactive protein (CRP), 2.20 mg/dL; and thyroid-stimulating hormone (TSH), 3.36 μIU/mL (reference range 0.5-5.0 μIU/mL). As a result, he was admitted to our hospital.

Nifedipine was stopped following admission due to possible side effects such as edema and severe hypotension. Although we suspected rheumatic disorders such as polymyalgia rheumatica or remitting seronegative symmetrical synovitis with pitting edema, the patient's symptoms improved with bed rest alone and his CRP decreased to the normal value within a few days. This ruled out rheumatic disorders as bed rest alone cannot improve the symptoms. Nevertheless, the patient's low blood pressure, low FPG (60-80 mg/dL), and low-grade eosinophilia (7.7-12.8%) persisted, and his symptoms deteriorated after he temporarily left the hospital and returned home.

We suspected hypoadrenalism. An adrenal function test revealed the following: adrenocorticotropic hormone (ACTH), <1.0 pg/mL; serum cortisol, <0.2 μg/dL; and plasma aldosterone, 28.3 ng/dL (reference range 3.6-24.0 ng/dL). The basal values of the other pituitary hormones and insulin growth factor-1 were normal or slightly elevated (Table 1). Brain magnetic resonance imaging revealed that the pituitary gland was normal in size and shape, the intensity of the posterior lobe was as high that which is normally observed, and regular enhancement was observed with contrast medium. No stalk thickening or empty-sella was detected (Fig. 2). A corticotropin-releasing hormone (CRH) test showed an inadequate ACTH/cortisol response (Table 2) and there was no response to a 250-μg ACTH stimulation test (Table 3). Tests for anti-pituitary antibody-1 and anti-thyroid autoantibodies were negative.

We diagnosed the patient with isolated ACTH deficiency

Table 1. Laboratory Findings on Admission.

Variables	Value	Reference range
White cell count (/μL)	5,600	3,300–9,000
Differential count		
Neutrophils (%)	48.0	40.0–71.9
Eosinophils (%)	7.7	0.2–6.8
Basophils (%)	0.2	0–1.0
Monocytes (%)	9.3	2.3–7.7
Lymphocytes (%)	34.8	26.0–46.6
Red cell count ($\times10^6$/μL)	4.19×10^6	4.00–5.40
Hemoglobin (g/dL)	12.5	13.0–17.0
Hematocrit (%)	36.8	40.0–50.0
Platelet count ($\times10^4$/μL)	16.0	15.0–35.0
Sodium (mEq/L)	139	135–147
Potassium (mEq/L)	3.7	3.4–4.4
Chloride (mEq/L)	106	99–112
Urea nitrogen (mg/dL)	14.6	8.0–22.0
Creatinine (mg/dL)	1.00	0.6–1.2
Total protein (g/dL)	6.1	5.8–8.1
Albumin (g/dL)	3.6	3.9–4.9
Total bilirubin (mg/dL)	1.3	0.2–1.2
Aspartate aminotransferase (IU/L)	32	7–38
Alanine aminotransferase (IU/L)	17	4–43
Lactate dehydrogenase (IU/L)	202	101–202
Glucose (mg/dL)	79	80–110
Erythrocyte sedimentation rate (mm/h)	22	2–10
C-reactive protein	2.20	0–0.30
Thyroid-stimulating hormone (μIU/mL)	3.36	0.5–5.0
Adrenocorticotropic hormone (pg/mL)	1.0	7.2–63.3
Growth hormone (ng/dL)	1.90	<0.13
Luteinizing hormone (mIU/mL)	8.7	0.8–5.7
Follicle stimulating hormone (mIU/mL)	10.2	2.0–8.3
Prolactin (ng/mL)	25.5	3.6–12.8
Anti-diuretic hormone (pg/mL)	2.7	<4.2
Free triiodothyronine (pg/mL)	3.14	2.3–4.0
Free thyroxine (ng/dL)	0.87	0.9–1.7
Cortisol (μg/dL)	<0.2	4.5–21.1
Aldosterone (ng/dL)	28.3	3.0–15.9
Insulin-like growth factor-1 (ng/mL)	58	48–177

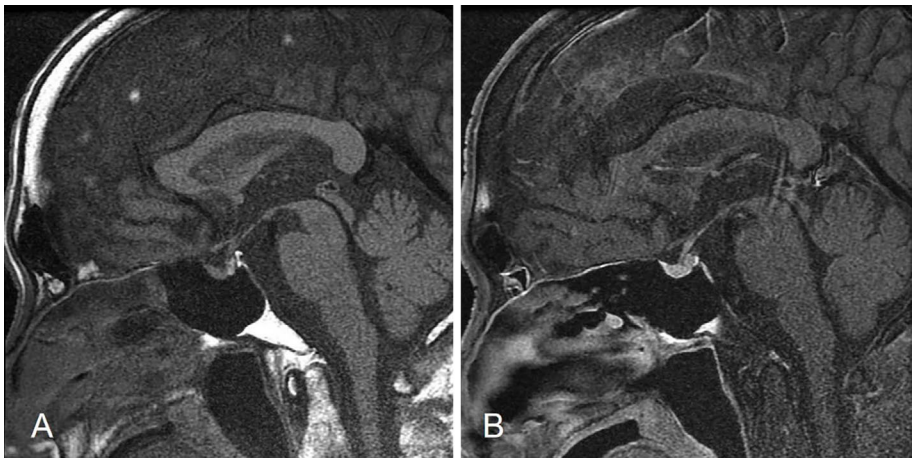

Figure 2. Pituitary MRI. A: T1WI image showed pituitary gland normal in size and shape, normally with a high intensity of the posterior lobe. B: Gadorinium enhancement image revealed homogenously enhanced pituitary gland.

Table 2. **Responses of CRH Stimulation Test.**

Variables	Basal	30 min	60 min	90 min	120 min
ACTH (pg/mL)	<1.0	<1.0	1.1	1.1	1.4
Cortisol (μg/dL)	0.6	0.5	0.4	0.5	0.5
Glucose (mg/dL)	72	70	71	73	74

CRH: corticotropin releasing hormone, ACTH: adrenocorticotropic hormone

Table 3. **Responses of 250 μg ACTH Stimulation Test.**

Variables	Basal	30 min	60 min	90 min
Cortisol (μg/dL)	<0.2	0.8	1.2	1.4
Glucose (mg/dL)	60	64	59	57

ACTH: adrenocorticotropic hormone

and started hydrocortisone (15 mg daily) treatment. Thereafter, the patient's blood pressure returned to normal (110/70 mmHg), his FPG increased to around 100 mg/dL the following day, and his symptoms gradually resolved. At three months after the initiation of glucocorticoid replacement therapy, he had made a complete recovery and could play golf as usual. A year after the initiation of hormone replacement therapy, the basal values of the other pituitary hormones were close to the normal range: TSH, 2.84 μIU/mL; GH, 0.04 ng/mL; luteinizing hormone (LH), 7.0 mIU/mL; follice stimulating hormone (FSH), 20.0 mIU/mL; and prolactin, 14.1 ng/mL.

Discussion

The incidence of IAD in adult patients is not well understood due to its rarity (7). A single Japanese cohort study estimated its prevalence at 3.8-7.3 per 100,000 (8). Between 1969 and 1994, more than 300 cases were reported in Japan; thus, IAD may not be as rare as indicated by the scarcity of literature (9). It is thought that the disease mostly affects elderly men (9).

Adult-onset IAD generally has an autoimmune etiology, as shown by its frequent association with other autoimmune endocrine disorders such as thyroiditis (2). Post-traumatic hypopituitarism was observed in 27.5-42.7% of patients with a history of TBI, presenting as an isolated deficiency in most cases (3-5). Growth hormone (GH) deficiency was the most prevalent type (pooled prevalence 30.1%), followed by gonadotropin and ACTH deficiency (28.8% and 18.5%, respectively) (4). Another study reported that the prevalence of hypopituitarism at 3 months after TBI was 56%, dropping to 36% at the 12-month follow-up examinations of those patients (10), indicating the spontaneous recovery of the pituitary function in some patients.

The pathophysiology of hypopituitarism after TBI is not completely understood. Aside from direct damage to the pituitary gland, several factors associated with TBI have been suggested to contribute to hypopituitarism, including vascular damage, hypotension, hypoxia, and brain swelling. However, recent research has indicated a possible role of autoimmunity in the development of post-traumatic hypopituitarism (3). Severe TBI has been suggested as a risk factor for post-traumatic hypopituitarism (5); however, other investigators did not find any association between injury severity and the prevalence of hypopituitarism (6).

Our patient had a history of chronic subdural hematoma, which occurred as a complication after a relatively mild traumatic head injury. Hána et al. investigated the relationship between chronic subdural hematoma and hypopituitarism in 59 patients after the evacuation of subdural hematoma (11): in the acute phase, approximately 50% of the patients presented with GH deficiency and 26% presented with hypogonadism; however, in the majority of cases, the symptoms resolved within 1 year. Transient partial hypocortisolism was present in two cases, but their symptoms soon resolved. The authors concluded that hormonal deficits of the pituitary gland in chronic subdural hematoma cases were less frequent in comparison to TBI cases (11).

A delayed diagnosis is common in patients with adrenal insufficiency, regardless of whether its cause is primary or secondary, due to its non-specific symptoms. Fatigue, which is the most common symptom, is seen in 73% of cases. Other common symptoms include weight loss, hypotension, loss of appetite, headache, and the loss of axillary and pubic hair; the prevalence of these symptoms ranges from 30 to 45% (1). The incidence of musculoskeletal symptoms has been reported to be 31% and 6-13% (1, 12); these musculoskeletal symptoms include myalgia, arthralgia, joint stiffness, muscle cramps, and flexion contracture (13, 14). To date, more than two-thirds of patients with adrenal insufficiency are diagnosed incorrectly, with psychiatric and gastrointestinal disorders being the most common incorrect diagnoses (1); rheumatic and neuromuscular diseases are the differential diagnoses in patients with musculoskeletal symptoms (13).

Our patient presented with sudden-onset symptoms after his trip; however, the results of the 250-μg ACTH stimulation test suggested that the atrophy of the adrenal cortex occurred after a certain period of time without adequate stimulation by ACTH (15). This was probably because adrenal insufficiency develops slowly over months and patients may not notice the physical changes at its onset unless they suffer from an acute adrenal crisis (1).

We did not perform other stimulation tests for GH, LH, FSH, TSH, or prolactin, thus limiting the diagnosis in our present case. GH and TSH abnormalities have been reported to occur in association with IAD; however, these abnormalities improved after the initiation of corticosteroid replacement (16). With the exception of prolactin, which approximately twice the upper normal limit, the other pituitary hormones were not suppressed: they were either normal (TSH, fT_4, fT_3, and insulin-like growth factor (IGF)-1) or slightly elevated (GH, LH, and FSH). The elevation of prolactin gave rise to the suspicion of lymphocytic hypophysitis or

the possibility that the patient's condition was drug-induced, as these are possible causes of hypopituitarism. However, the patient took no causative medications. The normal morphology of the pituitary gland on MRI and scarcity of symptoms such as headache and visual disturbance reduced the possibility of lymphocytic hypophysitis. Prolactin levels are increased in several other settings. Stress is one cause of hyperprolactinemia. After the initiation of hormone replacement therapy, the patient's prolactin level decreased to a near normal range; thus, we hypothesized that hypocortisolemia itself induced the patient's hyperprolactinemia. The result of a CRH stimulation test ruled out hypothalamic dysfunction and other rare etiologies such as hereditary proopiomelanocortin processing disorders are less likely to occur in elderly patients. Even if deficits of hormones other than TSH existed, glucocorticoid is the only hormone that clinically requires replacement in elderly patients — thus, we did not perform any other hormone stimulation tests.

In conclusion, we reported a case of IAD with a recent history of chronic subdural hematoma. No existing studies have reported any association between chronic subdural hematoma and hypopituitarism. However, because the diagnosis of patients with adrenal insufficiency is often delayed or incorrect, there may be more patients with a history of chronic subdural hematoma who remain undiagnosed.

A larger cohort study is necessary to conclusively determine the relationship between hypopituitarism and chronic subdural hematoma.

The authors state that they have no Conflict of Interest (COI).

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