Two Cases of Hypopituitarism Caused by Intrasellar Aneurysm

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Abstract:
Giant internal carotid artery aneurysms sometimes extend into the sellar region, which rarely but occasionally results in hypopituitarism due to the compression of the normal pituitary gland or hypothalamus. Hyponatremia is a known complication of hypopituitarism. We herein report two cases of hypopituitarism caused by intrasellar aneurysm of different origins, resulting in hyponatremia. Untreated hypopituitarism may lead to lethargy, coma, cardiac arrhythmia, and death. Therefore, we must be alert for the occurrence of giant intrasellar aneurysm, as it causes hypopituitarism. The prompt diagnosis and treatment of hypopituitarism are necessary to prevent this fatal outcome.

Key words: aneurysm, ACTH deficiency, hypopituitarism, hyponatremia

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Introduction
Hypopituitarism typically occurs because of the compression of the normal pituitary by pituitary adenomas or nonpituitary tumors. Giant internal carotid artery aneurysms sometimes extend into the sellar region and mimic pituitary tumors, resulting in hypopituitarism due to the compression of the normal pituitary or hypothalamus (1). Although it very rarely causes hypopituitarism, a previous study found that 7 (0.17%) of 4,087 patients with hypopituitarism were found to have hypopituitarism due to an intrasellar aneurysm (2). Hyponatremia is a known complication of hypopituitarism. Untreated hypopituitarism may lead to lethargy, coma, cardiac arrhythmia, and death due to hyponatremia or hypoglycemia. We must therefore be alert for the development of giant intrasellar aneurysm, as it causes hypopituitarism.

We herein report two cases of hypopituitarism caused by intrasellar aneurysm that resulted in hyponatremia.

Case Reports

Case 1
A 76-year-old woman was taken to a nearby hospital because of abdominal pain, appetite loss, and clouding of consciousness. A laboratory examination revealed hyponatremia (serum sodium: 108 mmol/L). She was referred to our department for the further evaluation and treatment of hyponatremia. Hormonal data on admission showed normal blood concentrations of adrenocorticotropic hormone (ACTH, 30 pg/mL), cortisol (7.8 μg/dL), and dehydroepiandrosterone sulfate (DHEA-S, 27 μg/dL) and low levels of growth hormone (GH, 0.07 ng/mL), insulin-like growth factor-1 (<10 ng/mL), luteinizing hormone (LH, 0.1 mIU/mL), and follicle-stimulating hormone (FSH, 0.3 mIU/mL) (Table 1A). The serum thyroid-stimulating hormone (TSH) level was not elevated, despite low free triiodothyronine (T₃) and free thyroxine (T₄) levels (Table 1A). The human corticotropin-releasing hormone (hCRH) and LH-releasing hormone (LHRH) test demonstrated a weak response of plasma cortisol, LH, and FSH levels and an exaggerated re-

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Table 1. Hormonal Laboratory Data.

| (A) Case 1 | (CRH 100 μg and LH-RH 100 μg, intravenous bolus) |
|-------------|-----------------------------------------------|
| ACTH        | 30 pg/mL (7-56)                               |
| Cortisol    | 7.8 μg/dL (3.8-18.4)                          |
| DHEA-S      | 27 μg/dL (13-264)                             |
| UFC         | 15.6 μg/day (11.0-80.0)                       |
| GH          | 0.07 ng/mL (<2.10)                            |
| IGF-1       | <10 ng/mL (50-160)                           |
| PRL         | 23.2 ng/mL (3.4-16.2)                         |
| LH          | 0.1 mIU/mL (0.3-7.1)                          |
| FSH         | 0.3 mIU/mL (1.6-10.6)                         |
| Estradiol   | <5 pg/mL (<47.0)                              |
| TSH         | 2.68 μIU/mL (0.38-3.64)                       |
| Free T3     | 1.24 pg/mL (2.30-4.00)                        |
| Free T4     | 0.70 ng/dL (0.90-1.70)                        |
| AVP         | 2.3 pg/mL (0.3-4.2)                           |

Table 2. Endocrinological Examinations.

| (A) Case 1: hCRH+LHRH test | (CRH 100 μg and LH-RH 100 μg, intravenous bolus) |
|-----------------------------|-----------------------------------------------|
| Time (min)                  | 0 | 30 | 60 | 90 | 120 |
| ACTH (pg/mL)                | 16 | 362 | 410 | 292 | 315 |
| Cortisol (μg/dL)            | 4.8 | 6.9 | 8.5 | 10.7 | 11.5 |
| LH (mIU/mL)                 | 0.1 | 0.3 | 0.4 | 0.4 | 0.4 |
| FSH (mIU/mL)                | 0.5 | 0.6 | 0.8 | 0.9 | 1.0 |

| (B) Case 1: GHRP-2 test     | (GHRP-2 100 μg, intravenous bolus) |
|-----------------------------|------------------------------------|
| Time (min)                  | 0 | 30 | 60 | 90 | 120 |
| GH (ng/mL)                  | 0.22 | 0.43 | 0.67 | 0.40 | 0.49 |
| ACTH (pg/mL)                | 7 | 72 | 68 | 33 | 43 |
| Cortisol (μg/dL)            | 1.4 | 2.0 | 5.6 | 6.8 | 6.3 |

| (C) Case 2: hCRH test       | (CRH 100 μg, intravenous bolus) |
|-----------------------------|--------------------------------|
| Time (min)                  | 0 | 30 | 60 | 90 | 120 |
| ACTH (pg/mL)                | 13 | 36 | 46 | 38 | 34 |
| Cortisol (μg/dL)            | 3.2 | 5.1 | 8.1 | 6.8 | 5.8 |

Normal basal ranges are indicated in parentheses.

ACTH: adrenocorticotropic, DHEA-S: dehydroepiandrosterone sulfate, UFC: urinary free cortisol, GH: growth hormone, IGF-1: insulin-like growth factor-1, LH: luteinizing hormone, FSH: follicle-stimulating hormone, PRL: prolactin, TSH: thyroid-stimulating hormone, T3: triiodothyronine, T4: thyroxine, AVP: arginine vasopressin

She was treated with hydrocortisone at 50 mg/day and 5% glucose acetated (Na 130 mEq/L) Ringer’s solution of 1,500 mL by an intravenous drip for 3 days, followed by hydrocortisone and levothyroxine replacement at 15 mg/day and 25 μg/day orally, respectively. There was no recurrence.

Case 2

A 74-year-old woman was taken to a nearby hospital because of a low-grade fever, nausea, and appetite loss. A laboratory examination revealed hyponatremia (serum sodium: 124 mmol/L). She was referred to our department for the further evaluation and treatment of hyponatremia. Hormonal data on admission showed normal blood concentrations of ACTH (28 pg/mL), cortisol (6.0 μg/dL), and DHEA-S (23 μg/dL) and elevated levels of prolactin (PRL, 104.4 ng/mL) (Table 1B). In addition, the data also showed low levels of urinary free cortisol (7.8 μg/day) and serum insulin-like growth factor (IGF)-1 (41 ng/mL) (Table 1B). Endocrine examinations demonstrated a weak response of plasma cortisol levels and a delayed response of plasma ACTH levels in the hCRH test (Table 2C). Coronal MRI of the pituitary and aneurysm revealed an aneurysm enhanced heterogeneously and compression of the right part of the pituitary gland (Fig. 2A). MR angiography of the pituitary and aneurysm revealed the three-dimensional structure of a giant aneurysm (23 mm) from the left internal carotid artery (Fig. 2B).

She was treated with 5% glucose acetated (Na 130 mEq/L) Ringer’s solution of 500 mL and 10% NaCl of 20 mL for 6 days, followed by dexamethasone at 0.25 mg/day orally for 7 days. Finally, she was treated with hydrocortisone replacement at 10 mg/day. There was no recurrence.
Discussion

Aneurysms extending into the sellar region are rare and account for 1-2% of all intracranial aneurysms (2). In this report, two giant intrasellar aneurysms with different origins were found: from the right cavernous sinus and from the left internal carotid artery. Furthermore, the intrasellar aneurysms caused hypopituitarism. Therefore, we speculated that these two hypopituitarism cases were caused by the intrasel-
lar aneurysm.

In case 1, the hCRH test results also suggested hypotha-
lamic ACTH insufficiency. The LHRH test and GHRP-2 test suggested hypogonadism and severe GH deficiency. Hormo-
nal data also indicated central hypothyroidism. Hanak et al. reported that ACTH deficiency and GH deficiency were de-
tected in 70% and 33%, respectively, of the 32 patients with intrasellar aneurysms (3). Furthermore, they reported that endocrinopathy and hyponatremia were found in 57% and 21% of patients with intrasellar aneurysms, respectively (3).

In patients with hypopituitarism, hyponatremia tends to develop under stressful conditions. Severe hyponatremia is a frequent indicator of hypopituitarism after 60 years of age (4). The serum arginine vasopressin (AVP) levels were maintained in case 1, despite a low serum sodium level. Syndrome of inappropriate antidiuretic hormone (SIADH) has been associated with multiple disease states and condi-
tions (5). Hyponatremia is frequently due to the SIADH (6). Inappropriate secretion of AVP/ADH can be caused by hy-
pocortisolism due to hypopituitarism even in patients with intrasellar aneurysms. Generally, hypovolemia and hypoten-
sion stimulate the release of AVP, resulting in a reduction in free water excretion in the kidney. An intravenous drip in-
creases the circulating volume, resulting in volume-expanded hyponatremia.

In case 2, the results of the hCRH test suggested hypotha-
lamic hypopituitarism. Hormonal data also indicated hypo-
gonadism, GH deficiency, and hyperPRLnemia. The aneu-
rysm compresses the hypothalamus or the pituitary stalk, likely leading to hyperPRLnemia. The thyroid function seems to have been maintained in this case. The thyroid function can sometimes worsen before the hypothalamo-
pituitary-adrenal axis in cases with hypopituitarism due to pituitary compression. However, hyperPRLnemia (90%), hy-
pogonadism (82%), ACTH deficiency (70%), and TSH defi-
ciency (60%) were noted in cases with infradiaphragmatic intrasellar aneurysms (3). Although the mechanism has not been determined, it may be related to the hypothalamic hy-
popituitarism due to the giant aneurysm or its position.

Giant internal carotid artery aneurysms sometimes mimic pituitary tumors, and recent imaging techniques, such as flow-related effects on standard MR angiography, have proven useful for the diagnosis of intrasellar aneu-
rysms (7, 8). Giant intrasellar aneurysms may rarely cause pituitary dysfunction, resulting in adrenal insufficiency (9). Two mechanisms have been suggested for the development of hypopituitarism due to giant intrasellar aneurysms (9). First, hypothalamic or pituitary stalk compression by aneu-
rysms may cause pituitary dysfunction. In case 2, only the PRL levels were high, and other pituitary hormone levels were low, suggesting hypothalamic or pituitary stalk com-
pression. Second, direct compression and destructive effects by an enlarging aneurysm may impair the normal pituitary function.

Most intrasellar aneurysms have a benign course (10). Aneurysm rupture has been considered rare, but 15% of cases were reported to present with acute aneurysm rupture (3). To prevent aneurysm rupture and reduce the mass effect on the pituitary, open surgery or endovascular treat-
ment may be employed to treat aneurysms (1). Open surgery methods are hazardous and technically challenging (10). In addition, hypopituitarism is usually permanent, and improve-
ment of the pituitary function is difficult to achieve, even af-
ter surgery (11, 12). Therefore, hormone replacement ther-
apy is required even after the operation. Thus, most recent cases have been followed without operation. However, the endovascular coil embolization has been developed and is now available for application. Good occlusion of the aneu-
rysm and partial recovery of the pituitary function has been reported in some cases of middle-aged and elderly pa-
patients (13, 14). The accumulation of more details on cases of hypopituitarism due to intrasellar aneurysms will be re-
quired in order to clarify the treatment and nature of this disease.

In summary, we reported two cases of hypopituitarism caused by intrasellar aneurysms of different origins. We have to closely monitor giant intrasellar aneurysm, as it causes hypopituitarism. The prompt diagnosis and treatment of hypopituitarism are necessary to prevent this fatal out-
come.

Informed consent was obtained for endocrinological examina-
tions.

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

References
1. Ono H, Inoue T, Kunii N, et al. Giant cavernous carotid aneurysm causing pituitary dysfunction: pituitary function recovery with high-flow bypass. Surg Neurol Int 8: 180, 2017.
2. Heshmati HM, Fatourechi V, Dagam SA, Piepgras DG. Hypopituitar-
tism caused by intrasellar aneurysms. Mayo Clin Proc 76: 789-
793, 2001.
3. Hanak BW, Zada G, Nayar VV, et al. Cerebral aneurysms with in-
trasellar extension: a systematic review of clinical, anatomical, and treatment characteristics. J Neurosurg 116: 164-178, 2012.
4. Chanson P. Severe hyponatremia as a frequent revealing sign of hypopituitarism after 60 years of age. Eur J Endocrinol 149: 177-
178, 2003.
5. Mesko TW, Garcia O, Yee LD, Villar MJ, Chan H. The syndrome of inappropriate secretion of antidiuretic hormone (SIADH) as a conse-
cuence of neck dissection. J Laryngol Otol 111: 449-453, 1997.
6. Barter FC. The syndrome of inappropriate secretion of antidiure-
tic hormone (SIADH). Dis Mon 1-47, 1973.
7. Lawson EA, Buchbinder BR, Daniels GH. Hypopituitarism associ-
ated with a giant aneurysm of the internal carotid artery. J Clin Endocrinol Metab 93: 4616, 2008.
8. Seok H, Park HN, Kim GH, Son HS, Sohn TS. A giant carotid aneurysm with intrasellar extension: a rare cause of panhypopitu-
tuitarism. Korean J Intern Med 30: 265-266, 2015.
9. Gungor A, Gokkaya N, Bilen A, et al. Pituitary insufficiency and hyperprolactinemia associated with giant intra- and suprasellar ca-
rotic artery aneurysm. Case Rep Med 2015: 536191, 2015.
10. Slaba S, Medlej R, Smayra T, et al. Endocrinologic recovery after
11. Tan LA, Sandler V, Todorova-Koteva K, Levine L, Lopes DK, Moftakhar R. Recovery of pituitary function following treatment of an unruptured giant cavernous carotid aneurysm using Surpass flow-diverting stents. J Neurointerv Surg 7: e20, 2015.

12. Verbalis JG, Nelson PB, Robinson AG. Reversible panhypopituitarism caused by a suprasellar aneurysm: the contribution of mass effect to pituitary dysfunction. Neurosurgery 10: 604-611, 1982.

13. Tan LA, Sandler V, Todorova-Koteva K, Levine L, Lopes DK, Moftakhar R. Recovery of pituitary function following treatment of an unruptured giant cavernous carotid aneurysm using Surpass flow-diverting stents. BMJ Case Rep 2014: bcr2014011233, 2014.

14. Fujii M, Tone O, Tomita H, et al. Endosaccular embolization of an intrasellar aneurysm with hypopituitarism: case report. No Shinkei Geka 6: 329-337, 2008 (in Japanese, Abstract in English).