A case of isolated hypothalamitis with a literature review and a comparison with autoimmune hypophysitis

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Abstract. Idiopathic hypothalamitis is a rare condition that can cause anterior pituitary dysfunction and central diabetes insipidus (CDI), occasionally accompanied by a disturbance of autonomic regulation known as hypothalamic syndrome. This condition has been described as a subtype of autoimmune (lymphocytic) hypophysitis; however, some cases of isolated hypothalamic involvement with no inflammatory lesions in either the pituitary gland or infundibulum have been reported. The detailed epidemiology and pathophysiology of isolated hypothalamitis have not been clarified. We herein report a case of a solitary hypothalamic lesion in a young woman who showed spontaneous development of CDI and panhypopituitarism accompanied by hyperphagia. The hypothalamic lesion increased from 11 × 7 to 17 × 7 mm over 16 months based on the sagittal slices of magnetic resonance imaging examinations. The negative results for anti-pituitary antibodies and anti-Rabphilin-3A antibodies suggested that upward extension of lymphocytic adenohypophysitis or infundibuloneurohypophysitis was unlikely. Infectious disease, granulomatosis, Langerhans cell histiocytosis, vasculitis, and systemic neoplastic diseases were excluded by the findings of a laboratory investigation, cerebrospinal fluid examination, and imaging studies. To make a definitive diagnosis, we performed a ventriculoscopic biopsy of the hypothalamic lesion. Histology revealed an infiltration of nonspecific lymphoplasmacytes with no evidence of neoplasm, which was consistent with a diagnosis of idiopathic hypothalamitis. Subsequently, the patient was treated with methylprednisolone pulse therapy followed by oral prednisolone. The hypothalamic lesion improved and remained undetectable after withdrawal of the prednisolone, suggesting that the glucocorticoid treatment was effective for isolated hypothalamitis while the patient remains dependent on the replacement of multiple hormones.

Key words: Hypothalamitis, Hypothalamus, Hypophysitis, Diabetes insipidus, Rabphilin-3A

HYPOTHALAMITIS is an extremely rare condition which can cause pituitary dysfunction, central diabetes insipidus (CDI), disturbance of autonomic regulation, and neuropsychiatric disorders. Hypothalamic involvement occurs in conjunction with inflammation of the pituitary gland [1]; however, there have been some reported cases of isolated hypothalamic involvement with no inflammatory lesion in the pituitary gland or infundibulum [2-7]. Idiopathic isolated hypothalamicitis [3-7] and autoimmune hypophysitis [8] share the similar histological features of predominant infiltration of lymphocytes accompanying plasma cells, eosinophils, and fibroblasts. It remains controversial whether the etiology/pathophysiology of isolated hypothalamitis is different from that of autoimmune (lymphocytic) hypophysitis.

Here, we present a case of isolated hypothalamitis diagnosed by endoscopic transventricular biopsy. We review the characteristics of patients with isolated hypothalamitis reported in the literature.

Case Report

A 31-year-old Japanese female patient was referred to our hospital due to amenorrhea. She had no remarkable medical history. She delivered twice by virginal delivery at the ages of 24 and 26. She developed polyuria and polydipsia followed by amenorrhea when she was 29 years old. She also noticed a craving for food, and her
body weight increased from 54 kg to 65 kg for 2 years. At the age of 31, she was diagnosed as secondary amenorrhea associated with hyperprolactinemia (serum prolactin 84.5 ng/mL) at a local obstetric clinic. Since her amenorrhea did not respond to cabergoline treatment, the obstetrician referred her to the department of obstetrics and gynecology in our hospital in consideration of a suprasellar space-occupying lesion causing her hyperprolactinemia.

A magnetic resonance imaging (MRI) examination at the age of 31 identified an isolated iso-intense hypothalamic lesion (11 × 7 mm on a sagittal slice) in the T1-weighted image (WI), and it was mildly hyperintense to normal white matter in the T2WI, and a postcontrast image displayed heterogenous enhancement with peripheral enhancement (Fig. 1A, B). However, the infundibular stalk and pituitary gland showed normal homogenous enhancement. The blight signal intensity of neurohypophysis was slightly observed in T1WI. An MRI examination repeated 16 months later showed an increase in the hypothalamic lesion (17 × 7 mm; Fig. 1C, D), and the bright signal of neurohypophysis in the T1WI had become undetectable. She complained of fatigue, and her polyuria and polydipsia had worsened. She was referred to our department at the age of 33.

On physical examination, she was obese with a height of 152.2 cm and a weight of 71.3 kg (body mass index, 30.8 kg/m$^2$). No visual field defect or memory disturbance was apparent. There were no abnormal neurological findings. Her liver enzymes were elevated (Supplementary Table 1), and an ultrasound examination revealed a severe fatty liver. The endocrinological examination showed partial panhypopituitarism with hyperprolactinemia caused by hypothalamic hormonal dysfunction and complete CDI (Supplementary Table 2). As shown in Fig. 2, she subsequently underwent replacement therapy with hydrocortisone, levothyroxine, and desmopressin acetate.

Laboratory investigations including a cerebrospinal fluid examination (Supplementary Table 1) and image tests including computed tomography scanning and bone scintigraphy excluded infectious diseases, granulomatous disorders, Langerhans cell histiocytosis, vasculitis, and systemic neoplastic diseases. Neither anti-pituitary antibodies [9] nor anti-Rabphilin-3A antibodies [10] were detected in the serum. To make a definitive diagnosis, she underwent a ventriculoscopic biopsy of the hypothalamic lesion. As shown in Fig. 3, the histological examination showed diffuse lymphoplasmacytic infiltration with granuloma. There were dominant infiltrations of CD3$^+$ lymphocytes rather than CD20$^+$ lymphocytes or CD138$^+$ histiocytes. Additional immunohistochemistry on the infiltrations of T lymphocytes showed that CD4$^+$ cells dominantly infiltrated the hypothalamus compared to CD8$^+$ or Foxp3$^+$ cells. Fibrosis was observed around those hematopoietic cells infiltrations. There was no restriction of the light chain in the immunoglobulin (Ig) staining, thus excluding lymphoproliferative disorders, and few IgG4-positive plasma cells, thus excluding IgG4-related disease. The architecture of the central nervous tissue was preserved, as shown by the presence of astrocytic glial fibrillary acidic proteins and neurofilaments. These pathological findings presumed that the hypothalamic lesion was induced by an autoimmune etiology.
Based on the histological findings, she underwent intravenous methylprednisolone pulse treatment (3 cycles of 500 mg × 3 days) followed by oral prednisolone at 20 mg. The administration of glucocorticoids caused her to develop glucose intolerance and her fatty liver to deteriorate. Treatment with metformin and liraglutide was insufficient to ameliorate the fatty liver issue, and she required somatropin treatment to decrease the levels of liver enzymes.

The hypothalamic lesion apparently responded to the glucocorticoid treatment (Fig. 1E, F). We gradually tapered and withdrew the prednisolone 16 months after the initiation of the glucocorticoid treatment. The MRI showed remission of the hypothalamitis 18 months after the withdrawal of prednisolone (Fig. 1G, H), and the lesion remained in complete remission in the latest MRI taken 30 months after the withdrawal of prednisolone (Fig. 1I, J). However, no clinical improvement in the endocrinological dysfunction was observed (Supplementary Table 2). She has continued to require hormone replacement up to the present (Fig. 2). The body weight and the levels of liver enzymes were increased after withdrawal of liraglutide and somatropin. We recently restarted administration of somatropin. Subsequently, the rising in these clinical parameters has stabilized (Fig. 2).

**Discussion**

We presented the rare case of a young woman with isolated hypothalamic lesion who underwent a hypothalamic biopsy by a transventricular endoscopic approach. Our case was the second in which the transventriculoscopic procedure was applied to diagnose hypothalaminis, following a case reported by Bertulli et al. [6]. Histology showed a diffuse infiltration of non-specific lymphoplasmacytes with neither glial proliferation nor monoclonal lymphoproliferation, which was identical to the cases reported previously [3-7]. The proportions of lymphocytes (T- and B-cell), plasmacytes, and histiocytes were variable by each report. Our case

Fig. 2  Clinical course of the patient.
ALT, alanine aminotransferase; mPSL, methylprednisolone; PSL, prednisolone.
showed a dominant infiltration of T lymphocytes similar to the case of Bertulli et al. [6]. In our case, CD4-positive T-cells were dominant more than CD8- or Foxp3-positive T-cells. It is unclear whether this distribution of T-cells was common in patients with primary hypothalaminitis, because no previous study has precisely evaluated the distribution of T-cell subsets in the infiltration of hypothalamic lesion.

The hypothalamic lesion showed a marked reduction in response to glucocorticoids and maintained a complete remission 30 months after the withdrawal of glucocorticoids. These findings might support the hypothalamic lesion having an immune mediated etiology.

The pathogenesis of hypothalaminitis remains unclarified. Wei et al. considered that hypothalaminitis might be a subtype of hypophysitis because the hypothalamus is closely associated with the pituitary gland and infundibulum in its anatomy, histology, and function [7]. The cases of solitary hypothalaminitis reported in the literature were almost identical to lymphocytic hypophysitis in their pathological findings, clinical manifestations, and therapeutic responses [8]. Bianchi et al. [3] described a case of hypothalaminitis in which the patient’s pituitary gland appeared atrophic with positive anti-pituitary antibodies, which are frequently detected in the sera of patients with autoimmune hypophysitis [11]. The patient’s hypothalamic lesion was considered to have evolved from autoimmune hypophysitis [3]. There was no decrease in the volume of the anterior pituitary gland in our patient’s clinical course (Fig. 1), and we did not detect anti-pituitary antibodies in her sera by an indirect immunofluorescence using the rat pituitary substrate (Supplementary Table 1). Ricciuti et al. reported that the human pituitary was the best substrate to detect anti-pituitary antibodies compared to other species including rat [12]. Although we need to consider that the sensitivity and specificity of the anti-pituitary antibodies, especially in the case using the rat substrate, for hypophysitis remains low [8], these findings suggested to us that the evolution of autoimmune hypophysitis to the hypothalamus was unlikely.

Iwama et al. recently reported that Rabphilin-3A was a major specific autoantigen in autoimmune infundibro-neurohypophysitis, and the antibodies against Rabphilin-3A could be detected in the sera of CDI patients with biopsy-proven infundibro-neurohypophysitis [10]. They demonstrated the expression of Rabphilin-3A in both the neurohypophysis and the arginine-vasopressin

**Fig. 3** The ventriculoscopic biopsy of the hypothalamic lesion. Histology showed diffuse nonspecific lymphoplasmacytic infiltration with granuloma.

GFAP, glial fibrillar acidic protein; NF, neurofilament.
neurons in the hypothalamus. The negative result for anti-Rabphilin-3A antibodies in our patient (Supplemen-
tary Table 1) might indicate that she had an etiology
different from those of patients with autoimmune
infundibro-neurohypophysitis.

De Bellis et al. reported the anti-hypothalamus anti-
bodies were detected in some patients with autoimmune
hypophysitis by an indirect immunofluorescence method
using young baboon hypothalamus [13]. We did not
examine the antibodies in our patient’s sera. Nor did we
determine the types of endocrine cells which were target-
ted by the infiltrated lymphocytes in the histology of
hypothalamus. These might be limitations when investi-
gating the etiology of the hypothalamic involvement of
our patient.

As summarized in Table 1, only 13 cases who pre-
sented with a localized lesion in the hypothalamus
without hypophysitis have been reported in the English
literature as far as we know. None of the patients
developed isolated hypothalamitis during pregnancy or

| Table 1 | Overview of known cases of isolated hypothalamitis including 14 patients with putative autoimmune hypothalamitis and a patient with anti-PD-L1 antibody-related hypothalamitis |
|---------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Case    | Sex/Age | Pituitary hormonal defect  | Other symptoms | APA | Bx            | Treatment          | Outcome* |
|---------|---------|----------------------------|----------------|-----|---------------|--------------------|----------|
| Our patient | F 29  | (+) (+) (+) (+) (+) (+) | Hyperphagia | ND  | ND (+)        | mPSL, PSL          | CR       |
| Wang 2008 [2][7] | F 70  | (+) (+) (+) (+) (+) (+) | None | ND  | ND (+)        | mPSL, PSL, AZT     | Died after relapse |
| Bianchi 2014 [3] | F 48  | (+) (+) (+) (+) (+) (+) | Bitemoral hemianopsia, Blurred vision | (+) (+) | PSL, AZT | PR |
| Zhang 2015 [4] | M 20  | (+) (+) (+) (+) (+) (+) | Hyperphagia, Personality change | ND  | (+) | DEX, PSL, AZT | PR |
| Zhang 2017 [5] | F 26  | (+) (-) (-) (+) (+) | ND | ND | ND (+) | ND | ND |
|           | F 34  | (+) (+) (+) (+) (+) | ND | ND | ND (+) | ND | ND |
|           | F 21  | (+) (+) (+) (+) (+) | ND | ND | ND (+) | ND | ND |
|           | F 19  | (-) (+) (+) (+) (+) | ND | ND | ND (+) | ND | ND |
|           | F 19  | (+) (-) (+) (+) (+) | ND | ND | ND (+) | ND | ND |
| Bertulli 2017 [6] | F 55  | (+) (+) (+) (+) (+) | ND | ND | ND (+) | mPSL, PSL, AZT | SD–PR |
| Wei 2019 [7]   | F 41  | (+) (+) (+) (+) (-) | None | ND  | ND (+) | mPSL, PSL, AZT, Radiation | Relapse |
|           | F 43  | (+) (+) (-) (+) (-) (+) | None | ND  | ND (+) | PSL | CR |
|           | F 39  | (+) (-) (-) (+) (+) | ND | ND | None | mPSL, PSL | CR |
|           | F 20  | (+) ND | ND | (-) ND | Hyperpyrexia | ND (-) | None | CR |
| Total (n = 14)*2 | 34.6 yrs | 93% 77% 77% 100% 71% 75% | | | | 71% | |

APA, anti-pituitary antibodies; AZT, azathioprine; Bx, biopsy; CR, complete remission; DEX, high dose of intravenous/oral
dexamethasone; Hyper-PRL, hyperprolactinemia; mPSL, intravenous methylprednisolone pulse therapy; ND, not described; PD-L1,
programmed cell death ligand 1; PR, partial remission; PSL, oral prednisolone; SD, stable disease.

*1 The outcomes were evaluated based on the changes in size of hypothalamic lesions according to MRI examinations.

*2 The means of the 14 patients with isolated autoimmune hypothalamitis including our case.

*3 The case developed isolated hypothalamitis after treatment with atezolizumab, a blocking antibody against PD-L1.
postpartum. The clinical characteristics of patients with hypothalamitis, including ours, were marked female predominance (93%) and young age of onset (34.6 ± 15.6 yrs) with deficiencies of multiple pituitary hormones. Similar clinical characteristics can be seen in autoimmune adenohypophysitis [8].

To describe the clinical difference between hypophysitis and hypothalamitis, CDI symptoms (polyuria and polydipsia) seemed to first become manifest in patients with hypothalamitis. CDI symptoms should not appear, since the posterior pituitary is spared in hypophysitis. The hypothalamus controls the autonomic nervous system including body temperature, satiety, thirst, sleep, and circadian rhythms. The dysregulations of these function are known as hypothalamic syndrome, which often occurs in hypothalaminus but not in hypophysitis. Our patient developed hyperphagia and CDI simultaneously; suggesting that the hypothalamus was directly impaired in our patient. The incidence of hyperprolactinemia in hypothalamitis (75%) was much higher than in hypophysitis (23%) [8]. This can be explained by the mechanism that prolactin secretion in adenohypophysis is controlled by inhibitory dopaminergic inputs produced in the infundibular region of the hypothalamus. The anterior pituitary hormone that is frequently impaired in patients with hypothalamitis has been reported to be gonadotropin (LH/FSH). Impaired pituitary function in autoimmune hypophysitis is typically ACTH > TSH > LH/FSH > GH in its frequency [14]. The different susceptibility of pituitary hormones in the two disorders suggests that isolated hypothalamitis may have a unique etiology different from that of autoimmune hypophysitis.

Glucocorticoids were frequently used as a treatment for hypophysitis in the reported cases, and they seemed generally effective to reduce the size of the hypothalamic lesion, with relapse after they are tapered or withdrawn in some patients [2, 7]. Azathioprine was reported to be effective in patients who relapsed or became resistant to glucocorticoid therapy [3, 4, 6, 7]. It has been reported that a good response in an MRI study does not necessarily indicate a good response in pituitary function in patients with hypophysitis. This was also the case in our patient. We observed a remission in the MRI for longer than 2 years, but there has been no improvement in the anterior or posterior pituitary dysfunction including hyperprolactinemia or the hypothalamic dysfunction of hyperphagia. It might suggest that the destruction of hypothalamus induced by hypophysitis was irreversible. The secretory capacities of adenohypophyseal hormones could not improve under the circumstances of decreased signals from hypothalamic hormones for a long time.

Recently, Tshima et al. reported a novel case that developed isolated hypothalamitis during treatment with atezolizumab, a monoclonal antibody against programmed cell death-ligand 1 (PD-L1) [15]. The patient developed CDI and panhypopituitarism accompanied by hypothalamic dysfunction including adipsia, sleep apnea, temperature dysregulation, and short-term memory disturbance (shown at the bottom of Table 1). Her hypothalamic inflammatory lesion promptly regressed after high-dose dexamethasone therapy along with the discontinuation of atezolizumab, suggesting an autoimmune etiology. Iervasi et al. demonstrated expression of the PD-L1 receptor on hypothalamic cells [16], which might explain the mechanism of hypothalamic immunotoxicity in patients receiving anti-PD-L1 inhibitors. On the other hand, it has recently been reported that approximately 10% of the patients treated with ipilimumab, a cytotoxic T-lymphocyte-associated antigen-4 inhibitor, developed autoimmune hypophysitis [17]. However, blocking antibodies against programmed cell death-1 or PD-L1 rarely causes autoimmune hypophysitis [18]. These studies may provide a clue to understanding the differences in autoimmune pathogenesis between hypothalaminus and hypophysitis.

**Conclusion**

We reported a case of isolated hypothalamitis in a woman who developed pituitary dysfunction and hyperphagia. We demonstrated the efficacy of glucocorticoid treatment to ameliorate inflammation in the hypothalamic lesion. Further investigations are needed to clarify the pathogenesis and clinical course of hypothalamitis.

**Disclosure**

The authors declare no conflict of interest associated with this manuscript.
## Supplementary Table 1  
Laboratory examinations at admission (before biopsy)

| Blood examinations | Case | Reference | Soluble interleukin-2 receptor (U/mL) | Case | Reference |
|---------------------|------|-----------|---------------------------------------|------|-----------|
| White blood cell (μL) | 5,700 | 3,300–8,600 | 189 | 122–496 |
| Red blood cell (<10^6/μL) | 441 | 386–492 | α-fetoprotein (ng/mL) | 3.3 | 10 |
| Hemoglobin (g/dL) | 13.3 | 11.6–14.8 | hCG-β (ng/mL) | <0.1 | <0.1 |
| Platelet (<10^9/μL) | 32.2 | 15.8–34.8 | Angiotensin-converting enzyme (U/L) | 11.4 | 7.0–25 |
| Sodium (mEq/L) | 143 | 138–145 | Lysozyme (μg/mL) | 3.4 | 5.0–10 |
| Potassium (mEq/L) | 4.2 | 3.6–4.8 | MPO-ANCA (U/mL) | <1.0 | <3.5 |
| Chloride (mEq/L) | 106 | 101–108 | PR3-ANCA (U/mL) | <1.0 | <2.0 |
| Triglyceride (IU/mL) | 184 | 50–149 | T-SPOT.TB | (–) | (–) |
| Cholesterol (IU/mL) | 274 | 150–219 | RPR test for Treponema pallidum | (–) | (–) |
| Blood urea nitrogen (mg/dL) | 18 | 8.0–20 | Anti-pituitary antibody*1 | (–) | (–) |
| Creatinine (mg/dL) | 0.78 | 0.46–0.79 | Rabphilin-3A antibody*2 | (–) | (–) |
| Aspartate aminotransferase (IU/L) | 94 | 13–30 | | |
| Alanine aminotransferase (IU/L) | 91 | 7.0–23 | | |
| γ-glutamyltransferase (IU/L) | 80 | <48 | White blood cell (μL) | | 1 |
| Glucose (mg/dL) | 75 | 73–109 | Glucose (mg/dL) | | 59 |
| Glycated hemoglobin (%) | 5.7 | 4.9–6.0 | Protein (mg/dL) | | 44 |
| IgA (mg/dL) | 293 | 90–400 | Lactate dehydrogenase (IU/L) | | 10 |
| IgG (mg/dL) | 1,298 | 820–1,740 | α-fetoprotein (ng/mL) | | <0.6 |
| IgG4 (mg/dL) | 4.0 | 5.0–117 | hCG-β (ng/mL) | | <0.3 |
| IgM (mg/dL) | 172.2 | 52–270 | PLAP (pg/mL) | | <8.0 |
| IgE (IU/mL) | 137.7 | <170 | | |

**ANCA, antineutrophil cytoplasmic antibody; hCG-β, human chorionic gonadotropin β subunit; Ig, immunoglobulin; MPO, myeloperoxidase; PLAP, placental alkaline phosphatase; RPR, rapid plasma regain; PR3, proteinase 3; T-SPOT.TB, type of ELISpot assay used for tuberculosis diagnosis; TPHA, Treponema pallidum hemagglutination**

*1 Anti-pituitary antibody was measured by an indirect immunofluorescence using rat pituitaries [9].

*2 Rabphilin-3A antibody was measured by a dot blotting method using recombinant human rabphilin-3A [10].
Supplementary Table 2  Results of pituitary functions before and after glucocorticoid treatment

| TRH, CRH, GnRH tests | Reference | At admission (Before treatment) | After withdrawal of glucocorticoid |
|-----------------------|-----------|---------------------------------|-----------------------------------|
|                       |           | 0      | 30     | 60     | 90 (min) | 0      | 30     | 60     | 90 (min) |
| TSH (μIU/mL)          | 0.48–5.08 | 1.24   | 8.33   | 6.13   | 8.0      | 0.11   | 1.06   | 1.06   | 0.95      |
| Free T3 (pg/mL)       | 2.37–3.91 | 0.92   |        |        |          |        |        |        |          |
| Free T4 (ng/dL)       | 0.95–1.57 | 0.80   |        |        |          |        |        |        |          |
| Prolactin (ng/mL)     | 6.1–30.5  | 163    | 215    | 170    | 186      | 118    | 160    | 147    | 137      |
| ACTH (pg/mL)          | 7.2–63.3  | 33.6   | 67.2   | 29.8   | 51.7     | 14.3   | 44.4   | 40.3   | 22.7     |
| Cortisol (μg/dL)      | 4.5–21.1  | 12.4   | 15.3   | 13.9   | 16.1     | 2.99   | 5.38   | 5.16   | 3.85     |
| LH (mIU/mL)           | 5.7–64.3  | 0.46   | 2.78   | 2.91   | 2.99     | 0.3    | 1.73   | 1.68   | 1.47     |
| FSH (mIU/mL)          | 1.47–16.60| 1.55   | 2.87   | 4.96   | 3.65     | 1.24   | 2.19   | 2.42   | 2.57     |
| Estradiol (ng/mL)     | 28.8–525.9| 8.2    |        |        |          |        |        |        |          |

GHRP-2 test

| Reference | 0 | 15 | 30 | 45 | 60 (min) | 0 | 15 | 30 | 45 | 60 (min) |
|-----------|---|----|----|----|----------|---|----|----|----|----------|
| GH (ng/mL)| 0.13–9.88 | 0.09 | 1.49 | 1.25 | 0.64 | 0.39 | 0.05 | 1.33 | 1.37 | 0.84 | 0.48 |
| IGF-1 (ng/mL) | 119–283 | 93 |

5% saline loading test

| Reference | 0 | 2h | DDAVP-2h* |
|-----------|---|----|----------|
| Serum Na (mEq/L) | 138–146 | 140 | 154 | 153 |
| Urine Na (mEq/L)  | 15 | 26 | 145 |
| Sosm (mOsm/kg)   | 276–292 | 282 | 313 | 306 |
| Uosm (mOsm/kg)   | 50–1,300 | 70 | 104 | 467 |
| ADH (pg/mL)      | 0.8–4.0 | <0.8 | <0.8 |

ACTH, adrenocorticotropic hormone; ADH, anti-diuretic hormone; CRH, corticotropin-releasing hormone; DDAVP, desmopressin acetate hydrate; FSH, follicle-stimulating hormone; IGF-1, insulin-like growth factor-1; GH, growth hormone; GnRH, gonadotropin-releasing hormone; GHRP-2, growth hormone-releasing peptide-2; LH, luteinizing hormone; Na, sodium; Sosm, serum osmotic pressure; T3, triiodothyronine; T4, thyroxine; TRH, thyrotropin-releasing hormone; TSH, thyroid-stimulating hormone; Uosm, urine osmotic pressure.

* “DDAVP-2h” indicates 2 hours after administering 5 μg of intranasal DDAVP, which was administered 2 hours after starting a 5% saline loading test.

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