WE EXPERIENCED a very rare case of hypothalamic adrenal insufficiency (AI), which clinically resembled but did not completely coincide with Sheehan’s syndrome (SS), because the patient lacked empty sella and experienced spontaneous resolution of the endocrinological abnormalities. To our knowledge, no case of remission of hypothalamic AI has been reported previously. The etiology in this patient was a suspected autoimmune mechanism when we considered the unusual clinical course and the coincidental complication of Basedow’s disease.

Case Report

The patient was a 37-year-old female. In August 2008, when she delivered her third child, she experienced a blood loss of 1,500 mL. She did not fall into hemorrhagic shock, therefore the blood transfusion and the glucocorticoid treatment were not required. She could feed her baby on breast milk. Two or three months after the delivery, she experienced general fatigue and loss of axillary and pubic hair but she did not consult a doctor. Her menstrual bleeding was resumed about 6 months after the delivery in spite of breast-feeding. In June 2009, because her symptoms had not resolved and leg edema developed, she consulted a doctor and testing revealed that her serum cortisol level was 5.7 μg/dL in a 0900 h sample. Adrenal insufficiency was suspected and 0.5 mg/day dexamethasone was prescribed for the week preceding admission to our hospital; however, the patient reported that she had not taken the medication. Head CT and MRI revealed no abnormalities in the hypothalamic-pituitary region. Basedow’s disease was also diagnosed based on a free-T4 level of 2.91 ng/dL, thyroid stimulating hormone (TSH) < 0.01 μIU/mL, and positive TSH receptor antibody (TRAb) and she was started on 15 mg/day methimazole (MMI). Her general physical examination findings were as follows: height 154 cm, BW 49.1 kg, BMI 20.7 kg/m², pulse 58/min (regular) and BP 94/58 mmHg. There was no pigmentation, and her axillary hair or pubic hair was lost. No other specific abnormalities, including the goiter and ophthalmopathy, were observed.
General laboratory examinations revealed no abnormalities in urine, complete blood cell count, and serum biochemistry testing including electrolytes. Endocrinological examinations revealed normal thyroid function after treatment with 15 mg methimazole for 2 weeks. However, serum TSH level was still undetectable (< 0.004 μIU/mL) with high titers of thyroid-stimulating antibody 319% and TRAb 28.7%. Basal plasma adrenocorticotropic hormone (ACTH) level and serum cortisol level measured immediately after admission to our hospital were 5.2 pg/mL and 1.9 μg/dL, respectively, suggesting that the patient had secondary adrenal insufficiency. Serum dehydroepiandrosterone-S level was extremely low at 4 μg/dL, which was compatible with the findings of loss of axillary and pubic hair. Because she complained of severe general fatigue on admission, 100 mg/day of hydrocortisone (HC) was administered intravenously for three consecutive days. On the fourth and the fifth days, 50 mg/day of HC was given orally, and from the sixth day, the dose was decreased to 20 mg/day. On the sixth day after admission, combined stimulation testing with corticotropin-releasing hormone (CRH), gonadotropin-releasing hormone, thyrotropin-releasing hormone (TRH), and GH-releasing hormone was performed. Basal hormone levels were almost within normal ranges: prolactin, 16.1 ng/mL; growth hormone (GH), 0.98 ng/mL; insulin-like growth factor-1, 171 ng/mL; luteinizing hormone (LH), 2.7 μIU/mL; follicle-stimulating hormone (FSH), 4.2 μIU/mL, and estrogen, 131.7 pg/mL. The responses of GH, prolactin, LH, and FSH to each stimulation were within normal ranges (Fig. 1). Because of Basedow’s disease, the basal TSH level was suppressed and showed no response to TRH (Fig. 1). Plasma ACTH response to CRH was normal whereas cortisol response to CRH was low (basal to peak; 1.6 to 4.0 μg/dL) (Fig. 1). Rapid ACTH testing with 250 μg Cortrosyn (Organon Inc., West Orange, NJ, USA) by intravenous injection performed on the eighth day after admission revealed a poor serum cortisol response (basal to peak; 4.5 to 10.0 μg/dL) (Fig. 2). However, serial stimulation with synthetic ACTH (Cortrosyn Z, Daiichi Pharmaceutical Co., Tokyo, Japan) by intramuscular injection once a day for 3 days resulted in a dramatic increase in urinary free cortisol (basal to peak; 18 to 370 μg/day), ruling out primary AI (Table 1). Hypothalamic AI was suspected. On the eighteenth day after admission, an
Recovery of hypothalamic adrenal failure

Recovery of hypothalamic adrenal failure of HC and 15 mg/day of MMI and finally discharged. Following discharge, endocrinological examinations were performed every 6 months and the doses of medications were modified, as needed. The poor response of cortisol to the CRH stimulation test gradually improved after 6 and 12 months (Fig. 3 a, b, c). GHRP-2 loading test, which is recognized to stimulate directly both hypothalamus and pituitary, was also performed 6 months after the discharge, and the lower responses of ACTH and cortisol were observed (basal to peak; 11.9 to 27.8 pg/mL, 4.3 to 7.7 μg/dL, respectively) than those to CRH. Responses of ACTH and cortisol to ITT clearly improved (Fig. 3 d, e, f). Changes in ACTH and cortisol, the clinical time course, and treatments are summarized in Fig. 4. Plasma ACTH and serum cortisol levels were measured between 1000 and 1100 h at an outpatient clinic without taking HC that morning. The patient’s symptoms gradually improved over 2 years, and replacement of HC was finally stopped in July 2011. No further replacement has been required. The dose of MMI was decreased gradually for 6 years, with no observation of hypothyroidism, and the medication was stopped in May 2015.

Discussion

This patient experienced postpartum hypothalamic AI and Basedow’s disease with the former gradually and spontaneously improving over a 2-year period. Our case clinically resembled SS on the onset after severe postpartum hemorrhage. However, she had several remarkable different conditions; normal lactation and menstruation after the delivery, isolated ACTH deficiency due to the impairment of the hypothalamus rather than the pituitary, and also no empty sella on serial MRI. Although lymphocytic hypophysitis has been recognized as one of causes of postpartum AI, this possibility is unlikely since the pituitary function and pituitary image on MRI were normal. Administration of supraphysiological doses of glucocorticoids or drugs used in intensive care, brain injury and subarachnoid hemorrhage have been reported to be possible causes for secondary AI, which may recover spontaneously [1, 2]. However, our case had no history of medication of any glucocorticoid or any other drug which may cause AI, or episodes like traumatic brain injury etc.

While the exact pathogenesis and natural history of SS are not completely understood [3–6], a role for

Table 1 Serial ACTH loading test (cortrosyn Z i.m. injection for 3 days)

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<th>Before</th>
<th>1st day</th>
<th>2nd day</th>
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<tr>
<td>Serum cortisol (μg/dL)</td>
<td>1.6</td>
<td>18.9</td>
<td>31.1</td>
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<tr>
<td>Urine cortisol (μg/day)</td>
<td>18</td>
<td>346</td>
<td>288</td>
<td>370</td>
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Insulin tolerance test (ITT) was performed and intravenous insulin injection (0.04 U/kg, 2U) caused serum glucose level to decrease to 40 mg/dL, indicating sufficient stimulation of the CRH-ACTH-cortisol axis. Although peak GH level was 7.8 ng/mL, ACTH and cortisol showed no response (Fig. 3d). Based on these findings, the patient was finally diagnosed as having hypothalamic AI.

Immunochemically, the patient showed negative results for anti-adrenocortical antibody and anti-pituitary antibodies (APAs) against rat anterior pituitary and intermediate lobe. Anti-hypothalamus antibody (AHA) could not be assessed.

The examination of Head MRI in July 2009 and January 2010 revealed no organic lesions, ruling out pituitary atrophy and hypothalamic-pituitary tumors.

We did not examine radioactive iodine uptake or thyroid scintigraphy. However, a thyroid echogram revealed a diffuse hypervascularity in her thyroid lobes.

Clinical Course

Under the diagnosis of hypothalamic AI and Basedow’s disease, she was medicated with 20 mg/day of HC and 15 mg/day of MMI and finally discharged. Following discharge, endocrinological examinations were performed every 6 months and the doses of medications were modified, as needed. The poor response of cortisol to the CRH stimulation test gradually improved after 6 and 12 months (Fig. 3 a, b, c). GHRP-2 loading test, which is recognized to stimulate directly both hypothalamus and pituitary, was also performed 6 months after the discharge, and the lower responses of ACTH and cortisol were observed (basal to peak; 11.9 to 27.8 pg/mL, 4.3 to 7.7 μg/dL, respectively) than those to CRH. Responses of ACTH and cortisol to ITT clearly improved (Fig. 3 d, e, f). Changes in ACTH and cortisol, the clinical time course, and treatments are summarized in Fig. 4. Plasma ACTH and serum cortisol levels were measured between 1000 and 1100 h at an outpatient clinic without taking HC that morning. The patient’s symptoms gradually improved over 2 years, and replacement of HC was finally stopped in July 2011. No further replacement has been required. The dose of MMI was decreased gradually for 6 years, with no observation of hypothyroidism, and the medication was stopped in May 2015.

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While the exact pathogenesis and natural history of SS are not completely understood [3–6], a role for
Fig. 3  Time course of ACTH-cortisol secretion by CRH-test or insulin-tolerance test

Time course of ACTH-cortisol secretion by CRH test were shown in (a), (b) and (c). Furthermore, those in response to insulin tolerance test were shown in (d), (e) and (f). The basal and peak values of plasma ACTH or serum cortisol were indicated in respective figures.

Fig. 4  Time course of changes in basal levels of plasma ACTH and serum cortisol

Dexamethasone (0.5 mg/day) was prescribed for one week by the patient’s previous doctor; however, the patient reported that she did not take the medication. Therefore, the prescription is not shown in this figure. The shadow indicates the dose of hydrocortisone (HC) administered in our hospital. On admission, HC was administered intravenously at a dose of 100 mg/day for three consecutive days. On the fourth and the fifth days, 50 mg/day of HC was given orally, and from the sixth day, the dose was decreased to 20 mg/day. HC, hydrocortisone; ACTH, adrenocorticotropic hormone.
pituitary or hypothalamic autoimmunity in the development of SS has been suggested. Recently, autoimmune mechanisms have been suggested as a cause of impairment in not only pituitary but also hypothalamic disease following ischemic change from brain trauma and massive bleeding [5–8]. Ischemia or necrosis of cells may produce antigens, leading to an immune response and production of cytokine-like interleukin 6 and nitrous oxide, which causes late-onset disorders in neuroendocrine cells. This immune response has been thought to produce APA and AHA. Recently, AHA detected in isolated ACTH deficiency was revealed to be antibody against CRH-secreting cells [8]. Among 20 patients with SS, 8 (40%) were AHA-positive and 7 were positive for APA [5]. Importantly, positive APA or AHA cases are frequently complicated with autoimmune thyroid diseases [5].

Basedow’s disease was also complicated almost at the same time with hypothalamic AI. SS is a well-known cause of postpartum autoimmune thyroiditis, and also the secondary AI of unknown origin were reported to be associated with autoimmune thyroid diseases [9]. Painless thyroiditis is recognized to occasionally occur following rapid development and/or progression of primary or secondary adrenal failure, as immune rebound phenomenon [10]. Therefore, the concomitant Basedow’s disease in our case might be caused by hypothalamic AI.

Remission of hypothalamic AI is also very unique in this case. To our knowledge, there are no previous case reports of remission of idiopathic hypothalamic AI in patients receiving only supplemental glucocorticoid therapy. Based on the unusual clinical course, remission of hypothalamic impairment, and the simultaneous complication of Basedow’s disease, an autoimmune mechanism may be a cause of the hypothalamic AI in this patient. Since we have not examined AHA, this possibility is currently speculative. Our report is valuable in that we showed the time-dependent recoveries of hypothalamic-pituitary adrenal (HPA) function by ITT. This careful tracking of HPA function strongly supports the gradual recovery of HPA function in this patient. The unique clinical time course showing remission may also raise a possibility of an autoimmune mechanism in this case. Conversely, we may have to consider the effect of glucocorticoid on autoimmune mechanisms, even though the dose was supplementary (15–20 mg/day of an HC-equivalent dose). Hashimoto et al. reported that a physiological dose of glucocorticoid (prednisolone-equivalent dose ≤ 7.5 mg/day) affected the reduction of pituitary masses in 16 (44.4%) of 36 patients with lymphocytic hypophysitis [11]; therefore, there is a possibility that even the supplementary dose of HC could have contributed to remission in our case.

There may be similar cases anywhere but unnoticed. We need to accumulate such cases in order to clarify what kind of endocrinological findings are associated with remission of AI.

In summary, ours may be the first case of remission of idiopathic hypothalamic AI in a patient receiving only supplemental glucocorticoid therapy. Further investigations are required to determine the underlying mechanism and clinical features.

Declaration of Interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

References

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