〈Case Report〉

A case of Sheehan syndrome with early postpartum panhypopituitarism and long-term partial improvement of endocrine function

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ABSTRACT Recently, there have been reports of Sheehan syndrome diagnosed within a short period after delivery. A 35-year-old woman underwent emergency cesarean section because of massive hemorrhage during delivery. Twenty-seven days after delivery, the patient was diagnosed with adrenal insufficiency. Magnetic resonance imaging of the pituitary revealed a subacute pituitary hematoma, which led to the diagnosis of Sheehan's syndrome. The symptoms improved with hydrocortisone and levothyroxine. Thyroid function improved with the resolution of the pituitary hematoma, but the adrenocorticotropic hormone response disappeared over time. Sheehan syndrome, diagnosed early postpartum, may show partial improvement in endocrine function and require many years of follow-up.

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Key words：Sheehan syndrome, Panhypopituitarism, Delivery, Adrenocorticotropic hormone, Thyroid-stimulating hormone

BACKGROUND

Sheehan syndrome, a common cause of delivery-related hypopituitarism, was first described by Sheehan in 1937[1]. Sheehan syndrome is generally diagnosed more than10 years postpartum and results in irreversible hypopituitarism due to an autoimmune mechanism involving pituitary necrosis at birth and pituitary autoantibodies[2]. In recent years, there has been an increase in reports of the rapid onset of Sheehan syndrome in the early postpartum period, triggered by postpartum pituitary apoplexy; some reports suggest that partial endocrine function may improve within the first year postpartum[3]. We present here a case of Sheehan syndrome in a patient who was admitted to the hospital because of early postpartum symptoms of adrenal insufficiency, and later tests suggested panhypopituitarism. More than 2 years after delivery, endocrine function partially improved with the disappearance of the pituitary hematoma.

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This case clearly demonstrates that partial pituitary function may improve over a long period in Sheehan syndrome, which develops in the early postpartum period.

CASE PRESENTATION

In a 35-year-old woman, a massive vaginal wall hematoma was observed during the delivery of her first child at another hospital, and she lost an estimated 5 L of blood during vaginal delivery. She received 800 mL of red blood cells and 800 mL of fresh frozen plasma after delivery. After delivery, she experienced anorexia, headache, fever, and diarrhea. Milk production did not occur after the delivery. Although she was temporarily discharged from the hospital, she was urgently admitted to our hospital 26 days after delivery because of a serum sodium level of 118 mmol/L at the 1-month postpartum checkup. Physical examination revealed that her height was 159 cm, weight 69.5 kg, body mass index 27.5 kg/m^2, blood pressure 109/74 mmHg, pulse 84 beats/min, and body temperature 37.0℃. Physical examination of the chest and abdomen revealed no significant findings. A visual field examination revealed bilateral hemianopsia. Blood test results on admission are presented in Table 1. Sodium was 118 mmol/L, blood glucose 64 mg/dL, and C-reactive protein 2.37 mg/dL. Endocrinology data were as follows: adrenocorticotropic hormone (ACTH) 4.2 pg/mL, cortisol < 0.2 μg/dL, thyroid stimulating hormone (TSH) 0.37 U/mL, free triiodothyronine 2.56 ng/mL, free thyroxine 0.46 ng/mL. Her IgG4 level was 28 mg/dL, and 24-hour urinary cortisol concentration was < 6.6 μg/day. A rapid ACTH stimulation test was performed for the suspected adrenal insufficiency (Fig. 1A). The serum cortisol concentration after an intravenous injection of 0.25 mg of tetracosactide was low, with a peak value of 2.8 μg/dL. Hydrocortisone (15 mg/day) administration was initiated on the evening of admission. Table 2 shows the results of a stimulation test performed to evaluate the endocrine function of the pituitary hormones. A corticotropin-releasing hormone (CRH), thyrotropin-releasing hormone (TRH), and luteinizing hormone-releasing hormone (LHRH) stimulation test was performed 32 days after delivery. The patient was diagnosed with secondary adrenal insufficiency, central

Table 1. Clinical data on admission in this subject

Peripheral blood	
Red blood cells	348×10^4 /μL
Hemoglobin	10.8 g/dL
Hematocrit	29.4 %
White blood cells	5,280 /μL
Neutrophils	66.6 %
Lymphocytes	22.0 %
Monocytes	6.8 %
Eosinophils	4.2 %
Basophils	0.4 %
Platelet	21.9×10^4 /μL

Electrolytes	
Sodium	118 mmol/L
Potassium	3.8 mmol/L
Chloride	86 mmol/L

Blood biochemistry	
Total protein	6.1 g/dL
Albumin	3.2 g/dL
Total bilirubin	1.4 mg/dL
AST	8 U/L
ALT	26 U/L
γ-GTP	6 U/L
LDH	299 U/L
ALP	146 U/L
Creatinine	0.60 mg/dL
BUN	6 mg/dL
UA	3.1 mg/dL
Blood glucose	64 mg/dL
CRP	2.37 mg/dL
IgG4	28 mg/dL

Endocrine examination	
TSH	0.37 μIU/mL
FT3	2.56 ng/mL
FT4	0.46 ng/mL
ACTH	4.2 pg/mL
Cortisol	< 0.2 μg/mL
GH	1.45 ng/mL
IGF-1	53 ng/mL
PRL	11.6 ng/mL
LH	0.85 mIU/mL
FSH	2.57 mIU/mL
ADH	0.7 pg/mL

Abbreviation: AST, aspartate aminotransferase; ALT, alanine aminotransferase; γ-GTP, γ-glutamyl transpeptidase; LDH, lactate dehydrogenase; ALP, alkaline phosphatase; BUN, blood urea nitrogen; UA, uric acid; CRP, C-reactive protein; TSH, thyroid-stimulating hormone; FT3, free triiodothyronine; FT4, free thyroxine; ACTH, adrenocorticotropic hormone; GH, growth hormone; IGF-1, Insulin-like growth factor; PRL, prolactin; LH, Luteinizing hormone; FSH, Follicle-stimulating hormone; ADH, antidiuretic hormone.

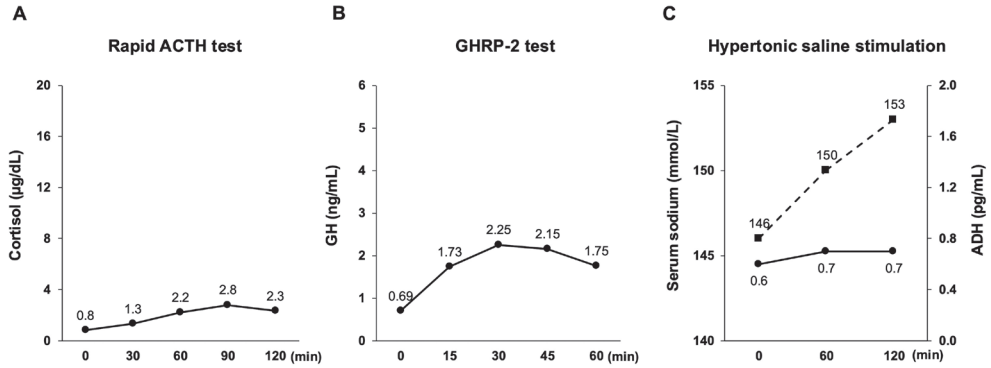

Fig. 1. The results of the rapid ACTH stimulation test (A), growth hormone-releasing peptide-2 (GHRP-2) test (B), and hypertonic saline stimulation (C).

Table 2. Result of CRH/TRH/LHRH stimulation test in this subject after delivery

Day 32	0 min	15 min	30 min	60 min	120 min	180 min
ACTH (pg/mL)	2.9	6.6	7.7	8.6	5.0	3.8
TSH (μIU/mL)	0.52	1.01	1.52	1.84	2.10	0.50
LH (mIU/mL)	0.85	2.06	2.53	2.83	2.57	−
FSH (mIU/mL)	2.57	3.30	3.81	4.32	6.09	−
PRL (ng/mL)	8.4	17.1	22.2	25.8	23.0	18.2
Day 168	0 min	15 min	30 min	60 min	120 min	180 min
ACTH (pg/mL)	1.5	2.2	2.4	2.0	1.5	1.9
TSH (μIU/mL)	0.77	1.87	3.64	5.30	4.35	2.90
LH (mIU/mL)	2.97	4.81	7.14	11.89	12.73	−
FSH (mIU/mL)	4.93	5.49	6.57	8.30	10.30	−
PRL (ng/mL)	17.9	29.1	41.9	48.6	32.0	26.7
Day 504	0 min	15 min	30 min	60 min	120 min	180 min
ACTH (pg/mL)	1.5	1.5	1.6	1.5	1.5	1.5
TSH (μIU/mL)	0.90	5.94	8.83	8.19	5.22	3.30
LH (mIU/mL)	3.08	7.74	12.68	16.32	20.86	−
FSH (mIU/mL)	5.69	5.78	6.56	7.59	10.34	−
PRL (ng/mL)	12.6	31.9	38.2	−	26.6	23.6

Abbreviation: CRH, corticotropin-releasing hormone; TRH, thyrotropic releasing hormone; LHRH, luteinizing hormone releasing hormone; ACTH, adrenocorticotropic hormone; TSH, thyroid-stimulating hormone; LH, Luteinizing hormone; FSH, Follicle-stimulating hormone; PRL, prolactin.

hypothyroidism, and central hypogonadism based on decreased responses of ACTH, TSH, luteinizing hormone (LH), and follicle-stimulating hormone (FSH). A growth hormone-releasing peptide-2 test performed 33 days after delivery revealed a decreased response of growth hormone secretion, leading to the diagnosis of adult growth hormone deficiency (Fig. 1B). The patient developed polyuria (6,000 mL/day after hydrocortisone administration). Hypertonic saline stimulation performed 35 days after delivery revealed no antidiuretic hormone response to the elevated sodium levels, leading to a diagnosis of central diabetes insipidus (vasopressin deficiency) (Fig. 1C). Magnetic resonance imaging (MRI) revealed that the pituitary gland was 19 × 14 × 15 mm, with equal signal intensity on T1-weighted images and high signal intensity on T2-weighted images, indicating a subacute hematoma (Fig. 2A). Based on these findings, we diagnosed the patient with early-postpartum-onset Sheehan syndrome. In addition to hydrocortisone, levothyroxine (50 mg/day) was initiated, and the patient was discharged on day 46 after delivery.

When she visited the endocrine outpatient clinic

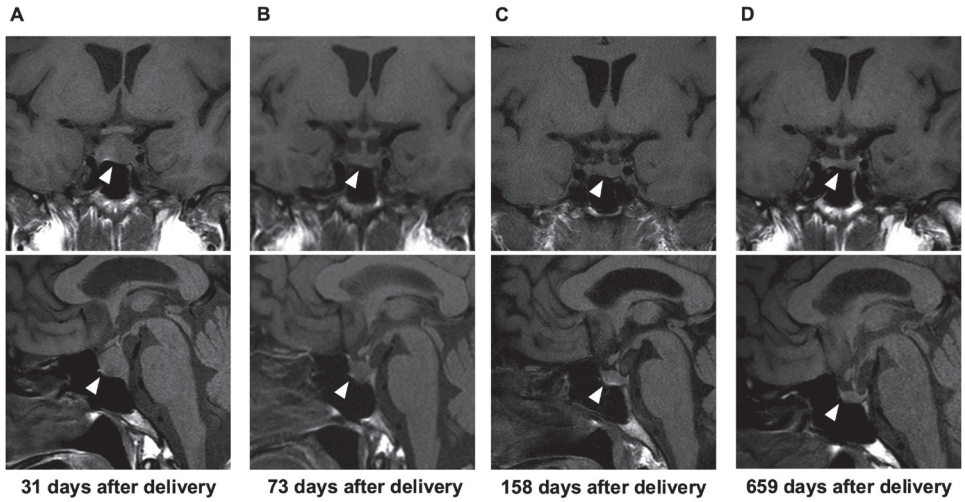

Fig. 2. Magnetic resonance imaging (MRI) of the pituitary gland. The upper panel is a coronal cross-sectional image, and the lower panel is a sagittal cross-sectional image. (A) MRI taken when Sheehan syndrome was diagnosed 31 days after delivery. The size of the pituitary gland was 19 × 14 × 15 mm. (B) MRI taken at the endocrine outpatient clinic 73 days after delivery. The size of the pituitary gland was 16 × 6.5 × 9.5 mm. (C) MRI taken at the endocrine outpatient clinic 158 days after delivery. The size of the pituitary gland was 14 × 7.5 × 9.5 mm. (D) MRI taken at the endocrine outpatient clinic 659 days after delivery. The size of the pituitary gland was 14 × 5.3 × 9.5 mm.

73 days after delivery, the polyuria and bilateral hemianopsia had mitigated. Pituitary MRI showed that the pituitary gland had decreased in size and the internal hematoma disappeared (Fig. 2B). In the CRH/TRH/LHRH stimulation tests, which were performed 168 and 504 days after delivery, TSH, prolactin, LH, and FSH secretion improved. In contrast, reactive secretion of ACTH gradually decreased (Table 2). MRI of the pituitary gland performed 158 and 659 days after delivery showed that the size of the pituitary gland had gradually decreased (Fig. 2C, 2D). The first postpartum menstruation occurred 422 days after delivery, and levothyroxine was discontinued 704 days later. She continues to take oral hydrocortisone (15 mg/day) for the ACTH deficiency.

DISCUSSION

Sheehan syndrome is a panhypopituitarism resulting from infarction and necrosis of the pituitary gland following massive hemorrhage or shock during delivery[1]. Our patient was diagnosed with adrenal insufficiency on postpartum day 32; however, it is possible that signs of adrenal insufficiency began to appear after cesarean delivery due to hypovolemic shock following massive hemorrhage associated with a massive vaginal wall hematoma. In typical cases, the time from delivery to diagnosis is 19.7 ± 10.2 years, and the hypopituitarism in Sheehan syndrome is considered irreversible[4]. However, owing to advances in endocrine testing and MRI, the number of cases diagnosed early is increasing. We searched PubMed and Google Scholar for Sheehan syndrome and summarize in Table 3 case reports in which Sheehan syndrome was diagnosed within the first month postpartum and pituitary MRI performed at the time of diagnosis[5–22].

To the best of our knowledge, there have been only 19 case reports of acute Sheehan syndrome in which pituitary MRI was performed at the time of diagnosis. Among these, eight had pituitary enlargement or pituitary apoplexy at the time of diagnosis, as observed in the present case. Pituitary

Table 3. Previous reports of acute Sheehan's syndrome evaluated by pituitary MRI

Authors	Age (years)	Time from delivery to diagnosis	Disrupted pituitary hormones	Improved hormone secretion	Pituitary MRI findings at diagnosis	Pituitary MRI follow-up (time from diagnosis to follow-up)	Follow-up pituitary MRI findings
Lavalle *et al.*[5]	30	6 hours	TSH, ACTH	TSH, ACTH	Intrasellar mass with suprasellar extension	48 days	Pituitary atrophy
Dejager *et al.*[6]	32	3 days	GH, LH, FSH, PRL, ADH	No	Pituitary mass	30 days	Normal
Lust *et al.*[7]	32	3days	TSH, ACTH	No	Pituitary enlargement	4 months	Empty sella
Bunch *et al.*[8]	23	6days	TSH, ACTH	Not stated	Pituitary enlargement	1 month	Normal
Vaphiades *et al.*[9]	40	Not stated	ACTH	ACTH	Pituitary enlargement	1 month	Normal
Wang *et al.*[10]	33	19days	LH, FSH, TSH, ACTH, PRL	Not stated	Normal	13 days	Empty sella
Kaplun *et al.*[11]	29	17 days	GH, LH, FSH, TSH, ACTH, PRL	No	Micro noncontrast areas within the pituitary gland	6 months	Empty sella
Kaplun *et al.*[11]	21	3 days	GH, LH, FSH, TSH, ACTH, PRL	No	Pituitary enlargement	11 months	Empty sella
Anfuso *et al.*[12]	35	8 days	GH, LH, FSH, TSH, ACTH, PRL	No	Poor contrast	Not stated	Pituitary atrophy
Kumar *et al.*[13]	36	4 days	TSH, ACTH, PRL, ADH	No	Normal	Not stated	Normal
Robalo *et al.*[14]	45	15 days	GH, LH, FSH, TSH, ACTH, PRL, ADH	No	Normal	None	
Sakai *et al.*[15]	37	6 days	GH, LH, FSH, TSH, ACTH, PRL	No	Slight pituitary enlargement	5 months	Empty sella
Hale *et al.*[16]	31	6 days	TSH, ACTH, PRL, ADH	No	Pituitary infarction	None	
Matsuzaki *et al.*[17]	27	8 days	GH, FSH, LH, TSH, ACTH, PRL	No	Normal	6 months	Pituitary atrophy
Windpessl *et al.*[18]	31	8 days	TSH, ACTH	No	Enhanced Pituitary Contrast Effect	1 months	Pituitary infarction
Meregildo-Rodriguez.[19]	24	4 days	GH, FSH, LH, ACTH, TSH, PRL	No	Normal	None	
Rahmani Tzvi-Ran *et al.*[20]	24	1 days	GH, FSH, LH, ACTH, PRL, ADH	No	Normal	None	
Pineyro *et al.*[21]	34	7 days	GH, ACTH, TSH	No	Pituitary enlargement	7 months	Pituitary atrophy
Olmes *et al.*[22]	28	2 days	FSH, LH, TSH, ADH	No	Pituitary infarction	None	

Abbreviation: MRI, magnetic resonance imaging; ACTH, adrenocorticotropic hormone; TSH, thyroid-stimulating hormone; GH, growth hormone; PRL, prolactin; LH, Luteinizing hormone; FSH, Follicle-stimulating hormone; ADH, antidiuretic hormone.

MRI retests were reported in 13 cases, with five cases of empty sella and three cases of pituitary atrophy. Only four cases have been reported in which the pituitary gland returned to its normal size, as observed in the present case. Early-onset Sheehan's syndrome has been reported in the postpartum period, in which pituitary function was restored by hormone replacement therapy; however, only one case of improved pituitary function has been reported[9]. Our patient presented with symptoms of Sheehan syndrome in the early postpartum period, but the size of the pituitary gland size returned to normal early on, and the patient had a very unusual course with partial improvement in pituitary function over a period of more than 1 year.

Pituitary function and MRI evaluation in the early postpartum period should be performed cautiously because of their impact on pituitary enlargement and endocrine function during pregnancy[23]. The pituitary is enlarged after delivery compared with its size in the nonpregnant state[24]. In the present case, the enlarged pituitary at the onset of Sheehan syndrome was reduced to a normal size without leaving an empty sella after a few months. Although pituitary signal changes are characteristic of pituitary stroke, contrast-enhanced pituitary MRI should be performed for a more detailed evaluation. During pregnancy, placental estrogen and progesterone levels increase, resulting in increased prolactin and ACTH levels and decreased LH, FSH, and TSH levels[25]. The patient had no milk production since delivery, and LH, FSH, and TSH levels improved over time; however, this took several years. However, ACTH secretory capacity did not improve, resulting in continued treatment for ACTH deficiency. These observations differ from those of physiological pituitary dysfunction after delivery.

In this case, Sheehan syndrome developed following massive blood loss requiring transfusion during delivery. If the correlation between Sheehan syndrome, diagnosed early postpartum and the amount of blood loss is clarified, it may be possible to promptly examine patients who are at high risk for hypopituitarism. On the other hand, few previous case reports of acute Sheehan syndrome have described in detail the amount of blood loss at delivery, and we were unable to review in detail the correlation between pituitary MRI findings and the degree of pituitary dysfunction and the amount of blood loss. Further accumulation of case reports is desirable to clarify the relationship between blood loss and Sheehan syndrome, diagnosed early postpartum.

We should bear in mind that patients with Sheehan syndrome diagnosed early in labor may have partial endocrine function improvement, although this may take a long time. Simultaneously, this case suggests that some endocrine dysfunction observed at the time of diagnosis may be permanent. Currently, there is no method to estimate improvement in endocrine function in Sheehan syndrome diagnosed in the early postpartum period. Therefore, periodic endocrine evaluations should ensure that progressive endocrine dysfunction is not overlooked.

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AUTHOR CONTRIBUTIONS

Y.I. and H.K. collected the data and wrote the manuscript. F.T., M.O., Y.K., T.K., M.S., S.N., and T.M. contributed to the discussion.

ETHICS STATEMENT

Written informed consent was obtained from the patient for the publication of this case report and the

accompanying images.

COMPETING INTERESTS

We do not have any potential conflicts of interest relevant to this article.

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