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Rare disease

Acute Sheehan's syndrome presenting as central *diabetes insipidus*

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Summary

Sheehan's syndrome occurs as a result of ischaemic pituitary necrosis due to severe postpartum haemorrhage. Improvements in obstetrical care have significantly reduced its incidence in developed countries, but postpartum pituitary infarction remains a common cause of hypopituitarism in developing countries. We report a case of severe postpartum haemorrhage followed by headache, central diabetes insipidus and failure to lactate, which prompted us to investigate and identify both anterior and posterior pituitary deficiency compatible with Sheehan's syndrome. A timely diagnosis allowed us to implement an adequate treatment and follow-up plan, which are known to improve clinical status and patient outcome.

BACKGROUND

Sheehan's syndrome occurs as a result of ischaemic pituitary necrosis due to severe postpartum haemorrhage. Improvements in obstetrical care have significantly reduced its incidence in developed countries, but postpartum pituitary infarction remains a common cause of hypopituitarism in developing countries.

Acute Sheehan's syndrome presenting as central diabetes insipidus is rare presentation and early recognition is paramount in improving a patient outcomes.

CASE PRESENTATION

A 45-year-old African-American woman, gravida 2 para 1, with multiple dichorionic pregnancy, was admitted to the obstetrics department at 21 weeks gestational age after a transvaginal ultrasound measurement had showed 10 mm of cervical length and high risk of preterm delivery. In vitro fertilisation with oocyte donation had been performed due to premature ovarian failure and early onset menopause. She had a history of chronic hypertension, and a previous full-term delivery with no complications. Her medical and family history was otherwise unremarkable.

At 26+4 weeks gestation one of the membranes of the first twin was ruptured prematurely, which was managed conservatively with a course of antenatal corticosteroids (betamethasone) and antibiotic prophylaxis (ampicillin/amoxicillin and erythromycin).

At 30 weeks gestation she entered spontaneous labour and had preterm vaginal delivery, with local anaesthesia and no other anaesthetic drugs. Live twins were born weighing 1365g and 1145g (first and second, respectively), both with Apgar score of 9 (1′) and 10 (5′) without any major interventions in the delivery room. Both neonates were admitted to the neonatal care unit for observation and postnatal care.

Within 1 h of delivery she suffered massive postpartum bleeding caused by retained placental fragments. Severe haemodynamic instability ensued, with an estimated 35–40% blood loss. There was need for fluid replacement (both colloid and crystalloid) and packed red blood cells. Haemoglobin declined from 13.6 g/dl prepartum to 7.6 g/dl 4 h postpartum (lowest value obtained). The placental fragments were manually removed followed by conventional uterine curettage within 2 h after delivery, and bleeding was controlled.

At about 8 h postpartum she began complaining of mild headache and photophobia. She had no nausea or vomiting, abdominal pain or any other symptoms. She had no history of migraine or headache.

On examination, she was alert and oriented, afebrile, pulse rate 98 bpm, and blood pressure 133/88 mm Hg. She was eupnaeic, the bleeding volume per vaginum was within normal limits and through abdominal palpation the uterus was contracted firmly and had approximately the equivalent of 18 weeks gestational age size. Neurological examination was unremarkable, including no pupillary changes, and no focal or meningeal signs.

Laboratory findings including renal and liver function, inflammatory markers and urinalysis were unrevealing and excluded pre-eclampsia.

She was started on paracetamol and metamizole with partial response, and pain slowly abated during the following days. No other symptoms were noted and she was discharged 5 days after delivery, with both analgesic drugs and a scheduled appointment within 1 week. Both twins were still at the neonatal unit with no major morbidity.

By the return visit on day 15 mild non-remitting headache was still persistent, and she was fatigued and had been unable to breastfeed due to poor milk production. She had also started noticing excessive thirst (>5 l of fluids/24 h), polyuria and mild visual disturbance. No other urinary symptoms were present. There were no psychiatric complaints and there did not seem to be a primary water-seeking behaviour.

INVESTIGATIONS

A targeted laboratory work-up including 24 h urinalysis after 12 h fluid restriction confirmed diuresis of 4.1 l, urine density 1.003 and urine osmolarity 88 mOsm/kg (simultaneous plasma osmolality 288 mOsm/kg). Plasma urea and creatinine were normal, potassium and calcium levels were normal and there were no significant changes in other serum laboratory tests. After consulting with the local endocrinologist an intranasal desmopressin challenge was performed by day 17. Urine osmolality increased up to 372 mOsm/kg which established a diagnosis of central diabetes insipidus (DI).

Basal serum hormonal tests were performed on day 22 postpartum (table 1).

There were low levels of thyroid-stimulating hormone (TSH) and free thyroxine, cortisol, prolactin and gonadotropins, all features suggestive of panhypopituitarism.

The patient was started on intranasally desmopressin with rapid response and reduction in diuresis.

A CT scan was performed the same day showing discrete enlargement of the right segment of the anterior pituitary lobe and hypoattenuation after intravenous contrast agent use. There were no significant sella turcica findings, and cerebral and vascular morphology was normal. MRI a few days later found normal anterior pituitary dimension and morphology, while the posterior pituitary gland was ectopic (infundibular region of the optic chiasm).

Hormonal stimulation tests were performed on day 42 postpartum at the endocrinology department. Results confirmed a complete deficiency of all pituitary hormones and reserve (table 2).

DIFFERENTIAL DIAGNOSIS

We considered lymphocytic hypophysitis and pituitary apoplexy as possible causes of postpartum hypopituitarism. However, imaging findings did not identify the features of any of these diagnoses, that is, respectively diffuse enlargement with contrast enhancement or a pituitary mass, or pituitary haemorrhage. Our final diagnosis was acute Sheehan's syndrome presenting as central diabetes insipidus.

TREATMENT

The patient was started on replacement treatment for individual pituitary and downstream hormonal deficiencies, which included prednisone (corticotropin and cortisol deficiency), levothyroxine (TSH and thyroxine deficiency), oestrogen-progestin (luteinising hormone (LH), follicle stimulating hormone (FSH) and oestrogen and progestin deficiency) and desmopressin (antidiuretic hormone deficiency). The patient was not interested in fertility and the oestrogen–progestin combination was given continuously. Prolactin deficiency has no standard treatment available. In our setting recombinant growth hormone replacement is not used routinely for adult-onset deficiency. We instructed the patient regarding the need for stress glucocorticoid doses in case of illness, trauma or surgery.

Table 1 Basal endocrine parameters, 22 days after delivery

Hormones (Plasma)	Units	Basal	Normal Value
TSH	μUI/mL	2.2	0.40–4.00
F T4	ng/dL	0.4	0.8–1.9
ACTH	pg/mL	13.3	10–48
Cortisol	μg/dL	5	5–25
Prolactin	ng/mL	14.2	>20 postpartum
17β Estradiol	pg/mL	34	..
FSH	mUI/mL	26	40–200
Na +	mEq/L	137	137–145

TSH: thyroid stimulating hormone; FT4: free thyroxine; FT3: free triiodothyronine; ACTH: corticotropin; FSH: follicle stimulating hormone.

Table 2 Dynamic test, 42 days after delivery

Hormones* (Plasma)	Units	0 min	30 min	60 min
TSH	μUI/mL	3,5	6,7	5,9
LH	mUI/mL	2	4,7	5
FSH	mUI/mL	5,5	6,1	6,9
Prolactin	ng/mL	5,9	17,7	2,3
GH	ng/mL	<0,05	<0,05	<0,05
Glucose	mg/dL	71	34	57
Cortisol	μg/dL	11,7	4	12

*Dynamic tests: Luteinizing hormone-releasing hormone (LHRH) and Thyrotropin-releasing hormone (TRH) for gonadotrope, prolactine and thyreotrope axis.
Insulin Hypoglycemia for growth hormone(GH) and corticotropin - cortisol axis.
TSH: thyroid stimulating hormone; LH: luteinizing hormone; FSH: follicle stimulating hormone.

OUTCOME AND FOLLOW-UP

The following year was uneventful and the patient has been well on replacement therapy. Both newborn twins were discharged at 37 days postnatal age, with autonomous feeding and no relevant morbidity. They were both doing well at regular follow-up visits with no developmental disabilities.

DISCUSSION

Sheehan's syndrome occurs as a result of ischaemic pituitary necrosis due to severe postpartum haemorrhage. It may be rarely seen without massive bleeding or after normal delivery.[1] Pituitary enlargement during pregnancy causes compression of the superior hypophyseal artery. Hypotension during delivery may result in arterial spasm of smaller vessels, apoplexy and subsequent pituitary necrosis.[2]

In developed countries postpartum haemorrhage rarely leads to Sheehan's syndrome, largely due to improvements in obstetrical care.[3] This case of Sheehan's syndrome was diagnosed soon after labour. Most cases have mild hypopituitarism, which may explain delays in recognition up to years after the inciting event.[4] Therefore, it is often misrecognised and not adequately treated.

The diagnosis of Sheehan's syndrome is based on a combination of patient's history and physical examination, laboratory tests (including hormone levels and hormone stimulation tests) and radiologic findings (preferably MRI scans). Clinical manifestations of the syndrome are most often caused by deficiencies of hormones of the anterior pituitary gland.

Involvement of the posterior lobe with central diabetes insipidus has been rarely described. Two published case series (n=20 and 28) found no cases of central diabetes insipidus.[5 6] Atmaca *et al*,[7] however, found subtle impairment of neurohypophyseal function on many patients with Sheehan's syndrome. The thirst centre might be

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affected by ischaemic damage and the osmotic threshold for the onset of thirst was increased, and 29% patients had partial central DI. In our case central diabetes insipidus symptoms was paramount in raising suspicion of Sheehan's syndrome, although other clinical features of this syndrome (headache, fatigue, absence of lactation and amenorrhoea) were also present.

Hyponatremia has been identified as the most common electrolyte disturbance, due to volume depletion, cortisol deficiency and hypothyroidism.[6] Our patient presented with borderline low natremia values and no serious symptoms, presumably due to an early stage of the disease.

Imaging findings of the pituitary gland may differ depending on the stage of the disease. Early CT and MRI scans usually demonstrate non-haemorrhagic enlargement of the pituitary gland, which are later followed by its involution, with an empty sella in late MRIs.[1 8] In our case there were early subtle anterior pituitary CT findings, while an ectopic posterior lobe suggested neurohypophysis dysfunction. The latter has been described in specific gene-associated congenital hypopituitarism or isolated hormone deficiencies, often accompanied by other cerebral malformations.[9] The history of this case did not suggest any premorbid hypopituitarism, but it does raise the issue of possible susceptibility.

In conclusion, we report a case of severe postpartum haemorrhage followed by headache, central diabetes insipidus and agalactia, which prompted us to investigate and identify both anterior and posterior pituitary deficiency compatible with Sheehan's syndrome. A timely diagnosis allowed us to implement an adequate treatment and follow-up plan, which are known improve clinical status and patient outcome.[10 11]

Learning points

- A history of severe postpartum haemorrhage is the key diagnostic feature.
- Classical manifestations include failure to lactate, amenorrhoea, asthenia, fatigue, headache and psychiatric disturbances.
- Complete central diabetes insipidus is rare, but can occur.
- Treatment of patients with hypopituitarism involves replacing individual pituitary hormonal deficiencies.
- Early treatment can improve clinical status and patient outcome.

Competing interests None.

Patient consent Obtained.

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