The price of a 15-year delay in diagnosis of Sheehan's syndrome

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We describe a case of a 48-year-old woman who presented with a 15-year history of recurrent episodes of hypoglycemia and hyponatremia leading to altered behavior and generalized seizures. She underwent full clinical assessment, endocrine tests, and a pituitary magnetic resonance scan that showed pananterior hypopituitarism secondary to postpartum pituitary necrosis (Sheehan's syndrome). She was commenced on appropriate hormone replacement therapy, which led to significant improvement in lethargy, anorexia, muscle weakness, and episodes of hypoglycemia. In addition to the alleviation of her physical symptoms, she experienced a significant improvement in her psychological well-being and reduction in hospital visits. This case illustrates the impact of delay in diagnosis of an easily treatable medical condition and its socioeconomic implications, especially for the population of a developing country like India.

Postpartum pituitary necrosis has an insidious course with varied manifestations. We present a case where a delay in its diagnosis resulted in significant morbidity to the patient.

CASE REPORT

A 48-year-old woman was brought to the endocrine clinic following transfer from an intensive care unit of another hospital, where she was being managed for lower respiratory infection complicated by severe hyponatremia (serum sodium 105 mEq/L [reference range 135–155 mEq/L]) and hypoglycemia (blood glucose 36 mg/dL [2 mmol/L]) leading to altered behavior and generalized seizures.

She had a long history of lethargy, anorexia, and episodic vomiting, which began insidiously a few months after her last pregnancy and had gradually progressed over the past 15 years. She had consulted local and regional specialists and had received symptom-driven management with no long-term benefit. Four years before presentation, she had developed persistent and progressive back pain, stooping posture, and reduced mobility. Imaging studies showed an osteoporotic spine with spondylolisthesis and deformity. She required two surgical operations over 2 years for spinal fixation, with short-term symptomatic relief. One year before presentation she was started on 50 mcg thyroxine for hypothyroidism but

discontinued it due to worsening of symptoms. Over the past 2 years during intercurrent illnesses or procedures, she developed hypotension, hyponatremia, and hypoglycemia requiring hospital admissions and had been managed with sodium and glucose replacement.

She delivered three children at home in a rural setting. Her last delivery had been complicated by significant bleeding, requiring hospitalization for blood transfusion. She had postpartum failure of lactation and her periods did not return after the delivery, but she never sought evaluation since she had completed her family.

On examination, she appeared well oriented but lethargic, withdrawn, and pale. She was tachycardic with a blood pressure of 110/70 mm Hg with a postural fall of >20 mm Hg systolic. She was weak and could not sit or stand due to dizziness. Axillary and pubic hair was scanty, and her skin was cold, pale, and wrinkled. Her hemoglobin was 10.3 g/dL, with normocytic blood tests, and her renal and liver function tests were normal. As a result of the treatment she had received, her serum sodium had risen to 121 mEq/L, and her serum potassium was normal. Anterior pituitary hormone values, listed in *Table 1*, confirmed the diagnosis of pananterior hypopituitarism.

Review of previous spinal x-rays showed spinal implant in situ extending from L4, L5 to S1 with osteopenic bones. Dual-energy x-ray absorptiometry confirmed significant osteoporosis, with a spinal T score of −2.9. Magnetic resonance imaging of the pituitary gland showed an empty sella.

A diagnosis of Sheehan's syndrome was made and the patient was commenced on 75 mcg of thyroxine and 20 mg of hydrocortisone in three divided doses. She was not started on estrogen in view of her age and was prescribed alendronate 70 mg once a week. Within 2 weeks, she showed marked improvement in general well-being with no hypoglycemia or hyponatremia. A repeat thyroid function test confirmed adequate replacement (*Table 1*). Three months later, she remained well and had regained full mobility.

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Table 1. The patient's pituitary function tests confirming anterior hypopituitarism

Hormone	Reference range	At presentation	On replacement
Thyroid-stimulating hormone (uIU/mL)	0.35–4.94	1.85	1.1
Free thyroxine (ng/dL)	0.70–1.48	0.73	1.40
Estradiol (pg/mL)	21–312	10	
Luteinizing hormone (mIU/mL)	0.90–9.33	0.95	
Follicle-stimulating hormone (IU/mL)	3.03–8.08	3.82	
Prolactin (ng/mL)	1.20–29.93	5.23	
Peak plasma cortisol (ug/dL) after intravenous injection of 250 ug synthetic adrenocorticotrophic hormone (cosyntropin)	Peak cortisol >20	0.28 at 0 min 1.36 at 30 min 2.23 at 60 min	

DISCUSSION

Sheehan's syndrome is caused by pituitary necrosis secondary to hemorrhagic hypovolemic shock during the peripartum period (1). Enlargement of the pituitary gland, small sella size, disseminated intravascular coagulation, and autoimmunity have been suggested to play a role in the pathogenesis of Sheehan's syndrome in women who suffer from severe postpartum hemorrhage (2). Improvement in obstetric care and the availability of blood transfusion have led to a significant reduction in the frequency of Sheehan's syndrome in the developed world. However, the entity remains one of the most common causes of hypopituitarism in the developing world (2).

Failure of postpartum lactation and failure of resumption of menses after delivery are the most common presenting symptoms (2). However, patients can present with a wide variety of symptoms, including feeling generally unwell, or with symptoms attributable to deficiency of individual hormones, e.g., constipation, fatigue, lethargy, dizziness, depression, or weight loss (3–7). Rarely, patients may present with hypoglycemic coma (5, 6). Although a small percentage of patients have an abrupt onset of severe hypopituitarism immediately after delivery, typically the onset of Sheehan's syndrome is insidious (7, 8). This could make an early diagnosis difficult, and a high index of suspicion is needed when patients present with a combination of the above symptoms with a history of peripartum hemorrhage. Once suspected, the diagnosis can be confirmed with pituitary

function tests and imaging, which are accessible and affordable for most patients, even in the developing world (2).

In our patient, there was a long delay in arriving at the diagnosis despite several clues, including secondary amenorrhea, premature osteoporosis, unexplained significant hyponatremia, hypoglycemia during acute stress, and worsening symptoms after thyroxine administration indicating concomitant hypocortisolemia. Several possible reasons could have contributed to this delay. Appropriate guidance was not provided on discharge after her eventful delivery and postpartum hemorrhage. The patient did not seek help for secondary amenorrhea for several years. Once she presented to health professionals, her management remained symptom-driven for a number of years without an attempt to diagnose the underlying cause.

The patient and her family had to pay a heavy price for this delay in diagnosis in the form of a physical, psychological, social, and financial burden. The patient endured poor health for several years, as well as impaired mobility, spinal deformity requiring two operations, repeated hospitalizations, and episodes of life-threatening acute illness related to adrenal crises. She had to frequently travel long distances, in a state of failing health, to seek specialist help. Her husband, who was her main caregiver, needed to be off work for a combined period of over 100 days during the previous 2 years. There was a considerable strain in family relationships due to the patient's chronic ill health. Lastly, the financial burden on the lower-middle-class family was immense, with a combined cost of Rs.600,000 (>US\$10,000), which was >2 years of the family's annual income. Once the correct diagnosis was made, her monthly cost for medications was reduced to Rs.700 (US\$14) a month.

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