Sheehan’s Syndrome: A Rare Cause of Delayed Recovery after Anesthesia

Abstract
Sheehan’s syndrome (SS) or adenohypophysal insufficiency is a rare but known complication of postpartum hemorrhage (PPH). It develops as result of ischemic pituitary necrosis secondary to a brutal and extended shock due to obstetric hemorrhage. The clinical presentation of this syndrome is variable and marked with abrupt or insidiously developing pituitary insufficiency. We report a case of 35-year-old female scheduled for laparoscopic appendicectomy under general anesthesia who developed delayed recovery. Proper history revealed that patient had history of severe PPH and was amenorrhoeic after that for last 4 years. Investigation revealed that pan hypopituitarism and neuroimaging (magnetic resonance imaging) showed reduced pituitary size. Replacement of deficient hormone leads to recovery and weaning from mechanical ventilation.

Keywords: Amenorrhea, electrolyte imbalance, hypopituitarism, postpartum hemorrhage, Sheehan’s syndrome

Introduction
Sheehan’s syndrome (SS) originally described by Sheehan in 1937 occurs as a result of ischemic necrosis of pituitary gland due to severe postpartum hemorrhage (PPH). Compression of the hypophyseal arteries, vasospasm, and thrombosis has also been described as possible causes of the syndrome. It is one of the most common causes of hypopituitarism in underdeveloped or developing countries, where the prevalence was found to be about 3% for women above 20 years of age. However, it is a rare cause of hypopituitarism in developed countries. In a study of 1,034 hypopituitary adults, SS was the sixth most frequent cause of growth hormone deficiency, being responsible for 3.1% of cases. In a retrospective nationwide analysis in Iceland, the prevalence of SS in 2009 was estimated to be 5.1 per 100,000 women.

SS is characterized by varying degrees of anterior pituitary dysfunction. Some degree of hypopituitarism occurs in nearly one-third of patients with severe PPH. Although symptomatic posterior pituitary function is uncommon, many patients have impaired neurohypophyseal function tests. The clinical presentation of this syndrome is variable; the patient can present abruptly with acute hypopituitarism or insidiously with nonspecific features. Its diagnosis is based on the clinical features of associated hormone deficiency, a suggestive obstetric history, laboratory finding of decreased hormone levels, and related radiological features. Its treatment requires lifelong replacement of the deficient hormones. We present a case of undiagnosed SS experiencing delayed recovery after anesthetic exposure which on further workup was attributed to SS.

Case Presentation
A 35-year-old, G6P6 female patient was admitted with complaint of nausea, vomiting, and diarrhea for last 2 days and fever with pain in abdomen for last 2 days. According to symptomatology, she suspected having gastroenteritis, appendicitis, cholecystitis, and pregnancy. On examination, she was looking dehydrated with sunken eyes and with generalized muscle and fat wasting [Figure 1]. The pulse was 76 bpm and blood pressure was 92/66 mmHg. Examination of abdomen revealed tenderness in right iliac fossa and rebound tenderness in left iliac fossa. Investigations revealed a hematocrit of 25.3% (with normocytic normochromic red blood cells), total leucocyte count of 9,350/μL with a normal differential count, blood

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urea 10 mg/dL, and serum creatinine 0.8 mg/dL and serum electrolytes Na⁺ 128 mmol/L, Cl⁻ 100 mmol/L, and K⁺ 3.5 mmol/L. Urine pregnancy test was negative. Upper gastrointestinal endoscopy was normal, whereas USG abdomen suggested acute appendicitis. One unit packed red cell was arranged and with the provisional diagnosis of acute appendicitis; she was posted for laparoscopic appendectomy under general anesthesia (GA) on second day of hospital admission; during this time, she was nil per oral and on iv fluids with iv ceftriaxone, metaclopramide iv, and iv paracetamol. GA was administered with endotracheal tube and controlled ventilation using fentanyl 2 μg/kg, propofol 2 mg/kg, atracuronium 0.6 mg/kg for intubation, and 0.1 mg/kg for maintenance and sevoflurane (MAC 0.8–0.9). The intraoperative course was uneventful. After the completion of one and half hour surgery, there was delayed awakening with inadequate power despite discontinuation of anesthetic agent and reversal of neuromuscular blocking agent with neostigmine (0.5 mg/kg) with glycopyrolate (0.1 mg/kg) after achieving TOF ratio 0.6 in NMT monitoring and spontaneous breathing efforts in capnograph. She was shifted to intensive care unit and put on mechanical ventilation. An arterial blood gas analysis was ordered, which revealed Na⁺ 122 mmol/L, Ca²⁺+0.588 mmol/L, Cl⁻ 84.9 mmol/L, and K⁺ 2.85 mmol/L. At this stage, delayed recovery was attributed to dyselectrolytemia due to recurrent vomiting. To correct this dyselectrolytemia, normal saline was started and K⁺ and Ca²⁺ were supplemented. In spite of electrolyte correction, condition of her remains the same. Further inquiry revealed history of progressively increasing weakness, skin pallor, and gradual loss of weight since past 4 years. Interestingly, there was history of severe PPH due to retained placenta leading to circulatory collapse following vaginal delivery 4 years back. At that time, PPH was managed conservatively with uterotonicics and blood transfusions. Since then, she was unable to breastfeed her child and was amenorrheic. MRI brain was done which revealed edema of brain and around 75% reduction in size of pituitary gland. The possible reason of brain edema was hyponatremia and laproscopic surgery in Trendelenburg position with pumoperitonium. There was no abnormality in hypothalamic, suprasellar, or para-sellar region. Hormonal profile showed in Table 1.

She was put on hormone replacement therapy: thyroxin 25 mg/day and hydrocortisone 50 mg/day. After 7 days, she become conscious and oriented with adequate muscle power and was extubated and shifted to postoperative ward on day 9 with hematocrit 30.5%, Hb 11.3 g/dL, urea 30 mg/dL and serum creatinine 0.79 mg/dL, Na⁺ 143 mmol/L, Ca²⁺+0.939 mmol/L, and K⁺ 3.45 mmol/L. Patient was referred to endocrinology OPD; there she was switched to oral prednisolone 10 mg/day and thyroxine 25 mg/day with oral contraceptives for sex hormone replacement.

**Discussion**

Clinical features of hypopituitarism and its association with destructive lesion in the pituitary was originally described by Simmonds in 1914. In 1937, Harold Leeming Sheehan reported 11 cases of hypopituitarism following intrapartum hypotension with postmortem confirmation of pituitary damage. The severity of the symptoms was related to the severity of the initial collapse. Hutchinson observed the occurrence of syndrome in early pregnancy with postmortem finding of pituitary necrosis in a woman who died at the 10th week of pregnancy following septic endometritis and pulmonary embolism.

In SS, necrotic damage to the anterior portion of the pituitary gland causes partial or complete loss of thyroid, adrenocorticoid, and gonadal functions. The diagnosis can be made reliably in the presence of lactation failure, prolonged amenorrhea and hypoglycemic crisis. However, other signs of pituitary insufficiency are often delayed and subtle leading to diagnosis being missed. In SS, inability to lactate after delivery due to prolactin deficiency and the development of amenorrhea from gonadotrophin deficiency classically occurs but clinical presentation of SS ranges from long-standing nonspecific features, such as weakness, fatigue, and anemia to profound abrupt hypopituitarism resulting in coma and death. The mean duration between

| Hormone                        | Result       | Normal range                             |
|--------------------------------|--------------|------------------------------------------|
| Serum cortisol                 | 75 ng/mL (at 9 am) | 100–200 ng/mL                           |
| Estrogen                       | 13.66 pg/mL  | Menstruating women: 15–350 pg/mL        |
| Follicle stimulating hormone   | 3.4 mIU/mL   | Postmenopausal: <10 pg/mL                |
| Luteinizing hormone            | 2.8 mIU/mL   | According to phase of menstrual cycle: 3.85–22.51 mIU/mL |
| Free T₄                        | 0.4 ng/mL    | Postmenopausal: 16.74–113.59 mIU/mL     |
| Free T₃                        | 1.3 pg/mL    | According to phase of menstrual cycle: 1.20–103.03 mIU/mL |
| Thyroid stimulating hormone    | 0.69 mIU/L   | Postmenopausal: 10.87–58.6 mIU/mL       |
| Prolactin                      | 0.4 ng/mL    |                                          |
postpartum bleeding and subsequent development of symptoms varies between 1 and 33 years. The diagnosis of SS is based on the features of hormone deficiency, a suggestive obstetric history, and decreased levels of basal hormones (free T3, T4, TSH, FSH, LH, estrogen, prolactin, cortisol, and insulin-like growth factor). Failure of postpartum menstruation due to deficiency of FSH and LH is quite common, but spontaneous pregnancies have been reported. MRI or CT of pituitary often shows empty sella turcica. Treatment is replacement of the deficient hormones.

In our case, patient developed nonspecific symptoms, inability to breastfeed her child, and amenorrhea following PPH complicated by circulatory collapse. Although the symptoms were suggestive of SS, but she remained undiagnosed till she had delayed recovery from anesthetic exposure. This case emphasizes the importance of eliciting detailed preoperative history which could have avoided the complication in this case. Following the diagnosis and hormone replacement, patient responded well and we could be able to save the patient. Few such cases have been reported sporadically with similar history and clinical finding and they responded well with hormone replacement therapy with good prognosis.

**Conclusion**

Postpartum pituitary necrosis is a known complication, but now it is rarely seen because of better obstetric care. Although presenting with vague constellation of nonspecific symptoms which are common to this age group of parous women; a strong suspicion and proper history with directed laboratory investigation can be helpful and lifesaving in such cases. It is necessary to consider this diagnosis in all patients having presented with a history of cardiovascular collapse during childbirth, whatever the cause, and in the presence of the classic signs of pituitary insufficiency. If not diagnosed early, it could cause increased morbidity and mortality.

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**Conflicts of interest**

There are no conflicts of interest.

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