

# Sheehan's Syndrome Presenting as Postpartum Psychosis

Harold Henrison C. Chiu, MD,<sup>1</sup> Ella Mae I. Masamayor, MD,<sup>2</sup> Ma. Belen B. Pilit-Hizon, MD,<sup>1</sup> Angelique Bea C. Uy, MD,<sup>1</sup> Ma. Cecille S. Añonuevo-Cruz, MD<sup>1</sup> and Gabriel V. Jasul Jr., MD<sup>1</sup>

<sup>1</sup>Division of Endocrinology, Diabetes and Metabolism, Department of Medicine, Philippine General Hospital, University of the Philippines Manila

<sup>2</sup>Department of Medicine, Philippine General Hospital, University of the Philippines Manila

## ABSTRACT

Sheehan's syndrome is characterized by hypopituitarism following ischemic necrosis of the pituitary gland caused by postpartum hemorrhage and impaired blood supply to the enlarged pituitary gland during pregnancy. The worldwide prevalence has since decreased due to improvements in obstetric care. Behavioral change is a rare presentation and is often misdiagnosed and managed as psychosis. We report a 42-year-old woman presenting with behavioral changes associated with postpartum failure of lactation and amenorrhea. Hormonal work-up revealed panhypopituitarism; serum cortisol, 98.93 (NV: 138–690 nmol/L); free T4, less than 5.15 (NV: 11.5–23.00 pmol/L); free T3, less than 2.30 (NV: 2.89–4.88 pmol/L); FSH, 3.63 (NV: 30–135 mIU/mL); LH, 3.88 (NV: 13–80 mIU/mL); serum estradiol, 3.89 (NV: 10.41–35.0 pg/mL); IGF-1, 13.13 (NV: 56–194 ng/mL); and serum prolactin, 1.8 (NV: 2.6–24.8 ng/mL). Cranial MRI with contrast revealed an atrophic pituitary gland consistent with Sheehan's syndrome. The symptoms improved substantially upon replacement with steroids and thyroid hormones and she was able to resume her routine activities. The psychiatric features of hypopituitarism can be attributed to a combination of hypothyroidism, hypoglycemia, and hypocortisolism and have been shown to reverse with adequate hormone replacement.

**Keywords:** hypopituitarism, psychosis, Sheehan's syndrome

## INTRODUCTION

Hypopituitarism following childbirth was documented more than a century ago in 1937 by British pathologist, Harold Sheehan. In a series of studies based on autopsies of women who had died in late pregnancy, at delivery, or in the puerperium, 12 out of 76 women had extensive destruction of the anterior pituitary and the common clinical feature was hemorrhagic shock rather than sepsis. He also observed that the longer the woman survived, the greater the degree of healing of the hemorrhagic areas and that, in virtually all cases, some islands of healthy pituitary tissue could be identified. The histological result consisting of mixed fibrosis and intact tissue could be distinguished from pituitary insufficiency of other causes. He interpreted that the necrosis was due to spasm or thrombosis of the arteries to the pituitary and not from embolism. After this publication, anterior pituitary infarction due to puerperal hemorrhage became known as Sheehan's syndrome.<sup>1</sup>

The prevalence of Sheehan's syndrome in the 20th-century ranged from 100–220 per 100,000 women but had since decreased due to improvements in maternal care.<sup>2</sup> Sheehan's syndrome (SS) is a relatively rare condition in the developed world. The prevalence of SS in Iceland in 2009 was 5.1 per 100,000 women.<sup>3</sup> However, the prevalence in the developing world is higher owing to poor obstetric

Corresponding author: Harold Henrison C. Chiu, MD  
Division of Endocrinology, Diabetes and Metabolism  
Department of Medicine  
Philippine General Hospital  
University of the Philippines Manila  
Taft Avenue, Ermita, Manila 1000, Philippines  
Email: harold.c.chiu@gmail.com

care and more home deliveries, as high as 3.1% of parous women more than 20 years of age who developed postpartum hemorrhage in Kashmir, India, with 66% having home births.<sup>2</sup> Furthermore, a local study done in a tertiary center in the Philippines showed a slightly lower percentage (8%) of patients diagnosed with hypopituitarism had Sheehan's syndrome as compared to a study conducted in Turkey (13.8%).<sup>4</sup> The current distribution of cases worldwide reflects the disparities in terms of healthcare services between the developed and developing world.<sup>2-4</sup>

The clinical presentation consists of a broad range of manifestations from immediate postpartum circulatory collapse among acute cases to nonspecific complaints many years after inciting event. Acquired hormone deficiency follows a typical pattern in which loss of growth hormone reserve foreshadows subsequent hormone deficits.<sup>1,5,6</sup> Thus, many population-based studies have been conducted to characterize the clinical and hormonal features of SS. Most of these studies were conducted in low to middle-income countries. The mean age at diagnosis and time from delivery varied but a majority manifest many years after the inciting event. A history of postpartum hemorrhage, failure of lactation, and amenorrhea were among the most common presenting features whereas anemia and hyponatremia are less common. Hypoglycemia, behavioral changes, and diabetes insipidus are considered rare presentations of this syndrome. Given the heterogeneous presentation of this syndrome, it is not surprising that laboratory findings are inconsistent when it comes to hormonal deficiencies with growth hormone and gonadotropins being the most commonly affected. However, no consistent pattern of deficiencies has been established.<sup>7-15</sup> In our institution, a case series of 19 patients with Sheehan's syndrome admitted from 1974–1984 revealed the mean age of diagnosis at 35.7 years, the average time of diagnosis from inciting event at 7 years, and the frequencies of manifestations and deficiencies as follows: gonadal insufficiency (100%), central hypocortisolism (95%), prolactin deficiency (84%), central hypothyroidism (79%), behavioral changes (21%), and diabetes insipidus (10%).<sup>16</sup>

## CASE PRESENTATION

A 42-year-old woman consulted our emergency room for behavioral changes. During her first pregnancy four years ago, she underwent a cesarean section for cephalopelvic disproportion. She required a transfusion of ten units of packed red blood cells for uterine atony. She noted a failure of lactation and prolonged amenorrhea post-partum but did not seek consult. During the interim, she noted new-onset dizziness, headache, mental sluggishness, pallor, fatigue, cold intolerance, loss of appetite, and weight gain. She did not have symptoms of polyuria, polydipsia, or nocturia. These symptoms persisted until one week before her admission when her husband noted mood swings, uncooperative behavior, incoherent speech, combativeness, and agitation.

She was brought to a local hospital and was managed as a case of central hypothyroidism and adrenal insufficiency from pituitary apoplexy. She was started on hydrocortisone 100 mg intravenously every 8 hours and levothyroxine 50 mcg once a day orally. She was then sent home on diazepam, levothyroxine, and prednisone but she was poorly compliant with her medications. Two weeks after her first admission, the behavioral symptoms persisted prompting her husband to bring her to our institution for further work-up and management. No baseline laboratories and imaging were available at the time of her consultation in our institution. She had an unremarkable past medical and family history. She had no known vices nor illicit drug use. At the time of consult, she was a homemaker and had a 4-year-old daughter who attended local daycare.

On admission, the patient was alert, well-groomed, but was also disoriented and with occasional inappropriate responses. She was combative requiring four-point restraints. She refused to follow commands. Anthropometrics were as follows: weight 64.5 kg, height 160 cm, BMI 25.2 kg/m<sup>2</sup> and BSA 1.673 m<sup>2</sup>. She had the following vital signs: blood pressure of 90/60 mmHg, heart rate of 72 beats per minute, respiratory rate of 20 breaths per minute, and temperature of 36.4°C. Pertinent physical examination findings included: small and atrophic breasts, grayish abdominal striae, previous low segment cesarian scar, scant pubic hair, grossly normal-appearing external genitalia, pallor, dry skin, poor skin turgor, weak pulses, cool extremities, absent axillary hair, and delayed deep tendon reflexes.

Her initial laboratory tests and hormonal work-up were consistent with panhypopituitarism, normocytic normochromic anemia, normal serum sodium, and normal urine specific gravity (Table 1). Imaging of the genital tract using transvaginal ultrasound showed an atrophic uterus with thin endometrium and atrophic ovaries. Cranial magnetic resonance imaging with contrast was performed which revealed an atrophic pituitary gland with an almost flattened shape for age and sex, and the presence of the posterior pituitary bright spot. The rest of the sellar structures, optic chiasm, third ventricle, and orbital apices all appeared normal (Figure 1).

The patient was initially seen and assessed by the psychiatry service, as part of our institution's behavioral change pathway. She was assessed to have acute delirium and was started on intramuscular haloperidol and oral risperidone on as-needed basis. However, none of these medications were administered to our patient. She was then managed as a case of panhypopituitarism from Sheehan's syndrome and was started on hydrocortisone 100 mg intravenously every 8 hours followed by oral levothyroxine 100 mcg daily. On her subsequent days of admission, she was more cooperative and was able to tolerate oral feeding. Hydrocortisone was eventually shifted to oral prednisone 10 mg given in the morning. Treatment with steroids and levothyroxine led to substantial improvement of her behavioral symptoms.

**Table 1.** Laboratory parameters and hormone levels on admission

	Patient	Normal values
<b>Serum Chemistry</b>		
FBS	112.5	70–100 mg/dL
Total cholesterol	420.27	< 200 mg/dL
HDL-C	35.14	40–60 mg/dL
LDL-C	343.04	100–127 mg/dL
Triglycerides	217.7	< 150 mg/dL
VLDL-C	43.24	12–30 mg/dL
Creatinine	84 (eGFR: 74)	46–92 $\mu$ mol/L
Sodium	135	137–145 mmol/L
Potassium	4.4	3.5–5.1 mmol/L
Chloride	99	98–107 mmol/L
Calcium (Corrected)	2.31 (2.33)	2.10–2.55 mmol/L
Magnesium	1.07	0.7–1.00 mmol/L
Albumin	39	35–50 g/L
<b>Urine Studies</b>		
Urine Specific Gravity	1.024	
<b>Hematology</b>		
Hemoglobin	112	120–160 g/L
Hematocrit	0.34	0.38–0.47
MCV	95.9	80–96 fL
MCH	31.9	27–31 pg
MCHC	333	320–360 g/L
RDW	15.5	11–16
Platelet Count	247	150–450 $\times 10^9$ /L
White Blood Cell Count	8.10	4.5–11 $\times 10^9$ /L
<b>Hormone levels</b>		
Serum cortisol (8 AM)	98.93	138–690 nmol/L
Free T4	< 5.15	11.5–23.00 pmol/L
Free T3	< 2.30	2.89–4.88 pmol/L
TSH	2.4761	0.3–3.8 mIU/mL
FSH	3.63	30–135 mIU/mL
LH	3.88	13–80 mIU/mL
Estradiol	3.89	10.41–35.0 pg/mL
IGF-1	13.13	56–194 ng/mL
Prolactin	1.8	2.6–24.8 ng/mL

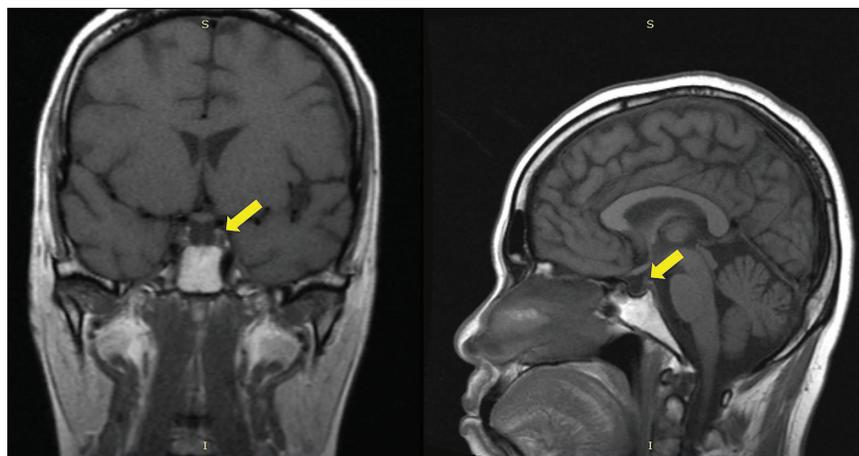
She was discharged on oral prednisone and levothyroxine without the need for any form of anti-psychotics. Following discharge, she had an improved sense of well-being and was able to resume her normal activities at home. One month post-discharge, she was started on oral hormone replacement therapy (HRT) using ethinyl estradiol and levonorgestrel on an outpatient basis following a discussion of the risks and benefits of HRT.

The study was carried out following the principles outlined in the 2008 Declaration of Helsinki. Informed consent was obtained from the patient before the beginning of the study.

## DISCUSSION

Psychosis in SS has been described as early as the time of its discovery in the 1930s. However, most of the published reports were started in the 1970s among patients admitted to psychiatric facilities but eventually turned out to be SS instead. These psychiatric features were initially treated with electroconvulsive therapy and anti-psychotics, both of which yielded poor results.<sup>17-18</sup> A summary of cases reported in literature on psychosis in SS is presented below (Table 2). All cases were given adequate steroid and thyroid hormone replacement with noted resolution of psychosis and without the need for antipsychotic medications. All patients reported an improvement in terms of quality of life and were able to resume their normal daily activities.

Behavioral change is a rare presentation of this syndrome and is often misdiagnosed and managed as a psychiatric illness. The psychiatric features can present as a combination of hallucinations, paranoid delusions, mania, depression, loss of affect, disorientation, excitability, combativeness, and aggression. These psychiatric manifestations were attributed to a combination of hypothyroidism, hypoglycemia, and hypocortisolism. These symptoms have been shown to spontaneously resolve with adequate hormone replacement.<sup>17-23</sup>



**Figure 1.** T1-weighted coronal (left) and sagittal (right) magnetic resonance images showing an atrophic pituitary gland (yellow arrows). The rest of the sellar structures, optic chiasm, third ventricle, and orbital apices all appear normal.

**Table 2.** Summary of cases reported in literature with psychosis as presenting feature of Sheehan's syndrome

Year	Age/Sex	Psychiatric Symptoms	Treatment
1970 <sup>17</sup>	55/F	Delusions and auditory hallucinations	Thioridazine
1976 <sup>18</sup>	48/F	Depression, auditory hallucinations, paranoid delusions and aggressive behavior	Electroconvulsive therapy
2011 <sup>19</sup>	49/F	Psychosis and signs of hypopituitarism	Prednisolone and levothyroxine
2013 <sup>20</sup>	31/F	Aggressive behavior	Hydrocortisone and levothyroxine
2015 <sup>21</sup>	45/F	Depression	Anti-depressants Steroids and levothyroxine
2015 <sup>22</sup>	44/F	Unwillingness to speak, nervousness, insomnia, and voice hallucinations	Steroids and levothyroxine
2017 <sup>23</sup>	46/F	Behavioral changes, talkativeness, talking to herself and insomnia	Steroids and levothyroxine

The general principles in the treatment of hypopituitarism apply to the treatment of Sheehan's syndrome and all deficient hormones should be replaced appropriately. However, hormonal replacement does not restore pituitary function and does not prevent the progression of pituitary necrosis. In addition, the pituitary function needs to be assessed at regular intervals as hypopituitarism can be progressive. Hence, lifetime follow-up with an endocrinologist is necessary to monitor the progression of hormonal deficiencies and adequacy of hormone replacement therapy.<sup>24</sup>

Lifelong glucocorticoid treatment is necessary for patients with Sheehan's syndrome. Among those who are in adrenal crises, glucocorticoid treatment should be started immediately with a parenteral injection of 50–100 mg hydrocortisone after taking serum cortisol levels. Once stable, the dose of glucocorticoid agent should be titrated according to the clinical findings instead of laboratory results. The daily physiological cortisol production in healthy individuals is about 5 to 10 mg per m<sup>2</sup> of body surface area, roughly around 15 to 20 mg per day. However, there is no reliable marker to determine the exact dose, and requirements are largely estimated. Dose adjustments are made depending on clinical status, patient preferences, and comorbidities. Currently, no available glucocorticoid treatment regimen is capable of accurately simulating the normal cortisol circadian rhythm. Hydrocortisone at 15–20 mg total daily dose in single or divided doses remains to be the recommended replacement regimen: highest dose in the morning at awakening and the second in the afternoon (two-dose regimen) or second and third dose at lunch and late afternoon, respectively (three-dose regimen). There is no superiority of one glucocorticoid over the other and more physiological replacement strategies are preferred to mimic the circadian endogenous steroid production. All patients should receive detailed information on their disease and adjustments for stressful situations such as infection, surgery, and trauma and patient education are key towards the prevention of an adrenal crisis.

Levothyroxine is the treatment of choice for lifelong thyroid hormone replacement to target serum free thyroxine levels in the mid- to upper half of the reference range. Liothyronine, thyroid extracts, or other formulations of thyroid hormones are not recommended for replacement

therapy. Furthermore, serum thyroid-stimulating hormone levels cannot be used to adjust thyroid hormone replacement doses. Caution, however, must be exercised among elderly patients and those with cardiac disease. These subsets of patients should receive levothyroxine at lower doses and each dose adjustment should be slowly titrated.<sup>24</sup>

Among premenopausal women who, in the absence of contraindications, are willing to take menopausal hormone therapy, estrogen replacement therapy may be given for those without a uterus while an estrogen plus progestogen therapy is given for those with a uterus. Among the definite benefits of estrogen and progesterone replacement therapy in Sheehan's syndrome are the prevention of premature osteoporosis and the alleviation of menopausal symptoms and cardiovascular disease.<sup>24,25</sup> Unlike the lifelong replacement of glucocorticoids and thyroid hormones, the need for gonadal replacement therapy is assessed annually by targeting the shortest total duration possible. In general, for premenopausal women without contraindications, the duration of hormone replacement lasts until the time of anticipated natural menopause, and reassessment is performed if continuation is necessary after individual risk assessment. However, hormonal replacement therapy alone is not sufficient to restore fertility. For women who desire fertility and future pregnancies, ovulation induction and assisted reproductive technologies may be employed following consultation with a fertility specialist.<sup>25</sup>

## CONCLUSION

The psychiatric features of hypopituitarism can be attributed to a combination of hypothyroidism, hypoglycemia, and hypocortisolism and have been shown to spontaneously resolve with adequate hormone replacement. As Sheehan's syndrome remains common in the developing world, a high index of suspicion, thorough medical and obstetric history, and physical examination are of paramount importance in the diagnosis as most patients will present with nonspecific symptoms which cause delays in management. Treatment remains to be lifelong and adequate hormone replacement has been shown to reduce mortality, morbidity and improve quality of life. Although adequate replacement of thyroid hormone and corticosteroids are

paramount, replacement of estrogen in young premenopausal women should not be neglected. Lifetime monitoring of anthropometrics, development of diabetes mellitus, lipid and cardiovascular abnormalities, sexual dysfunction, and quality of life are warranted.

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All authors participated in the conceptualization of work, acquisition and analysis of data, drafting and revising, and final approval of the version to be published.

### Author Declaration

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