A case of Sheehan syndrome six years postpartum with hypothyroidism and mild hyponatremia

Priya Mishra (priyam251197@gmail.com)
Ganesh Shankar Vidyarthi Memorial Medical College, Kanpur, India

Himanshu Jindal
Ganesh Shankar Vidyarthi Memorial Medical College, Kanpur, India https://orcid.org/0000-0003-0364-8147

Efa Khan
Ganesh Shankar Vidyarthi Memorial Medical College, Kanpur, India https://orcid.org/0000-0003-3800-7657

Dr. Sandeep Singh Palawat
Ganesh Shankar Vidyarthi Memorial Medical College, Kanpur, India

Case Report

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Abstract

Sheehan syndrome, also referred to as postpartum hypopituitarism is often a sequela of massive post-partum hemorrhage in resource poor healthcare settings where blood loss during delivery is often neglected. The diagnosis of this rare but fatal is disease is often delayed because the symptoms are vague and the pituitary dysfunction is insidious in nature. This condition sometimes takes more than a decade before it is diagnosed. The classic signs and symptoms include agalactia, secondary amenorrhea and dry wrinkling skin. Often an empty or a partially empty sella is seen on magnetic resonance imaging of the brain. We present the case of a 35-year-old multiparous female with anhedonia and raised serum transaminases who presented to our side with mild hyponatremia and hypothyroidism. She got diagnosed with Sheehan syndrome at our set up six years after her last obstetric event. Through this case report, we intend to provide a clinical account of the patient's condition and management.

Introduction

First described by HL Sheehan in 1937, Sheehan syndrome refers to an ischemic necrosis of the adenohypophysis due to severe hypotension usually resulting from a massive post-partum haemorrhage (PPH) [1]. It can present acutely (post-partum) or months to years after the PPH complicated delivery, with symptoms of partial or pan-hypopituitarism [2]. A study conducted in Kashmir (India) estimated the prevalence of Sheehan syndrome in India to be 2.7–3.9% in parous females aged 20–39 years [3, 4]. Most of the case load of Sheehan Syndrome is in underdeveloped or developing nations where the risk of obstetric complications is high with limited availability of skilled obstetric care, predominantly in rural regions.

Certain factors have been linked with the pathogenesis of Sheehan syndrome –pituitary enlargement in pregnancy (a two to three-fold increase in volume) via oestrogen mediated hyperplasia of lactotrophs or prolactin cells. An enlarged pituitary may compress the superior hypophyseal artery, a predisposition to severe ischemia in the case of massive blood loss[1, 5]. A small sella turcica, hypercoagulability disorders, genetic predisposition and pituitary autoimmunity are other notable contributory factors [2].

Clinical presentations vary depending on the deficient pituitary hormones, ranging from a selective hormonal insufficiency to classic pan-hypopituitarism. Agalactia and secondary amenorrhea after complicated delivery are the most common presenting symptoms to look for in making a provisional diagnosis of Sheehan syndrome [6]. Magnetic resonance imaging (MRI) of the brain is the diagnostic test of choice, an empty or partially empty sella being the characteristic finding except in acute cases. Some remarkable findings include sparse pubic and axillary hair, dry skin, fine wrinkling around the mouth, involution of breast and vaginal atrophy. Adrenocortical insufficiency due to corticotroph failure is an important consequence of Sheehan syndrome that can result in hypotension, asthenia, hypopigmentation, hyponatremia and hypoglycemia [2].

The mean interval between a complicated delivery and diagnosis of Sheehan syndrome is reported to be around 13 years [7, 8]. Delayed diagnosis can be explained by non-specific presentations such as fatigue, anemia and asthenia during the post-partum period which may be misdiagnosed as having baby blues [7]. Most patients remain asymptomatic for prolonged duration, their condition may worsen during acute stressors resulting in adrenal crisis, myxoedema, coma or death. Herein, we report a case of Sheehan syndrome in a woman who presented to a tertiary care hospital with hypothyroidism six years postpartum.

Case Presentation

A 35-year-old female, gravida three para three (G3P3), presented to the emergency medicine department with generalized body weakness for two months, fever for three days and loss of appetite for 15 days. On admission, the patient was found to be hypotensive (BP: 64/30 mm of Hg) with a pulse rate of 112/min and oxygen saturation of 95% on room air. On presentation to our side, she also had mild hyponatremia (serum sodium: 136 mEq/L, reference range: 137–140 mEq/L). She had menarche at 15 years of age with normal subsequent sexual development. She admitted to having recurrent episodes of jaundice that resolved upon the local practitioner's intervention. She also admitted that she had multiple episodes of jaw spasms in the past. Her history did not reveal hospitalization for any medical condition in the past except for her deliveries. She was on anti-tubercular therapy (ATT) for the past three months as prescribed by a physician for suspicion of tuberculosis. Her obstetrical history revealed that she was multiparous with two successful vaginal deliveries that were uneventful. However, her last vaginal delivery (six years back) at a primary health care (PHC) center yielded a stillbirth child and she was kept under observation for two days for unknown reasons. The delivery took place with the help of drugs to augment labor for a vaginal delivery. When asked, neither the patient nor the patient's attendant could confirm whether or not PPH occurred during this time. However, we anticipate that a massive PPH could have occurred during this time due to which the doctors at the PHC center had kept her under observation. This was her last delivery. She began losing weight and her health deteriorated after this delivery. Her menstrual cycle did not resume and she had had amenorrhea since then. During this time, she also lost weight and her appetite reduced significantly. She gradually had progressive body weakness and anhedonia to the extent that she could not perform day to day activities and was essentially bed ridden.

Her physical examination revealed anasarca, generalized pallor and, asthenia. She had thinning of limbs, facial edema, hair fall and dryness of skin (Fig. 1).

The CBC (complete blood count) revealed thrombocytopenia (135,000 cells/mm^3) and erythropenia (3.51 $x10^6/mm^3$). She was thus transfused with two units of blood on the third day of admission.

Table 1
Results of complete blood count (CBC), kidney panel and liver panel enzymes of the patient.

Parameter	Day 1 (On admission)	Day 4	Day 7	Day 14	Reference Range
Hemoglobin, g/dL	6.3	10.5	9.9	10.0	12-16.5
Total leukocyte count, cells/mm^3	8,700	7,500	6,600	12,100	4,000–10,000
Platelet count, cells/mm^3	135,000	79,000	61,000	38,000	150,000-450,000
Red blood cells, x 10^6 cells/mm^3	2.91	4.11	4.1	4.22	3.8–4.8
MCV, fL	62.8	62.2	72.1	72.5	80–100
MCH, pg	21.7	25.6	24.1	23.8	27–32
MCHC, g/dL	34.5	41.1	33.5	32.9	32–35
Hematocrit, %	18.2	25.6	29.5	30.6	36–46
Serum urea, mg/dL	44	-	-	46	13–43
Serum creatinine, mg/dL	1.6	-	-	1.2	0.6–1.2
Serum bilirubin (total), mg/dL	3.8	2.7	-	-	0-1.2
Serum bilirubin (direct), mg/dL	1.0	1.5	-	-	0-0.2
Serum bilirubin (indirect), mg/dL	2.8	1.2	-	-	0.2–0.7
Serum protein, g/dL	6.2	6.4	-	5.8	6.0-8.3
Serum albumin, g/dL	3.4	4.2	-	4.0	3.8–5.5
SGOT, IU/L	71	74	-	33	< 40
SGPT, IU/L	14	12	-	63	< 34
Serum ALP, IU/L	398	406	-	220	< 240

Her chest X-ray (CXR) revealed an enlarged cardiac silhouette that raised the suspicion of a massive pericardial effusion or a massive cardiomegaly (Fig. 3). A 2D echocardiography confirmed that it was a massive pericardial effusion. Her pericardial fluid was sent for examination. The following test results were insignificant or inconclusive: Ziehl-Neelsen staining, adenosine deaminase (ADA) and gram staining. The cytopathology of the pericardial fluid indicated moderate cellularity with few polymorphs and macrophages in the background of an eosinophilic proteinaceous material and red blood cells.

Her electrocardiography (ECG) findings revealed the presence of short-wave complexes. An ultrasonography of the thorax revealed mild left pleural effusion with underlying lung consolidation and right basal lung consolidation.

For further evaluation, a battery of endocrinological tests were ordered (Table 2). The hormone levels pointed towards adrenal insufficiency and hypopituitarism. A gadolinium enhanced MRI of the brain was thus advised to the patient.

Table 2
Results of hormonal investigations of the patient

Parameter	Value	Reference Range
Serum TSH, μIU/mL	0.63	0.35–5.5
Serum free T3, pg/mL	1.28	2.30-5.0
Serum free T4, pmol/mL	0.82	12–32
ACTH, pg/mL	< 5	0–46
Prolactin, ng/mL	0.689	4.79–23.3
Serum Cortisol (morning), μg/dL	1.50	3.70–19.40
Serum FSH (post-menopausal), mIU/mL	4.82	23.00-116.30
Serum LH (post-menopausal), mIU/mL	1.89	5.16–61.99

Her gadolinium enhanced MRI of the brain revealed thinning of the pituitary gland (atrophic pituitary gland) with partially empty sella (Fig. 2).

Discussion

Pituitary gland present in the sella turcica of the brain, is divided into anterior and posterior pituitary. The blood supply of the posterior pituitary comes from the inferior hypophyseal artery while the anterior pituitary is supplied indirectly by portal vessels coming from hypothalamus and posterior pituitary [9]. This low pressure system feeding the anterior pituitary makes it more susceptible to ischemia after any vascular insult [10].

During pregnancy, this gland undergoes hyperplasia, increasing the nutritional and metabolic demands of the gland. In case of a massive PPH, this gland undergoes ischemic necrosis in 1–2% of women who lose 1–2 L of blood with associated hypotension [2].This condition is known as Sheehan syndrome.

Sheehan syndrome or postpartum pituitary necrosis, is a rare complication of PPH, indicating that there are other factors responsible for its causation apart from the compromised blood supply to the gland. These include enlargement of the pituitary gland, small size of the sella, disseminated intravascular coagulation and autoimmunity [11].

The clinical manifestations associated with this condition can result from selective loss of pituitary function or even panhypopituitarism. There is often a delay of months to years in the diagnosis of the condition due to the late presentation of vague and non-specific symptoms including fatigue, weakness and anemia after the initial vascular insult [12]. Our patient presented six years after her last obstetric event because the signs of adenohypophyseal insufficiency are often delayed and subtle [13]. She gave birth to a still born and thus could not provide a history of failure to lactate. Her amenorrhea and gradual deterioration after the delivery was, to most extent, neglected until she was hospitalized.

Owing to pituitary dysfunction and hypoprolactinemia, failure to lactate can occur along with low serum level of prolactin as seen in this patient. In our patient, the history was also notable for six years of amenorrhea and low serum levels of follicle stimulating hormone (FSH) and luteinizing hormone (LH) compared to the post-menopausal levels, indicating pituitary dysfunction as the cause of early menopause. Another less frequent cause of panhypopituitarism is Lymphocytic Hypophysitis, which needs to be ruled out in the diagnosis of Sheehan syndrome. Lymphocytic Hypophysitis is an autoimmune condition leading to impaired pituitary hormonal secretion and is also associated with other autoimmune diseases, such as Hashimoto's thyroiditis, autoimmune polyglandular syndrome type 2, Grave's disease, and systemic lupus erythematosus [6]. Low serum prolactin level in this patient along with a history of PPH makes Sheehan syndrome a more likely diagnosis.

Hypothyroidism from the deficiency of thyroid stimulating hormone (TSH) secreted by the anterior pituitary is responsible for a majority of clinical manifestations in our patient. Fatigue, loss of appetite, edema, hair loss and dry wrinkling skin seen here, can be explained by the deranged thyroid profile. A major cause of pericardial effusion is hypothyroidism, which usually gets corrected on achieving a euthyroid state [14]. Pericardiocentesis was performed to rule out infectious and malignant effusion.

Pituitary dysfunction leads to disruption of normal adrenocorticotropic hormone (ACTH)-cortisol axis seen as adrenocortical insufficiency. Common features of adrenal insufficiency like weight loss, anorexia, nausea, vomiting, lethargy and fatigue along with skin pigmentation over the elbows, knuckles, lips and gingival mucosa, and loss of axillary and pubic hair have been observed in people with primary adrenal failure [15]. Hypotension, tachycardia and hyponatremia, accompanied by impaired consciousness at the time of admission of our patient, indicate that she was in a state of adrenal crisis secondary to ACTH deficiency which was confirmed by low serum levels of ACTH and cortisol on analysis (Table 2).

According to a cohort study in Costa Rica, approximately 50% of patients with Sheehan syndrome develop panhypopituitarism, whereas only adrenal insufficiency is seen in around 33% patients and the remaining present with just hypothyroidism [16].

Confirmation of diagnosis of Sheehan Syndrome is done by imaging of pituitary gland and sella turcica where an empty sella is present in about 70% of patients, and a partially empty sella is present in about 30% of patients on MRI [17].

After the establishment of diagnosis, the aim of the treatment is to correct the endocrine imbalances such as hypoglycemia and adrenal insufficiency that warrant urgent care [18]. Normal function of the thyroid, adrenals and ovaries can be maintained by hormone substitution for life. It is important to have regular follow ups for response assessment and dose regulation of the medications.

Though the occurrence of Sheehan syndrome has slowly declined over time with better management of labour and delivery, in the resource poor healthcare settings of developing countries, its cases are still witnessed owing to neglected blood loss during delivery and poor management. The late presentation of this condition can result in a delay in diagnosis. It is important to note that mild hyponatremia should not be missed as a presenting sign of adrenal failure secondary to ACTH deficiency in a patient with Sheehan syndrome as in this case. The condition can be fatal and warrants an early diagnosis through recognition of symptoms as well as blood workup in a female with massive PPH.

Declarations

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References

1. Sheehan HL. Post-Partum Necrosis of the Anterior Pituitary. Trans Edinb Obstet Soc 1938;58:13–28.
2. Keleştimur F. Sheehan's Syndrome. Pituitary 2003;6:181–8. https://doi.org/10.1023/B:PITU.0000023425.20854.8e.
3. Zargar AH, Singh B, Laway BA, Masoodi SR, Wani AI, Bashir MI. Epidemiologic aspects of postpartum pituitary hypofunction (Sheehan's syndrome). Fertility and Sterility 2005;84:523–8. https://doi.org/10.1016/j.fertnstert.2005.02.022.
4. Azeez T. Sheehan's syndrome: A descriptive case series from a developing country. Journal of Clinical and Molecular Endocrinology 2020;5:3. https://doi.org/10.36648/2572-5432.5.1.16.
5. Scheithauer BW, Sano T, Kovacs KT, Young WF, Ryan N, Randall RV. The Pituitary Gland in Pregnancy: A Clinicopathologic and Immunohistochemical Study of 69 Cases. Mayo Clinic Proceedings 1990;65:461–74. https://doi.org/10.1016/S0025-6196(12)60946-X.
6. Sethuram R, Guilfoil DS, Amori R, Kharlip J, Berkowitz KM. Sheehan Syndrome: An Unusual Presentation Without Inciting Factors. Women's Health Reports 2020;1:287–92. https://doi.org/10.1089/whr.2019.0028.
7. Ramiandrasoa C, Castinetti F, Raingeard I, Fenichel P, Chabre O, Brue T, et al. Delayed diagnosis of Sheehan's syndrome in a developed country: A retrospective cohort study. European Journal of Endocrinology / European Federation of Endocrine Societies 2013;169. https://doi.org/10.1530/EJE-13-0279.
8. Sert M, Tetiker T, Kirim S, Kocak M. Clinical Report of 28 Patients with Sheehan's Syndrome. Endocrine Journal 2003;50:297–301. https://doi.org/10.1507/endocrj.50.297.
9. Laway BA, Baba MS. Sheehan syndrome. JPMA The Journal of the Pakistan Medical Association 2021;71:1282–12568.
10. Schury MP, Adigun R. Sheehan Syndrome. StatPearls, Treasure Island (FL): StatPearls Publishing; 2022.
11. Shivaprasad C. Sheehan's syndrome: Newer advances. Indian J Endocrinol Metab 2011;15:S203–7. https://doi.org/10.4103/2230-8210.84869.

12. Matsuzaki S, Endo M, Ueda Y, Mimura K, Kakigano A, Egawa-Takata T, et al. A case of acute Sheehan's syndrome and literature review: a rare but life-threatening complication of postpartum hemorrhage. BMC Pregnancy and Childbirth 2017;17:188. https://doi.org/10.1186/s12884-017-1380-y.
13. Kumar N, Singh P, Kumar J, Dhanwal DK. Recurrent hypoglycaemia: a delayed presentation of Sheehan syndrome. BMJ Case Reports 2014;2014:bcr2013200991. https://doi.org/10.1136/bcr-2013-200991.
14. Chahine J, Ala CK, Gentry JL, Pantalone KM, Klein AL. Pericardial diseases in patients with hypothyroidism. Heart 2019;105:1027–33. https://doi.org/10.1136/heartjnl-2018-314528.
15. Pazderska A, Pearce SH. Adrenal insufficiency – recognition and management. Clinical Medicine 2017;17:258–62. https://doi.org/10.7861/clinmedicine.17-3-258.
16. Gei-Guardia O, Soto-Herrera E, Gei-Brealey A, Chen-Ku CH. Sheehan Syndrome in Costa Rica: Clinical Experience With 60 Cases. Endocrine Practice 2011;17:337–44. https://doi.org/10.4158/EP10145.OR.
17. Kanekar S, Bennett S. Imaging of neurologic conditions in pregnant patients. Radiographics 2016;36:2102–22. https://doi.org/10.1148/rg.2016150187.
18. Mittal A, MITTAL B, Mittal N. Sheehan's Syndrome: A Case Report and Literature Review. J Med Dent Sci 2020;19:28–9. https://doi.org/10.9790/0853-1904022829.

Figures

Figure 1

Photographs of the patient showing:

(A) Coarse facial features with facial edema, wrinkles, scanty scalp hair on forehead and partial loss of both eyebrows

(B) Dry, scaly and pale skin of legs

(C) Dry and scaly skin of hands

Figure 2

(a) T1 weighted MRI of the coronal section of the brain

(b) T1 weighted MRI of the saggittal section of the brain

The scans reveal thinning of the pituitary gland with partially empty sella (arrows). However, the pituitary stalk is normal in length & width.

Figure 3

Plain chest X-ray of the patient showing enlarged cardiac silhouette (arrow)