Case Report

Unusual presentation of Sheehan's Syndrome with recurrent vomiting: A case report

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Abstract

Sheehan's syndrome is often a sequela of massive postpartum hemorrhage in resource-poor developing countries where blood loss during delivery is often neglected. The diagnosis of this rare yet fatal disease is often delayed because the symptoms are vague, insidious in nature and partial deficiencies are often difficult to determine. We report the case of a 30-year-old multiparous female with recurrent vomiting and severe hyponatremia. This report highlights the subtle manifestations of Sheehan's syndrome to help clinicians establish a prompt diagnosis which can play role in improving the quality of life of the patient while also saving her from impending adrenal crisis.

Keywords:
Sheehan's syndrome, Hormones, Hypopituitarism, Hypotension, Hypovolemic shock, Postpartum Hemorrhage, Adrenal insufficiency.

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Introduction:

Sheehan's syndrome is hypopituitarism due to postpartum ischemic necrosis of the pituitary gland. It was first described in 1937 by Sheehan.[1] It is reported that Sheehan's syndrome accounts for 0.5% of all known cases of hypopituitarism in females.[2] The disease is deemed "rare" in industrialized nations, but in developing nations, due to a lack of access to sophisticated medical procedures, skilled professionals, and medical resources, which contributes to a higher prevalence of postpartum hemorrhage and subsequent Sheehan's syndrome, it is reported to occur in 5 out of every 100,000 births.[3,4] The rate is much higher in developing countries, with a prevalence of 3.1% in a state in India where more than half of the affected individuals had home deliveries.[5] The underlying mechanism leading to Sheehan's syndrome is the infarction of the physiologically enlarged anterior pituitary lobe (due to hyperplasia of prolactin-secreting cells resulting from elevated estrogen secretion) and secondary to the compression of the blood vessels supplying the gland by the enlarged gland itself or due to grossly impaired blood supply during intrapartum or postpartum events, which is therefore highly vulnerable to ischemia in the setting of hypotension and hemorrhage during delivery. Apart from adenohypophysal necrosis, other etiologies are noted: autoimmunity, tumoral, immunological, iatrogenic, traumatic, infectious and genetic.[6] Pituitary dysfunction, which slowly progresses, is thought to be due to an inflammatory or autoimmune process triggered by released antigens during pituitary necrosis and autoantibodies have been detected in patients with Sheehan syndrome, but not consistently.[7] Sheehan's syndrome can present during the postpartum period or several months or even years following delivery. A study in France showed a delay of 9 ± 9.7 years in the diagnosis of Sheehan's syndrome,[8] and a longer delay of 20.37 ± 8.34 years was noted in developing countries.[9] Women with Sheehan's syndrome have varying degrees of hypopituitarism, ranging from panhypopituitarism to only selective anterior pituitary deficiencies even sometimes in posterior pituitary hormones deficiency, causing diabetes insipidus.[10,11] The most common initial symptoms are agalactia and/or amenorrhea. Uncommonly, it can present as an emergency condition like adrenal crisis, myxedema coma, hypoglycemia, and hyponatremia precipitating by an infection or surgery.[12] Differential diagnoses include pituitary adenoma and lymphocytic hypophysitis. There may be a long delay to diagnosis; even over a decade because symptoms are often vague and pituitary dysfunction progresses gradually. We describe a case of a patient with chronic presentation of Sheehan's syndrome 6 years after the obstetric event and with no clear precipitating event.

Case Presentation:

A 30-year-lady with recurrent vomiting, generalized fatigability and chronic severe hyponatremia of unclear origin sought care at our gastroenterology outdoor department. She was hospitalized for further evaluation and treatment. During her hospital stay, physical examination raised some concerns. The patient exhibited generalized skin pallor suggesting true hypopigmentation with mild anemia (Figure 1). Her skin appeared dry; she had fine wrinkling around the mouth and eyes and her hair was thin. Initial laboratory evaluations showed anemia, with a hemoglobin level of 10.30 g/dL, random blood sugar at 3.5 mmol/L and severe hyponatremia, with a level of 109 mmol/L and potassium level at 3.10 mmol/L. All of the following tests were within normal ranges or had negative results: basic metabolic panel, lipase level, creatinine level, liver function test, urinalysis and imaging like abdominal ultrasound, upper GI Endoscopy.

To evaluate recurrent hyponatremia, further tests were given which fulfilled the diagnostic criteria of SIADH with urinary sodium 76 mmol/L, blood osmolality 236.14 mOsmol/Kg, urine osmolality 573 mOsmol/Kg. She continued to have orthostatic symptoms even after fluid resuscitation. Given the absence of an alternative cause of her symptoms, additional endocrine testing was undertaken (Table 1). Her TSH was 1.27 mIU/L, and free triiodothyronine (T3) and free thyroxine (T4) levels were 1.12pg/ml and 0.24ng/dl respectively. A 9 am cortisol level was 8.73 mcg/dL, and adrenocorticotropic hormone (ACTH) level was 15.93 pg/ml necessitating for short synachthen test which confirmed a diagnosis of adrenal insufficiency (cortisol after 30 min and 60 min were 10.20 mcg/dl and 14.70 mcg/dl). Her prolactin level was inappropriately normal at 75.64 mcIU/L. Her level of Luteinizing hormone was low at 2.64 mIU/L with Follicular stimulating hormone at 8.93 mIU/L, indicating gonadotropin hormone deficiency. Magnetic resonance imaging of the brain was consistent with partial empty sella (Figure 2).

Further inquiries during her treatment revealed that she had experienced a severe postpartum hemorrhage following the delivery of her last child 6 years prior, with an estimated blood loss of 700 mL and required two units of blood transfusion. She had delivered at home, and bleeding subsided without intervention. After childbirth, she had difficulty in lactating but her menstrual cycle was regular. She was having OCP since her childbirth; that's why having withdrawal bleeding mimicking regular menstrual cycle and flow. This was actually masking her amenorrhea with altered picture of gonadotropin deficiency. She also reported symptoms of anhedonia and light-headedness. Over the years, her primary care practitioners had evaluated her condition by TSH levels, which had remained in the normal range.

The patient was diagnosed with Sheehan's syndrome, which was associated with PRL deficiency, gonadotropin deficiency, adrenal insufficiency and secondary hypothyroidism. The patient was rehydrated with normal saline (NS), and standard dosage of oral contraceptives, prednisolone and thyroxin were started following consultation with the endocrinology department. She was initially given hydrocortisone, 5 mg in the morning and 2.5 mg in the evening, followed by levothyroxine supplementation, 75 mcg daily started 3 days later. She was strictly instructed on the nature of her illness and to take these medications for the rest of her life. Her orthostatic symptoms got resolved and significant improvement was noted following the commencement of hormone replacement.

Discussion:

The diagnosis of Sheehan's syndrome is determined by the patient's history and physical examination, and later confirmed by laboratory tests. Failure to lactate is often a common initial complaint.[13] Many of them also report amenorrhea after delivery.[14] The diagnosis of Sheehan's syndrome is not made until several years later in certain cases, when the features of hypopituitarism gradually become apparent in a woman who had postpartum bleeding.[15] Patient presents with varied symptoms depending on the specific hormone deficiencies. Growth hormone deficiency causes fatigue, decreased quality of life, and weight loss. Prolactin deficiency can cause lactation failure. Gonadotropin deficiency will often cause amenorrhea, loss of libido or genital hair loss. Corticotrophin deficiency can result in generalized fatigue, weakness, hypoglycemia, dizziness or vomiting. Symptoms of secondary hypothyroidism are clinically similar to primary hypothyroidism while having low triiodothyronine and thyroxine levels, with low or even inappropriately normal thyroid-stimulating hormone levels. Diagnosis of panhypopituitarism is straightforward, but partial deficiencies are often difficult to determine.[16] Our patient developed chronic Sheehan's syndrome, which include clinical manifestations of growth hormone deficiency, prolactin deficiency, gonadotropin deficiency and partial involvement of adrenocorticotropic and thyroid stimulating hormone. The French study found that the delay in diagnosis in patients presenting with hypothyroidism was 8.1 ± 8.5 years and in those presenting with acute adrenal insufficiency was 10.6 ± 9.4 years.[8] In our patient, the first clue to her diagnosis was her lactational failure and postpartum haemorrhage, and the next clue was the manifestation of symptoms of adrenal insufficiency in subtle ways with fatigue and anorexia which progressed to dizziness, nausea, and recurrent vomiting, all of which were unfortunately missed as findings in making a diagnosis. This can be attributed to a lack of awareness, especially given that patients with panhypopituitarism present with nonspecific symptoms, coupled with a lack of a thorough history and physical examination required to diagnose a rare disease. Laboratory tests can reveal many other abnormalities, including hyponatremia. This is the most common electrolyte imbalance, occurring in 33–69% of cases.[17,18] As a presenting manifestation of Sheehan's syndrome, severe hyponatremia causing altered level of consciousness has rarely been described in the literature. This might be due to the slow evolution of the disease into its chronic form.[19] Punwell and colleagues found mild to severe hyponatremia in 9 of 13 patients with Sheehan's syndrome.[20] The pathology behind hyponatremia in Sheehan's syndrome is still open to debate. Cases of severe hyponatremia, with serum sodium levels below 125 mmol/L, developing 16 years after postpartum haemorrhage have been reported. SIADH may be responsible for hyponatremia in Sheehan's syndrome.[12,22] Inappropriate secretion of ADH is known to occur in states of adrenocorticotropin deficiency. Animal experiments and clinical observations suggest that glucocorticoids tonically inhibit the secretion of ADH. A sudden loss or decrease in the inhibitory control may lead to rapid serum elevations of ADH. Another potential mechanism for the elevation in ADH is the uncontrolled release of the hormone from the posterior hypophysis in the setting of ischemia.[23] In our patient's case, we found hypo-osmolar hyponatremia with euvolemia, and increased urinary sodium. Low serum osmolality and elevated urine osmolality suggested SIADH. There are several other possible mechanisms by which hypopituitarism can result in hyponatremia. Hypothyroidism can cause decreased free-water clearance and subsequently hyponatremia occurs. Glucocorticoid deficiency can also cause decreased free-water clearance, independent of ADH. The potassium level in these situations is normal, because adrenal production of aldosterone is independent of pituitary. In this case, the initial hypokalemia noted could be due to gastrointestinal loss following recurrent vomiting. The patient's sodium level was subsequently normalized with commencement of hydrocortisone, and potassium was corrected with KT syrup. Anemia is a well-recognized feature of hypopituitarism. Gokalp et al. recently reported hematological abnormalities in 65 patients with Sheehan's syndrome, 80% of whom presented with anemia, compared with 25% of controls.

Many hormonal deficiencies, including hypothyroidism, adrenal insufficiency, and gonadal hormonal deficiency, can explain normochromic anemia in hypopituitarism.[24] Dynamic pituitary MRI may reveal different features depending on the stage of the disease. While early scans are not usually helpful for diagnosis, they may demonstrate a non-hemorrhagic enlargement of the pituitary gland, leading to its subsequent involution, and late scans typically show an empty sella. A secondary empty sella is considered a classical finding of Sheehan's syndrome.[25] Treatment of young female with hypopituitarism usually includes replacement of hydrocortisone first and then replacement of thyroid-stimulating hormone and estrogen with or without progesterone, depending on having a uterus. Hydrocortisone is replaced first because thyroxin therapy can exacerbate glucocorticoid deficiency and induce life threatening adrenal crisis.[14,26]

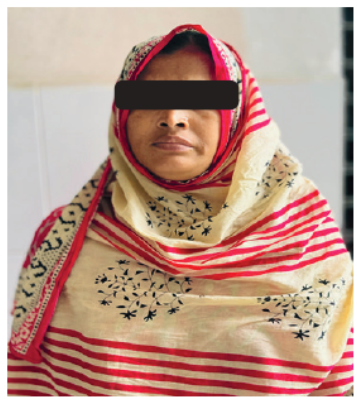

Figure I: Facial features showing fine wrinkling, skin hypopigmentation.

The standard dose of hydrocortisone is 20 mg/day for an adult (15 mg every morning and 5 mg every evening). Both gonadotropin and thyroxin replacement are titrated to each individual. Replacement of growth hormone is necessary in children with hypopituitarism but controversial in adults. Some people with severe growth hormone deficiency may derive great benefit from replacement, but standard recommendations are not available.[27] For our patient, since the clinical symptoms were caused by combination of multiple pituitary hormone deficiencies, the diagnosis was made based on the presence of specific hormone deficiency symptoms, an established obstetric history, and lowered basal hormone levels such as prolactin, luteinizing hormone, cortisol and free thyroid hormones.

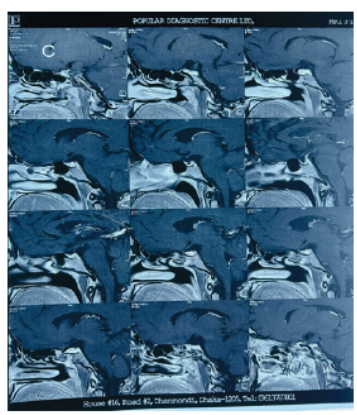

Figure II: Dynamic pituitary MRI showing partial empty sella

The investigation of choice was MRI of sella and parasellar region, which revealed a partial empty sella turcica following pituitary atrophy. We replaced relevant hormones considering her age and fertility desire.

Table: Results of endocrine evaluation

Laboratory Test	Result	Reference range, units	Interpretation
TSH	1.27	0.30-4.80 mIU/L	Inappropriately normal
Free T3	1.12	2.20-4.20 pg/ml	Low
Free T4	0.24	0.79-1.70 ng/dl	Low
9am cortisol	8.73	>15 mcg/dL	Inconclusive
ACTH	15.93	5.00-46.00 pg/mL	Low normal
Luteinizing hormone (LH)	2.64	8.70-76.30 mIU/L	Low
Follicular stimulating hormone (FSH)	8.93	3.40-33.40 mIU/L	Low normal
Prolactin	75.64	59.00-619.00 mcIU/L	Inappropriately normal
Short synacthen test (cortisol after 30min and 60 min)	10.20 14.70	>18.1 mcg/dl	Positive

Conclusion:

A high index of suspicion for Sheehan's syndrome by primary care physicians is warranted in patients with a bad obstetric history of intrapartum or postpartum hemorrhage. Signs of adenohypophysal insufficiency are often delayed and subtle leading to the diagnosis being easily missed. In some cases, the pituitary necrosis is partial and the syndrome can present in atypical and incomplete forms further complicating the diagnostic pathway. Awareness among clinicians is crucial so that such cases are not overlooked, especially in developing nations, where home delivery is still common and obstetric care is limited.

Conflict of Interest:

There is no conflict of interest of any authors in this study.

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