Original Research Article

Sheehan's syndrome: a retrospective analysis

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Abstract

Introduction: Sheehan's syndrome is defined by varying degrees of anterior pituitary hormones deficiency due to postpartum ischemia of the pituitary gland after massive postpartum haemorrhage and shock. It can present during postpartum or several months or years following delivery. Endocrinologic manifestations of hypopituitarism reveal the deficiencies of specific hormones secreted from pituitary gland including hypoadrenalism, hypothyroidism and hypogonadism.**Aims and Objectives**:To highlight the under diagnosed cases of Sheehan's syndrome. **Materials and Methods**: A retrospective analysis of Sheehan's syndrome was done over a period of 3 months from June 2019 to August 2019, at Reproductive Medicine department, IGIMS, Patna, Bihar, India; after clearance from institutional ethics committee. Case from 2010 to 2019 were taken. All the patients attending Reproductive Medicine OPD, Endocrinology OPD or presenting in Emergency with acute episodes of diarrhoea & vomiting and not maintaining BP, at IGIMS, Patna, were included. Se FSH, Se LH, Se Estradiol, Se Thyroid profile, Se Cortisol and ACTH stimulated cortisol along with CT Scan were done.We aimed to highlight the under diagnosed cases of Sheehan's syndrome (≥2 hormonal axis impairment).**Result:** A retrospective analysis was done. Total 15 cases were diagnosed. The mean age of presentation was 38.31±5.9 years.Year of presentation following last delivery was 4-16 years. Mean duration was 7.67± 3.76 years. Secondary amenorrhea and lactation failure were the most common clinical presentations. 11 patients presented with failure to resume menses following delivery and 3 had oligomenorrhea following secondary amenorrhea. 12 patients presented with lactation failure. All the 15 patients had history of severe PPH and 10 had home deliveries.The mean total tetraiodothyronine (T4), peak stimulated cortisol, stimulated growth hormone (GH), and prolactin (PRL) levels were low. Even in the presence of amenorrhoea the gonadotropins [follicle stimulating hormone (FSH) and luteinizing hormone (LH)] were inappropriately normal. Estrogen levels were low in 14 patients(93.33%). The most common hematological abnormality seen was anemia (53.33%) in 8 patients, while 5 patients (33.33%) had hyponatermia. 9 patients(60%) had empty sella turcica while 6 patients (40%) were having normal CT scan. BMD assessment (n = 15) was suggestive of low bone mass. After one year of hormonal replacement therapy, the QoL improved significantly ($P < 0.05$). **Conclusion:** Sheehan's syndrome is a frequent cause of hypopituitarism in developing countries and usually present with Subtle clinical features. It causes multiple pituitary hormone deficiencies in all patients. It is prone to be missed and delayed diagnosis is common.Severe PPH, failure to lactate and cessation of menses are important clues. In patients with Sheehan's syndrome anemia, hyponatremia, and low bone mass were frequently seen. It is eminently treatable with gratifying response. The QoL improved significantly ($P < 0.05$) after one year of hormonal replacement therapy. With improved obstetric care we canprevent it.

Keywords: PPH, Sheehan's syndrome, Secondary amenorrhoea, lactation failure.

Introduction

Sheehan's syndrome remains a frequent obstetric complication in underdeveloped or developingcountries due to relatively high prevalence of moderate to severe postpartum hemorrhage (PPH) and hypovolemic shock during or just after delivery[1,4]. Sheehan's syndrome (SS), a post partum pituitary necrosis, was first described by HL Sheehan in 1937.[5] The pituitary is one of the highly vascularized tissues in the body. Elevated concentration of estrogen during pregnancy results in hyperplasia of prolactin secreting cells or lactotrophs, leading to increase in pituitary volume by two-folds[6]. The pathophysiology of Sheehan's syndrome has been classically attributed to a transient hypoperfusion that provokes infarction, necrosis, and consequent dysfunction in a physiologically enlarged pituitary gland (due to pregnancy)[5,7,9].

At least 75-80% of pituitary is destroyed before clinical manifestations become evident. The extent of anterior pituitary hormone deficiency varies in different studies. The secretion of growth hormone (GH) and prolactin get affected in 90-100% cases, while deficiencies in cortisol secretion, gonadotropins and thyroid stimulating hormone (TSH) ranged from 50 to 100%[10-12]History of postpartum hemorrhage, failure to lactate and cessation of menses are important clues to the diagnosis. The frequency of Sheehan's syndrome has gradually decreased in developed countries due to improved obstetric care including treatment of hemodynamic complications with rapid blood transfusion and/or fluid replacement. In developing countries like India, home deliveries are still widely practised, thus, it is one of the leading causes of hypopituitarism [13].The prevalence of Sheehan's syndrome in India is estimated to be 2.7-3.9% among parous women older than 20 years.[14]It's diagnosis usually takes months to years after the event[5,11]. Due to its delayed diagnosis, clinical presentation (which usually impairs quality of life), and potentially life-threatening complications (e.g. coma or death), sheehan's syndrome still remains important to pregnant women, clinicians, and public health services around the world[11]. Recently, several studies have assessed the role that autoimmunity could have in the pathophysiology of Sheehan's syndrome[15-18]. De Bellis et al. retrospectively detected anti-hypothalamic antibodies and anti-pituitary antibodies in the serum of

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patients diagnosed with Sheehan's syndrome (40% and 35%, resp.)[17].

Materials and Methods

The present study was conducted in the Department of Reproductive Medicine at IGIMS, Patna, Bihar, India, from June 2019 to August 2019 after clearance from institutional ethics committee. Cases from July 2010 to July 2019 were taken. Based on patient's history (profound bleeding during or following the delivery, absence of postnatal lactation etc), physical examination, deficiency of one or more pituitary hormone and a CT scan for evaluation of the pituitary, diagnosis of Sheehan's syndrome was done. Routine investigations like complete blood counts (CBC), thyroid function tests and basal hormone levels (for FSH, LH, prolactin, cortisol and GH) were performed for diagnosis.

For insulin tolerance test(ITT), regular insulin was used at a dose of 0.1 U/kg. The moment at which blood glucose level fell below 40 mg/dl or less(criterion of hypoglycaemia)was accepted as the 0time point and accordingly blood samples were taken at 0, 30, 60, 90 and 120 minutes for cortisol and GH determination. An increase in cortisol level of more than 21 g/dl and increase in GH level of more than 10g/dl,during the ITT test was consider significant. An MRI (1.5T) of pituitary was done. The patients were evaluated for BMD by dual energy x-ray absorptiometry (DEXA) of femoral neck, and lumbar spine (postero-anterior projection L1-4) at the time of the diagnosis of sheehan's syndrome. With the help of Burckhardt questionnaire,[19] assessment of the quality of life was done; sixteen questions were asked to each patientboth before and after hormonal replacement therapy for one year (Prednisolone, levothyroxine and estrogen/progesterone in appropriate dosage).

Statistical analysis

Continuous data were summarized as Mean ± SD and discrete (categorical) values as numbers and percentages.

Results

The results are summarized in the tables below.

The mean age at diagnosis was 38.31±5.9 years, and mean diagnostic delay was 7.67± 3.76 years . Mean height, mean weight, mean BMI, mean systolic and diastolic BP, mean waist: hip circumference ratio and mean QOL are given in Table 1.

Anemia was the most common haematological abnormality found in 8 patients (53.33%). The most common electrolyte imbalance was hyponatremia seen in 5 patients (33.33%). Hypoglycaemia was seen in 2 patients (13.33%).

The common clinical manifestations found, were history of post partum haemorrhage in 100% of the patients, followed by secondary amenorrhea in 93.33% of patients, and lactation failure in 80% of patients.

Gonadotropins deficiency (LH and FSH) and estrogen deficiency was the most common hormonal abnormality found in the patients of Sheehan's syndrome (93.33%), followed by prolactin deficiency and growth hormonal in 86.67% of patients, ACTH deficiency in 73.33% and TSH deficiency in 66.67% of patients.

Table 5 shows the bone mineral characteristics of patients with Sheehan's syndrome. T-score, were found to be significantly reduced in lumbar spine (−2.9 ± 0.7) and femoral neck (−1.8 ± 0.7) as also the Z score; these were −1.7 ± 0.5, -1.3 ± 0.4 respectively in the patients of Sheehan's syndrome. Severe osteoporosis (osteoporosis with fracture) was found in two patients (13.33%), osteoporosis in three patients (20%), osteopenia in four patients (26.67%), while the rest of the six patients had normal BMD.

Table 6 shows the quality of life in the patients of Sheehan's syndrome before and after hormonal replacement therapy for one year. Before the start of therapy the score was 23 ± 7and it increased to 58.4 ± 7.6 after one year of hormonal replacement therapy.

Table 1: showing baseline parameters

Parameters	Mean±SD
Age at diagnosis(years)	38.31±5.9 years
Diagnostic Delay(years)	7.67± 3.76 years
Height(cm)	151±6.2
Weight(Kg)	46.4±7.2
BMI(Kg/m2)	21.6±3.4
Systolic BP(mmHg)	103.6±21.8
Diastolic BP(mmHg)	71.6±11.4
Waist: Hip circumference ratio	0.86±1.4
Quality of life scale (QOL) 112	26±7

Table 2: showing biochemical parameters

Biochemical Parameters	Mean±SD
Serum Sodium(135-145 mmol/L)	128.4±8.7
Serum Potassium(3.5-5.0 mmol/L)	4.1±1.3
Serum Calcium (8.7-10.2 mg/dL)	9.3±2.3
Serum Phosphorus(2.5-4.3 mg/dL)	3.1±0.7
Fasting plasma glucose (<100 mg/dL)	75.5±21.3
Hemoglobin (12-15 g/dL)	9.7±2.4

Table 3: showing signs and symptoms at presentation

Parameters	Number of patients	Percentage
Postpartum hemorrhage	15	100%
Secondary amenorrhea	14	93.33%
Lactation failure	12	80%
Asthenia	9	60%
Anemia	8	53.33%
Hyponatremia	5	33.33%
Hypoglycemia	2	13.33%

Table 4: Anterior Pituitary assessment (hormonal assessment of patients with Sheehan's syndrome)

Parameters	Affected Patients	Percentage

LH (3-12 IU/L) FSH (2-10 IU/L)	14/15 14/15	93.33% 93.33%
Estrogen(<40 pg/ml)	14/15	93.33%
Stimulated GH (>3 ng/mL)	13/15	86.67%
PRL (9-21 ng/mL)	13/15	86.67%
Basal cortisol (<3 µg/dL)	11/15	73.33%
T4 (55-135 ng/mL)	10/15	66.67%
T3 (0.8-2 ng/mL)	10/15	66.67%

LH: Luteinizing hormone, FSH: Follicle stimulating hormone, PRL: Prolactin, GH: Growth hormone

Table 5: BMD

Cases	Age(years)	**Lumbar spine (T- score)**	**Lumbar spine (Z- score)**	**Femoral neck (T- score)**	**Femoral neck (Z- score)**
Sheehan's Syndrome BMD	38.31±5.9 years	(−2.9± 0.7) Severe Osteoporosis	−1.7 ± 0.5, Osteoporosis	(−1.8 ± 0.7) Osteopenia	−1.3±0.4 Normal

Table 6: QOL

Cases	Age(years)	Before HRT	After HRT for 1 year
Sheehan's Syndrome		23±7	58.4±7.6

Discussion

This retrospective study was done in the Department of Reproductive Biology at IGIMS, Patna, Bihar, from June 2019 to August 2019. Cases from July 2010 to July 2019 were included. Total fifteen patients were diagnosed; patients were evaluated for the baselines parameters, clinical presentation, hormonal assessment, bone mineral density and quality of life assessment during the study. The prevalence of Sheehan's syndrome among women of reproductive age in the Kashmir valley (Indian subcontinent) was estimated to be 3.2%[14]

Sheehan's syndrome's presentation may be acute or chronic. The diagnosis of the chronic form may be delayed for many years while acute form is very rare. This interval may be as long as 15 to 20 years[20] In the present study, the diagnostic delay was 7.67± 3.76 years, with the earliest detection after 4.8 years and the longest being a duration of 17 years. The delay in diagnosis is common because most of the patients with Sheehan's syndrome, don't show frank symptoms suggestive of pituitary involvement. Also, another contributing factor in the delay in diagnosis is the lack of awareness about Sheehan's syndrome among physicians.

In the present study the most common presentations of patients with Sheehan's syndrome was history of post partum haemorrhage (100%), followed bysecondary amenorrhea (93.33%), lactation failure in 80% of patients, asthenia in 60% of patients, anemia in 53.33% of patients, hyponatremia in 33.33% and hypoglycemia in 13.33% of patients. The results of our study correspond to various studies done previously[14,21-27].

Thus, the most common electrolyte imbalance was hyponatremia (33.33%), corresponding to the study done by Dokmetas *et al*[11] The cause of anemia is believed to be due to deficient anterior pituitary hormones or absence of some other yet unidentified factors normally secreted from the pituitary.

Somatotropes (GH) and lactotrophs (PRL) are the most common cells involved in Sheehan's syndrome, followed by the gonadotrophs (LH and FSH), corticotrophs and thyrotopes. Various studies have reported partial insufficiency in 10-30% of the patients and complete pituitary insufficiency in 70-90% of the patients[14,28] Involvement of posterior pituitary is very rare but may be present in small number of patients[29,30]. In the present study, the most common hormone deficiency was of gonadropins in 93.33% of patients followed by GH, prolactin, ACTH, and thyrotropes in 86.67%, 86.67%, 73.33% and 66.67% of patients. Diabetes insipidus was not found in any of the patients.

The BMD of all the patients were recorded after diagnosis. Severe osteoporosis (osteoporosis with fracture) was seen in two patients (13.33%), osteoporosis in three patients (20%), osteopenia in four patients (26.67%), and normal BMD was found in the rest of six patients. Results of the present study are comparable to the study done by Gokalp *et al*.[31] radiological imaging also aids in the diagnosis of Sheehan's syndrome;An empty sella, as typical feature of Sheehan's syndrome was described by Fleckman *et al*.[32] It has been shown by various studies that compared to the normal controls, sella volumes decrease in patients with Sheehan's syndrome.[33] CT scan of the pituitary was done in all the patients. Nine patients(60%) had an empty sella while six patients(40%) had a normal CT scan. With the help of Burckhardt questionnairethe quality of life assessment was done;[34] sixteen questions were asked to each patient both before and after hormonal replacement therapy for one year. After one year, the score improved significantly from 23±7 to 58.4±7.6. Previously an improvement in score was reported only with GH replacement therapy[35] but in the present study, patient's scores for quality of life improved significantly without GH replacement therapy i.e after substitution with levothyroxine, prednisolone, and estrogen/progesterone.

Conclusion

Sheehan's syndrome has been usually described to affect pregnant woman after moderate to profound hypovolemic shock during delivery. However, it is usually diagnosed months to years after the hemorrhagic event due to its subtle symptoms and clinicians ignorance. We can prevent Sheehan's syndrome with improved obstetric care. Also it is eminently treatable with gratifying response. Thus, in developing countries obstetric care should be upgraded.

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