Original Article:

Sheehan's syndrome: a single centre experience

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ABSTRACT

Background: Sheehan's syndrome (SS) occurs as a result of ischaemic pituitary necrosis due to severe postpartum haemorrhage. It is one of the most common causes of hypopituitarism in developing countries.

Objective: To study the clinical profile of patients with SS presenting to the Endocrinology Department at a tertiary care teaching hospital in South India.

Methods: All patients diagnosed as SS during the study period of 2007-2012 were identified. Their clinical, biochemical, hormonal, radiological and bone mineral density (BMD) data were collected.

Results: Eighteen patients were identified. Median age of diagnosis was 40 years [interquartile range (IQR = 32-51years); median (IQR) diagnostic delay was 11 (5-17 years)]. Failure to resume menstruation and lactation failure was the most common clinical presentation. The median total tetraiodothyronine (T4), peak stimulated cortisol, stimulated growth hormone (GH), and prolactin (PRL) levels were low. The gonadotropins [follicle stimulating hormone (FSH) and luteinizing hormone (LH)] were inappropriately normal in the presence of amenorrhea. Hyponatremia was the most common electrolyte abnormality seen in 14 patients. Seven patients had anaemia and five of them had normocytic normochromic anaemia. BMD assessment (n = 9) was suggestive of low bone mass.

Conclusion: SS resulted in multiple pituitary hormone deficiencies in all the patients. Hyponatremia, anaemia, and low bone mass were frequently seen in patients with SS.

Key Words: *Sheehan's syndrome, Hypopituitarism, Simmonds disease*

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INTRODUCTION

Sheehan's syndrome (SS), which was first described by HL Sheehan, classically refers to postpartum hypopituitarism due to pituitary necrosis occurring during severe hypotension or shock secondary to massive bleeding at or just after the delivery.[1] But, before Sheehan, Glinski and Simmonds had already published autopsy findings of patients who had died after severe postpartum bleeding. It was named as Simmonds disease until 1939 when Sheehan stated that Simmonds disease was due to necrosis of the anterior pituitary following postpartum haemorrhage.[1] Thus, the condition was named after Sheehan.

The pituitary is one of the highly vascularized tissues in the body. Its volume increases two-folds during pregnancy; mostly due to the massive hyperplasia of lactotrophs as a result of elevated estrogen secretion.[2] Enlarged pituitary gland is vulnerable to ischaemia and does not have the ability to regenerate. Scar tissue substitutes the necrotic cells.[3] The presence of 50% of pituitary gland is sufficient for the maintenance of normal functions. Partial or total hypopituitarism develops with necrosis of 70% - 90% of the gland.[3] Growth hormone (GH) and prolactin (PRL) involvement is seen in 90%-100% of the patients; whereas, involvement of gonadotrophs, thyrotrophs and corticotrophs may be seen in 50%-100% of the patients.[4-6] GH deficiency is very common in SS as somatotrophs, located in the lower and lateral regions of the pituitary, are most likely to be damaged by ischaemic necrosis of pituitary.[7]

Half a century ago, the prevalence of SS was 10-20 per 100,000 women.[8] The frequency of SS

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has gradually decreased all over the world particularly in developed countries. This decrement was contributed to improved obstetric care including treatment of haemodynamic complications with rapid blood transfusion and/or fluid replacement. Thus, SS has received little attention in recent years.[9] But, in an international database [Kabi International Metabolic Study (KIMS) database] containing 1034 patients with GH deficiency, SS was the cause in 3.1% of the patients, and in a Spanish cross-sectional study, SS was the cause of GH deficiency in 6%-10% of the hypopituitarism patients.[10,11] Also, in a study done in Iceland, a prevalence of 5.1 per 100,000 women was found.[12] These data suggest the presence of SS in recent years.

The prevalence of SS in India is estimated to be 2.7%-3.9% among parous women older than 20 years.[13] Hence, in developing countries like India, where home deliveries are widely practised and obstetric care is poor, it is one of the leading causes of hypopituitarism.[14] The data from southern part of India is lacking, and no case series have been published. This dearth of data inspired us to present a case series of patients with SS.

MATERIAL AND METHODS

We retrospectively studied the case-records of patients diagnosed to have and treated for hypopituitarism in the Department of Endocrinology and Metabolism during the period 2007-2012. SS was defined as the absence of resumption of menstruation even one year after the parturition and/ or failure of lactation in the presence of documented evidence of hypopituitarism.[9] Evidence of empty sella on computed tomography (CT) or magnetic resonance imaging (MRI) was taken as corroborative evidence of pituitary necrosis in the past. Hypopituitarism was defined by presence of one or more of the following: (i) inappropriately normal or low gonadotropins; (ii) peak GH during insulin tolerance test less than 3 ng/mL; (iii) post-stimulation cortisol less than 20 μg/dL; and (iv) total triiodothyronine (T3) less than 0.8 ng/mL, and total tetraiodothyronine (T4) less than 55 ng/mL in the presence of low or inappropriately normal thyroid stimulating hormone (TSH).

Case-records of patients with SS were reviewed for clinical presentation, age at diagnosis, duration of amenorrhea, history of postpartum hemorrhage, lactation failure, height, weight, body mass index (BMI), systolic and diastolic blood pressure (BP), haemoglobin, peripheral blood smear, biochemical and hormonal data, and imaging characteristics.

Biochemical analysis

Serum luteinizing hormone (LH), T4, and T3 levels were determined by radioimmunoassay using commercially available kits [RIAK10, BRIA Mag4, BRIA Mag3; Bhabha Atomic Research Centre (BARC), Mumbai, respectively]. Serum TSH levels were measured by immunoradiometric assay (IRMAK-9; BARC, Mumbai). Serum cortisol levels were determined by radioimmunoassay using commercially available kit (Gamma CoatTM; Diasorin, USA). Immunoradiometric assays were used for analyzing serum levels of follicle stimulating hormone (FSH) (Immunotech, Czech Republic), PRL (Immunotech, Czech Republic) and GH (Izotop, Budapest) respectively.

Dynamic tests

All GH stimulation tests were performed after the patients were rendered euthyroid and were on adequate glucocorticoid replacement. For stimulated GH levels, a standard insulin tolerance test was performed using regular insulin given at 0.1 U/kg of body weight intravenously. Blood samples for GH determination were taken at 0, 30, 60, 90 and 120 minutes after the injection of insulin. Blood glucose level of 40 mg/dL or less with symptoms suggestive of hypoglycaemia such as sweating or palpitations was considered as hypoglycaemia. For assessing the hypothalamic-pituitary-adrenal axis, 250 μg of injection Synacthen was administered intramuscularly and blood was collected at 30 min and 60 min after the injection for cortisol.

Imaging

MRI (1.5T; Symphony Maestro, Siemens-Germany), or CT (Somatom definition AS+, Siemens-Germany) of pituitary was done. At the time of the diagnosis of SS, patients were evaluated by dual energy x-ray absorptiometry (DEXA) (Hologic, Discovery QDRS) to determine BMD, T-score and Z-score using the Asian BMD database. Measurements included DEXA of femoral neck, total hip and lumbar spine (postero-anterior projection L1-4). The data collected was anonymized. All results are expressed as median with interquartile range (IQR).

RESULTS

During the study period, 18 patients with SS were diagnosed. The median age of presentation was 40 years (IQR = 32-51). The median time elapsed between the obstetrical event and the diagnosis of SS was 11 years with a minimum of 6 months to maximum of 28 years. Clinical, biochemical, anthropometric characteristics of the patients are shown in Table 1. The BMI, systolic BP, diastolic BP and fasting plasma glucose, were on the lower side of normal.

Salient clinical manifestations were as described below. Failure to resume menstruation even 1 year after the last delivery was present in 17 patients. One patient presented with lactation failure and amenorrhoea six months following delivery of a live baby. Of the total 18 patients, four had SS following still birth and one following an abortion. The prevalence of various symptoms and signs at presentation are shown in Table 2. Metabolic encephalopathy and secondary adrenal crisis was seen in five and four patients respectively. Hyponatremia (serum sodium < 130 mmol/L) was the most common electrolyte abnormality seen in our study. Anaemia (haemoglobin < 10 g/dL) was seen in seven patients and five of the seven anaemic patients had normocytic normo chromic anaemia on peripheral smear.

The results of serum levels and a review of anterior pituitary function tests are given in Table 3. All the values were below the reference range. In the presence of amenorrhea with multiple pituitary hormone deficiencies the normal levels of FSH and LH was suggestive of hypogonadotropic hypogonadism. No patient had clinical features of diabetes insipidus, so the posterior part of the pituitary was not evaluated further.

Imaging features could be retrieved in 12 patients only. Ten patients had empty sella on CT/MRI and the remaining two had normal radiologic appearance on CT. However, both of them were amenorrheic and had multiple pituitary hormone deficiencies.

Table 1: Clinical, biochemical, anthropometric characteristics

Variable	Median (IQR)
Age at diagnosis (years)	40.0 (32-51)
Height (cm)	152 (145.5-158.5)
Weight (Kg)	44 (41-50)
BMI (Kg/m2)	19.3 (17.6-21.6)
Systolic BP (mm of Hg)	100 (87-112)
Diastolic BP (mm of Hg)	70 (60-72)
Serum sodium (135-145 mmol/L)	127 (120-130)
Serum potassium (3.5-5.0 mmol/L)	4 (3.7-4.5)
Serum calcium (8.7-10.2 mg/dL)	9.3 (9.0-9.8)
Serum phosphorous (2.5-4.3 mg/dL)	3.2 (2.5-3.7)
Fasting plasma glucose (70-110 mg/dL)	80 (72-100)
Haemoglobin (12-15 g/dL)	10.5 (8.8-11.4)

IQR=interquartile range; BMI=body mass index

Table 2: Symptoms and signs at presentation (n=18)

Symptoms	No. (%)
Amenorrhea	18 (100)
PostPartum Haemorrhage	16 (89)
Lactation failure*	10 (76)
Asthenia	9 (50)
Encephalopathy	5 (28)
Shock	4 (22)
Hyponatremia	14 (82)
Anaemia	7 (41)
Hypoglycaemia	4 (22)

* Out of 18 patients, 4 had still birth and 1 had abortion, hence lactational failure was recorded only in the 13 remaining patients

Table 3: Anterior Pituitary assessment

Hormone (reference range)	No.	Median (IQR)
T3 (0.8-2 ng/mL)	18	0.3 (0.3-0.4) ng/ml
T4 (55-135 ng/mL)	18	17.5 (15-34) ng/ml
Stimulated Cortisol (>20 µg/dL)	18	4.85 (2.8-7.5) µg/dL
LH (3-12 IU/L)	9	3 (2-5) IU/L
FSH (2-10 IU/L)	13	3.2 (1.2-5.8) IU/L
Stimulated GH (>3 ng/mL)	4	0.5 (0.35-0.5) ng/mL
PRL (9-21 ng/mL)	8	2.3 (2.3-2.9) ng/mL

T3=total triiodothyronine; T4 = total tetraiodothyronine; LH=luteinizing hormone; FSH=follicle stimulating hormone; GH=growth hormone; PRL=prolactin; IQR=interquartile range

Table 4: Bone mineral density characteristics

Case No.	Age (years)	Lumbar spine T- score	Lumbar spine Z- score
1	40	–2.6	–2.1
2	48	–1.4	–0.3
3	54	–2.6	–1.6
4	55	–3.0	–2.5
5	34	–1.2	–1.2
6	54	–2.9	–1.9
7	39	–3.3	–3.1
8	38	–2.5	–2.4
9	59	–1.6	–0.3

Lumbar spine T-scores and Z-scores were available in 9 patients at the time of the diagnosis of SS. The bone mineral densities are shown in Table 4. All patients had low bone mass (T-score < –1). Four patients had a Z score of < – 2.0.

DISCUSSION

Estimated prevalence of SS in India is 2.7%-3.9% among parous women older than 20 years.[13] This is in sharp contrast to the prevalence studies from developed countries where it is seen in 5 per 100000 women.[12] Poor obstetrical care and poor access to health care are the underlying differences between the two.[15] Failure to resume menstruation and agalactia were the most common symptoms and were reported in 100% and 72 % of the patients respectively. This is in line with the findings of Dokmetas et al (amenorrhoea in 100%, agalactia in 70%).[5] History of post partum haemorrhage was elicited in 89% of the patients which was similar to Dokmetas et al (90%).[5] Pituitary necrosis is attributable to the hypotension following post partum haemorrhage at the time of child birth. Disseminated intravascular coagulation and autoimmunity in addition to pituitary necrosis have been suggested to play a role in the development of SS.[3,16]

A diagnostic delay of more than ten years was seen in 10 of our patients, which is higher than the numbers reported by Banzal et al (27%).[6] Decade long diagnostic delay is most probably due to the vague symptoms of asthenia seen in 50% of our patients and poor access to health care. This diagnostic delay can lead to life threatening presentations such as metabolic encephalopathy and secondary adrenal crisis as occurred in nearly a quarter of our patients.

The most common electrolyte abnormality seen in our series was hyponatremia (82%) which is high in contrast to the series by Dokmetas et al (35%).[5] This is probably due to the deficiency of thyrotropins and corticotropins in all of our patients while these were deficient in 90% and 55% of the patients respectively in the series by Dokmetas et al.[5]

Anaemia was seen in seven of our patients, and our observations were similar to that reported by Dokmetas et al (45%).[5] Of the anaemic patients, five had a peripheral smear suggestive of normocytic normochromic anaemia which is consistent with the pattern expected in patients who are deficient in thyroxine and cortisol.[17] Pancytopenia is associated with hypocellular bone marrow and complete recovery has been shown to occur after achieving euthyroid and eucortisolemic state.[17] Further, it has been shown that achieving eucortisolemic status is more important in reversing the pancytopenia than achieving euthyroid status.[18]

Thyrotropin and corticotropin deficiency was documented in all our patients which was similar

to that reported by Sert et al.[4] In the background of multiple pituitary hormone deficiencies with amenorrhea, inappropriately normal levels of LH and FSH are suggestive of central hypogonadism, and were seen in all of our patients similar to that reported in other studies.[5,6] GH and PRL levels were available in 4 and 8 patients respectively and all values were below the reference range. GH and PRL deficiency has been documented in all the patients reported in two other studies.[4,5]

Imaging features could be retrieved only in 12 patients and 10 of the 12 patients had an empty sella by CT (6 of the 8) and by MRI (4 of the 4). Similar observations were documented in another study.[19] In our series, two patients had a normal sella on imaging by CT which is not the ideal imaging tool for the evaluation of pituitary as it lacks the soft tissue resolution obtainable by MRI.[20]

BMD assessment of the nine patients was suggestive of low bone mass. Further four of our patients had a Z score less than 2 suggestive of a possible secondary cause of osteoporosis. These observations are in line with the series described in another study[21] where the possible mechanism responsible for osteoporosis was suggested to be hypogonadism, GH deficiency and disorders of parathyroid hormone and calcium metabolism.

We conclude that SS was associated with multiple hormone deficiencies of at least four anterior pituitary function tests (related to the activities of lactotrophs, gonadotrophs, thyrotrophs, and corticotrophs) in our series. Failure to resume menstruation and lactation failure were the most common and earliest symptoms suggestive of SS. Thus women failing to lactate postpartum should be evaluated by measurements of serum PRL for early and timely diagnosis, as a low prolactin at this stage strongly raises the possibility of SS.[12] Our study shows that even in women presenting in the acute setting with encephalopathy or hyponatremia the possibility of SS should be kept in mind if the previous obstetric history is suggestive of the same. Asthenia was present for years before the diagnosis of SS was made in our series. A large proportion of our patients with SS also had anaemia and low bone mass which may have significant impact on their health and quality of life. A high index of suspicion is thus required to diagnose SS and the same should be looked for in all women if there is a prior history of postpartum haemorrhage with subsequent lactation failure or secondary amenorrhoea. All women who go through severe postpartum bleeding should be followed up periodically for SS.

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