Original Article

# Clinical, Endocrine, Metabolic Profile, and Bone Health in Sheehan's Syndrome

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## Abstract

**Background:** Sheehan's syndrome (SS) occurs due to ischemic pituitary necrosis resulting from severe postpartum hemorrhage (PPH). SS is characterized by varying degrees of pituitary insufficiency involving mostly the anterior lobe. Comprehensive data on SS apart from endocrine dysfunction is scarcely available. **Materials and Methods:** Thirty-eight subjects previously diagnosed with SS were enrolled in this observational study. Their clinical, biochemical, hormonal, radiological data at presentation were recorded from past records and bone density was measured in all. **Results:** Mean (±SD) age was 39 (±8.7) years and diagnostic delay was 9.3 (±5.5) years. All had history of PPH and lactation failure. About 47% were referred from emergency, and rest 53% were diagnosed from outpatient's department. Mean free T4, TSH, prolactin, morning cortisol, FSH, LH, and IGF-1 were mostly low. Panhypopituitarism was present in 97%. Hyponatremia was most common electrolyte imbalance found in about 53%. More than 40% had elevated transaminases. Dyslipidemia especially low HDL was found in 31 (81.5%) subjects. MRI of hypothalamus–pituitary region showed empty sella in 53% and partial empty sella in 47%. About 13% subjects had diabetes mellitus. Low bone mass (BMD Z-Score ≤-1) was seen in 80% and it was more severe (BMD Z-Score ≤-2) in 44% subjects, affecting predominantly lumbar spine. Bone loss at femoral neck was less prominent. **Conclusion:** Apart from variable spectrum of clinical presentation, subjects with SS have significant abnormalities in serum electrolytes, metabolic parameters. Low bone mass is also a frequent accompaniment.

**Keywords:** Hypopituitarism, low bone mass, Sheehan's Syndrome

## Introduction

Sheehan's syndrome (SS) occurs due to ischamic pituitary necrosis resulting from severe postpartum hemorrhage (PPH) first described in 1937.[1] Vasospasm, thrombosis, and vascular compression of the hypophyseal arteries have been suggested as possible causes of the syndrome. Enlargement of pituitary gland during pregnancy, small size of sella, disseminated intravascular coagulation have been thought to play a role in the pathogenesis of SS. Patients may present in the emergency with altered sensorium, loss of consciousness, seizure, shock, intractable vomiting or more commonly with chronic complaints like asthenia and weakness, dizziness, anorexia, weight loss, nausea, vomiting with typical history of failure to resume menses and lactational failure following last child birth. SS is characterized by varying degrees of pituitary dysfunction involving mostly the anterior lobe.[2] Although symptomatic posterior pituitary dysfunction is uncommon, some patients may have impaired neurohypophyseal function tests.[3] In last few decades, SS has become a rare occurrence in developed world but it is still prevalent in developing countries like ours. An epidemiological study from Kashmir valley estimated the prevalence to be about 3% for women above 20 years of age, almost two-thirds of whom had delivered babies at home.[4] In many affected patients, symptoms appears gradually over many months and even years that they are often diagnosed late after the inciting event. In a study of 60 subjects, the average time between the previous obstetric event and diagnosis of SS

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was 13 years.[5] Lack of suspicion, inertia for testing pituitary function from clinicians' part is also partly responsible for delay in diagnosis as well as treatment.

Though several studies on endocrine dysfunction in SS are available in literature, data regarding metabolic derangement and bone health in this subgroup is relatively scarce. Hence we conducted this study to assess subjects of SS more comprehensively. The objective of our study was to assess the demographic and clinical profile, endocrine dysfunction, metabolic state and most importantly the bone health in subjects of SS.

## Materials and Methods

This study was conducted in the department of Endocrinology of IPGME&R over a period of 1 year. The data was collected retrospectively in subjects with age more than 18 years having documented SS who were diagnosed and being treated with replacement therapy in the Endocrine Clinic of this institute since 2010. They must have done all necessary investigations at the time of presentation which was required by the protocol of this study. All subjects were on oral calcium supplement daily and cholecalciferol supplement at a dose of 60,000 IU monthly since the diagnosis of SS. Twenty-six subjects were on combined oral contraceptive pill and rest 12 subjects were not on oestrogen containing hormone replacement therapy voluntarily.

The diagnosis of SS was based on following criteria: history of failure of lactation and/or amenorrhea following PPH during last child birth and hypopituitarism was diagnosed by the presence of deficiency of one or more pituitary hormones.[6]

The following parameters were recorded from their treatment records at the time of their presentation: complete blood count, creatinine, liver function test, fasting lipid profile, fasting blood glucose, 2 h 75 g blood glucose , HbA1c , serum sodium, serum potassium, serum calcium, serum phosphate . Hormonal profile that was recorded retrospectively at diagnosis was: serums free T4, TSH, 8 am cortisol, prolactin, LH, FSH, and IGF-1. MRI of the hypothalamo-pituitary region that was done in subjects with biochemical evidence of hypopituitarism to exclude any structural lesion was also recorded. All subjects included in the study were subjected to assessment of bone mineral density by performing DXA at dual hip and L1-L4 region.

The institutional protocol which was followed for diagnosing hypopituitarism was documentation of deficiency of one or more anterior pituitary cell types, that is, corticotrophs, thyrotrophs, gonadotrophs, lactotrophs, and somatotrophs. Central hypothyroidism was defined by having low free T4 (Normal Range 0.8–1.9 ng/ml) with a low/normal TSH level (NR 0.4-5.0 μIU/ml). Adrenal insufficiency was defined as a cortisol level <3 mcg/dl with low or inappropriately normal ACTH or a cosyntropin stimulated cortisol level <18 mcg/dl. Hypoprolactinemia was defined as a serum prolactin <5.0 ng/mL. Hypogonadism was defined in subjects with a low or inappropriately normal FSH (NR 3–10 IU/L) and LH (NR 3–10 IU/L) in the background of amenorrhoea. IGF1 deficiency was defined as levels lower than the lower limit of the age and sex specific normal range (lower limit for detection was 25 ng/ml). Low age specific IGF -1 was taken as an evidence of GH deficiency in presence of deficiency of other hormones.

All the hormone assays in the institute were done by using the solid phase, competitive chemiluminescent immunometric assay except free T4, cortisol which were done by competitive immunoassays (Immulite-1000, Siemens' Healthcare Diagnostics).

BMD was measured by DXA (Lunar) [enCore-based X-ray bone Densitometer, Prodigy advance, version 17.0, GE Healthcare Lunar, LU43616EN, GE Medical Systems, Madison, WI, USA] using the standard protocol. Z-score and T-score at L1- L4 vertebrae, left and right femur neck were taken for analysis.

Subjects having hypopituitarism due to any other cause except SS or any other chronic disease, for example, chronic kidney disease were excluded from this study.

Statistical Package for the Social Sciences (SPSS version 21.0, SPSS Inc) was used for data processing and analysis. Shapiro–Wilk test was applied to check the normality of the parameters. Accordingly, continuous data with normal distribution were expressed as mean ± SD. Categorical data were expressed as counts and percentage. Correlation between between variables was assessed by Spearman's Rho.

Written informed consent was taken from all subjects. The study was approved by Institutional Ethics Committee of Institute of Post Graduate Medical Education and Research. Kolkata, West Bengal, India.

## Results

In this observational study, 38 subjects with SS were included. Mean (±SD) age of the participants was 39 (±8.7) years. The mean interval between inciting event to the diagnosis of SS was 9.3 (±5.5) years. The mean duration of treatment was 4.5 ± 3.6 years. At initial presentation, their mean body weight was 49.7 ± 4.8 Kg. The mean body mass index was 20.3 ± 2.7 kg/m$^2$. The mean systolic and diastolic blood pressures were 116 ± 5.1 and 74 ± 4.7 mm Hg during time of diagnosis. The baseline features are presented in Table 1.

All 38 subjects had history of PPH and lactation failure. Five out of 38 subjects presented with history of loss of consciousness or seizure, shock and documented hypoglycemia. Two of them had history of both shock and documented hypoglycemia, 1 patient had history of both loss of consciousness and shock in the emergency, 6 patients had history of repeated loss of consciousness only, 3 had repeated shock like features which resolved with IV normal saline, and 1 had hypoglycemia as the only presenting feature. Remaining 20 subjects (53%) visited OPD with chronic complaints of anorexia, nausea,

frequent vomiting, weight loss, dizziness and depression and subjectively poor quality of life. All 38 subjects had history of asthenia before presentation. Overall, loss of consciousness, shock and hypoglycemia were present in 12, 11, and 8 subjects, respectively.

Thirty-seven (97.4%) subjects had history of secondary amenorrhoea and only 1 patient (2.6%) had regular menses. All those 37 subjects were found to have panhypopituitarism, that is, all anterior pituitary cell lines were affected in them. Thirty (78.9%) subjects had IGF1 level below detection limit, that is, <25 ng/ml, and 8 subjects had detectable level of IGF1 though below the age and sex specific normal range. Only 1 subject had preserved gonadotroph axis. Eighteen subjects (47.3%) had morning cortisol below detection limit, that is, <1 mcg/dl, rest of them had detectable level but far below the lower normal limit. The mean values of other anterior pituitary hormones are given in Table 2. None of our subjects presented with features of polyuria or diabetes insipidus. Twenty-one subjects (53.33%) had empty sella in MRI of hypothalamus-pituitary region and remaining 17 subjects had partial empty sella. None of them had any evidence of mass lesion in MRI. Figure 1 and Figure 2 show T1 and T2 weighted sagittal image of a subject with empty sella in MRI.

**Table 1: Demographic and Clinical parameters of the study participants**

| Parameters ($n$=38) | Mean±SD |
|---|---|
| Age (years) | 39±8.7 |
| Body weight (Kg) | 49.7±4.8 |
| BMI (Kg/m$^2$) | 20.3±2.7 |
| Systolic BP (mmHg) | 116±5.1 |
| Diastolic BP (mmHg) | 74±4.7 |
| Diagnostic delay (years) | 9.3±5.5 |
| Duration of treatment (years) | 4.5±4.6 |
| Haemoglobin (gm/dl) | 10.1±1.6 |
| Serum Sodium (mEq/L) | 129±12.3 |
| Serum Potassium (mEq/L) | 4.0±0.6 |
| Serum Calcium (mg/dL) | 8.7±0.9 |
| Serum Phosphorous (mg/dL) | 3.5±0.5 |
| Fasting Plasma Glucose (mg/dl) | 89±23.3 |
| ALT (IU/L) | 34.7±29.2 |
| AST (IU/L) | 41.0±36.1 |
| Total Cholesterol (mg%) | 187±36 |
| LDL (mg%) | 84±30 |
| HDL (mg%) | 43±8 |
| Triglyceride (mg%) | 144±47 mg |
| Non-HDL Cholesreol (mg%) | 144±37 |

**Table 2: The mean values anterior pituitary hormones**

| Pituitary Hormones ($n$=38) | Mean±SD |
|---|---|
| FreeT4 (ng/dl) | 0.5±0.4 |
| TSH (micro IU/ml) | 3.1±3 |
| Prolactin (ng/ml) | 2.7±2 |
| FSH (IU/L) | 4.1±2 |
| LH (IU/L) | 2.17±1.3 |

Serum cortisol was <1 µg/dl in 17 subjects and below 3 µg/dl in rest. IGF-1 was <25 ng/ml in 30 subjects. Hence mean value of these two parameters could not be calculated

Hyponatremia (<135 mEq/L) was found in 20 subjects (52.6%) but hyperkalemia (>5 mEq/L) in only 1 subject (2.6%). The mean sodium and potassium was 129 ± 12.3 mEq/L and 4.02 ± 0.98 mEq/L, respectively. Hypocalcaemia was seen (<8 mg/dl) in 6 subjects (15.7%) and hypophosphatemia (>4.5 mg/dl) in one subject (2.6%). The mean sodium and potassium levels were 8.76 ± 0.82 mg% and 4.3 ± 1.3 mg%, respectively. The mean albumin and albumin corrected calcium were 3.9 ± 0.44 gm% and 8.76 ± 0.89 mg%.

Elevated ALT and AST were found in 16 and 12 subjects (42.1% and 31.57%, respectively) with levels above the upper normal limit for adult females (Normal level of ALT in women used in this study was 19 to 25 IU/L as per American College of Gastroenterology, Clinical Guideline: Evaluation of Abnormal Liver Chemistries 2017). Striking elevation of ALT and AST (above three times of the upper normal limit) were in found only in 5 subjects (13.1%) and 4 subjects (10.5%), respectively. However, there was no clinical suggestion of liver disorders in them. The mean ALT and AST levels were 34.7 ± 29.2 IU/L and 41.0 ± 36.1 IU/L.

Serum triglyceride was elevated (>150 mg%) in 12 subjects (31.57%), elevated LDL (>100 mg%) in 5 (13.15%), low HDL (<50 mg%) in 31 (81.5%) subjects. Non-HDL cholesterol was found to be raised (>130 mg%) among 25 (65.8%) subjects. The mean total cholesterol, LDL, non-HDL cholesterol, HDL and triglyceride of the subjects were 187 ± 36 mg%, 84 ± 30 mg%, 144 ± 37 mg%, 43 ± 8 mg%, 144 ± 47 mg%, respectively. Five subjects (13%) were diagnosed to have diabetes mellitus as per fasting blood glucose or $HbA_1c$ criteria.

Seventeen subjects (44.7%) had low bone mass in L1–L4 spine with an age matched BMD Z-score ≤-2. BMD Z-score value of ≤-1 in L1- L4 spine was present in 31 subjects (81.5%). BMD Z-score in either of the femur ≤-1 was present in 11 (28.9%) subjects. Sixteen subjects (42.1%) had a BMD T-score ≤-2.5 in L1–L4 spine. BMD T-score value ≥-2.5 and ≤-1 in L1- L4 spine was present in 19 subjects (50%). BMD T-score in either of the femur <-2.5 was present in 3 subjects. The mean BMD Z score and BMD T score in lumbar spine were 1.67 ± 0.98 and 2.3 ± 1.08, respectively. Statistically significant and moderately strong correlation was seen between the duration of untreated period in SS patients and BMD Z-score at L1–L4 spine (Spearman's Rho -0.553, $P < 0.001$). All the subjects in this cohort were on daily calcium supplement and monthly supplementation of cholecalciferol at a dose of 60,000 IU.

## Discussion

SS, as etiology of hypopituitarism, is presently very rare in developed countries due to advancement of obstetric care.

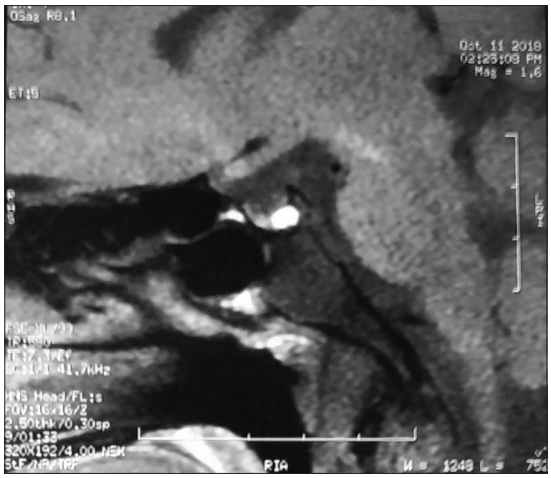


**Figure 1:** T1 weighted sagittal MRI of a subject with Sheehan's Syndrome showing compressed pituitary and presence of CSF in pituitary fossa

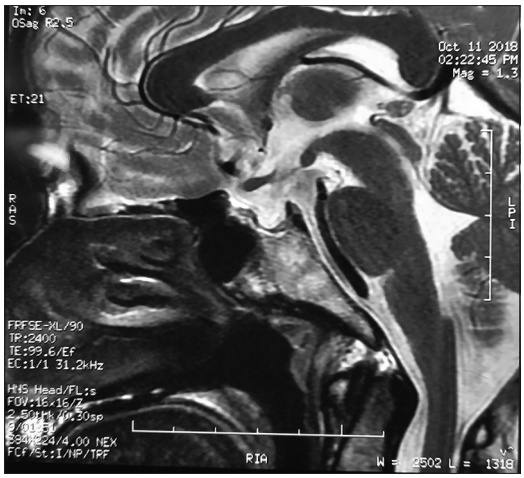


**Figure 2:** T2 weighted sagittal MRI of the same subject showing hyperintensity due to presence of CSF in pituitary fossa

However this is still one of the most important long-term obstetric complications in developing countries. In this study, mean age of the participants was 39 (±8.7) years with a range of 24–51 years which is similar to other Indian studies.[4,7] The mean interval between inciting event to diagnosis of SS in our study population was 9.3 (±5.5) years. However, other studies have documented more delay in diagnosis of SS from the previous obstetric event.[5,8] This delay between the inciting event and diagnosis suggests that most of the subjects are asymptomatic for several years or have nonspecific symptoms overlooked by both subject and the treating clinician.

PPH and lactation failure was present in 100% cases corroborating with findings from other studies.[7-9] Forty-seven percent subjects were referred from emergency presenting with features of loss of consciousness/seizure, shock, hypoglycemia alone or in combination. Similar percentage of acute presentation in emergency is reported by other investigators.[8]

Panhypopituitarism was present in 97.3%. Only one subject had preserved gonadotroph axis in the form of regular menses. Similar occurrence of panhypopituitarism is also documented by other investigators.[9,10] Selective preservation of anterior pituitary function was little higher in other studies.[7,8] The higher occurrence of panhypopituitarism in our study may be due to presentation of only severe cases at our institute. About 84% subjects are found to have anemia and this is also supported by findings in other studies.[11,12]

Most of our subjects were found to have normal glycemic profile. Only 5 (13%) of them had type 2 diabetes mellitus. However, Dokmetas *et al*.[13] found diabetes mellitus in 30% (6 out of 20) subjects and Lim *et al*. found in 10.3% (8 of 78) subjects.[14]

Hyponatremia was the most common electrolyte imbalance in our series, occurring in about 53% subjects, similar to the study by Lim *et al*.[14] However, other studies have documented much less occurrence of hyponatremia.[8,13,15] The higher occurrence of hyponatremia in our study can be explained by presence of both cortisol and thyroxine insufficiency in almost all the subjects in comparison to other studies. Empty sella in MRI was found in about 53% and 47% had partial empty sella. However, other studies showed variable results with empty sella found in 28–75%.[8,10,13] Figures 1 and 2 show MRI features corroborating with empty sella in a subject with Sheehan's syndrome.

Elevated ALT and AST were fairly common. Though data on liver dysfunction in SS per se is scarce, study by Nishizawa *et al*.[16] showed significantly higher levels of ALT and AST in subjects with hypopituitarism other than SS compared to controls.

Serum triglycerides and LDL were elevated respectively in 31.5% and 13% subjects. Low HDL was the commonest lipid abnormality, occurring in more than 80% of subjects with SS. This finding is also in keeping with other studies.[17,18] Altered lipid profile in SS, in part, could be attributed to oestrogen and growth hormone deficiency.

Age matched BMD Z-score value of ≤-1 in L1–L4 spine was present in more than 80% subjects suggestive of low bone mass, whereas 44.7% subjects had age matched BMD Z-score ≤-2 suggestive of significantly poor bone health. However, the BMD Z-score in either of the femur ≤-1 in 29% subjects. This is certainly not a usual finding. This might indicate more severe osteoporosis in lumbar spine as compared to femoral neck. However, the lumbar spine was more frequently affected by low bone mineral mass in a study by Chihaoui M *et al*.[19] This is in contrast to the study by Agarwal *et al*., who have demonstrated that subjects with SS had significantly lower BMD compared to controls at all three sites.[20] Significant osteoporosis (T-score ≤-2.5 in L1–L4 spine) was present in about 42% subjects. Duration of untreated period in SS subjects and Z-score at L1–L4 spine also had moderate correlation. The discordance may be explained by the fact that all subjects in

our cohort were receiving Vitamin D and calcium supplement and many of them were also on oestrogen containing oral pills.

### Limitations of this study

The main limitation of our study is that the sample size was not very large. Also we did not check serum 25 OH vitamin D levels while assessing the bone density. However, all subjects were on regular daily oral calcium and monthly cholecalciferol supplement. Also, we could not measure anti pituitary antibody in our subjects

## Conclusion

SS may have variable spectrum of clinical presentation SS mostly present with panhypopituitarism. Posterior pituitary dysfunction is rare. Hyponatremia is the most common electrolyte abnormality. Dyslipidemia, altered liver functions are fairly common. Low bone mass involving mainly the lumbar spine also augments the morbidity of these subjects.

### Declaration of patient consent

The authors certify that they have obtained all appropriate participant consent forms. In the form, the participants have given their consent for clinical information to be reported in the journal. The participants understand that their names will not be published and due efforts will be made to conceal their identity.

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### Conflicts of interest

There are no conflicts of interest.

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