Original Article

Sella Turcica Size in Women with Sheehan Syndrome—A Case–Control Study

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Abstract

Introduction: Sheehan syndrome is a common cause of hypopituitarism in developing countries. Among risk factors, in addition to post-partum haemorrhage, a smaller sellar volume is also believed to predispose to pituitary necrosis. Some earlier studies have reported smaller sellar volume in these patients but involved a small number of patients and lacked matched controls. The main of the present study was to study the sellar volume in a large cohort of patients with Sheehan syndrome and compare it with age- and parity-matched controls. **Methods:** Fifty women with Sheehan syndrome and an equal number of age- and parity-matched controls were studied. Baseline investigations, relevant hormonal assay, and MRI of pituitary were studied in all. **Results:** Sellar volume was significantly lower in patients with Sheehan syndrome (334.50 ± 129.08 mm^3 in patients as against 456.64 ± 169.25 mm^3 in controls, $P = 0.000$). Far more women with Sheehan syndrome than controls had decreased sellar volume (40% vs. 12%). **Conclusions:** Patients with Sheehan syndrome have a smaller sellar volume that may be a non-modifiable risk factor for the development of post-partum pituitary necrosis.

Keywords: Hypopituitarism, MRI, post-partum haemorrhage, sellar size, Sheehan syndrome

Introduction

Sheehan syndrome (SS) refers to post-partum necrosis of the pituitary gland usually precipitated by post-partum haemorrhage (PPH).[1,2] Normally pituitary gland enlarges during pregnancy under the influence of placental hormones mainly oestrogen. The enlargement of the pituitary results in the compression of small hypophyseal arteries and in the presence of PPH causes necrosis of the gland.[3,4] In addition to PPH, pituitary autoimmunity and coagulation disturbances are believed to be risk factors for the development of SS.[5-7]

Sheehan syndrome mainly involves the anterior pituitary and typically presents with failure of lactation, non-resumption of menstrual cycles after the puerperium, features of hypothyroidism, and cortisol deficiency.[8] Pituitary hormone deficiency may occur in different combinations (and order) and sometimes gonadotroph and corticotroph may be preserved in the so-called partial SS.[9,10] Involvement of the posterior pituitary in the form of clinical diabetes insipidus requiring treatment is extremely rare.[11] Magnetic resonance imaging (MRI) of the pituitary gland shows partial or complete empty sella in almost all of these patients, making it an important tool for diagnosis.[12]

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In past, several authors have reported lower sellar volume in women with SS using plain skull X-rays to modern-day tools like computed tomography (CT) or MRI[13-16] and a small sellar volume has been postulated as a predisposing factor for the development of SS. These studies, however, are limited by small number of patients or lack of controls and this prompted us to undertake the present study. The main aim of the present study was to study the sellar size on MRI in a large cohort of patients with Sheehan syndrome compared with matched controls.

Methods

Study participants

Fifty patients with SS attending the outpatient department of a tertiary care hospital in north India were recruited between 2018

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and 2020. SS is common in our area.[17] and any woman clinically suspected to be affected is admitted to the hospital for evaluation as per a pre-defined protocol.[18] The present cohort of patients was recruited from those on follow-up. All patients were on standard replacement therapy of levothyroxine (50–100 µg/day), physiological dose of glucocorticoids (prednisolone 2.5–7.5 mg/day or hydrocortisone 7.5–20 mg/day) for varying time duration (6 months to 19 years). None of the patients ever received growth hormone therapy. All participants underwent detailed clinical examinations. Parameters like height, weight, waist, and hip circumference were measured using standard procedure. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared (kg/m^2). Blood pressure was measured as the average of three readings taken 3 min apart with a standard manual sphygmomanometer. Baseline blood samples were taken in all patients in a fasting state for complete blood count, glucose, lipids, liver, and kidney function in addition to estimation of serum total T4. Basal hormone profile at the time of diagnosis included serum thyroid stimulating hormone (TSH), total thyroxine (T4), follicle stimulating hormone (FSH), luteinizing hormone (LH), cortisol, prolactin (PRL), and growth hormone (GH). As per protocol, on follow-up, after documenting euthyroid state (total T4 in 6th to 8th decile of normal range and/or free T4 in the upper half of the reference range), patients are put on oral hydrocortisone in place of prednisolone. After stopping hydrocortisone for a day, patients are subjected to insulin tolerance test (ITT). All the hormones were estimated by Chemiluminescence Immunoassay on (BECKMAN COULTER, Acess-2 Analyzer, USA). The patient group was compared with equal number of apparently healthy age- and parity-matched women with a baseline normal T4 and TSH.

MRI pituitary

Both the patients and controls underwent an MRI scan with a 1.5 tesla (Siemens, Germany) MR Scanner using a standard protocol. Both T1-weighted sagittal and coronal images were taken before and after the injection of gadolinium contrast. Only two radiologists evaluated all the MRI images. Sella turcica volumes were measured by using the Di Chiro–Nelson formula {0.5 × (length × width × depth)}.[19]

The diagnosis of SS was based on the history of PPH and/or failure of lactation and/or amenorrhea following the last childbirth, varying grades of loss of pituitary hormone reserve, and demonstration of empty sella on MR imaging.[2] Pituitary-dependent hormone failures were defined as follows: lactotroph failure as a failure of lactation with low basal/stimulated prolactin, thyrotroph failure as low T4 with inappropriately normal TSH, corticotroph failure as low morning cortisol (≤5 µg/dl) with inappropriately normal ACTH and/or peak cortisol <20 µg/dl after ITT, gonadotroph failure as amenorrhea with low estradiol associated with normal LH, and somatotroph failure as non-stimulable GH (peak GH less than 3 ng/ml) on ITT.[20] Informed consent was obtained from all participants and the study was approved by the institutional ethics committee (IEC/SKIMS Protocol #RP/2021).

Statistical analysis

The statistical software SPSS version 20 (IBM SPSS statistics for windows, version 20 Armonk, NY: IBM corp.) was used to analyse the data. The distribution of variables was verified by means of Shapiro–Wilk's test. The Student's independent *t* test and Wilcoxon–Mann–Whitney U test were used to compare the parameters between cases and controls at baseline. Chi-square and Fischer's exact tests were used to analyse the categorical type of data. All results have been described on a 5% level of significance, i.e., value <0.05 is considered as significant.

Ethical Clearance Statement

The study was approved by Institutional Ethics Committee, Sher-I-Kashmir Institute of Medical Sciences, Srinagar vide IEC/SKIMS protocol # RP 65/2021 on 9.4.2021. Written informed consent was obtained for participation in the study and use of the patient data for research and educational purposes. The procedures follow the guidelines laid down in Declaration of Helsinki (1964).

Results

Over a period of three years, 50 patients with SS attending either the outpatient or emergency services of the hospital were taken in the study. The mean age of patients was 46.8 ± 8.52 (range 30–69 years) and the mean parity was 3.06 ± 1.46 (range1–6). For comparison, 50 controls were recruited from among the attendants of patients in the outpatient clinic; their age and parity were comparable with those of patients with SS and none had evidence of hypothyroidism [Table 1]. The mean time since the last childbirth was 19.44 ± 8.38 years (range 9–45 years). Thirty-four women (68%) delivered their last child at home (a history of PPH was present in 21 of these women, eight of whom received a blood transfusion after being shifted to the hospital). Ten out of 16 women who delivered in the hospital also had PPH and all of them received blood transfusions. Forty-seven of the 50 patients had lactation failure

Table 1: Comparison of clinical, biochemical parameters, and MRI findings between cases and controls

Parameter	Cases	Control	*P*
Number	50	50	–
Age (year)	46.8±8.52	43.9±6.58	0.060
Parity	3.00±1.45	2.72±0.94	0.258
Height (cms)	152.64±5.41	153.71±2.97	0.480
Weight (kgs)	52.07±8.76	56.71±3.81	0.059
BMI	22.43±3.84	23.85±1.56	0.186
T4(µg/dl)	3.66±2.85	8.99±1.84	0.000*
TSH (mu/L)	3.16±3.14	3.64±2.95	0.645
MRI sella			
Length (mm)	8.84±1.81	10.40±1.43	0.000*
Width (mm)	9.61±2.20	11.86±2.20	0.000*
Height (mm)	7.90±1.81	12.65±1.59	0.038*
Sellar volume (mm^3)	334.50±129.08	456.64±169.25	0.000*

T4=thyroxine, TSH=thyroid stimulating hormone. *Statistically significant. Data were expressed as mean±SD

and 49 never resumed menstrual cycles after delivery. All these women had frank clinical features of hypothyroidism like slowness and marked delay in deep tendon jerks and features of hypogonadism in the form of amenorrhea and sparse axillary and pubic hair while many had features of ACTH deficiency in the form of hypopigmentation and hypotension. None of the patients had polyuria. Over three-fourths (78%) had anaemia, 30% had bicytopenia, and 9.5% had pancytopenia [Table 2]. All the patients had thyrotroph and somatotroph failure while gonadotroph and corticotroph failure was documented in 98%, and lactotroph failure in 94% of patients. Table 3 depicts the mean/stimulated hormone levels after ITT.

MRI findings

All the patients had features suggestive of complete or partial empty sella, while none of the control women had empty sella. All the parameters of sellar size like length, width, and height were significantly lesser in patients with SS than in controls. Mean sellar volume was 334.50 ± 129.08 mm^3 in patients with SS as against 456.64 ± 169.25 mm^3 in controls, $P = 0.000$.

Table 2: Clinical characteristics of the patients with Sheehan syndrome

Parameter	Mean/percent
Number	50
Age (years)	46.8±8.52
Parity	3.06±1.46
Time since last delivery	20 years
APH	6.1%
PPH	59.2%
Blood transfusion history	35.4%
Anaemia	78%
Bicytopenia	30%
Pancytopenia	9.5%
Absent cycles after LCB	98%
Lactotroph failure	94%
Thyrotroph failure	100%
Somatotroph failure	100%
Corticotroph failure	98%
Gonadotroph failure	98%

APH=antepartum haemorrhage, PPH=post-partum haemorrhage, LCB=last childbirth

Table 3: Hormonal parameters in patients with Sheehan syndrome at the time of diagnosis

Parameter	Value	Normal value
T4 (µg/dl)	3.66±2.85	5.5-13.5
TSH (mu/L)	3.16±3.14	0.5-6.5
LH (IU/L)	2.24±2.09	3-12
FSH (IU/L)	6.73±8.36	2-6.6
*PRL µg/l	7.12±15.88	>25
*GH (µg/l)	0.512±0.75	>3
*Cortisol (µg/dl)	3.10±3.65	>20

T4=thyroxine, TSH=thyroid stimulating hormone, LH=luteinizing hormone, FSH=follicle stimulating hormone, PRL=prolactin, GH=growth hormone. *peak after ITT. Data were expressed as mean±SD

Taking 287.39 mm^3 (mean minus 2SD of sellar volume in controls) as a cut-off, 40% of women with SS had low sellar volume as against 12% of the controls [Table 1].

Discussion

Sheehan syndrome continues to be a common cause of hypopituitarism in many developing countries.[1] In a large epidemiological study from Indian Kashmir, SS was seen in 2.8% of adult parous women of 20 years or older.[17] Sequential MRI studies in women with SS reveal an initial enlargement of the gland up to a month post-partum and a progressive decrease thereafter leading to the appearance of empty sella in 6 months to one year.[21] In established cases of SS, empty sella on MR imaging is a universal finding.[1,2,10,13] During the past half century, assessment of the size of sella turcica using tools from X-rays to present-day MR imaging has interested many physicians. Present study consisted of a series of 50 women with SS and an equal number of age- and parity-matched healthy women. Using MRI, we demonstrated that all the measurements of sella turcica, such as length, width, and height, were significantly lower in patients with SS as compared to matched controls. The sellar volume calculated as 0.5 × (L × W × H) was significantly lower in patients with SS as compared to matched controls (sellar volume of 334.50 ± 129.08 mm^3 in cases against 456.64 ± 169.25 mm^3 in controls, $P = 0.000$). As early as 1966, Meador *et al*. studied lateral sellar volume on plain X-ray skulls in 14 women with SS compared with 59 female controls. The mean lateral sellar volume was 76 ± 33.4 mm^2 in SS patients as against 104.3 ± 17.6 mm^2 in controls. There was no correlation of age or parity with the lateral sellar area.[14] This seminal study, however, involved few patients and controls that were not matched for age and parity. Using computed tomography, Fleckman *et al*. studied content and size of sella turcica in seven patients of suspected SS and compared the sellar content with ten normal women. Empty sella with partial or complete absence of pituitary tissue was demonstrated in all women with suspected SS and in none of the normal women. The size of the sella turcica was within normal limits in six out of seven patients.[22] This study, though the first to demonstrate empty sella in SS, included only a handful of patients and provided no details on sellar size in controls, making it impossible to draw any meaningful conclusion. Sherif *et al*. assessed sellar size and contents in 57 patients with SS and 17 controls. Sellar volume in patients with SS (565 ± 292 mm^3) was significantly lower than in controls (sellar volume of 922 ± 155 mm^3, $P < 0.01$).[15] Less number of controls that were not matching for age and parity has been the main limitation of the study. Bakiri *et al*. demonstrated a significantly smaller sellar size in 54 women with SS than in 12 women matched for age and number of pregnancies. No correlation was seen between sellar size and extent of hormonal deficiencies.[16] Inclusion of a lesser number of controls that too with endocrinological disorders and two-dimensional rather than three-dimensional measurements of sella were some of the limitations of the

Table 4: Review of studies on sellar size in women with Sheehan syndrome

Author	Year	Cases	Controls	Imaging	Sellar volume	Limitations
Meador *et al*.[14]	1966	14	59	Skull X-ray	Decreased, 7/14 had SV BLC	Use of X-rays
Fleckman *et al*.[22]	1983	7	10	CT scan	Normal	Small sample size
Sherif *et al*.[15]	1987	57	17	CT scan	Decreased, 8/57 had SV BLC	Controls, not age-matched.
Bakiri *et al*.[16]	1991	54	12	CT scan	Decreased, 16/54 had SV BLC	Calculated area only, Controls not matched
Diri *et al*.[13]	2014	67	29	MRI	Decreased, 35/67 had SV BLC	Fewer controls
Simsek *et al*.[23]	2020	21	13	MRI	Decreased, all had SVBLC	Controls, not age and parity matched

SVBLC=Sellar volume below lower limit of controls, CT=computed tomography, MRI=magnetic resonance imaging

study. In an extensive investigation of 114 patients, using MRI, Diri *et al*. studied sellar volume in 67 patients of SS and compared it with 29 age- and gender-matched controls. Mean sellar volume in patients with SS (340 ± 214 mm^3) was significantly lower than matched controls (sellar volume of 602.5 ± 92 mm^3, $P < 0.001$); half of the women with SS had sellar volume smaller than the smallest value among controls.[13] In a retrospective study, Simsek *et al*. using MRI assessed sellar volume in 21 women with SS and compared it with 13 controls. Sellar volume in SS patients was significantly lower as compared to that of controls (125 ± 50.8 mm^3 in cases as against 679.5 ± 129.5 mm^3 in controls).[23] Less number of cases limited the study as well as controls that were not age and parity matched. Table 4 summarizes the results and limitations of previous studies on sellar size in SS. Whether the small sellar size is present before the onset of SS or is a consequence of pituitary infarction is a matter of debate with all previous studies pointing against the latter. We did not demonstrate any correlation between sellar volume and either age of the women or time since the diagnosis of SS. Moreover, we did not find any statistically significant difference between sellar volume among patients with ages below or above 50 years. None of the above studies has noted any relationship between sellar size and age and duration or extent of the disease.[14-16,23] These findings suggest that decreased sellar size is possibly not the sequel of pituitary necrosis. It is suggested by the fact that Sheehan found no difference in sellar volume on post-mortem examination in women with SS of varying duration.[24] The mean ± SD sellar volume in healthy age- and parity-matched women in our series was 456.64 ± 169.25 mm^3 and 20 out of 50 (40%) patients had a sellar volume of less than 287.39 mm^3. Diri *et al*. also observed low sellar volume in only 52% of women with SS. Many authors are of the opinion that a smaller sellar volume is a non-modifiable risk factor for the development of post-partum pituitary necrosis.[13-16,23] A small sella turcica would direct the physiological enlargement of the pituitary during pregnancy superiorly, leading to compression of the superior hypophyseal artery and subsequent predisposition to ischemic necrosis.[2] Women with a small sellar volume are at a greater risk of developing pituitary necrosis in the presence of a preventable risk factor of PPH. Therefore, the prevention of PPH is the key for the elimination of SS from the community.

Summary

Women with SS have smaller sella turcica volume as compared to normal women. This may be a non-modifiable risk factor for post-partum pituitary necrosis.

Limitations

The study has some limitations. As part of the initial diagnosis, we did not estimate ACTH and IGF-1 in all the patients included in the present study. However, we believe this will not affect the diagnosis of SS as we have previously shown that the presence of central hypothyroidism and low basal GH in the presence of PPH or lactation failure or amenorrhea together with empty sella on MR imaging is sufficient to make an accurate diagnosis of SS in resource-poor settings.[10] Furthermore, it would have been desirable to have even more women with SS.

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Conflicts of interest

There are no conflicts of interest.

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