Clinical, hormonal and radiological features of partial Sheehan's syndrome: an Indian experience

Bashir Laway[1], Raiz Misgar[2], Shahnaz Mir[3], Arshad Wani[4]

[1] Sher-i-Kashmir Institute of Medical Sciences, Endocrinology, Srinagar, Kashmir, India
[2] Sher-i-Kashmir Institute of Medical Sciences, Endocrinology, Srinagar, Kashmir, India
[3] Govt Medical College, Srinagar, Medicine, Srinagar, India
[4] Sher-i-Kashmir Institute of Medical Sciences, Endocrinology, Srinagar, Kashmir, India

Correspondence to:
Bashir Ahmad Laway,
Department of Endocrinology,
Sher-i-Kashmir
Institute of Medical Sciences,
Soura, Srinagar, Jammu and Kashmir, India
drlaway@gmail.com

Received on Oct/9/2015
Accepted on Nov/1/2015

DOI: 10.1590/2359-3997000000137

ABSTRACT

Objective: The objective of this study was to describe clinical presentation, hormonal profile and imaging characteristics of 21 patients with partial Sheehan's syndrome. **Subjects and methods:** This prospective study was carried out over a period of six years (2008-2013). The evaluation of patients included clinical assessment, hormone estimations and contrast enhanced magnetic resonance imaging of pituitary. **Results:** We documented preservation of gonadotroph, corticotroph and lactotroph function in 71.4, 61.9, and 9.5% of patients respectively. **Conclusion:** To conclude some of the pituitary functions can be preserved in Sheehan's syndrome and this has important implications from the treatment and long term morbidity point of view. Arch Endocrinol Metab. 2016;60(2):125-9

Keywords
Sheehan's syndrome; post partum hemorrhage; partial Sheehan's syndrome

INTRODUCTION

Postpartum pituitary necrosis results from severe hypotension or shock secondary to blood loss at the time of childbirth (1). Sheehan's syndrome (SS) is the most common cause of hypopituitarism in women from developing countries (2). Improvement in the obstetric care has considerably decreased the prevalence of SS in western world (3). An epidemiological study from India (Kashmir) has documented a prevalence of around 3.1% in adult women (4). Though SS is rare in the west, recently the disease has been reported from some developed countries. Sheehan's syndrome was the sixth common cause of adult growth hormone (GH) deficiency comprising of 3.1% of total patients of adult hypopituitarism, who were administered GH (5). The largest series of patients with SS seen over a period of more than two decades was published recently (6). The clinical presentation of hypopituitarism in SS varies from subtle symptoms to severe hypocortisol crisis. The extent of hypopituitarism (the number of trophic hormones deficient) and the severity of deficiency of a given hormone are variable. The detailed description of preservation of anterior pituitary functions in these patients is limited to case reports (7). With limited data available on clinical profile of partial SS, we present a large series of such patients from North Indian region.

SUBJECTS AND METHODS

This prospective study was carried at an endocrine center in North India over a period of six years (2008-2013). The study was approved by institutional ethical committee and an informed consent was obtained from each subject. Twenty one patients fulfilled the criteria for partial SS and were included in the study. The diagnosis of SS was based on: (a) history of postpartum hemorrhage (PPH) or failure of lactation and/or amenorrhea following last child birth; (b) deficiency of more than one anterior pituitary hormone and (c) empty sella on pituitary MRI (2). Partial SS was defined as hypopituitarism following an obstetric insult with preservation of one or more of five trophic hormone producing cell lines i.e. lactotroph, somatotroph, corticotroph, thyrotroph and gonadotroph with empty sella on MR imaging. General physical and systemic examination was performed on all subjects.

The clinical assessment was specifically focused on seeking the findings suggestive of deficiency of various pituitary hormones. The patients were admitted in the

hospital and evaluated according to a pre-defined protocol. Fasting blood samples were obtained for complete blood count, liver and kidney function tests, electrolytes and glucose. Hormone estimations included serum thyroid stimulating hormone (TSH), total thyroxine (T4), follicle-stimulating hormone (FSH), luteinizing hormone (LH), cortisol, prolactin (PRL) and GH. A baseline sample was drawn for estimation of all anterior pituitary hormones, serum cortisol and total serum T4. Patients were put on injectable hydrocortisone and oral thyroxine. After stabilizing and correcting the acute metabolic derangements like hypoglycemia, hyponatremia, hypokalemia and dehydration, patients were discharged on oral thyroxine (50–100 µg/day), prednisolone (5–7.5 mg/day) and were followed monthly. Corticosteroids were withdrawn on follow up in women with basal cortisol of 18 µg/dL or more. Women younger than 40 years were also administered cyclic estrogen/progesterone pills in case of loss of gonadotroph function. After documenting euthyroid state, women with corticotroph involvement were put on oral hydrocortisone in place of prednisolone. Hydrocortisone was stopped for two days and insulin tolerance test (ITT) was performed to assess for lactotroph, somatotroph and corticotroph function; magnetic resonance imaging (MRI) sella was also done in the same admission. The preservation of pituitary function was defined as: resumption of menstrual cycles after delivery with normal basal gonadotropins for gonadotrophs, a serum cortisol of 18 µg/dL or more, either basally or at any time during the ITT for corticotrophs, normal lactation in puerperium and an increase in serum prolactin of at least 100% over the basal value on ITT for lactotrophs, normal baseline T4 and TSH for thyrotrophs, and a peak serum GH of least 3 µg/l on ITT for somatotrophs Serum concentrations of T4, TSH, LH, FSH, PRL, and GH were measured by immunoradiometric assay (IRMA) using commercially available kits (Siemens Medical solutions, Los Angles USA, CA 90045-6900). Serum cortisol was measured by radio immunoassay (RIA) using commercially available kits (Diasorin Stillwater, Minnesota 55082-0285 USA).

RESULTS

A total of 21 patients qualified for the definition of partial SS. Mean age of the patients was 39.3 ± 8.4 years with a parity ranging from 1-4 deliveries. The mean time since last delivery was 11.81 ± 8.48 years (range 1-30 years). All but three patients had PPH at the time of last delivery and 14 had received blood transfusion. Two patients lactated normally. Twelve patients resumed regular menstrual cycles, another 3 patients having oligomenorrhea after last delivery, one of whom had a successful pregnancy subsequently. Table 1 gives the details of clinical features, trophic hormone deficiencies and MRI findings of all the 21 patients. All had low serum T4 with inappropriately normal TSH in 16 and mildly increased TSH in five patients. Insulin tolerance test revealed subnormal GH response in all the patients and subnormal prolactin response in all except two patients; 10 of 21 patients had a normal cortisol response to ITT. One patient had a normal basal cortisol and in one, ITT could not be done, instead short synacthene test was done which confirmed a normal cortisol response. Table 2 gives the details of hormonal analysis in all the women with partial Sheehan's syndrome. Overall, 85% of women had history of PPH and 66% had received blood transfusion. Lactation failure was seen in 90% of women, corticotroph failure in 38% of the women, and gonadotroph failure in 28% of women. All these women had somatotroph and thyrotroph failure. Contrast enhanced MRI revealed evidence of empty sella in all the patients. All the patients are on replacement treatment appropriate for the deficiency of their pituitary hormones.

DISCUSSION

The diagnosis of SS in these patients was based on PPH, lactation failure, trophic hormone deficiency and presence of empty sella on MRI. In recent times many series of cases with SS have been published and the presentation of the cases has been variable (6,8-10). Here we present the clinical, hormonal and radiological details of a series of 21 patients with partial SS. In the present series, all patients had growth hormone and thyroid hormone deficiency. Inappropriately normal or increased TSH secretion has been demonstrated in women with SS. After the development of pituitary necrosis, initially TSH levels decrease which results in decreased T4 which in turn stimulates TSH production and secretion by the remaining thyrotrophs. Low levels of cortisol and growth hormone also contribute to increase in TSH release in these patients. The increased TSH produced has low intrinsic bioactivity and decreased metabolic clearance (11,12). Prolactin deficiency was seen in 19 out of 21 patients. Anatomically lactotroph and somatotroph cells are situated in the lower and lateral regions of the pi-

Table 1. Clinical features, trophic hormone deficiencies and MR imaging features of patients

Case	Age	Parity	PPH	BT	LTF	TTF	STF	CTF	GTF	MRI
1	36	4	+	+	+	+	+	–	–	ES
2	35	1	+	+	+	+	+	–	+	ES
3	45	3	+	+	+	+	+	–	+	ES
4	50	3	+	+	+	+	+	–	–	ES
5	30	2	–	–	–	+	+	+	–	ES
6	45	4	+	–	+	+	+	+	–	ES
7	45	3	–	–	+	+	+	–	–	ES
8	40	4	+	+	+	+	+	+	–	ES
9	42	1	+	+	+	+	+	–	–	ES
10	40	3	+	–	+	+	+	–	–	ES
11	50	3	+	+	–	+	+	+	–	ES
12	40	2	+	+	+	+	+	–	+	ES
13	60	3	+	–	+	+	+	+	–	ES
14	35	1	+	+	+	+	+	-		ES
15	30	1	+	+	+	+	+	_	_	ES
16	35	2	+	+	+	+	+	+	-	ES
17	45	2	+	+	+	+	+	+	-	ES
18	25	3	+	+	+	+	+	+	-	ES
19	30	4	-	-	+	+	+	-	+	ES
20	38	4	+	-	+	+	+	-	+	ES
21	30	3	+	+	+	+	+	-	+	ES

PPH: post partum hemorrhage; BT: blood transfusion; LTF: lactotroph failure; TTF: thyrotroph failure; STF: somatotroph failure; CTF: corticotroph failure; GTF: gonadotroph failure; MRI: magnetic resonance imaging; ES: empty sella.

Table 2. Hormonal profile of the patients

Hormone	T4 µg/dL	TSH µIU/mL	LH IU/L	FSH IU/L	PRL µg/L	GH µg/L	Cortisol µg/dl
Normal value	5.5-13.5	0.5-6.5	3-12	2-6.6	> 2 fold* increase	> 3*	> 20*
Case 1	3.2	5.9	6.5	10.2	4*	2.2*	20.1*
Case 2	1	4.9	11.28	1.47	2.03*	1*	21.83*
Case 3	4.35	3.6	5.22	8.9	5.41*	1*	20.22*
Case 4	3.7	7.9	1.6	6.2	4.79*	1*	28*
Case 5	1	7.7	4.89	9.49	22*	1*	15*
Case 6	2.7	5.9	6.7	9.8	4.6*	1*	8.25*
Case 7	1	5.86	6.3	8.3	3.85*	1*	24.75*
Case 8	3.2	6.2	4.5	5.8	3.45*	1*	3.8*
Case 9	1.7	2.54	1.62	2.75	0.5*	1*	21.2*
Case 10	2	4.6	4.24	3.54	3.84*	1*	22.6*
Case 11	1.6	8.2	5.9	10.2	14.2*	1*	13*
Case 12	2.3	4.9	3.8	4.7	3*	0.8*	24*
Case 13	1.2	9.2	8.52	13.3	2.83*	0.7*	11.2*
Case 14	1.4	5.2	3.4	5.3	2.3*	< 1*	19.5*
Case 15	2.26	1.8	2.24	4.94	2.04	< 1*	26.05±
Case 16	2.1	6.2	5.3	4.2	2	< 1*	5.2*
Case 17	< 1	4.63	5.8	3.2	3.58*	< 1*	8.25*
Case 18	< 1	6.7	1	3.79	3.49*	< 0.25*	9.96*
Case 19	1.50	3.45	0.98	3.15	-	1.25	17.41*
Case 20	1.15	0.15	1.71	2.06	< 1.5*	< 0.25*	20.74*
Case 21	2.91	3.24	< 1.5	< 1.5	-	< 0.25	21.3

T4: total thyroxine; TSH: thyroid stimulating hormone; FSH: follicle stimulating hormone; LH: luteinizing hormone; GH: growth hormone. * Peak after ITT; ± peak after Short synacthene test.

tuitary gland and are damaged predominantly during the ischemic necrosis (13). There is a consensus among different series that GH deficiency is a universal finding in SS (2,7-9,14). Normal lactation and preservation of lactotroph function has been reported in different series. One study reported normal lactation in 30% yet all had GH and prolactin deficiency on dynamic testing (9). In yet another series, 2 out of 28 patients had normal lactation and both had a normal prolactin response to ITT (8). Previously prolactin deficiency was reported in 85.2% of women with SS on ITT (5). In a recent large series of 114 patients, 37% of women had normal lactation which included 6% of women having a blunted response to TRH test (6). In the present series 9.5% of women had normal lactation and a normal prolactin response to ITT. There is some discordance between prolactin deficiency documented biochemically and failure of lactation. It has been reported that lactation can be normal even in women with lactotroph failure documented on dynamic tests (10). Rarely, lactotroph function may recover after its initial loss (15). The most consistent finding in SS is the loss of somatotroph and thyrotroph function; though the loss of somatotroph function is universal, there are varying reports about involvement of thyrotroph function. Several previous series reported thyrotroph failure in 90% of patients (6,8,9,13) and one reported it in all the patients (8). All of our patients had thyrotrophs failure. Our data are consistent with recent Indian studies, wherein most of the patients with SS have thyrotroph failure (7,14,16).

Preservation of gonadotroph function in women with SS has been widely reported in the literature. Loss of gonadotroph function has been reported in all the patient series from Turkey (6,8,9). On the other hand Indian data reveal that preservation of gonadotroph function and subsequent pregnancy is not an uncommon phenomenon (8,17-20). We previously reported preservation of gonadotroph function in 30% of women with partial SS (7), and 71% of our patients in the present series had preserved gonadotrophs. There seems to be no explanation for this disparity between Indian and Turkish patients.

Preservation of corticotroph function has important implication on the long term management of women with SS. Corticotroph involvement has been reported in 50-100% of women in different series (6,7,9). In the present series, 62% of women had preservation of corticotroph function. Corticotroph failure is the main cause of hypoglycemia and is easily correctable with glucocorticoid administration; glucocorticoid replacement in presence of severe hypothyroidism predisposes them to severe psychosis (21). Preservation of corticotroph function spares these women from the undesirable effects of exogenous glucocorticoids. Several mechanisms have been invoked to explain the sparing of corticotrophs. In human pituitary corticotrophs comprise around 10-20% of cells and are most numerous around mid sagittal region, with some of the cells concentrated in lateral wings and zona intermedia. Zona Intermedia is situated between anterior and posterior pituitary, and some of these cells extend into the posterior pituitary which is known as basophilic invasion. Mid sagital region is least damaged during pituitary infarction. Because of dual blood supply to posterior pituitary, it is likely that these cells escape damage and will be responsible for preservation of some of corticotroph function (22). None of the patients in the present series had involvement of posterior pituitary function in the form of polyuria. Diabetes insipidus is quite rare in these patients, though subtle features of posterior pituitary involvement have been reported (23). Table 3 summarizes the anterior pituitary involvement in reported series of patients with SS.

Table 3. Summary of loss of anterior pituitary functions (%) in women with Sheehan's syndrome

Author	Year	No	Somatotroph	Lactotroph	Gonadotroph	Thyrotroph	Corticotroph
Dash and cols.	1993	19	100	90	85	100	100
Zargar and cols.	1996	86	100	94.19	92.6	85.7	84.4
Goswami and cols.	2002	19	-	-	94.8	100	94.8
Sert and cols.	2003	20	100	92.8	100	100	100
Dökmetaş and cols.	2006	28	100	93	100	90	100
Laway and cols.	2011	10	100	100	30	100	50
Gei-Guardia and cols.	2011	60	100	69.2	75	80	96.6
Diri and cols.	2014	114	100	71.1	100	90.4	71.9
Present series	2014	21	100	90	28	100	38

We conclude that in areas where SS is still common, atypical and partial presentation are also quite common. Though GH and TSH deficiencies are universal in SS, gonadotropin and corticotropin secretion may be preserved in these patients. The preservation of ACTH secretion, in particular, has important therapeutic implications given the difficulties and the risks of long term glucocorticoid replacement; hence every effort should be made to assess the corticotroph function.

Contributions: the authors alone are responsible for the content and writing of the paper.

Disclosure: no potential conflict of interest relevant to this article was reported.

REFERENCES

1. Sheehan HL. Postpartum necrosis of anterior pituitary. J Pathol Bacteriol. 1937;45:189-214.
2. Kelestimur F. Sheehan's syndrome. Pituitary. 2003;6(4):81-8.
3. Soares DV, Conceição FL, Vaisman M. [Clinical, laboratory and therapeutics aspects of Sheehan's syndrome]. Arq Bras Endocrinol Metabol. 2008;52(5):872-8.
4. Zargar AH, Singh B, Laway BA, Masoodi SR, Wani AI, Bashir MI. Epidemiologic aspects of postpartum pituitary hypofunction (Sheehan's syndrome). Fertil Steril. 2005;84(2):523-8.
5. Abs R, Bengtsson BA, Hernberg-Ståhl E, Monson JP, Tauber JP, Wilton P, et al. GH replacement in 1034 growth hormone deficient hypopituitary adults: demographic and clinical characteristics, dosing and safety. Clin Endocrinol (Oxf). 1999;50(6):703-13.
6. Diri H, Tanriverdi F, Karaca Z, Senol S, Unluhizarci K, Durak AC, et al. Extensive investigation of 114 patients with Sheehan's syndrome: a continuing disorder. Eur J Endocrinol. 2014;171(3):311-8.
7. Laway BA, Mir SA, Gojwari T, Shah TR, Zargar AH. Selective preservation of anterior pituitary functions in patients with Sheehan's syndrome. Indian J Endocrinol Metab. 2011;15 Suppl 3:S238-41.
8. Sert M, Tetiker T, Kirim S, Kocak M. Clinical report of 28 patients with Sheehan's syndrome. Endocr J. 2003;50(3):297-301.
9. Dökmetaş HS, Kilicli F, Korkmaz S, Yonem O. Characteristic features of 20 patients with Sheehan's syndrome. Gynecol Endocrinol. 2006;22(5):279-83.
10. Gei-Guardia O, Soto-Herrera E, Gei-Brealey A, Chen-Ku CH. Sheehan syndrome in Costa Rica: clinical experience with 60 cases. Endocr Pract. 2011;17(3):337-44.
11. Abucham J, Castro V, Maccagnan P, Vieira JG. Increased thyrotrophin levels and loss of the nocturnal thyrotrophin surge in Sheehan's syndrome. Clin Endocrinol (Oxf). 1997;47(5):515-22.
12. Oliveira JH, Persani L, Beck-Peccoz P, Abucham J. Investigating the paradox of hypothyroidism and increased serum thyrotropin (TSH) levels in Sheehan's syndrome: characterization of TSH carbohydrate content and bioactivity. J Clin Endocrinol Metab. 2001;86(4):1694-9.
13. Shahmanesh M, Ali Z, Pourmand M, Nourmand I. Pituitary function tests in Sheehan's syndrome. Clin Endocrinol (Oxf). 1980;12(3):303-11.
14. Zargar AH, Masoodi SR, Laway BA, Shah NA, Salahuddin M, Siddiqi MA, et al. Clinical spectrum of Sheehan's syndrome. Ann Saudi Med. 1996;16(3):338-41.
15. Laway BA, Mir SA, Zargar AH. Recovery of prolactin function following spontaneous pregnancy in a woman with Sheehan's syndrome. Indian J Endocrinol Metab. 2013;17(Suppl 3): S696-9.
16. Goswami R, Kochupillai N, Crock PA, Jaleel A, Gupta N. Pituitary autoimmunity in patients with Sheehan's syndrome. J Clin Endocrinol Metab. 2002;87(9):4137-41.
17. Zargar AH, Masoodi SR, Laway BA, Sofi FA, Wani AI. Pregnancy in Sheehan's syndrome: a report of three cases. J Assoc Physicians India. 1998;46(5):476-8.
18. Dash RJ, Gupta V, Suri S. Sheehan's syndrome: clinical profile, pituitary hormone responses and computed sellar tomography. Aust N Z J Med. 1993;23(1):26-31.
19. Algun E, Ayakta H, Harman M, Topal C, Aksoy H. Spontaneous pregnancy in a patient with Sheehan's syndrome. Eur J Obstet Gynecol Reprod Biol. 2003;110(2):242-4.
20. Laway BA, Ganie MA, Wani IR, Butt TP, Zargar AH. Multiple spontaneous pregnancies in Sheehan syndrome with preserved gonadotropin function. Endocrinologist. 2009;19(6):253-4.
21. Laway BA, Shah TR, Bashir MI, Dada AH, Zargar AH. Acute onset psychosis following steroid replacement in Sheehan's syndrome. Acta Endocrinologica (Buc). 2010;6(4):533-8.
22. Laway BA, Mir SA, Dar MI, Zargar AH. Sheehan's syndrome with central diabetes insipidus. Arq Bras Endocrinol Metabol. 2011;55(2):171-4.
23. Atmaca H, Tanriverdi F, Gokce C, Unluhizarci K, Kelestimur F. Posterior pituitary function in Sheehan's syndrome. Eur J Endocrinol. 2007;156(5):563-7.