

# Sheehan Syndrome: Clinical and laboratory evaluation of 20 cases\*

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## Abstract

Sheehan syndrome (SS) or post-partum pituitary necrosis is a pituitary insufficiency secondary to excessive post-partum blood losses. SS is a very significant cause of maternal morbidity and mortality in developing countries although it is a rarity in developed countries in which obstetrical care has been improved. In this study, we reviewed 20 cases retrospectively who were diagnosed as SS in our clinic.

The patients aged 40 to 65 years with a mean age of  $51.12 \pm 9.44$  years (mean  $\pm$  SD). Time to make a definitive diagnosis of the disease ranged between 5 and 25 years with a mean of  $16.35 \pm 4.74$  years. Three of our patient (15%) had a previous diagnosis of SS. Three patients (15%) were referred to emergency service for hypoglycemia, three patients (15%) for hypothyroidism and one patient (5%) for hyponatremia. Dynamic examination of the pituitary revealed GH, Prolactin, FSH, TSH and ACTH insufficiency in all of the patients. One of our patients had a sufficient LH response to LHRH challenge. All of the patients were imaged with pituitary MRI. Eleven patients had empty sella and 9 patients had partial empty sella.

SS is still a common problem in our country, especially in rural areas. Considering the duration of disease, important delays occur in diagnosis and treatment of the disease.

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## Introduction

Sheehan syndrome (SS) or post-partum pituitary necrosis is an adeno-pituitary insufficiency from hypovolemia secondary to excessive blood losses during or after the delivery. It was first described by Sheehan in 1937. Sheehan's studies based on autopsy findings of the patients died

of uterine bleeding immediately after the delivery and hypopituitarism findings in the patients who survived despite massive bleeding during the delivery [1].

Although the pathogenesis of SS is not clear, it is clear that the basic event is infarct in the ante-

rior pituitary due to decreased blood volume [2]. It is not clear whether this infarct is due to vasospasm, thrombosis or a vascular compression.

Pituitary volume increases two fold during pregnancy. This is due to hyperplasia of prolactin secreting cells from elevated estrogen secretion. Enlarged pituitary gland may be compressing the blood vessels supporting it or there may be a predisposition in pregnant women compared with non-pregnant women or these two conditions may concur [2]. Pituitary gland doesn't have ability to regenerate. Scar tissue substitutes the necrotic cells. Presence of 50% of pituitary gland suffices for maintenance of normal functions [2]. Partial or total hypopituitarism develops with necrosis of 70 to 90% of the gland. It is believed that 32% of women with severe post-partum bleeding develop hypopituitarism [3].

SS is a very significant cause of maternal morbidity and mortality in developing countries although it is a rarity in developed countries in which obstetrical care has been improved. It is prevalent especially in eastern regions of our country. We aimed in this study to evaluate the patients with SS we diagnosed in our own clinic.

## Material and method

Firat Medical Center is a regional hospital under Medical School of Firat University that serving to a population of approximately 1 million peoples. In the present study, 20 patients followed up with a diagnosis of SS in our clinic between January 1998 and October 2003 was evaluated retrospectively. The diagnosis of SS was based on the patient history (profound bleeding during or following the delivery, absence of postnatal lactation etc), physical examination, laboratory investigations and radiological and magnetic resonance imaging (MRI) evaluation of the pituitary.

Routine biochemical examinations, complete blood counting (CBC), thyroid function tests and basal hormone levels (for FSH, LH, Prolactin, E2, Cortisol and GH) were performed for diagnosis.

In dynamic investigation of the pituitary 20 patients underwent to TRH, LHRH and long-ACTH tests and 16 patients to insulin hypoglycemia test and 4 patients to L-dopa stimulation test. For the patients referred from emergency service with such diagnoses as hypoglycemia, coma, hypothyroidism and hypotension, dynamic investigations were performed the general health status of the patient was improved and insulin tolerance test (ITT) was performed after the patients became eucortisolemic and euthyroid.

For each patient, blood samples were obtained between 08.00 and 09.00 am and then 200 µg of TRH and 100 µg of GnRH (LHRH) was given and blood samples were obtained at 0, 20, 40, 60, 90 and 120<sup>th</sup> minutes for determinations of TSH, prolactin, FSH and LH.

1 mg of Synacthen depot was used intramuscularly for ACTH stimulation test and blood samples for cortisol determination were taken at 0, 30, 60, 90 and

120<sup>th</sup> minutes and at 4<sup>th</sup>, 12<sup>th</sup> and 24<sup>th</sup> hours. For tests lasting more than 24 hours, Synacten i.m was applied at a dose of 1 mg/day and then blood sample was taken for cortisol measure 24 hours later.

For ITT, crystallized insulin was used at a dose of 0.1 U/kg. Blood glucose level of 40 mg/dl or less was considered as a criterion of hypoglycemia and the moment at which blood glucose level fell below this limit was accepted as the "0" time point and accordingly blood samples for cortisol and GH determination were taken at 0, 30, 60, 90 and 120<sup>th</sup> minutes. In L-dopa test applied to the patients for which ITT couldn't be applied, blood samples for GH measurement were taken at the minutes 20, 40, 60, 90 and 120.

All of the hormonal investigations were performed at Biochemistry Department of Research Hospital of Firat University using electrochemiluminescence immunoassay (ECLIA) method. TSH (Normal: 0.27–4.2 mIU/L), fT<sub>3</sub> (Normal: 1.8–4.6 pg/dl), fT<sub>4</sub> (Normal: 0.93–1.71 ng/dl), FSH (post-menopausal Normal: 25.8–134.8 mIU/mL), LH (post-menopausal Normal: 7.7–58.5 mIU/mL), E2 (post-menopausal N: 10–40 pg/ml), prolactin (3.4–24.1 ng/ml) levels were determined by Elecsys E170 device using a commercial kit with elecsys brand and cortisol (morning normal: 6.2–19.4 µg/dl) and GH (0.06–5.00 ng/ml) levels were studied with Immunit 2000 device using immulite kit.

An increase of 5–35 mIU/ml in TSH response to TRH and an increase of 32 ng/ml in prolactin levels, an increase more than 21 µg/dl in cortisol level and more than 10 µg/dl in GH level in ITT test, an increase of at least 2.5 times in FSH and LH levels compared to basal levels in LHRH test were all considered as normal [4,5].

## Results

Ages of the patients ranged between 40 and 65 years with a mean of  $51.12 \pm 9.44$  years (mean  $\pm$  SD). The interval between the beginning of the disease and a definitive diagnosis varied between 5 and 25 years with a mean of  $16.35 \pm 4.74$  years. All of the patients had a history of a serious bleeding during or after delivery. Six patients had received blood transfusions for severe bleeding. All of the patients described that they couldn't nurse their child and their menstrual cycles didn't return to normal patterns.

Three of our patients (15%) had a previous diagnosis of SS. 3 patients (15%) were referred to emergency service for hypoglycemia and three patients for hypothyroidism and 1 patient (5%) for hyponatremia. Other patients were those appealed to outpatient departments of Internal Medicine of Endocrinology and were diagnosed as a consequence of investigations following suspicion of SS. Ten patients had appealed to a medical center for some complaints such as fatigue. These patients were diagnosed as hypothyroidism or anemia and none of them was referred with a pre-diagnosis of SS.

**Table 1:** Basal hormone levels and disease duration of the patients with Sheehan Syndrome.

Patients	Disease duration (year)	FSH (mIU/mL)	LH (mIU/ml)	E2 (pg/ml)	PRL (ng/ml)	Cortisol ( $\mu$ g/dl)	GH (ng/ml)	TSH (mIU/L)	fT3 (pg/dl)	fT4 (ng/dl)
1	13	3.97	1.09	14.5	3.24	1.56	<0.05	2.69	0.1	0.1
2	12	1.1	0.29	20	2.01	1.0	0.09	0.02	3.8	1.73
3	20	1.34	0.48	20	2.73	2.6	<0.05	1.55	0.77	0.03
4	22	2.81	0.75	17.5	2.02	<1	<0.05	4.09	0.861	0.09
5	18	1.57	1.04	20.4	2.66	4.74	<0.05	3.0	0.9	0.11
6	21	3.6	1.6	5.71	5.02	<1	0.07	0.2	0.7	0.5
7	5	2.24	1.54	20	4.2	<1	<0.05	0.43	1.01	0.91
8	15	0.33	0.75	11.64	6.44	<1	<0.05	0.10	1.17	1.1
9	25	2.19	0.42	18.22	5.17	2.45	<0.05	3.18	0.85	0.22
10	16	2.12	1.35	12.2	2.50	<1	0.05	1.75	1.20	0.60
11	18	2.30	0.50	20	4.25	1.85	0.71	1.56	0.40	1.5
12	14	1.86	0.94	11.5	3.7	1.75	0.7	0.08	0.80	1.2
13	12	2.20	1.12	3.25	5	4.2	<0.05	3.2	1.7	0.15
14	20	0.52	1.05	18.4	2.0	5.0	0.09	0.2	0.7	0.17
15	8	3.72	0.32	19.25	3.5	<1	<0.05	3.5	0.9	0.92
16	24	2.10	0.86	20	3.25	<1	0.1	0.10	0.1	0.42
17	14	1.56	1.20	12.5	3.25	1.25	<0.05	0.85	0.65	0.96
18	18	3.46	1.35	4.7	2.45	4.20	0.65	1.26	1.70	0.80
19	20	2.11	0.46	11.7	4.75	2.6	<0.05	1.50	1.25	0.90
20	12	1.87	0.65	5.65	2.75	1.25	0.06	0.10	1.40	1.20

Our patients had a moderate hyperlipidemia. Average blood lipids were as follows: total cholesterol:  $220.91 \pm 38.08$  mg/dl, LDL-Cholesterol:  $139.11 \pm 32.80$  mg/dl, HDL-Cholesterol:  $39.82 \pm 5.20$  mg/dl, Triglyceride:  $206.21 \pm 97.20$  mg/dl. Mean blood sodium level was  $132 \pm 9.9$  mEq/l. The sodium level of the patient referred to emergency service was 116 mEq/L. Six patients had normochrom normocytic anemia.

Mean basal hormone levels of the patients were as follows: TSH:  $1.46 \pm 1.36$  mIU/L, fT<sub>3</sub>:  $1.04 \pm 0.77$  pg/dl, fT<sub>4</sub>:  $0.68 \pm 0.51$  ng/dl, FSH:  $2.14 \pm 0.99$  mIU/mL, LH:  $0.881 \pm 0.40$  mIU/ml, E2:  $14.35 \pm 5.88$  pg/ml, Prolactin:  $3.54 \pm 1.24$  ng/ml, cortisol:  $2.07 \pm 1.34$   $\mu$ g/dl, GH:  $0.17 \pm 0.24$  ng/ml. Table 1 shows duration of disease and basal hormone values of the patients.

In regard to basal hormone levels, FSH, LH and cortisol levels of all patients were below normal limits. E2 levels in 16 patients, prolactin levels in seven patients, GH levels in 4 patients, TSH in eleven patients, fT<sub>3</sub> in 1 patient and fT<sub>4</sub> in 5 patients were within normal range.

All of patients had GH, prolactin, FSH, TSH and ACTH insufficiency on dynamic examination of the pituitary. One of our patients had sufficient LH response to LHRH test. All of the patients were underwent MRI scanning of pituitary. Eleven patients had empty sella and 9 patients had partial empty sella.

## Discussion

Known as postpartum pituitary necrosis, SS is diagnosed based on medical history of the patient, clinical findings, detection of low levels of pituitary and target gland hormones and visualizing partial or

complete empty sella by imaging procedures. SS is one of the leading causes of hypopituitarism in developing countries while it is responsible for only a minority of the hypopituitarism cases in developed countries [6,7].

Pituitary insufficiency in SS may be in the form of partial or complete hormone insufficiency [8]. Symptoms and signs of SS is generally due to insufficient levels of hormones secreted from the anterior pituitary. The skin is dry, pale and light colored and the face is wrinkled. Axillary and pubic hair decrease and amenorrhea develops as a result of gonadotropin insufficiency. Thyroid gland is shrunk as thyroid stimulation ceased. No sufficient breast milk can be produced because of hypoprolactinemia [9]. The patients with SS usually are presented to emergency service due to such situations as coma of hypothyroidism, adrenal insufficiency, hypoglycemia and hyponatremia following a serious stressful event [10]. Among our patients 3 patients came to emergency service due to hypothyroidism, 3 patients with hypoglycemia and 1 patient with hyponatremia. Hyponatremia is the most common electrolyte disorders in SS and it has been estimated that it occurs in 33% to 69% of the patients. It develops due to volume depletion, cortisol insufficiency, hypothyroidism and probably syndrome of inappropriate ADH secretion (SIADH). It may emerge in the post-partum period as well several years after delivery [10–13].

We found normochromic normocytic anemia in 6 patients. Anemia may develop in SS due to cortisol insufficiency, hypothyroidism and hypogonadism [14]. SS patient may show hyperlipidemia due to

hypothyroidism and GH insufficiency. Our patients had also moderate hyperlipidemia.

It is believed that the functions altered by SS most frequently are prolactin and GH secretions. However, secretion of other hormones may also be affected adversely. Haddock and colleagues reported complete insufficiency in 86% of the patients and partial insufficiency in 14% of the patients [8]. In a study by Bayram et al. on 30 cases, 23 complete insufficiency and 7 partial insufficiency cases were reported [15]. It has been reported that diabetes insipidus may also be seen in some of the patients with SS [14,16–19]. Among our patients, only one patient had sufficient LH response to LHRH while the entire of remaining patients had insufficient pituitary hormone levels. Accordingly, all of our patients had deficient growth hormone, hypogonadotropic hypogonadism, secondary hypothyroidism and secondary surrenal deficiency. None of our patients had diabetes insipidus.

In regard to basal hormone levels of the patients, it can be seen that eleven patients had normal TSH levels. Being below normal levels of free T3 and free T4 levels, however, suggests that the situation is secondary hypothyroidism. One of the patients, of whom both fT3 and fT4 levels were within normal limits hadn't sufficient TSH response to TRH test. These findings suggest that one may overlook the diagnosis of secondary hypothyroidism as a consequence of evaluating the patients solely by TSH level.

With introduction of tomographic imaging procedures in diagnosis of SS, Fleckman et al. suggested that empty sella was a typical feature of SS [20]. Studies showed that sella volumes of the patients with SS were smaller compared to the normal controls [21, 22]. All of our patients were scanned with pituitary MRI. Eleven patients had empty sella and 9 patients had partial empty sella.

SS may be acute or chronic. Its acute form is rarer. SS diagnosis is usually made several years after the postpartum bleeding. This interval may be as long as 15 to 20 years [9]. Among our patients, the one of whom the diagnosis was made earliest had disease duration 5 years and of whom the diagnosis was made latest had disease duration of 25 years. Time interval between post-partum bleeding and SS diagnosis was averagely  $16.35 \pm 4.74$  years. The reason for delay in diagnosis is that most of the patients don't have symptoms suggesting the diagnosis in the early periods of the disease. However, the fact SS is not known well among the physicians is another contributing factor in delay. Eleven (68.75%) of our patients had gone to physician before SS diagnosis was made and had had several diagnoses such as anemia, hypothyroidism and their diagnosis of SS had been overlooked. This indicates us that SS is not known well among physicians.

In conclusion, Sheehan syndrome is more common in especially rural parts of our country. Considering the duration of disease, one may conclude that diagnosis and treatment are delayed. This may be originat-

ing from natural course of the disease. However, the fact that the physicians don't know SS well or don't give enough attention and time to the examination of the patients seems an important factor. Thus, we consider that SS should be emphasized in training of the physicians.

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