MULTIFACETED EVALUATION OF 72 PATIENTS WITH PITUITARY FAILURE

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Objective. We aimed to reach a diagnosis for patients with pituitary failure (PF) with more detailed multifaceted examination, to obtain new gains in this way and to apply this experience to our future patients.

Patients and Method. The study included 72 patients with pituitary failure diagnosis. Patients were divided into two groups of 32 female patients with Sheehan syndrome (SS) and 40 non-Sheehan syndrome patients (20 female and 20 male).

Results. The mean age of the 32 patients with Sheehan syndrome was 56.1 ± 11.7 years with mean disease duration 20.3 ± 8.3 years and mean age at disease onset 34.3 ± 7.6 years. For the 40 non-SS pituitary failure patients mean age was 46.5 ± 16.6 years, mean disease duration was 4.7 ± 5.1 years and mean age at disease onset was 41.8 ± 18.2 years. The prolactin response (PRL) on the TRH test was found to be significantly lower in SS patients compared to non-SS patients ($p < 0.05$). Both patient groups had low basal pituitary hormones, with mean PRL level in SS patients 4.9 ± 4.0 ng/mL which was significantly low compared to non-SS patients with 36.8 ± 84.7 ng/mL ($p = 0.022$).

Conclusion. Pituitary failure patients may present with a broad range of clinical symptoms and findings. Early diagnosis and timely replacement treatment have vital importance for SS patients.

Key words: Sheehan syndrome, hypopituitarism, pituitary adenoma, pituitary failure, DEXA.

INTRODUCTION

Pituitary failure (PF) is full or partial deficiency of hormone secretion from the anterior and/or posterior pituitary. The causes of PF are generally divided into hereditary and acquired causes. Among acquired causes are neoplastic, traumatic, infiltrative/inflammatory, infection, vascular (Sheehan syndrome, pituitary apoplexy, aneurysm), postoperative, radiation exposure, medications, functional and other causes (1, 2).

In spite of developed surgical techniques and

advanced imaging methods, the most common cause of PF is still pituitary adenoma (3, 4). In addition, Sheehan syndrome (SS) is a rarely-observed health problem in developed countries but is a continuing problem in less developed and developing countries, due to insufficient postpartum care conditions (5). For diagnosis of SS generally good anamnesis and physical examination are sufficient, with basal hormone levels, dynamic tests and radiological investigations confirming diagnosis. Treatment is cheap and easy but has vital importance, making diagnosis of this disease very important.

Patients with pituitary failure may apply to hospital with complaints like hyponatremia, hypoglycemia, hypotension, loss of consciousness and confusion. Non-specific complaints may include weakness, fatigue and shivering. Female patients may have irregular menstruation or amenorrhea, loss of lactation, infertility, and anemia, while male patients may have disrupted sexual functions and erectile dysfunction and infertility with delayed puberty and growth retardation in children (2, 5).

Anamnesis, physical examination and low basal hormones ensure suspicion of PF. For diagnosis, ACTH stimulation test or insulin tolerance test (ITT) in non-contraindicated patients, TRH test and LH-RH test are commonly used. The ITT is accepted as the gold standard to assess the hypothalamus-pituitary-adrenal axis (HPA) (6, 7). Patients with PF may have variations in hemogram and biochemical parameters and basal hormone variations (2, 8). Lymphocytic hypophysitis cases, especially, may have autoimmune source, while SS patients have higher anti-pituitary antibodies and anti-hypothalamic antibodies compared to a control group (8, 9). With PF the risk of osteopenia and osteoporosis is theoretically expected to increase due to hormone deficiencies (10).

For pituitary region imaging, magnetic resonance (MR) imaging is commonly used. PF patients with hereditary cause are most commonly reported to

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have pituitary macroadenoma appearance (11).

With this study we divided our PF patients into two groups as SS and non-SS patients to better assess and compare our patients. Thus, we compared the differences between these two groups in terms of clinical picture at admission to the hospital, hemogram and biochemistry values, autoantibodies, basal hormone levels, their response to dynamic tests, DEXA values and pituitary magnetic resonance (MR) images. We aimed to create a database of PF patients, to reach multifaceted detailed diagnosis of PF patients, and in this way to obtain new gains and to apply our experience to future patients.

MATERIAL AND METHOD

The study included 72 patients with pituitary failure. As this study assessed patients monitored for pituitary failure from multiple aspects and compared the data, ethics committee permission was obtained for analytical research as a retrospective and cross-sectional study. Patients were divided into two groups as 32 female patients with Sheehan syndrome (SS) and 40 patients (20 female and 20 male patients) with non-Sheehan syndrome pituitary failure. Groups were compared in terms of anamnesis data, laboratory characteristics, basal hormone levels, dynamic test results, DEXA results of patients and radiological imaging.

SS diagnosis was made with history (such as excessive hemorrhage during or after birth, agalactia, prolonged amenorrhea after birth, hypotension, breast atrophy, history of miscarriage or stillbirth, blood transfusion history, wrinkling of skin around eyes and mouth, cold intolerance, constipation, loss of axillary and pubic hair), physical examination, laboratory investigations, low basal hormone levels, radiological tests and dynamic tests.

Diagnosis of patients with non-SS pituitary failure was placed with relevant pituitary history physical examination, laboratory tests, basal hormone levels, radiological tests and dynamic tests.

The patients' diagnosis, height, weight, body mass index (BMI), systolic and diastolic pressure, hemogram, serum iron, serum iron binding capacity and ferritin levels in patients with anemia were studied. Biochemical parameters of blood urea nitrogen (BUN), creatinine, fasting blood glucose (FBG), sodium, chlorine, potassium, calcium, magnesium, phosphorus, lactate dehydrogenase enzyme (LDH), alanine transferase (ALT), aspartate transferase (AST),

triglycerides, total cholesterol, HDL cholesterol, and LDL cholesterol were studied. Basal hormones of free T3, free T4, TSH, FSH, LH, ACTH, GH, estradiol (E2), testosterone (T), IGF-1, PRL and cortisol levels were studied. Additionally, in terms of accompanying autoimmune disease, patients had antinuclear antibody (ANA), double-stranded DNA antibody (anti-dsDNA), anti-microsomal antibody (anti-M) and anti-thyroglobin antibody (anti-Tg) levels examined. Dynamic tests (the ACTH stimulation test, TRH test, LH-RH test and ITT values) used for pituitary failure diagnosis recorded values in the 0, 30th, 60th, 90th and 120th minutes. All patients had bone densitometry values measured before beginning replacement therapy using a Hologic QDR4500 W device. The radiological imaging method of pituitary MR images was obtained with a Toshiba Excelart 1.5 Tesla device.

Dynamic tests of SS and non-SS patients included the ACTH stimulation test, TRH test, LH-RH test and ITT values. For the ACTH stimulation test, following overnight fasting, samples were taken for basal cortisol levels in the morning from 08.00-09.00, then 250 µg synthetic ACTH was administered and blood samples were taken for cortisol in the 30th, 60th, 90th and 120th minute. Peak cortisol levels above 20 µg/dL were accepted as normal response, in other words as no adrenal failure (12).

For the TRH test, basal TSH and PRL samples were taken from 08.00-09.00 in the morning, then 200 µg TRH ampoule was administered intravenously and blood samples were taken for serum TSH and PRL in the 30th, 60th, 90th and 120th minutes. On the TRH test, TSH value above 20 µIU/mL and PRL values above 30-35 ng/mL were accepted as normal response (13).

The LH-RH test had samples taken for basal FSH and LH in the morning from 08.00-09.00 and then 100 µg LH-RH ampoule was administered intravenously and blood samples for serum FSH and LH were taken again at the 30th, 60th, 90th and 120th minute. On the test, peak LH and FSH passing 10 IU/L were accepted as normal response (13).

ITT was used for patients with no contraindications such as ischemic heart disease history, epilepsy, fainting with unknown cause, glycogen storage disease or advanced age and who responded to the ACTH test. Patients fasting from midnight had an iv catheter inserted at 08.00 in the morning and the patient was left in a calm room with 50% dextrose and fruit juice beside them in case of unexpected severe hypoglycemia. Later patients were administered 0.10-0.15 ü/kg crystallized insulin bolus and blood glucose

was carefully monitored. In addition to hypoglycemia symptoms, the 0 minute was accepted as the time when blood glucose dipped below 40 mg/dL and blood samples were taken for blood glucose, cortisol and GH, with samples taken in the 30th, 60th, 90th and 120th minute for the same parameters. A positive cortisol response to ITT was accepted as a peak cortisol value above 18 µg/dL (13).

Statistical Analysis

The data from the study were uploaded to the SPSS (Version 22.0, Inc. Illinois, Chicago, USA) program for analysis with the significant difference test for two means and the chi-square test used. Data are presented as arithmetic mean $\pm$ standard deviation, number of subjects (n) and percentage on tables with level of error 0.05. $P < 0.05$ was accepted as significant.

RESULTS

The findings of the study are dealt with in six sections listed below.

I. Clinical findings of SS and non-SS pituitary failure patients included in the study.

II. Hemogram values, serum electrolyte levels, serum triglyceride and cholesterol levels, thyroid autoantibodies and ANA, anti-dsDNA values.

III. Basal hormone levels of the patients

IV. ACTH stimulation test, LH-RH test, TRH test, and ITT test results of patients.

V. Bone mineral density (BMD) values obtained with DEXA for patients

VI. Pituitary MR imaging results of patients.

Section I: The study included a total of 72 patients with pituitary failure diagnosis. Of these patients, 32 were SS female patients and 40 were non-SS patients comprising 20 males (50%) and 20 females (50%). The patient groups are shown in Table 1.

The age interval for SS patients was 29-77 years with disease duration varying from 4 to 36 years. Mean age was 56.1 ± 11.7 years, with mean disease duration 20.3 ± 8.3 years and mean age at disease onset 34.3 ± 7.6 years. The age interval for non-SS pituitary failure patients was 20-78 years, with disease durations varying from 1 to 20 years. Mean age was 46.5 ± 16.6 years, mean disease duration was 4.7 ± 5.1 years and mean age at disease onset was 41.8 ± 18.2 years. The mean BMI in the SS group was 26.4 ± 4.7 kg/m², with mean systolic blood pressure 108.1 ± 20.2 mmHg and mean diastolic blood pressure 69.2 ± 14.8 mmHg. For the non-SS group, mean BMI was 27.8 ± 7.0 kg/m², mean systolic blood pressure was 119.7 ± 14.7 mmHg and mean diastolic blood pressure was 78.3 ± 9.4 mmHg. When the two groups are compared, mean age was higher in the SS group ($p=0.008$), with mean disease duration longer in the SS group ($p=0.0001$) and mean age at initial onset younger in the SS group ($p=0.0001$) and mean systolic blood pressure ($p=0.009$) and diastolic blood pressure lower in the SS group ($p=0.004$). The difference between the groups in terms of BMI was insignificant ($p=0.375$) (Table 2).

The comparison of clinical characteristics of both patient groups is given in Table 3. In the SS group, of patients attending hospital for the first time, complaints were hyponatremia in seven patients (21.8%), hypoglycemia in three patients (9.4%), confusion or coma + hypotension tableau in seven patients (21.9%), infection and fever in three patients (9.4%), weakness-fatigue in 11 patients (34.4%), and abdominal pain and secondary hypothyroidism in one patient (3.1%). Advanced tests and investigations were performed and it was found that 2 patients with hyponatremia also had hypoglycemia, and one patient with hypoglycemia also had pericardial effusion. In the non-SS group, four patients applied with hyponatremia (10%), one patient with infection and fever (2.5%), one

Table 1. Patient group with pituitary failure

Patient diagnosis		n	%
Non-SS (n=40)	Sheehan syndrome	32	44.4
	Postoperative pituitary failure	24	33.3
	Lymphocytic hypophysitis	1	1.4
	Empty sella syndrome	8	11.1
	Idiopathic causes	2	2.8
	Pituitary adenoma	1	1.4
	Ectopic neuropituitary + pituitary hypoplasia	1	1.4
	Langerhans cell histiocytosis	1	1.4
	Pituitary stem compression (1 patient pseudo tumor cerebri, 1 patient germ cell tumor)	2	2.8
	TOTAL	72	100

SS: Sheehan Syndrome, n: number.

Table 2. Comparison of patient age, BMI, age at disease onset, disease duration and blood pressure values

Variables	SS (n=32)	Non-SS (n=40)	P value
Age (year)	56.1 ± 11.7	46.5 ± 16.6	0.008
BMI (kg/m ²)	26.4 ± 4.7	27.8 ± 7.0	0.375
Disease duration (year)	20.3 ± 8.3	4.7 ± 5.1	0.0001
Disease onset age (year)	34.3 ± 7.6	41.8 ± 18.2	0.0001
Systolic blood pressure (mmHg)	108.1 ± 20.2	119.7 ± 14.7	0.009
Diastolic blood pressure (mmHg)	69.2 ± 14.8	78.3 ± 9.4	0.004

SS: Sheehan Syndrome, BMI: body mass index

Table 3. Comparison of patients in terms of clinical features

	SS (n=32) n%		Non-SS (n=40) n%		P value
Weakness-fatigue	32	100	36	50	0.124
Nausea-vomiting	24	75	15	37.5	0.002
Weight loss	20	62.5	11	27.5	0.003
Headache	10	31.3	33	82.5	0.001
Hypertension	11	34.4	10	25	0.384
Hypotension	8	25	8	20	0.612
Dry hair	27	84.4	22	52.5	0.004
Hair-eyebrow loss	25	78.1	26	65	0.223
Pale skin	24	75	13	32.5	0.001
Constipation	23	71.9	22	55	0.142
Drowsiness	28	87.5	32	80	0.396
Cold intolerance	29	90.6	26	65	0.011
Facial edema	8	25	7	17.5	0.436
Loss of libido	29	90.6	30	75	0.087
Diabetes insipidus	1	3.1	15	37.5	0.001
Diabetes mellitus	2	6.3	5	12.5	0.451
Axillary-pubic rash	30	96.8	21	52.5	0.010
Wrinkles around mouth and eyes	24	75	13	32.5	0.001

SS: Sheehan syndrome, n: number.

patient in a coma (2.5%), six patients with weakness-fatigue (15%), sixteen patients with low postoperative basal hormones (40%), three patients with growth-development retardation (7.5%), one patient with loss of vision and hair loss, six patients with headache and secondary hypothyroidism (15%), one patient with diabetes insipidus (DI)+ hypernatremia (2.5%) and one patient with DI+vision disorders (2.5%) and advanced tests and investigations were performed.

Section II: In this section, the hemogram values, serum electrolytes and lipid levels, serum iron, serum total iron binding capacity and ferritin levels in patients with anemia are dealt with in SS and non-SS pituitary failure patients. The mean values for hemogram and biochemical parameters and statistical comparison between the groups are given in Table 4.

Section III: In this section, basal hormone levels and thyroid autoantibody levels among SS and non-SS pituitary failure patients are examined. Of 32 SS patients, 27 had secondary hypothyroidism according to basal hormone levels, while after the TRH test, all SS patients appeared to have hypothyroidism. Sixteen patients had hypocortisolemia, and 16 patients had

basal cortisol levels in the normal interval. When the ITT or ACTH test responses of SS patients are assessed together with basal cortisol levels, 28 patients (87.5%) had adrenal failure. When the menopausal FSH and LH values of patients are considered as basis, all 32 patients had lower than necessary FSH and LH levels. Seventeen patients had basal PRL levels lower than normal, while 14 patients were in the normal interval. Anti-M values were normal for 22 patients, and higher than normal in 7 patients. Anti-Tg values were normal for 5 patients and higher than normal for 24 patients.

According to basal hormone levels of 40 patients with non-SS pituitary failure, all patients had a secondary hypothyroidism tableau. Twenty-three patients had hypocortisolemia, 17 patients had basal cortisol levels in normal interval. When the ITT or ACTH test responses of patients with non-SS pituitary failure are assessed together with basal cortisol levels, 32 patients (80%) had adrenal failure. Considering the basal FSH and LH values for male and female patients according to age group, 31 patients had lower FSH values and 35 patients had lower LH values than normal. When the E2 and testosterone values

Table 4. Comparison of mean hemogram and biochemical values of patients

	SS (n=32) Mean $\pm$ sd	Non-SS (n=40) Mean $\pm$ sd	P value
Hemoglobin (g/dL)	11.9 $\pm$ 1.4	12.9 $\pm$ 1.3	0.006
RBC (10 ⁶ / μ L)	4.0 $\pm$ 0.6	4.4 $\pm$ 0.6	0.003
WBC (10 ³ / μ L)	7.9 $\pm$ 3.7	8.1 $\pm$ 2.8	0.766
Hematocrit (%)	34.8 $\pm$ 4.3	38.0 $\pm$ 4.2	0.003
MCV (fL)	89.7 $\pm$ 5.3	85.8 $\pm$ 5.2	0.003
MCH (pg)	30.9 $\pm$ 2.2	29.2 $\pm$ 1.6	0.001
MCHC (g/dL)	34.4 $\pm$ 2.0	34.0 $\pm$ 1.1	0.204
BUN (mg/dL)	17.6 $\pm$ 8.3	15.0 $\pm$ 8.6	0.207
Creatinine (mg/dL)	1.2 $\pm$ 0.4	0.9 $\pm$ 0.3	0.008
FBG (mg/dL)	84.2 $\pm$ 25.1	101.6 $\pm$ 36.5	0.025
Sodium (mmol/L)	135.9 $\pm$ 7.4	136.0 $\pm$ 8.6	0.954
Potassium (mmol/L)	4.1 $\pm$ 0.5	4.1 $\pm$ 0.4	0.871
Chlorine (mmol/L)	100.5 $\pm$ 7.0	100.7 $\pm$ 8.4	0.918
Calcium (mg/dL)	8.8 $\pm$ 0.8	9.1 $\pm$ 0.8	0.098
Phosphorus (mg/dL)	3.0 $\pm$ 0.8	3.7 $\pm$ 0.9	0.001
Magnesium (mg/dL)	2.0 $\pm$ 0.3	2.2 $\pm$ 0.4	0.213
ALT (IU/L)	24.3 $\pm$ 11.8	25.9 $\pm$ 16.5	0.645
AST (IU/L)	39.3 $\pm$ 23.5	32.3 $\pm$ 27.2	0.263
LDH (IU/L)	297.9 $\pm$ 115.7	243.8 $\pm$ 84.3	0.034
Triglyceride (mg/dL)	144.2 $\pm$ 62.7	157.1 $\pm$ 95.2	0.549
Cholesterol (mg/dL)	210.4 $\pm$ 55.4	208.1 $\pm$ 71.6	0.892
LDL (mg/dL)	136.5 $\pm$ 54.2	121.3 $\pm$ 49.2	0.275
HDL (mg/dL)	40.5 $\pm$ 16.6	42.5 $\pm$ 16.2	0.647
Iron (μ g/dL)	61.1 $\pm$ 32.9	58.8 $\pm$ 31.5	0.833
SDBK (ng/dL)	274.1 $\pm$ 103.3	334.8 $\pm$ 100.5	0.082
Ferritin (ng/dL)	140.0 $\pm$ 86.3	97.9 $\pm$ 68.4	0.109

Mean: mean, sd: standard deviation, n: number, SS: Sheehan syndrome MCV: Midcorpuscular volume MCH: Midcorpuscular hemogram, MCHC: Midcorpuscular hemogram concentration, BUN: Blood Urea Nitrogen, FBG: Fasting blood glucose, ALT: Alanine transferase, AST: Aspartate transferase, LDH: Lactate dehydrogenase, LDL: Low density lipoprotein, HDL: High density lipoprotein, SIBC: Serum iron binding capacity.

Table 5. Comparison of mean basal hormone values and thyroid autoantibodies of patients

	SS (n=32) Mean $\pm$ sd	Non-SS (n=40) Mean $\pm$ sd	P value
FT3 (pg/mL)	1.1 $\pm$ 0.6	1.7 $\pm$ 0.8	0.001
FT4 (ng/dL)	0.4 $\pm$ 0.2	1.1 $\pm$ 2.5	0.107
TSH (μ IU/mL)	1.7 $\pm$ 1.4	1.0 $\pm$ 1.0	0.025
Anti M (IU/mL)	15.7 $\pm$ 36.9	8.7 $\pm$ 30.5	0.401
Anti Tg (IU/mL)	34.6 $\pm$ 40.2	37.1 $\pm$ 41.3	0.805
FSH (μ IU/mL)	2.1 $\pm$ 1.9	2.3 $\pm$ 2.5	0.816
LH (μ IU/mL)	0.7 $\pm$ 0.8	0.9 $\pm$ 1.2	0.280
Cortisol (μ g/dl)	5.8 $\pm$ 5.7	5.0 $\pm$ 4.9	0.509
ACTH (pg/mL)	12.7 $\pm$ 11.2	17.5 $\pm$ 17.4	0.211
Prolactin (ng/mL)	4.9 $\pm$ 4.0	36.8 $\pm$ 84.7	0.022
GH (ng/mL)	0.1 $\pm$ 0.0	0.9 $\pm$ 2.7	0.074
E2 (pg/mL)	17.7 $\pm$ 11.8	12.8 $\pm$ 14.8	0.228
IGF-1 (ng/mL)	9.6 $\pm$ 11.1	130.2 $\pm$ 85.9	0.001
Testosterone (ng/mL)	---	10.7 $\pm$ 22.7	

SS: Sheehan syndrome FT3: Free T3, FT4: Free T4, TSH: Thyroid stimulating hormone Anti-M: Anti-Microsomal antibody, Anti-Tg: Anti-Thyroglobulin, FSH: Follicular stimulating hormone, LH: Luteinizing hormone, ACTH: Adrenocorticotrophic hormone, GH: Growth hormone, E2: estradiol, IGF-1: Insulin like growth factor-1.

of these patients are also assessed, 34 patients had hypogonadism. Eleven patients had lower than normal basal PRL values, 15 patients were normal and 14 patients had high values. Anti-M values were normal for 13 patients and higher than normal for 6 patients.

Anti-Tg values were normal for 13 patients and higher than normal for 24 patients. The mean basal hormone levels and thyroid autoantibody levels were statistically compared between the groups and are shown in Table 5.

Section IV: In this section, the ACTH test, TRH

test, LH-RH test and ITT results of suitable patients were compared between SS and non-SS pituitary failure patients and are shown in Table 6. However, due to general status disorder and beginning emergency treatment, dynamic tests could not be performed for some patients.

ACTH stimulation test; when the SS and non-SS groups are compared in terms of cortisol levels at all times (0, 30th, 60th, 90th, 120th minute), there was no significant difference between the two groups ($p>0.05$).

TSH response to TRH test: when the SS and non-SS groups are compared in terms of TSH values at all times (0, 30th, 60th, 90th, 120th minute), there was no significant difference between the two groups ($p>0.05$).

PRL response to TRH test: in terms of PRL values at all times (0, 30th, 60th, 90th, 120th minute) in both groups, mean PRL values were lower in the SS group ($p<0.05$).

FSH response to LH-RH test: when the SS and non-SS groups are compared in terms of FSH values at all times (0, 30th, 60th, 90th, 120th minute), there was no significant difference found between the two groups ($p>0.05$).

LH response to LH-RH test: when the SS and non-SS groups are compared in terms of LH values at all times (0, 30th, 60th, 90th, 120th minute), there was no significant difference between the two groups ($p>0.05$).

Cortisol response to ITT: when the SS and non-SS groups are compared in terms of cortisol values at all times (0, 30th, 60th, 90th, 120th minute), there was no significant difference identified between the two groups ($p>0.05$).

GH response to ITT: when the SS and non-SS groups are compared in terms of GH levels at all times (0, 30th, 60th, 90th, 120th minute), there was no significant difference between the two groups ($p>0.05$).

According to basal hormone values and dynamic test results, we assessed 28 SS patients (87.5%) as having total hypopituitarism while 4 patients (12.5%) had partial hypopituitarism. In the non-SS pituitary failure patients, 32 patients (80%) were assessed as having total hypopituitarism and 8 patients (20%) had partial hypopituitarism.

Section V: In this section, the BMD values obtained with DEXA were compared in SS and non-SS pituitary failure patients. Thirty SS patients had BMD measured in the L1-L4 lumbar vertebrae and femur neck with DEXA. Six patients (20%) had normal BMD, seven patients (23.3%) had osteopenia and 17 patients (56.6%) had osteoporosis. Two patients did not have DEXA performed. Thirty-nine non-SS pituitary failure patients had DEXA performed. Nine patients (23.1%) had normal BMD, 14 patients (35.9%) had osteopenia and 16 patients (41%) had

Table 6. Comparison of mean values on dynamic tests for both groups

ACTH Stimulation test	SS (n=28)	Non-SS (n=28)	P value
	Mean± sd	Mean± sd	
Cortisol (0 min)	6.3±6.5	4.6±4.1	0.261
Cortisol (30 th min)	13.1±12.5	11.5±8.4	0.583
Cortisol (60 th min)	15.4±14.7	15.0±10.3	0.903
Cortisol (90 th min)	17.1±15.0	15.8±10.8	0.726
Cortisol (120 th min)	15.9±11.1	19.4±17.2	0.386
TRH Test	SS (n=22)	Non-SS (n=28)	P value
TSH (0 min)	1.8±1.0	1.3±1.2	0.117
TSH (30 th min)	2.7±1.6	5.2±9.2	0.176
TSH (60 th min)	2.8±1.5	5.9±9.4	0.108
TSH (90 th min)	2.9±1.6	5.8±9.2	0.123
TSH (120 th min)	2.8±1.5	5.4±8.0	0.117
TRH Test	SS (n=22)	Non-SS (n=27)	P value
PRL (0 min)	4.8±3.4	25.7±8.4	0.020
PRL (30 th min)	6.3±4.6	32.9±8.7	0.006
PRL (60 th min)	5.9±4.1	31.9±9.1	0.009
PRL (90 th min)	5.7±4.2	30.8±9.2	0.012
PRL (120 th min)	5.4±3.6	29.4±8.9	0.013
LH-RH Test	SS (n=25)	Non-SS (n=32)	P value
FSH (0 min)	2.5±2.2	2.3±2.6	0.744
FSH (30 th min)	2.8±2.7	2.8±2.8	0.934
FSH (60 th min)	2.9±2.8	3.1±3.1	0.749
FSH (90 th min)	3.1±3.0	3.4±3.3	0.749
FSH(120 th min)	3.1±2.9	3.5±3.4	0.608

Table 7. Comparison of mean values on dynamic tests for both groups (cont'd)

LH-RH Test	SS (n=25)	Non-SS (n=32)	P value
LH (0 min)	0.7±0.9	1.5±2.9	0.233
LH (30 th min)	2.1±2.9	4.5±2.1	0.351
LH (60 th min)	2.4±0.6	4.1±1.4	0.350
LH (90 th min)	2.2±2.5	4.8±1.6	0.201
LH (120 th min)	2.4±3.1	4.1±1.2	0.281
ITT	SS (n=11)	Non-SS (n=14)	P value
Cortisol (0 min)	5.3±2.4	4.8±3.8	0.692
Cortisol (30 th min)	10.3±7.1	9.0±7.0	0.668
Cortisol (60 th min)	10.4±6.0	9.7±7.7	0.598
Cortisol (90 th min)	9.4±5.2	9.0±8.1	0.429
Cortisol (120 th min)	8.8±5.8	7.3±6.4	0.391
ITT	SS (n=4)	Non-SS (n=4)	P value
GH (0 min)	0.1±0.1	1.2±1.7	0.149
GH (30 th min)	0.1±0.1	1.0±0.7	0.468
GH (60 th min)	0.1±0.1	1.0±0.9	0.885
GH (90 th min)	0.1±0.0	0.9±0.8	0.887
GH (120 th min)	0.1±0.0	0.9±0.8	0.855

Mean: mean, sd: standard deviation, n: number, SS: Sheehan syndrome, min: minute, TSH: Thyroid stimulating hormone, PRL: prolactin, LH-RH: luteinizing hormone-releasing hormone, ITT: insulin tolerance test, FSH: Follicular stimulating hormone, LH: Luteinizing hormone, ACTH: Adrenocorticotrophic hormone, GH: Growth hormone.

Table 8. Mean DEXA values and comparison of patients

	SS (n=30) Mean± sd	Non-SS (n=39) Mean± sd	P value
Lumbar T	-2.0±1.3	-1.7±1.4	0.306
Lumbar Z	-0.9±1.2	-1.1±1.5	0.529
Femoral T	-1.4± 1.5	-1.2±1.3	0.686
Femoral Z	-0.3±1.3	-0.3±2.2	0.500

Mean: mean, sd: standard deviation, n: number, SS: Sheehan syndrome.

Table 9. Pituitary MR imaging results of patients

	Groups				Total	
	SS (n=32) n%		Non-SS (n=40) n%		S%	
-Empty sella	25	78.1	3	7.5	28	38.8
-Partial empty sella	7	21.8	5	12.5	12	16.6
-Microadenoma	0	0	2	5	2	2.7
-Macroadenoma	0	0	21	52.5	21	29.1
-Lymphocytic hypophysitis	0	0	1	2.5	1	1.3
-Ectopic neuropituitary+pituitary hypoplasia	0	0	1	2.5	1	1.3
-Langerhans cell histiocytosis	0	0	1	2.5	1	1.3
-Craniopharyngioma**	0	0	1	2.5	1	1.3
-Normal	0	0	2	5	2	2.7
-Pituitary stalk compression (pseudotumor cerebri, germ cell tumor)	0	0	2	5	2	2.7
-Mass in dorsum sella and clivus region (small round cell tumor)**	0	0	1	2.5	1	1.3
TOTAL	32	100	40	100	72	100

SS: Sheehan syndrome n: number, **Postoperative pituitary failure group patients.

osteoporosis. One patient with platinum implants did not have DEXA performed. When the groups are compared in terms of BMD values obtained with DEXA, there appeared to be no significant differences between the two groups in terms of osteopenia and osteoporosis ($p>0.05$) (Table 7).

Section VI: In this section, the results of pituitary

MR radiological imaging for diagnosis of pituitary failure in SS and non-SS pituitary failure patients were compared and are shown in Table 8. Among SS patients, 78.1% had empty sella and 28.1% had partial empty sella identified. The majority of non-SS pituitary failure patients had pituitary macroadenoma (52.5%).

DISCUSSION

There are many known reasons for pituitary failure. Sheehan syndrome is undoubtedly one of the most common causes. In developing countries such as ours, obstetric conditions are shown to be important. Additionally, autoimmune events are held responsible for pathogenesis and lymphocytic hypophysitis picture is important for differential diagnosis of SS. Imaging methods and advanced surgical techniques have ensured rapid diagnosis and early treatment opportunities for pituitary and suprasellar region tumors, space-occupying lesions, congenital or acquired pituitary anomalies. In spite of all this, both preoperative and postoperative pituitary failure picture have not been fully prevented.

The 32 SS cases investigated in this study had mean age, mean disease duration and mean age at disease onset similar to previous studies (14). This study emphasized that there may be a long interval between the postpartum process and diagnosis (14). In our study, one patient was diagnosed 10 years later, while 32 patients had been diagnosed more than 10 years from the event. The ages, disease duration, mean age, mean disease duration and mean age at disease onset of non-SS patients were slightly higher than the mean values of other studies (15, 16). The reason for this is the inclusion of all pituitary failure patients in the non-SS pituitary failure group.

Studies have found systolic and diastolic blood pressure values in SS are significantly low compared to a control group (17). This is expected to be low in patients with adrenal failure (15). In our study, mean systolic and diastolic blood pressure values of patients were low compared to normal healthy individuals.

In our study, one patient was primipara while 31 patients (96.8%) were multipara. SS patients are generally expected to have birth history at early ages, lack of menstruation after last birth (14). In our SS patient group, the high birth rate and high number of births may be explained as reflecting low socioeconomic level or that high numbers of births may increase obstetric complications. Additionally, a study by Purnell *et al.* reported the incidence of SS and degree of severity of hypopituitarism is not associated with the number of pregnancies (18).

Of SS patients, 19 patients (59.4%) had stillbirth or infant dying within a year of birth, with 19 patients (59.4%) having blood transfusion after their last birth. SS pathogenesis includes excessive hemorrhage after birth and secondary to this postpartum pituitary

necrosis is expected to form (14). Studies have stated there are high maternal and infant deaths in SS, with infants dying in the first months considered to be linked to lactation loss (19). In the non-SS pituitary failure group, two patients (13.3%) had blood transfusion after their last births, six patients (42.9%) had stillbirths and 15 patients (100%) stated they could not breastfeed after their final birth. Six female patients with stillbirths and newborn deaths are considered to be linked to homebirth anamnesis, low socio-economic level, inappropriate health conditions and inappropriate birth technique.

Patients with hypopituitarism attend hospitals under emergency conditions and with different clinical picture (20). In our study patients attending the emergency or endocrinology clinics had different biochemical disorders in terms of initial complaints and metabolic values. In SS patients these findings were higher compared to the non-SS pituitary failure group. According to these results, in our study together with emphasizing that female patients applying with clinical complaints and metabolic disorders should be initially suspected of SS, we recommend inquiring about other pituitary failure causes.

There are publications stating that hypoglycemia and associated symptoms and coma are the first symptoms of SS. Dökmetaş *et al.* in a study of 20 SS patients, identified seven patients had hyponatremia (35%), three patients had adrenal crisis (15%) and one patient had hypoglycemia (5%) (21). Bayram *et al.* in an SS series found that 7 out of 30 patients (23%) attended hospital with hypoglycemia (22). The series published by Sert *et al.* found nine out of 28 SS patients (32.1%) applied to hospital with confusion, coma and hyponatremia (23). Patients with pituitary failure may attend with advanced clinical situations like adrenal crisis, hyponatremia, hypovolemic shock, lethargy, and hypoglycemia linked to corticotropin deficiency and secondary adrenal failure, but may also attend with clinical situations like weight loss, non-specific abdominal pain, fatigue, headache and sweating (20, 24). The cause of hyponatremia in hypopituitarism may be hypocortisolemia or hypothyroidism forming a picture similar to ADH syndrome (25).

There are publications stating that in SS patients, autoimmune marker positivity and hypothyroidism may accompany SS (14, 26). In the non-SS pituitary failure group, one patient had lymphocytic hypophysitis, and one patient had Langerhans cell histiocytosis. These patients had very high titrations of positive thyroid autoantibodies. We think this association was present in

2 of our patients due to autoimmune diseases occurring together.

One of the most important tests for SS diagnosis in the lack of PRL response to the TRH test (27). The reason for this is that the first and most disrupted pituitary functions in SS are PRL and GH secretion disorder. As the cells secreting these hormones are located in the lateral external section of the adenohypophysis, they are the first regions affected by ischemic necrosis (14). Similar to our study, Özbey *et al.* obtained no sufficient PRL response in any of their 21 patients, while Jialal *et al.* found similar results for their 10 patients (27, 28). Many researchers have emphasized that PRL deficiency is the most commonly encountered hormone deficiency in SS (14, 19). They reported the PRL response to the TRH test is the most appropriate and reliable screening test to research SS (28). In our case series, the high rate of PRL deficiency among SS patients (100%) supports this view.

There are many tests used to measure the ACTH reserve in the pituitary. The most commonly used is the ITT test which is accepted as the gold standard (12, 29). This test is especially beneficial to determine individuals with limited pituitary reserves (13). The normal cortisol response to ITT has been defined differently in various studies. Lindholm *et al.* accepted cortisol values passing 18 µg/dL as normal response (30), while Plumpton and Bese accepted that cortisol values above 19.8 µg/dL were sufficient (31). Study by Dökmetaş *et al.* accepted cortisol response to ITT passing 20 µg/dL peak cortisol values as positive response (12). In our study, the standard ACTH test was performed with cortisol response; however, there were four patients in the SS group and three patients in the non-SS pituitary failure group without response on ITT among the same patients. These results support the view that for assessment of the hypothalamo-pituitary axis (HPA) in those with pituitary failure, ITT is superior to the standard ACTH test.

In 30 patients in the SS group with DEXA performed 17 patients (56.6%) had osteoporosis, while in 39 patients in the non-SS pituitary failure group with DEXA performed 16 patients (41%) had osteoporosis identified. All of our SS patients were female and the longer mean disease duration, longer low GH and gonadotropin interactions, early menopause and insufficient protective effect of E2 may explain the higher rate of osteoporosis observed in our SS patients compared to the other group. The study by Dökmetaş *et al.* assessed 20 SS patients and identified osteoporosis in 2 of nine patients assessed

with DEXA (22.2%) (21). In our study, the higher number of osteoporosis cases among SS patients (56.6%) may be due to our higher patient numbers and that nearly all of our cases were assessed for BMD with DEXA.

Though empty sella was observed in all our SS patients, a total of eight patients in the non-SS group had total-partial empty sella observed. Empty sella occurs due to sellar expansion and damage to the sellar diaphragm resulting in herniation of the arachnoid region. With more than 90% of the pituitary gland compressed, hypopituitarism develops. Secondary empty sella may be caused by infection in the region, trauma, autoimmunity, radiotherapy, surgery and spontaneous necrosis of pituitary adenoma (32).

In conclusion, due to home births and inappropriate birth conditions in less developed regions of Turkey, SS continues to be a serious problem in our country. As a result, diagnosis of asymptomatic and atypical cases may be reached through serious anamnesis. Female patients attending emergency services with hypoglycemia, hyponatremia and loss of consciousness should be insistently considered for SS. Early diagnosis and timely replacement therapy has vital importance for SS patients. This study reveals the need to assess basal hormone levels together with dynamic tests for diagnosis of pituitary failure.

Conflict of interest

The authors declare that they have no conflict of interest.

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