Extensive investigation of 114 patients with Sheehan’s syndrome: a continuing disorder

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Abstract

Objective: Sheehan’s syndrome (SS) is a well-known cause of hypopituitarism resulting from postpartum pituitary necrosis. Because of its rarity in Western society, its diagnosis is often overlooked. We aimed to investigate the clinical, laboratory, and radiological aspects of SS in a large number of patients.

Study design: A retrospective assessment of the medical records of 114 patients with SS was conducted. In addition, sella turcica volumes of 29 healthy women were compared with those of patients by magnetic resonance imaging examinations.

Results: The mean period of diagnostic delay was 19.7 years in patients with SS. It was found that 52.6% of patients had nonspecific complaints, 30.7% had complaints related to adrenal insufficiency, and 9.6% had complaints related to hypogonadism when diagnosed. At the time of diagnosis, 55.3% of the patients had panhypopituitarism, while 44.7% had partial hypopituitarism. The number of deficient hormones was found to be increased over the years. None of the patients whose basal prolactin was below 4.0 ng/ml had adequate prolactin responses to TRH test, while all patients whose basal prolactin was above 7.8 ng/ml had adequate responses. Mean sella volume was found to be significantly lower in the SS group (340.5 ± 214 mm³) than that in the healthy group (602.5 ± 192 mm³).

Conclusions: SS is a common cause of hypopituitarism in underdeveloped and developing countries. The main reasons for diagnostic delay seem to be the high frequency of patients with nonspecific complaints and neglect of SS. In addition, the TRH stimulation test was found to have a high sensitivity and specificity to recognize PRL deficiency. Furthermore, small sella size may have an important contributing role in the etiopathogenesis of SS.

Introduction

Sheehan’s syndrome (SS) can be defined as partial or complete hypopituitarism occurring due to massive postpartum uterine hemorrhage that leads to pituitary infarction (1). It is a common disorder particularly in underdeveloped and developing regions of the world. It was estimated by the World Health Organization (WHO) in 1996 that SS was taking the lives of 100 000 women a year, and at that time affected more than 3 million women in the world (2). In one cohort study, the prevalence of SS was estimated to be 3.1% among women who were older than 20 years in Kashmir, India (3).

SS is not rare in developing countries; even so, delay in diagnosis has been a common problem. A recent study carried out in Turkey has shown that the frequency of SS was 13.8% among 773 patients with hypopituitarism (4). The main reason for diagnostic delay of SS seems to be nonspecific and thus unnoticed symptoms, such as fatigue, weakness, and anorexia. For this reason, there may be a great number of patients with SS who remain undiagnosed and thereby untreated. However, it should be kept in mind that SS may also develop acutely and lead to coma and even death due to severe hypopituitarism (5). Furthermore, clinical and laboratory findings vary according to whether pituitary deficiency is partial or complete (6, 7, 8).

The etiopathogenesis of SS is also not clear. Physiological enlargement of the pituitary gland during
pregnancy makes it more vulnerable to ischemic necrosis; however, some other factors have also been suggested to have a contributing role. Thrombosis in the pituitary arteries due to hypercoagulation, arterial vasospasm due to severe hypotension during delivery, pituitary autoimmunity, and smaller sella turcica size have been hypothesized for the etiopathogenesis of the disease (9, 10, 11, 12). Herein, we aimed to investigate the initial clinical and laboratory findings with subsequent course in patients with SS. In addition, we investigated the difference between SS patients and healthy women with regard to sella volumes.

**Subjects and methods**

**Study design**

The medical records of 114 SS patients who were followed up in the Endocrinology Department of Erciyes University Medical School between 1985 and 2013 were assessed in this retrospective study after obtaining approval from the Local Ethics Committee. The diagnosis of SS was based on the criteria proposed previously: i) typical obstetrical history of severe postpartum vaginal bleeding; ii) severe hypotension or shock for which blood transfusion or fluid replacement is necessary; iii) failure of postpartum lactation; iv) failure to resume regular menses after delivery; v) varying degree of anterior pituitary failure, partial or panhypopituitarism; and vi) empty sella discovered on computed tomography (CT) scan or magnetic resonance imaging (MRI) (13).

The demographic data, clinical findings at diagnosis and during follow-up, obstetric histories, endocrinological investigations, pituitary MRI, and CT findings of the patients were recorded from their hospital files. The initial complaints of patients at diagnosis were classified into four groups: i) nonspecific complaints (fatigue, weakness, anorexia, arthralgia, and headache); ii) adrenal insufficiency (hypoglycemia, hyponatremia, hypotension, fever, loss of consciousness, nausea, vomiting, and diarrhea); iii) hypothyroidism (somnolence, edema, cold intolerance, and constipation); and iv) hypogonadism (amenorrhea).

In addition, 29 healthy women were enrolled in the study as a control group to compare their sella turcica volumes with the patients with SS. The demographic data and past medical and obstetric histories of the healthy women were also recorded. The obstetric and reproductive histories of all healthy women were normal.

**Hormonal assessment**

Basal levels of hormones and, if indicated, dynamic tests were carried out to determine hormonal failures in all patients. During the last 30 years, different methods and commercial kits have been used to measure hormone levels. Hence, reference ranges of hormones were taken according to the values suggested by commercial kits used at that time.

Diagnosis of gonadotropin deficiency was established by reduced basal estradiol levels with reduced or inappropriately normal gonadotropin levels. Menstrual irregularities, amenorrhea in particular, in addition to biochemical data were also taken into account for the diagnosis of gonadotropin deficiency. Thyroid-stimulating hormone (TSH) deficiency was diagnosed by low free thyroxine levels with normal or decreased TSH levels. Adrenocorticotropic hormone (ACTH) deficiency was determined as low serum cortisol level (≤3.0 μg/dl) in the presence of a low or normal ACTH level. Blood samples were taken at 0800 h for analyzing ACTH and cortisol levels. The 1 μg ACTH stimulation test was carried out in 49 patients to confirm the diagnosis of secondary adrenal insufficiency. Adrenal failure was defined as peak cortisol levels below 18 μg/dl (14). The basal PRL level and responses to the thyrotropin-releasing hormone (TRH) stimulation test were evaluated together to detect PRL deficiency. Patients with peak PRL values that did not double according to baseline values were accepted as having PRL deficiency in TRH test (15). Growth hormone (GH) deficiency was diagnosed by low insulin-like growth factor 1 level in the presence of greater than or equal to three pituitary-deficient hormones or insulin tolerance test (ITT). ITT was carried out in 52 patients. A peak GH level of <3 μg/l after ITT was accepted as GH deficiency (16). The diagnosis of antidiuretic hormone (ADH) deficiency was established by measuring serum and urine osmolalities in patients with polyuria (>3 l/day) and confirmed by the response to desmopressin therapy in patients with low urine osmolality.

**Radiological evaluation**

Three dimensional volumetric MRI (Philips, Gyroscan Intera 1.5 Tesla; Eindhoven, The Netherlands) was used to evaluate pituitary gland and sella turcica volumes at the Radiology Department of Erciyes University Medical School. The same MRI scan was performed for both the control and the SS groups. Sella turcica volumes (mm³) were measured by using the
DiChiro formula \((0.5 \times (\text{length} \times \text{width} \times \text{depth}))\) (17). Two experienced neuroradiologists evaluated the images (A C Durak and S Senol).

**Statistical analysis**

All statistical analyses were performed with the SPSS 15.0 Software. Descriptive data are presented as mean±S.D., percentages, and occasionally as a range of minimum–maximum. Distribution of data was tested by the Kolmogorov–Smirnov test before comparison and correlation tests. The independent samples t-test was used for normally distributed data. The Spearman’s test was used for correlation analysis, because data were not normally distributed. In addition, the \(\chi^2\) test was used to evaluate a relationship between partial hormone deficiency and partially empty sella. Receiver operating characteristic (ROC)-curve analysis was performed in order to find a cut-off value for prolactin responses to TRH stimulation test. A probability (\(P\)) value of \(<0.05\) was considered as statistically significant.

**Results**

The mean age of 114 patients previously diagnosed with SS between 1985 and 2013 was 63.2±12.5 years, and age at diagnosis was 52.1±12.7 years. When the past histories of patients with SS were analyzed, mean age at the last delivery was 32.4±6.5 years and thereby the period of diagnostic delay was 19.7±10.2 years. After diagnosis, the follow-up time was 7.4±6.9 years. Nine (7.9%) cases had died and 55 (48.2%) were alive. The other 50 (43.9) patients did not attend follow-up visits in the last 3 years, and therefore it was not known whether they were still alive.

The complaints of the patients at presentation were nonspecific in 60 patients (52.6%), while complaints related to adrenal insufficiency were noted in 35 patients (30.7%), complaints related to hypogonadism in 11 patients (9.6%), and complaints related to hypothyroidism in eight patients (7.0%). Nine (7.9%) patients with SS were initially admitted to hospital due to hypoglycemia, and five (4.4%) due to concomitant severe hyponatraemia and hypoglycemia.

The past obstetric history of the patients showed that the mean number of pregnancies was 5.59±3.2, that of deliveries was 4.56±2.4, live births was 4.37±2.4, stillbirths was 1.22±0.4, miscarriages was 1.98±1.5, and curettages to end pregnancy was 1.55±1.0. All patients had a past history of pregnancy and delivery, while two (1.8%) did not have a history of live birth. Twenty-seven (23.7%) patients had a history of stillbirth, 54 (47.4%) had a history of miscarriage, and nine (7.9%) had a history of curettage during their lives. One patient became pregnant through induction of ovulation after the diagnosis of SS, and had a healthy baby.

Obstetric histories of the last delivery revealed that 89 (78.1%) patients had delivered at home. Eight (9%) out of these 89 patients were subsequently admitted to a hospital and given a blood transfusion because of severe postpartum hemorrhage. On the other hand, 25 (21.9%) patients reported that they had delivered at a hospital, but two (8%) of them had not been given a blood transfusion at hospital in spite of massive hemorrhage. Analyses of dates and places of their last deliveries are summarized in Table 1.

Frequencies of complications at last deliveries were reported as follows: 20 (17.5%) stillbirths, two (1.8%) miscarriages, one (0.9%) uterine rupture, two (1.8%) retained placentas, and two (1.8%) abdominal trauma-induced stillbirths. Furthermore, five (4.4%) patients had a history of hysterectomy due to massive uterine bleeding or uterine rupture at the last delivery, three (2.6%) patients had a C-section, and one (0.9%) patient had a history of curettage to end pregnancy. In addition, six (5.3%) patients reported that they had had twins in their last pregnancy, but four out of these six pregnancies resulted in stillbirths.

Ninety-seven (85.1%) patients reported amenorrhea starting immediately after delivery, while 17 (14.9%) patients had regular menses for 32.2±32 (6–120) months after the last delivery. In addition, 48 (42.1%) patients had postpartum agalactia, and 43 (37.7%) patients reported that they had breastfed normally for 15.1±7 (6–30) months. Twenty-three (20.2%) patients did not remember whether they had breastfed, mainly due to stillbirths or miscarriages.

The results obtained from evaluating histories of postpartum lactation, basal serum PRL levels, and PRL responses to TRH stimulation test (TRH test) together are presented in Table 2. According to these results, in 31 out of 71 patients whose basal PRL levels were below 4.0 ng/ml, a TRH test was performed, but none of them had adequate responses. Thirteen out of those 71 patients had a history of normal lactation after their last delivery. In addition, 11 out of 29 patients whose basal PRL levels were higher than 7.8 ng/ml had adequate responses to TRH test and a history of normal breastfeeding after their last delivery. Therefore, diagnosis of PRL deficiency in patients who had basal PRL levels between 4.0 and

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Table 1  Distribution of patients (n(%)) with SS according to dates and places of last delivery.

<table>
<thead>
<tr>
<th>Dates</th>
<th>Total number of patients</th>
<th>Last delivery at hospital</th>
<th>Last delivery at home</th>
</tr>
</thead>
<tbody>
<tr>
<td>1960–1969</td>
<td>12 (10.5)</td>
<td>1 (8.3)</td>
<td>11 (91.7)</td>
</tr>
<tr>
<td>1970–1979</td>
<td>39 (34.2)</td>
<td>4 (10.3)</td>
<td>35 (89.7)</td>
</tr>
<tr>
<td>1980–1989</td>
<td>37 (32.5)</td>
<td>7 (18.9)</td>
<td>30 (81.1)</td>
</tr>
<tr>
<td>1990–1999</td>
<td>21 (18.4)</td>
<td>8 (38.1)</td>
<td>13 (61.9)</td>
</tr>
<tr>
<td>&gt;2000</td>
<td>5 (4.4)</td>
<td>5 (100)</td>
<td>0</td>
</tr>
</tbody>
</table>

7.8 ng/ml was established according to their TRH stimulation test and/or history of postpartum agalactia. Fourteen patients had basal PRL levels between 4.0 and 7.8 ng/ml. Seven of them did not have adequate PRL responses to TRH test, while five patients had adequate responses. The basal PRL levels of six patients with postpartum agalactia were between 4.0 and 7.8 ng/ml, and four of them had blunted responses to TRH test. As TRH tests were not performed in the other two patients, they were diagnosed as having PRL deficiency according to postpartum agalactia. In addition, when the cut-off value was taken as 10.84 ng/ml in ROC curve analysis to determine adequate peak PRL response to TRH test, its sensitivity was found as 97.2% and specificity was 94.1% (Fig. 1).

Overall hormonal assessment at the date of diagnosis revealed that all of the patients had GH and follicle-stimulating hormone (FSH)–luteinizing hormone (LH) deficiencies, while 103 (90.4%) patients had TSH deficiency, 82 (71.9%) patients had ACTH deficiency, and 81 (71.1%) patients had PRL deficiency. In addition, five (4.4%) patients had ADH deficiency and were regularly using desmopressin replacement therapy.

As a result, 63 (55.3%) patients had panhypopituitarism, while 51 (44.7%) patients had partial hypopituitarism. The rates of deficient hormones at the date of diagnosis are shown in Table 3. No significant correlation was found between the number of deficient hormones and sella volumes in 67 patients whose MRIs were available (P: 0.104). Similarly, no significant relationship was detected between partial hypopituitarism and partially empty sella when the 114 patients were considered together (P: 0.079).

The number of deficient hormones was found to be increased in 10 (19.2%) out of the 51 patients with partial hypopituitarism (Table 4), whereas the hormone profile of 19 (36.5%) out of those 51 patients remained the same after a mean 13.1 ± 7.0 years follow-up period. The course of hormonal deficiency was not assessed in the other 22 patients due to their being diagnosed recently or not attending follow-up visits regularly. Recovery of deficient hormones was not detected in any of the patients.

Sixty-seven patients had pituitary MRI performed in Erciyes University Medical School, 38 patients had MRI performed in other hospitals, and nine patients had pituitary CT reports. According to CT and MRI findings, 86 (75.4%) patients with SS had a completely empty sella, while 28 (24.6%) patients had a partially empty sella. The mean age of the 29 healthy women was 60.4 ± 8.5 years, which was not statistically different from the SS group. Furthermore, no significant difference was found in the mean number of deliveries of the healthy group (4.28 ± 1.9) and the SS group (4.56 ± 2.4). The mean sella volume of the 67 patients with SS was 340.5 ± 214 mm³ (range, 40–1008) and this was significantly lower than that of the healthy group (602.5 ± 192 mm³; range, 308–1040; P<0.001). The minimum sella size in healthy women was found to be 308 mm³, and 35 out of 67 patients in the SS group had sella volumes below 308 mm³.

**Discussion**

Hypopituitarism due to SS is a rarely encountered disease in developed countries due to modern obstetric care. In previous cohort studies performed in Spain, Japan, and the USA, it was found that SS was an uncommon disorder among women (18, 19, 20). Therefore, SS has become a neglected and unnoticed syndrome because of its rarity in developed countries. However, it seems that SS has recently become more frequent in Western society, probably due to the influx of migrant populations with

Table 2  Distribution of patients according to TRH tests, basal PRL values, and history of postpartum agalactia. Data are presented as n(%).

<table>
<thead>
<tr>
<th>History of postpartum lactation/response to TRH test</th>
<th>Basal PRL (ng/ml)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;4.0</td>
<td>&gt;7.8</td>
</tr>
<tr>
<td>Agalactia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adequate</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Blunted</td>
<td>18 (15.8)</td>
<td>4 (3.6)</td>
</tr>
<tr>
<td>Not available</td>
<td>24 (21.1)</td>
<td>2 (1.8)</td>
</tr>
<tr>
<td>Normal lactation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adequate</td>
<td>0</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>Blunted</td>
<td>5 (4.4)</td>
<td>2 (1.8)</td>
</tr>
<tr>
<td>Not available</td>
<td>8 (7.0)</td>
<td>0</td>
</tr>
<tr>
<td>Not known</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adequate</td>
<td>0</td>
<td>4 (3.6)</td>
</tr>
<tr>
<td>Blunted</td>
<td>8 (7.0)</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>Not available</td>
<td>8 (7.0)</td>
<td>2 (1.8)</td>
</tr>
<tr>
<td>Total</td>
<td>71 (62.3)</td>
<td>14 (12.3)</td>
</tr>
</tbody>
</table>
poor socioeconomic status and health care problems. Supporting this idea, in 1034 GH-deficient patients, the majority of whom were living in developed countries, the frequency of SS was found to be 3.1% (21). In another study from Iceland, the prevalence of SS was 5.1/100,000 women in 2009, which indicates that SS should not be ignored in Western society either (22).

An important issue regarding SS which has been reported in all retrospective studies is delay in diagnosis. The mean period of diagnostic delay was found to be 19.7 years in 114 patients with SS in this study. Other retrospective studies performed in India, France, and Turkey have also found long periods of delay in diagnosis, such as 7, 9, and 27 years respectively (3, 7, 8). We can conclude from the evaluation of our results that the main reason for delay in diagnosis is the high frequency of patients who have nonspecific complaints: 52.6% of our patients had nonspecific complaints at the time of diagnosis and they had histories of being admitted to hospitals with those complaints, but no diagnosis had been established. In a study carried out by Güven et al. (23), 126 patients who were admitted to a hospital because of severe hypoglycemia were evaluated, and it was found that SS was the second most common cause of hypoglycemia after diabetic treatments. Presumably the most important reasons underlying the delayed diagnosis are insufficient medical education in doctors and their subsequent unawareness of the syndrome.

Partial hypopituitarism and histories of normal lactation and regular menses that continued after the last delivery also seem to be contributing factors to diagnostic delay. A total of 44.7% of patients had partial hypopituitarism in this study. Seventeen patients reported that they had continued to menstruate for a mean period of 32.2 months and 43 patients had lactated for a mean period of 15.1 months after their last delivery.

Diagnostic delay of SS also causes delay in administration of replacement therapies. Although gonadal steroids and GH are not vital replacement therapies as glucocorticoid and thyroid hormone therapies are, they have some beneficial effects in SS. Kelestimur et al. (24) demonstrated that GH therapy had significant beneficial outcomes in terms of body composition, lipid profile, and quality of life measures in 91 patients with SS. In another study, they also reported that the severity of GH deficiency in patients with SS was related to the degree of hypopituitarism (25).

It was detected in this study that the frequency of giving birth at home has decreased over time (Table 1). All five patients who delivered after 2000 had given birth at a hospital. Interestingly, these five patients and 25 patients overall who delivered at a hospital had massive bleeding and were given a blood transfusion except for two patients. In addition, eight of the patients who had their last delivery at home were subsequently admitted to a hospital due to massive uterine bleeding. These patients were also given a blood transfusion. However, there were no data regarding the amount of bleeding or whether they were given sufficient blood transfusion. The question of how did SS develop in women who experienced massive bleeding and received blood or fluid transfusion at a

### Table 3 deficient hormones of anterior pituitary gland in patients with SS.

<table>
<thead>
<tr>
<th>Deficient hormones</th>
<th>Number (%) of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>All hormones</td>
<td>63 (55.3)</td>
</tr>
<tr>
<td>FSH–LH + GH + ACTH + TSH</td>
<td>17 (14.9)</td>
</tr>
<tr>
<td>FSH–LH + GH + TSH + PRL</td>
<td>12 (10.5)</td>
</tr>
<tr>
<td>FSH–LH + GH + TSH</td>
<td>11 (9.6)</td>
</tr>
<tr>
<td>FSH–LH + GH + PRL</td>
<td>5 (4.4)</td>
</tr>
<tr>
<td>FSH–LH + GH</td>
<td>4 (3.5)</td>
</tr>
<tr>
<td>FSH–LH + GH + ACTH + PRL</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>FSH–LH + GH + ACTH</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>Total</td>
<td>114 (100)</td>
</tr>
</tbody>
</table>
branches of the inferior hypophyseal artery (10). Anastomoses between these two main pituitary artery systems remain to be answered.

The rates of patients who had an obstetric history of miscarriage (47.3%) or stillbirth (23.6%) at any time in their lives were very high. Furthermore, 20 (17.5%) patients had a history of stillbirth, while two (1.75%) patients had a miscarriage in their last pregnancy. In a cohort study involving 7405 women in Turkey, the rate of miscarriage was 25% and the rate of stillbirth was 4% during their lifetimes (26). High frequencies of stillbirths and miscarriages in patients with SS may be explained by a disorder such as hypercoagulation (9).

As it is well known, the main arteries of the adenohypophysis are branches of the superior hypophyseal artery, and those of the neurohypophysis are branches of the inferior hypophyseal artery (10). Anastomoses between these two main pituitary artery systems are mainly located in the middle-posterior regions of the adenohypophysis. It can be speculated that in a case of obliteration in the superior hypophyseal artery, blood supply to the adenohypophysis via anastomoses of the inferior hypophyseal artery may cause partial hypopituitarism. In a case of a complete and sudden obliteration these anastomoses may not be sufficient.

Sheehan & Whitehead (27) previously reported that the neurohypophysis and hypothalamic nuclei were atrophic in over 90% of women with SS at autopsy. Although clinically manifest diabetes insipidus is uncommon in SS, the frequency of partial diabetes insipidus was found to be 29.6% in SS patients who did not have polyuria (28). In that study the osmotic threshold for the onset of thirst in patients with SS was found to be increased. Thus, it seems that the thirst center is also affected due to ischemic damage. In addition, GH replacement therapy in patients with SS-induced GH deficiency did not improve the subtle abnormalities in posterior pituitary functions (29).

Partial hypopituitarism due to SS has also been reported in other studies (3, 7, 30, 31). In our study, all of the patients had GH and gonadotropin deficiencies, while 90.4% of patients had TSH deficiency, 71.9% had ACTH deficiency, and 71.1% had PRL deficiency at the time of diagnosis. The most common intact hormones were ACTH and PRL in this study. PRL deficiency was not found in 28.9% (33 patients). However, there are contradictory reports about PRL deficiency in SS. Many studies have reported that PRL deficiency was sine qua non for the diagnosis of SS (7, 30, 32, 33). On the other hand, Ramiandrasoa et al. (8) reported that ten out of 24 (42%) patients with SS did not have lactotroph insufficiency, defined by a basal PRL level below 3 ng/ml. Similarly, PRL deficiency was found in 85.2% of females with SS in the study performed by Zargar et al. (3).

It was revealed in our study that 16 patients with SS had adequate PRL responses to TRH (Table 2). In contrast, some studies have revealed that PRL was the most common and the first hormone to be deficient in patients with SS who were tested with TRH stimulation (30, 32, 33). It is noteworthy that the TRH stimulation test was more compatible with histories of postpartum galactasia than that with baseline PRL levels to detect lactotroph deficiency in patients whose basal PRL levels were between 4.0 and 7.8 ng/ml in this study. This point shows the necessity of the TRH stimulation test to avoid diagnostic errors. None of the 22 patients with postpartum galactasia were found to have adequate PRL responses to TRH (Table 2). Hence, we can recommend the TRH stimulation test as a more sensitive test than basal PRL level to recognize PRL deficiency. Furthermore, for peak PRL in TRH tests, a cut-off value of 10.84 ng/ml was found to have a high sensitivity and specificity in the diagnosis of hypoprolactinemia.

Patients who had breastfed for a period of time after their last delivery may have had PRL deficiency at the time of diagnosis. Overall, 43 patients had normal breastfeeding after their last delivery, but 15 of them had PRL deficiency at the time of diagnosis in our study. This situation might have been due to the progressive course of SS that is encountered in some patients (3). The progressive course is probably due to the antibodies which develop against pituitary necrotic tissue (11, 34). Relatedly, another result obtained from our study was the decrease in number of intact pituitary hormones, particularly shown in ten patients (Table 4). However, none of the patients followed up regularly in our cohort recovered

### Table 4 Progression of hormonal deficiency in ten patients with SS.

<table>
<thead>
<tr>
<th>Patient Nos</th>
<th>Intact hormones at date of diagnosis</th>
<th>After a period of (years)</th>
<th>Intact hormones in last clinical visit</th>
</tr>
</thead>
<tbody>
<tr>
<td>21</td>
<td>ACTH</td>
<td>18</td>
<td>None</td>
</tr>
<tr>
<td>31</td>
<td>ACTH + TSH + PRL</td>
<td>15</td>
<td>ACTH + PRL</td>
</tr>
<tr>
<td>35</td>
<td>ACTH</td>
<td>22</td>
<td>None</td>
</tr>
<tr>
<td>60</td>
<td>ACTH</td>
<td>6</td>
<td>None</td>
</tr>
<tr>
<td>64</td>
<td>ACTH + PRL</td>
<td>9</td>
<td>None</td>
</tr>
<tr>
<td>66</td>
<td>PRL + TSH</td>
<td>12</td>
<td>None</td>
</tr>
<tr>
<td>81</td>
<td>PRL</td>
<td>22</td>
<td>None</td>
</tr>
<tr>
<td>90</td>
<td>ACTH</td>
<td>11</td>
<td>None</td>
</tr>
<tr>
<td>95</td>
<td>ACTH</td>
<td>10</td>
<td>None</td>
</tr>
<tr>
<td>109</td>
<td>ACTH + TSH</td>
<td>8</td>
<td>TSH</td>
</tr>
</tbody>
</table>

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any of the insufficient hormones. Therefore, it seems that hypopituitarism is progressive in SS and, if indicated, replacement therapies should be started early when a hormonal insufficiency is diagnosed.

In this study, all the patients had a completely or partially empty sella. Hence we conclude that a partial or complete empty sella is sine qua non in the late phase of SS; in other words an empty sella on CT or MRI is a characteristic feature of SS. Bakiri et al. (12) found that all 54 patients with SS had an empty sella, while 72% of them had a completely empty sella. Dash et al. (35) reported that the degree of postpartum pituitary necrosis was poorly correlated with the severity of clinical expression in SS. Similarly, no significant correlation between the number of deficient hormones and sella volumes, and no relationship between partial hypopituitarism and partial empty sella, was found in this study. Empty sella is a frequent finding in imaging studies (36, 37), but it should be kept in mind that SS is a rare cause of empty sella. Brismar & Efendic (38) found that SS was present in only one out of 50 patients with empty sella and Jara-Albarran et al. (39) diagnosed SS in none of the 41 patients with empty sella.

Lymphocytic hypophysitis (LyH) should also be considered in the differential diagnosis of SS. LyH, which is another pregnancy-related disorder, also generally develops at first in the peripartum period and causes hypopituitarism and finally empty sella (40). Some findings which differentiate LyH from SS may be hyperprolactinemia, diabetes insipidus, increase in thickness of infundibulum, loss of the neurohypophyseal bright spot on MRI, and absence of massive uterine hemorrhage; these findings are not so frequently encountered in SS (41).

A relatively smaller sella turcica volume has been suggested to play an important role in the etiopathogenesis of SS (12, 42). Smaller sella turcica volume may lead to a larger suprasellar pituitary enlargement, which leads to compression of the infundibulum and thereby of the superior hypophyseal artery during pregnancy. The sella, turcica volume of patients with SS was significantly lower than that of the healthy women in our study, which is similar to previous studies (12, 42). It is noteworthy to add that approximately half of our patients, not all of them, had small sella size.

In conclusion, SS is still a worldwide public health problem. In our study, 52.6% of the patients investigated had nonspecific complaints initially, and SS was first recognized in physical examinations related to hypogonadism, particularly fine wrinkling around the eyes and mouth, and as a result of questions about postpartum amenorrhea/agalactia. We therefore believe that training physicians about SS is very important, particularly in Western society. In order to eradicate SS, obstetric care should be adequately improved and among young doctors awareness of the syndrome needs to be increased. The TRH stimulation test seems to be more useful than baseline serum PRL levels in the detection of lactotroph deficiency, particularly in patients whose basal PRL levels are between 4.0 and 7.8 ng/ml. Lastly, our results also demonstrate that small sella size may have an important contributing role in the etiopathogenesis of SS.

Declaration of interest
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