

CLINICAL STUDY

Sheehan's syndrome in modern times: a nationwide retrospective study in Iceland

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Abstract

Background and objective: Half a century ago the prevalence of Sheehan's syndrome (SS) was 10–20 per 100 000 women. With better obstetric help the prevalence is assumed to have decreased, especially in developed countries. The aim of this study is to estimate the prevalence of SS in modern times in Iceland.

Design: We studied the prevalence of SS in 2009 in a nationwide retrospective population-based study.

Methods: All patients with diagnosed SS were identified, and information regarding obstetric care, clinical presentation and hormonal assays was collected. Correlation was calculated with Kendall's tau-b. Significance level: $P < 0.05$.

Results: Eight women were identified with SS; thus, the prevalence of SS in 2009 was 5.1 per 100 000 women. The mean age at delivery and diagnosis was 33.0 and 36.6 respectively, resulting in a diagnostic delay (DD) of 1–240 months. Four women had low blood pressure during delivery, and five had massive blood loss (> 1000 ml). Six had complicated deliveries. The most common clinical presentation was failure to lactate and failure to resume menstruation. The patients had three to five failing pituitary axis. There was no correlation between bleeding at delivery or the number of hormonal axes affected and DD.

Conclusion: The prevalence of SS in Iceland was higher than we expected in a country with modern obstetric care. Long DD and incidental diagnosis indicate that women might be lacking correct diagnosis and treatment, and thus the prevalence of SS is even higher. As SS is easily diagnosed and treatable, but can be life-threatening if unrecognised, doctors need to be aware of the disease.

European Journal of Endocrinology 164 349–354

Introduction

Sheehan's syndrome (SS) is a pituitary failure occurring in women after labour (1). Half a century ago, the prevalence of SS was 10–20 per 100 000 women (2). With better obstetric help, it is assumed the incidence and prevalence has decreased, especially in the developed countries, and has therefore received little attention in recent years (3). The current incidence and prevalence of SS in developed countries is thus not well known. In the underdeveloped countries where home deliveries are widely practised and obstetric help is poor, SS is a big health issue. The prevalence of SS in India is estimated to be 2.7–3.9% among parous women older than 20 years (4). In an international database (KIMS database) containing 1034 patients with GH deficiency (GHD), SS is the cause in 3.1% of the cases, and in a Spanish cross-sectional study, SS is the culprit of GHD in 6–10% of the cases (5, 6). It is

therefore possible that SS is more common in the western world than was previously thought. The aim of this study is to estimate the prevalence of SS in modern times in Iceland.

Materials and methods

Patients

This is a retrospective study of the prevalence of SS in Iceland. The study population ($n = 157\,300$) was composed of all women in Iceland on 1st of January 2009. The fertility rate in Iceland is 2.11 for the years 1981–2005, and still births per 1000 live births for the same years are 3.1 (Hagstofa Íslands, hagtolur.hagstofa.is). The patients were identified by asking all practicing endocrinologists in Iceland ($n = 9$) to provide

information about their patients with SS. Patients were further identified through the electronic medical record system (from 1983) at the Landspítali University Hospital in Iceland, by scanning for the diagnosis of hypopituitarism (E23) under the *International Classification of Diseases*, 10th edition (ICD-10), where patients with SS were extracted.

The study protocol was approved by the National Bioethics Committee (ethical licence no: VSNb2009060004/03.15) and Data Protection Committee in Iceland.

Data collection, hormonal measurements and statistical analysis

Data on demographic and obstetric features, mode of presentation, diagnostic delay (DD), and blood and radiographic test results were collected. *Post-partum* haemorrhage (PPH) was defined as little if < 500 ml, medium if 500–1000 ml and gross if more than 1000 ml had occurred in the first 24 h after delivery. Transfusion was documented if needed in the first 24 h after delivery. Hypotension at delivery was defined as documented systolic blood pressure below 90 mmHg. Results of hormonal blood values were from the time of diagnosis. All diagnostic testing was done in a standardised manner at that time. No attempt was made to criticise the methods used for investigation of the patients; values are presented with given reference values as provided in a respective patient's medical record. Information on the results of hormonal measurements in relation to the menstrual cycle was not available for any of the women. Synacthen testing was performed with 250 µg Synacthen, and in the insulin tolerance tests, an injection of Actrapid 0.1 U/kg was given intravenously according to the clinical guidelines.

A professional statistician was consulted for statistical analysis. Excel was used for calculating prevalence. Numerical variables are presented as averages with the range. Correlation calculations were done with Kendall's tau-b, a non-parametric rank test, and results were considered significant if $P < 0.05$.

Results

We found 8 women with confirmed SS, leading to a prevalence of 5.1 per 100 000 women.

Demographic and obstetric features

One patient was excluded from further investigation as clinical data was largely missing. She was born in 1928 and gave birth in the 1960s. For seven patients, detailed histories were available and are referred to as numbers 1–7 (see Table 1). The age range at the time of the research was 41–55 years, and the women gave birth between the years 1985 and 2008. The DD was from 1

Table 1 Demographic features, mode and complications of delivery and clinical outcome of seven patients with Sheehan's syndrome.

Pat no.	Age	Year of birth	Year of delivery	Year of diagnosis	Diagnostic delay (months)	Low blood pressure	Blood loss ^a	Blood transfusion (units)	Mode of delivery	Loss of lactation	Menstr.	Later pregnancy	CT/MRI (year taken)	Hormonal deficiency
1	55	1954	1985	1993	93	No	+	0	ACS	Yes	No	No	MRI:CES (1993)	S/A/T/P/G
2	55	1954	1987	1988	8	Yes	++	8	ACS	Yes	No	No	CT:PES (1988)	S/A/T/P/G
3	41	1968	1989	2009	240	Yes	++	10	Vaginal	Yes	No	No	MRI:PES (2009)	S/P/T/G
4	49	1960	1996	1997	14	Yes	++	2 ^b	Vaginal	Yes	Yes ^c	No	MRI:PES (1997)	S/P
5	46	1963	1998	2000	21	No	++	7	Vaginal	Yes	No	No	CT:PES (1998)	S/A/T/P/G
6	45	1964	2000	2002	23	Yes	++	4	ACS	— ^d	No	Yes w. ART	MRI:PES (2008)	S/A/T/G
7	40	1969	2008	2008	1	No	+	2	Vaginal	Yes	No	No	MRI:NS (2008)	A/T ^e /P/G

Age refers to the age when included in the study. ACS, acute C-section; Menstr., menstruation; ART, assisted reproductive technology; N, normal sella; PES, partially empty sella; CES, completely empty sella; S, somatotrop insufficiency; A, corticotrop insufficiency; T, thyrotrop insufficiency; P, prolactin insufficiency; G, gonadotrop insufficiency; Pat, patient.

^aEstimated blood loss: —, not significant; +, 500–1000 ml; ++, > 1000 ml.

^bPatient had heat reaction to the blood transfusion and therefore did not receive more transfusions.

^cPolycystic ovary syndrome with irregular menstruation before and after delivery.

^dPatient had Cabergoline after delivery to stop lactation.

^ePrior primary hypothyroidism already treated with thyroxin.

month to 20 years. Four of the women gave birth at Landspítali University Hospital (tertiary hospital), two in smaller hospitals and one in a birth centre. Four patients had documented low blood pressure. All seven women had medium to gross blood loss, and six of them received blood transfusions. Most of these deliveries were complicated (see Table 1). Patient no. 1 had an acute Caesarean section (C-section) and medium blood loss. Patient no. 2 had an acute C-section and gross blood loss. Patient no. 3 had a vaginal delivery, inversion of the uterus and gross blood loss. Patient no. 4 had a vaginal delivery that resulted in rupture of the cervix and gross blood loss. Patient no. 5 had atonic bleeding with gross blood loss after vaginal delivery of twins, and patient no. 6 had a ruptured uterus and an acute C-section with intra-partum fetal death. Patient no. 7 had an uncomplicated vaginal delivery with medium blood loss. A summary of demographic and obstetric features can be seen in Table 1.

Symptoms and radiographic features

Loss of lactation (n=6) and failure to resume menstruation (n=6) were the most common symptoms. All of the women had various unspecific symptoms such as lethargy, intolerance of cold, heat flushes, decreased libido, dry skin and mood changes. Some had diminished genital and axillary hair. One patient conceived again with assistive reproductive technology. Six of seven patients had partially or completely empty sella on computed tomography/magnetic resonance imaging (CT/MRI) though patient no. 7 had a normal pituitary on MRI that was taken 6 weeks after delivery.

Pituitary function

The results of serum levels and a review of hormonal axis are given in Tables 2-4. Patient nos 1, 2 and 5 had deficiency of all anterior pituitary hormones, and another four women had failure of two to four of the five pituitary axes. Patient no. 7 had low prolactin (PRL) level, and all of the other women had low-normal or normal PRL levels. As none of the women were able to lactate after delivery, a relative PRL deficiency was assumed. Patient no. 6 had received Cabergolium to hinder lactation after delivery, and analysis of serum levels of PRL was not performed. In patient no. 1, serum IGF1 was low, and she was assumed to have GHD, and no further testing for GHD was done. Patient no. 2 had normal cortisol at diagnosis (1988), but due to persistent symptoms she was repeatedly evaluated for cortisol deficiency and treated with hydrocortisone due to low urinary cortisol excretion in 1998 (89 nmol/24 h, reference value 97-330 nmol/24 h). Patient no. 3 had four pituitary axes affected. Her TSH axis was first assumed to be normal according to reference values, but due to her symptoms she was re-evaluated as having subclinical hypothyroidism, and

Table 2 Results of hormonal assays of seven patients with Sheehan's syndrome.

Pat no.	Cortisol (nmol/l)		ACTH (ng/l)		Prolactin (µg/l)		IGF1 (µg/l)		fT ₄ (pmol/l)		TSH (mU/l)	
	Value	RV	Value	RV	Value	RV	Value	RV	Value	RV	Value	RV
1	4.0	250-830	8.0	10-50	1.3	1.0-28.0	30	110-450	3.7	9.0-19.0	2.9	0.30-4.0
2	577	220-700	-	-	4.3	1.3-20.8	68 ^a	170-370	6.2	8.8-23.2	1.16	0.35-3.35
3	397	200-800	-	-	7.40	3-20	86	101-267	13.6	10.0-25.0	3.72	0.4-4.0
4	319	200-700	-	-	5.6	4.0-32.0	80	110-450	13.7	10.0-25.0	1.53	0.4-4.0
5	218	220-700	-	-	11.4	3.9-29.5	-	-	3.2	13.0-23.0	2.28	0.27-4.2
6	152	200-700	14.3	10-50	5.9	4.0-32.0	30	110-450	3.7	10.0-25.0	3.67	0.4-4.0
7 ^b	<1	200-700	<10	0-46	<0.5	5.0-30.0	76	109-284	18.6	12.0-22.0	<0.01	0.3-4.2

Pat., patient; RV, reference value.

^ang/ml.

^bPatient had previous hypothyroidism after removal of colloid cysts and was being treated with levothyroxin at the time of diagnosis of SS.

Table 3 Results of hormonal analysis of gonadotropins in seven patients with Sheehan's syndrome.

Pat no.	Oestradiol (pmol/l) ^a		FSH (U/l)		LH (U/l)	
	Value	Reference value	Value	Reference value	Value	Reference value
1	82	FP 73–515 Ovul. 180–1030	7.0	Women 1.0–8.0 Ovul. 8–30	3.5	Women 3.0–10.0 Ovul. 15–45
2	52	FP 73–515 Ovul. 180–1030	5.4	Women 1.0–8.0 Ovul. 8–30	3.9	Women 3.0–10.0 Ovul. 15–45
3	103	Women 130–930	7.8	Women 1.1–7.6	8.3	Women 0.8–10.8
4	132	FP 25–700 Ovul. 150–1500	4.3	Women 1.0–12.0	2.3	Women 1–12
5	82	FP <37–650 Ovul. 176–1422	2.6 ^b	FP 3–20 Ovul. 9–26	1.0 ^b	FP 1–10 Ovul. 10–100
6	75	FP 80–700 Ovul. 200–1500	9.3	Women 1–12	4.2	Women 1–12
7	53.6	FP 46–607 Ovul. 315–1828	8	FP 3.5–12.5 Ovul. 5.0–21.0	4.5	FP 2.4–12.6 Ovul. 14.0–96.0

Pat., patient; FP, follicular phase; Ovul., ovulation; LP, luteal phase; PM, postmenopausal.

^aInformation on oestradiol value in relation to menstrual cycle was not available.

^bU/l.

as her clinical response to treatment was undoubtful, she was assumed to have central hypothyroidism. Patient no. 4 had two axes affected. Patient no. 7 was taking levothyroxin (L-T₄) before delivery, as most of her thyroid gland had been removed years earlier because of colloid cysts, but as she had normal serum levels of free T₄ (fT₄) and very low levels of TSH, it was assumed she had central hypothyroidism as well.

There was no correlation between bleeding at delivery or number of hormonal axes affected or DD. Significant correlation ($P=0.042$, Kendall's tau-b correlation coefficient=0.767) was seen between adrenal axis failure and the number of axes affected but not between adrenal axis failure and bleeding at delivery or DD. No patient had clinical symptoms of diabetes insipidus, so the posterior part of the pituitary was not evaluated further.

Discussion

The prevalence of SS in the Icelandic population in 2009 is 5.1 per 100 000 women. This, as expected, is much lower than results from India but higher than expected in a developed country with good obstetric help, indicating that SS should not be ignored in modern societies (4).

Our study is a nationwide population-based study in a well-defined population. Few endocrinologists (altogether nine) are responsible for treatment of adult patients in Iceland, and there is only one University Hospital. The most advanced obstetric department in the country is at this hospital as well as the only Department of Endocrinology. Furthermore, Iceland has a complete birth registry since 1972 and a complete national registry since 1914 (Hagstofa Íslands, hagtolur. [cited 14th of February 2010]; Available from www.hagstofa.is, Landlæknir. [cited 1st of May 2010]; Available from www.landlaeknir.is/Heilbrigdistolfraedi/Gagnasofn/Faedingraskra). We therefore believe the study is a reliable source of descriptive data on patients with SS as well as representative of the prevalence of SS in western countries with modern obstetric help. For the sake of comparison, the population in our study was defined as all women alive, as Dr Sheehan did in his publication, which has often been cited (2).

We found great variation in DD, from 1 month to 20 years, which is in line with the few published data (4, 7–9). The patient with the longest DD was incidentally diagnosed (no. 3) even though she was found to have four pituitary axes affected. This indicates that women with SS might be lacking correct diagnosis and treatment. Thus, the prevalence of SS in western countries may be even higher than presented in this study.

We did not find a correlation between DD and bleeding at delivery or the number of hormonal axes affected. PPH and/or hypotension causing pituitary necrosis have been thought to be the main cause of SS,

Table 4 Results on further evaluation of hormonal axis with insulin tolerance test and Synacthen test.

Patient	Insulin tolerance test						Synacthen test		
	Glucose (mmol/l)		Cortisol (nmol/l)		GH		Cortisol (nmol/l)		
	BV	LV	BV	HV	BV	HV	BV	30 min	60 min
1	–	–	–	–	–	–	6	20	20
2 (1988/1990) ^a	5/4.3	2.3/2.0	577/385	658/577	0.6/0.6 µg/l	0.1/<0.1	532	525	660
3	5.3	1.4	508	796	1.5 mUI/l	5.1	–	–	–
4	4.2	1.4	181	540	0.94 µg/l	2.27	320	671	719
5 ^b	4.8	1.7	32	77	0.2 mUI/l	0.4	–	–	–
6	3.8	1.6	220	224	0.03 µg/l	0.04	–	–	–
7	3.7	1.5	<1	2	1.3 mUI/l	21	0.1	20	29

BV, basal value; LV, lowest value; HV, highest value.

^aTest performed in the year 1988 and 1990 respectively. Synacthen test performed in 1988 on this patient.

^bPerformed in 2006.

which is in line with Sheehan's definition made in 1937 (1, 10). Five of the women had more than 1000 ml PPH and would therefore fit Dr Sheehan's definition well. Two of the women had less PPH (nos 1 and 7) and interestingly woman No. 7 had the shortest DD and the most serious symptoms. She did not have a traumatic delivery or hypotension during or after the delivery, and the estimated blood loss was 700 ml. On the other hand, she had psoriasis diagnosed before pregnancy, indicating that the cause of her post-partum hypopituitarism might be autoimmune hypophysitis. As antibodies against the pituitary are not on the open market, we have not been able to test this theory. Theoretically, women with autoimmune diseases might be at higher risk for post-partum hypopituitarism.

All women in this study failed to resume menstruation and were not able to lactate, which is in line with earlier studies (7, 11, 12). Serum levels of PRL were not measured until the time of diagnosis or 1–240 months post delivery. Only one patient (no. 7), the one with the shortest DD (1 month), had low PRL at the time of diagnosis. It is therefore impossible to interpret the PRL levels post delivery for the other patients, but as none of the women could lactate, they are assumed to have had PRL deficiency. Evaluation of the serum levels of PRL is a simple and relatively inexpensive method to test for the cause of failure to lactate, and by responding to these specific and obvious early symptoms of SS by evaluating PRL, the DD can be shortened considerably. Failure to lactate should therefore lead to evaluation of serum PRL levels and thereby hinder the long DD of SS.

We found a significant correlation between the number of hormonal axes affected and failure of the adrenal axis; thus, women with more severe hypopituitarism are more likely to have adrenal axis failure. The woman with the longest DD, 240 months, did not have adrenal axis failure, but the one with the shortest DD (1 month) did and presented with serious symptoms. Failure of the adrenal axis is of course the most important complication of SS and the type of hormonal deficiency most likely to require emergency treatment as it can be life-threatening. Women with adrenal axis

failure due to SS are thus more likely to be diagnosed correctly earlier.

We conclude that the prevalence of SS in modern times, where obstetric help is good, is higher than we expected – 5.1 per 100 000 women in Iceland. The variation in DD and incidental diagnosis of SS found in our study indicates that SS might be underestimated. We most often found SS after moderate or severe PPH, but autoimmune hypophysitis is a possible cause of SS in one of our women with less severe PPH. Women failing to lactate should be evaluated by measurements of serum PRL levels. Doctors should be aware of symptoms of SS as it can be easily diagnosed and treated, and it causes increased morbidity and can be life-threatening if unrecognised.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Funding

This work was funded by the Science Fund of Landspítali University Hospital.

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Received 16 December 2010

Accepted 22 December 2010