

## CLINICAL STUDY

## Posterior pituitary function in Sheehan's syndrome

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### Abstract

**Objective:** We studied posterior pituitary function in 27 patients with Sheehan's syndrome and 14 controls. **Design:** All patients were investigated by water deprivation test and 26 of them by 5% hypertonic saline infusion test. None of the patients had symptoms of diabetes insipidus and all patients were on adequate glucocorticoid and thyroid hormone replacement therapy before testing.

**Results:** According to dehydration test, 8 (29.6%) patients had partial diabetes insipidus (PDI group) and 19 (70.3%) had normal response (non-DI group). During the 5% hypertonic saline infusion test, the maximal plasma osmolality was higher in PDI ( $305 \pm 4.3$ ) and non-DI ( $308 \pm 1.7$ ) groups when compared with controls ( $298 \pm 1.7$  mOsm/kg;  $P < 0.005$ ), but the maximal urine osmolality was lower in PDI group ( $565 \pm 37$ ) than in non-DI ( $708 \pm 45$ ) and control ( $683 \pm 17$  mOsm/kg) groups ( $P < 0.05$ ). The osmotic threshold for thirst perception was higher in PDI ( $296 \pm 4.3$ ) and non-DI ( $298 \pm 1.4$ ) groups when compared with control group ( $287 \pm 1.5$  mOsm/kg) ( $P < 0.005$ ). Basal plasma osmolalities were also higher in PDI ( $294 \pm 1.0$ ) and non-DI ( $297 \pm 1.1$ ) groups than in controls ( $288 \pm 1.2$  mOsm/kg;  $P < 0.001$ ).

**Conclusions:** Our findings demonstrated that patients with Sheehan's syndrome have an impairment of neurohypophyseal function. The thirst center may be affected by ischemic damage and the osmotic threshold for the onset of thirst in patients with Sheehan's syndrome is increased.

*European Journal of Endocrinology 156 563–567*

### Introduction

Sheehan's syndrome occurs as a result of ischemic pituitary necrosis due to severe postpartum hemorrhage. It is one of the most common causes of hypopituitarism in underdeveloped or developing countries. Sheehan's syndrome is characterized by varying degrees of anterior pituitary dysfunction (1). Diabetes insipidus is considered to be an uncommon complication of Sheehan's syndrome, despite the fact that Sheehan and Whitehead demonstrated lesions in the neurohypophysis and the hypothalamic nuclei in over 90% of their patients (2, 3). However, little attention has been given to the neurohypophyseal function in patients with Sheehan's syndrome, probably because such patients rarely manifest signs of neurohypophyseal insufficiency (4–6). There are not enough data about posterior pituitary function in patients with Sheehan's syndrome. In this study, our aim was to investigate the posterior pituitary function by water deprivation test (WDT) and hypertonic saline infusion test in patients with Sheehan's syndrome.

### Materials and methods

Twenty-seven patients with Sheehan's syndrome and 14 age-matched healthy control women were

included in this cross-sectional study. The diagnosis of Sheehan's syndrome was based on the typical obstetrical history, physical examination, laboratory evaluation and radiological investigation of the pituitary gland by magnetic resonance imaging (MRI). The mean age of the patients was  $48.6 \pm 2.3$  years (range 29–75) and the mean duration of the disease was  $15.4 \pm 1.8$  years (range 4–34). The mean age of the controls was  $49.1 \pm 2.2$  years (range 40–72). Laboratory evaluation included basal hormone ( $fT_3$ ,  $fT_4$ , thyroid-stimulating hormone (TSH), prolactin (PRL), cortisol, estradiol ( $E_2$ ), follicle-stimulating hormone (FSH), luteinizing hormone (LH), and insulin-like growth factor-I (IGF-I) levels and dynamic pituitary function tests, including TSH and PRL responses to TRH, FSH and LH responses to gonadotropin-releasing hormone (GnRH), cortisol responses to adrenocorticotrophic hormone (ACTH), and growth hormone (GH) and cortisol responses to insulin tolerance test. Eighteen (66.7%) patients had panhypopituitarism and nine (33.3%) had partial hypopituitarism. Gonadotropins, GH, PRL, TSH, and ACTH deficiencies were 100, 100, 92.5, 85.1, and 81.4% respectively. Eighteen (66.6%) patients had complete and nine (33.3%) had partial empty sella on pituitary MRI.

The study was approved by the local ethics committee and informed consent was obtained from all subjects. The WDT and hypertonic saline infusion test were carried out in patients and controls. All the patients were euthyroidic and eucortisolemic during the WDT and the hypertonic saline infusion test. To eliminate the possible pharmacological effect of thyroid hormone and glucocorticoid on vasopressin release, the patients were given their usual doses of prednisolone and/or L-thyroxine until the evening before each test. None were receiving estrogen or progesterone. None of the patients had overt polyuria and daily urine output was below 2500 ml in all patients. Four patients had nocturia less than two episodes. Blood urea nitrogen, serum creatinine, plasma glucose and serum sodium, calcium and potassium levels were within normal limits. The dehydration test was performed according to the protocol for a modified Dashe dehydration test (7). Tea, coffee, alcohol and cigarettes, which can interfere with vasopressin secretion, were excluded after midnight on the day before the test. Fluids were allowed *ad libitum* until 0700 h and the patients were asked to void their bladders. All patients were monitored closely with hourly measurements of weight, plasma osmolality, urine output and urine osmolality. After 8-h fasting, subjects were allowed to drink (but avoided excessive fluid intake) and were given 2 µg desmopressin (DDAVP) subcutaneously; urine output and osmolality were recorded hourly for an additional 4 h. The 5% hypertonic saline infusion test was performed on another day. Hypertonic saline was infused into an antecubital vein for 2 h at a rate of 0.05 ml/kg per min. Blood for osmolality measurements was taken at -15, 0, 30, 60, 90, 120 and 135 min from the other arm. Urine volume and osmolality were recorded at the beginning and at the end of the test (8). The time of onset of thirst was recorded. Plasma and urinary osmolality were measured using a freezing-point depression osmometer (Micro Osmometer Model 3300, Advanced Instruments, Inc., Norwood, MA, USA).

Serum GH levels were measured using immunoradiometric assay (IRMA) with commercial kit (DSL, Webster, TX, USA); intra- and inter-assay coefficient of variation (CV) were 3.1 and 5.9% respectively. IGF-I level was measured by IRMA after formic acid-ethanol extraction (DSL); intra- and inter-assay CV were 3.4 and 8.2% respectively. E<sub>2</sub> levels (ACS:180, Bayer) were determined by an automated chemiluminescence system; intra- and inter-assay CV were 9.9 and 11.8% respectively.

All the other serum hormones (except TSH) were measured using RIA with the following commercial kits: cortisol (DSL; intra- and inter-assay CV: 8.4 and 9.1%), FSH (ICN Biomedicals, Costa Mesa, CA, USA; 2.4 and 7.3%), LH (ICN Biomedicals; 3.6 and 7.8%), FT<sub>3</sub> (ZenTech, Angleur, Belgium; 2.7 and 8.3%), FT<sub>4</sub> (ZenTech; 3.7 and 4.5%), PRL (ICN Biomedicals; 7.0

and 8.9%), and TSH-IRMA (Bio-source, Nivelles, Belgium; 6.0 and 4.1%).

Results are expressed as mean ± S.E.M. in the text and tables. Statistical analysis was performed by Kruskal-Wallis H and Mann-Whitney U-tests for comparison between groups.  $P < 0.05$  was considered as statistically significant.

## Results

Basal serum sodium level was slightly higher in patients ( $142 \pm 1$  mEq/l) when compared with controls ( $139 \pm 0.2$  mEq/l) but without statistical significance. All the controls and 19 patients had peak urine osmolality exceeding 750 mOsm/kg at the end of WDT. The mean percentage increase of urine osmolality in response to DDAVP was <9% in 19 patients and controls. Eight patients had peak urine osmolality <750 mOsm/kg, and the maximal percentage increase of urine osmolality in response to DDAVP was 23%. According to WDT, 8 (29.6%) patients had partial diabetes insipidus (PDI group) and 19 (70.3%) had normal response to WDT (non-DI group). Basal plasma osmolality was higher in PDI and non-DI groups when compared with controls ( $P < 0.001$ ). Although it did not reach a significant level, maximal plasma osmolality was also higher in PDI and non-DI groups when compared with controls. Basal and maximal urine osmolalities were lower in PDI group than in non-DI and control groups ( $P < 0.01$  and  $0.001$  respectively). The mean maximal urine-plasma osmolality ratio was also lower in PDI group than in non-DI and control groups ( $P < 0.001$ ). However, only three patients with PDI had urine-plasma osmolality ratio <2, the remaining five patients had urine-plasma osmolality ratio  $\geq 2$  (2, 2.1, 2.2, 2.4, and 2.5). On the other hand, all subjects in non-DI and control groups had urine-plasma osmolality ratios  $\geq 2$  (range 2.5–3.9). The percentage increase in urine osmolality in response to DDAVP within 1 h remained 5% in PDI patients, but 13, 18, and 23% increases were observed in urine osmolalities at second, third and fourth hours respectively. The maximal percentage increase in urine osmolality was 2% in non-DI group and 3% in control group within 4 h. The results of WDT are shown in Table 1 and Fig. 1.

One patient from non-DI group had hypertension and was not included in hypertonic saline infusion test. No individual developed nausea during the hypertonic saline infusion. The maximal plasma osmolality was higher in PDI and non-DI groups when compared with controls ( $P < 0.005$ ), but the maximal urine osmolality was lower in PDI group than in non-DI and control groups ( $P < 0.05$ ). None of the patients included in this study had medical conditions or medications known to cause nephrogenic diabetes insipidus and none of them had persistent polyuria known to be associated with renal concentrating defect. On the other hand, the

**Table 1** Comparisons of water deprivation test results of groups.

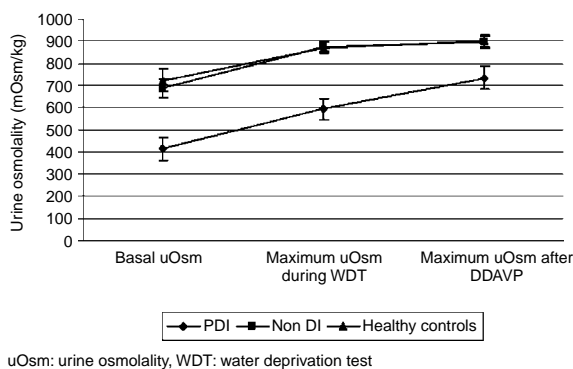
	PDI (n=8)	Non-DI (n=19)	Controls (n=14)
Basal plasma osmolality (mOsm/kg)	294 ± 1.0	297 ± 1.1	288 ± 1.2*
Maximal plasma osmolality (mOsm/kg)	296 ± 1.3	298 ± 0.9	294 ± 1.7
Basal urine osmolality (mOsm/kg)	415 ± 52 <sup>†</sup>	686 ± 43	724 ± 50
Maximal urine osmolality (mOsm/kg)	594 ± 47*	874 ± 23	869 ± 24
Urine-plasma osmolality ratio	2.0 ± 0.1*	2.9 ± 0.0	2.9 ± 0.0
Maximal urine osmolality after DDAVP (mOsm/kg; % increase)	733 ± 51 <sup>†</sup> (23)	895 ± 27 (2)	901 ± 29 (3)

Non-DI, non-diabetes insipidus; PDI, partial diabetes insipidus. \**P*<0.001. <sup>†</sup>*P*<0.01, significance between groups.

results of WDT are not compatible with nephrogenic diabetes insipidus. Therefore, although plasma arginine vasopressin (AVP) levels were not measured, nephrogenic diabetes insipidus is unlikely in those patients. All the patients and controls became thirsty during the hypertonic saline infusion test. The osmotic threshold for thirst perception was higher in PDI (296 ± 4.3) and non-DI (298 ± 1.4) groups when compared with control (287 ± 1.5 mOsm/kg) group (*P*<0.005). The results of hypertonic saline infusion test are shown in Table 2 and Fig. 2. Figure 3 illustrates the median osmotic threshold for the onset of thirst perception.

**Discussion**

In most of the reported studies of Sheehan's syndrome, diagnosis of diabetes insipidus was based solely on clinical ground and assessment of posterior pituitary function was inadequate. Little attention has been given to the posterior pituitary function (9–12). Clinical diabetes insipidus is apparently an uncommon complication of postpartum pituitary necrosis. The frequency of clinical diabetes



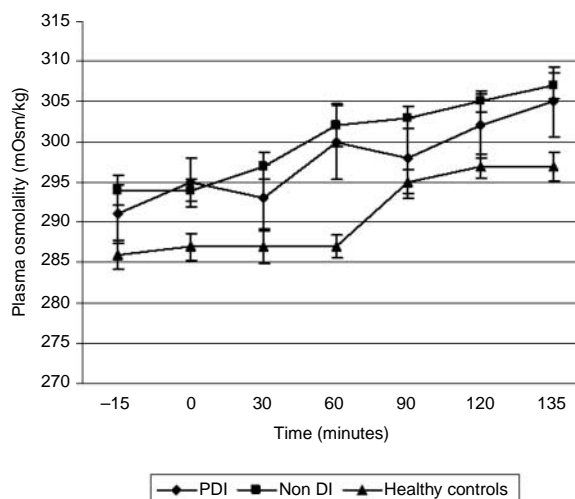
**Figure 1** Changes in urine osmolality during the water deprivation test and the responses to DDAVP.

**Table 2** Comparisons of hypertonic saline infusion test results of groups.

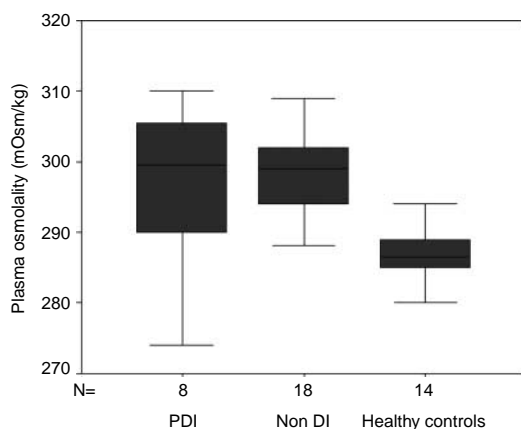
	PDI (n=8)	Non-DI (n=18)	Controls (n=14)
Maximal plasma osmolality (mOsm/kg)	305 ± 4.3	308 ± 1.7	298 ± 1.7*
Maximal urine osmolality (mOsm/kg)	565 ± 37 <sup>†</sup>	708 ± 45	683 ± 17
Osmotic threshold for thirst	296 ± 4.3	298 ± 1.4	287 ± 1.5*

Non-DI, non-diabetes insipidus; PDI, partial diabetes insipidus. \**P*<0.005. <sup>†</sup>*P*<0.05, significance between groups.

insipidus is estimated to be about 5% in Sheehan's syndrome (1). PDI was reported to be much more frequent in postpartum hypopituitarism than previously believed (13, 14). The neurohypophyseal functions in patients with postpartum hypopituitarism were investigated only in a few studies systematically (13–17). These studies indicate that the neurohypophyseal functions are frequently affected in patients with Sheehan's syndrome, but the majority of patients do not manifest diabetes insipidus (13–16). Arnaout *et al.* (14) have demonstrated an impaired osmoregulation of vasopressin secretion in 12 out of the 15 patients with postpartum hypopituitarism using hypertonic saline infusion test. Eight of the patients showed reduced maximum urine osmolality after WDT. Similarly, Iwasaki *et al.* (16) have found an impaired osmoregulation of vasopressin secretion in 10 out of the 12 patients using hypertonic saline infusion test. Six out of the eleven patients showed reduced maximum urine osmolality after WDT. Consistent with previous studies, we also found that patients with Sheehan's syndrome showed higher serum osmolality during hypertonic saline infusion test. Eight out of the twenty seven patients had reduced maximum urine osmolality during WDT. After administration of DDAVP, the percentage increase in urine



**Figure 2** Changes in plasma osmolality during the hypertonic saline infusion test.



Non DI: non diabetes insipidus, PDI: partial diabetes insipidus

**Figure 3** The osmotic threshold for the onset of thirst perception.

osmolality was 23% in these patients, consistent with PDI. Patients with PDI had lower maximum urine osmolality during the hypertonic saline infusion test when compared with non-DI patients and controls. The gold standard method of confirming PDI is the measurement of AVP, which has not been measured in the present study. Jialal *et al.* (17) studied 16 patients with Sheehan's syndrome and demonstrated that the patients have lower maximum urine osmolality and higher plasma osmolality during WDT (according to the protocol of Miller's test). However, only three patients with polyuria had maximum urine osmolality lower than 600 mOsm/kg, and following DDAVP all had an increment in urine osmolality which exceeded 9%. Thus, 19% of patients had diabetes insipidus. Although the dehydration protocol was different, we found that 30% of patients without polyuria have PDI. Diabetes insipidus is manifest only when the function of more than 80% of vasopressinergic magnocellular neurons is lost (18). Otherwise, the findings in most patients indicate that urine output may be virtually normal in spite of an impairment in ADH secretion. The demonstration of ADH deficiency in Sheehan's syndrome is consistent with the histopathological observations of Sheehan and Whitehead. They reported atrophy and scarring in the posterior pituitary and anterior hypothalamus in most of the patients (2, 3). The limitation of the present study is the possible effect of prednisolone therapy on AVP release. Although prednisolone was stopped 24 h earlier, it might have interfered with AVP release. This issue remains to be determined.

In healthy adults, a rise in effective plasma osmolality to 2–3% above basal levels produces a strong desire to drink. The absolute level of plasma osmolality at which a desire for water is first perceived is termed as the osmotic threshold for thirst. The mean osmotic threshold for thirst perception is around 281 mOsm/kg. As with osmoregulated vasopressin release, the characteristics of osmoregulated thirst remain consistent

within an individual on repeated testing despite wide inter-individual variation (18, 19). The osmoreceptors that regulate thirst appear to be located in the anterior hypothalamus near, but distinct from, the supraoptic nucleus. Both the osmoreceptors that regulate AVP secretion and the thirst osmoreceptors are located in or around the organum vasculosum of the lamina terminalis and the anterior wall of the third ventricle (20). The osmoregulation of thirst is also normal in more than 90% of patients with cranial diabetes insipidus (18, 19, 21). It was shown that patients with Sheehan's syndrome had normal basal serum sodium concentrations and have become thirsty during the hypertonic saline infusion test. It was postulated that thirst center appears to be spared from ischemic damage (14, 16). Despite the fact that sensation of thirst is preserved, we found that both basal serum osmolality and the osmotic threshold for the onset of thirst in patients with Sheehan's syndrome were higher when compared with controls. The close anatomical relationship between the osmoregulatory centers for thirst and vasopressin release mean that adipsic syndromes are often associated with defects in osmoregulated vasopressin release (18). We think that even in subclinical situations, the thirst center can be affected by ischemic necrosis.

In conclusion, Sheehan's syndrome may be characterized by impaired posterior pituitary function. The thirst center may be affected by ischemic damage and the osmotic threshold for the onset of thirst in patients with Sheehan's syndrome is increased.

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Received 6 December 2006

Accepted 13 February 2007