Impaired osmoregulation in anorexia nervosa: a case–control study

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Abstract

Background. Anorexia nervosa (AN) has been associated with abnormal osmoregulation and impaired urinary concentrating capacity. Conflicting results suggest that the disorder may be related to hypothalamic dysfunction and/or a primary renal defect. The role of antidepressants, which are increasingly prescribed in AN patients, has not been evaluated.

Methods. We analysed renal function as well as electrolyte disturbances and osmoregulation parameters at baseline and following a water deprivation test in 12 well-defined AN patients (all females, 10 taking antidepressants) vs 12 age-matched controls and 11 young female patients taking antidepressants.

Results. In comparison with matched controls, patients with AN were characterized by a significant alteration of osmoregulation both at baseline [lower plasma sodium and osmolality, abnormally high levels of antidiuretic hormone (ADH) and tendency towards more concentrated urine] and after water deprivation (impaired ADH reaction and lower urinary concentrating ability). The AN patients had no electrolyte abnormalities. The two patients with the shortest duration of AN showed a normal urinary concentrating ability. Patients taking antidepressants showed similar but less marked changes than AN patients, including a lower urinary concentrating ability.

Conclusions. These results show that AN patients are characterized by abnormal osmoregulation at baseline and a lack of reactivity of ADH with a significant urinary concentrating defect after water deprivation. The origin of these defects in AN patients is probably multifactorial, but the duration of the disease and the prescription of antidepressants could play a role.

Keywords: antidepressants; eating disorders; vasopressin; water deprivation test

Introduction

Anorexia nervosa (AN) is an increasingly common psychiatric syndrome consisting primarily of serious restriction of food intake leading to marked weight loss, intense fear of weight gain, inaccurate perception of one’s own body size, and amenorrhea [1]. Among its many complications, AN has been associated with various renal function abnormalities, including a decline in glomerular filtration rate (GFR), an impaired water diuresis, a decreased urinary concentrating capacity and various electrolyte abnormalities [2–6].

The abnormal osmoregulation in AN has been described in three landmark studies published >25 years ago [2,3,6]. There has been a significant evolution in the diagnostic criteria of AN over time, with the definition of the American Psychiatric Association (Diagnostic and Statistical Manual of Mental Disorders, DSM-IV) now being the reference [7]. The potential problem of diagnostic criteria is illustrated by the fact that three different definitions of AN were used in the initial studies [2,3,6]. A second difficulty is the lack of determination of the endogenous antidiuretic hormone (ADH) arginine vasopressin, which complicates the interpretation of these earlier studies [2,3,6]. Thus, the reduced urinary concentrating ability of AN patients was attributed to hypothalamic dysfunction (partial neurogenic diabetes insipidus) in one study [6], whereas the variable and incomplete response to exogenous ADH suggested a primary renal origin in another investigation [3]. A third element is that the antidepressant drugs, which are increasingly prescribed in AN patients [1], have not been considered previously. The antidepressants are clearly associated with hyponatraemia and impaired osmoregulation [8], and they should be considered when analysing water and electrolyte disturbances in AN patients.
In order to characterize the osmoregulation in AN further, we conducted a case–control study to (i) investigate the osmoregulation at baseline and the urinary concentrating ability in a well-defined series of female patients with AN; and (ii) distinguish between the effect of AN itself and the effect of antidepressants that are increasingly prescribed in these patients.

**Patients and methods**

**Patients and controls**

Twelve successive patients suffering from AN hospitalized at Saint-Luc Academic Hospital (Brussels, Belgium) for weight correction were included from October 2000 to June 2001. All patients met the standard DSM-IV diagnostic criteria for AN [7]. All patients were female and their age ranged from 17 to 33 years (mean 21.6 years). They were chronically (≥3 months) underweight (<85% of the expected body weight) and amenorrheic (5 out of 12 AN patients were taking oral contraceptives). Ten out of 12 AN patients were taking antidepressants, including selective serotonin re-uptake inhibitors (SSRIs) (n = 5), the serotonin-norepinephrine re-uptake inhibitor (SNRI) venlafaxine (n = 3), imipramine (n = 1) and mianserine (n = 1), and 6 were taking benzodiazepine drugs. The psychopharmacological therapy was not interrupted during the study. A single AN patient was intermittently taking laxatives. No documented case of chronic hypokalaemia was noted among the AN patients.

Two control groups were included in the study: (i) an age-matched group of 12 women without medical history and without any psychotropic therapy; and (ii) a group of 11 young women taking antidepressant (either alone, n = 6; or in combination, n = 5) but without any other medical history. The antidepressants in the latter group included SSRIs (n = 7), SNRIs (n = 4) and risperidone (n = 3); the drugs were taken chronically for at least 2 months. The protocol of the study has been approved by the Ethics Committee of the Université Catholique de Louvain Medical School. Patients and controls gave informed consent for the study.

**Clinical and biological evaluation and water deprivation test**

Patients with AN and their matched controls, as well as the patients taking antidepressants, underwent a baseline clinical and biological evaluation (evening sample, day 1) that was followed by a 12 h, overnight water deprivation test. The water deprivation test was performed on the day of arrival, independently of refeeding therapy. Clinical and biological parameters were again obtained immediately after the water deprivation test (morning sample, day 2). Plasma levels of sodium, potassium, chloride, carbon dioxide, calcium, urea, creatinine, haematocrit, urate and total protein were measured, as well as plasma osmolality (Posmo). Urine samples obtained simultaneously were analysed for sodium, potassium, chloride, glucose, proteins, osmolality (Uosmo) and density. All biological determinations were performed routinely according to standard methods. Plasma levels of ADH were determined by radioimmunoassay (Nichols Institute Diagnostics, San Juan Capistrano, CA). The ADH levels were analysed simultaneously for the matched AN patients and controls, and a posteriori for the patients taking antidepressants.

**Statistical analysis**

Data are presented as the mean ± SEM. Comparison of clinical parameters (Table 1) and baseline biological values (Table 2) between the three groups was performed using ANOVA and the appropriate parametric (Bonferroni) or non-parametric (Dunn) corrections for multiple comparisons. Comparison between day 1 and day 2 values within each group (before vs after water deprivation) was performed using the paired t-test (two-tailed). The values for data grouping (Figure 2) were those situated in the middle of the range for each parameter (Posmo, 270–300 mOsm/kg; Uosmo, 0–1200 mOsm/kg; ADH, 0–12 pg/ml), and Fisher’s exact test was used for statistical analysis of the contingency table. The relationship between Posmo and ADH levels was evaluated by Spearman rank correlation. All calculations were performed using the Instat 3.0 software (GraphPad, San Diego, CA).

**Results**

The relevant clinical parameters in AN patients and their age-matched controls are shown in Table 1. As expected, the body mass index (BMI) of the AN patients was significantly (almost 30%) lower than in controls. The weight loss in AN patients averaged 26 ± 3% (range 8–40%) over a mean period of 36 ± 16 months (range 3–180 months). Five out of 12 AN patients reported polyuria/nycturia and polydipsia, whereas no such symptoms were reported by the controls. None of the AN patients showed clinical signs of dehydration at baseline. Their mean systolic and diastolic blood pressure (supine) was 94 ± 4 and 58 ± 3 mmHg, respectively. Ten AN patients had bradycardia (<60 b.p.m.), and 58% of them complained of dizziness and syncope. The clinical parameters of the 11 women taking antidepressants were similar to

<table>
<thead>
<tr>
<th>Table 1. Clinical parameters in the matched controls and patients with anorexia nervosa, and in patients taking antidepressants</th>
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</thead>
<tbody>
<tr>
<td>Controls (n = 12)</td>
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<tr>
<td>-------------------</td>
</tr>
<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>Height (cm)</td>
</tr>
<tr>
<td>Body weight at baseline (kg)</td>
</tr>
<tr>
<td>BMI</td>
</tr>
<tr>
<td>Weight loss after water deprivation (% from baseline)</td>
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</tbody>
</table>

*Patients subsequently included as a second control group. Data are mean ± SEM; ANOVA was used for statistical analysis. *P < 0.05, AN patients vs patients taking antidepressants; **P < 0.05, AN patients vs controls.
those of the controls (Table 1). The water deprivation test resulted in a similar weight loss in matched AN patients and controls; the weight loss was slightly higher in patients taking antidepressants, but the difference was not statistically significant ($P = 0.08$).

Biological analyses obtained at baseline (Table 2) showed no significant differences in plasma urea and creatinine levels among the three groups. However, patients with AN were characterized by significantly lower plasma sodium and chloride concentrations, as well as significantly lower Posmo than controls, although the three parameters remained within the normal range. Of note, plasma levels of ADH were identical in matched controls and AN patients, despite the significantly lower Posmo values in the latter group. The AN patients also showed a tendency towards more concentrated urine, as shown by increased Uosmo ($P = 0.07$ vs controls) and urinary sodium concentration (data not shown). Urinalysis was unremarkable and showed no proteinuria or glucosuria in all patients.

Water deprivation in controls yielded a significant increase in Posmo (mean +2 mOsm/kg), as well as a significant rise in ADH levels (mean +1.2 pg/ml). As expected, these modifications were associated with a significant increase in Uosmo (Table 2, Figure 1).

In contrast, despite a significant increase in Posmo (mean +3 mOsm/kg), water deprivation in AN patients induced a minor, non-significant increase in ADH levels (mean +0.2 pg/ml) and a lack of significant urinary concentration. As a consequence, Uosmo at day 2 was lower in AN patients than in their matched controls (Uosmo 515 ± 6 vs 725 ± 57 mOsm/kg, respectively, $P = 0.06$). An intermediate situation was observed in patients taking antidepressants: water deprivation led to a significant but mild increase in Uosmo. Comparison of the individual values of urinary concentrating ability in the three groups (Figure 1) revealed a significant increase of Uosmo in controls, and a milder (still significant) increase in patients taking antidepressants, contrasting with the lack of significant increase in AN patients. It must be noted that the decreased values of Uosmo at day 2 in some controls and patients could not be attributed to water intake during the test, since they showed decreased body weight and/or increased Posmo on day 2. A single AN patient (Uosmo at day 1 = 348 mOsm/kg; day 2 = 220 mOsm/kg) had no increase in Posmo at day 2 (day 1 = 284 mOsm/kg; day 2 = 282 mOsm/kg) and showed the same body weight at day 2. Censoring this AN patient (who did not confess to water intake during the test) does not change the conclusions drawn from Figure 1.

An analysis of Posmo, ADH and Uosmo parameters obtained after water deprivation was performed for the AN patients and their matched controls (Figure 2). The analysis showed that AN patients were characterized by ADH levels similar to controls, despite significantly lower Posmo values (Figure 2A). Furthermore, 10 out of 12 AN patients were characterized by a lower urinary concentrating ability, as evidenced by lower Uosmo levels, than controls (Figure 2B). Two AN patients showed a normal urinary concentrating ability (Uosmo = 1079 and 1017 mOsm/kg, respectively). These patients had higher levels of ADH (6.9 and 10 pg/ml, respectively). Both patients were taking antidepressant; they had a similar cumulative weight loss (26 and 20%) to the other 10 patients. However, these two patients were characterized by the shortest duration of AN (3 months in both) in our series. Conversely, the two AN patients that were not taking antidepressant drugs showed a very low Uosmo after water deprivation (Uosmo = 102 and 364 mOsm/kg, respectively).

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**Table 2. Biological parameters at baseline (day 1) and after water deprivation (day 2)**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Controls ($n = 12$)</th>
<th>AN patients ($n = 12$)</th>
<th>Patients taking antidepressants ($n = 11$)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Day 1</strong></td>
<td><strong>Day 2</strong></td>
<td><strong>Day 1</strong></td>
<td><strong>Day 2</strong></td>
</tr>
<tr>
<td><strong>Plasma</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urea (15–40 mg/dl)</td>
<td>30 ± 2</td>
<td>27 ± 2 (t)</td>
<td>26 ± 3</td>
</tr>
<tr>
<td>Creatinine (0.6–1.4 mg/dl)</td>
<td>0.83 ± 0.03</td>
<td>0.83 ± 0.03</td>
<td>0.83 ± 0.05</td>
</tr>
<tr>
<td>Na(^+) (135–145 mEq/l)</td>
<td>139 ± 0.6</td>
<td>140 ± 0.4 (t)</td>
<td>136 ± 0.9* (#)</td>
</tr>
<tr>
<td>Cl(^-) (97–107 mEq/l)</td>
<td>104 ± 0.7</td>
<td>106 ± 0.7</td>
<td>101 ± 1.3* (#)</td>
</tr>
<tr>
<td>K(^+) (3.5–5 mEq/l)</td>
<td>3.9 ± 0.3</td>
<td>3.8 ± 0.2</td>
<td>3.9 ± 0.2</td>
</tr>
<tr>
<td>HCO(_3)(^-) (22–29 mEq/l)</td>
<td>26.5 ± 0.6</td>
<td>27.2 ± 0.4</td>
<td>27.3 ± 0.9</td>
</tr>
<tr>
<td>Osmolality (280–300 mOsm/kg)</td>
<td>288 ± 1</td>
<td>290 ± 1 (t)</td>
<td>281 ± 2* (#)</td>
</tr>
<tr>
<td>ADH (0–8 pg/ml)</td>
<td>5.3 ± 0.7</td>
<td>6.5 ± 0.7 (#)</td>
<td>5.3 ± 0.8</td>
</tr>
<tr>
<td><strong>Urine</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Osmolality (mOsm/kg)</td>
<td>276 ± 47</td>
<td>725 ± 57 (t)</td>
<td>474 ± 90</td>
</tr>
</tbody>
</table>

\(t\)Normal limits are in parentheses.

\(\#\)The ADH values were determined simultaneously in the matched AN patients and controls, and \textit{a posteriori} in patients taking antidepressants.

Data are means ± SEM; ANOVA was used for comparison between baseline values among the three groups; the paired \(t\)-test was used for comparison between day 1 and day 2 values in each group. \(* / \# P < 0.05\) AN patients vs controls (\(*\)) or patients taking antidepressants (\(#\)); \(\dagger P < 0.05\) day 1 vs day 2 (intra-group).
The analysis of the correlation between Posmo and ADH values (combined day 1 and day 2 values) revealed a positive correlation in AN patients (Spearman $r = 0.51$; $P = 0.007$), and a positive but weaker correlation in patients taking antidepressants (Spearman $r = 0.43$; $P = 0.05$).

**Discussion**

This study indicates that, in comparison with controls, patients with AN show a significant alteration of their osmoregulation both at baseline (normal ADH levels despite lower plasma sodium and osmolality)
and after water deprivation (lower urinary concentrating ability). These modifications in AN patients occur in the absence of hypokalaemia or acid–base abnormalities. Young female patients taking antidepressant drugs showed similar but less marked changes than AN patients, including an impaired urinary concentrating ability.

Alterations in water balance and osmoregulation have long been reported in AN patients. Russell and Bruce [2] first documented an impaired water diuresis in AN patients. Having no evidence for adrenal failure and excessive or inappropriate secretion of ADH and aldosterone, they concluded that malnutrition was involved [2]. Mecklenburg et al. [6] evidenced partial neurogenic diabetes insipidus in 4 out of 5 patients with AN. These results were interpreted as indicating hypothalamic dysfunction, either primary or secondary to starvation [6]. The hypothesis of an abnormal osmoregulation of ADH of central origin in AN patients was supported by the studies of Gold et al. [9]. In a minority of patients (1 out of 4 cases), they described a subnormal rise in plasma ADH relative to the osmotic stimulus, consistent with the partial neurogenic diabetes insipidus reported earlier [6]. In a majority of patients (3 out of 4 cases), however, they showed an erratic or osmotically uncontrolled release of ADH. These modifications, associated with increased levels of ADH in the cerebrospinal fluid, were attributed to an intrinsic defect in the hypothalamic–posterior pituitary axis [9]. It must be noted that the changes were no longer observed in patients who had corrected their body weight for 6 months or more [9]. Aperia et al. [3] documented a lower GFR (using insulin clearance) and urinary concentrating ability in nine patients with AN (including three males). In contrast to a previous study [6], they showed that administration of exogenous ADH did not improve the concentrating capacity in 7 out of 9 patients, and concluded that the defect was of renal rather than central origin [3]. In addition to the fact that different diagnostic criteria of AN were used in the above studies, interpretation of these conflicting data is hampered by the absence of endogenous ADH levels and the lack of consideration of a potential effect of antidepressants in these patients.

Our studies at baseline indicate that, although remaining within normal limits, both plasma sodium concentration and osmolality are significantly lower in AN patients than controls. This abnormality could be due to primary or psychogenic polydipsia (5 out of 12 AN patients reported polydipsia and polyuria). However the latter hypothesis is not supported by the higher baseline Uosmo values observed in AN patients (Table 2). Conversely, AN patients were characterized by ADH levels similar to controls, despite significantly lower Posmo, and a trend towards more concentrated urine. These characteristics are compatible with a lack of suppression of endogenous ADH, which may be part of a complex hypothalamic–pituitary dysfunction [1,9], and they could explain the reduced water clearance observed in AN patients [2]. Furthermore, low basal blood pressure, which may lower the set of the osmostat or increase its sensitivity to plasma osmolality, may induce an inappropriate release of ADH at baseline [10]. Such a mechanism could certainly play a role in AN patients, in which a lower metabolic state is reflected by a low blood pressure [9,10].

The water deprivation test unambiguously demonstrated that most AN patients have an impaired ability to concentrate urine (Table 2, Figures 1 and 2). The origin of this abnormal response to water deprivation is probably multifactorial.

First, the impaired urinary concentrating ability in AN patients could reflect a blunted reactivity of ADH (+0.2 pg/ml from day 1 to day 2), possibly related to the lower Posmo at baseline and a post-test increase that is not sufficient to trigger the release of ADH. In that respect, the positive correlation between Posmo and ADH levels argues against an intrinsic defect in ADH reaction but provides some evidence for a reset osmostat in AN patients [10]. This is supported further by the demonstration that, within a similar range of ADH levels, AN patients consistently show lower Posmo values (Figure 2A). Of interest, 2 out of 12 AN patients showed a normal urinary concentrating ability in relation to higher levels of plasma ADH (Figure 2B). Although they had a similar weight loss to the others, these two patients were also characterized by a lower duration of AN.

Secondly, patients with AN may also have an intrinsic renal defect. Chronic renal failure has been reported in 5% of AN patients in a prospective long-term follow-up study [11]. Aperia et al. have shown that AN patients have an incomplete response to exogenous ADH and a reduced GFR [3]. Analysis of the relationship between ADH levels and Uosmo after water deprivation (Figure 2B) also suggests that, within a similar range of ADH levels, AN patients have lower Uosmo values than controls. Renal failure in AN patients could be due to malnutrition per se [12], as suggested by the improvement of renal function after refeeding and weight gain [4]. Chronic hypokalaemia could also be involved [13]. However, hypokalaemia appears to be limited to the subgroup of AN patients who vomit or purge or abuse diuretics or laxatives [14]. The patients studied here showed normal acid–base status and plasma potassium levels, in the absence of clinical or biological signs of dehydration. Similarly, very low levels of plasma urea, which may also impair urinary concentration [3,12], were not observed. The trend for decreased plasma urea levels observed in the three groups after water deprivation (Table 2) may primarily reflect the reduced exogenous protein intake during the overnight test. Because no GFR formula has been validated in patients with profound modifications of body weight and/or body composition [15,16], we do not have a valid estimation of GFR in the AN patients studied here.

A third element to consider is the potential influence of antidepressants. Although antidepressant and neuroleptic agents have not been shown to improve symptoms of AN in controlled trials, they are increasingly
used in treating the disorder [1]. Different classes of antidepressant drugs have been associated with hyponatraemia, the risk being apparently increased with SSRIs [17]. Severe cases of hyponatraemia have also been reported with the newest class of SNRI venlafaxine [18]. The risk of hyponatraemia is particularly high during the first weeks of antidepressant treatment, as well as in older patients with co-morbidity and/or polymedication [8,19]. Since the majority (10 out of 12) of AN patients in our series were taking antidepressants at the time of investigation, a direct effect of these medications on the release of ADH should be considered [19]. At baseline, patients taking antidepressants showed a trend for lower plasma sodium and osmolality, as well as a slight increase in Ωosm in comparison with controls (Table 2). Patients taking antidepressants also showed a blunted ability to concentrate urine in comparison with controls (Figure 1). However, the defect was less marked than in AN patients, probably reflecting a better reactivity in the ADH levels. Thus, the modifications induced by antidepressants are similar to, although much less marked than, those observed in AN patients. Also, patients taking antidepressants showed a positive correlation between plasma ADH and Posmo similar to AN patients.

In conclusion, we have documented significant alterations of the osmoregulation at baseline and following water deprivation in a case–control study including well-defined patients with AN. Similar changes, although less marked, were observed in patients taking antidepressants. In the absence of other electrolyte abnormalities, the cause of the defective osmoregulation in the AN patients studied here is probably multifactorial. The duration of AN as well as the prescription of antidepressants may also play a role in the abnormal osmoregulation.

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