Cyclical Edema in a Patient with Hypothalamic Disorders and Chronic Glomerulonephritis: Arginine Vasopressin-Dependent Atrial Natriuretic Hormone Release

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Abstract. A 28-year-old woman had hypothalamic disorders (amenorrhea, obesity, psychiatric abnormalities, polydipsia and fever) and chronic glomerulonephritis. She also suffered from general edema associated with cyclical oliguria and polyuria. Her body weight and plasma osmolality increased during the oliguria phase lasting 2 to 8 days and decreased after paroxysmal polyuria accompanied by the natriuresis. These episodes occurred repeatedly, regardless of the treatment with or without diuretics. The release of arginine vasopressin in response to increased plasma osmolality was exaggerated, but changes in plasma volume did not affect arginine vasopressin release. Plasma atrial natriuretic hormone increased in response to a rise in plasma arginine vasopressin and plasma volume during the oliguria phase, thereby resulting in the diuresis and natriuresis. The renin-angiotensin-aldosterone system was secondarily activated by body fluid depletion and diuretics, and this might play an additive role in general swelling. Plasma gonadal hormones did not change to explain the edema. The mechanism of this cyclical edema remains unknown, but it is likely that hypothalamic dysfunction related to psychiatric abnormalities may exaggerate arginine vasopressin release, and enhanced renal sympathetic activity may cause retention of Na and water, and the increase in atrial natriuretic hormone release responding to the plasma volume expansion may bring about the diuresis and natriuresis.

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It is well known that idiopathic edema occurs almost exclusively in women and is neither due to cardiac, hepatic, renal, or allergic diseases nor to any drugs. Edema may be aggravated in the legs and feet after prolonged orthostasis and be accompanied by diurnal weight gain in excess of 1.4 kg [1]. Its pathogenesis is unknown, but it has been argued that a fall in plasma volume due to increased vascular permeability, microangiopathy or impaired protein synthesis activates the renin-angiotensin-aldosterone (RAA) system and the release of arginine vasopressin (AVP), thereby resulting in the retention of salt and water [2-5]. On the other hand, cyclical edema has been reported to be concerned with abnormalities in the release of gonadal, hypophysioadrenocortical and thyroid hormones [6-10].

We recently observed a rare case of cyclical edema in a female patient with hypothalamic disorders and glomerulonephritis. Paroxysmal polyuria occurred repeatedly following oliguria lasting 2 to 8 days, and the edema was not dependent on the body posture. In this case, we investigated the behavior of the RAA system, AVP, atrial natriuretic hormone (ANH) and...
gonadal hormones during the course of cyclical edema and discussed its pathophysiology.

**Case report**

A 28-year-old amenorrheal woman suffered from fatigue and general edema, and was admitted to the 2nd Department of Internal Medicine in Tohoku University Hospital on November 11, 1988. She complained of general edema with increases of 3 to 5 kg in body weight during oliguria lasting 2 to 8 days followed by paroxysmal polyuria.

In the past, she was diagnosed as hypothalamic amenorrhea 7 years ago and her amenorrhea has lasted since then. In March, 1988, purpura appeared in the right upper limb and macrohematuria was noticed. Open renal biopsy was performed in April 1988. Diffuse proliferative glomerulonephritis was diagnosed, but changes in the tubules and interstitium were mild. Thickening of the endothelium and lamina media in the renal artery was also found. On the third day after the renal biopsy, she suddenly presented with polyuria of about 5 L a day, and ever since she has suffered from polyuria occurring every 3 to 9 days followed by general edema with the gain of body weight associated with oliguria lasting 2 to 8 days.

Glucocorticoid had no effect on these cycles. In August, 1988, hypothyroidism was suspected, but sodium thyroxin (50 µg/d) replacement failed to improve the cyclical edema. The administration of furosemide (120 mg) and spironolactone (75 mg) had no effect either on the gain of body weight associated with oliguria. Finally, she was transferred to our department to receive further examinations on these abnormalities and their treatment.

At the physical examination on admission, body weight was 82.4 kg, body length 161 cm, temperature 37.5°C, blood pressure 114/78 mmHg and heart rate 88 beats/min. Consciousness was clear and intelligence was normal, but she was emotionally labile and childish in speech and behavior. She had polydipsia and showed peculiar behavior in eating. Her skin was wet, and mild non-pitting edema was observed. Neurological findings were normal.

She had 4.72×10^10/L of RBC with 122 g/L of Hb and 0.37 of Hct and 7.2×10^9/L of WBC and 367×10^3/L of Plt. The erythrocyte sedimentation rate was 19 mm (1 h) and 44 mm (2 h), and C-reactive protein was negative. She had 143 mmol/L of serum Na, 3.9 mmol/L of K, 108 mmol/L of Cl, 2.3 mmol/L of Ca and 1.3 mmol/L of phosphate. Twenty-four hour creatinine clearance and para-aminohippurate clearance were 1.45 and 9.45 mL/s, respectively, and PSP (15 min) was 29%. Total protein was 63 g/L with 0.59 of albumin, 0.04 of α₁-globulin, 0.09 of α₂-globulin, 0.11 of β-globulin and 0.18 of γ-globulin. In liver function, total bilirubin was 8.6 µmol/L with 6.3 µkat/L of AST, 6.3 µkat/L of ALT, 6.3 µkat/L of LDH, 1.3 µkat/L of ALP and 2.9 µkat/L of γ-GTP. Fasting blood sugar was 5.8 mmol/L, total cholesterol 4.32 mmol/L and triglyceride 1.38 mmol/L. Plasma and urine osmolalities were 285 and 661 mmol/kg, respectively. The urine volume was 1.15 L/d, and urinary Na, K and Cl excretion were 214, 48 and 188 mmol/d, respectively. Urolysis was not remarkable. In the arterial blood gas analysis, acid-base balance was normal. Electrocardiogram was within normal limits and chest and abdominal X-rays were not remarkable. No abnormalities were observed in the renoscintigram. The brain and abdominal CTs were also normal except for the fatty changes in the liver.

Urinary excretion of 17-hydroxycorticosteroids and 17-ketosteroids were 10.5 and 9.0 µmol/d, respectively. Under 50 µg of sodium thyroxin treatment, T₃ and T₄ were high and TSH was not detectable. However, T₃ and T₄ became normal (2.0 nmol/L and 88.8 nmol/L, respectively) 3 months after withdrawal of sodium thyroxin replacement. Plasma estradiol (E₂) and progesterone (PGS) were normal. Plasma renin activity (PRA) and the plasma aldosterone concentration (PAC) were within normal limits, but plasma AVP and ANH increased. TSH was slightly increased at the basal level and hyperresponded to TRH. Plasma PRL and growth hormone (GH), cortisol (CS), LH and FSH were normal and their responses to GH releasing hormone (GHRH), ACTH or LHRH were also normal (Table 1).

As shown in Fig. 1, her daily urine volume was less than 1.2 L/d for the initial 3 days, but her body weight gradually increased by 1.8 kg in 3 days and reached 84.2 kg, accompanied by general swelling. On the 4th day, she suddenly showed signs of polyuria (5.45 L/d) with a subsequent reduction of 4.4 kg in body weight, and the general edema disappeared. After this episode, she had repeated
Table 1. LHRH + TRH + GHRH + ACTH test

<table>
<thead>
<tr>
<th></th>
<th>TSH (µU/L)</th>
<th>GH (µg/L)</th>
<th>PRL (µg/L)</th>
<th>CS (nmol/L)</th>
<th>LH (IU/L)</th>
<th>FSH (IU/L)</th>
<th>PAC (pmol/L)</th>
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</thead>
<tbody>
<tr>
<td>Base</td>
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<td>0.4</td>
<td>8.2</td>
<td>234.5</td>
<td>12.9</td>
<td>6.8</td>
<td>768.4a</td>
</tr>
<tr>
<td>Peak</td>
<td>51.4a</td>
<td>19.6</td>
<td>36.3</td>
<td>717.3</td>
<td>108.9</td>
<td>25.0</td>
<td>1550.7a</td>
</tr>
</tbody>
</table>

a: high value.

similar cycles of edema and polyuria every 2 to 8 days throughout the period of her admission. The polyuria was associated with the natriuresis, and the plasma Na concentration and osmolality decreased after polyuria. Indeed, plasma osmolalities during oliguria were significantly higher than those observed after polyuria (285.3 ± 1.1 mmol/kg in oliguria vs. 278.6 ± 1.1 in polyuria, p<0.01). Although paroxysmal polyuria periodically occurred during her admission, serious hypotension did not occur and polyuria spontaneously subsided within half a day. Diuretics were not administered during the polyuria phase. After treatment with diuretics, the basal body weight gradually decreased in inverse proportion to the increase in the dose of diuretics, but cyclical edema and changes in body weight continued during the observation.

Plasma AVP and ANH concentrations were maintained at relatively high levels during her admission compared to normal subjects. PRA and PAC were relatively suppressed during the early phase of admission, but gradually increased as the basal body weight decreased. Plasma E2 and PGS did not change greatly during the observation (Table 2). Figure 2 shows changes in plasma AVP and ANH in detail in November, 1988 and in January, 1989. Plasma AVP changed in accordance with changes in plasma osmolality, and...
Table 2. Endocrinological data

<table>
<thead>
<tr>
<th>Date</th>
<th>PRA (ng/L/s)</th>
<th>PAC (pmol/L)</th>
<th>AVP (pmol/L)</th>
<th>ANH (pmol/L)</th>
<th>F2 (pmol/L)</th>
<th>PGS (nmol/L)</th>
<th>ACTH (pmol/L)</th>
<th>CS (nmol/L)</th>
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<td>264</td>
<td>6.7</td>
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<tr>
<td>12.01</td>
<td>3.1</td>
<td>283</td>
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<td>32.5</td>
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<td>—</td>
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<td>152</td>
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<tr>
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<td>89.1.05</td>
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<td>652</td>
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<td>26.8</td>
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<td>5.7</td>
<td>9.9</td>
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<tr>
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<td>1207</td>
<td>11.6</td>
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<td>&lt;2.2</td>
<td>199</td>
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<tr>
<td>2.27</td>
<td>—</td>
<td>768</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>212</td>
</tr>
</tbody>
</table>

Normal range: PRA 0.2–1.7, PAC 50–330, AVP 1.4–5.5, ANH 3.4–27.6, F2 37–294, PGS 0.3–4.8, ACTH <11, CS 80–360.

F: follicular phase, L: luteal phase.

Fig. 2. Clinical course of the patient in November, 1988 and in January, 1989. PAVP: plasma AVP concentration, PANCE: plasma ANH concentration, PRA: plasma renin activity, PAC: plasma aldosterone concentration, Cosm: osmolar clearance. Shaded area represents the polyuria phase. The other abbreviations are the same as in Fig. 1.
neither a large fall in body fluid and plasma volume nor their rises entirely affected plasma AVP. Indeed, there was a significant correlation between all plasma AVP values recorded during her admission and their corresponding plasma osmolalities (Fig. 3, A), and the slope of the calculated regression line was steeper in this patient than in normal subjects. Plasma ANH appears to change in parallel with changes in body weight, but no significant correlation was noticed between them. There was a significant correlation between plasma AVP and ANH (Fig. 3, B). An acute water load test (15 ml/kg body weight) was undertaken in the supine position after an overnight fast. Plasma AVP decreased from 16.0 to 7.1 pmol/L at 90 min and changes in plasma ANH were quite comparable to changes in plasma AVP. Total water excretion was less than 200 ml, and urinary dilution was only transiently observed from 45 to 75 min associated with slight rises in plasma ANH and AVP followed by hypertonic urine formation (Fig. 4).

An oral diuretic, azosemide, was administered to prevent the formation of edema and the gain in body weight, but the treatment was not effective. In Feb. 1989, spironolactone was added to azosemide, but these regimens had no effect either on the edema. She always had a low fever without any inflammatory or infectious disorders detected in laboratory findings throughout her admission.

Plasma AVP and ANH were determined by radioimmunoassays previously reported elsewhere [11, 12]. Other hormones were measured with conventional commercial kits.

Discussion

In the present case, oliguria and general swelling developed despite bed rest and treatment...
with diuretics, and polyuria suddenly started and lasted for half a day. Similar episodes were observed repeatedly throughout her admission and menstruation never appeared. This finding was quite different from idiopathic edema, usually elicited by adopting an upright posture, as well as from cyclical edema associated with the menstrual cycle. Cyclical edema has also been reported to occur in patients who abuse diuretics or laxatives [13, 14]. In the present case, diuretics were administered to prevent body fluid retention, but had no effect on the cyclical formation of fluid accumulation. She did not suffer from any constipation requiring laxatives.

On the other hand, Kuchel et al. [10] reported that cyclical edema and hypokalemia occurred in patients with occult episodic hypercorticism, and Chajek et al. [8] found that cyclical edema was noticed in patients with ectopic ACTH producing tumor. However, endocrinological data for our patient were not compatible with disorders of these hormones. Al-Khader et al. [9] reported that subclinical hypothyroidism might produce edema, and treatment with thyroxin improved it. Indeed, in the present case, subclinical hypothyroidism was diagnosed, but thyroxin replacement never kept

Fig. 4. Acute supine water load test. WL: water load, UF: urine flow rate, CH₂O: free water clearance. The other abbreviations are the same as in Figs. 1 and 2.
her from the formation of cyclical edema. Hyperprolactinemia associated with decreased central dopaminergic control has been documented in idiopathic edema and increased plasma PRL has been reported to produce excess fluid retention [15]. Young et al. [16] found that the responses of PRL to TRH, and the release of LH and FSH stimulated by LHRH were exaggerated in idiopathic edema. However, in the present case, the basal levels of these hormones and their responses to TRH and LHRH were normal.

In her past history, chronic glomerulonephritis was suspected. However, the impairment of renal function was mild and could not explain the formation of general swelling and cyclical polyuria. In the present case, plasma osmolality and the Na concentration increased in parallel with weight gain during the oliguria phase, but decreased after polyuria associated with natriuresis. In these situations, AVP release responded to changes in plasma osmolality, but, neither a rise in plasma volume nor its fall, which usually affects AVP release [17, 18], had any effect on AVP release, suggesting that the volume regulation of AVP release may be impaired. On the other hand, plasma ANH, which increases in response to plasma volume expansion and induces natriuresis, apparently increased in parallel with the retention of Na and water, but there was no significant correlation between changes in body weight and plasma ANH. Moreover, plasma ANH changed in parallel with plasma AVP, and decreased despite blood volume expansion (Fig. 4). Therefore, it is likely that increased plasma osmolality during oliguria stimulates AVP release, which may, in turn, enhance ANH release. However, it still remains unclear whether increased plasma ANH brings about the paroxysmal natriuresis and concomitant decreased oliguria, but it is possible that ANH is one of the humoral and physical factors which produce the natriuresis induced by the increase in the extracellular fluid volume [19].

The causes of cyclical edema in the present case remained unclear, but hypothalamic dysfunction may be one of them. Thorn [1, 6] suggested that patients with idiopathic or cyclical edema have psychologic and psychiatric abnormalities with disturbed central nervous system function. In the present case, low grade fever, obesity, emotional lability, hypothalamic amenorrhea, hyperdipsia and enhanced AVP release were noticed. Indeed, impaired AVP release and water excretion have been reported to occur in patients with anorexia nervosa accompanied by hypothalamic disorders and psychological abnormalities [20, 21]. Moreover, the central nervous system has been reported to modulate renal Na and water excretion via the renal sympathetic activity [22]. In the present case, therefore, it is plausible that abnormalities of the central nervous system exaggerated AVP release and enhanced the renal sympathetic activity, thereby resulting in enhanced renal water and Na reabsorption, leading to the formation of edema.

In the present case, RAA system activity was rather low in the initial period associated with increased basal body weight, but gradual decreases in body weight due to diuretics secondarily stimulated the RAA system. However, increased aldosterone release might not play an essential role in producing edema, since spironolactone did not affect the formation of edema. However, it is likely that the activated RAA system plays an additional role in Na and water retention during the oliguria phase.

In conclusion, the cause of cyclical edema in the present case remains unclear, but increased AVP release and enhanced renal Na and water reabsorption related to abnormalities of the central nervous system may elicit excess body fluid retention and oliguria, and increased AVP release in the overhydrated state may stimulate ANH release. On the other hand, gonadal hormones and the RAA system might not play an essential role in the cyclical edema in the present case.

Acknowledgments

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References