A deficient response of atrial natriuretic peptide to volume overload in Gordon's syndrome

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Abstract. Gordon's syndrome was diagnosed in a 19-year-old woman who had hypertension, hyperkalemia and hyperchloremic acidosis. In family screening, hyperkalemia and hyperchloremic acidosis were also found in the patient's mother and brother. The proband and her brother were studied and showed normal glomerular function with normal renal sodium conservation and urine acidification mechanisms. The levels of plasma aldosterone were normal in both subjects. The renin activity was low in the proband but normal in the brother. Both the basal and the volume-stimulated plasma concentration of atrial natriuretic peptide was low in the two patients. As compared with controls, the kaliuretic response to infusion of sodium chloride was not decreased in the patients. Hydrochlorothiazide promptly corrected the acidosis and the hyperkalemia as well as normalized the raised blood pressure of the proband. We suggest that a deficiency of atrial natriuretic peptide rather than an unusual avidity for sodium chloride reabsorption by the renal tubules plays a significant pathogenetic role in Gordon's syndrome.

Gordon's syndrome (hypertension and hyperkalemia with normal glomerular filtration rate) is a rare disorder in which hyperkalemia of renal origin occurs in the absence of glomerular insufficiency or renal sodium wasting and in which hyperchloremic acidosis, hypertension, and hyporeninemia coexist (Schambelan et al. 1981). Since 1964 altogether 28 patients have been reported (Paver & Pauline 1964; Arnold & Healy 1969; Gordon et al. 1970; Spitzer et al. 1973; Weinstein et al. 1974; Brautbar et al. 1978; Farfel et al. 1978a,b; Grekin et al. 1979; Lee et al. 1979; Bravo et al. 1980; Iitaka et al. 1980; Lee & Morgan 1980; Sauder et al. 1981; Schambelan et al. 1981; Sanjad et al. 1982; Licht et al. 1985; Gordon & Hodsman 1986; Soppi et al. 1986). Eleven of them have been sporadic (Paver & Pauline 1964; Arnold & Healy 1969; Gordon et al. 1970; Spitzer et al. 1973; Weinstein et al. 1974; Grekin et al. 1979; Sauder et al. 1981; Schambelan et al. 1981; Sanjad et al. 1982; Gordon & Hodsman 1986; Soppi et al. 1986), whereas the others are members of four separate families (Brautbar et al. 1978; Farfel et al. 1978a,b; Lee et al. 1979; Bravo et al. 1980; Iitaka et al. 1980; Lee & Morgan 1980; Licht et al. 1985). The inheritance seems to be consistent with an autosomal dominant trait. Sodium chloride volume overload appears to be a common feature of the syndrome, whereas the underlying mechanism remains obscure. Schambelan et al. (1981) have suggested that the primary abnormality in Gordon's syndrome is an increased reabsorptive avidity of the distal nephron for chloride. This enhances sodium chloride reabsorption, resulting in volume expansion and decrease of the intratubular electronegativity required for the excretion of potassium and hydrogen ions. This results in hyperkalemia and acidosis. Another hypothesis maintains that hypervolemia in patients with Gordon's syndrome results from a lack of natriuretic or chloruretic factors, for instance owing to deficient action of the atrial natriuretic peptide (ANP) (Gordon 1986).

We have tested these hypotheses in two Finnish patients meeting the criteria of Gordon's syndrome. They were children of a mother who also had the same abnormality. Our results favour the
suggestion that deficient response of atrial natriuretic peptide to volume overload may have a central pathophysiologic role in the genesis of the syndrome.

Patients and Methods

Patient No. 1. The proband

The patient, a 19-year-old woman, was referred to the University Central Hospital of Helsinki for evaluation of mild hypertension (150/105 mmHg) discovered one year previously. She was symptomless and well fit, playing football regularly three times a week.

The results of physical examination were normal except an elevated blood pressure of 138/100 mmHg. Her height was 163 cm and weight 65 kg. The optic funds were normal.

Initial laboratory investigations revealed a normal white cell count and a normal hemoglobin level. There was no proteinuria. The specific gravity of urine was 1.019 and pH 5.0. Serum creatinine was 82 µmol/l (reference range < 115), serum sodium 140 mmol/l (137–149), serum potassium 5.8 mmol/l (3.7–5.3), serum chloride 112 mmol/l (99–111), plasma pH 7.36 (7.35–7.45) with pCO₂ 36 mmHg (35–45) and plasma total CO₂ content 20 mmol/l (22–26). Within normal limits were serum calcium, phosphorus, magnesium, and albumin. No signs of hemolysis were found, and blood thrombocyte count was normal. Thyroid function was normal. Plasma cortisol level was normal and showed appropriate circadian variation. Values for urinary excretion of calcium, phosphorus, magnesium, and amino acids were normal. The chest X-ray finding was normal as was the iv pyelogram. Electrocardiogram was normal.

On hydrochlorothiazide, 50 mg daily, for 4 days the patient's blood pressure was 130/90 mmHg, serum potassium 3.7 mmol/l, serum chloride 100 mmol/l and plasma CO₂ content 24 mmol/l.

The family was screened by studying the parents and two brothers of the proband (Fig. 1). The father and one brother had normal values for serum potassium and plasma total CO₂ content. The mother had previously used antihypertensive drugs. Having been off treatment for 2 weeks the blood pressure was 130/100 mmHg and serum potassium 4.9 mmol/l. She had mild metabolic acidosis (plasma total CO₂ content 19 mmol/l). Similar findings were made in one brother of the proband. The mother refused further studies but the brother was willing to participate in examinations carried out in the metabolic ward.

Patient No. 2. Brother of the proband

He was 18 years old, quite healthy and no abnormalities were found at the physical examination. The blood pressure was 115/70 mmHg. His height was 172 cm and weight 51 kg. Initial laboratory investigations revealed mild hyperkalemia (serum potassium 5.3 mmol/l), metabolic acidosis (plasma total CO₂ content 20 mmol/l) and hyperchloremia (serum chloride 112 mmol/l). Serum creatinine level was 76 µmol/l and urinanalysis disclosed a specific gravity of 1.012, pH 5.5 and no protein. The laboratory and radiologic studies carried out in the sister were performed also in the brother and gave normal results.

Methods

All investigations were carried out in the metabolic ward. The patients were on isocaloric diet (30 kcal/kg per day) containing approximately 100 mmol potassium. The sodium content of the basic diet was approximately 10 mmol/day and was varied with sodium chloride tablets to provide 100 mmol of sodium chloride a day.

The glomerular filtration rate was estimated by the endogenous creatinine clearance. Renal conservation of sodium was evaluated by measurement of the 24-h urinary excretion rate of sodium during a 5-day period on low sodium diet (10 mmol daily). Renal acidification was evaluated by oral administration of ammonium chloride, 0.1 g/kg.

Studies of the renin-angiotensin-aldosterone activity were carried out on 100-mmol sodium diet for 3 days. The studies comprised determination of the 24-h urinary excretion of aldosterone and electrolytes. In addition, plasma samples were taken at 08.00 h after overnight rest and at 12.00 h after 4 h of upright activity for determination of plasma aldosterone, renin, sodium, and potassium concentrations.

The response of atrial natriuretic peptide to volume overload was studied in the patients and in 4 female and 4 male healthy volunteers (aged 18 to 22 years). These studies were done separately from the other investigations. Before the examinations both the patients and the controls were ambulatory and on their normal diet. At the time of the examination the proband had been off treatment for 6 months. Neither her brother nor the controls had a history of alcoholic drinking at the time of the examination.

Fig. 1.
Family pedigree for Gordon's syndrome.
trols used any drugs. The blood pressure and pulse rate of the controls were normal and clinically they were in the normal hemodynamic state. During the whole study the subjects were in a half-sitting position. Two litres of sodium chloride, 0.9%, were infused iv within 60 min through an indwelling catheter placed in a cubital vein. Venous blood samples for determination of the concentrations of atrial natriuretic peptide were collected into chilled EDTA tubes kept in ice -15, 0, 15, 30, 45, 60, 75, 90 and 120 min after the start of the infusion. Plasma was separated in a cooled centrifuge and stored at -70°C.

To evaluate the integrity of the hydrogen ion secretory mechanism and the effect of anion permeability on non-sodium cation secretion, the sodium salts of sulphate and chloride were infused on separate occasions. For comparison, sodium chloride was administered to 2 healthy subjects, a 21-year-old woman and a 17-year-old man. The patients were on low sodium diet (10 mmol/day) for 5 days before sodium sulphate infusion. One milligram of fludrocortisone (Florinef®, Squibb, Princeton, NJ) was administered orally at 19.00 h the day before each infusion. On the next morning urine was collected for 2 h (from 08.00 to 10.00 h) for the determination of basal excretion of sodium, potassium and creatinine and for urine pH determinations. Blood samples for determination of serum electrolytes, creatinine and acid-base levels were obtained at 08.00 and 10.00 h. Thereafter either sodium chloride, 0.9%, plus sodium bicarbonate, 25 mmol/l, at a rate of 16.7 ml/min or sodium sulphate, 0.15 mmol/l, plus sodium bicarbonate, 25 mmol/l, at rate of 8.3 ml/min was infused for 2 h. After the start of the infusions five 1-h samples of urine were collected for measurement of potassium, sodium, creatinine, and pH. At the end of each collection, blood was obtained for measurement of serum sodium, potassium, creatinine, and acid-base levels.

Plasma and urine aldosterone were measured by a RIA kit form Sorin International CIS (St. Quentin Yvelines Cedex, France). In plasma renin assay angiotensin I was measured using a RIA kit obtained from Medix (Espoo, Finland). Plasma atrial natriuretic peptide was determined as described before (Tikkanen et al. 1985).

### Table 1.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Plasma renin</th>
<th>Plasma aldosterone</th>
<th>Urine excretion/24 h</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rest (µg l⁻¹ h⁻¹)</td>
<td>Upright (µg l⁻¹ h⁻¹)</td>
<td>Rest (pmol/l)</td>
</tr>
<tr>
<td>1</td>
<td>0.1</td>
<td>0.6</td>
<td>210</td>
</tr>
<tr>
<td>2</td>
<td>1.7</td>
<td>4.3</td>
<td>341</td>
</tr>
<tr>
<td>Reference range</td>
<td>0.9–2.0</td>
<td>2.0–5.0</td>
<td>85–470</td>
</tr>
</tbody>
</table>

### Results

The glomerular filtration rate was normal in both patients (1.4 and 2.0 ml/sec, respectively). On a diet containing 100 mmol sodium and 100 mmol potassium, the urinary excretion of potassium varied in the patients from 74 to 100 mmol/24 h (Table 1). Urinary sodium excretion decreased promptly to 12 and 3 mmol/24 h, respectively, when dietary sodium chloride intake was restricted to 10 mmol/day. Both patients showed a normal capacity to acidify the urine. Thus, in response to the acute administration of ammonium chloride, the urine pH was 4.8 in both patients.
The results of studies of the renin-angiotensinaldosterone system are presented in Table 1. Plasma renin levels were low in patient No. 1 but normal in patient No. 2. Plasma aldosterone levels and their responses to upright position as well as urine aldosterone excretion were normal in both patients.

Fig. 2 illustrates the response of atrial natriuretic peptide to the infusion of sodium chloride. In the patients both the basal and volume-stimulated plasma ANP concentrations were clearly lower than the mean values for the controls. In the proband no response of ANP to sodium chloride was seen, whereas in her brother there was a slight response (Fig. 2).

The response of the urinary excretion of potassium to the infusion of sodium chloride was similar in the patients and controls (Table 2). In the patients plasma CO₂ content increased and serum potassium concentration decreased to minimal value of 4.8 and 4.6 mmol/l, respectively (Table 2). The infusion of sodium sulphate also clearly decreased serum potassium levels, the lowest values recorded being 3.8 and 3.4 mmol/l, respectively (Table 3). Plasma CO₂ content increased in both patients, and more so in patient No. 2 (Table 3).

**Table 2.**

<table>
<thead>
<tr>
<th>Subject</th>
<th>Urine excretion (mmol/h)</th>
<th>Urine pH</th>
<th>Plasma CO₂ content (mmol/l)</th>
<th>Serum potassium (mmol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>K</td>
<td>Na</td>
<td>K-Na-ratio</td>
<td>Before</td>
</tr>
<tr>
<td>Patient 1</td>
<td>5.2</td>
<td>7.3</td>
<td>4.4</td>
<td>30.5</td>
</tr>
<tr>
<td>Patient 2</td>
<td>4.3</td>
<td>7.6</td>
<td>4.2</td>
<td>14.7</td>
</tr>
<tr>
<td>Control 1</td>
<td>3.3</td>
<td>5.6</td>
<td>5.8</td>
<td>30.2</td>
</tr>
<tr>
<td>Control 2</td>
<td>3.5</td>
<td>5.9</td>
<td>4.5</td>
<td>16.2</td>
</tr>
</tbody>
</table>

* = mean hourly excretion during a 2-h control period (before) and during 5 h after the start of the infusion (after); 1 = the mean of two control samples obtained before the infusion; 2 = the lowest value in five samples obtained after the start of the infusion; 3 = the highest value in five samples obtained after the start of the infusion.

**Table 3.**

<table>
<thead>
<tr>
<th>Subject</th>
<th>Urine excretion (mmol/h)</th>
<th>Urine pH</th>
<th>Plasma CO₂ content (mmol/l)</th>
<th>Serum potassium (mmol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>K</td>
<td>Na</td>
<td>K-Na-ratio</td>
<td>Before</td>
</tr>
<tr>
<td>Patient 1</td>
<td>2.6</td>
<td>12.8</td>
<td>2.2</td>
<td>29.2</td>
</tr>
<tr>
<td>Patient 2</td>
<td>4.0</td>
<td>17.9</td>
<td>4.2</td>
<td>26.6</td>
</tr>
</tbody>
</table>

* = mean hourly excretion during a 2-h control period (before) and during 5 h after the start of the infusion (after); 1 = the mean of two control samples obtained before the infusion; 2 = the lowest value in five samples obtained after the start of the infusion; 3 = the highest value in five samples obtained after the start of the infusion.

**Discussion**

This report describes two siblings who most likely had Gordon's syndrome (hypertension and hyperkalemia with normal glomerular filtration rate). The proband had all the main characteristics of the disorder, including hyperkalemia without glomerular insufficiency and without renal sodium wasting, hyperchloremic acidosis, hypertension and hyporeninemia (Schambelan et al. 1981). The brother had hyperkalemia and hyper-
chloremic acidosis, but he was normotensive and normoreninemic. The mother of the patients had hypertension, hyperchloremic acidosis, and mild hyperkalemia, indicating that the disorder in the family was inherited with an autosomal dominant trait (Fig. 1).

Normal aldosterone levels of the patients indicate that they did not have aldosterone deficiency. Low or normal plasma activity of renin and the absence of renal sodium wasting show that the aldosterone in the patients was biologically active and that aldosterone-responsive tissues were not resistant to its effects. A hyperkalemic form of distal renal tubular acidosis is excluded since, in contrast to our patients, patients with that disorder are unable to lower their urinary pH after administration of ammonium chloride or sodium sulphate. Also, such patients are unable to increase fractional potassium excretion in response to infusion of sodium sulphate and to reduce sodium excretion to the level of intake when on a low sodium diet (Batlle 1981; Batlle et al. 1981).

Deficiency of any natriuretic or chloroureatic factor, including atrial natriuretic peptide, could explain the pathophysiologic mechanism of the syndrome. Our results are compatible with this suggestion. In our patients the basal plasma concentrations of atrial natriuretic peptide tended to be low even in absolute terms, but surely they were appropriately low in the face of the fact that patients with Gordon's syndrome are hypervolemic (Gordon 1986) in which case a raised basal concentration of atrial natriuretic peptide would rather be expected. A deficient response of atrial natriuretic peptide to volume overload in our patients was further ascertained by saline infusion, which stimulated ANP secretion only to a slight extent. Our findings are in accordance with those reported by Tunny et al. (1988) in one earlier patient. This patient showed an inappropriately elevated basal level and a blunted response of ANP to saline infusion. Seemingly, Gordon's syndrome is the first disease entity in the pathogenesis of which deficient action of atrial natriuretic peptide plays a role.

How can deficiency of atrial natriuretic peptide explain the characteristics of Gordon's syndrome? Firstly, because ANP is a potent vasodilator (Ballermann & Brenner 1986), reduced secretion of this polypeptide may contribute to vasoconstriction and increase systemic vascular resistance, which would favour a rise in blood pressure. Secondly, a relative lack of ANP would result in sodium chloride and volume retention, also acting in a hypertensive direction. By increasing glomerular filtration rate, atrial natriuretic peptide increases sodium delivery to the distal nephron which determines to a great extent the secretion of potassium and hydrogen (Batlle et al. 1987). Accordingly, deficient secretion of the hormone may result in a reduced distal delivery of sodium and further in the failure to secrete potassium and hydrogen ions, which leads to hyperkalemia and metabolic acidosis. Of course, hyperchloremic acidosis may also be the result of a volume expansion-induced bicarbonaturia and retention of chloride. Moreover, owing to several interactions between potassium and hydrogen ions, actual degrees of hyperkalemia and acidemia are highly dependent on each other.

In patients with Gordon's syndrome plasma and urine levels of aldosterone have varied from low to high (Schambelan et al. 1981; Gordon 1986). It has been suggested that the actual aldosterone levels in the disorder are the net result of stimulation by hyperkalemia and inhibition by co-existing hyporeninemia (Schambelan et al. 1981). Atrial natriuretic peptide suppresses both aldosterone secretion and renin release (Ballerman & Brenner 1986). Thus, on the basis of the present data the actual aldosterone levels in patients with the syndrome may depend on the degree of the deficiency of atrial natriuretic peptide, too.

The speculation about the increased rate of reabsorption of chloride by the renal tubule as the primary abnormality in the syndrome has been based on the findings of different kaliuretic responses of some patients to infusion of the highly reabsorbable anion, chloride, and the poorly absorbed anion, sulphate. The response to sulphate in these patients has been of the same magnitude as in controls, whereas that to chloride has been either deficient or absent (Schambelan et al. 1981; Licht et al. 1985). We were not able to confirm the presence of any 'chloride shunt' in our patients because they responded properly to the infusion of sodium chloride. Although it is conceivable that Gordon's syndrome may have several pathophysiological mechanisms, the severe deficiency of atrial natriuretic peptide could, via reduced distal delivery of sodium, explain a deficient kaliuretic response of some patients (Schambelan et al. 1981; Licht et al. 1985) to infusion of chloride.
In accordance with previous findings (Arnold & Healy 1969; Gordon et al. 1970; Lee et al. 1979; Schambelan et al. 1981; Sanjad et al. 1982; Licht et al. 1985; Soppi et al. 1986), hydrochlorothiazide readily corrected the acidosis and the hyperkalemia, and normalized the raised blood pressure of the proband. The favourable response to treatment with thiazides may explain that there are patients with the syndrome who are never admitted to hospital for their hypertension. Therefore, Gordon's syndrome may be far more common than expected from the rare reports published until now.

References


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