NOTE
Factitious Bartter's Syndrome Induced by Surreptitious Intake of Furosemide

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Abstract

Studies on the electrolyte metabolism and the renin-angiotensin-aldosterone system were made in a 47-year-old female patient with factitious Bartter's syndrome induced by surreptitious use of furosemide. The diagnosis was confirmed later by detection of the diuretic in the urine. In metabolic studies patient exhibited abnormalities similar to those reported in Bartter's syndrome; viz, hypokalemic alkalosis, blunted response to exogenous angiotensin II, which reverted to normal by volume expansion with an albumin solution, and diminished fractional free water clearance per fractional distal sodium delivery. The above data, along with the known pharmacological effects of furosemide, suggest that the abnormality in Na+ or Cl- reabsorption in the ascending limb of Henle's loop is a primary cause of Bartter's syndrome.

Bartter's syndrome was first described by Bartter et al. in 1962 (Bartter et al. 1962). This syndrome is characterized by hypokalemic alkalosis, increased level of plasma aldosterone, normal blood pressure, decreased sensitivity to exogenous angiotensin II (A II), and juxtaglomerular hyperplasia. The pathogenesis is still a matter of active debate.

In a recent review, Bartter proposed that Bartter's syndrome results from abnormalities of the electrolyte metabolism caused by various pathological conditions (Gill & Bartter 1978). One of the most likely causes of the syndrome is impairment of the Cl- reabsorption in the thick ascending limb of Henle's loop. The combination of metabolic abnormalities similar to that seen in Bartter's syndrome has been known to occur in patients who abuse laxatives or diuretics and is called "Pseudo-Bartter Syndrome" (Trübestein et al. 1972) or factitious Bartter's syndrome (Rosenblum et al. 1977).

Recently, we had a female patient who exhibited symptoms and signs compatible with Bartter's syndrome. A later survey disclosed that she had been taking furosemide surreptitiously. This report is an outline of the clinical course of the patient and the results of metabolic studies. The data seem to support the hypothesis that the inhibition of Na+ or Cl- reabsorption (by furosemide in this case) causes most of the metabolic disturbances observed in Bartter's syndrome.

Case Report

A 47-year-old licensed nurse was admitted to the hospital on June 19th, 1980, for evaluation of hypokalemia. On history-
taking, she revealed that she had taken hydrochlorothiazide from 1962 to 1968 and then furosemide until the summer of 1979 for mild hypertension. She stated that she had taken no diuretics thereafter because of the normalization of her blood pressure. Starting in May 1980, she had weakness, malaise, episodes of nausea and anterior chest discomfort. In August, moderate hypokalemia (2.6 mEq/l) was detected in a routine check-up performed in her hospital. Her past and family histories were non contributory. On admission, she was active. She weighed 48 kg and stood 153 cm tall. The pulse was 68/min and irregular, and the blood pressure 112/60 mmHg. Otherwise, the results of a complete physical examination were not revealing. The arrhythmia was due to premature ventricular contraction which disappeared after control of the hypokalemia.

Material and Methods

A diet containing 100 meq of sodium and 70 meq of potassium was given throughout. Examination was started after a week of adaptation to this dietary regimen. Plasma samples were drawn at 9 : 00 a.m. in the supine position after an overnight fast except when stated otherwise in the text.

Renin-Aldosterone study

Plasma renin activity (PRA) and plasma aldosterone were determined by radioimmunoassay. Plasma volume and blood volume were measured by the use of 131I-human serum albumin (Williams & Fine 1962). Urinary furosemide was measured by high-performance liquid chromatography (Uchino et al. 1978).

Pressor response to A II

Studies were made as described before (Fujita et al. 1977). In short, after an overnight fast, the patient was kept supine for 2 hours before and during the administration of A II. The A II was infused intravenously at rates of 1, 2, 3, 5, 10, 20, 30 and 35 ng/kg/min until the diastolic pressure rose by 20 mmHg. The responsiveness to A II was re-evaluated after an albumin solution had been infused intravenously (4.4 g per day) for 5 days.

Renal tubular function

Studies were made as described before (Fujita et al. 1977). In short, 20 ml/kg body weight of water was administered during a one-hour period, followed by intravenous administration of 0.45% saline at a rate of 5 ml/min. The rate of saline infusion was subsequently adjusted to exceed the urinary flow by 5 ml or more per minute. Urine was collected by an indwelling catheter. Free water clearance (CH2O) and fractional free water clearance per fractional distal sodium delivery were calculated as follows (Stein et al. 1967):

\[
\text{CH}_2\text{O} = \frac{V - \frac{U_{osm}}{P_{osm}}}{V} \quad \text{V: volume of urine} \\
\text{fractional free water clearance per fractional distal sodium delivery:} \quad \text{CH}_2\text{O} = \frac{C_{\text{H}_2\text{O} + C_{\text{Na}}}}{C_{\text{H}_2\text{O}}}
\]

Asn1-, Val1–Angiotensin II amide (Hypertensin, Ciba) was obtained from Ciba-Geigy Co, Takarazuka, Japan.

Results

The results of serum electrolytes, blood gas analysis, renin study and plasma and

Fig. 1. Daily urinary Na, K, Cl and furosemide excretion. Urinary furosemide was determined by high performance liquid chromatography.
blood volume are shown in Table 1.

The time courses of urinary Na, K, Cl and furosemide are shown in Fig. 1, which indicates that, although salt intake was restricted to 100 meq per day, the actual levels of urinary sodium were between 120 and 215 meq, indicating that the patient had failed to follow our instructions.

To increase diastolic pressure by 20 mmHg, 35 ng/kg body weight/min of A II was needed (Fig. 2). After the albumin infusion, the dose of A II for this purpose was diminished to 24 ng/kg/min.

Discussion

Bartter et al. initially suggested that a decrease in the sensitivity of blood vessels to circulating A II is the fundamental abnormality in Bartter’s syndrome (Bartter et al. 1962). This hypothesis was soon challenged by the observation that similar findings (normotension, high PRA and poor responsiveness to exogenous A II) were detected in many patients who suffered from diseases obviously different from Bartter’s syndrome (nephrosis and liver cirrhosis, for example) (Cannon et al. 1968). As an alternative, increased activity of prostaglandin synthesis in the kidney (Gill et al. 1976) and/or a defect of reabsorption of sodium or chloride at the ascending limb of Henle’s loop (Fujita et al. 1977; Gill & Bartter 1978) are suggested as the cause of this syndrome.

Our patient showed signs of hypokalemic alkalosis, an increased level of PRA, and decreased sensitivity to the pressor effect of exogenous A II. The plasma aldosterone level was in the high normal range. The patient strongly denied vomiting, diarrhea and intake of any drugs. Thus, at first, we suspected Bartter’s syndrome as her condition.

Table 1. Summary of the laboratory data.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
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<tbody>
<tr>
<td>Serum electrolytes (mEq/l)</td>
<td>Na 138.2±0.5 K 2.82±0.08 Cl 92.4±0.7</td>
</tr>
<tr>
<td>BUN</td>
<td>19 mg/dl</td>
</tr>
<tr>
<td>UA</td>
<td>11.7 mg/dl</td>
</tr>
<tr>
<td>Creatinine</td>
<td>1.0 mg/dl</td>
</tr>
<tr>
<td>Arterial blood gas analysis</td>
<td>pH 7.538 HCO₃⁻ 31.0 mEq/l BE +7.9 PCO₂ 36.5 mmHg</td>
</tr>
<tr>
<td>Renin-Aldosterone system</td>
<td>PRA 15.8 ng/ml/hr (normal range 0.5–2.0) Aldosterone 11.7 ng/dl (2–14)</td>
</tr>
<tr>
<td>Plasma volume</td>
<td>1866 ml (normal: 2160; 45 ml/kg)</td>
</tr>
<tr>
<td>Blood volume</td>
<td>3039 ml (normal: 3840; 80 ml/kg)</td>
</tr>
<tr>
<td>Cl₂H₂O²⁻/Cl₂H₂O²⁻+CNa⁺</td>
<td>47.3±5.0% (mean±S.E.M. n=4, control: 60–80%)</td>
</tr>
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</table>

Plasma renin activity (PRA) and plasma aldosterone were determined after overnight fast and in the supine position. Cl₂H₂O²⁻/(Cl₂H₂O²⁻+CNa⁺) indicates the fractional free water clearance per fractional distal sodium delivery.
Examinations were then designed in an attempt to clarify the pathophysiology of Bartter's syndrome as reported previously (Fujita et al. 1977). The results indicated first that the plasma volume tended to be diminished (Table 1), and volume expansion by albumin infusion caused improvement in the sensitivity of the blood vessels to the pressor effect of exogenous A II. Secondly, a decrease in the fractional free water clearance per fractional distal sodium delivery was demonstrated. These findings are exactly in line with the results obtained in patients with genuine Bartter's syndrome. However, in view of the unexpected results of urinary sodium chloride examinations, surreptitious intake of salt was strongly suggested. This led us to suspect that she was taking potent diuretics surreptitiously. Thus, we re-examined her urine. The results disclosed that she must have been taking at least one or two tablets (1 tablet = 40 mg) of furosemide a day in secret. It is well known that abuse of laxatives or diuretics, vomiting and diarrhea evoke a state similar to that of Bartter's syndrome (Trüebstein et al. 1972). Such a state is described as "Pseudo-Bartter Syndrome" or factitious Bartter's syndrome. On long term follow-up by a psychiatrist, the patient finally confessed to abuse of diuretics. Her metabolic abnormalities cleared up one month after the discontinuation of this habit.

From the results of this study, two points have been found relevant. The first concerns diagnosis. Before establishing a diagnosis of Bartter's syndrome, we must exclude any condition that mimicks Bartter's syndrome. When potassium loss is not through the kidney and is instead, for example, through the gastrointestinal tract as a result of vomiting, diarrhea and laxative abuse, reduction in the urinary potassium excretion is of value in making the diagnosis. But when surreptitious intake of diuretics, such as furosemide, causes this condition, urinary potassium excretion is not decreased and, therefore, differentiation from Bartter's syndrome is difficult. This case illustrates the usefulness of the measurement of urinary excretion of these diuretics. The second point concerns the pathogenesis of Bartter's syndrome. This case revealed that metabolic abnormalities similar to those of Bartter's syndrome can occur in patients who take diuretics, the action of which is known to inhibit the Na⁺ or Cl⁻ reabsorption at the thick ascending limb of Henle's loop specifically. Thus, the hypothesis that the basic abnormality in Bartter's syndrome resides in a defect in the Na⁺ or Cl⁻ reabsorption at the thick ascending limb of Henle's loop seems to be supported.

References


