A Case of Pseudo-Bartter's Syndrome Associated with Hypergastrinemia, Thrombocytosis and Increased Serum Thyroxine-Binding Globulin

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Abstract

A housewife, 40 years of age, was admitted with dysesthesia of the extremities, muscle weakness, and attacks of adynamia and thirst. She had been taking a laxative for more than 20 years. On physical examination, blood pressure was 94/56 mmHg. Laboratory tests revealed thrombocytosis, low serum K and marked increases in both plasma renin activity and serum aldosterone. Serum TBG was increased. Serum gastrin was also markedly increased and could not be enhanced by exogenous secretin. Both angiotensin 11 loading test and noradrenalin loading test failed to increase blood pressure. Ammonium chloride loading to examine the disturbance of urinary acidification was abnormal in the short term test and borderline in the long term test. Following a diagnosis of pseudo-Bartter's syndrome induced by long term intake of laxative and repeated diarrhea, the administration of laxative was interrupted and potassium, indomethacin and spironolactone were administered. However, serum K remained low. Hypergastrinemia, thrombocytosis and a high serum TBG level also persisted, the causes of which remain unknown. This is the first reported case of pseudo-Bartter's syndrome associated with hypergastrinemia, thrombocytosis and increased serum TBG.

Bartter's syndrome is characterized by an increase in plasma renin activity, an increase in serum aldosterone, hypokalemia, metabolic alkalosis, normo- to hypotension and decreased responsiveness of blood pressure to exogenous angiotensin 11 (Bartter et al., 1962). Chronic vomiting (Veldhuis et al., 1979), chronic diarrhea, long term administration of laxative (Fleischer et al., 1969) or diuretics (Tajiri et al., 1981; Jamison et al., 1982) and anorexia nervosa (Wolff et al., 1968) also induce a state similar to Bartter's syndrome, and such a syndrome is called pseudo-Bartter's syndrome (Meurer et al., 1968). Recently, cystic fibrosis (Davison and Snodgrass, 1983), cystinosis (Whyte et al., 1985), jejunoileal bypass for obesity (Julkunen et al., 1982) and chemotherapy (Lieber et al., 1984) also
have been reported to induce so called pseudo-Bartter's syndrome.

In this paper, we report a case of pseudo-Bartter's syndrome induced by long term intake of laxative and chronic diarrhea, with impaired urinary acidification and which was associated with hypergastrinemia, thrombocytosis and an increase in serum TBG.

Case Report

History
A 40-year-old housewife had been taking a laxative (Dokusogan) for constipation 3 times a week, since she suffered from peritonitis at 14 years of age. Stools were passed every 3 to 10 days accompanied by several episodes of diarrhea for one day. In May, 1982, nausea, vomiting, cold sweating and spasms of the hands as well as dull back pain appeared, then disappeared within half a day. Since September, 1982, attacks of adynamia appeared every 2-3 months, and her local doctor pointed out a renal stone. In March, 1985, hypokalemia, hyperreninemia and hyperaldosteronemia were pointed out at a hospital and she was admitted to this department for further examinations in July, 1985.

Physical Examination.
Body height was 149 cm and body weight 41 kg. Blood pressure was 94/56 mmHg. The right kidney was palpable for a half fingerbreadth. Tenderness and knock pain were present in bilateral lumbar regions. Purpura was observed on the extremities. Neurological examination revealed slight decreases in deep tendon reflexes, paresthesia and a decrease in muscle power.

Laboratory Tests
Peripheral blood examination revealed Hb 13.0 g/dl, RBC $418 \times 10^4$, Hct 38.1%, platelets $59.7 \times 10^4$ and WBC 14,500 (Band 12, Seg 70, Eosino 0, Baso 0, Mono 5, Lymph 13%). ESR was 57 mm (1 h). Wasserman test, CRP, RA test, LE test, antinuclear antibody and HBs antigen were negative. HBs antibody was 64×. IgG was 1,073 mg/dl, IgA 286 mg/dl and IgM 165 mg/dl. Urinalysis revealed a specific gravity of 1.005, no sugar, traces of protein, a moderate degree of blood and normal urobilinogen. In sediment, RBC 8-10/svf and WBC 3-5/svf were observed. Fecal examination revealed no occult blood and no parasitic ova. Coagulation tests were normal. Blood chemistry revealed TP 7.7 g/dl (Alb 61.4, α₁-Glb 2.8, α₂-Glb 11.2, β-Glb 11.4, γ-Glb 13.0%), Na 131 mEq/l, K 2.0 mEq/l, Cl 91 mEq/l, Ca 9.1 mg/dl, P 2.9 mg/dl, Mg 2.7 mg/dl, creatinine 1.4 mg/dl, BUN 24 mg/dl, Osm 277 mOsm/kg, total bilirubin 0.6 mg/dl, GOT 10 mU/ml, GPT 10 mU/ml, LDH 304 mU/ml, Al-P'ase 183 mU/ml, γ-GTP 11 mU/ml, LAP 31 mU/ml, total cholesterol 336 mg/dl, triglyceride 311 mg/dl, phospholipid 379 mg/dl, chyromicron 10 mg/dl, VLDL-cholesterol 155 mg/dl, LDL-cholesterol 1049 mg/dl, HDL-cholesterol 75 mg/dl, amylase 200 SU/ml, CEA 1.1 ng/ml and AFP below 20 ng/ml. Urinary chemistry revealed Na 44 mEq/day, K 18.7 mEq/day, Cl 57.9 mEq/day, Ca 110 mg/day and P 270 mg/day.

Among renal function tests, Fishberg's test revealed a maximum specific gravity of 1,012. PSP excretion was 7% (15 min.) and 45% (120 min.). Twenty-four h endogenous creatinine clearance was 13.2 l/day. Serum BMG was 8.5 μg/l and urinary BMG 19, 950 μg/l. FENa was normal (1.9), FEK increased (55.2) and FECl normal (4.3). Excretion of bicarbonate was normal (0.11%). Intravenous pyelography revealed calcification of the bilateral renal medulla. Renogram revealed bilateral renal dysfunction. Analysis of arterial blood gas revealed pH 7.46, PCO₂ 37.7 mmHg, PO₂ 104.2 mmHg, HCO₃⁻ 26.4 mEq/l, and SAT 97.6%. Culture
Fig. 1. Renal biopsy specimen (PAS stain, 400X).
of urine was negative. ECG showed a low T wave, U wave and depression of ST segment. The circulating plasma volume was 44.3 ml/kg (normal 45 ± 5) and circulating blood volume 66.6 ml/kg (normal 80 ± 10).

Roentgenological examination of the skull and hands were normal. Cranial CT scan was normal. Chest X-ray film revealed an abnormal calcified density posterior to the heart. Plain abdominal X-ray film, abdominal CT scan and abdominal echogram revealed atrophy and calcification of bilateral kidneys. Fluoroscopy of the upper GI tract and opaque enema were negative. Endoscopy of the upper GI tract revealed hypertrophic gastritis, but biopsy of the gastric mucosa was normal. In the examination of the gastric juice, BAO was 7.30 mEq/h and MAO 17.56 mEq/h after pentagastrin injection, indicating normal acidity. As shown in Fig. 1, renal biopsy did not reveal distinct hyperplasia of the juxtaglomerular complexes, but interstitial nephritis was suspected. Bone marrow puncture revealed that megakaryocytes were increased in number and small in size.

In endocrinological tests, as shown in Table 1, serum GH and serum PRL were slightly increased. Serum T₄ and TBG were increased and resin uptake and %TRP were decreased. Serum cortisol was increased, while urinary 17-OHCS was normal. The dexamethasone suppression test revealed normal suppression of the serum cortisol level. Both plasma renin activity and the serum aldosterone level showed marked increases. The angiotensin 11 level was high. Serum gastrin was markedly increased and was not enhanced by exogenous secretin. 75 g OGTT exhibited impaired glucose tolerance, while HbA₁c was normal

<table>
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<tr>
<th>Table 1. Endocrinological tests</th>
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<tr>
<td>Pituitary: serum GH 7.8 ng/ml (below 5.0), plasma ACTH 83 pg/ml (15–85), serum LH 3.3 mIU/ml (4–19), serum FSH 15.1 mIU/ml (10–17.3), serum PRL 27.6 ng/ml (2–20)</td>
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<td>Thyroid: serum TSH 2.6 µU/ml (1–10), serum T₄ 14.0 µg/dl (5.6–11.2), Resin uptake 22.0% (23.2–38.4), serum T₃ 1.0 ng/ml (0.9–2.0), TBG 43.4 µg/ml (12–28)</td>
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<td>Parathyroid: serum PTH-C 0.78 ng/ml (0.20–1.00), %TRP 74.3% (85–98)</td>
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<td>Adrenal: plasma renin activity 50.8 ng/ml/h (0.5–2.0), serum aldosterone 1044.9 pg/ml (below 180), serum cortisol 24.7 µg/dl (4–15), plasma angiotensin II 620 pg/ml (below 110), urinary 17-OHCS 5.0 mg/day (1.9–6.1), urinary total 17-KS 1.1 mg/day (3.1–8.8), plasma adrenalin below 10 pg/ml (below 120), urinary adrenalin 4.4 µg/day (below 12), plasma noradrenalin 556 pg/ml (40–350), urinary noradrenalin 71.6 µg/day (10–90), plasma dopamine below 200 pg/ml (below 700), urinary dopamine 40 µg/day (100–700)</td>
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<td>Dexamethasone suppression test serum cortisol (23:00) 23.6 (8:00) 5.0 µg/dl</td>
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<td>GI Tract: serum gastrin 2362.3 pg/ml (42–200), serum secretin 94 pg/ml (60–120)</td>
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<td>Secretin loading test (before) serum gastrin 4123.8 pg/ml (3832.6–4463.4), (5 min) 3754.0, (10 min) 3049.6, (20 min) 3754.0, (40 min) 3754.0 pg/ml</td>
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<td>Pancreas: 75 g OGTT (before) serum insulin 3.5 (5.5), (30 min) 41.3 (41.3), (60 min) 167.1 (164.1), (90 min) 167.8 µU/ml (180min)</td>
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<td>Plasma glucose (88) 237 328 396 429 365 mg/dl</td>
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<td>HbA₁c 5.1% (4.0–6.5), plasma glucagon 227 pg/ml (70–160)</td>
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<tr>
<td>Miscellaneous: plasma PGE 538 pg/ml (below 320), urinary PGE 120 ng/day (below 200), urinary kallikrein 1.08 U/day (below 1.4)</td>
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Normal values are indicated in parentheses.
Fig. 2. Angiotensin II loading test.

Fig. 3. Noradrenalin loading test.
and glucose in 24 h urine was 0.24 g/day. The plasma PGE level was high, while urinary PGE and kallikrein levels were within normal limits. As shown in Fig. 2, the angiotensin II loading test did not cause an increase in blood pressure. As shown in Fig. 3, the noradrenalin loading test also did not increase blood pressure. The water loading chloride clearance test, which indicates chloride reabsorption by renal tubules, showed a slight decrease. In the ammonium chloride loading test, as shown in Fig. 4, the 8-h method (left panel) revealed a decrease in blood HCO$_3^-$ from 24.8 mEq/l to 18.8 mEq/l and disturbance of urinary acidification, while the 3-day method (right panel) revealed that urinary pH was decreased to the normal level (5.2) on the first day and second day but remained above 5.5 on the third day.

**Course**

This case was diagnosed as pseudo-Bartter’s syndrome induced by long-term administration of a laxative and chronic diarrhea. As shown in Fig. 5, the laxative was withdrawn and potassium, indomethacin and spironolactone were administered. However, the serum K level remained low. Serum gastrin, the number of peripheral blood platelets and serum TBG also remained increased. Body weight was decreased by 4 kg in 2 years and remained constant thereafter.

**Discussion**

Pseudo-Bartter’s syndrome is described as a syndrome which is caused by chronic vomiting (Veldhuis et al., 1979), chronic diarrhea, long term administration of laxative (Fleischer et al., 1969) or diuretics...
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(Tajiri et al., 1981; Jamison et al., 1982), anorexia nervosa (Wolff et al., 1968), cystic fibrosis (Davison and Snodgrass, 1983), cystinosis (Whyte et al., 1985), jejunoileal bypass for obesity (Julkunen et al., 1982) and chemotherapy (Lieber et al., 1984), and displays the same findings as those of Bartter's syndrome, namely an increase in plasma renin activity, an increase in serum aldosterone, hypokalemia, metabolic alkalosis, normo- or hypotension and decreased response of blood pressure to angiotensin 11 infusion (Bartter et al., 1962). The present case was diagnosed as pseudo-Bartter's syndrome induced by the long term administration of laxative and repeated diarrhea.

With regard to the pathogenesis of Bartter's syndrome, congenital hyporesponsiveness of peripheral arterioles to angiotensin 11 (Bartter et al., 1962), overproduction of prostaglandins in the kidney (Fichman et al., 1976; Gill et al., 1976) and disturbance of chloride reabsorption in
Henle’s loop (Gill and Bartter, 1978) have been reported. However, details of the pathogenesis remain unclear. In regard to the pathogenesis of pseudo-Bartter’s syndrome, especially that caused by chronic laxative abuse (Oster et al., 1980), cyclic vomiting or diuretic abuse, these factors induce sodium chloride and potassium depletion, leading to hypovolemia and hypokalemia, respectively. Hypovolemia causes hyper-reninemia, an increase in angiotensin 11 production and finally an increase in aldosterone production. Hypokalemia caused by these factors and hyperaldosteronemia induce an increase in vascular prostacyclin production (Galveg et al., 1977), leading to pressure insensitivity to angiotensin 11 and noradrenalin. The suppressive effects on blood pressure of hypovolemia and pressure insensitivity to angiotensin 11 and noradrenalin and the enhancing effects on blood pressure of increased blood angiotensin 11 and aldosterone levels were counterbalanced, leading to the maintenance of normal blood pressure. Hypovolemia causes constipation, which in turn obligates the use of laxatives and invites a vicious circle.

It has been reported that renal tubular dysfunction leading to impaired renal acidification is present in Bartter’s syndrome (Stein, 1985). Bartter’s syndrome happens to present features resembling renal tubular acidosis and vice versa (Rodriguez-Soriano et al., 1978; Takeda et al., 1973). Impaired renal acidification has also been reported in pseudo-Bartter’s syndrome induced by furosemide abuse (Tajiri et al., 1981). It is known that urine pH does not necessarily decrease in the ammonium chloride loading test in a potassium deficient state because hypokalemia enhances the production of ammonia, and that such an impaired renal acidification is normalized by potassium supplementation. In the present case, the acidification of urine in the ammonium chloride loading test was slightly disturbed and chloride reabsorption by renal tubules was slightly decreased, although the urinary excretion rate of sodium bicarbonate and the serum Mg level were normal. The plasma PGE level was high, while urinary PGE and kallikrein levels were normal. The kind of tubular dysfunction observed in this case is thought to be due to functional changes in renal tubules or tubular nephropathy caused by long-standing hypokalemia (Relman and Schwartz, 1956).

Hypergastrinemia has been reported to be caused in Zollinger-Ellison’s syndrome (Zollinger and Ellison, 1955), pernicious anemia, duodenal ulcer (Tam, 1988), carcinoid syndrome and chronic renal failure (Muto et al., 1988). In this case, Zollinger-Ellison’s syndrome was ruled out, because gastrin secretion was not enhanced by exogenous secretin, and upper gastrointestinal endoscopy and abdominal CT scan as well as the examination of gastric juice revealed no abnormalities. Renal function tests including Fishberg’s tests, PSP excretion, urinary BMG and renogram revealed renal dysfunction in this case, although serum creatinine and BUN levels showed slight increases. However, the hypergastrinemia observed in this case could not be explained by such a degree of renal dysfunction. As to the cause of hypergastrinemia in this case, further investigations are being performed. There has been no report associating Bartter’s syndrome or pseudo-Bartter’s syndrome with hypergastrinemia.

The hyperlipemia (Fredrickson type IIb) observed in this case might be caused by renal dysfunction or have occurred incidentally, independently of pseudo-Bartter’s syndrome. Although hyperglycemia was observed in 75 g OGTT, HbA1c was normal and analysis of 24 h urine revealed a small amount of sugar, suggesting that such a hyperglycemia is transient after meals and secondary to hypokalemia in pseudo-Bartter’s syndrome.

In regard to the thrombocytosis observed
in this case, we could not detect any definite cause inducing thrombocytosis, such as hematopoietic disorders, inflammatory diseases, neoplasm or essential thrombocytemia (Murphy, 1983), although polycythemia vera and chronic myeloblastic leukemia cannot be completely ruled out. There has been no report in which pseudo-Bartter’s syndrome is associated with thrombocytosis.

As to the causes of the increase in serum TBG, pregnancy, estrogen administration, acute intermittent porphyria, hypogammaglobulinemia, acute hepatitis and hepatoma as well as familial increase in serum TBG have been reported (Ross et al., 1983; Ramsden et al., 1983). In this case, however, we could not detect any cause of the increase in serum TBG except for a familial trait, which is now under investigation. There has been no report in which pseudo-Bartter’s syndrome is associated with an increase in serum TBG.

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