Pseudo-Bartter’s Syndrome due to Furosemide Abuse: Report of a Case and an Analytical Review of Japanese Literature

Junichi Tajiri, MD, Mahito Nakayama, MD, Tatsuo Sato, MD, Sadao Isozaki*, PhD and Katsuyoshi Uchino*, MD

Bartter’s syndrome characteristically exhibits the constellation of hypokalemic alkalosis, normotensive hyperreninism, hyperaldosteronism, hyporesponsiveness to pressor agent and juxtaglomerular cell hyperplasia. Recently, metabolic mimicry of Bartter’s syndrome by vomiting, diarrhea, laxatives and diuretics abuse has been reported. We had a 30 year-old female patient who developed so-called pseudo-Bartter’s syndrome as the result of surreptitious self-administration of furosemide for about six years. In this case, calcification of bilateral renal medulla was demonstrated. Such adverse reaction has not been reported to date. Moreover, a total 14 cases of pseudo-Bartter’s syndrome reported in Japanese literature is reviewed.

Key Words: Hypokalemia, Normotension, Plasma renin activity, Plasma aldosterone concentration, Nephrocalcinosis

Furosemide, a potential diuretic agent, has been widely used for edematous disorders. However, it is known that a variety of untoward effects, primarily electrolyte disturbance and volume depletion, has been attributed to the drug. Recently, furosemide dependence has been reported. The following case report describes a patient with pseudo-Bartter’s syndrome due to surreptitious self-administration of furosemide. This case had bilateral nephrocalcinosis, which was probably brought about by long-term administration of furosemide. Such adverse reaction had not been reported previously. We have collected a total 14 cases of pseudo-Bartter’s syndrome from Japanese literature to date and discuss on some interesting points.

CASE REPORT

A 30-year-old married woman was admitted to the 3rd department of Internal Medicine, Kumamoto University Hospital, on July 10, 1980, because of hypokalemia, muscle weakness and tetany. In 1974, she was in her second pregnancy, and edema in the face and bilateral legs, which was treated with furosemide for several weeks. After delivery, she was pointed out edematous face by her friends. Then, self-administration of furosemide, 80 mg daily, started. In 1976, she entered the local hospital with chief complaint of tetany, where hypokalemia was detected. However, she was discharged within several days, because the symptom disappeared. Although several attacks of tetany have been developed, she had neither been hospitalized nor stopped furosemide until June, 1980. She had been hospitalized elsewhere, and her serum potassium level was pointed out to be 2.0 mEq/L. Then she was referred to our clinic for evaluation of hypokalemia.

On admission, she was lean and some-
what nervous in appearance, but otherwise healthy woman. There was history of appendectomy and probe laparotomy for suspicion of ovarian tumor, but no tumor was found. She denied diarrhea, vomiting, and on repeated questioning any ingestion of laxatives, licorice, and diuretics. Her father died of prostatic cancer and her mother is now hospitalized because of cerebro-vascular diseases, but in normokalemia.

Her temperature was 36.8°C, the pulse 72; and the respiration 20. Multiple supine blood pressure determinations were in around 96/60 mmHg. Neither anemia nor jaundice was observed. Cervical lymph node and the thyroid gland were not enlarged. The heart and lungs were normal. There was no tenderness on abdomen, and the liver, spleen and kidneys were not palpable. No edema on the face and legs was found. The following laboratory tests were normal: blood count, urinalysis, blood sugar, serum creatinine, blood urea nitrogen, alkaline phosphatase, serum protein, plasma cortisol, T3, T4, TSH, PTH, 24 hours urinary excretion of 17-KS, and 17-OHCS.

Electrolyte values were as follows: serum Na was 139 mEq/L, K 2.0 mEq/L, Cl 88 mEq/L, Ca 9.1 mg/dl, P 2.9 mg/dl. Serum uric acid was 8.3 mg/dl. Urinary excretion of Na for 24 hours was 110-130 mEq, K 26-36 mEq, Ca 3.0-6.7 mEq, and Cl 112-135 mEq. Blood gas was disclosed metabolic alkalosis <pH 7.56, B.E. +9.9 mEq/L, bicarbonate 32.9 mEq/L). Plasma renin activity and plasma aldosterone concentration at the resting supine position were 6 ng/ml/hr (normal 0.25-1.4 ng/ml/hr) and 59.4 ng/dl (2.5-14.0 ng/dl), respectively. Plasma angiotensin I (AI) and angiotensin II (AII) as measured by radioimmunoassay were 56872 pg/ml (less than 200 pg/ml) and 5683 pg/ml (less than 60 pg/ml), respectively. Urinary excretion of prostaglandins E and F were 237 ng/L (less than 200 ng/L) and 668 ng/L (100-1500 ng/L), which were also measured by radioimmunoassay.

An angiotensin II infusion test was performed and the response curve of diastolic pressure is shown in Fig. 1. In this patient, critical dose was 100 ng/kg/min (body weight 59 kg), which caused a sustained elevation of diastolic pressure by 20 mmHg above the averaged control values. Normally, a hypertensive response with 20 mmHg elevation of the diastolic pressure is elicited with the infusion of less than 10 ng/kg/min of angiotensin. After infusion of normal saline 1000 ml for hour, critical dose decreased to 40 ng/kg/min, which caused the same effect (Fig. 1). In addition, the effect of AII converting enzyme inhibitor (SQ 14,225), 25 mg by mouth, was studied on blood pressure. Ten minutes later, her blood pressure decreased from 76/61 to 70/43 mmHg, and 30 minutes later, decreased to 62/32 mmHg. But 60 minutes later, it returned to 80/62 mmHg.

The result of renal function tests were as fellows: phenolsulfonphthalein excretion for the first 15 minutes was 12%, creatinine clearance 66.8 ml/min, and Fishberg's concentration test disclosed poor concentration ability, and maximum was only 269 mOsm/L. Renal response to ammonium chloride, 0.1 g/kg, revealed an impaired renal acidification. Urinary pH never become lower than 6.76. An electrocardiogram demonstrated T...
wave depression and presence of U wave. X-ray film of the chest was normal, but of the abdomen disclosed multiple calcific deposits in both kidneys. Drip infusion pyelogram showed a normal calyces and ureters, but the calcifications were present in the region of renal medulla. CT scan and ultrasonogram of the kidney also disclosed calcification of bilateral renal medulla (Fig. 2). The needle biopsy specimen from the kidney showed a hyperplasia of the juxta-glomerular apparatus and a focal vacuolisation of the tubular epithelium as shown in Fig. 3.

DISCUSSION

Bartter’s syndrome is a rare disorder characterized by hypokalemia, hyperreninism, hyperaldosteronism, normotension, juxta-glomerular cell hyperplasia, and resistance to the pressor effect of exogenous angiotensin. Recently, the majority of reports have emphasized prostaglandin mediation of the characteristic metabolic disturbance.

More precise evaluation of renal pathophysiology in Bartter’s syndrome has suggested a defect of chloride reabsorption in ascending-limb.

On the other hand, metabolic mimicry of Bartter’s syndrome by covert vomiting, diuretics abuse, and excessive laxatives taking has been reported. The syndrome caused by these agents was so called pseudo-Bartter’s syndrome. So far as we know, a total 14 cases of pseudo-Bartter’s syndrome have been reported in Japan up to date. Our case was the 15th. Table I summarizes sex, age and underlying cause of these cases. Fourteens of 15 cases were female, and ranged in age from 21 to 66 years. It was of interest that the patients suffering from anorexia nervosa were 9 of 15 cases.

In our case, many of the features of Bartter’s syndrome were present. Thus, the furosemide abuse could lead to the full constellation of metabolic abnormalities resembling Bartter’s syndrome. Since our patient denied vomiting, diarrhea, and laxatives, licorice or diuretics abuse, we diagnosed this patient as Bartter’s syndrome initially. She persisted in her denial of diuretic ingestion until her friend suggested us her furosemide intake. Then, furosemide in plasma and urine of the patient was determined by high performance liquid chromatograph using a spectrofluorometric detector and we obtained positive result, 0.85 µg/ml and 18 µg/ml, respectively. Careful subsequent inquiry revealed that she had self-administered furosemide 80 mg daily for four years and 300 mg per day for the last two years. Total dose of furosemide could be estimated about 330 g. Although the distinction between diuretics abuse and Bartter’s syndrome could be extremely difficult if patient denied, it is important to consider that the discontinuation of the drugs is associated with reversal of most abnormalities of the disorder. Thus, careful supervision and measurement of urinary output of the drugs should be necessary to differentiate such patient from Bartter’s syndrome.
Pseudo-Bartter’s syndrome

Table 1. Pseudo-Bartter’s syndrome reported in Japan.

<table>
<thead>
<tr>
<th>No</th>
<th>Author</th>
<th>Sex</th>
<th>Age</th>
<th>Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Nishimura. S, et al. (1973)</td>
<td>Male</td>
<td>18</td>
<td>Vomiting</td>
</tr>
<tr>
<td>3</td>
<td>Fujishiro. N et al. (1974)</td>
<td>Female</td>
<td>25</td>
<td>Anorexia nervosa</td>
</tr>
<tr>
<td>7</td>
<td>Sato. A, et al. (1978)</td>
<td>Female</td>
<td>42</td>
<td>Anorexia nervosa, Diuretics, Laxatives</td>
</tr>
<tr>
<td>8</td>
<td>Torii. S, et al. (1978)</td>
<td>Female</td>
<td>30</td>
<td>Anorexia nervosa, Diuretics, Laxatives</td>
</tr>
<tr>
<td>10</td>
<td>Matsuda. T, et al. (1979)</td>
<td>Female</td>
<td>33</td>
<td>Anorexia nervosa, Vomiting, Diarrhea</td>
</tr>
<tr>
<td>11</td>
<td>Mori. H, et al. (1979)</td>
<td>Female</td>
<td>27</td>
<td>Anorexia nervosa, Vomiting</td>
</tr>
<tr>
<td>12</td>
<td>Isok. K, et al. (1979)</td>
<td>Female</td>
<td>24</td>
<td>Furosemide abuse</td>
</tr>
<tr>
<td></td>
<td>Our patient (1980)</td>
<td>Female</td>
<td>30</td>
<td>Furosemide abuse</td>
</tr>
</tbody>
</table>

There have been eleven case reports concerning diuretics abuse. Of interest in this regard are data indicating that all cases are females, from 21 to 47 year-old. Young women are usual, like this case and most of them were anorexia nervosa. Accordingly, it seemed likely that psychiatric abnormalities such as anorexia nervosa, terror to weight gain, and depression state are closely related to development of pseudo-Bartter’s syndrome. Our patient was self-willed, not co-operative, and mentally immature. Unfortunately, Na-K balance study failed because the patient did not take hospital diet regularly.

Another interesting finding of this patient was calcification of bilateral renal medulla, nephrocalcinosis. She had no disorder, which developed nephrocalcinosis, for example, hyperparathyroidism, hypervitaminosis D, hypercalciuria, oxalosis, Milk-alkali syndrome, chronic pyelonephritis, and so on. In addition, no abnormal calcification except for the kidney was demonstrated.

There are some possibilities that caused nephrocalcinosis. Firstly, it is reported that furosemide has inhibitory effect on carbonic anhydrase like acetazolamide and nephrolithiasis. Since this usually established under acidosis, the cause seems unlikely because of her alkalosis. Secondly, it is well known that serum uric acid increases by administration of furosemide. The hyperuricemia could be brought about renal calculi. Most uric acid stone is radio-lucent, but in some cases, radio-opaque. Our patient had also slight hyperuricemia, but exact mechanism remained obscure. Thirdly, Tambyah and Lim reported increased urine calcium during the first 4–8 hours following administration of furosemide. Knapp and Heath confirmed furosemide induced hypercalciuria during the first 8 hours post furosemide but stated that, during the 8–24 hour post-dosage period, urinary calcium was decreased and that the 24 hour net calcium excretion was essentially unchanged. In this case, stone formation might occur during the first 8 ours. Finally, this patient has impaired renal acidification. Bartter’s syndrome associated with impaired renal acidification was often reported. In the original paper of Bartter et al, the second case had bilateral renal stone. However, in patients with pseudo-Bartter’s syndrome impaired renal acidification has never been reported. The nephrocalcinosis of this case

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might be due to, in part, renal tubular acidosis. Since previous abdominal X-ray films were not available, we could not certify when her nephrocalcinosis did start. Therefore, her nephrocalcinosis might be due to long-standing and abnormally large amount of furosemide abuse rather than renal tubular acidosis. Her impaired renal acidification might be secondary to concomitant nephrocalcinosis.

In conclusion, surreptitious diuretic usage has to be carefully excluded in an adult patient, particularly in female patients with weakness, tetany and normal blood pressure together with laboratory data consisted with Bartter’s syndrome. Simple screening test for the drugs in urine should be necessary.

REFERENCES


