

Bartter's Syndrome with Type 2 Diabetes Mellitus

Ting-Ting See¹, Siu-Pak Lee^{2*}

¹Section of Endocrinology and Metabolism, and ²Section of Neurology, Department of Internal Medicine, Far Eastern Memorial Hospital, Panchiao, Taipei, Taiwan, R.O.C.

We report a rare case of Bartter's syndrome in a 35-year-old woman with type 2 diabetes mellitus. The patient presented with leg weakness, fatigue, polyuria and polydipsia. Hypokalemia, metabolic alkalosis, and high renin and aldosterone concentrations were present, but the patient was normotensive. Gitelman's syndrome was excluded because of the presence of hypercalciuria, secondary hyperparathyroidism and bilateral nephrocalcinosis. The patient's condition improved upon administration of a prostaglandin synthetase inhibitor (acemetacin), oral potassium chloride and potassium-sparing diuretics. Five months later, the patient discontinued acemetacin because of epigastric discomfort; at the same time, severe hypokalemia and hyperglycemia developed. Glucagon stimulation and water deprivation tests were performed. Type 2 diabetes mellitus with nephrogenic diabetes insipidus was diagnosed. To avoid further gastrointestinal complications, the patient was treated with celecoxib, a selective cyclooxygenase 2 inhibitor. This case serves as a reminder that Bartter's syndrome is associated with various metabolic derangements including nephrogenic diabetes insipidus, nephrocalcinosis and diabetes mellitus. When treating Bartter's syndrome, it is also prudent to remember that the long-term use of nonsteroidal anti-inflammatory drugs and potassium-sparing diuretics may result in serious adverse reactions. [*J Chin Med Assoc* 2009;72(2):88–90]

Key Words: Bartter, diabetes mellitus, hypokalemia, syndrome

Introduction

Bartter's syndrome, a constellation of renal tubular disturbances, is characterized by hypokalemia, metabolic alkalosis with hyperreninemia, and hyperaldosteronism.¹ Clinically, patients may present with fatigue, polyuria and polydipsia. These signs and symptoms overlap with those manifested by patients with diabetes mellitus. Furthermore, hypokalemia may serve to promote glucose intolerance.² A MEDLINE search using "Bartter's syndrome" and "diabetes mellitus" as key words revealed 1 report of a case of Bartter's syndrome concurrent with type 1 diabetes mellitus over the past 40 years.³ The present report describes a rare case of Bartter's syndrome with type 2 diabetes mellitus and the various treatment modalities, including a selective cyclooxygenase 2 (COX-2) inhibitor, utilized. The relationship between Bartter's syndrome and diabetes mellitus is explored.

Case Report

A 35-year-old woman with bilateral leg weakness, fatigue, polyuria and polydipsia consulted the outpatient clinic of Far Eastern Memorial Hospital. Routine blood tests revealed a serum potassium level of 2.2 mmol/L. Her fasting blood glucose was 108 mg/dL, serum calcium was 9.6 mg/dL, serum sodium was 134 mmol/L, and serum chloride was 87 mmol/L. Physical examination was unremarkable. She was normotensive with normal hearing ability. Her blood pressure was 102/70 mmHg, body weight was 58 kg, and height was 162 cm. She was not on any medications, including diuretics. She denied family history of hypokalemia, diabetes mellitus or renal stone.

Further work-up was performed to evaluate the hypokalemia (Table 1). Venous blood gas measurements revealed metabolic alkalosis. Her urinary potassium, calcium and chloride excretion rates were increased.



*Correspondence to: Dr Siu-Pak Lee, Section of Neurology, Department of Internal Medicine, Far Eastern Memorial Hospital, 21, Section 2, Nan-Ya South Road, Panchiao, Taipei 220, Taiwan, R.O.C.
E-mail: siupakmd@ms1.hinet.net • Received: April 14, 2008 • Accepted: September 9, 2008

Table 1. Laboratory workups to evaluate hypokalemia

	Results	Normal values
Urine potassium (mmol/d)	53.2	<25
Urine chloride (mmol/d)	38.1	<20
Urine calcium (mg/kg/d)	7.47	<4
Renin (pg/mL)	142	1.80–59.40
Aldosterone (pg/mL)	792	38–313
Serum pH	7.475	7.30–7.45
PCO ₂ (mmHg)	47.9	32–46
HCO ₃ ⁻ (mmol/L)	34.5	21–29

There was hyperreninemic hyperaldosteronism. Serum creatinine, calcium, phosphate and magnesium levels were normal. Intact parathyroid hormone was 196 pg/dL (normal, 12–65 pg/dL). A parathyroid scan with Tc-99m MIBI injection showed bilateral parathyroid hyperplasia, but bone mineral density was normal. Renal ultrasound revealed bilateral nephrocalcinosis. A diagnosis of Bartter's syndrome was made.

A prostaglandin synthetase inhibitor (acemetacin, 60 mg), oral potassium chloride (600 mg), and spironolactone (25 mg) were administered 3 times daily. One week following initiation of this regimen, polyuria and polydipsia were relieved and the potassium value had increased to 3.3 mmol/L. Four months later, the patient discontinued acemetacin because of epigastric discomfort.

Five months later, however, she visited the emergency room due to epigastric pain, vomiting and general weakness. Her potassium was 1.9 mmol/L, random blood glucose was 383 mg/dL, and hemoglobin A1c (HbA1c) was 11.8%. Arterial blood gas measurements revealed metabolic alkalosis; ketones were not present in serum or urine. Upon admission for further management, fluid and potassium replacements were administered. The patient's blood glucose and potassium values improved. A glucagon stimulation test was performed. Fasting C-peptide level was 6.5 ng/mL (normal, 1.00–7.60 ng/mL); 6 minutes after glucagon injection, this value rose to 8.2 ng/mL. Although blood glucose values stabilized, polyuria remained. The patient then underwent a water deprivation test. After 12 hours of water deprivation, serum osmolality was 298 mOsm/kg and urine osmolality was 175 mOsm/kg. One hour after injection of vasopressin, urine osmolality was 198 mOsm/kg. These findings supported the presence of nephrogenic diabetes insipidus. Glimepiride (2 mg) and metformin (500 mg) were administered twice daily to control blood glucose. To decrease the possibility of epigastric pain while controlling potassium, the selective COX-2 inhibitor celecoxib (200 mg once daily)

was substituted for acemetacin. The patient's condition stabilized, with potassium values maintained at approximately 3 mmol/L and HbA1c values maintained at approximately 7%.

Discussion

In Bartter's syndrome, a transporter defect at the thick ascending limb of Henle's loop disrupts sodium and chloride reabsorption.⁴ Decreased sodium reabsorption also reduces the electrical gradient driving calcium and magnesium reabsorption, resulting in hypomagnesemia and hypercalciuria.⁴ The resultant hypercalciuria favors formation of renal stones and secondary hyperparathyroidism.⁵ An increase in circulating parathyroid hormone concentrations can promote bone resorption such that osteopenia or osteoporosis may develop. However, our patient with high parathyroid hormone concentrations exhibited normal bone mineral density of the lumbar spine as detected by dual-energy X-ray absorptiometry. The reason why our patient maintained a normal lumbar spine bone mineral density is probably due to the fact that the spine is rich in trabecular bone. It has been reported that the usual pattern in hyperparathyroidism is lower bone mineral density at sites rich in cortical rather than trabecular bone (forearm > hip > spine).⁶

The hypokalemia of Bartter's syndrome can be highly refractory to pharmacotherapy. Although potassium administered orally at high doses usually does not suffice as single therapy, addition of potassium-sparing diuretics may prove helpful. Reduction of prostaglandins with indomethacin has proven efficacious in maintenance of potassium values.³ Long-term use of this cyclooxygenase inhibitor in subjects with Bartter's syndrome, however, is associated with gastrointestinal bleeding and renal failure.¹ The angiotensin-converting enzyme inhibitors (ACEIs) enalapril and captopril have also been used to treat Bartter syndrome.⁷ However, hypotension was observed in some type 2 diabetic patients during the first few days of treatment with these agents.⁸ Propranolol has been used successfully in some patients to alleviate hypokalemia through reductions in renin and aldosterone.⁹ It should be noted, however, that ACEIs and propranolol were not found to be beneficial in the treatment of Bartter's syndrome in other studies.⁴

There was probably a delay in the diagnosis of glucose intolerance in our patient because her fasting blood glucose was 108 mg/dL during her initial visit. The disability of urinary concentration in Bartter's syndrome aggravated the patient's hyperglycemia. Patients

with Bartter's syndrome display elevated insulin concentrations, with hyperplasia of the islets of Langerhans as noted at autopsy.³ However, insulin secretion is decreased in hypokalemia,^{2,3} and potassium infusions improve glucose tolerance by increasing insulin and proinsulin concentrations.¹⁰ We should be aware of the fact that Bartter's syndrome is associated with various metabolic and electrolyte derangements. Treatment can be complicated, and the long-term use of NSAIDs and potassium-sparing diuretics in this disorder remains a challenging issue for clinicians.

References

1. Vaisbich MH, Fujimura MD, Koch VH. Bartter syndrome: benefits and side effects of long-term treatment. *Pediatr Nephrol* 2004;19:858-63.
2. Zillich AJ, Garg J, Basu S, Bakris GL, Carter BL. Thiazide diuretics, potassium, and the development of diabetes: a quantitative review. *Hypertension* 2006;48:219-24.
3. Venkat Raman G, Albano JD, Millar JG, Lee HA. Bartter's syndrome and diabetes mellitus. *J Intern Med* 1990;228:525-31.
4. Shaer AJ. Inherited primary renal tubular hypokalemic alkalosis: a review of Gitelman and Bartter syndromes. *Am J Med Sci* 2001;322:316-32.
5. Watanabe T, Tajima T. Renal cysts and nephrocalcinosis in a patient with Bartter syndrome type III. *Pediatr Nephrol* 2005;20:676-8.
6. Silverberg SJ, Bilezikian JP. Evaluation and management of primary hyperparathyroidism. *J Clin Endocrinol Metab* 1996;81:2036-40.
7. Hene RJ, Koomans HA, Dorhout Mees EJ, vd Stolpe A, Verhoef GE, Boer P. Correction of hypokalemia in Bartter's syndrome by enalapril. *Am J Kidney Dis* 1987;9:200-5.
8. Chen HS, Wu TE, Jap TS, Lee SH, Wang ML, Lu RA, Chen RL, et al. Decrease heart rate variability but preserve postural blood pressure change in type 2 diabetes with microalbuminuria. *J Chin Med Assoc* 2006;69:254-8.
9. Schwartz GJ, Cornfeld D. Letter: Propranolol in Bartter's syndrome. *N Engl J Med* 1974;290:966.
10. Gorden P, Sherman BM, Simopoulos AP. Glucose intolerance with hypokalemia: an increased proportion of circulating proinsulin-like component. *J Clin Endocrinol Metab* 1972;34:235-40.