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CASE REPORT

Renal Sodium Handling Study in an Atypical Case of Bartter's Syndrome Associated with Mitochondriopathy and Sensorineural Blindness

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ABSTRACT

Bartter's syndrome is a disorder that has been linked to mutations in one of three ion transporter proteins: NKCC2 (type I), ROMK (type II) and CCLNKB (type III), which affects a final common pathway that participates in ion transport by thick ascending limb cells. We present an atypical case of mitochondriopathy combined with tubule functional disturbances compatible with Bartter's syndrome and definitive sensorineural blindness. Our patient had a peculiar clinical presentation with signs of salt and volume depletion, low blood pressure and secondary hyperaldosteronism, associated with hypokalemic metabolic alkalosis, hypocalcemia and severe hypomagnesemia, uncommon in genetic forms of Bartter's syndrome. The enhanced absolute and fractional sodium excretion in our patient compared to volunteers was accompanied by increased post-proximal sodium rejection, suggesting a striking ion transport dysfunction in these nephron segments. These findings lead to the Bartter's syndrome diagnosis, accompanied by a suppose mitochondrial tick ascending loop of Henle epithelium dysfunction that may reflect the high energy supplied by mitochondria electron transport chain, required for this nephron segment to maintain normal ion transport.

Key Words: Bartter's syndrome; Mitochondriopathy; Sodium excretion; Lithium clearance.

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INTRODUCTION

Mitochondrial cytopathies are caused by genetic alterations of nuclear or mitochondrial encoded genes involved in the synthesis of subunits of the electron transport chain.[1] Mutations of mitochondrial DNA have long been regarded as neuromuscular diseases. However, the ubiquitous nature of mitochondria and their role in cellular metabolism may give rise to dysfunction in other organs or tissues, which are dependent upon mitochondrial supply, including renal dysfunction.[2] The most frequent is proximal tubular dysfunction, with various degrees of Fanconi syndrome. A few patients have been reported with tubular acidosis, chronic tubulointerstitial nephritis, nephrotic syndrome, focal-segmental glomerulosclerosis and renal failure.[2–4] The diagnosis of these disorders is made through careful clinical evaluation, coupled with biochemical, morphologic, and molecular biologic techniques.

In 1962, Bartter and his colleagues described a syndrome consisting of hypokalemia, chronic metabolic alkalosis, salt wasting and extra cellular fluid volume depletion, hyperreninemia, hyperaldosteronism, and juxtaglomerular apparatus hyperplasia.[5] The patients are usually normotensive despite the hyperactivity of the renin-angiotensin aldosterone system. Resistance to the pressor effects of angiotensin II and norepinephrine is characteristic. The primary defect in this rare disorder is considered to be renal tubular dysfunction. Its occurrence in siblings, with involvement of a single generation, is consistent with autosomal recessive heredity. Bartter's syndrome has been diagnosed early in childhood as well as later in life. Occasionally, it may be discovered in a patient who was incidentally noted to have hypokalemia.

Bartter's syndrome is a disorder that has been linked to mutations in one of three ion transporter proteins: NKCC2 (type I), ROMK (type II) and CCLNKB (type III), which affects a final common pathway that participates in ion transport by thick ascending limb cells.

CASE REPORT

Our patient is a 45-year-old white woman that has been followed at State University of Campinas Clinical Hospital and referred to Internal Medicine ambulatory for investigation of persistent hypokalemia. She had a history of subnormal vision, anemia, muscular weakness, cramps and recurrent infections (pulmonary and urinary) in childhood, managed and treated in her hometown with blood transfusions and antibiotic therapy until the age of 19, when she came to this hospital for further investigation. She was admitted with cramps and was not taking the prescribed treatment (KCl solution, calcium carbonate, spironolactone and pidolate magnesium). In the course of the physical examination she was tachycardiac, dehydrated and her arterial pressure was 90×60 mmHg. There was a history of tobacco addiction, 1 pack/day for 20 years. Her pertinent laboratory findings were hyponatremia (129 mmol/L), hypokalemia (2.1 mmol/L), hypocalcemia (0.85 mmol/L), hypomagnesemia (0.96 mmol/L), hypochloremia (79 mmol/L) and inorganic hyperphosphatemia (5.3 mmol/L), with moderate alkalosis (serum pH 7.51, PCO2 41.9 mmHg, PO2 87.1 mmHg, and HCO3 33.9 mmol/L). The anion gap was 16.2 mmol/L and osmolality 260 mmol/kg. Urine analysis showed sodium (88 mEq/L), potassium (42 mEq/L), calcium (10 mg/dL) and creatinine (25 mg/dL). Urinary sediment was normal with a pH of 6.0 and density of 1015. Protein, glucose, TSH, T4 and T3 plasma levels were normal. A high plasma renin level at rest was found (19.5 ng/mL/h) at a normossodic diet intake (normal range: 0.15 – 2.33 ng/mL/h). Autoimmune screening and HCV serology were negative and positive, respectively. Creatinine clearance (CCr), used to estimate the glomerular filtration rate and

Table 1. Characteristics of urinary sodium handling (UNaV), studied by CLi, CCr and urine potassium (UKV) excretion in control individuals as compared with the bartter's syndrome patient.

Parameters	Control subjects (n=11)	Bartter's syndrome patient
UNa V, mmol/min	0.1±0.03	0.25
UK V, mmol/min	0.05±0.01	0.05
CLi, mL/min	32±4.2	10
CCr, mL/min	137±11.7	113
FENa, %	0.63±0.19	1.62
FENa proximal, %	23±2.2	8.9
FENa distal, %	2.6±0.8	18.2

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lithium clearance (CLi),[6,7] used to estimate the sodium output from the proximal tubule were calculated by standard formulas. Fractional excretions (FE) were calculated as FENa=CNa/CCr, FENa proximal=CLi/CCr, and FENa distal=CNa/CLi (Table 1). Our patient was also submitted to tests of urinary and plasmatic concentration. The initial levels (274 mmol/kg and 291 mmol/kg) for plasmatic and urinary osmolarity, respectively, reach a urinary (265 mmol/kg) and plasmatic level (324 mmol/kg) six hours after water privation. A muscle biopsy showed mitochondrial myopathy (mitochondrialis) with lipid accumulation in muscle fibers and preponderance of type I muscle fibers. Blood marrow biopsy disclosed sideroblastic anemia. Her vision deteriorated to definitive sensorineural blindness when she was 25 years old. A funduscopy revealed just bilateral optic nerve atrophy.

DISCUSSION

We present an atypical case of mitochondriopathy combined with tubule functional disturbances compatible with Bartter's syndrome and definitive sensorineural blindness. The patient had a peculiar clinical presentation with signs of salt and volume depletion, low blood pressure and secondary hyperaldosteronism, associated with hypokalemic metabolic alkalosis, hypocalcemia and severe hypomagnesemia, uncommon in genetic forms of Bartter's syndrome. The glomerular filtration rate estimated by creatinine clearance and the calculated filtrated sodium load were unchanged compared to control volunteers. The enhanced absolute and fractional sodium excretion in our patient compared to volunteers was accompanied by increased post-proximal sodium rejection, suggesting a striking ion transport dysfunction in these nephron segments. Despite accentuated hypokalemia, the urinary potassium excretion was normal and similar to that observed in control subjects, probably as result of secondary hyperaldosteronism. In the present case, increased FENa associated with normal urinary potassium excretion despite secondary hyperaldosteronism also confirm a tubule transport disorder in the loop of Henle. The increased proximal sodium reabsorption may reflect an additional homeostatic effort to keep the hydrosaline body balance (see Table 1) of the patient. Consistently with a defect of thick ascending limb cells, the patient shows persistent hypocalcemia and hypomagnesemia suggesting also incapacity of the NKCC2 and/or ROMK ion transporter proteins to create a transepithelial lumen-positive voltage potential related to passive paracellular calcium and magnesium influx to basolateral tubule side. Although urinary calcium and potassium are in the normal range, this could be explained by a state of chronic depletion of these electrolytes, and would reflect a disproportionate waste in view of low plasmatic concentrations of these cations. These findings taken together lead to the Bartter's syndrome diagnosis, accompanied by mitochondrial tick ascending loop of Henle epithelium dysfunction that may reflect the high energy supplied by mitochondria electron transport chain, required for this nephron segment to maintain normal ion transport.

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