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Severe hyponatremia occurring after surgical stress in a patient with mitochondrial disease

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Abstract
A 53-year-old man with mitochondrial disease underwent gastrectomy because of gastric cancer. Three days after the surgery, he developed severe hyponatremia (Na, 106 mmol·l^{-1}) together with hypovolemic shock and lactic acidosis. Despite the hyponatremia, his urine sodium concentration was high, suggesting renal salt wasting. Although mitochondrial diseases are not common and hyponatremia in patients with these diseases is not well known, clinicians should pay close attention to serum sodium levels and maintain them properly.

Key words Mitochondrial disease · MELAS · Hyponatremia · Renal salt wasting · Na/K-ATPase

Introduction

Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS), one of the most common maternally inherited mitochondrial diseases, is a multisystem disorder caused by dysfunction of oxidative phosphorylation in mitochondria. MELAS is clinically characterized by: (1) encephalopathy, frequently manifesting as dementia, seizures, or both; (2) evidence of mitochondrial dysfunction in the form of lactic acidosis, ragged-red fibers, or both; and (3) stroke-like episodes [1]. Other clinical features include hearing loss, muscle weakness, short stature, diabetes mellitus, peripheral neuropathy, visual disturbance, external ophthalmoplegia, and cardiomyopathy, among others [2]. We describe severe hyponatremia, possibly due to excessive renal sodium wasting, occurring after gastrectomy in a patient with MELAS.

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Case report

A 53-year-old man underwent gastrectomy because of advanced gastric cancer. He had a medical history of diabetes mellitus of more than 20 years' duration and had had sensorineural hearing loss for 10 years. Starting in his thirties, he began having episodes of dizziness and limb weakness. At the age of 45, he had undergone muscle biopsy and genetic testing at another hospital, and was diagnosed at that time with MELAS.

A preoperative physical examination revealed that the patient had a short stature (147 cm), cachexia, and severe muscle wasting (body weight, 30 kg). He could not walk on his own and showed no tendon reflex. He had not been taking any medications. Preoperatively, laboratory data showed anemia (hemoglobin [Hb], 9.9 g·dl^{-1}), hyperglycemia (glucose, 191 mg·dl^{-1}), and normal concentrations of electrolytes (Na, 135 mmol·l^{-1}; K, 4.9 mmol·l^{-1}; Cl, 98 mmol·l^{-1}; Ca, 9.2 mg·dl^{-1}), normal renal function (blood urea nitrogen [BUN], 18 mg·dl^{-1}; creatinine [Cre], 0.6 mg·dl^{-1}), and slightly high lactate (29 mg·dl^{-1}). A pulmonary function test revealed decreased vital capacity (2000 ml; 63%) and normal forced expiratory volume (FEV) 1.0% of 88%. His ECG was normal, and an ultrasound cardiography examination showed good contractility in the left ventricle.

This patient's anesthetic management has been reported in detail previously [3]. The operating time was 2 h and 20 min, and the surgical procedure was uneventful, with blood loss of 127 ml. Because the patient showed respiratory insufficiency with mild hypercarbia (Pa_{CO_2}, 55 mmHg) probably due to both respiratory muscle weakness and residual anesthetics, and because he also required dopamine, at 5 μg·kg^{-1}·min^{-1}, he was treated in the intensive care unit (ICU). Three hours after the surgery, he was successfully weaned from a ventilator and his trachea was extubated. The next day he was transferred to the surgical

Table 1. Laboratory examination on the third postoperative day

pH 7.40	Na 106 mmol·l^{-1}	WBC 5500 mm^{-3}
Pa_{CO_2} 17 mmHg	K 3.6 mmol·l^{-1}	RBC 3.8×10^6 mm^{-3}
Pa_{O_2} 63 mmHg	Cl 85 mmol·l^{-1}	Ht 34.3 %
Base excess –12 mmol·l^{-1}	Ca 8.2 mmol·l^{-1}	Hb 12.6 g·dl^{-1}
	BUN 10 mg·dl^{-1}	Plt 111×10^3 mm^{-3}
	Cre 0.5 mg·dl^{-1}	
	Glu 152 mg·dl^{-1}	
	CRP 2.7 mg·dl^{-1}	
	Lac 80 mg·dl^{-1}	
	sOsm 242 mOsm·kg^{-1}	

BUN, blood urea nitrogen; Cre, creatinine; Glu, glucose; CRP, C-reactive protein; Lac, lactate; sOsm, serum osmolarity; Ht, hematocrit; Hb, hemoglobin; Plt, platelets

ward, where he presented with slight hyponatremia (Na, 132 mmol·l^{-1}).

On the third postoperative day, he developed respiratory failure and circulatory collapse, with blood pressure 60/40 mmHg and heart rate (HR) 110 bpm. He was afebrile (body temperature, 36.5°C). Arterial blood gas analysis showed hypoxia and metabolic acidosis. Laboratory examination revealed severe hyponatremia, hyperlactatemia, and hypotonic serum osmolarity (Table 1). Chest roentgenography showed no remarkable abnormality. Ultrasound cardiography showed good left ventricle contraction, and collapse of the inferior vena cava, indicating hypovolemic shock.

The patient was returned to the ICU. He was conscious. Because of his severe respiratory distress, his trachea was intubated and his lungs ventilated. His central venous pressure was 2 cmH_2O. Despite the hyponatremia, his urine sodium concentration was 78 mmol·l^{-1} with urine osmolarity of 257 mOsm·kg^{-1}, which was almost the same as the serum osmolarity and implied renal sodium wasting. Urine output was more than 6000 ml in the first 2 days after surgery, suggesting salt and water depletion, which caused hypotonic hyponatremia with a decrease in the extracellular fluid volume. In the ICU, 500 ml of 0.9% saline was administered in the first 1 h in addition to a maintenance fluid (Na, 35 mmol·l^{-1}) infusion. Then, an additional 500 ml of 0.9% saline and 1000 ml of bicarbonated Ringer's solution (BICARBON injection; Ajinomoto, Tokyo, Japan; Na, 135 mmol·l^{-1}), which has a physiologic concentration (25 mmol·l^{-1}) of bicarbonate, were administered in the next 5 h, followed by 500 ml of 0.9% saline and 500 ml of bicarbonated Ringer's solution administration for 24 h (Fig. 1). To maintain his blood pressure, dopamine administration at 8 μg·kg^{-1}·min^{-1} was required. The metabolic acidosis soon recovered, to a base excess of –1 mmol·l^{-1}, in 6 h. The hyperlactatemia gradually resolved in 30 h, to a lactate level of 22 mg·dl^{-1}. The hyponatremia also slowly resolved in 3 days, to a serum sodium level of the order of 130 mmol·l^{-1}. He remained normokalemic throughout. He developed pneumonia and required respiratory support for 7 days because of respiratory muscle weakness. Subsequently, he was successfully weaned from ventilatory support and extubated. He was transferred to the surgical ward with a minitracheostomy tube in his trachea for the suction of sputum.

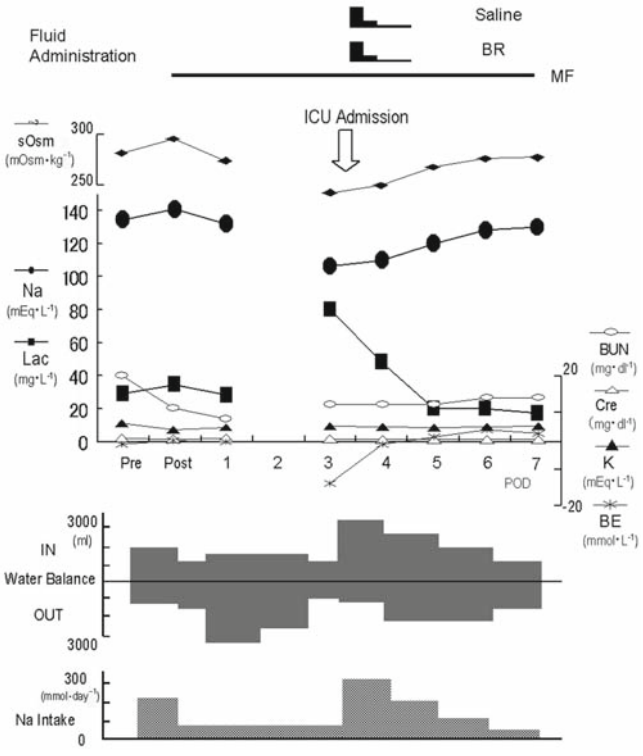

Fig. 1. Time course of laboratory data and water balance. The patient developed polyurea on postoperative day (*POD*) 1 and POD 2. On POD 3, the patient developed circulatory collapse and severe hyponatremia. *BR*, Bicarbonated Ringer's solution (Na, 135 mEq·l^{-1}; K, 4 mEq·l^{-1}; Ca, 3 mEq·l^{-1}; Mg, 1 mEq·l^{-1}; Cl, 113 mEq·l^{-1}; HCO_3, 25 mEq·l^{-1}; citrate, 5 mEq·l^{-1}); *MF*, maintenance fluid (Na, 35 mEq·l^{-1}; K, 20 mEq·l^{-1}; Ca, 5 mEq·l^{-1}; Mg, 3 mEq·l^{-1}; Cl, 28 mEq·l^{-1}; acetate, 20 mEq·l^{-1}; gluconate, 5 mEq·l^{-1}; P, 10 mmol·l^{-1}; glucose, 100 g·l^{-1}); *sOsm*, serum osmolarity; *Lac*, lactate; *Pre*, preoperation; *Post*, postoperation; *BUN*, blood urea nitrogen; *Cre*, creatine; *BE*, base excess; *ICU*, intensive care unit

While awaiting transfer to a referring hospital, the patient remained stable in the ward for 3 weeks, with a serum sodium level of 133–138 $mmol \cdot l^{-1}$, until he suddenly died, from probable aspiration.

Discussion

Patients with mitochondrial disease present to the ICU with a variety of neurological, metabolic, and respiratory impairments in various combinations [4]. In most mitochondrial diseases, the impairment of energy supply caused by mitochondrial DNA mutations appears to be the central pathogenic factor. Consequently, these patients present with a wide variety of multisystemic degenerative disorders across tissues. Brain and muscle are usually affected, and other tissues that have high-energy requirements can often be affected. In addition, organs or cells that contain a high proportion of mutant mitochondrial DNA can manifest symptoms [5].

In general, the causes of hypotonic hyponatremia with decreased volume of extracellular fluid include renal sodium loss caused by diuretic agents, osmotic diuresis (glucose, urea, mannitol), adrenal insufficiency, salt-wasting nephropathy, bicarbonaturia (renal tubular acidosis, disequilibrium stage of vomiting), ketonuria [6], and cerebral salt-wasting syndrome [7]. Causes also include extrarenal sodium loss caused by diarrhea, vomiting, blood loss, excessive sweating, and fluid sequestration in the "third space" (caused by bowel obstruction, peritonitis, pancreatitis, muscle trauma, and burns) [6].

Although mitochondrial diseases have been reported to present renal symptoms such as nephropathy, de Toni-Debré-Fanconi syndrome, Bartter syndrome, tubulointerstitial nephritis, and tubular acidosis [8], hyponatremia has not received much attention. Kubota et al. [9] demonstrated that four of seven MELAS patients developed episodic hyponatremia due to renal salt wasting, which, the authors concluded, could have multiple etiologies, such as relative adrenal insufficiency, acute renal failure, and cerebral salt wasting. Southgate and Penney [10] reported that a patient with Kearns-Sayer syndrome, another mitochondrial cytopathy, developed recurrent acute hyponatremia with natriuretic episodes. The patient showed polyurea followed by dehydration and hyponatremia, i.e., salt and water depletion. They concluded that the failure of the energy-dependent sodium reabsorption pump, i.e., Na/K-ATPase, in the renal tubular cells might have been the cause of the recurrent renal salt wasting [10]. Howard et al. [4] reported two cases of hyponatremia due to the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) in patients with mitochondrial diseases during treatment in the ICU.

It is noteworthy that all of these hyponatremic episodes occurred in patients who had some acute illness, such as stroke-like episodes and/or exacerbated heart failure [9] and infection [4,10]. These acute illnesses probably increased their energy demand, which in turn may have affected mitochondrial ATP synthesis in the renal tubular cells and, hence, reduced energy-dependent sodium reabsorption (Na/K-ATPase) in the kidneys [10]. This may have been the case in the present patient. Increased energy demand as a result of surgical stress may have caused a mismatch between energy requirements and availability, particularly in the renal tubular cells, and, hence, reduced sodium reabsorption via Na/K-ATPase.

Another possible cause of hyponatremia in the present patient could have been cerebral salt-wasting syndrome. MELAS patients develop central nervous system disorders. Cerebral salt-wasting syndrome, defined as renal sodium loss during intracranial disease, leads to hyponatremia and to a decrease in extracellular fluid volume [7].

In general, postoperative hyponatremia is mainly caused by elevated antidiuretic hormone (ADH) levels [6] as part of the stress response, which causes free water to be retained. This was unlikely to have occurred in the present patient, because the patient had polyurea and developed hypovolemia. His urine was not concentrated, which is inconsistent with the effects of ADH. Similarly, SIADH was unlikely in the present patient. SIADH is associated with a normal or increased volume of extracellular fluid and higher urine osmolarity than serum osmolarity [6,7], neither of which factors was consistent with the findings in the present patient.

Hyponatremia together with circulatory collapse implies adrenal insufficiency. The pathologic condition of MELAS could cause disorder somewhere in the hypothalamic-pituitary-adrenal axis, causing adrenal insufficiency. This does not seem to have been the case in the present patient, considering his smooth, rapid recovery from circulatory collapse through only fluid resuscitation and inotrope administration and without steroid supplementation, although no hormonal data were available.

For the treatment of hyponatremia, it is important to evaluate the volume status together with the urine sodium level. When hypovolemia and renal salt wasting are detected, external fluid resuscitation and careful sodium replacement are essential. Administration of 0.9% saline will be effective in patients with mitochondrial diseases as well, as described by Southgate and Penney [10]. Administration of lactated Ringer's solution should be avoided because lactate metabolism is impaired in patients with mitochondrial disorders [11]. Bicarbonated Ringer's solution may be beneficial to correct a base deficit when it is accompanied by severe

metabolic acidosis [12]. Rapid correction of hyponatremia by administering hypertonic saline should also be avoided, in order to prevent osmotic demyelination [6].

In conclusion, patients with mitochondrial diseases present with various symptoms. Although mitochondrial diseases are not common, and hyponatremia in these patients is not well known, clinicians should pay close attention to serum sodium levels and maintain them properly, especially in cases where there are stressful events in patients with mitochondrial diseases.

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