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BRIEF REPORT

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Pseudo-Bartter syndrome in a pregnant mother and her fetus

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Abstract Pseudo-Bartter syndrome presents the same clinical and biological characteristics as Bartter syndrome but without primary renal tubule abnormalities. We relate the case of a premature baby presenting at birth with severe hypokalemic metabolic alkalosis associated with hyponatremia and hypochloremia. Maternal blood at the time of delivery showed the same electrolyte perturbations. The baby's mother had suffered from anorexia and vomiting during pregnancy. A few weeks after birth the baby's blood abnormalities had almost returned to normal. Chloride depletion is at the origin of both maternal and fetal hypokalemic alkalosis.

Keywords Pseudo-Bartter syndrome · Eating disorders · Hypokalemia · Hypochloremia · Metabolic alkalosis · Placental electrolyte exchange · Fetus · Neonate

Introduction

It was in 1962 that Bartter et al. first described the cases of two patients presenting with biochemical disorders (i.e., hypokalemic metabolic alkalosis, hyperreninemia and hyperaldosteronism), normal blood pressure, and hyperplasia of the juxtaglomerular apparatus [1]. Molecular biology allowed the determination of four Bartter genotypes. These genotypes share the same combination of biochemical abnormalities but proceed from different molecular defects at the renal tubule level. Mutations in four genes have been identified to date: the Na-K-2Cl cotransporter (NKCC2), the K channel (ROMK), and the chloride (CIC-Kb) and (ClC-Ka) (Barttin) channels [2, 3]. A variety of other clinical conditions has been anecdotally described in the literature under the terms "secondary Bartter syndrome" (due to diuretic abuse and prostaglandin infusion) or "pseudo-Bartter syndrome" (due to chloride deficient diets, chronic vomiting, and laxative abuse) [4–6].

In this article the unexpected occurrence of severe pseudo-Bartter syndrome is described at birth in both a mother and her neonate. These disorders appear to be related to a state of anorexia associated with chronic vomiting during the pregnancy, which was denied by the mother. Some hypotheses are advocated to explain the electrolyte abnormalities observed in the mother and her fetus.

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Case report

A 39-year-old woman was seen for her fourth pregnancy. Previous pregnancies had been normal. The patient usually weighed 46 kg and was 1.66 m tall. Her body mass index (BMI) was 16.7 kg/m^2. She was a physician. Her family background and personal and medical history were unremarkable. She would, however, later reveal that she was suffering from a "slight eating disorder with vomiting events". The course of the pregnancy was uneventful until 34 weeks' gestation, at which time routine fetal monitoring showed signs of fetal distress. The mother was neither dehydrated nor hypotensive (110/55 mmHg) on admission into the maternal intensive care (MIC) unit. An emergency cesarean section was performed. The baby girl's birth weight was 2,330 g (50th percentile); her height was 45.5 cm (25th to 50th percentile) and her head circumference 31 cm (25th percentile). The Apgar score was 7-8-9, respectively, at 1 min, 5 min and 10 min. She exhibited respiratory distress soon after birth, requiring a CPAP device for respiratory assistance. Initial clinical examina-

tion showed generalized hypotonia. Blood pressure was within the normal range. Glycemia was very low (<20 mg%). An intravenous glucose perfusion and afterwards glucagon and hydrocortisone were together unable to control the glycemia at a sufficiently safe level. A supply of diazoxide allowed stabilization of the glucose level. Diazoxide and glucose supplementation were stopped after a few days in view of the normal level of glycemia. CPAP respiratory assistance was stopped after 41 h.

Laboratory investigations after her admission into the neonatal intensive care unit (NICU) showed (Table 1) hyponatremia (126 mmol/l), hypochloremia (66 mmol/l) and severe hypokalemia (2.2 mmol/l), together with metabolic alkalosis [pH 7.46; pCO_2 72 mmHg; base excess (BE) 23 mmol/l; HCO_3 53 mmol/l, pO_2 78 mmHg)]; calcemia was normal but phosphatemia was low (Table 1). The first 24 h urinary output was 3.74 ml/kg per hour. Urinalysis showed hypernatriuria, hyperkaliuria, and normal calciuria for age. An exhaustive investigation was undertaken later to find an explanation for these ionic problems: assessments of blood and urinary concentrations of amino acids, ammonium ion, pyruvate, beta-OH-hydroxylbutyrate, fatty acids, carnitin, insulin-like growth factor (IGF)-1, 17-OH-progesterone, aldosterone, and renin, were normal. Lactic acid, liver enzymes, and creatine kinases were transitorily elevated just after delivery, but those metabolic abnormalities were rapidly normalized and remained so without medical intervention. This transitory increase was attributed to fetal distress.

A maternal biology analysis (Table 1) before any ion supplementation had been instigated revealed metabolic alkalosis (pH 7.53; pCO_2 60.9 mmHg; BE 27 mmol/l; HCO_3 51 mmol/l) associated with hypokalemia (1.4 mmol/l), hyponatremia (131 mmol/l) and hypochloremia (76 mmol/l). Her urinary chloride excretion was low (21 mmol/l). The mother would tell the neonatal team later about “her little eating disorder”. Such a description, playing down the severity of the problem, would indicate that she also minimized her frequent episodes of vomiting. The biochemical abnormalities observed in the mother were rapidly corrected after the delivery and remained as such without any

Table 1 General characteristics

Parameter	Mother	Neonate				
	Day 0	Day 0	Day 1	Day 2	Day 5	Day 19
Blood gas						
pH	7.53	7.46	7.48		7.33	
pCO_2 (mmHg)	60.9	72.0	56.0		48.0	
BE +	27.0	23.0	14.0		0.0	
HCO_3 (mEq/l)	51.0	53.0	42.0		26.0	
Plasma levels						
Urea (g/l)	0.58	0.54	0.51		0.43	0.08
Creatinine (μmol/l)	92.9	114	110.6	76.1	48.7	35.3
Sodium (mmol/l)	131.0	126.0	132.0	140.0	141.0	137
Potassium (mmol/l)	1.4	2.2	2.1	3.0	4.4	4.4
Chloride (mmol/l)	76.0	66.0	84.0	95.0	112.0	110
Calcium (mmol/l)	1.82	2.40	1.92	1.92	2.27	2.45
Phosphate (mmol/l)		1.12	1.28	1.38	1.76	2.20
Renin (ng/ml per hour)				3.0		
Urinary levels						
Creatinine (μmol/l)	3,730[a]	592[a]	999	3,217		1,352
Na (mmol/l)	68[a]	86[a]	62	67		20
K (mmol/l)	13[a]	4[a]	19	49		14
Cl (mmol/l)	21[a]	10[a]	13	20		28
Ca (mmol/l)	0.52[a]	0.5[a]	0.4	0.7		
Urinary output						
(ml/kg per hour)		3.74				
Ion supplementation						
Supply of Na (mmol/kg per day)		3.41	5.35	5.74	6.30	No more
Supply of K (mmol/kg per day)		0.73	1.90	2.40	1.24	No more
Calculation of						
FE Na^+ (%)	1[a]	12.9[a]				0.4
FE Cl^- (%)	0.55[a]	2.8[a]				0.76
FE K^+(%)	18.5[a]	34.5[a]				9.5
Urinary Ca^{++}/Creatinine ratio (mmol/mmol)		0.82[a]	0.38	0.21		

[a]Measurement and calculation on the first urinary sample before any ion supplementation

other treatment. She did, however, refuse any psychiatric help.

The baby was given supplementation of sodium, potassium and phosphorus. At the same time, hydrocortisone was temporarily added in view of the observed hyponatremia. As a result of a transitorily disrupted coagulation profile, the child benefitted from transfusions of both platelets and fresh plasma on days O and 1. Progressively, all these initial signs disappeared and were also attributed to the delayed consequences of perinatal distress. After 2 weeks, the baby left the hospital without any further treatment needed. At present, the baby is a pretty 3-year-old girl, who is developing perfectly.

Discussion

Both the mother and her fetus experienced the same dramatic metabolic abnormalities at the time of delivery, thereby mimicking a Bartter syndrome. Prompt resolution of the biochemical abnormalities in the baby and her mother suggests that these problems were caused by a pseudo-Bartter syndrome induced by the mother's eating disorder and chronic vomiting. Vomiting may lead to severe chloride and hydrogen ion losses and is the most likely cause of metabolic alkalosis. Indeed, the maternal urinary chloride excretion was low while the mother was hospitalized, rendering unlikely the hypothesis of chloride wastage due to loop diuretics abuse. Owing to the relative well-being of the mother before the delivery (she had told her obstetrician only of "feeling a little bit more tired for a few weeks"), these biochemical abnormalities must have been progressively and chronically induced.

Eating disorders in pregnant women are known to induce problems, ranging from polyhydramnios, increased risk of pre-term delivery, fetal cleft palate, increased risk of stillbirth, lower Apgar score, and lower birth weight, to an increased risk of other obstetric complications (breech delivery, higher numbers of cesareans). Except for a previous article reporting a case of transplacental hypochloremia [7], we found no cases similar to ours in the literature [8, 9]. Previously Voyame et al. [10] reported the case of a full-term baby presenting with hypokalemic metabolic alkalosis, whose mother had untreated Bartter syndrome. The situation spontaneously resolved.

Metabolic alkalosis is the consequence of chronic hypokalemia observed in the mother, and maternal hypochloremia is the original explanation of both biochemical abnormalities. Velasquez et al. studied the relationship between various factors and renal K^+ secretion [11]. In the presence of hypochloremia (at constant luminal Na^+ and constant flow rate), the renal distal secretion of K^+ is stimulated via a K^+Cl^- co-transport pathway [12], thus causing a hypokalemic state, which could, in turn, be responsible for maternal metabolic alkalosis. Metabolic alkalosis increases distal delivery of bicarbonate, and increased luminal Na^+ could lead to K^+ secretion [13]. Amorim et al. also showed that K^+ secretion is increased when the pH of the control perfusate is raised [14]. This appears to be linked to the kaliuretic effect of the luminal bicarbonate, independent of low urinary Cl^- concentration. The urinary concentration of potassium observed in the mother on her admission to the MIC unit before she had received any ion supplementation is, indeed, relatively elevated, compared with her very low kalemia.

Based on animal studies, especially those on rats, transplacental movement of Cl^- is known to be bidirectional and almost symmetrical [15]. This therefore explains fetal hypochloremia, as there is no way in which the fetus can correct the defect in the presence of insufficient chloride supply via the placenta. While animal studies show that the fetus is able to maintain normal or near-normal potassium levels, despite severe maternal hypokalemia, thanks to an active process through the ATP-ase pump [15], the maternal kalemia in this case is probably at too low a level to maintain normal fetal K^+ levels. In spite of the lack of any electrolyte analysis of an amniotic sample, we further postulate that fetal hypochloremia also induces potassium wastage into the amniotic fluid, thereby increasing the fetal pre-existing hypokalemic state. The decreased kalemia observed at birth in the neonate, and the concomitant relatively high urinary potassium excretion in the sample obtained before any ion supplementation (FeK^+ at the time of delivery was, indeed, relatively elevated in both mother and baby), must be kept in mind and could support this point of view. We hypothesize, therefore, that the mechanism of hypochloremia-induced renal potassium urinary loss described in the mother does also exist in the fetus.

Prostaglandins play a fundamental role in renal sodium excretion, causing higher fractional excretion of sodium in pre-term infants but also in patients with Bartter syndrome [16]. The supply of exogenous prostaglandins in neonates is associated with the development of a secondary Bartter syndrome [5, 6]. Hornych et al. demonstrated that Bartter syndrome could be dissociated from secondary Bartter syndrome because, in the latter, the urinary prostaglandin E_2 (PGE_2) excretion is always shown to be within a normal range [17]. Unfortunately, due to technical difficulties, we did not measure urinary prostaglandins in this case.

Conclusion

The case outlined here is likely to be a unique neonatal pseudo-Bartter syndrome due to a maternal eating disorder. Maternal hypochloremia appears to be the key feature explaining the mother's biochemical disorders. The hypotheses that are presented here to explain the same chloride handling abnormalities in the fetus deserve further research interest.

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