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ANTENATAL BARTTER SYNDROME: Analysis of Two Cases with Placental Findings

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□ *The prenatal diagnosis of Bartter syndrome can be based on the high chloride level in the amniotic fluid. Microscopic examination of the placenta in untreated cases showed extensive mineralization in the chorionic villi in previous studies. Two cases were presented at 26–29 weeks of gestation with severe polyhydramnios. The mothers were treated with Indomethacin, KCl, and serial amniocentesis in order to reduce the amniotic fluid volume and prevent fetal hypokalemia. The microscopic examination of the placenta revealed focal calcification and acute atherosis in placental vessels. The treatment with Indomethacin in the antenatal period can prevent severe nephrocalcinosis.*

Keywords Bartter syndrome, prenatal diagnosis, polyhydramnios, nephrocalcinosis

INTRODUCTION

Bartter Syndrome is an inherited renal tubular disorder associated with hypokalemic alkalosis. Hyperreninemic hyperaldosteronism with normal blood pressure, increased excretion of urinary prostaglandin, and hyperplasia of the juxtaglomerular apparatus are other features of this syndrome [1]. The syndrome is subdivided into three clinical phenotypes: the classic syndrome described by Bartter et al. (Classic Bartter syndrome); the hypocalciuric- hypomagnesemic variant (Gitelman syndrome); and the antenatal hypercalciuric variant (hyperprostaglandin E syndrome) [2]. In the antenatal form, the pregnancy is complicated with severe polyhydramnios and preterm delivery due to fetal polyuria. The diagnosis may be suspected

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prenatally on the basis of high chloride concentrations in the amniotic fluid [3].

Nonsteroidal anti-inflammatory agents (Indomethacin) as the main drug of the children with hyperprostaglandin E syndrome inhibit cyclooxygenase and diminish prostaglandin synthesis. Prenatal Indomethacin prevents the progression of polyhydramnios and extreme prematurity. Early diagnosis and treatment also prevents hypovolemic renal failure induced by excessive renal loss of salt and water and severe neonatal nephrocalcinosis at neonatal period [4]. Only one published report includes placental pathology [5]. The clinical and pathologic findings in two cases of Bartter syndrome detected antenatally and treated in our clinic are presented.

CASE REPORTS

Case 1

A 25-year-old woman, (G1) was referred to the Department of Obstetrics with a diagnosis of placental abruption at 29 weeks. Sonographic and tocographic examinations revealed severe polyhdramnios and fetal bradycardia. The fetal anatomy and placenta were found to be normal. Fetal doppler and biophysical score were normal. The patient was treated with potassium chloride (KCl) containing intravenous fluid for a serum K level (3.9 mEq/l). The amniotic fluid had a high chloride concentration (Cl: 116 mEq/l) (Table 1). Biochemical, serological tests and karyotype were normal. The mother was treated with Indomethacin 2 mg/kg/d and KCl 4 mg/d. Repeat amniocenteses was performed at weekly intervals. At 33 weeks gestation, a preterm rupture of membranes occurred. A Cesarean section was performed for fetal bradycardia during the labor. The birth weight was 1640 g, and the Apgar score was 7–9. Bartter syndrome, associated with severe polyuria, increased renal excretion of sodium, chloride, potassium, calcium, and high levels of plasma renin and aldosterone, was confirmed. Indomethacin was started after 2 weeks of age. In the third week spontaneous intestinal perforation required surgery.

TABLE 1 Amniotic Fluid and Serum Levels of the Cases with Bartter Syndrome

Amniotic Fluid	Case 1	Case 2	Normal Levels*
Cl (mEq/l)	116	111	108 ± 3.2
Ca (mg/dl)	7.1	7.3	7.4 ± 2.2
Na (mEq/l)	135	133	136 ± 6.8
K (mEq/l)	3.91	3.5	4 ± 0.2
Serum levels			
Renin (pg/ml)	1228	1114	5–33
Aldosterone (pg/ml)	>2000	>2000	34–273

*From Benzie et al. [6].

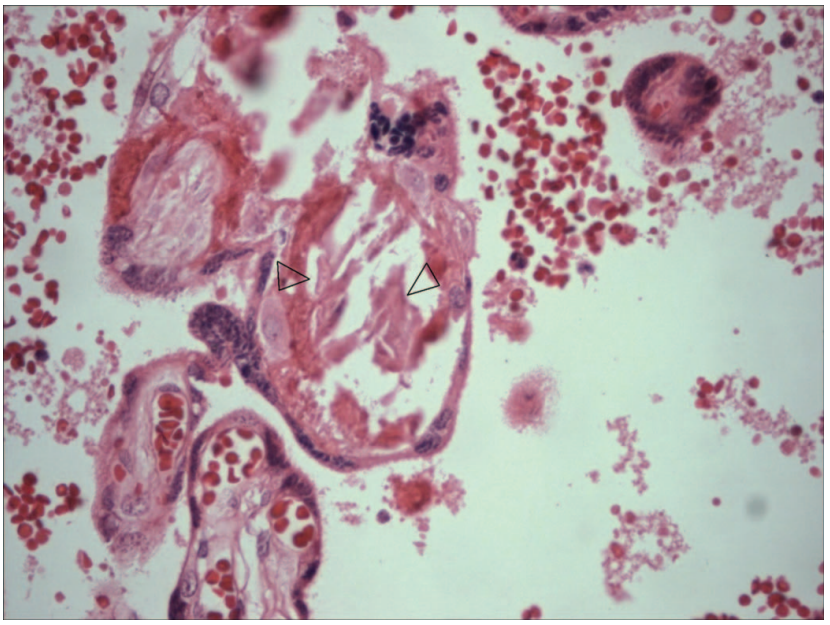

FIGURE 1 Early focal calcification in placenta.

The placenta was large for its gestational age (weighing 780 g). Examination of the placenta did not reveal any change related to the abruption, but focal calcifications of the chorionic villi (Figure 1) and prominent atherosis in placental vessels (Figure 2). The Indomethacine treatment was restarted

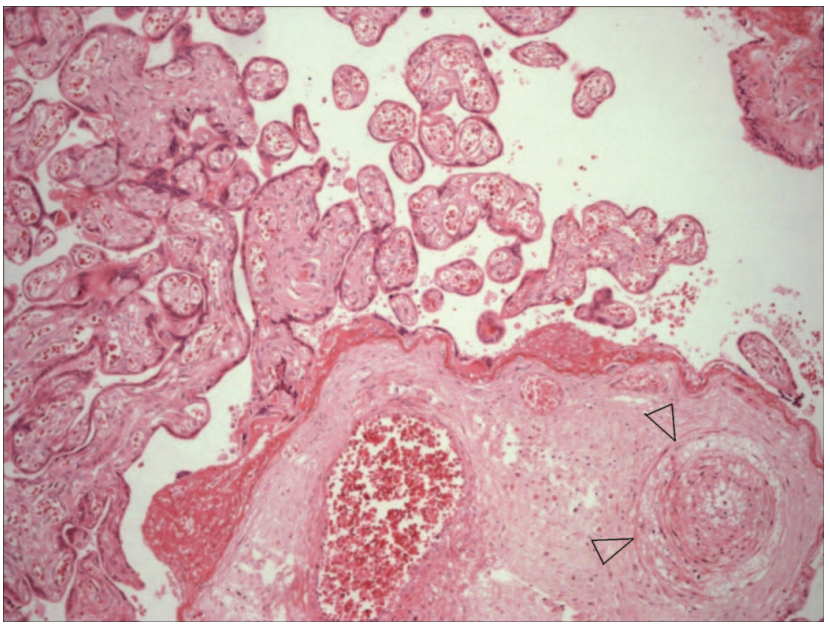

FIGURE 2 Acute atherosis in the stem villus.

at 2 months postnatally. The baby underwent a second operation at 8 months of age. He is still alive at 22 months of age and has a physical growth below the average and normal neurologic status. At 18 months of age a sonographic examination of the baby revealed minimal calcification at the medullar region of the kidneys.

Case 2

A 30-year-old woman (G4, P3) presented with severe polyhydramnios at 26 weeks of gestation. A previous pregnancy was complicated with polyhydramnios and the baby died at home after 1 month in the intensive care unit. The records of this baby were not available. The fetal anatomy, biochemic, and serologic examinations were normal. The amniotic fluid revealed normal chromosomes and a chloride level of 111 mEq/l (Table 1). The mother was treated with Indomethacin 1 mg/ kg/d and KCl 4 mg/g. Serial amnio drains were performed until 34 weeks of gestation. The repeated chloride level was 114 mEq/l. A Cesarean section was performed due to placental abruption and rupture of the fetal membranes at 35 weeks. The birth weight was 2420 g and Apgar score 4–7. Severe polyuria and high levels of plasma renin and aldosterone confirmed the diagnosis was Bartter syndrome. The Indomethacin treatment was started at day 16.

The placenta was large for gestational age (weighing 950 g). The microscopic examination of the placenta revealed only the changes related to the abruption. Sonographic examinations of the kidneys were normal at 18 months of age. The baby is alive at 21 months of age with an average growth and normal neurologic status.

DISCUSSION

Intestinal perforations in the neonatal period are usually related to necrotizing enterocolitis (NEC) or intestinal occlusion. Intestinal perforation in the absence of these conditions is called isolated perforation (IP). In a recent study antenatal indomethacin exposure in infants with very low birth weight was not associated with a significant increase in the incidence of NEC [7]. Indomethacin treatment for longer than 2 days with a daily or cumulative dosage $\geq$150 mg is associated with a significantly higher incidence of NEC [8]. Necrotizing enterocolitis and IP are difficult to distinguish based on clinical parameters. The association between IP and maternal use of indomethacin in the prenatal period has been demonstrated in previous studies [9,10]. Risk factors and pathologic findings seemed to support an ischemic pathogenesis in both diseases [11]. Both Indomethacin and dexamethasone have been shown to alter prostaglandin metabolism leading to a loss of the cytoprotection and promoting intestinal perforations [12,13]. After the elective cessation of Indomethacin, the amniotic fluid volume is rapidly increased in our cases. The high daily dosage of Indomethacin (>150 mg)

TABLE 2 Comparison of the Cases with Bartter Syndrome

	Case 1	Case 2	Case 3*	Case4*
Time of delivery (weeks)	33	35	30	32
Management				
Prenatal	Indomethacin+ serial AS	Indomethacin+ serial AS	None	Serial AS
Postnatal	Electrolyte abnormalities Intestinal perforation	Electrolyte abnormalities	Electrolyte abnormalities	Electrolyte abnormalities
Status of the patient				
Physical growth	Below average	Average	Below average	Below average
Nephrocalcinosis	Focal medullar	None	present	Present
Placental features				
Weight	LGA	LGA	LGA	LGA
Calcification	Early focal	none	Subtrophoblastic basal membrane mineralization (iron and calcium)	Subtrophoblastic basal membrane mineralization (iron and calcium)
Specific feature	Acute atherosis in the stem villi	None	Chorangioma (<1 cm)	None

*From Ernst et al. [5]
AS = amniocenteses; LGA = large for gestational age.

in the first case might be a risk factor of the intestinal perforation, although it was discontinued 1 week before the delivery.

In a previous report the placental pathology of two cases with Bartter syndrome are presented [5]. The findings of their cases are compared with our cases in Table 2. The placentas were large for gestational age (weighing greater than the 95th percentile). Microscopic examination showed extensive subtrophoblastic basement membrane mineralization in the chorionic villi. The excesses of calcium in the placenta may be due to a overloading of the transport system deposited beneath the trophoblastic layer. Cases were not treated with intrauterine Indomethacin and developed nephrocalcinosis. Although both our cases were large for gestational age placentas, the microscopic examination revealed only focal calcification. Serious nephrocalcinosis did not occur. Indomethacin in the antenatal period may prevent diffuse calcification in the placenta and kidneys. Atherosis was defined as the presence of clearly identifiable foam cells in the intimae or within fibrinoid material in the vessel wall. It is a significant pathologic marker associated with preeclampsia, molar pregnancy, maternal hyperhomocysteinemia, antiphospholipid syndrome, diabetes, systemic lupus erythematosus, and small-for-gestational-age infants. Acute atherosis is described as the typical lesion

at maternal side of the fetoplacental unit in preeclamptic patients which may be responsible for placental underperfusion [14]. In a previous study, the following two placental lesions were found to be inversely related to chronic lung disease in infants with very low birth weight [15]: 1) histologic chorioamnionitis and 2) acute atherosis. Atherosis localized at the maternal side of the placenta is a marker for the maternal disease. Acute atherosis in Bartter syndrome may indicate the ischemic changes also in mesenteric vessels of the fetus.

Indomethacin prevents serious nephrocalcinosis in antenatally detected cases of Bartter syndrome. It might have serious side effects including intestinal ischemia and NEC.

DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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