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CASE REPORT

Fetal urine biochemistry in antenatal Bartter syndrome: a case report

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Key Clinical Message

Bartter syndrome is a severe inherited tubulopathy responsible for renal salt wasting, and hence electrolyte disorders and dehydration. Prenatally, it is characterized by severe polyhydramnios caused by fetal polyuria. We studied for the first time fetal urine in a Bartter syndrome case and demonstrated that the tubulopathy is already present at 24 weeks of gestation.

Keywords

Introduction

Bartter syndrome is a severe inherited tubulopathy responsible for renal salt wasting. It is caused by alterations in ion channels located in the thick ascending limb of Henle's loop. Five mutations in four genes – *SLC12A1*, *KCNJ1*, *CLCNKB*, and *BSND* – coding for transporters and one specific mutation (L125Q) in the *CASR* gene, which encodes the calcium-sensing receptor, have been identified [1,2]. First described in 1962 [3], two presentations are currently recognized. The classic form develops in childhood and is characterized by severe polyuria, dehydration, hypokalemic metabolic alkalosis, secondary hyper-aldosteronism, and hypercalciuria sometimes leading to nephrocalcinosis. The second presentation is antenatal, more severe [4,5] and is revealed by refractory polyhydramnios (caused by fetal polyuria) during the second trimester of pregnancy, without morphological anomalies. The major consequences are preterm birth,

growth retardation, and severe dehydration at birth due to salt loss. In children with Bartter syndrome, urinalysis highlights increased sodium, potassium, chloride and calcium excretion, and as a consequence hyponatremia, hypochloremia, and hypokalemia [4,6]. However, until now, no studies have been published about fetal urinalysis in antenatal Bartter syndrome.

A 28-year-old woman in a consanguineous marriage (first cousins), gravida 1, para 0, presented severe polyhydramnios at routine ultrasound examination at 22.6 weeks of amenorrhea. Megacystis was observed in a female fetus, without any other malformation. After genetic counseling, invasive procedures were offered to the parents and accepted: amniotic fluid sampling for karyotyping and biochemistry and fetal urine sampling for renal function evaluation. The karyotype was normal, 46,XX. A second amniocentesis was secondarily performed at 26.3 weeks for amniodrainage. Amniotic fluid alpha-fetoprotein and total protein were decreased at both

Table 1. Fetal urine and amniotic fluid electrolytes (mmol/L), β2-microglobulin (β2 m), and total protein in Bartter syndrome and controls.

	Gestational age	Na	Cl	Ca	P	β2 m (mg/L)	Protein (g/L)	AFP (MoM)
Fetal urine								
Bartter syndrome case	24.3	160	157	5.6	18.86	0.1	0.09	
Control with normal renal function	24.4	53	47	0.25	0.01	1.6	0.03	
Control with renal failure	24.3	132	105	1.71	1.52	13	0.28	
Amniotic fluid								
Bartter syndrome case	22.6	138	116	1.7	0.78		1.6	0.53
Bartter syndrome case	26.3	138	116	1.17	0.72		1.5	0.47
Polyhydramnios control	23	135	113	1.64	0.44		3.6	0.77
Polyhydramnios control	26.3	133	111	1.49	0.37		4.1	0.69

AFP, alpha-fetoprotein; MoM, multiple of median.

22.6 and 26.3 weeks (Table 1), giving a Bartter index (total protein expressed in g/L x alpha-fetoprotein in MoM) of 0.85 and 0.71, respectively [7]. These values were strongly suggestive of Bartter syndrome. In fetal urine we assayed electrolytes, beta-2 microglobulin, and total protein. Results are presented in Table 1 in comparison with two fetal urine controls (one with renal failure and one with normal renal function, both performed because of megacystis). Electrolytes were significantly increased in Bartter syndrome compared with controls ($P < 0.001$). A weekly check-up was planned. The patient delivered a girl at 33.6 weeks of gestation. The baby presented clinical and laboratory signs of Bartter syndrome. Postnatal screening for Bartter syndrome mutations detected a homozygous mutation in the *SLC12A1* gene.

This was a rare opportunity to obtain fetal urine samples in a case of antenatal Bartter syndrome. To our knowledge, there is no other report of such sampling. Indeed, fetal urine sampling is an invasive procedure reserved for the case of bladder dilation for renal function evaluation [8,9]. Here, the megabladder observed at ultrasound scan at 24.3 weeks suggested obstructive uropathy requiring renal function evaluation, whereas this megabladder was the reflection of massive fetal urine excretion. In Bartter syndrome, abnormal urine electrolytes are due to mutations in the cotransporter located in the thick ascending limb of Henle's loop. Sodium and chloride or potassium cannot be reabsorbed and are therefore excreted in urine. In addition, because the transmembrane potential difference observed physiologically is absent, the calcium, which follows a paracellular reabsorption, can no longer follow this pathway and is also excreted in urine. Phosphorus reabsorption probably follows a similar process, thus explaining the huge value observed. As a consequence, the salt loss leads to loss of water which corresponds to polyuria. During fetal life, this polyuria is responsible the early and severe polyhydramnios, generally observed from 24 to 26 weeks of gestation. This fetal urinalysis confirms that a tubulopathy, characterized by electrolyte loss, is present as early as

24 weeks of gestation. The fetal urine electrolyte profile we observed in Bartter syndrome is specific and differs from the profile observed in fetal urine with normal renal function, but also from the profile observed in fetal renal failure. The low β2-microglobulin and protein values (similar to the control with normal renal function) reflected normal glomerular filtration.

Amniotic fluid in the second half of gestation is largely a product of fetal urine and lung fluid. Fluid is reabsorbed via fetal swallowing and the intramembranous pathway. Aquaporins (a family of 13 proteins) are membrane proteins that play a major role in water permeability. In the case of polyhydramnios, it has been demonstrated that a compensatory response due to a significant increase in aquaporin 1 expression is observed [10], increasing intramembranous absorption and decreasing the maternal-to-fetal water flow to maintain amniotic fluid homeostasis. However, in Bartter syndrome the permanent and massive flow of water probably exceeds the capacity of aquaporins. In contrast to fetal urine, amniotic fluid electrolyte concentrations were normal in Bartter syndrome. This observation can be explained by the quick restoration of balance between amniotic fluid and maternal plasma through the placenta, so there is no difference between Bartter syndrome cases and healthy controls. This therefore excludes the hypothesis of an osmotic difference to explain the severe polyhydramnios observed in fetal Bartter syndrome.

Our results show that, in Bartter syndrome, tubulopathy is present from 24 weeks of gestation and is responsible for severe polyhydramnios.

Conflict of Interest

None declared.

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