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Case Report

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A case with prenatal molecular diagnosis of X-linked transient antenatal Bartter syndrome

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Abstract

Early-onset polyhydramnios during pregnancy can be caused by X-linked transient antenatal Bartter syndrome. Most of the reported cases were molecularly diagnosed after birth, whereas few cases were diagnosed in the fetus period. We received a pregnant woman who had polyhydramnios detected by ultrasound imaging at 25 weeks of gestation, and treated with magnesium sulfate, indomethacin and an amnioreduction at 30 weeks of gestation, whereas amniotic fluid decreased spontaneously since 32 weeks of gestation. Prenatal molecular testing showed the fetus carried *MAGED2* hemizygous variant c.967C>T [p. (Asp323*)] inherited from the mother. The preterm boy did not present with polyuria and electrolytes and acid-base imbalance in the early neonatal period, and had good development without polyuria at the age of 20 months. We presented the phenotypes of a Chinese case with a prenatal diagnosis of X-linked transient antenatal Bartter syndrome and his response to prenatal indomethacin treatment. Early identification of the condition helps to provide appropriate prenatal genetic counseling and postnatal management.

Keywords: Polyhydramnios, Bartter syndrome, *MAGED2* pathogenic variant, prenatal diagnosis

INTRODUCTION

Polyhydramnios is a common complication of pregnancy, with an incidence rate of 1 to 2 percent and is

associated with increased morbidity and mortality[1-3]. It was reported that 12 percent of these cases were diagnosed as severe polyhydramnios[4]. The most common mechanisms for polyhydramnios are decreased fetal swallowing and fetal polyuria[5], which may be idiopathic or caused by a variety of diseases. Approximately 40% of polyhydramnios is idiopathic[6]. However, 25 percent of infants with a prenatal diagnosis of idiopathic polyhydramnios are diagnosed with an abnormality after birth, such as Bartter syndrome (BS)[7]. Antenatal BS typically presents with severe polyhydramnios, premature delivery, hypokalemic alkalosis, and secondary hyperaldosteronism. Most antenatal BS patients require lifelong treatment with mineral supplementation and nonsteroidal anti-inflammatory drugs, and some may have severe chronic kidney disease progression[8]. In 2016, Kömhoff *et al.* reported that pathogenic variants in the *MAGED2* (melanoma-associated antigen D2) gene result in mislocalization of both NKCC2 (sodium-potassium-2-chloride cotransporter) and NCC (sodium chloride cotransporter)[9]. The mutant MAGED2 proteins cause a severe but transient X-linked antenatal BS (BS type 5), which mainly affects male infants[10]. Up to now, fewer than 50 cases with BS type 5 have been reported all over the world. Although some patients died in utero or shortly after birth[10,11], most of them had a normal estimated glomerular filtration rate at last follow-up[10-18]. Individual cases of BS type 5 with positive outcomes after serial amniocentesis therapy have been reported[11,15,17,18], and one fetus has spontaneous remission of polyhydramnios after two amnioreductions[18]. Prenatal indomethacin therapy has been reported to decrease amniotic fluid in some fetuses with antenatal BS[19-21], whereas its effects on fetuses with BS type 5 are still uncertain. To date, only a male infant with BS type 5 treated with prenatal indomethacin has been reported[13]. He had severe progressive polyhydramnios since 21 weeks of gestation (WG); despite several courses of indomethacin, amnioreductions on five separate occasions were required, and he was born at 29 WG after premature rupture of membranes. However, the dose of indomethacin and the genotype have not been described. Although antenatal BS is quite rare, it should be considered in the differential diagnosis of polyhydramnios if a structural abnormality and maternal diabetes are excluded. Accurate prenatal diagnosis may help to provide appropriate prenatal consultation and postnatal management.

CASE REPORT

A previously healthy 33-year-old G2P1 female was referred at 29 WG due to polyhydramnios detected by ultrasound imaging since 25 WG. Ultrasonography at 28 WG indicated severe polyhydramnios, with amniotic fluid index (AFI) of 43 cm (normal AFI: 5-24 cm)[22]. There were no structural abnormalities in the fetus. Screening for Down's syndrome was negative. The result of 75 g oral glucose tolerance test (OGTT) was normal. She gave birth to a healthy full-term girl in 2018. There was no family history of severe polyhydramnios or hereditary diseases. Ultrasonography at 29 WG in our hospital also indicated polyhydramnios, with the single deepest pocket (SDP) of 15.2 cm (normal SDP: 2-8 cm), and cervical shortening (13.3 mm). Owing to premature rupture of membranes at 30 WG, the woman received a short course of magnesium sulfate infusion and oral indomethacin (a dose of 25 mg six times daily for the first week and four times daily for the second week) for tocolysis and its amniotic fluid-reducing effects. A course of dexamethasone was also administered to reduce the possibility rate of neonatal respiratory distress syndrome. An amnioreduction was performed under continuous US guidance at 30 + 2 WG, and the volume drained was 2,200 mL. Amniotic fluid leakage ceased within a week after the amnioreduction. The SDP at 32 WG+, 33 WG+ and 34 WG+ were 13 cm, 9.4 cm and 8.7 cm, respectively [Figure 1]. After obtaining the couple's informed consent for the genetic analysis, genomic DNA of the fetus was extracted from amniotic fluid, and the couple's DNAs were extracted from peripheral white blood cells. No chromosomal abnormalities were detected using Karyotype analysis and chromosomal microarray. Whole-exome sequencing (WES) followed by Sanger sequencing analysis showed the fetus carried *MAGED2* (NM_177433.1) hemizygous nonsense variant c.967C>T [p. (Asp323*)] inherited from the mother [Figure 2]. This variant has been reported previously[11], and was classified as pathogenic (PVS1, PM2, PP4) according to the American College of Medical Genetics and Genomics guidelines[23].

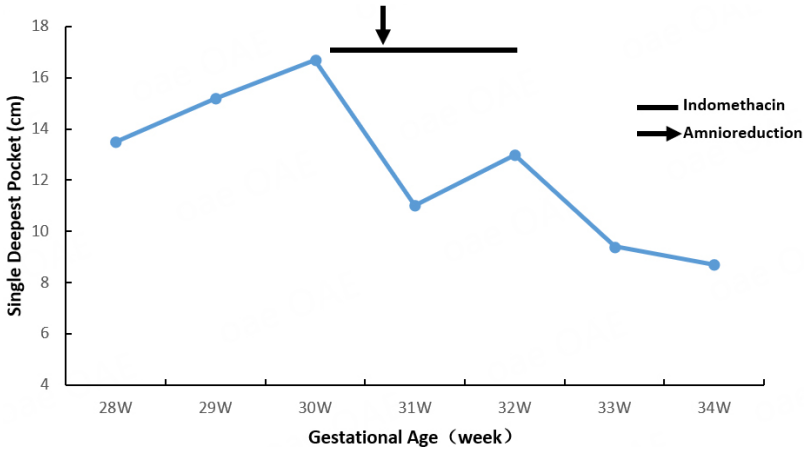

Figure 1. Treatment and changes in single deepest pocket during pregnancy.

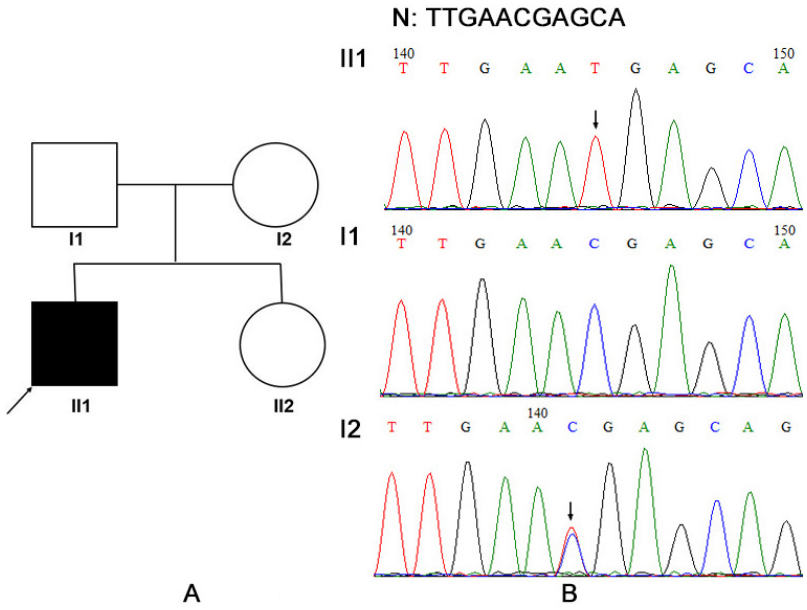

Figure 2. Pedigree of the case in this report (A) and Sanger sequencing of exon 6 in the *MAGED2* gene (B). The proband is indicated by a slope arrow, and the changed nucleotide is indicated by the vertical arrows. N: normal sequence.

The female gave birth to a preterm male baby infant born via vaginal delivery at 34 + 6 WG with birth weight of 2,900 g (P85) and length of 50 cm (P50). The newborn baby's 1 min Apgar score was 9 (muscle tone-1) and the 5 min Apgar score was 10. He did not develop obvious polyuria. Although he had a high blood level of renin (> 500 mU/L, reference range 2.8-39.9 mU/L) and aldosterone (> 100 ng/dL, reference range 3.0-23.6 ng/dL), his postnatal blood pressure (60/39 mmHg) and biochemical blood data were normal [Table 1]. Head ultrasound showed mild bilateral intraventricular hemorrhage. Kidney ultrasound and newborn hearing screening did not detect any abnormalities. At the age of 20 months old, he showed good development (height was 91.5 cm and weight was 13 kg) without polyuria.

Table 1. Clinical and postnatal blood biochemical characteristics of the boy

Parameters	Normal value	Age		
		1 day	4 days	45 days
Urine volume-mL/kg/h	3-4 (First week)	4.1	3.8	normal
Potassium-mmol/L	3.5-5.3	4.91	4.01	4.81
Sodium-mmol/L	137-147	138.80	137.37	137.7
Chloride-mmol/L	99-110	109.9	108.6	106
Bicarbonates-mmol/L	22-30	24	15.9	26.4
Magnesium-mmol/L	0.75-1.02	0.84	1.01	0.83
Creatinine-μmol/L	44-133	81.8	78.1	32.6
Urea-mmol/L	1.8-7.1	2.97	1.17	2.56

DISCUSSION

Severe polyhydramnios has been associated with an increased risk of several adverse maternal and newborn outcomes, such as maternal respiratory compromise, premature rupture of membranes and preterm birth[24]. The specific underlying etiology of the polyhydramnios guides intrapartum management and timing of birth. For example, polyhydramnios of fetal origin should raise the clinical suspicion of BS[8]. It was reported that BS accounts for 6% of cases with isolated polyhydramnios[25]. Because of different prognoses of BS, it is important to perform prenatal genetic testing to confirm the diagnosis. When prenatal genetic testing is not available or not sufficient to make a definite diagnosis, the assessment of the "Bartter index" (total protein × alfa-fetoprotein) is suggested[25]. In addition, the use of serial amniocentesis with or without prenatal indomethacin therapy has been reported to prolong gestational age at birth in a few cases of antenatal BS[26,27]. However, there was no report of successful prenatal treatment of fetal BS type 5 with indomethacin alone. Indomethacin is a potent inhibitor of prostaglandin synthesis and decreases salt wasting. This, in turn, can reduce fetal urine output and thereby controls the polyhydramnios[28]. Moreover, indomethacin can delay preterm birth by suppressing uterine contractions[29]. After an amnioreduction and two weeks of maternal indomethacin therapy, the recovery of polyhydramnios was observed in our case, which may be related to prenatal indomethacin therapy. Meanwhile, no serious side effects, such as fetal ductus arteriosus constriction and neonatal necrotizing enterocolitis, were observed. In our case, the response of indomethacin is better than that reported by Meyer *et al.*, which may be related to the older fetal age or *MAGED2* different genotypes[13]. In addition, the polyhydramnios symptoms can be relieved spontaneously with the increase of gestational age in patients with BS type 5[18]. This is the first report on the successful application of maternal indomethacin therapy in the fetus with BS type 5 to prevent the progression of polyhydramnios.

The most common form of antenatal BS is the autosomal recessive inheritance pattern. The infants exhibit postnatal polyuria and persistent renal salt wasting, requiring lifelong treatment. Some parents may terminate pregnancy due to concerns about poor prognosis. In contrast, favorable prognosis of BS type 5 caused by *MAGED2* pathogenic variants results in pregnant women choosing ongoing pregnancy. *MAGED2* pathogenic variants explained 9% of cases with antenatal BS[11]. In BS type 5, the onset of severe polyhydramnios (18-27 WG) and gestational age at birth [median (IQR): 29 (21-37) WG] are typically earlier than in other types, but signs and symptoms of renal impairment resolve spontaneously postnatally[30]. Polyhydramnios was detected in our case during the routine antenatal ultrasonic examination at 25 WG, which is similar to the previous report[11]. Since earlier routine antenatal ultrasonic examination in our hospital is performed in early pregnancy and 11-13 WG, respectively, and the proband's mother had no complaints of discomfort, we speculated that polyhydramnios might develop at 14-24 WG. As an inherited salt-losing tubulopathy, the transient nature of BS type 5 remains unclear. Two mechanisms may

be involved[10]. First, the sensitivity of adenylate cyclase activity to vasopressin gradually increases with fetal age, making the expression of NKCC2 and NCC independent of MAGED2 beyond a certain period of renal development. In addition, MAGED2 is required for cAMP generation and induction of the transcription factor HIF-1α under hypoxia[31]; the significant increase of oxygenation after birth may promote the synthesis of NKCC2 and NCC. Whether *MAGED2* pathogenic variants interfere with the expression of other proteins and cause extra kidney manifestations or may have some impact on female carriers[11] is still unknown.

The dominant presentation of our case was severe polyhydramnios, which led to the mother presenting with premature rupture of membranes at 30 WG. However, after treatment with amnioreduction and indomethacin, the amniotic fluid decreased since 32 WG. These dynamic changes in amniotic fluid volume indicated polyhydramnios was not related to fetal structural abnormalities. As we were initially unaware of antenatal BS due to its quite rare feature, biochemical analyses of amniotic fluids were not performed, which was a limitation of our report. Prenatal genetic testing demonstrated that polyhydramnios was caused by BS type 5, which provided evidence for timely genetic counseling and postnatal management of the patient. In addition, our case's postnatal mild symptoms may be associated with his gestational age at birth relatively close to term. A French boy with antenatal BS postnatally got a genetic diagnosis by identified *MAGED2* De novo variant c.967C>T, while the detailed manifestations were not described[11]. Our case complemented the phenotype of *MAGED2* variant c.967C>T. Besides our case, there were three cases prenatally diagnosed as BS type 5 caused by *MAGED2* splice site variant, deletion of the entire *MAGED2* gene and frameshift variant, respectively[14,15,18]. Different variant types of *MAGED2*, including nonsense, missense, splice site, frameshift, and large deletion, had been reported, but fortunately, most of the patients had a favorable outcome[10-13,15-18]. Prenatal genetic diagnosis and subsequent amnioreduction and prenatal indomethacin therapy seem to have a beneficial effect in the fetus with BS type 5, especially on the progression of polyhydramnios; therefore, extreme prematurity and related complications could be prevented.

In conclusion, we report a case of prenatal molecular diagnosis of BS type 5, which extends the phenotypic spectrum. Meanwhile, we share our experience of prenatal indomethacin therapy and discuss the optimal management approach for fetuses with BS type 5. Timely prenatal identification of BS type 5 could guide the management of polyhydramnios and postnatal symptoms.

DECLARATIONS

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Authors' contributions

Conception and design of the work, interpretation of the results, editing of the manuscript, and final approval of the version to be published: Wang F

Drafting of the manuscript, data acquisition, and final approval of the version to be published: Xu K

Administrative, technical, and material support, critical revision of the manuscript, and final approval of the version to be published: Zhang Y, Hou X, Yang H, Ding J

Availability of data and materials

All datasets generated for this study are included in the manuscript material.

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

The study involving human participants was reviewed and approved by the Ethical Committee of Peking University First Hospital (2021 Scientific Research 074). Written informed consent to participate in this study was provided by the participants.

Consent for publication

Written informed consent was obtained from the participants for the publication of any potentially identifiable images or data included in this manuscript.

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