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Diagnosis of antenatal Bartter syndrome

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Summary

Established facts: Bartter syndrome is a rare heterogeneous group of autosomal-recessive salt-losing renal tubular disorders that can present in fetal life (antenatal Bartter syndrome; ABS) as "unexplained" early-onset polyhydramnios, often associated with growth restriction. Prenatal diagnosis of the condition involves assessment of amniotic fluid biochemistry in a setting of polyuric polyhydramnios; with elevated chloride levels considered a consistent and diagnostic finding. Other amniotic fluid biochemical markers have been described, notably increased aldosterone levels, and low total protein levels. *Novel insight:* Antenatal Bartter syndrome is a heterogeneous group of renal disorders. While certain biochemical features in amniotic fluid might heighten suspicion, final diagnosis can only be made in the postnatal setting. In the setting of unexplained severe polyhydramnios, clinicians should continue to entertain the diagnosis of antenatal Bartter Syndrome and maintain neonatal surveillance, even if amniotic fluid markers do not support the diagnosis.

Key words: Antenatal Bartter syndrome.

Introduction

Bartter syndrome describes a group of autosomal recessive salt losing renal tubulopathies where affected neonates are usually born premature, have postnatal polyuria, vomiting, failure to thrive, hypercalciuria, and subsequently nephrocalcinosis. Some forms of Bartter syndrome manifest in the antenatal period by causing severe polyhydramnios at 24-30 weeks gestation [1-4]. The polyhydramnios is considered a function of fetal polyuria [1, 5, 6] secondary to hyperreninemia, hyperaldosteronism, and excess prostaglandin production resulting in hypokalemia, impaired urine concentration ability, and renal tubular sodium loss [7].

Gene mutations have been identified in affected individuals, and prenatal genetic diagnosis is theoretically feasible. However, this usually relies on the availability of an index case, and is further hampered by genetic heterogeneity [4] and laboratory considerations. As a consequence, diagnosis of antenatal Bartter syndrome relies on the finding of polyuric polyhydramnios and analysis of amniotic fluid, in which elevations of chloride [1, 6, 8, 9] and/or aldosterone [3, 5] are considered consistent and diagnostic findings. Other alterations of amniotic fluid include low total protein levels [10].

This case study highlights the difficulty of antenatal diagnosis of Bartter syndrome, and the need to maintain postnatal surveillance for the neonatal manifestations of the condition, even when antenatal amniotic fluid analysis does not appear to support the diagnosis.

Case Report

This 38-year-old woman was in her first spontaneous pregnancy. She had no relevant medical history and her blood group was O positive and negative for agglutins. The woman and her partner were non-consanguineous Ashkenazi Jews. Both had tested negative for common cystic fibrosis gene mutations. A 12-week nuchal translucency and first trimester serum screening assessment returned a low risk for trisomy 13, 18, and 21. Fetal anatomy survey at 19 weeks revealed no ultrasonic evidence of structural abnormality and amniotic fluid volume was assessed as normal.

Due to maternal abdominal discomfort and increased symphysio-fundal height at 30 weeks gestation, an ultrasound assessment was performed with the finding of a normally grown fetus with polyhydramnios (AFI 43 cm with the deepest pool of fluid 12 cm) in the absence of other demonstrable structural or placental abnormality. A 75-gram oral glucose tolerance test at 26 weeks was normal. The cervix measured 31 mm in closed length.

Bartter syndrome was considered the most likely diagnosis on the basis of severe polyhydramnios, considered to be polyuric, in the absence of other obvious cause. The patient underwent a 2.5 L amnio-reduction at the initial assessment.

A karyotype was requested on amniotic fluid and returned as 46 XX. Amniotic fluid chloride level was 120 mmol/L (normal range 107.4 ± 3.4 mmol/L at 31 weeks), sodium 142 mmol/L (normal range 133.2 ± 6.6 mmol/L at 31 weeks) [11], total protein 3.0 g/L (normal range 2.3 – 9.9 g/L) [10], and aldosterone level 14.4 pg/ml (normal range 36-240 pg/ml) [5].

After discussion of therapeutic options, serial amnio-reduction was preferred to medical amnio-reduction with indomethacin [12].A further amnio-reduction of three L was performed at 34 weeks' gestation due to increasing maternal discomfort. The pregnancy proceeded without further need for amnio-reduction until 38 weeks when elective caesarean was performed due to polyhydramnios and unstable lie. The patient delivered a female infant with a birth weight of 2,714 grams (14th centile) and APGAR scores

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of 9 at one minute and 9 at five minutes of age. Approximately seven litres of amniotic fluid was drained at the time of delivery.

The neonate was noted to have polyuria from day one (4.5 ml/kg/day). The serum Na reached a nadir of 126 mmol/L (normal range 132–145 mmol/L) on day 3 and bicarbonate to 17 mmol/L (normal range 22–32 mmol/L) on day 5. Serum potassium peaked at 6.5 mmol/L (normal range 4–6.2 mmol/L). Plasma renin was 455 mU/L (expected normal 32.5 mU/L). Plasma protein levels were normal range at 56 g/L (normal range 50–70 g/L), and the 17-hydroxyprogesterone level was not increased. Urine osmolality was low and urine Ca/creatinine ratio was elevated. A renal tract ultrasound and BP measurements were normal. The infant passed a baseline SWISH hearing screen.

The neonate underwent clinical geneticist review and is being managed as Bartter syndrome. At five weeks of age the infant is stable and thriving, and continues to receive sodium chloride and bicarbonate supplementation. The parents declined genetic testing.

Discussion

Bartter's syndrome comprises a group of renal tubular disorders, first described by Bartter in 1962 [13]. It is rare, although an improved understanding of the nature of the condition, and its genotypic and phenotypic variations, have led to a sound classification system [14].

Antenatal Bartter syndrome is a severe form of the condition, which manifests in the antenatal setting as "unexplained" early-onset and severe polyhydramnios, with its attendant complications of preterm labour, prematurity, and postnatal dehydration. It can be a cause for serious perinatal morbidity and mortality, if undiagnosed and untreated. Due to the serious nature of this condition, prenatal consideration of the diagnosis is important in formulating both antenatal and postnatal management.

The fetal medicine literature is confused with regards to the sensitivity and diagnostic clarity afforded by the finding of altered biochemistry and hormone levels in amniotic fluid [1, 3, 5, 6, 8-10] when compared with normal levels [11]. There is a commonly held misconception, repeated in review articles [1, 6, 8, 9] that amniotic fluid chloride levels are consistently elevated and diagnostic for Bartter syndrome. Amniotic fluid chloride levels were indeed elevated in this case. However, in the largest cohort of antenatal Bartter syndrome cases studied [10], no significant differences in chloride levels in amniotic fluid were noted on comparison of Bartter-affected versus non-affected pregnancies. Instead, those workers suggested a significant reduction in the total protein level in the amniotic fluid of Bartter-affected fetuses as the most useful antenatal indicator, a finding not present in this case. Furthermore, because Bartter syndrome is associated with hyperreninemia, and hyperaldosteronism, increased amniotic fluid aldosterone levels have been described in the setting of antenatal Bartter syndrome [3, 5]. However, amniotic fluid aldosterone levels were reduced in this case.

This case report highlights the inconsistency of abnormal findings on analysis of amniotic fluid in the setting of Bartter's syndrome, and the diagnostic uncertainty that may accompany these varied results. While findings of elevated chloride or reduced protein levels would strengthen the provisional antenatal diagnosis, it would be unwise to discount the possibility of the condition in the event of "normalcy" of these values. It is suggested that in the setting of severe and early-onset polyhydramnios in a karyotypically normal fetus without evidence of structural anomaly, and where the fetus is either normally grown or growth restricted, that antenatal Bartter syndrome remains the working diagnosis both antenatally and in the neonatal period, until such time that a more likely diagnosis emerges.

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