Antenatal Bartter Syndrome: A Rare Case Report with Successful Management

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Abstract

Bartter Syndrome (BS) is a rare renal tubular disorder. Of all the forms, the antenatal form is associated with the worst clinical outcome. A case of antenatal BS is discussed to illustrate that diagnosis in early neonatal period through a meticulous step- wise approach leading to timely initiation of treatment is possible. Extensive review suggests a possibility of diagnosis in antenatal period by simple biochemical analysis of amniotic fluid with implications to further improve perinatal outcomes.

Keywords: **Antenatal Bartter Syndrome, dehydration, hyponatremia, hpokalemia, hypochloremia, metabolic alkalosis.**

Introduction

Bartter Syndrome is a group of rare disorders of infancy or childhood transmitted by autosomal recessive mode of inheritance and clinically characterized by polyuria and an excessive renal loss of sodium and chloride associated with secondary hyperaldosteronism with normal or low blood pressure and resulting hypokalemic, hypochloremic metabolic alkalosis. Two distinct clinical forms namely "classical" and "antenatal" forms are known to exist. The classical variant is a milder phenotype, with diagnosis frequently delayed even up to adolescence. The severe antenatal variant is associated antenatally with polyhydramnios (due to fetal polyuria) resulting in premature delivery. Postnatally, such a baby presents with typical serum biochemical anomalies as above along with polyuria complicated clinically by recurrent episodes of severe dehydration and vomiting, growth retardation, failure to thrive and later hypercalciuria with nephrocalcinosis and possible progressive renal failure and death which are mostly inevitable. [1]

We report a rare case of antenatal BS which was diagnosed and managed successfully in neonatal period. [2] After extensive review of literature, we suggest a possibility of diagnosis in antenatal period by simple biochemical analysis of amniotic fluid with implications to further improve perinatal outcomes.

Case report

A 2100g female baby was delivered by emergency caesarian section to a Muslim consanguineous couple at 34 weeks of gestation. Antenatally, pregnancy had been complicated by severe polyhydramnios (amniotic fluid index 40). The work up for polyhydramnios including glucose tolerance, thyroid functions, VDRL, TORCH serology, antiphospholipid, anticardiolipin and lupus anticoagulant antibody, fluorescent in situ hybridization analysis were normal. Karyotype was 46 XX. Mother was symptomatically managed antenatally with Indomethacin. Previous pregnancy had been complicated with polyhydramnios and resulted in intrauterine death of the fetus.

Baby was roomed in with mother and was accepting breast feeds. At 48 hours, baby was brought to nursery with moderate dehydration (15% cumulative loss since birth) despite good urine output. Sensorium, perfusion and blood

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pressure were normal. Sepsis screen was negative. Serum sodium was 124mEq/L, potassium 3.8mEq/L, blood urea 90mg/dL, serum creatinine 0.7mg/dL, uric acid 15.6mg/dL, blood sugar150mg/dL and no glycosuria. A low serum osmolarity of 268mosm/kg confirmed true hyponatremia. Hyponatremic dehydration was corrected.

Baby clinically appeared well and was accepting and retaining breast feeds. However, unexplained recurrent episodes of symptomatic hyponatremia started occurring. There were no clinical features of sepsis/ diarrhea/ vomiting. Blood pressure was normal and cumulative weight loss reached 22% by day 5 despite repeated deficit corrections. In view of episodes of retrocollis and ophisthotonus posturing, cranial USG and MRI brain were done and were normal.

Further investigations revealed spot urinary sodium of 92mEq/L, establishing sodium loss site to be renal. Normal value of serum 17 hydroxy-progesterone level of 20.20ng/ml (normal<55.0ng/ml) and absence of virilization ruled out congenital adrenal hyperplasia. Hypokalemia (serum K^+ 2.4meq/L), hypochloremia (76meq/L) and metabolic alkalosis appeared by day 7 of life. Serum aldosterone was raised {878.22pg/ml (normal range 25 – 315pg/ml)} with normal plasma rennin activity (0.25ng/ml/h). Spot urinary calcium, spot urinary calcium creatinine ratio and serum magnesium level were 13.2mg% (normal<4mg %), 0.7 (normal <0.5 for 35wk gestation) and 1.90 mg/dL (normal range 1.70 – 2.30 mg/dL) respectively.

In view of hyponatremia, natriuresis, hypokalemic- hypochloremic metabolic alkalosis with hyperaldosteronism and normal blood pressure, a renal salt losing tubulopathy was considered. Additionally, in the presence of hypercalciuria and normomagnesemia associated with idiopathic polyhydramnios and preterm delivery, a diagnosis of antenatal BS was made.

Baby was managed with fluid correction, sodium and potassium supplementation. Baby required fluid up to 300ml/kg/d and sodium and potassium up to 20mEq/kg/d each. Oral indomethacin was started at low dose of 0.5mg/kg/d. Further dose was titrated against serum Na^+ and K^+. Indomethacin dose needed to be increased up to 4mg/kg/d. Baby started gaining weight and sodium- potassium requirements decreased after initiating therapy with Indomethacin. Serial values of serum electrolytes, platelet count and renal function tests on follow up were normal. However, there was suggestion of specks of nephrocalcinosis on ultrasonography. At 34 months of corrected age, she weighs 11.5 kg with a normal neuro-motor- sensory (visual and auditory) development.

Discussion

Bartter Syndrome (BS), a rare form of renal salt losing tubulopathy was discovered by Dr. Frederic Bartter in 1960. [3]Incidence of neonatal BS is 1.2-1.7 per million live births and varies with prevalence of consanguineous marriage. However, antenatal form is even rarer with no available incidence data. [4]Of the reported infants, most succumb in neonatal period itself, possibly due to delay in diagnosis or management. [2]

We describe this case to illustrate that an early diagnosis based on a sequential logical step- wise approach, followed by prompt initiation of appropriate therapy and early enrolment for a strict vigilant follow up leads to a reasonably good overall outcome in cases of antenatal BS.

BS is caused by loss of function mutations in genes encoding for proteins of various channels involved in sodium potassium chloride channel transport in the renal tubule. The type of channel involved characterizes the onset, severity and prognosis. NaK2Cl or ROMK channel is defective in antenatal Bartter. [1]

The genetic diagnosis of BS is performed only after a clinical diagnosis in an affected newborn. For a first pregnancy with idiopathic polyhydramnios, or when mutations are unknown in the index case, prenatal genetic diagnosis is not possible and in such cases amniotic fluid analysis may help in predicting diagnosis of antenatal bartter syndrome. In event of the index case, mutation being known prenatal, diagnosis may be possible for subsequent case by mutational analysis of genomic DNA from cultured amniocytes. However, it is not possible because of the delay that occurs in gene sequencing for four genes, prohibitive cost and poor accessibility in our country. [7]

It has been shown that antenatal BS can be prenatally diagnosed with simple biochemical analysis of amniotic fluid markers with good diagnostic accuracy, even in the absence of a family history. All cases of idiopathic maternal polyhydramnios should have amniotic fluid analysis (AFA) for protein and alphafetoprotein levels to diagnose the index case. Amniotic fluid Bartter index = (protein MoM) x (AFP MoM) x 1000 Bartter index (calculated as patient's protein

x patient's AFP/ mean protein x mean AFP for respective gestation age, all values in g/L measured in amniotic fluid) cut off value less than 0.25g/L has a sensitivity of 93%, specificity 100%, positive predictive value of 100% and negative predictive value of 98% to diagnose BS antenatally. [8]Hence, possibility of accurately diagnosing antenatal BS, based on a simple biochemical analysis of amniotic fluid offers opportunity for early specific maternal and neonatal management of such cases with chances of better outcomes for a disease with otherwise dismal outcome. 10

Key Messages

- Antenatal form is a severe variety of Bartter Syndrome (BS).
- Antenatal BS should be suspected in every case of idiopathic maternal polyhydramnios.
- Antenatal management of mother with indomethacin and postnatal management of neonate with indomethacin along with appropriate fluids and electrolytes can lead to better outcome of a baby with BS.
- Recent methods of simple biochemical amniotic fluid analysis in cases of idiopathic polyhydramnios offer an easy and accurate way to diagnose antenatal Bartter Syndrome for appropriate pregnancy follow up and optimal neonatal outcomes.

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