Case Report

A case report of antenatal bartter syndrome

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Abstract

Bartter syndrome is a rare renal tubulopathy first described by Frederic Bartter in 1962. The primary pathogenic mechanism is defective transepithelial chloride reabsorption in the thick ascending limb of loop of Henle (TALH). The disease is characterized by hypokalemia, metabolic alkalosis, and secondary hyperaldosteronism with normal to low blood pressure due to renal loss of sodium and hyperplasia of juxtaglomerular apparatus. The two distinct presentations of Bartter syndrome are antenatal bartter syndrome (ABS) and classical Bartter syndrome.We present a rare case of antenatal bartter syndrome.

Key words: bartter syndrome, polyhydraminos , ante natal.

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INTRODUCTION

Mrs S, G3 P2 L0 at 24 weeks plus 6 days of gestational age came to the OPD of our hospital for routine antenatal check up. First trimester was uneventful. She felt quickening at 5 months of amenorrhea. At 20 weeks of gestational age anomaly scan was done which showed polyhydraminos with no gross foetal congenital anomalies. At 24 weeks plus 6 days a repeat scan was done for her at our hospital which showed polyhydramnios with single vertical pocket of liqour 13.8 cms. Her blood sugar levels were normal. All other routine investigation for the patient were normal. During her first pregnancy she had PPROM at 32 weeks and she delivered vaginally a girl baby of weight 1.7 kg with poor Apgar score. Baby had early neonatal death on day 3 of life .During her second pregnancy she was diagnosed to have polyhydramnios at 26 weeks and amnioreduction was done twice. She went into pre term labour at 30 weeks and was diagnosed to have intra uterine foetal demise and expelled a girl baby of 1.2 kg by assisted vaginal breech delivery. In view of her past obstetric history and also recurrence of un explained polyhydramnios she was suspected to have antenatal bartter syndrome. Patient and attainders were counselled regarding the plan of management and the possible outcomes and prognosis of the baby, in consultation with the foetal and perinatal medicine specialists. Patient was closely observed and was admitted at 30 weeks of gestational age. In view of amniotic fluid index of 54.8,patient was planned for amnioreduction after giving antenatal corticosteroids (injection betamethasone 12mg intramuscularly two doses 24 hours apart).Detailed counseling was given about the further plan of action. Ultrasound guided amnioreduction was done, 2 litres of fluid was removed and same sent for biochemical analysis. Amniotic fluid analysis which showed the following Na+143-Meq/L,K+-3.4Meq/L,Cl-121Meq/L,HCO3-18Meq/L. Modified biophysical profile was done biweekly. Growth scan was repeated at 31 weeks which showed rapidly increasing polyhydramnios .In view of precious pregnancy with bad obstetric history and AFI of 56.8cms patient was planned for Elective LSCS at 32 weeks of gestational age. Intra operatively 2000 ml of amniotic fluid was drained. A alive baby girl with birth weight of 2.25 kg and APGAR score of 8/10, 9/10 was delivered. Postnatally baby was in NICU care for 2 months and was discharged and is on follow up.

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DISCUSSION

Antenatal Bartter syndrome has four variants [5, 6] with mild differences in phenotype and genotype. Principal clinical features in most of them include early onset polyhydramnios, failure to thrive, prematurity, and nephrocalcinosis. Types I, II, and III have severe antenatal symptoms, prematurity, and failure to thrive, while type IV is a mild salt losing nephropathy with mild antenatal symptoms. Type IV involves chloride channels which are present in distal nephron as well as in inner ear resulting in sensorineural hearing loss in addition. The pathophysiology involves mutation of the genes coding for ionic channels in the thick ascending limb of loop of Henle.Such mutations result in impaired channel function and defective electrolyte absorption. Thick ascending loop of Henle (TAL) has channels, namely, Na-K-2Cl cotransporter, K+ (ROMK: rat outer medulla potassium), and chloride (CIC-Kb) channels which are responsible for electrolyte absorption. K+ transport occurs through ROMK channel, whereas Na+ and Cl− get absorbed from the luminal space. Passage of Cl− from the cell into the interstitium can take place through kidney-specific chloride channels (CIC-Kb) and via K+/Cl− cotransport system. In the apical membrane, there is also an exchange of Na+/H+. Thus, the handling of chloride ions by the thick ascending loop of Henle (TALH) is an intimate part of the normal function of Na+ K+ 2CI− electroneutral cotransport, as well as K+ channels (ROMK) and Cl− channels (CIC-Kb). Any loss or altered function of Na+-K+-2CI− cotransporter and/or K+ channels as well as chloride channels results in defective Cl− transport. This defect will result in malreabsorption of Na+, K+, Cl−, and Ca2+ in the TALH and delivery of large volumes of urine with a high content of Na+, K+, Cl−, and Ca2+ to the distal tubule. In the distal tubule, part of the delivered Na+ will be reabsorbed in exchange for intracellular K+. Hence, potassium wasting occurs. Impaired Na absorption in TALH will result in increased levels of prostaglandin E2. Increased PGE2 will exacerbate primary defect of chloride transport in TALH which will stimulate renin angiotensin-aldosterone axis causing hypokalemia (due to hyperaldosteronism), and impede water reabsorption in collecting ducts leading to hyposthenuria. Hyperaldosteronism increases K wasting and stimulates exchange of intracellular H ions for K ions for intraluminal K (distal tubule and collecting duct) resulting in exaggeration of metabolic alkalosis. The normal blood pressure despite high levels of renin and angiotensin is thought to be due to nonresponsive of their blood vessels to angiotensins [1–7] Continuous loss of calcium in urine results in nephrocalcinosis [2–4] Mothers of fetuses with Bartter syndrome often present with unexplained polyhydramnios between 24 and 30 weeks of gestation [3, 4, 7] Intrauterine growth restriction may also be associated. Inability of the kidney tubule to retain salt and water results in fetal polyuria. Important biochemical abnormality in amniotic fluid is normal sodium and potassium but consistently elevated chloride levels [4, 8–12] Infants are usually born preterm. After birth, important diagnostic finding is hyposthenuria and rapid weight loss. Poor feeding and lethargy are the other symptoms. Urine examination shows low specific gravity, normal potassium but high sodium and chloride levels. However, after 1–3 weeks, level of potassium considerably rises above normal with relatively less sodium than in the first week of life. Prostaglandin levels are high in blood and urine as a secondary phenomenon [5, 6, 9, 13] Impaired sodium absorption in TALH will result in increased levels of prostaglandin E2 [13, 14] If the diagnosis gets delayed, infants may present with poor feeding, dehydration, and severe electrolyte imbalance. Transient hyperkalemia may be observed in type II ABS. Blood pressure is usually normal. Growth faltering, dwarfism, polydipsia, and weakness may be present in older children. Mild mental retardation is reported in few patients. Facial features such as triangular face, prominent forehead, large eyes, protruding ears, and drooping mouth may be present [15, 16] Sensorineural deafness is seen in type IV Bartter syndrome. Strabismus, convulsions, and increased susceptibility to infections are also reported [15, 16] Urinary electrolytes except potassium in second trimester are low in mother's urine in cases of Bartter syndrome [17] When there is early onset unexplained maternal polyhydramnios, ultrasonography should be performed to confirm structurally normal fetus and placenta. If ABS is strongly suspected, one should do amniocentesis and subject amniotic fluid for biochemical analysis. High chloride in amniotic fluid is a consistent finding and diagnostic of ABS [4, 9, 17]Mutational analysis of the genomic DNA extracted from cultured amniocytes will identify the fundamental defect [5 ,18-19 ,20] Once ABS is confirmed, mother should be treated antenatally at the earliest with indomethacin (1 mg/kg/day) in two divided doses [22] Indomethacin inhibits prostaglandin synthetase, decreases renal salt wasting, reduces fetal urine output, and thereby controls polyhydramnios. Indomethacin may lead to constriction of ductus arteriosus. Hence, patency of ductus arteriosus needs to be monitored in all such fetuses. Rapidly increasing hydramnios may require therapeutic amniocentesis. Indomethacin therapy and therapeutic amniocentesis usually allow the pregnancy to continue. Following birth, neonate should be monitored for urine output, hydration, weight loss, and electrolyte balance. Correction of dehydration and electrolyte imbalance are the important aspects of management. Potassium supplements are usually needed by 2-3 weeks.

Prostaglandin synthetase inhibitors are usually required for the disease control. Indomethacin at a dose of 1–5 mg/kg is usually recommended and well tolerated [18, 22, 23] Early initiation of indomethacin may be required in neonatal Bartter syndrome caused by mutations at gene coding for the NKCC2 transporter. Benefit from initiation of indomethacin therapy at 4–6 weeks and doses below 1 mg/kg/day is likely in patients with mutations at the ROMK channel gene [19] Colonic perforation after indomethacin administration has been reported emphasizing the importance of careful monitoring [24] Other drugs used are acetylsalicylic acid (100 mg/kg/day), ibuprofen (30 mg/kg/day), or ketoprofen (20 mg/kg/day). Addition of potassium sparing diuretics may be initially effective in the control of hypokalemia, but their effect is transient. Caution in such treatment is required as treatment with potassium sparing diuretics may be dangerous in situations of gross salt and water wasting and circulatory volume contraction. Long-term prognosis is guarded. Lack of satisfactory control may lead to morbidity, growth failure, and renal insufficiency [2, 18] Untreated ABS patients may succumb to dehydration, dyselectrolytemia, and intercurrent infections. Timely and appropriate therapy results in clinical improvement and catch up growth in majority of children. Bartter and Gitelman syndromes are autosomal recessive disorders, and neither is curable. The degree of disability depends on the severity of the receptor dysfunction, but the prognosis in many cases is good, with patients able to lead fairly normal lives. The effects of prostaglandin synthetase inhibition include an increase in the plasma potassium concentration (however, this rarely exceeds 3.5 mEq/L), a decrease in the magnitude of polyuria, and improved general well-being. With treatment, plasma renin and aldosterone levels normalize. Therapy improves the patient's clinical condition and allows catch-up growth. Bone age is usually appropriate for chronological age, and pubertal and intellectual development are normal with treatment.The effectiveness of long-term use of prostaglandin synthetase inhibitors is well established. Some patients may experience a recurrence of hypokalemia, which can be managed by adjusting the indomethacin dose or with potassium supplementation. The disease does not recur in the patient with a transplanted kidney. Significant morbidity and mortality occur if Bartter syndrome is untreated. With treatment, the outlook is markedly improved; however, long-term prognosis remains guarded because of the slow progression to chronic renal failure due to interstitial fibrosis. Sensorineural deafness associated with Bartter syndrome IV is due to defects in the barttin subunit of the ClC-Ka and CIC-Kb channels. A review of 61 cases of Bartter syndrome reported 29 with nephrocalcinosis, a condition that is often associated with hypercalciuria. Renal failure is fairly uncommon in Bartter syndrome. In a review of 63 patients, 5 developed progressive renal disease requiring dialysis or transplantation. Brochard et al. 19 reported chronic renal failure in 3 out of 42 children with a median follow-up of 8.3 years. Satisfactory prognosis after a median follow-up of more than 10 years and gallstones representing a uncommon in Bartter syndrome. Brochard et al. [19] reported chronic renal failure in 3 out of 42 children with a median follow-up of 8.3 years. Satisfactory prognosis after a median follow-up of more than 10 years and gallstones representing a new complication of ABS has also been reported [20] Benefits from renal transplantation have been mentioned. Spontaneous recovery of ABS following a period of treatment has been recognized [21]Nearly all patients with Bartter syndrome have growth retardation. In a review of 66 patients, 62 had growth retardation, often severe (below the fifth percentile for age). Treatment with potassium, indomethacin, and growth hormone (GH) has been effective. Other complications in Bartter syndrome include cardiac arrhythmia and sudden death - resulting from electrolyte imbalances and failure to thrive, and developmental delay .These are common in untreated patients. Significant decrease in bone mineral density has been documented in patients with either the neonatal or classic form.

CONCLUSION

Antenatal Bartter Syndrome though a rare case can present as unexplained, rapidly increasing polyhydraminos in late second trimester especially in the setting of bad obstetric history. High index of clinical suspicion and prompt referral to a tertiary care facility go a long way in establishing the diagnosis. Early intervention and specific treatment options play a great role in reducing the complication rates of the affected neonates though long term prognosis is still guarded.

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