Neonatal Bartter Syndrome

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Abstract

The neonatal form of Bartter syndrome is characterized by intrauterine onset of polyuria leading to severe polyhydramnios. We report a case of a 31 weeks, male baby was born by emergency Caesarean Section due to severe polyhydramnios (AFI 54). Postnatally, baby had polyuria, dehydration, hyponatremia, hypokalemia and hypochloremic metabolic alkalosis. Possibility of neonatal Bartter syndrome was supported by high serum renin and aldosterone levels. Correction of electrolytes and dehydration along with indomethacin constituted the treatment. This syndrome is reported to make paediatricians aware about the severe neonatal form of the disease.

Key words: Polyhydramnios, Bartter Syndrome, Preterm neonate, Indomethacin.

Introduction

Bartter syndrome is an autosomal recessive disorder characterized by severe polyuria and defective reabsorption of chloride in Thick Ascending limb of Loop of Henle. Prenatally, fetal polyuria leads to polyhydramnios and preterm delivery. After birth, polyuria can lead to life-threatening dehydration[1,2].The disease is characterized by hypokalemia, hypochloremia, metabolic alkalosis, hyperplasia of juxtaglomerular apparatus, hyperreninaemia, secondary hyperaldosteronism and normal blood pressure. High index of suspicion is necessary as typical biochemical changes may be masked with co-existent dehydration and infection[2].

The Case

A preterm (31 weeks), appropriate for gestational age (1.27 Kg), male baby was born of a consanguineous marriage to a 2nd gravida mother by an emergency LSCS for severe polyhydramnios (AFI 54). The baby did not require any resuscitation at birth. The previous sibling was near-term, small-for-date who died in early neonatal period for obscure reasons.

In the postnatal period, baby was noted to have triangular facies, prominent forehead, large eyes, bulb-shaped nose, and normal blood pressure. Baby had polyuria with urine output of 5 ml/Kg/hour on day1of life which increased to 7 ml/Kg/hour on day 3 and 11.7% weight loss

by day 5. Routine investigations for urine revealed a low specific gravity of 1.005. As the baby was lethargic with poor suck, relevant investigations were done to rule out sepsis. Diagnosis of neonatal Bartter was considered as baby had metabolic alkalosis, hypochloremia, hyponatremia, hypokalemia and normocalcaemia. Spot urine sodium, potassium and chloride were raised. As the serum renin and aldosterone levels were raised, diagnosis of neonatal Bartter's syndrome was confirmed on the 5thdayof life. Chest X Ray and Ultrasound of kidneys were normal.

Electrolyte abnormalities were corrected by supplementation and IV fluids were relaxed up to 220 ml/Kg/day. Nasogastric tube feeds were gradually hiked and baby achieved full nasogastric tube feeds on day 10 of life. Baby required sodium replacement up to 6 mEq/kg/day and potassium up to 8 mEq/kg/day. Indomethacin (2 mg/kg/day) was started from day 21 of life with strict monitoring of renal function and electrolyte levels. Gradually, baby improved over the next two weeks and at present two months old, thriving with adequate weight gain, developmentally normal and without nephrocalcinosis on USG.

Discussion

Primary or secondary hyperaldosteronism can lead to hypokalemic hypochloraemic metabolic alkalosis. Primary hyperaldosteronism was excluded as there was no hypertension[3]. Causes of secondary hyperaldosteronism like vomiting, diarrhea, diuretics and laxative were excluded from history in our case. Thus, Bartter syndrome (BS) and Gitelman's syndrome were considered as possibilities. The absence of tetany and near-normal serum calcium and magnesium levels ruled out Gitelman's syndrome[4].

Federic Bartter in 1962 first described BS as a combination of juxtaglomerular complex hyperplasia, hyperaldosteronism and hypokalaemic metabolic alkalosis with normal blood pressure[5]. It was traditionally classified as (a) Classic BS, (b) neonatal BS and (c) Hypocalciuric, hypomagnesemic variant described by Gitelmanet. Al[6].Seyberthet. al. suggested that neonatal BS as Hyperprostaglandin E syndrome[7].

BS is caused by mutations of genes encoding proteins causing defective chloride reabsorption in the Thick Ascending limb of Loop of Henle (TALH)[8]. The result is large volume urine and increased sodium and potassium loss at the distal tubule with activation of the renin-angiotensin-aldosterone system which increases excretion of potassium and hydrogen ions leading to hypokalaemic, hypochloraemic metabolic alkalosis[2]. Spectrum of disease includes hyperphosphatemia, hypercalciuria, nephrocalcinosis[9], magnesium deficiency[10], excess renal prostaglandin production and defects in platelet aggregation[11]. Thomas et al.[12] have described typical characteristic facies in two infants with this syndrome.

Table 1: Electrolyte levels during follow-up

Days	Na	K	Cl	HCO3	pH
Day 3 (on maintenance IV Fluid)	118	2.9	78	29	7.49
Day 10 (on EBM and IV Na/ K supplementation for 7 days)	124	3.3	88	26	7.41
Day 35 (on Indomethacin 2 mg/Kg/day for 2 weeks and Na/K supplementation for 5 weeks)	128	3.6	101	24	7.34

Table 2: Biochemical Investigations during follow-up

Parameters	Results on admission (Day 3)	Reports after treatment (day 35)
Serum Urea	69	31
Serum Creatinine	1.8	0.7
Serum Calcium	6.8	7.6
Serum Phosphate	6.5	5.5
Serum Chloride	78	101
Urinary calcium	9.1	7.2
Urinary Creatinine	7.8	6.2
Urinary chloride	30	22
FE Na	17 (normal <4%)	8
FE K	111 (normal <30%)	76
Plasma Renin	7.6 ng/ml (normal 0.2-2 ng/ml)	-
Plasma Aldosterone	3520 pg/ml (normal 50-250 pg/ml)	-

In 1971 Fanconiet. al first reported the neonatal variant of BS in two preterm babies with hypercalciuria, nephrocalcinosis and polyhydramnios[13].History of consanguineous marriage, polyhydramnios and a previous sibling death suggest autosomal recessive pattern of inheritance in our case.

BS can be autosomal recessive (BS type 1 to 4) or autosomal dominant (BS type 5). BS type 1 is linked to mutations of *SLC12A1* gene (chromosome 15)[14]. BS type 2 is linked to gene *KCNJ1* on chromosome 11q while BS type 3 is linked to the *ClCNKb*gene (chromosome 1p36). The last two genes produce proteins, ROMK and ClCN-Kb respectively, special "channels" for K and Cl[14]. The fourth gene responsible for BS type 4, *BSND*, encodes a protein product called Barttin also associated with sensorineural hearing loss[15]. The fifth gene, linked to BS type 5, is *CASR* (chromosome 3q) which produces cell-membrane Ca-sensing receptor (CaR). The neonatal type is characterized by fever, diarrhea, vomiting, osteopenia and elevated urinary excretion of prostaglandin E[14].

Prenatal diagnosis can be made by the high chloride content of the amniotic fluid and mutational analysis of genomic DNA obtained by amniocentesis. Postnatally, neonate should be monitored for dehydration, weight loss, and electrolyte balance. Sodium and Potassium supplements are usually needed by 2-3 weeks. Prostaglandin synthetase inhibitors, Indomethacin at a dose of 1–5 mg/kg is usually recommended till growth is complete[16]. Other drugs used are acetylsalicylic acid, ibuprofen, or ketoprofen[17].

Untreated patients may succumb to dehydration, dyselectrolytemia, and intercurrent infections. Hypokalemia, hypercalciuria, and nephrocalcinosis may lead to chronic tubulointerstitial nephropathy[4]. Mouraniet. Al[18] reported a preterm girl who developed nephrocalcinosis by one month despite indomethacin treatment whereas Mastumuto et al showed resolution of nephrocalcinosis despite indomethacin therapy[19]. Chan has comprehensively reviewed BS and concluded that patients with BS types 1, 2 and 4 present at a younger age than classic type like in our case[20].

Conclusion

This case is intended to alert the obstetricians and paediatricians about neonatal variant of BS which is a rare entity with life threatening postnatal course and should be suspected in every preterm baby born with a history of polyhydramnios. Early initiation with indomethacin prevents life threatening complications, decrease possibility of nephrocalcinosis and restitute normal growth. Genetic counseling for future pregnancies is helpful.

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