

# Neonatal Bartter Syndrome

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## SUMMARY

**We report a case of neonatal Bartter syndrome in a 31 weeks premature baby girl with antenatal unexplained polyhydramnios requiring amnioreduction. She presented with early onset E. coli septicaemia and severe dehydration leading to pre-renal renal impairment which obscure the typical biochemical changes of hypokalaemic hypochloreaemic metabolic alkalosis.**

## KEY WORDS:

*Bartter syndrome, Neonatal*

## INTRODUCTION

Neonatal Bartter syndrome is a rare condition resulting in defective absorption of sodium and chloride in the thick ascending loop of Henle resulting in excessive loss of urinary electrolytes and fluid. Delayed diagnosis can result in severe dehydration with increased morbidity and mortality. High index of suspicion is necessary as typical biochemical changes with hypokalaemic hypochloreaemic metabolic alkalosis may not be present early on especially with the presence of dehydration and infection.

## CASE REPORT

Infant M is the fifth child of non-consanguineous parents. She was born premature at 31 weeks and 6 days period of gestation with a birth weight of 1550 grams following an antenatal history of unexplained polyhydramnios requiring amnioreduction. She had a good Apgar score at birth with mild respiratory distress syndrome requiring nasal CPAP for 4 days. She was nursed in a double wall incubator with a humidity of 80% and was started on standard fluid regime. She was found to have early onset E. coli bacteraemia and was started on intravenous C-penicillin and gentamicin which was later changed to cefotaxime due to renal impairment. Her blood sugar and blood pressure were normal. However she was noted to be polyuric since birth with initial urine output of 4ml/kg/hour at D1 of life which increased to more than 10ml/kg/hour at 1 week of life. She rapidly became dehydrated with a weight loss of 16.7 % at D5 of life with pre-renal renal impairment and metabolic acidosis despite being on higher fluid replacement and multiple fluid boluses.

Following fluid correction and total maintenance fluid of more than 220ml/kg/day, her dehydration was gradually corrected and her renal function recovered. She remained polyuric at 2 weeks of life and was investigated further.

Biochemical investigations showed hypokalaemic hypochloreaemic metabolic alkalosis (pH 7.58, bicarbonate 28mEq/L, pCO<sub>2</sub> 20mmHg, potassium 2.8mEq/L, chloride 94mEq/L) with normal serum level of calcium and magnesium. Urine electrolytes showed increased urinary loss of sodium, chloride and potassium (urine sodium 72mEq/L, chloride 85mEq/L, potassium 31mEq/L). Ultrasound kidneys done at 2 weeks of life showed normal kidneys with no calcification. She required potassium supplementation of more than 6mmol/kg/day. Spironolactone and captopril was later added resulting in better potassium retention. There were problems clinching an early diagnosis as the serum renin and aldosterone sample were rejected twice due to sampling error. She remained polyuric with poor weight gain and only achieved back her birth weight at 1 month of life. She subsequently developed a late onset sepsis with klebsiella pneumonia and stage 2 necrotizing enterocolitis of which she was treated medically.

At 6 weeks of life, she was still polyuric and required high fluid and potassium supplementation. Based on the clinical picture and biochemical abnormalities, she was treated as suspected neonatal Bartter syndrome and indomethacin was started. This resulted in a remarkable drop in urine output to 3-4ml/kg/hour with better fluid and potassium retention. Results of the serum renin and aldosterone were finally available after 2 months of life which showed markedly elevated level of renin 55.35ng/ml in supine position (normal 0.2-2.8) and aldosterone 6155pmol/L (normal 180-2386) and with this confirmed the diagnosis of neonatal Bartter syndrome.

Soft dysmorphism described with triangular facies, prominent forehead, large eyes, protruding ears and drooping mouth were observed in this child and became more obvious with time. Subsequent ultrasound kidneys at 3 months chronological age showed nephrocalcinosis.

## DISCUSSION

Bartter syndrome was first described by Federic Bartter in 1962 as a combination of hyperplasia of the juxtaglomerular complex, hyperaldosteronism and hypokalaemic metabolic alkalosis with normal blood pressure. It was traditionally classified as neonatal, classical and Gitelman syndrome. It is caused by mutations of genes encoding proteins that transport ions across renal cells in the thick ascending limb of loop of Henle (TALH)<sup>1</sup>. A large proportion of sodium and potassium filtered in the kidneys is reabsorbed, 70% in the proximal tubule and 20% in the TALH via Na-K-2Cl co-

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transporter driven by low intracellular concentration of sodium. When these are defective, the cumulative result is a large volume of urine and increased amounts of sodium and potassium loss at the distal part of the tubule with activation of the renin-angiotensin-aldosterone system which enhances excretion of potassium and hydrogen ions leading to hypokalaemic hypochloaemic metabolic alkalosis.

Bartter syndrome is inherited as autosomal recessive and classified into 4 variants<sup>2</sup>. In neonatal Bartter syndrome type 1, mutations occur in the gene located on chromosome 15q15-q21 encoding for Na-K-2Cl co-transporter (NKCC2) of the TALH. Mutations in ROMK gene located on chromosome 11q24-25 encoding adenosine triphosphate (ATP) sensitive K<sup>+</sup> channels that recycle and reabsorb K<sup>+</sup> back into tubular lumen results in neonatal Bartter type 2. Classical Bartter syndrome type 3 and Bartter syndrome type 4 (with sensorineural hearing loss) involves the chloride channel due to mutations in the gene localized at chromosome 1p31 or 1p36, encoding for Barttin which is expressed in the TALH and inner ear.

In neonatal Bartter syndrome, maternal polyhydramnios due to fetal polyuria frequently occurs and results in premature birth as in this case. Biochemical changes of hypokalaemic hypochloaemic metabolic alkalosis, which is important for the diagnosis, may not be apparent in the first week of life due to dehydration. The condition is diagnostic with marked elevation of renin and aldosterone with normal blood pressure<sup>3</sup>. A definitive diagnosis of genetic mutation analysis is not available in Malaysia. In this case, the infant is likely to have neonatal Bartter syndrome of either type 1 or 2 due to the early age of onset, presence of nephrocalcinosis and high urinary loss of sodium, potassium and chloride.

Differential diagnoses considered and excluded were Gitelman's syndrome as there was a normal serum magnesium level; primary hyperaldosteronism as there was no hypertension and pseudo-Bartter syndrome as there were no other apparent losses from vomiting, diarrhoea or use of diuretics.

Management of neonatal Bartter syndrome include fluid hydration, potassium supplementation and indomethacin therapy which will reduce prostaglandin E overproduction and correct underlying biochemical changes and result in better growth. Indomethacin at a dose of 1.5-2.5 mg/kg/day in 3 divided doses is usually started at 4-6 weeks after birth due to the inherent risk in a premature infant<sup>3</sup>. There is no recommendation on the duration of treatment but a study had reported indomethacin use up to 12 years<sup>4</sup>. Spontaneous recovery following period of treatment has also been reported<sup>5</sup>.

### CONCLUSION

Neonatal Bartter Syndrome should be considered in any neonate with antenatal history of unexplained polyhydramnios presenting early in the neonatal period with polyuria and severe dehydration.

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