

## Failure to Thrive, Can this be Bartter's Syndrome?

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### ABSTRACT

A case series of four children, of different age groups, having complaints of polyuria and failure to thrive. These cases include two infants, a toddler and a child and investigations revealed that they had hyponatremia, hypokalemia, hyperchloremia and metabolic alkalosis, leading to a diagnosis of Bartter's syndrome. Two of the patients also had hypomagnesemia. All the children were put on treatment for Bartter's Syndrome, and they responded well but unfortunately one of them was lost to follow-up.

**Key words:** Failure to thrive, Bartter's Syndrome, Polyuria, Metabolic alkalosis.

### INTRODUCTION

Bartter's Syndrome is a rare form of renal potassium wasting characterized by hypokalemia, normal blood pressure and elevated plasma concentration of renin and aldosterone.<sup>1</sup> Bartter's Syndrome in Pakistan is a much neglected disease as it is thought to be quite rare here. 'What mind doesn't know, eyes don't see!' This phrase truly applies to Bartter's syndrome. All children with failure to thrive, polyuria and polydipsia should be investigated for this problem. Quite a number of cases might just be missed if we particularly do not look for it.

Bartter's Syndrome was first observed by Dr. Fredric Bartter. In 1962, Bartter et al. described a new disease entity in two African Americans who presented with metabolic alkalosis, hyperplasia of juxtaglomerular apparatus, and normotensive hyperaldosteronism.<sup>2</sup> It is nowadays evident that this term does not represent a unique entity but encompasses a variety of disorders of renal electrolyte transport all characterized by a biochemical picture of "hyperreninemic, hypokalemic metabolic alkalosis". Recent molecular biology findings have demonstrated that most of these patients have

an inherited defect in NaCl transport in the distal nephron either at the gene encoding the renal bumetanide sensitive Na-K-Cl co-transporter (NKCC2) or the gene encoding an ATP-sensitive inwardly rectifying K-channel (ROMK). These mutations, however, have not been found in some patients and genetic heterogeneity is suspected.<sup>3</sup>

The biochemical features of Bartter's syndrome, including hypokalemic metabolic alkalosis with hypercalciuria, resemble those seen with loop diuretic use and reflect a defect in sodium, chloride and potassium transport in the ascending loop of Henle. The loss of sodium and chloride, with resultant volume contraction, stimulates the renin/angiotensin II/aldosterone (RAA) axis. Aldosterone promotes sodium uptake and potassium secretion, exacerbating the hypokalemia. It also stimulates hydrogen ion secretion distally, worsening the metabolic alkalosis.

Hypokalemia stimulates prostaglandins, which further activates the RAA axis.<sup>1</sup>

Three forms have been described which are:

- 1 Neonatal (or Antenatal) Bartter's Syndrome,
- 2 Classic Bartter's Syndrome,
- 3 Gitelman's Syndrome.<sup>4</sup>

The incidences of Bartter's syndrome varies from country to country.<sup>22</sup>

Kwait	1.7/100,000
Sweden	1.2/100,000
CostaRica	1.2/100,000

The incidence of neonatal Bartter's Syndrome is 1 case per 50,000-100,000 newborns.<sup>6</sup>

Both familial and sporadic forms seen with mostly being autosomal recessive. There is no racial predisposition.

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Gitelman's syndrome is a much more common disease than Bartter's syndrome.<sup>7-8</sup> The magnitude of difference was evaluated in a report from the Framingham Heart Study in which the estimated prevalence was approximately 1 per 40,000 for Gitelman's syndrome and 1 per million for Bartter's syndrome.<sup>8</sup> However, the prevalence of heterozygotes may be as high as 1 percent.

Unfortunately we could not find enough local data to quote the exact incidence of the disease in our country. Few case reports are published in Pakistan and India.<sup>9-13</sup>

The diagnosis is usually made on the basis of the clinical presentation and laboratory findings. Because features of Bartter's syndrome resemble chronic loop diuretic use, diuretic abuse should be considered in the differential diagnosis, even in young children.

## CASE REPORT 1

Two months old male infant weighing 2.7 kg was admitted with severe pneumonia. He was a term baby with a birth weight of 3.4 kg and issue of a consanguineous marriage. Since birth there was complaint of failure to thrive for which top feed with cup and spoon along with breastfeed was instituted. History of polyuria was also present. On examination, he was an emaciated baby with anthropometric measurements at <5<sup>th</sup> percentile. He was tachypnoeic and had subcostal and intercostals recessions. Rest of the systemic examination was unremarkable. Lab investigations showed a high TLC and a positive C-reactive protein for which I/V antibiotics were started. Electrolytes showed hyponatremia, hypochloremic alkalosis and hypokalemia (Na-107, K-2.3, Cl-70, and HCO<sub>3</sub>-28). S.renin and Aldosterone levels were done which came out to be high despite a normal BP (S.renin-24 ng/dl, aldosterone-120 ng/dl). Serum Magnesium was normal (1.9 mg/dl) and there was no evidence of hypercalciuria. Serum urea and creatinine and ultrasound KUB were normal. The baby was put on oral rehydration therapy to which he responded and his electrolytes improved. Indomethacin was started and the general condition of the baby improved. He started gaining weight and his serum aldosterone and renin levels showed tremendous improvement after 8 weeks of therapy (s.renin:12 ng/dl, s.aldosterone:65 ng/dl). He is on aregular followup showing satisfactory growth.

## CASE REPORT 2

Four years old boy weighing 7 kg was admitted with complaints of fever, cough, vomiting and loss of appetite

for about ten days. This malnourished boy was thriving well till his first birthday when his problem of not gaining weight despite adequate nutrition started. His mother also noticed that he was passing excessive urine. At the age of two years he was hospitalized with diarrhoea, vomiting and tetany. He was managed for acute gastroenteritis and was treated for rickets. Although he never had tetany since then but still he was not thriving and always seemed to be thirsty and dehydrated. He is an issue of a consanguineous marriage and has three siblings. None of the siblings have any problem. On examination, severely dehydrated, malnourished, febrile child. H/R was 120/min., R/R was 36/min., BP was 80/60mmhg and the temperature was 103F. He had sunken eyes and was very irritable. The systemic examination revealed nothing significant. On investigations, his S.Electrolytes were deranged showing hyponatremia (112meq/l), hypokalemia (1.2meq/l), hypochloremia (80meq/l) and metabolic acidosis (HCO<sub>3</sub>-10meq/l). His CBC revealed mild neutrophilia and CRP was raised(60). There were few patchy infiltrates on the right side in the CXR. S.Calcium was very low (4.4mg/dl) and so was the magnesium (1.2mg/dl). There was no evidence of hypercalciuria. The child was rehydrated and was put on I/V Ceftriaxone after sending the blood for C/S. He was also given I/V calcium gluconate 8 hourly and therapeutic doses of Inj. Magnesium sulphate. After rehydration, his Ca and Mg levels improved but there was persistent hypokalemia (1.2-2.6meq/dl) and bicarbonate started increasing. With the history of polyuria, failure to thrive and persistent hypokalemia, Bartter's syndrome was suspected. His Renin was very high (>38ng/dl) and so was the Aldosterone (137.5ng/dl). U/S KUB was normal. The PTH level was high (probably due to a low calcium level).

We started treating him with the Oral Rehydrating Solution and oral Indomethacin (2mg/kg in three divided doses). The boy showed remarkable improvement within a week of therapy; his urinary output decreased and the overall condition improved. Within six weeks he started gaining weight and the Renin and Aldosterone levels improved. We discontinued oral magnesium and calcium after six weeks once the levels were normal. After two months we repeated the investigations which revealed decreasing levels of calcium, magnesium and persistently high levels of renin and aldosterone. At this point we increased the dose of Indomethacin and restarted calcium and magnesium.

### CASE REPORT 3

One and a half years old female child weighing 8.4 kg came to the OPD with the complaints of not gaining weight, polyuria and polydipsia for the last six months, with a history of head injury about eight months back for which a CT scan brain and an X-ray skull was done which were normal. She was a pretty looking lean-built child, issue of a consanguineous marriage and younger of the two siblings. Older sister is healthy. She had a normal BP but was slightly pale and quite irritable. Her general physical and systemic examinations did not reveal anything significant. On investigations, her RBS (both random and fasting) were normal. Hb was 9.6 g/dl, TLC was normal with a normal differential count. Urine D/R was also normal with a normal specific gravity. Serum electrolytes were deranged showing hyponatremia and hypokalemia. Serum rennin and aldosterone were raised (renin-9.33 ng/dl and aldosterone-36 ng/dl). Serum Magnesium, Calcium and U/S KUB were normal. She started improving within six weeks of starting the treatment with oral Indomethacin (2 mg/kg in 3 divided doses).

### CASE REPORT 4

Forty days old male infant, was admitted through the emergency ward with the history of fever, chronic diarrhea and failure to thrive since birth. This was his third admission in the last one month with similar complaints. He is the only child of this young couple who are first cousins. The baby was a full-term SVD, with a birth weight of 2.5 kg. He was breast fed up till 15 days of life after which he was supplemented with top feed through bottle in proper dilution. He had loose frequent stools since birth and also had polyuria as the mother had to change him every 15 minutes. On examination, he was a severely malnourished and had mottling all over the body. He had a toxic look, was dehydrated and very irritable. He had acidotic breathing, tachycardia with weak feeble pulses and was hypotensive. He was also hypothermic. There was oral thrush and angular stomatitis. The abdomen was distended with a tympanic note on percussion. There was no visceromegaly. Gut sounds were exaggerated. Investigations revealed signs of sepsis. His TLC was high with predominant neutrophilia. CRP was raised but the blood culture showed no growth. There was hypoglycemia (Random Blood Sugar 30 mg/dl), Hyponatremia (Na 112 mEq/L), hypokalemia (1.3 mEq/L), Metabolic acidosis (HCO<sub>3</sub>: 8 mEq/L). He was rehydrated, antibiotics were started and his hypoglycemia and hypothermia were corrected. Subsequent electrolytes showed persistent hypokalemia.

After he improved from sepsis his HCO<sub>3</sub> level also started rising. On this basis we investigated him for Bartter's Syndrome. His Renin was high (22 ng/dl) but the aldosterone level was surprisingly normal (12 ng/dl). Mg was also low (1.4 mg/dl) but the Calcium level was normal (8.6 mg/dl). Renal U/S was also non significant. Labeling him as Gittleman we started treating him with oral indomethacin. The baby got better; he recovered from sepsis and was feeding well. His diarrhoea improved and urinary output decreased. After 2 weeks of the indomethacin therapy his electrolytes started improving but unfortunately we lost this patient to followup.

### DISCUSSION

These case reports show the prevalence of different variants of Bartter's Syndrome. Cases 1 and 2 are the Classical ones; Case-1 being the neonatal variant. Although case 2 has decreased magnesium levels but we cannot exactly classify it as Gittleman's since the serum aldosterone and renin are very high in our patient and usually these levels are not that high in Gittleman's. A few cases of classical Bartter's do present with hypomagnesemia and hypocalcemia and we think that Case 2 belongs to this group. Since there is no hypercalciuria the low calcium in this case could be due to low magnesium levels. Case 4 is not a typical case of Bartter's Syndrome. In this case the S.Aldosterone level is within the normal range but renin shows mild elevation. Although the electrolytes and magnesium levels improved with the prostaglandin inhibitor (Indomethacin) but still a proper follow up was required to put a final label of Gittleman's on this baby.

All our cases, although with different disease presentations had one thing in common and that was failure to thrive! All were undernourished, height and weights below or on the 3<sup>rd</sup> centile despite being on adequate diets.

There is no definite cure for Bartter's syndrome. The mainstay of therapy is to replace what is lost. There is a great variability of pharmacologic treatment. In a lot of cases prostaglandin inhibitors have been used with success. Recently, a selective cyclooxygenase 2 inhibitor was introduced for therapy of pediatric and adult patients with Bartter's syndrome as an alternative to indomethacin. It was shown to have comparable efficacy and better tolerability profile.<sup>15</sup> Indomethacin has no direct effect on inherited renal tubular abnormality. It is beneficial because it neutralizes the amplifying effect of prostaglandins on features of Bartter's syndrome. However, Indomethacin therapy has been reported to be associated with gastrointestinal side effects like vomiting, stomachache, chronic diarrhoea,

gastriculcer, chronic gastritis and gasterocolic fistula.<sup>14</sup> On the other hand, it has been suggested that nephrocalcinosis might only be reversed by indomethacin in the early stages of development.<sup>10,15</sup>

Alongwith Prostaglandin inhibitors, angiotensin converting enzyme inhibitors such as Captopril may give additional control.<sup>11</sup>

Some patients with pharmacologic treatment recover growth velocity and improvement in other symptoms while other patients have reduced growth percentiles and serum potassium and bicarbonate do not attain adequate levels. In younger patients growth hormone may be used to prevent short stature.<sup>17</sup>

Dillon et al. used indomethacin in six of ten children for 6 to 24 months.<sup>19</sup> In the study by Abdel-al et al., all patients were treated with an aldosterone antagonist (spironolactone) and a prostaglandin synthetase inhibitor (indomethacin or aspirin) sequentially.<sup>20</sup> Growth hormone therapy was not given to our children. But studies have shown that nearly all patients with BS have growth retardation and are given growth hormone therapy along with potassium and indomethacin. A case report showed an association between BS and isolated familial growth hormone deficiency, with growth hormone therapy providing good results.<sup>21</sup>

The study by Dillon et al. showed catch-up growth in all patients treated with indomethacin therapy with remarkable clinical and biochemical improvement.<sup>18,20</sup>

Usually prognosis in many cases is good, with patients being able to lead fairly normal lives.<sup>3</sup>

## CONCLUSION

BS should be suspected in any child with history of failure to thrive and metabolic alkalosis. Early diagnosis and treatment with NSAIDs are lifesaving.

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