

## Neonatal Bartter Syndrome in association with congenital adrenal hyperplasia in a neonate — a rare combination

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### Abstract

Neonatal Bartter syndrome (NBS) is an autosomal recessive renal tubulopathy characterized by hypokalaemic, hypochloraemic metabolic alkalosis associated with increased urinary loss of sodium, potassium, calcium and chloride. There is hyperreninaemia and hyperaldosteronaemia but normotension. Congenital adrenal hyperplasia (CAH), another autosomal recessive condition, may present in the neonatal period with vomiting, hypovolaemia, failure to gain weight or ambiguous genitalia.

We report a case of NBS and CAH combination in a neonate. A male neonate born at term was admitted with history of recurrent vomiting and dehydration episodes. Investigations revealed electrolytes imbalance, metabolic alkalosis, raised aldosterone and renin levels suggestive of NBS. He was treated successfully and discharged. He was re-admitted with the same symptoms. Further evaluation confirmed the presence of CAH as well.

We report this case because of the rarity of this combination (NBS plus CAH) and to the best of our knowledge this is the first such case report from Pakistan.

**Keywords:** Neonate, Bartter syndrome, Congenital adrenal hyperplasia, Combination, Pakistan.

### Introduction

CAH is caused by enzymatic defect of one of the five steps required for synthesis of cortisol from cholesterol in adrenal cortex. In > 90% cases the deficient enzymes are 21-hydroxylase (21-OH) and 5-8% 11- beta hydroxylase whilst remaining enzymes constitute only 1% of cases. Deficiency of 21-OH enzyme leads to overproduction and accumulation of precursors proximal to the blocked enzymatic step, deficient production of cortisol, increased ACTH, increased adrenal androgens and adrenal hyperplasia. Approximately 75% of patients with classic 21-OH deficiency also have a defect in their ability to synthesize aldosterone.<sup>1</sup> Clinical features depend upon

degree of 21-OH deficiency.

Mainly three clinical phenotypes have been described in literature

- a) Classic salt losing (SW-21-OH)
- b) Classic non-salt-losing (simple-virilizing) (SV-21-OH)
- c) Non-classic (late-onset)

Male neonates with salt-losing variant present with vomiting, dehydration, failure to thrive, hyponatraemia, and hyperkalaemia typically in the second week of life.<sup>2</sup>

Since enzyme assay studies are not available in Pakistan, diagnosis of CAH depends upon clinical judgment augmented by specific biochemical abnormalities. Treatment consists of lifelong synthetic glucocorticoid and mineralocorticoid supplementation. Salt wasters also require mineralocorticoid, flurohydrocortisone, therapy. Breast fed babies need extra sodium supplementation till weaning is established.<sup>3</sup> Newer modalities of treatment consist of combination of an anti-androgen, an aromatase inhibitor and lower dose hydrocortisone. Adrenalectomy with replacement medication is under trial.

The reported prevalence of NBS in western world is one per million. Hyponatraemia, though common, is seen in only severe cases.<sup>4</sup> These neonates are usually born prematurely, may have signs of RDS, dehydration and sepsis in the neonatal period. Laboratory abnormalities include hyposthenuria, hyponatraemia, hypokalaemia, and hypochloraemic metabolic alkalosis associated with increased urinary loss of sodium, potassium, chloride and calcium. Renin, aldosterone and Prostaglandin (PGE2) levels are markedly raised in serum and are reversible. Prostaglandin (PGE2) level is also elevated in urine. In spite of all above endocrine abnormalities blood pressure is normal. Antenatal diagnosis can be established by finding raised levels of chloride and aldosterone in amniotic fluid.<sup>5</sup> Hypercalciuria is an important distinguishing marker between Bartter's and Gitelman syndrome.

### Case Report

A 25 day old male neonate was admitted with episodes of

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**Table:** Laboratory values.

Serial No.	Investigation	Result	Normal Value
1	Serum Electrolytes;		
	Sodium	125	(130-145 mEq/L)
	Potassium	3.0	(3.6-6.5 mEq/L)
2	Chloride	92	(101-111 mEq/L)
	ABGs;		
	PH	7.60	(7.35-7.45)
	PO2	96	(60-80mm Hg)
3	PCO2	38	(35-50 mm Hg)
	HCO3	35	(17-28 mmol/l)
	Urine R/E;		
4	Specific Gravity	1.001	(> 1.003)
	Urine Electrolytes;		
5	Sodium	350	(40-120 mEq/l/day)
	Potassium	276	(25-125 mEq/l/day)
	Chloride	450	(110-250 mEq/l/day)
	Calcium	422	(100-300 mEq/l/day)
6	Plasma Renin	148	(4-37 pg/ml)
7	Plasma Aldosterone	720	(40-310 pg/ml)
8	17OH progesterone	36.84	(0.03-0.90 ug/dl)
9	Serum cortisol level	0.1	(0.6-20 ug/dl)
10	Serum ACTH	↑ 80	(7-28pg/ml)
11	Urinary 17-Ketosteroids	11	(< 2mg/ 24 hrs)
	Testosterone	220	(1-170 ng/dl)

vomiting and dehydration from day 8 of life. He was being treated as a case of sepsis before referral to this hospital. He was delivered full term at home to consanguineous parents. According to the father one sibling of this baby died in the neonatal period with similar illness but remained undiagnosed.

On examination the baby was lethargic, dehydrated and afebrile. Weighed 2.3kg, FOC 35cm, length 50cm. Vital signs were within normal limits and systemic examination was unremarkable. Initial investigations showed neutrophil leukocytosis, thrombocytopenia, raised C Reactive Protein whereas Renal function tests, Liver Function Test, X-Ray Chest and Arterial Blood Gases were normal. He was managed as a case of sepsis. Patient improved progressively and was discharged from the neonatal unit. His condition deteriorated on 5th day of discharge to such an extent that he was hospitalized again. He was re-evaluated and reinvestigated. This time investigations revealed normal blood counts, normal CRP value, marked hypokalaemia, hyponatraemia, hypochloroemia and metabolic alkalosis. Ultrasonography images of abdomen (including kidney, ureter and urinary bladder) revealed no abnormality. A diagnosis of NBS was suspected and confirmed by further investigations as shown in table. Renal biopsy was planned but parents refused the procedure. Patient was

managed by correction of electrolytes and dehydration along with Indomethacine. He responded well and was discharged on 10th day of hospitalization. Parents were counseled regarding disease and treatment, advised to continue oral indomethacin and potassium chloride supplementation. He was screened for hearing loss (due to aminoglycosides toxicity and NBS association but no evidence of sensorineural deafness found) and visual impairment. After two weeks he was re-admitted a third time as vomiting and dehydration were not relieved. His laboratory investigations that included sepsis screening, electrolyte values, blood gases analysis, rennin/aldosterone, serum ammonia and lactate level all were within the normal range. Here we suspected CAH due to recurrent vomiting and dehydration. Decreased level of serum cortisol, raised 17-hydroxy progesterone, raised ACTH and raised urinary 17-ketosteroids levels confirmed the diagnosis. Electrolytes levels were not consistent with CAH. A plausible explanation for this may be coexistence of NBS. Hydrocortisone was added to therapy. His symptoms improved. At age of 4 month, parents stopped all medicines as per advice of some Hakim. Patient's clinical condition deteriorated. He was admitted, reinvestigated on parents request and again the diagnosis was confirmed. This time again renal biopsy was planned but parents refused the procedure. Follow up of patient by different ways like telephonic calls and clinic visits was possible till 8 month of age only. During follow up visits we monitored his growth, hematological and radiological parameters. At 8 month follow up his growth parameters were at 50th centile, laboratory investigations including electrolytes and hormonal assays were within normal limits and no radiological evidence of nephrocalcinosis or urogenital anomalies was present.

## Discussion

Bartter et al in 1962 described a new disease entity in two African Americans and it is now recognized as Bartter syndrome. Pathologically the primary defect is impairment in one of the transporters involved in sodium chloride reabsorption in the thick ascending limb of loop of Henle or distal convoluted tubule viz, Na-K-2Cl cotransporter (NKCC2) or apical K channel (ROMK) or basolateral chloride channel (ClCNKB).<sup>6</sup> Defect in these channels leads to impaired absorption of Na<sup>+</sup>, K<sup>+</sup>, Cl<sup>-</sup> and calcium in thick ascending loop of Henle. This cause's defective re absorption of water in descending loop of Henle. As a consequence of these defects, a large quantity of urine with high content of Na<sup>+</sup>, K<sup>+</sup>, Cl<sup>-</sup>, and Calcium is presented to distal convoluted tubule. In the distal tubule incomplete concentration of intraluminal fluid (urine) occurs at the cost of K<sup>+</sup> loss. Incomplete Na<sup>+</sup> absorption

in thick ascending loop of Henle results in raised level of PGE2 that further aggravates primary defect of Cl-transport in the thick ascending loop of Henle.

Ultimate effects of these defects are

(1) Hypokalaemia- as a result of stimulation of Renin-Angiotensin-aldosterone axis

(2) Decreased NaCl transport due to impairment of ROK channel activity and

(3) Decreased H2O re absorption in collecting ducts and hyposthenuria (urine of low osmolality) due to vasopressin

Hypovolaemia as a result of above factors activates rennin- aldosterone axis leading to hyperaldosteronism that causes K+ wasting (hypokalaemia) and metabolic alkalosis.

(4) Hypercalciuria results due to the opening and closure of K+ channels which is under control of intracellular calcium and cell ATPase.

(5) Normal blood pressure in spite of raised rennin-aldosterone levels is due to volume loss.<sup>7</sup>

NBS is managed by correction of fluid deficit and electrolyte imbalance. Prostaglandin synthetase inhibitor, indomethacine, is commonly used drug. However if indomethacine therapy is ineffective, rofecoxib (a new cyclooxygenase-2 inhibitor) may be used.<sup>8</sup> Long-term prognosis of NBS should always be guarded as far as primary disease and associated co morbidities are concerned.<sup>9</sup> Medullary nephrocalcinosis along with persistent hypercalciuria, sooner or later, will develop in nearly all NBS patients.

There is scanty amount of literature available regarding the uniqueness of this combination (NBS and CAH). In literature one case report of a girl with BS and CAH is

available.<sup>10</sup> What about the prognosis of a patient with coexistence of NBS and CAH, the literature is silent. Typical investigation abnormalities of NBS and CAH are usually not present due to overlapping of two disease processes at a same time in the same patient. How much one disease process overshadows the other is also not clear. Hyperaldosteronemia of NBS may minimize/mask the symptoms and laboratory abnormalities of CAH. But cortisol deficiency and over production of androgen precursors /metabolites are not compensated and leads to symptomatology of CAH as well.

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