DOI: 10.7860/JCDR/2018/36189.11965

Case Series

Paediatrics Section

Pseudo-bartter Syndrome as the Initial Presentation of Cystic Fibrosis in Infants: A Series of Three cases and Review of Literature

PRAWIN KUMAR[1], NEERAJ GUPTA[2], DAISY KHERA[3], KULDEEP SINGH[4]

ABSTRACT

Cystic Fibrosis (CF) is predominantly a disease of Caucasians, but it is increasingly being recognised in India. The typical presentations of CF are recurrent pneumonia and malabsorption. Atypical presentations are also increasingly being reported from India due to the differences in genotype and environmental factors. Pseudo-Bartter syndrome (PBS) is one of these atypical presentations which can present at any time after the diagnosis of CF but its presentation as an initial manifestation is rare. We hereby report three infants who presented with dehydration without obvious external losses. The investigations revealed metabolic alkalosis with hypochloraemia. A stepwise approach towards metabolic alkalosis revealed possibility of cystic fibrosis which was confirmed by sweat chloride test. All infants completely recovered with initial fluid and electrolyte therapy, following which supportive therapy for CF was started and subsequently they were discharged from the hospital.

Keywords: Hypochloraemia, Metabolic alkalosis, Pseudo-Bartter Syndrome

CASE SERIES

In this case series, we have described three infants in the age group of 5-10 months from western Rajasthan, India, who presented with features of dehydration, without any evidence of obvious external fluid loss. Parental consent was taken for all the cases for this publication.

The first case presented in Paediatrics OPD with complaints of excessive cry since one and half months of age and weight loss of 1 kg in last one month. There was no history of fever, cough, vomiting, loose motions or increased frequency of urine but on examination there was evidence of some dehydration.

The second case presented in paediatric emergency with generalised tonic-clonic seizure. There was clinical evidence of severe dehydration with shock. There was no history of loose motions, vomiting and increased urinary frequency. He had history of passing oily stool and was admitted in hospital once, for pneumonia.

The third case presented in Paediatrics OPD with complaints of poor weight gain for the last four months. He was born at term, appropriate for gestational age, birth weight was 2.7 kg, gaining adequate weight till two months and since then, he had poor weight gain. On examination, apart from failure to thrive he also had clinical evidence of severe dehydration.

The demographic profiles of all the three infants are summarised in [Table/Fig-1]. In summary, all the three infants had clinical features of dehydration without any obvious evidences of external fluid loss at the time of hospital visit.

The initial investigation in these infants revealed metabolic alkalosis with varying degree of hypoelectrolytaemia viz., hyponatraemia, hypokalaemia and hypochloraemia [Table/Fig-2]. The further work-up for metabolic alkalosis was initiated as per standard guideline [Table/Fig-3] [1,2]. The first step was to estimate 24-hours urinary chloride level. All the infants had low urinary chloride (<15 mEq/L) level i.e., chloride responsive metabolic alkalosis. There was no evidence of gastric and renal loss and they were not on any diuretics. They were not on chloride deficient formula and they did not have recent history of ventilator requirement.

After excluding common conditions for chloride responsive metabolic alkalosis, a possibility of cystic fibrosis was kept. As the sweat chloride test was not available at our centre so they were sent to paediatric pulmonology division, AIIMS, New Delhi where sweat chloride test was performed (pilocarpine iontophoresis method), which turned out to be positive (sweat chloride >60 mEq/L) in all three infants [Table/Fig-2]. Genetic test for cystic fibrosis (only 4 genes, including F508 mutation), was also sent, that was negative in all the three infants.

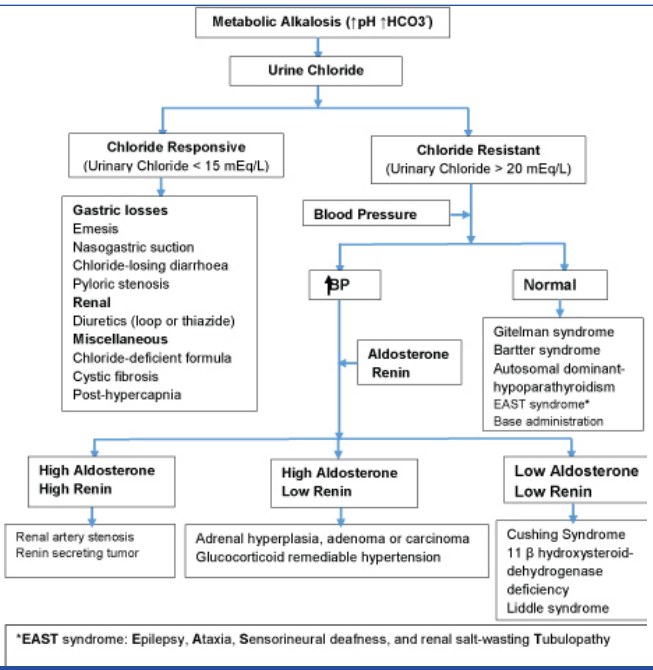
Demographic variables	Case 1	Case 2	Case 3
Age of presentation	five months	10 months	six months
Sex	Female	Male	Male
Birth weight (kg)	3.5	3.1	2.9
Perinatal period	Uneventful	Uneventful	Physiological jaundice
History of consanguinity	No	No	No
Weight at admission: kg (Z score)	5.4 (-2 SD)	6.8 (-3 SD)	4.1 (-3 SD)
History of recurrent respiratory infection	No	Yes	No
History of polyuria	No	No	No
History of diuretic use	No	No	No
History of oily stool	No	Yes	No
Blood pressure; mm of Hg (centile)[1]	90/58 (50^{th}-90^{th})	98/60 (50^{th}-90^{th})	86/54 (50^{th}-90^{th})
Family history	No similar history	One elder sibling died at 18 months with similar presentation	No similar history

[Table/Fig-1]: Demographic profile of infants with pseudo-bartter syndrome [3].

They were managed initially with parenteral fluids and with establishment of the diagnosis, the management for CF was started (Enzyme Panlipase, vitamin A, D, E, K, B-complex, extra salt along with inhalational medications (Asthalin, 3% saline and Budecort) followed by chest therapy). On the first six months of follow-up, they improved symptomatically and were compliant to therapy. The first case (youngest one) developed pneumonia with empyema on follow-up for which he required hospitalisation.

Variables	Case 1 Values (Normal)	Case 2 Values (Normal)	Case 3 Values (Normal)
Blood Gases (ABG) (at admission)			
pH	7.68 (7.35-7.45)	7.53 (7.35-7.45)	7.56 (7.35-7.45)
PO_2 (mmHg)	97.9 (80-100)	78 (80-100)	84 (80-100)
PCO_2 (mmHg)	28.8 (35-45)	36 (35-45)	32 (35-45)
HCO_3 (mmol/L)	35.7 (22-24)	32 (22-24)	33.4 (35-45)
Serum Electrolyte (mmol/L)			
Sodium (Na)	125 (136-146)	126 (136-146)	124 (136-146)
Potassium (K)	2.7 (3.5-5.1)	2.8 (3.5-5.1)	2.6 (3.5-5.1)
Chloride (Cl)	73 (98-107)	76 (98-107)	80 (98-107)
Renal function test			
Blood urea (mmol/L)	55 (10-38)	77 (10-38)	34 (10-38)
Creatinine (µmol/L)	0.31 (0.16-0.39)	0.46 (0.16-0.39)	0.28 (0.16-0.39)
Liver function test (U/L)			
SGPT	39 (<35)	103 (<35)	24 (<35)
SGOT	30 (<35)	59 (<35)	20 (<35)
24 hour urinary output (ml/kg/hour)	2.7	3.1	3.0
24 hour Urinary Chloride (mEq/day)	3.3 (<15)	5.0 (<15)	3.8 (<15)
Sweat chloride (mEq/L)	70 (<30)	121 (<40)	111 (<40)
Genetic mutations (4 genes including F508)	Negative	Negative	Negative

[Table/Fig-2]: Investigations of infants with pseudo-bartter syndrome.
SGPT: Serum glutamic pyruvic transaminase; SGOT: Serum glutamic oxaloacetic transaminase



[Table/Fig-3]: Approach to metabolic alkalosis.

DISCUSSION

Cystic fibrosis is the most common life-limiting inherited disorder in Caucasians [1]. It is now increasingly being recognised in India due to increased awareness and better availability of diagnostic facilities [4]. The typical presentations of CF are recurrent pneumonia and malabsorption. Due to differences in genotype and environmental factors, increased frequency of unusual clinical features of CF are being reported from India. PBS is one of such unusual initial presentation of CF [5]. PBS is characterised by metabolic alkalosis and a combination of varying degree of hyponatraemia, hypochloraemia or hypokalaemia [2,6]. The prevalence of PBS varies from 6.6 to 16.5 % in different CF series [7].

The underlying mechanisms of PBS are multifactorial. The most important mechanism is defective Cystic Fibrosis Transmembrane conductance Regulator (CFTR) protein leading to excessive loss of sodium and chloride in sweat which results in hypochloremia and hyponatraemia. Hypokalaemia results from excessive potassium losses in sweat as well as in urine due to secondary hyperaldosteronism in response to Extra Cellular Fluid (ECF) contraction. Metabolic alkalosis results from ECF contraction which leads to decrease filter load to glomeruli as well as increase renal absorption of bicarbonate. Hypokalaemia can also contribute to the development of metabolic alkalosis as less potassium is available to exchange with sodium in distal renal tubules which result in bicarbonate retention. All these mechanisms are more pronounced during summer when the sweat production is at maximum [2,8]. Western Rajasthan is one of the hottest regions in India so extreme temperature exposure might have contributed to the presentation of PBS.

A stepwise approach is essential in the evaluation of children with metabolic alkalosis. The first step is the measurement of 24-hours urine chloride level [9]. A value <15 mEq/day in absence of obvious evidence of volume depletion with no diuretic use favour the possibility of PBS due to CF even in absence of its common signs and symptoms.

In CF, due to defective chloride channel there is increased sweat production which leads to excessive fluid and electrolyte loss from the skin especially in young infants, who have a large body surface area in comparison to older children and adults. Since breast milk has low salt content so breastfeeding infants are especially at increased risk for PBS. Other precipitating factors for PBS in CF are diarrhoea, vomiting or respiratory infection, which are very common in CF [10]. In this case series also, all were infants and the first case was on exclusive breastfeeding. The second case had severe dehydration and shock in absence of any apparent external fluid loss at the time of emergency visit which might have precipitated PBS. Seizure, in this case may be due to severe hyponatraemia (Na:119 meq/dL) or may be the first episode of febrile convulsion.

The most common differential of PBS is Bartter syndrome as both can have metabolic alkalosis, hypochloremia, increased aldosterone and renin level, but urine chloride will be less (<15 mEq/day) in PBS while its level increased (>20 mEq/day) in Bartter syndrome. Other close differentials of PBS are pyloric stenosis, diuretic use and Gitelman syndrome.

The treatment of PBS is appropriate fluid and electrolytes administration usually by IV route but, now there is increasing evidence of treatment with modified oral rehydration solution. A retrospective study from Turkey by Yalçin E et al., had described a series of 29 CF children and PBS with median age of four months in which all initially responded with intravenous fluid therapy while 12 of them had recurrent episodes of PBS and required hospitalisation [11]. In present case series, all infants responded with initial parenteral fluid and electrolyte administration and only one of them required repeat hospitalisation for recurrent PBS.

CONCLUSION

The Pseudo-bartter syndrome could be the initial presentation of CF. A high degree of suspicion, especially in the hot climate should be kept and a stepwise approach to metabolic alkalosis will help in timely diagnosis and appropriate treatment especially in resource limited regions where the facility for sweat chloride and genetic testing are not widely available.

REFERENCES

[1] Eagan M, Green D, Voynow J. Cystic Fibrosis. In: Nelson Textbook of Paediatrics. First. South Asia Edition: Elsevier; 2016. pp. 2098-2112.
[2] Vilotijević-Dautović G, Stojanović V. Pseudo-Bartter's syndrome in patients with cystic fibrosis: a case series and review of the literature. Srp Arh Celok Lek. 2015;143(11-12):748-51.
[3] Report of the Second Task Force on Blood Pressure Control in Children-1987. Task Force on Blood Pressure Control in Children. National Heart, Lung, and Blood Institute, Bethesda, Maryland. Pediatrics. 1987;79(1):01-25.
[4] Kabra SK, Kabra M, Lodha R, Shastri S. Cystic fibrosis in India. Paediatr Pulmonol. 2007;42(12):1087-94.
[5] Wallis C. Diagnosis and Presentation of Cystic Fibrosis. In: Kendig and Chernick's Disorder of the Respiratory Tract in Children. 8th ed. Elsevier, Saunders; 2012. pp. 763-69.
[6] Kintu B, Brightwell A. Episodic seasonal Pseudo-Bartter syndrome in cystic fibrosis. Paediatr Respir Rev. 2014;15(Suppl 1):19-21.
[7] Nahida ER, Mohammed H, Guy L. Pseudo-Bartter's syndrome revealing cystic fibrosis in an infant caused by 3849+1G>A and 4382delA compound heterozygosity. Acta Paediatr Oslo Nor. 2011;100(11):e234-235.
[8] Devlin J, Beckett NS, David TJ. Elevated sweat potassium, hyperaldosteronism and pseudo-Bartter's syndrome: a spectrum of disorders associated with cystic fibrosis. J R Soc Med. 1989;82(Suppl 16):38.
[9] Greenbaum L. Electrolyte and Acid-Base Disorders. In: Nelson Textbook of Paediatrics. 8th ed. South Asia Edition: Elsevier; 2016. pp. 346-91.
[10] Fustik S, Jakovska-Maretti T, Spirevska L. 198 Electrolyte depletion with metabolic alkalosis in infants with cystic fibrosis. J Cyst Fibros. 2015;14: S108.
[11] Yalçin E, Kiper N, Doğru D, Ozçelik U, Aslan AT. Clinical features and treatment approaches in cystic fibrosis with pseudo-Bartter syndrome. Ann Trop Paediatr. 2005;25(2):119-24.

PARTICULARS OF CONTRIBUTORS:
1. Assistant Professor, Department of Paediatrics, All India Institute of Medical Sciences, Jodhpur, Rajasthan, India.
2. Associate Professor, Department of Paediatrics, All India Institute of Medical Sciences, Jodhpur, Rajasthan, India.
3. Associate Professor, Department of Paediatrics, All India Institute of Medical Sciences, Jodhpur, Rajasthan, India.
4. Professor, Department of Paediatrics, All India Institute of Medical Sciences, Jodhpur, Rajasthan, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Prawin Kumar,
Assistant Professor, Department of Paediatrics, All India Institute of Medical Sciences, Jodhpur-342005, Rajasthan, India.
E-mail: drprawin484@gmail.com

FINANCIAL OR OTHER COMPETING INTERESTS: None.

Date of Submission: **Feb 28, 2018**
Date of Peer Review: **Apr 18, 2018**
Date of Acceptance: **May 11, 2018**
Date of Publishing: **Sep 01, 2018**