

Pseudo-Bartter's syndrome in cystic fibrosis

J D Kennedy, R Dinwiddie, C Daman-Willems, M J Dillon, D J Matthew

Abstract

Seven cases of cystic fibrosis complicated by chronic salt depletion and failure to thrive were studied. After replacement of the salt deficit, the metabolic abnormalities resolved, and weight gain was rapid. This should be considered as a differential diagnosis in children who have been diagnosed as having cystic fibrosis, but who fail to thrive despite standard treatment.

thrive without severe dehydration is less widely recognised. Though most cases have been reported from North America, the syndrome has also been described in the United Kingdom.¹ We describe seven cases who presented to this hospital over the five year period May 1983 to October 1988. All cases presented during the warmer months May to October.

Hospital for Sick Children, Great Ormond Street, London, Respiratory Unit
J D Kennedy
R Dinwiddie
D J Matthew

Renal Unit
C Daman-Willems
M J Dillon

Correspondence to:
Dr M J Dillon,
Renal Unit,
Hospital for Sick Children,
Great Ormond Street,
London WC1N 3JH.

Accepted 19 December 1989

(Arch Dis Child 1990;65:786-7)

Metabolic alkalosis in association with low serum electrolyte concentrations (hyponatraemia, hypokalaemia, and hypochloreaemia) is uncommon in infancy. In the United Kingdom the more common causes included pyloric stenosis, gastric drainage without electrolyte replacement, and—less common—chloride losing nephropathy, the use of thiazide diuretics, and Bartter's syndrome. Acute salt loss in cystic fibrosis is well known, but the gradual development of abnormally low serum electrolyte concentrations, metabolic alkalosis, and failure to

Patients and methods

Seven patients, four boys and three girls, were referred for investigation (table 1). Five had already been diagnosed by sweat test (sweat sodium concentration >60 mmol/l, sweat weight >100 mg) as having cystic fibrosis. Birth weight had been normal in all cases, ranging from 2600 to 3800 g. Two (cases 1 and 3) presented with meconium ileus in the neonatal period, and three (cases 4-6) presented with recurrent chest infections, loose stools, and failure to thrive.

Despite treatment with pancreatic supplements, low solute proprietary cows' milk feeds,

Table 1 Details of patients and treatment

Case No	Birth weight (g)	Age at referral (months)	Weight (kg) at referral (centile)	Blood pressure (mmHg)	Treatment (kg/day)*	Age treatment discontinued (months)	Outcome	
							Age (years)	Weight centile
1	3150	7	4.2 (3rd)	85/60	NaCl 2 mmol decreasing to 1 mmol at 10 months, and to 0.5 mmol at 15 months	18	1 6	25th-50th 10th
2	3500	7	6.3 (3rd)	95/60	NaCl 1 mmol KCl 3 mmol initially then 1 mmol	14	2 6	50th 50th
3	2800	14	6.6 (<3rd)	110/70	NaCl 2 mmol, KCl 1 mmol	60	6.5	25th-50th
4	2600	6	4.3 (<3rd)	Not recorded	NaCl 2 mmol decreasing to 1 mmol at 20 months	24	4.5	25th
5	3500	7	5.3 (<3rd)	90/65	KCl 2 mmol	On treatment	0.9	3rd-10th
6	3400	7	4.9 (<3rd)	90/50	NaCl 3 mmol, KCl 3 mmol	10	1.6	10th
7	3800	22	12.0 (50th)	110/70	No treatment recorded	21	2	50th

*NaCl, sodium chloride; KCl, potassium chloride.

Table 2 Biochemical profiles

Case No	Age (months)	Plasma								Urine	
		Sodium (mmol/l)	Potassium (mmol/l)	Chloride (mmol/l)	Total carbon dioxide (mmol/l)	Urea (mmol/l)	Creatinine (μmol/l)	Renin activity in ng AI/l/sec (ng AI/l/hr) [†]	Aldosterone (pmol/l) [†]	Sodium (mmol/l)	Potassium (mmol/l)
1	7	127	2.5	76	36	3.2	50	4.35 (15658)	400	9	134
2*	5	121	3.2	64	41.4	3.7	—	—	—	—	—
	7	136	2.5	96	26	1.6	42	0.48 (1710)	1000	3	17
3	14	137	2.6	87	32	6.6	30	5.60 (20145)	511	37	151
4	6	130	2.4	74	39	9.2	39	4.80 (17275)	>2220	6	22
5	7	124	1.9	82	—	2.8	35	6.50 (23402)	—	6	10
6	7	133	1.8	—	—	4.3	38	—	—	3	31
7	4	—	2.3	87	34	—	—	—	—	6	149
	22	140	4.3	102	24	3.6	27	0.48 (1710)	—	—	—

*Values from referring hospital.

[†]Reference values: mean plasma renin activity <1 year 0.41 ng AI/l/sec (1459 ng AI/l/hour), range 0.13-0.87 (472-3130), 1-4 years 0.21 (757), range 0.03-0.73 (110-2610). Mean (range) plasma aldosterone concentration <1 year 788 (164-2292); 1-4 years 294 (69-946).

and physiotherapy, all the children with positive sweat tests had failed to thrive. Two children were thought to have Bartter's syndrome (cases 2 and 7). Case 2 developed failure to thrive and mild vomiting and was admitted to her local hospital at the age of 5 months. On examination her temperature was normal, and she was wasted but not dehydrated. A mid stream specimen of urine grew a pure culture of *Escherichia coli* $\times 10^5$ /ml. She had in addition metabolic alkalosis and abnormally low plasma electrolyte concentrations (table 2). She was treated with co-trimoxazole and sodium supplements. She had two further admissions with similar electrolyte disturbances that were associated with mild vomiting. On each occasion her temperature was normal and she was not dehydrated. Case 7 was also referred with a provisional diagnosis of Bartter's syndrome. He had failed to thrive, and had a positive sweat test (sweat sodium 75 mmol/l; sweat weight 429 mg) at the age of 2 months. In addition he was found to be alkalotic and had abnormally low plasma electrolyte concentrations (table 2). With potassium supplementation he rapidly gained weight and subsequently followed the 50th centile.

None of the patients were feverish when referred, and all were wasted but not dehydrated. Case 5 had a lower respiratory tract infection. A positive sweat test confirmed the diagnosis of cystic fibrosis in each case. Their electrolyte abnormalities resolved when they were given electrolyte supplements and they rapidly gained weight. Cases 2, 3, and 6 required sodium and potassium supplements, cases 1 and 4 sodium supplements alone, and case 5 potassium supplements alone. Case 7 did not require any supplements.

Discussion

In the United Kingdom, cystic fibrosis is usually considered in the differential diagnosis of metabolic alkalosis, as most children present with either respiratory or gastrointestinal symptoms. Chronic salt depletion, with failure to thrive and only mild respiratory or gastrointestinal symptoms, is not a well known complication of cystic fibrosis. In a period of five years we have seen seven cases, which prompted us to speculate that it may be commoner than previously thought.

Although the biochemical hallmark of both Bartter's and pseudo-Bartter's syndrome is abnormally low plasma electrolyte concentrations, there are important differences between the two diseases. In Bartter's syndrome, the sweat electrolyte profile is normal (MJ Dillon, personal communication) and the renal handling of electrolytes is defective. In cystic fibrosis, sweat electrolyte loss is increased, and intensive reabsorption occurs in the renal tubules. The effect of this electrolyte loss is contraction of the extracellular space and activation of the renin-angiotensin system.² In some of our patients plasma renin activity was high but plasma

aldosterone concentrations were normal, as low plasma potassium concentrations may suppress the release of aldosterone.³

Pseudo-Bartter's syndrome in cystic fibrosis has more than one cause. Chronic sweat electrolyte loss, particularly in high environmental temperatures, may be aggravated by an acute intercurrent illness with mild vomiting or diarrhoea. The intercurrent illness is not severe enough in itself to account for the metabolic upset, but acts as a precipitating event.⁴ This may be aggravated by an insufficient salt intake to compensate for the increased electrolyte losses through the skin. Affected children are not severely dehydrated but show varying degrees of hyponatraemia.

Most children with cystic fibrosis probably compensate for excess losses of sodium and potassium in sweat by increasing the rate of aldosterone secretion² and the salt intake. A few children seem to be more biochemically vulnerable, which may be the result of above average sweating⁵ and a higher potassium loss in the sweat.⁶ Alternatively, increased loss of potassium in sweat may be secondary to increased concentrations of aldosterone.

All our cases presented during the warmer months when it is likely that they had increased electrolyte losses in sweat. It is also important to note that low solute formula milks have only half the salt content of older formula milks, and the apparently increasing number of children with pseudo-Bartter's syndrome and cystic fibrosis may be partly a consequence of the change to low solute milks in the mid 1970s.

It is difficult to lay down rigid guidelines about the duration of treatment with electrolyte supplements that is required. Sodium or potassium supplements, or both, were given as needed to maintain a normal plasma electrolyte profile. They were continued until the growth curve had returned to normal and stopped when it was clear that plasma electrolyte concentrations remained satisfactory without the need for supplements.

In conclusion, pseudo-Bartter's syndrome should be considered in children with cystic fibrosis who are failing to thrive despite conventional treatment. In children presenting with metabolic alkalosis and abnormally low serum electrolytes, cystic fibrosis should be included in the differential diagnosis.

- 1 Devlin J, Beckett NS, David TJ. Elevated sweat potassium, hyperaldosteronism and pseudo-Bartter's syndrome: a spectrum of disorders associated with cystic fibrosis. *JR Soc Med* 1989;82(suppl 16):38-43.
- 2 Simopoulos AP, Lapey A, Boat TF, di Sant'Agnese PA, Bartter FC. The renin-angiotensin-aldosterone system in patients with cystic fibrosis of the pancreas. *Pediatr Res* 1971;5:626-32.
- 3 Dillon MJ, Shah V, Mitchell MD. Bartters syndrome: 10 cases in childhood. *Q J Med* 1979;48:429-46.
- 4 Nussbaum E, Boat TF, Wood RE, Doershuk CD. Cystic fibrosis with acute hypoelectrolytemia and metabolic alkalosis in infancy. *Am J Dis Child* 1979;133:965-6.
- 5 Sibinga MS, Barbero GJ. Studies in the physiology of sweating in cystic fibrosis. II. Elevated night sweating rates. *Arch Dis Child* 1961;36:537-9.
- 6 Arvanitakis SN, Lobeck CC. Metabolic alkalosis and salt depletion in cystic fibrosis. *J Pediatr* 1973;82:535-6.