Elevated sweat potassium, hyperaldosteronism and pseudo-Bartter's syndrome: a spectrum of disorders associated with cystic fibrosis

J Devlin MRCP DCH **N S Beckett** Medical Student **T J David** MD FRCP
Department of Child Health, University of Manchester, Booth Hall Children's Hospital, Manchester

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Introduction

Infants and children with Bartter's syndrome present with a history of failure to thrive, anorexia, vomiting, polyuria and hypotonia. There is a characteristic biochemical picture of low serum potassium, low serum chloride and usually a low serum sodium, accompanied by a metabolic alkalosis. The cause of Bartter's syndrome is uncertain, but increased renin and aldosterone secretion without hypertension are present[1,2]. There are other disorders in which the metabolic findings may mimic those of Bartter's syndrome, so-called pseudo-Bartter's syndrome (PBS), and it is not always appreciated that cystic fibrosis (CF) can present as PBS.

We present three cases of CF with PBS, and a closely related fourth case of CF with hyponatraemia, hypochloraemia and metabolic alkalosis but with a normal level of serum potassium. This biochemical picture may be caused by secondary hyperaldosteronism, for which a high sweat potassium may be a marker. It has been our impression that a marked elevation of the sweat potassium is often seen in otherwise well infants with CF. We have, therefore, included a fifth case which illustrates this point. In addition, we have investigated the sweat potassium in a group of patients with CF and a sample of non-CF children.

Case reports

Case 1

A 14-week-old boy presented with an 8-week history of noisy breathing, poor weight gain and frequent loose stools. His Mother had noted a salty taste to his skin. Sweat sodium and chloride were 120 and 88 mmol/l respectively, and a diagnosis of CF was made. (For further details see Tables 1 and 2.) Treatment with pancreatic supplements and chest physiotherapy was started. He was admitted to hospital at the age of 4 months with a respiratory infection, poor feeding, vomiting and failure to thrive. His condition deteriorated despite treatment with antibiotics and he was transferred to Booth Hall Children's Hospital at 5½ months of age.

On admission he was cyanosed and dyspnoeic with finger clubbing. His chest was hyperinflated with widespread expiratory rhonchi. He was grossly wasted (Figure 1), and his weight of 4.5 kg was well below the third centile. He was nursed in oxygen and was treated with intravenous ceftazidime and hydrocortisone. On admission, his serum electrolytes were within normal limits (sodium 135 mmol/l, potassium 3.9 mmol/l, chloride 91 mmol/l). Over the next 48 h, the sodium and chloride fell to 128 and 79 mmol/l, respectively. Arterial blood gases showed an increasing metabolic alkalosis over the same period (pH 7.57, standard bicarbonate 33 mmol/l.) He was rehydrated with 0.9% saline intravenously, but as his serum sodium and chloride returned to normal, his serum potassium fell to 1.8 mmol/l, requiring intravenous replacement.

After a further 24 h of intravenous fluid and electrolyte replacement, his serum electrolytes and acid-base status returned to normal (sodium 137 mmol/l, potassium 4.2 mmol/l, standard bicarbonate 28.5 mmol/l, pH 7.39). His general condition improved over the next 2 weeks, and electrolyte supplements were stopped. However, by 6½ months of age, he again showed depletion of serum electrolytes (sodium 134 mmol/l, potassium 2.1 mmol/l, chloride 80 mmol/l) and oral supplements of sodium chloride (20 mmol/day) and potassium chloride (7.5 mmol/day) were started, which resulted in normal serum electroylytes after 48 h.

Table 1. Sweat test results in patients described in case reports (see text)

Case	Age (months)	Sodium (mmol/l)	Potassium (mmol/l)	Chloride (mmol/l)	Weight (mg)
1	3	120	–	88	41
	4	97	–	171	44
	5	73	21	83	600
2	3	99	–	–	–
	5	53	37	50	286
	5	89	92	145	140
	5	85	48	109	280
	5	109	65	145	210
	10	107	38	128	284
	62	118	21	–	–
3	3	61	–	102	448
	3	58	–	110	'adequate'
	4	64	49	106	307
4	2	84	19	82	150
5	3	51	58	95	232
	3	56	53	110	'adequate'
	4	48	32	77	418

Table 2. Clinical details of patients described in case reports (see text)

Case	Presentation● 1	2	3	Age at diagnosis (months)	Age at metabolic alkalosis (months)	■ 1	2	3	Lowest serum Na (mmol/l)	K	Cl	Highest pH	HCO_3
1	+	+	+	3	5	+	+	−	128	1.8	79	7.57	34
2	−	+	−	3	9	+	+	−	127	1.9	58		
					10	−	−	−	128	1.7	42	7.67	51
3	−	+	−	3	4	+	+	−	128	2.3	75		38
4	+	+	−	2	3	+	+	+	131	5	77	7.52	52
5	+	+	−	3									

●Symptoms at presentation: 1, respiratory infections; 2, failure to thrive; 3, loose stools.
■ Symptoms at time of metabolic alkalosis: 1, poor feeding; 2, vomiting; 3, loose stools

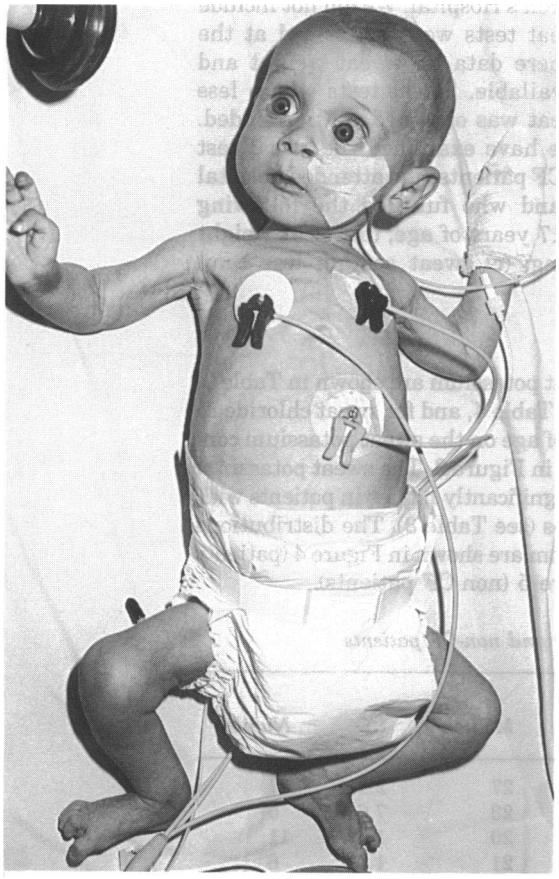

Figure 1. Case 1, aged 5½ months, showing gross wasting

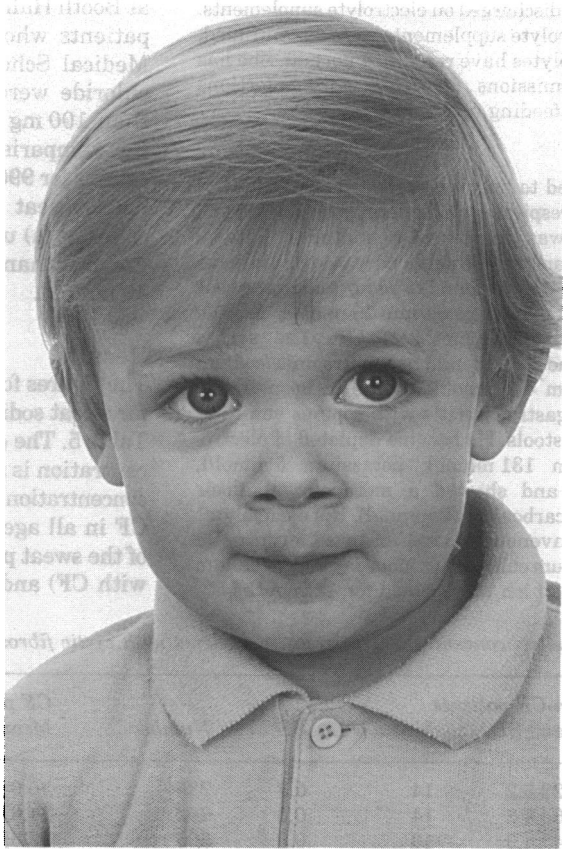

Figure 2. Case 1, aged 26 months

His subsequent progress has been excellent (Figure 2). His weight has risen steadily, and by 23 months was above the 75th centile. He has a productive cough, and his sputum is colonized with mucoid *Pseudomonas aeruginosa* for which he receives regular 3-monthly courses of intravenous ceftazidime.

An attempt to stop electrolyte suplements at 17 months again led to hypokalaemia, and at 24 months he remains on oral sodium and potassium chloride supplements.

Case 2

An 8-week-old boy presented with failure to thrive. His stools were described as normal, and there were no respiratory symptoms. A sweat sodium at 13 weeks was 99 mmol/l, and a diagnosis of CF was made. He was referred for a gastroenterology opinion because he was thought to have coexistent coeliac disease, but this was excluded by jejunal biopsy. He was found to have mild hyponatraemia (serum sodium 131 mmol/l, potassium 4.1 mmol/l, chloride 92 mmol/l) and repeated sweat tests confirmed CF but showed a high sweat potassium (for further details see Table 1).

He was readmitted at the age of 9 months, following measles. He was vomiting and refusing feeds, and his weight of 5.1 kg was well below the 3rd centile. He was found to have severe electrolyte depletion (serum sodium 127 mmol/l, potassium 1.9 mmol/l, chloride 58 mmol/l) and he was treated with intravenous fluid and electrolyte replacement, with correction of his electrolyte imbalance after 5 days.

One month later he was admitted with constipation, and was again found to have electrolyte depletion and metabolic alkalosis (serum sodium 128 mmol/l, potassium 1.7 mmol/l, chloride 42 mmol/l, pH 7.55, standard bicarbonate 51 mmol/l). Intravenous replacement again corrected his electrolyte imbalance, and on discharge he was supplied with an oral supplement of sodium chloride and potassium chloride to be

used during periods of illness. A repeat sweat test at 5 years of age confirmed a high sweat sodium and chloride, but the potassium had fallen to a lower level (see Table 1).

By the age of 12 years he had had no further metabolic disturbances.

Case 3

A 14-week-old girl was admitted to hospital for investigation of failure to thrive, which had first been noted at 4 weeks of age at the infant welfare clinic. Sweat electrolytes showed elevated levels of sodium and chloride (see Table 2) but the potassium was not measured.

While in hospital, she continued to lose weight and vomited her feeds, and she was transferred to Booth Hall Children's Hospital at 18 weeks of age. She was found to have electrolyte depletion and a metabolic alkalosis (serum sodium 128 mmol/l, potassium 2.4 mmol/l, chloride 75 mmol/l, actual bicarbonate 38.5 mmol/l). The sweat sodium and chloride were found to be similar to the referring hospital's measurements, but the sweat potassium was elevated (see Table 1).

Oral sodium chloride and potassium chloride supplements were started, and the serum electrolytes returned to normal after 3 days (serum sodium 135 mmol/l, potassium 4.0 mmol/l, chloride 96 mmol/l). Her feeding and weight gain improved and she was discharged on electrolyte supplements. At 7 months the electrolyte supplements were discontinued, and her serum electrolytes have remained normal. She has required several admissions for respiratory infections associated with poor feeding and vomiting.

Case 4

This boy was admitted to hospital three times in the first 3 months of life with respiratory infections, poor feeding and failure to thrive. He was transferred to another children's hospital because total anomalous pulmonary venous drainage was suspected. His heart was found to be normal, but sweat electrolytes (sodium 84 mmol/l, potassium 19 mmol/l, chloride 82 mmol/l) suggested a diagnosis of CF. The serum electrolytes at this time showed mild hyponatraemia (sodium 133 mmol/l, potassium 4.9 mmol/l). While in hospital, he developed rotavirus gastroenteritis with copious vomiting and frequent watery stools. He became depleted of electrolytes (serum sodium 131 mmol/l, potassium 5 mmol/l, chloride 77 mmol/l) and showed a metabolic alkalosis (pH 7.52, standard bicarbonate 52 mmol/l). His electrolytes were corrected intravenously, and he was eventually discharged on oral sodium chloride 10 mmol/day and potassium chloride 6 mmol/day which he received for 12 months.

He is now aged 3 years, and he has had no further metabolic problems.

Case 5

This 6-week-old boy had a troublesome cough and failure to thrive, and his family doctor suspected CF. He was referred to his local hospital where a sweat test was performed and the result (sodium 51 mmol/l, potassium 58 mmol/l, chloride 95 mmol/l) was interpreted as 'borderline'.

He was referred to Booth Hall Children's Hospital, and a sweat test gave similar results (see Table 1) and CF was diagnosed. At that time his weight was on the 3rd centile. He has not required electrolyte supplements, and his progress has been good. His weight was above the 75th centile at 17 months, though his chest was colonized with *Pseudomonas aeruginosa* by 9 months and he has required regular admissions for intravenous antibiotics ever since.

Patients and methods

We examined the sweat test results of all 98 children under the age of 17 years with CF who have attended the CF clinic at Booth Hall Children's Hospital from 1968 to 1988, and who have had sweat tests performed at Booth Hall Children's Hospital. We did not include patients whose sweat tests were performed at the Medical School, where data for sweat weight and chloride were unavailable. Sweat tests where less than 100 mg of sweat was obtained were excluded. For comparison, we have examined the sweat test results for 990 non-CF patients who attended hospital for a sweat test, and who fulfilled the following criteria: (a) under 17 years of age; (b) sweat weight greater than 100 mg; (c) sweat sodium less than 40 mmol/l.

Results

The figures for sweat potassium are shown in Table 3, for sweat sodium in Table 4, and for sweat chloride in Table 5. The effect of age on the sweat potassium concentration is shown in Figure 3. The sweat potassium concentration was significantly higher in patients with CF in all age groups (see Table 3). The distributions of the sweat potassium are shown in Figure 4 (patients with CF) and Figure 5 (non-CF patients).

Table 3. Sweat potassium concentration (mmol/l) in patients with cystic fibrosis (CF) and non-CF patients

	Non-CF patients				*CF patients*			
Age (months)	*Mean±SD*	*Median*	*SE*	*Number*	*Mean±SD*	*Median*	*SE*	*Number*
0-6	15.2±5.2	14	0.3	236	30.0±12.5[a]	27	2.1	37
7-12	14.6±4.2	14	0.3	202	24.6±3.4[b]	23	7.6	5
13-24	14.4±4.9	13	0.3	205	22.6±6.1[c]	20	1.8	11
25-48	14.0±4.2	13	0.3	179	19.5±3.7[d]	21	1.5	6
49+	13.6±4.4	13	0.3	168	18.2±6.0[e]	17	1.0	39

[a] $t=-7.11$, df 38.01, $P<0.005$ (separate variance estimate)
[b] $t=-2.91$, df 4.06, $P=0.043$ (separate variance estimate)
[c] $t=-5.38$, df 214, $P<0.0005$ (pooled variance estimate)
[d] $t=-3.11$, df 183, $P=0.002$ (pooled variance estimate)
[e] $t=-4.48$, df 47.90, $P<0.0005$ (separate variance estimate)

Table 4. Sweat sodium concentration (mmol/l) in patients with cystic fibrosis (CF) and non-CF patients

	Non-CF patients				*CF patients*			
Age (months)	*Mean±SD*	*Median*	*SE*	*Number*	*Mean±SD*	*Median*	*SE*	*Number*
0-6	16.5±7.2	15	0.5	236	86.8±17.7	87	2.9	37
7-12	17.9±6.9	17	0.5	202	75.8±10.6	80	4.8	5
13-24	21.0±7.7	20	0.5	205	94.3±11.8	92	3.6	11
25-48	23.6±7.6	23	0.6	179	109.0±36.0	99	14.7	6
49+	26.1±7.9	27	0.6	168	117.5±16.9	114	2.7	39

Table 5. Sweat chloride concentration (mmol/l) in patients with cystic fibrosis (CF) and non-CF patients●

Age (months)	Non-CF patients Mean±SD	Median	SE	Number	CF patients Mean±SD	Median	SE	Number
0-6	11.8±6.5	10	0.4	234	105.1±15.2	103	2.5	36
7-12	11.8±5.4	11	0.4	200	95.0±7.5	93	3.3	5
13-24	13.6±7.1	13	0.5	205	107.5±10.1	107	3.0	11
25-48	14.5±6.5	14	0.5	178	114.8±23.0	109	9.4	6
49+	15.1±6.2	15	0.5	168	120.0±13.4	119	2.1	39

●The total numbers of patients with and without CF is not quite the same as in Tables 3 and 4 because a few results for chloride were unobtainable

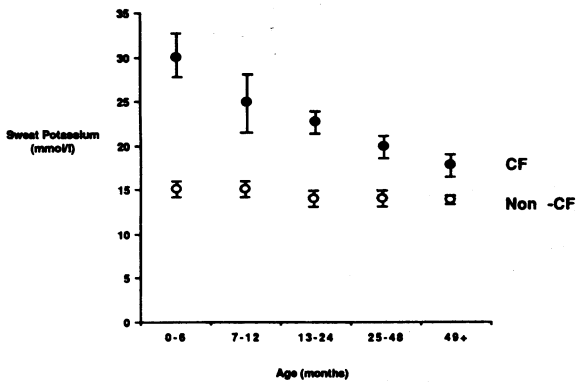

Figure 3. The effect of age on the sweat potassium concentration in patients with cystic fibrosis and non-cystic fibrosis children

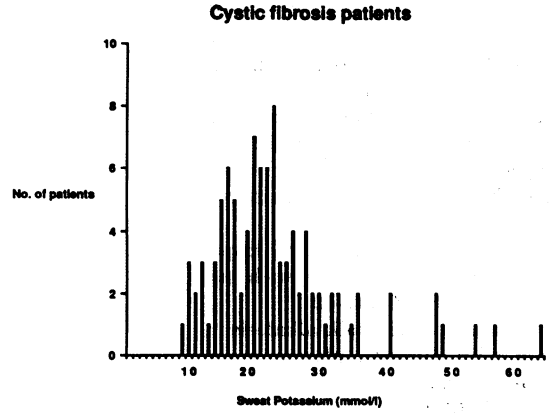

Figure 4. The distribution of sweat potassium in patients with cystic fibrosis

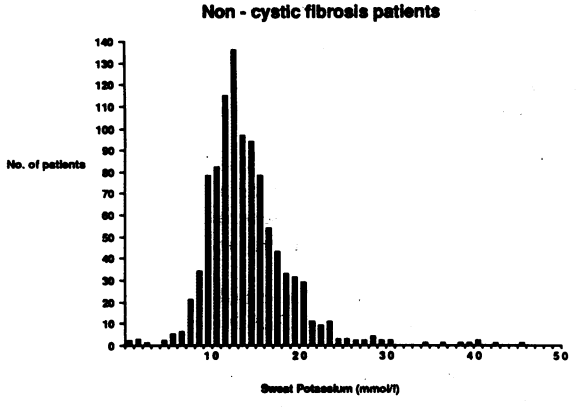

Figure 5. The distribution of sweat potassium in non-cystic fibrosis patients

Discussion

Four of our patients with CF developed metabolic alkalosis with electrolyte depletion, mimicking Bartter's syndrome. This biochemical picture in CF has been previously noted[3-8], and we have designated it Pseudo-Bartter's syndrome (PBS). It has been suggested that the two principal factors contributing to the development of metabolic alkalosis are an increase in sodium delivered to the distal renal tubule and increased reabsorption of sodium in the distal tubule with exchange for potassium and hydrogen ions[9]. Both of these conditions may be met in CF as a result of chronic loss of sodium and chloride ions in the sweat. Electrolyte depletion may be exacerbated by a low dietary intake, increased sweating or gastrointestinal losses.

Increased sodium delivery to distal tubule

It has been shown that primary dietary chloride deficiency can cause a PBS picture similar to that we have described[10,11]. It has been postulated that a decrease in chloride in the glomerular filtrate results in decreased sodium and chloride reabsorption in the loop of Henle[12]. A high concentration of sodium is, therefore, delivered to the distal tubule, where sodium is exchanged for hydrogen ions, causing a metabolic alkalosis, and for potassium ions causing hypokalaemia. A similar mechanism is likely to be present due to the chloride depletion in CF.

Increased cation exchange in distal tubule

Aldosterone causes retention of sodium and increased urinary excretion of potassium. Simopoulos and colleagues investigated the renin-angiotensin-aldosterone system in 5 patients with CF aged 13-21 years[13]. They found elevated plasma renin and aldosterone levels in all five, and they postulated that the state of secondary hyperaldosteronism was secondary to increased renin release, resulting from frequent and excessive losses of sodium in the sweat, leading to depletion of the extracellular fluid volume. In her report, however, Gottlieb showed only a slight elevation of aldosterone levels of twins with CF and a metabolic alkalosis[5], but her patients showed only borderline hypokalaemia and hypochloraemia and hence did not exhibit the full picture of PBS.

Arvanitakis and Lobeck noted that their patient with CF had a high sweat potassium and suggested that potassium loss in the sweat may contribute to the hypokalaemia and alkalosis[6]. It has been shown that patients with CF respond to exogenous aldosterone by retaining sweat sodium and increasing sweat potassium[14]. Thus the high sweat potassium

seen in two of our patients (cases 2 and 3), that of Arvanitakis and Lobeck[6] and those of Davison and Snodgrass[8], may be a marker of secondary hyperaldosteronism - that is, an effect rather than the primary cause of electrolyte depletion. The fact that our other two patients (cases 1 and 4) had normal sweat potassium levels suggests that in these patients hyperaldosteronism was not a cause of PBS. However, we suggest that a high concentration of potassium in sweat may identify CF patients who are at particular risk of PBS. When measurement of sweat potassium is not routinely available, a discrepancy between the sweat sodium and chloride concentrations (with a lower sweat sodium) should suggest the possibility of an elevated sweat potassium. Some laboratories only measure the sweat sodium concentration, and a hazard here is that in the presence of a high sweat potassium concentration, the sweat sodium level may be misleadingly low. In case 5 reported above, the sweat sodium was low enough to raise doubts about the diagnosis of CF at the referring hospital. In the case reported by Davison and Snodgrass, the sweat sodium was initially not diagnostic of CF, but the sweat potassium was relatively high (30 mmol/l)[8]. The sweat chloride was not reported. Difficulties of this sort are easily avoided if the laboratory measures sodium, chloride and potassium in all sweat samples.

Patients with CF should have their serum electrolytes and acid-base status measured at the time of diagnosis, and during subsequent acute illnesses, particularly if associated with pyrexia, vomiting or loose stools. Patients who have presented with PBS will require oral sodium, potassium and chloride supplementation. The duration for which such supplementation is necessary will differ for each patient, but may exceed 12 months as in our first patient.

There are possible long-term renal and developmental effects of PBS. Glomerular and interstitial nephritis with nephrocalcinosis leading to renal failure have been reported in patients with Bartter's syndrome[15], but have also been seen in congenital chloride diarrhoea[16], suggesting that the changes are due to the common biochemical disorder. None of our patients showed any sign of renal disease, and renal problems were not reported to accompany PBS, in previously reported cases of CF with PBS[3-8]. Katz and colleagues have recently reported a high incidence of nephrocalcinosis in CF[17]. Of 38 patients with CF who came to necropsy, 35 had evidence of nephrocalcinosis on microscopy of the kidneys, and this series included two neonates and on stillborn infant. The finding of microscopic nephrocalcinosis near the time of birth was interpreted as suggesting a primary abnormality of calcium metabolism in the kidney[17]. Katz and colleagues also found hypercalciuria in 5 of 14 patients with CF. Hypercalciuria has also been described in patients with Bartter's syndrome[18] and dietary chloride deficiency[19].

Developmental or learning difficulties are further possible consequence of PBS. Mental retardation was found in two thirds of patients with Bartter's syndrome in one series[20]. Roy and colleagues described a delay in expressive language ability in 6 of 31 infants who had developed chloride depletion as a result of receiving a milk formula deficient in chloride[21]. Poor scores in tests for learning ability and social maturity[22] and overall intelligence[23] have been reported in subjects followed up after pyloric stenosis in infancy. It is unclear whether these developmental problems are due to the electrolyte and hydrogen ion depletion which can occur in all of these conditions, or to the malnutrition which may accompany them.

Our data show that the level of potassium in the sweat is significantly higher in patients with CF than in non-CF children, and that this elevation of sweat potassium is most marked in the first two years of life. Schwarz has pointed out that as the clinical symptoms improve or disappear with treatment, the sweat sodium tends to rise and the sweat potassium to fall[24]. Our findings (see Figure 3) suggest that in patients with CF in general, a fall in the sweat potassium is an effect of increasing age.

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