Discussion

Copper deficiency has been noted in infants of low birthweight, in malnourished babies, in infants fed with a milk formula of low copper content, in patients receiving prolonged parenteral nutrition or alkali medication for renal acidosis, or on long-term zinc therapy. All these causes could be excluded in our patient and in his family.

The face and the curly hair of the propositus suggested Menkes's syndrome. However, this inherited copper deficiency is characterised by severe neurological deterioration leading to death by 3 to 4 years, by pili torti, tortuosity of arteries, and decreased caeruloplasmin levels. None of these features was found in our patient, and in Menkes's syndrome oral administration of copper is generally ineffective.[2] Considering the normal mental development and the normal caeruloplasmin levels of the child, his condition does not correspond to the 'mild form of Menkes's syndrome'[3] nor does it correspond to so called pseudo-Menkes's syndrome.[4][5]

We were not able to clarify the mechanism of copper deficiency in the family reported here. Excessive renal loss of copper and insufficient dietary intake could be ruled out, and the underlying cause is probably a defect in the absorption of copper. Considering the mild and reversible symptoms the mechanism must certainly differ from that of true Menkes's syndrome.[6][7]

The inheritance of copper deficiency in the family examined may represent an autosomal or an X-linked dominant trait.

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Pseudohypoaldosteronism. Response to long-term treatment with indomethacin

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SUMMARY A 6-month-old boy presented with features of pseudohypoaldosteronism. Considerable quantities of supplemental sodium failed to compensate his natriuresis but indomethacin, a prostaglandin inhibitor, greatly reduced his sodium requirement. Treatment was maintained for 9 months when re-evaluation showed him to be dependent on indomethacin for satisfactory control.

A boy of consanguineous Saudi-Arabian parents, birthweight 3 kg, presented from a few weeks of age with lethargy, vomiting, recurrent hyponatraemic, hyperkalaemic dehydration (for example serum sodium 109 mmol/l, potassium 7 mmol/l). There was no response to 15 µg/24 h 9α-fludrocortisone or to 2 mg/24 h DOCA but large supplements of sodium corrected the biochemical abnormalities.

He was referred to us aged 6 months, weighing 4·8 kg. Apart from a slightly raised (110/65 mmHg) blood pressure (BP) his clinical condition was normal. The principal biochemical findings are shown in the Table. Levels of urinary urea, creatinine, calcium, and phosphate, and amino-acid excretion were normal.

During a vomiting, hyponatraemic episode his resistance to 30 µg/24 h 9α-fludrocortisone was demonstrated and it was with difficulty that the

Table *Biochemical findings at age 6 months*

| Investigation	Sodium		Normal
	Depleted	Replete	
Serum			
Sodium (mmol/l)	120	135	132–135
Potassium (mmol/l)	7	4	3·3–4·5
Urinary sodium (mmol/l)	±160	±150	<30
sodium: potassium ratio	3·2	3·4	3, but <1 in hyperaldosteronism
Salivary sodium (mmol/l) fed	?	23	20–45
sodium: potassium ratio		0·78	0·3–1·0
Sweat sodium (mmol/l)	?	17	<60
sodium: potassium ratio	?	1·54	±3
Wet faeces (μmol/g)	?	25	±30
Plasma ACTH (ng/l) at 0800 h	?	54	<60
at 2400 h	?	36	<10
Cortisol (nmol/l) at 0800 h	?	275	130–550
at 2400 h	?	113	55–415
Aldosterone (pmol/l)	3120	719	150–3000 (infants)
Renin activity (pmol/ml per hour)	29·3	14·0	3–5 (infants)
17-OH-progesterone (mmol/l)	120·0	33	<15
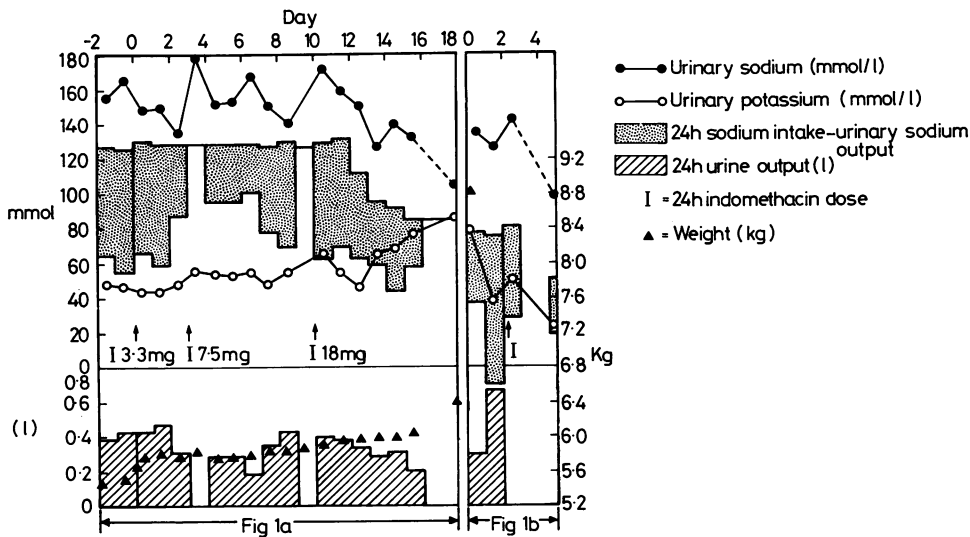
Figure *Effect of indomethacin on renal water and electrolyte excretion* (a) *at first admission* (b) *at second admission.*

osmotic diuresis was eventually compensated by large intakes of sodium 25 mmol/kg and fluid (milk) 200 ml/kg daily. His balance remained precarious however, so indomethacin was started to try to facilitate control (Fig. 1a). After a transient response to smaller doses, 1 mg/kg three times daily resulted in reduced sodium and fluid requirements after 48 hours, with improved potassium excretion and a slight drop in BP from 110/60 to 100/60 mmHg. Plasma indomethacin was 0·8 mg/l (adult therapeutic range 1–3 mg/l). Blood urea and serum creatinine levels remained normal. Four days later he became fluid overloaded, with plasma aldosterone reduced to 590 pmol/l and plasma renin activity (PRA)

reduced to 5·35 pmol/ml per hour. Daily sodium and fluid intakes were reduced to 8 mmol/kg and 150 ml/kg respectively. He was discharged on indomethacin, weighing 6·4 kg.

On review at age 18 months he had required a few brief admissions for vomiting. BP was 100/60 mmHg. He had been receiving 2·1 mg/kg daily indomethacin with a sodium intake up to 9 mmol/kg. PRA was 22·4 pmol/ml per hour, plasma aldosterone 840 pmol/l, and aspartate transaminase 58 IU/l (normal <40). His length (74·7 cm) and weight (8·8 kg) were just below the 3rd centile but were appropriate as his parents were small.

When indomethacin was stopped without altering

sodium or fluid intake, he entered negative sodium balance within 48 hours and became dehydrated (Fig. 1b). The pseudohypoaldosteronism (PHA) had clearly not remitted so he was discharged on indomethacin 2 mg/kg daily with sodium 6 mmol/kg, and fluid about 120 ml/kg.

Discussion

This patient differs from others previously reported by the severity of his osmotic diuresis and by his maintenance treatment with indomethacin. The pattern of response raises questions about the pathophysiology of PHA.

Since 1958, 42 cases of PHA have been described.[1] Common features have been vomiting, lethargy, and failure to thrive from early infancy; there is salt-wasting and hyperkalaemia with raised levels of plasma aldosterone and PRA.[1-4] Most cases have presented with natriuresis, but one report demonstrated multiple aldosterone end-organ resistance, and another showed only sweat and salivary gland insensitivity.[3] Control has been achieved by large dietary sodium supplements.[1-4] Some cases have been familial.[1 2]

(1) **Aldosterone end-organs.** The membrane-bound enzyme system Na, K-ATPase, is normally stimulated by an increased sodium work load on the nephron.[4] Support was therefore given to the concept of intrinsic tubular abnormality when Bierich and Schmidt found deficient Na, K-ATPase activity throughout the renal tubule in a case of PHA.[4] At least distal tubular aldosterone insensitivity must be present to explain the hyperkalaemia; effects of aldosterone on the proximal tubule are controversial.[6] Further evidence for end-organ resistance is given by involvement of other aldosterone targets in PHA[3] and by its resistance to exogenous mineralocorticoids.[1]

(2) **Renin-aldosterone axis.** Raised aldosterone levels could be explained partly by a direct positive feedback from the end-organ or from hyperkalaemia, and partly by activation of the RA-Aldos axis in response to impaired renal perfusion.[5] Excess PRA is reflected in hyperplasia of the juxtaglomerular apparatus in PHA.[4] In our patient, raised plasma 17-OH progesterone and aldosterone (Table) in a salt-depleted state supports an increased renin-aldosterone drive, rather than an 18-oxidation defect. Urinary adrenal androgen and corticosterone metabolites were also slightly raised in the depleted state.

(3) **Prostaglandins.** The renal PGs were first incriminated in PHA by Rampini *et al*.[2] Their patient had less natriuresis during a 4-day course of indomethacin. Renal PGs E1 and E2 promote vasodilatation, saliuresis, kaliuresis, and hydromosis. During hypovolaemia, they probably contribute to renovascular homeostasis by redistributing blood to the juxtamedullary nephrons, which are in fact predominantly natriuretic.[5] PGE_2 inhibits Na, K-ATPase[5] so its overactivity would partly explain the findings of Bierich and Schmidt.[4] Water loss is promoted by PGE_1 through inhibition of cyclic-AMP-mediated collecting duct sensitivity to vasopressin and PGE_2 can stimulate the RA-Aldos system.[6]

PHA involves multiple, complex interactions between aldosterone end-organs, renal PGs, and the RA-Aldos system, creating a vicious circle. Salt-wasting seems to persist in adulthood but the tendency to negative sodium balances is ameliorated by age 2 years in most cases, possibly through the combined effects of an improved salt appetite and maturation of end-organ ATP-ase function.[1-4] The persistently raised PRA at 18 months in our patient illustrates that, although the clinical effects of PHA were controlled, biochemical compensation remained incomplete.

The potential toxicity of indomethacin precludes its recommendation for routine treatment of PHA (our patient's AST levels, for example, were slightly raised) but in severe, life-threatening cases it may be a valuable adjunct to sodium supplementation.

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