Salt-losing syndrome in 2 infants with defective 18-dehydrogenation in aldosterone biosynthesis

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SUMMARY Two infants presented with a salt-losing syndrome, the presenting features of which were subtle. One case appeared to be transient. Deficient production of aldosterone was shown by plasma renin activity and plasma aldosterone profile. Gas chromatography-mass spectrometry of urine indicated a defect in 18-dehydrogenation of 18-hydroxycorticosterone. Treatment with salt supplements and 9α-fludrocortisone reversed the salt-losing state and in one case treatment was later stopped. Although the disease may appear transient, the biochemical defect is persistent and for adequate growth a positive salt-balance is necessary.

Salt loss of adrenal origin is due to defective production of aldosterone. This may be associated with deficient production of other adrenal steroids or can be an isolated defect of 18-oxidation of corticosterone. This study concerns 2 children with hypoaldosteronism due to defective 18-dehydrogenation of 18-hydroxycorticosterone. The presenting features of failure to thrive, anorexia, vomiting, loose stools, and intermittent pyrexia were subtle. Abnormalities of the serum electrolytes were transient. Plasma renin activity (PRA) and aldosterone concentration (PAldo) profiles showed an inappropriate secretion of aldosterone at a time of salt loss. These findings were helpful in making an early diagnosis in one child and confirming a suspected diagnosis in the other.

Case reports

Case 1. A male infant was born at term, birthweight 2.8 kg. There were 2 healthy male sibs. He was fed with a cows' milk formula, and remained well until the end of the first week of life. He then began to vomit his feeds. A urinary tract infection was diagnosed and the symptoms resolved with antibiotic treatment. Throughout the following months he fed poorly and vomited frequently. Growth retardation was prominent in spite of the introduction of solids. He was investigated at the age of 8 months. He was then a small infant of 5.3 kg and height 63 cm. There was no abnormal pigmentation. Blood pressure 80/50 mmHg. The male external genitalia were normal.

Initial investigations showed a normal blood count and plasma electrolytes; blood urea 8.5 mmol/l (51 mg/100 ml). Urine was sterile and an intravenous pyelogram normal. Shortly after admission he became dehydrated after a minor episode of diarrhoea and vomiting. At this time, plasma Na was <122 mmol/l (<122 mEq/l), K 6.6 mmol/l (6.6 mEq/l), and blood urea 15.1 mmol/l (91 mg/100 ml). Urinary Na excretion was 36 mmol/24 h, and K 8 mmol/24 h when Na intake was 77 mmol/24 h. During the initial salt-wasting period inappropriately low levels of PAldo were found compared with extremely high PRA. These investigations together with others of adrenal function are summarized in Table 1. Serial 24-hour urine collections during the salt-wasting period were assayed for excretion of aldosterone metabolites and precursors (Table 2).

Na balance and clinical progress are shown in Fig. 1. Several episodes of pyrexia, vomiting, and loose stools occurred for which no infective cause could be found. During these episodes excessive urinary salt loss occurred. Initial management consisted of increasing salt intake to correct excessive salt loss until preliminary investigations were complete. PRA/PAldo profiles strongly suggested a deficient aldosterone secretion, and replacement therapy was started with 9α-fludrocortisone (9αFC), 0.05 mg/day. In spite of this, further episodes of salt-
Table 1 18-dehydrogenase defect

<table>
<thead>
<tr>
<th>Case 1</th>
<th>Case 2 (aged 2 years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRA 48 000 ng/l per h (normal mean 1459, range 472–3130)</td>
<td>PRA 26 720 ng/l per h (normal mean 757, range 110–2610)</td>
</tr>
<tr>
<td>PAldo 611 pmol/l (normal mean 789, range 164–2936)</td>
<td>PAldo 486 pmol/l (normal mean 295, range 69–948)</td>
</tr>
</tbody>
</table>

**Urinary excretion (mg/24 h)**
- 17-oxo: 3.1
- 17-hydroxy: 5.6
- Oxy-index: 0.1

**Synacthen 0-125 mg**
- Plasma cortisol: 557 nmol/l Before / 1327 nmol/l After

<table>
<thead>
<tr>
<th>ACTH 40 units/day × 3 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma cortisol: 449 nmol/l Before / 1021 nmol/l After</td>
</tr>
<tr>
<td>Urine 17-oxo: 3.5 µmol/24 h Before / 10.5 µmol/24 h After</td>
</tr>
<tr>
<td>, 17-hydroxy: 7.0 µmol/24 h Before / 49.0 µmol/24 h After</td>
</tr>
<tr>
<td>, pregnanetriol: 0.6 µmol/24 h Before / 12.6 µmol/24 h After</td>
</tr>
<tr>
<td>, oxy-index: 0.29 Before / 0.71 After</td>
</tr>
</tbody>
</table>

PRA = plasma renin activity; PAldo = plasma aldosterone.

Table 2 Urinary excretion of aldosterone precursors and metabolites with plasma electrolyte and treatment data

<table>
<thead>
<tr>
<th>Case 1</th>
<th>Case 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma sodium (mmol/l)</td>
<td>124</td>
</tr>
<tr>
<td>Plasma potassium (mmol/l)</td>
<td>48</td>
</tr>
<tr>
<td>9αF (mg/24 h)</td>
<td>124</td>
</tr>
<tr>
<td>Salt (mmol/24 h)</td>
<td>&lt;3.5</td>
</tr>
<tr>
<td>Steroid excretion (mg/24 h)</td>
<td>—</td>
</tr>
<tr>
<td>Aldosterone metabolites</td>
<td>—</td>
</tr>
<tr>
<td>Tetrahydroaldosterone</td>
<td>—</td>
</tr>
<tr>
<td>Corticosterone metabolites</td>
<td>—</td>
</tr>
<tr>
<td>Tetrahydrocorticosterone</td>
<td>89</td>
</tr>
<tr>
<td>Allo-tetrahydrocorticosterone</td>
<td>645</td>
</tr>
<tr>
<td>18-OH corticosterone metabolites</td>
<td>—</td>
</tr>
<tr>
<td>18-OH tetrahydro compound A</td>
<td>165</td>
</tr>
<tr>
<td>18-OH tetrahydrocorticosterone</td>
<td>150</td>
</tr>
</tbody>
</table>

Wasting occurred associated with pyrexia and vomiting (Fig. 1) and 9αFC was increased in a stepwise manner. Na balance was eventually achieved as indicated by a normal PRA on 77 mmol supplemental NaCl per day and 0.5 mg 9αFC per day. At this time plasma Na and K had returned to normal. Blood pressure remained normal on the large dose of mineralocorticoid used, and no further episodes of pyrexia and vomiting occurred. This was followed by a period of catch-up growth.

At the age of 1 year it was possible to reduce the dose of 9αFC though the child still required the same salt supplementation to maintain sodium balance.

**Case 2.** A female infant was born at term, birthweight 4.06 kg. She was the first child of healthy unrelated parents. From birth she vomited her feeds frequently and weight gain was poor. She was eventually investigated at the age of 5 months, in view of persistent vomiting and marked growth retardation. She was then small, weight 4.8 kg, height 58 cm. Blood pressure 90/60 mmHg. External genitalia normal.

Initial investigations showed a normal blood count, sterile urine, and a normal intravenous pyelogram. A barium swallow and meal was also normal. Plasma Na was 120 mmol/l, and urinary Na concentration 109 mmol/l.

A salt-wasting state was diagnosed and treated with increased salt supplements (Fig. 2). Na balance was achieved on a daily intake of 70 mmol. When the Na intake was reduced to 12 mmol daily, plasma Na fell to 125 mmol/l, and at this time PAldo was inappropriately low at 250–278 pmol/l. Further investigations of adrenal function are summarized in Table 1.

Treatment with 9αFC (0.025 mg daily) and NaCl (40 mmol daily) was started. Na balance and subsequent progress are shown in Fig. 2. 9αFC was
stopped after 3 weeks and salt balance maintained by dietary Na supplements of 40 mmol daily. Negative Na balance ensued and she was restarted on 9aFC (0.05 mg daily) and NaCl (66 mmol daily) as shown in Fig. 2.

At the age of 23 months she was reinvestigated. She had enjoyed a period of catch-up growth; height and weight were now 81 cm and 10.3 kg respectively. Na balance and PRA/PAldo profile studies were undertaken while on treatment with 9aFC and NaCl, a normal diet, and a low-salt diet.

**Laboratory methods**

Plasma and urine electrolytes were measured by flame photometry in a simultaneous 5-channel

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**Fig. 1** Case 1. Sodium balance, clinical progress, PRA/PAldo profiles, and treatment. PRA = plasma renin activity; PAldo = plasma aldosterone; 9aFC = 9afluorocortisone.

**Fig. 2** Case 2. Sodium balance, clinical progress, PRA/PAldo profiles, and treatment.
Auto-Analyser. Standard methods were used for the estimation of urine 17-hydroxycorticoids (Clayton et al., 1963), 17-oxosteroids (Prout and Snaith, 1958), and the 11-oxygenation index (Clayton et al., 1971). Competitive protein-binding methods were used to determine plasma cortisol (Barnes et al., 1972) and 17-hydroxyprogesterone (Barnes and Atherden, 1972). Plasma ACTH was determined by radioimmunoassay (Rees et al., 1971). PRA was measured by the radioimmunoassay of generated angiotensin I (Dillon, 1975); PAIodo was measured by radioimmunoassay after extraction and chromatographic steps (Dillon and Ryness, 1975). Urine aldosterone metabolites and precursors were analysed by gas chromatography-mass spectrometry; the technique is described in detail in a separate communication (Shackleton et al., 1976).

Results

The PRA/PAIodo profiles in both patients in the presence of salt-wasting indicated a defect in the secretion of aldosterone. Congenital adrenal hyperplasia due to 21-hydroxylase deficiency and congenital hypoadrenalism were excluded by the appropriate investigations.

Urinary excretion of aldosterone precursors was abnormal and is given in detail in Table 2. Corticosterone metabolite excretion, particularly allo-tetrahydrocorticosterone, was grossly raised suggesting a defect in the 18-oxygenation of corticosterone. A defect in 18-dehydrogenation was implied by the increased urinary excretion of 18-hydroxy-corticosterone metabolites.

Quantitative data from Case 1 during periods of treatment with salt supplements and when both salt and 9αFC were administered are summarized in Table 2. Urinary tetrahydroaldosterone secretion correlated with the low PAIodo measured at the same time. Excretion of corticosterone and 18-hydroxy metabolites was high during the initial salt-wasting period. After administration of 9αFC and salt (Fig. 1) the excretion of both groups of metabolites fell to 'normal' values (Table 2).

Quantitative data were obtained from Case 2 while on treatment with a normal diet and a low salt diet. Similar results to those of Case 1 were obtained (Table 2). PRA/PAIodo profiles during control and treatment periods are given in Table 3 and show the inappropriately low levels of PAIodo in relation to PRA at times of negative Na balance in both patients.

In Case 1, after treatment with salt supplements and 9αFC, PRA fell to normal and the PAIodo, though initially normal, decreased further. The level of PRA indicated precisely when Na balance had been achieved. In Case 2, after treatment with salt and 9αFC, PRA was only marginally raised with a normal PAIodo. On normal and low salt diets the PRA was markedly increased with normal PAIodo.

Discussion

Both infants presented initially with persistent vomiting and growth retardation and were ultimately shown to have isolated aldosterone deficiency due to defective 18-dehydrogenation of 18-hydroxy-corticosterone. Superficially Case 2 appeared to have only a transient defect.

The existence of transient states of adrenocortical insufficiency in infancy were first suggested by Jaudon in 1946. Russell et al. (1963) described 2 infants with a transient salt-wasting syndrome who responded well to salt-retaining hormones. A temporary biosynthetic defect in aldosterone production was postulated by these authors. In the light of current knowledge of the natural history of 18-oxygenation defects, these infants may in reality have suffered from this type of condition.

The conversion of corticosterone to aldosterone is assumed to be a two-step process, a hydroxylation forming 18-hydroxy-corticosterone which in turn is dehydrogenated to aldosterone. Greengard et al. (1967) showed that cytochrome P450 is necessary for this step, thus providing evidence that hydroxylation is involved. In the dog, adrenal mitochondria have been shown to require both NADPH and air for the conversion of both corticosterone and 18-hydroxy-corticosterone to aldosterone suggesting that the reaction is carried out by mixed function oxidases (Marusic et al., 1973).

Assuming that two enzymes are involved, then absence or inactivity of either of them would lead
to deficient aldosterone synthesis. If the deficiency was of dehydrogenation of 18-hydroxycorticosterone then this would produce high urinary excretion of 18-hydroxytetrahydro compound A (the major metabolite of 18-hydroxycorticosterone), 18-hydroxytetrahydrocorticosterone, and metabolites of corticosterone such as alloetrahydrocorticosterone. If the deficiency was of 18-hydroxylation then only raised amounts of corticosterone metabolites would be excreted.

In 1964, Visser and Cost described a family with a urinary salt-wasting disease similar to the infants described here, and found evidence for an 18-oxidation defect in the biosynthesis of aldosterone. The disease was later (Degenhart et al., 1966) shown to be due to a defect in 18-hydroxylation. At about the same time Ulick et al. (1964) described a 5-month-old infant with an identical illness and showed that it was due to defective dehydrogenation of 18-hydroxy-corticosterone.

Since that time several reports have appeared of defects in 18-oxidation of corticosterone. Of these, two describe defects in 18-hydrogenation (David et al., 1968; Rappaport et al., 1968), and one describes a defect in 18-hydroxylation (Jean et al., 1969). In two further reports it was not possible to define which defect was present (Polonovski et al., 1965; Forsyth (quoted by Cathro), 1967).

In all the reported cases similar correction of the biochemical abnormalities and satisfactory catch-up growth occurred with replacement therapy. However, the amount of mineralocorticoid necessary to suppress production of aldosterone precursors and to control the excessive salt loss in some patients is much greater than that conventionally used in the treatment of salt-losing forms of congenital adrenal hyperplasia or Addison’s disease, suggesting perhaps precursor competitive inhibition of the Na⁺ K⁺ ATPase transport system of both kidney tubule and gut. The latter is further suggested by the fact that some of the patients during salt-wasting episodes experience diarrhoea and vomiting. In addition, DOCA and aldosterone have been shown in rats to increase the Na⁺ and K⁺ ATPase activity and electrolyte and water transport in both the tubule and colon (Charney et al., 1974, 1975). In experimental hypoadrenal states in rats renal tubular Na⁺ K⁺ ATPase is profoundly depressed, but after administration of aldosterone, enzymatic activity is completely restored (Schmidt et al., 1975). It is likely that depression of Na⁺ K⁺ ATPase of both kidney and colon due to deficient secretion of aldosterone is the major factor in the salt-wasting state of these patients.

The course of Case 1 was marked clinically by episodes of salt-wasting associated with mild gastrointestinal symptoms and pyrexia (Fig. 1). These features were also noted by Visser and Cost (1964) in the 3 patients they described with a defect of 18-hydroxylation. Episodes of pyrexia have also been noted in patients with the 21-hydroxyase deficiency form of congenital adrenal hyperplasia, and in some cases ascribed to the pyrogenic effect of steroids such as aetiocholanolone (Cara et al., 1963). The pyrogenic effect of aetiocholanolone was first described by Kappas et al. (1956), who showed that other C-19 and -21 steroids with a 3α-hydroxy-5β H configuration had the same pyrogenic effect. Some of the tetrahydro metabolites excreted by Case 1 also have this configuration, and this may explain the episodes of pyrexia in association with episodes of salt-wasting.

In 3 cases reported by David et al. (1968), Jean et al. (1969), and Rappaport et al. (1968) PRA was noted to be raised, but the PRA/PAldo profile was not used to provide an indication of the probable cause of the salt loss. In Case 1, the PRA/PAldo profile, determined early after hospital admission, permitted a speedy diagnosis, and the sequential measurement of PRA also indicated when normal salt balance had been achieved. In Case 2, the PRA/PAldo profile led us to examine the urine sometime after she had been treated empirically with fludrocortisone and salt, but was receiving no treatment for aldosterone precursors, and thus allowed a precise diagnosis. The value of the PRA/PAldo profile in discriminating between renal and adrenal causes of salt loss in childhood has been previously reported (Dillon and Ryness, 1975).

In both patients improvement of the salt-wasting appeared to take place with age, though Case 1 still required salt supplements. The mechanism of age-dependent adaptation is not known. After the first year of life the small amount of aldosterone secreted together with mild salt-retain properties of precursor metabolites may be sufficient, under normal conditions, to maintain salt balance. At about this time, salt craving may become a recognizable stimulus to the child and together with the change to a toddler’s diet the daily intake of salt may increase sufficiently to cope with normal life. In addition, maturation of the proximal renal tubule’s sodium reabsorption mechanism occurs at about this time. Certainly in the 2 cases described by David et al. (1968) the administration of salt seemed to be a crucial factor.

The initial presenting features are often subtle and in many cases the disease may appear to be transient. In a few patients studied longitudinally (Rappaport et al., 1968), though there was improvement of salt-wasting and the defect appeared to be transient superficially, the biosynthetic defect persisted.
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apparent temporary nature of the condition may mask its true incidence and the defect may be commoner than might be suspected from the existing reports.

During salt-wasting episodes either at initial presentation or later during intercurrent infections, relatively high doses of salt and mineralocorticoid are necessary to achieve positive Na balance. Once suppression of precursors has been achieved positive Na balance can be obtained with more conventional doses of mineralocorticoid and salt. Growth rate however may remain abnormally low unless positive Na balance is assured either by treatment or by a self-selected diet by the patient.

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References


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Addendum

The patients we have described certainly suffer from the same condition as the family recently described by Hamilton et al. (1976). This latter family emphasizes that though salt-wasting may improve, the biosynthetic defect persists, and growth requires adequate sodium homeostasis to be maintained. If the diagnostic techniques now available had been established at the time of initial presentation of the older sibling earlier diagnosis undoubtedly would have been made. PRA/PAldo profile coupled with urinary gas liquid chromatography/mass spectrometry is a very powerful tool for the rapid evaluation of the less common salt-losing disorders of childhood. The technique of GLC/mass spectrometry is extremely useful in situations where poorly characterized metabolites may be encountered for which reference compounds are not available. The technique also enables a complete profile of the metabolites excreted to be obtained at one examination.

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