Prostaglandin excretion in pseudohypoaldosteronism type I

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Abstract

In an infant with pseudohypoaldosteronism type I increased urinary excretion of PGE2 (1.32 ng/mg creatinine; normal mean ± SE: 0.50 ± 0.10) and PGF2α (6.15 ng/mg creatinine; normal mean ± SE: 2.93 ± 0.91) was found. Prostaglandin excretion as well as the typical hyperkalemia, hyperreninemia and hyperaldosteronism normalized with adequate dietary salt supplementation. An abnormally high excretion of the renal prostaglandins was again present at age 4.4 years when the child was thriving although additional salt was withheld. These abnormalities are considered to be secondary to this condition's basic defect which remains to be elucidated.

Pseudohypoaldosteronism was first described by Cheek and Perry (1958) as a rare cause of salt loss in infancy. Salt wasting occurs despite high levels of plasma renin activity and aldosterone (Dillon et al. 1980). Several familial cases have been described, but the mode of inheritance is not clearly defined. At present, both the autosomal recessive as well as the autosomal dominant transmission appear possible. A similar disorder with hyperkalemia, but characterized by low renin hypertension, was termed pseudohypoaldosteronism type II by Schambelan et al. (1981) in distinction to the more common condition of infantile onset designated as type I. Rampini et al. (1978) reported that the latter disorder is amenable to treatment with indomethacin, a potent inhibitor of prostaglandin synthesis. Therefore, these authors assumed that the production of the saluretic renal prostaglandins might be increased. In the present study urinary prostaglandin excretion was measured in an infant with the typical features of pseudohypoaldosteronism type I.

Case report

The affected boy is the first child of young Turkish parents. The birth weight was 3720 g. The infant was breast-fed for two weeks and thereafter received formula feeding. Because of failure to thrive and vomiting he was admitted to hospital at the age of 7 1/2 weeks weighing only 3820 g. He appeared slightly dehydrated and showed marked muscular hypotonia. Blood pressure was 70/30 mmHg. Salt depletion with hyponatremia and hyperkalemia was found: serum sodium was 119, chloride 82 and potassium 7.0 mmol/l. Urinalysis and serum creatinine (44 μmol/l) were normal. Serum calcium was repeatedly elevated (2.6 to 3.0 mmol/l), parathyroid hormone was 24 ng/ml (normal: below 40). The following steroid determinations gave normal results: plasma cortisol (593 mmol/l, 1 hr after 0.25 mg/m2 ACTH i.v. 1275 mmol/l), 17-hydroxyprogesterone.
(1.43 nmol/l), 17-ketosteroids (0.4 mg/d), 17-hydroxycorticoids (2.6 mg/d). The profile of individual urinary steroids analyzed by gas chromatography on glass capillary columns (Völlmin 1970) was normal (pregnanetriol 0.18 µmol/d, pregnanetriolone 0.66 µmol/d, tetrahydro-S 1.08 µmol/d). Plasma ACTH was 56 ng/l (normal: below 50).

The infant's condition did not respond to treatment with 50 mg/d hydrocortisone succinate and 25 µg/d 9β-fludrocortisone acetate.

When 3 g/d sodium chloride (12.7 mmol/kg Na⁺) was added to the milk feeding the infant started to gain weight and the serum electrolytes normalized. At 9 months of age, the salt supplement was gradually discontinued without adverse clinical effects. At 4.4 years, the boy still tolerated normal feeding and appeared healthy with normal stature and weight.

Before starting treatment by adding salt to the diet plasma renin activity (Haber et al. 1969), aldosterone (Vetter et al. 1973), serum electrolytes and urinary prostaglandins PGE₂ and PGF₂α (Bürr et al. 1979; Godard et al. 1982), aldosterone (New et al. 1969) and electrolytes were measured. These studies were repeated before discontinuing the salt supplement and 1 week thereafter and again at later follow-up.

Results (Table I)

Urinary excretion of prostaglandins PGE₂ and PGF₂α relative to creatinine excretion was clearly above normal, while total daily prostaglandin excretion was not increased, when the infant of 8 weeks was in severe salt depletion. Plasma renin activity and plasma and urinary aldosterone were grossly elevated.

At the age of 9 months, during oral salt supplementation, and at 10 months, one week after its withdrawal, PGE₂ was nearly and PGF₂α (ng/mg creatinine) was completely suppressed to normal. Plasma renin activity and aldosterone were normal in the sodium repleted state at 9 months of age, but urinary aldosterone remained slightly elevated.

When the added salt was withheld a brisk increase in plasma renin activity and aldosterone was observed. At the age of 4.4 years, plasma and urine aldosterone were normal, but renin activity and prostaglandin excretion (ng/mg creatinine) were still definitely increased.

Discussion

In the present case of pseudohypoaldosteronism type I we found high amounts of urinary PGE₂ and PGF₂α in relation to creatinine excretion while absolute values of prostaglandin excretion were not increased. In view of the difficulty to obtain 24 hour urine specimens in infants and small children values related to creatinine are more reliable. Nevertheless, abnormally high values of PGE₂ excretion were reported by two groups of investigators in two untreated infants with pseudohypoaldosteronism (Hogg et al. 1978, Usberti et al. 1975). The finding of increased prostaglandin excretion was to be expected, since treatment with indomethacin which inhibits prostaglandin synthesis from arachidonic acid effectively reduces saluresis in pseudohypoaldosteronism as well as in Bartter's syndrome (Ram-pini et al. 1978; Bommen & Brook 1982; Usberti et al. 1985). Excessive renal prostaglandin synthesis may not be looked upon as the primary defect. Evidence has been presented that pseudohypoaldosteronism is due to a defect in sodium reabsorption in the proximal renal tubules (Postel-Vinay et al. 1974). The salt wasting is asso-
<table>
<thead>
<tr>
<th>age</th>
<th>8 weeks</th>
<th>9 months</th>
<th>10 months</th>
<th>4.4 years</th>
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<tr>
<td>salt added to diet</td>
<td>-</td>
<td>6.1</td>
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<tr>
<td>(mmol Na⁺/kg/d)</td>
<td></td>
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<tr>
<td>K (mmol/l)</td>
<td>5.6</td>
<td>4.4</td>
<td>4.7</td>
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<tr>
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<tr>
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<td>0.9</td>
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<td>69</td>
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<td>(16-58)</td>
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<td>(135.4±15.6)</td>
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<tr>
<td>(ng/mg creat.)</td>
<td>1.32</td>
<td>0.68</td>
<td>0.86</td>
<td>0.90</td>
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<td>PGF₂α (ng/d)</td>
<td>209</td>
<td>221</td>
<td>205</td>
<td>385</td>
</tr>
<tr>
<td>(46-668)</td>
<td>(231.7±77.6)</td>
<td>(625.8±57.1)</td>
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<tr>
<td>(ng/mg creat.)</td>
<td>6.15</td>
<td>2.17</td>
<td>2.27</td>
<td>2.59</td>
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<td>778.3</td>
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<td>(8.7-46.2)</td>
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<td>8030.3</td>
<td>144.3</td>
<td>1821.7</td>
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<td>(pg/ml)</td>
<td>(48-1320)</td>
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<td>(µg/ml/3h)</td>
<td>(2.4-26.5)</td>
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<td>(1.1-10.3)</td>
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*normal range and mean ± SE given in parentheses (identical for 8 weeks to 10 months) (New et al. 1966; Stark et al. 1975; Godard et al. 1982)
ciated with a decrease in extracellular volume which stimulates al-
dosterone secretion by activating the renin-angiotensin system as
well as renal prostaglandin synthesis. The saluretic effect of the
prostaglandins cannot be fully compensated even by maximal aldoste-
renception. Alternatively, mineralocorticoid unresponsiveness
was suggested to be the cause of salt wasting in pseudohypoaldoste-
ronism (Oberfield et al. 1979; Savage et al. 1982). Recent studies
by Armanini et al. (1985) support this hypothesis. These authors
demonstrated in three cases the absence or a reduced number of mi-
neralocorticoid receptors on monocytes. They speculated that the
renal target cells of aldosterone may have an equally reduced num-
ber of these receptors.
The follow-up studies in our patient who seemed no longer to be de-
pendent on additional dietary salt showed abnormally high prosta-
glandin excretion and renin activity. This confirms previous eviden-
ce of a persisting defect in pseudohypoaldosteronism (Postel-Vinay
et al. 1974; Oberfield et al. 1979; Satayaviboon et al. 1982; Rösler
1984; Armanini et al. 1985).

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