Pseudohypoaldosteronism

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SUMMARY 10 infants are described with pseudohypoaldosteronism, 5 in detail and a further 5 briefly. They all presented with hyperkalaemia, urinary salt-wasting disease, and ostensibly normal renal and adrenocortical function. Diagnosis was established by demonstrating the greatly increased values of plasma renin activity and plasma aldosterone concentration, plus the increased excretion of aldosterone and its metabolites on gas chromatographic and mass spectrometric analyses of urine. The children were treated with sodium chloride supplements, up to 60 mmol/day, but by the time most of the infants were about a year old these could be stopped. Exogenous mineralocorticoids were without effect in those to whom they were administered. The precise aetiology of the condition remains conjectural; lack of renal tubular response to aldosterone seems probable. Pseudohypoaldosteronism may be more common than has been thought and new techniques for investigating salt-wasting disorders may show its true incidence.

Salt loss in infancy is often due to gastrointestinal disease and in such cases there is renal conservation of sodium. In contrast, urinary salt loss occurs in certain renal tubular disorders and in adrenal insufficiency. Severe salt loss in infancy has been described despite ostensibly normal renal and adrenocortical function, and has been attributed to lack of response of the renal tubule to endogenous mineralocorticoids. This syndrome has been called pseudohypoaldosteronism and since 1958, when it was first described by Cheek and Perry,¹ 30 cases have been described.²⁻¹⁹ In one report²⁰ 7 additional but atypical cases were described and these patients were shown subsequently to have a defect of aldosterone biosynthesis.²¹

This paper describes in detail 5 more children with PHA, and briefly refers to a further 5 cases in whom diagnostic investigations were undertaken in our laboratories. The diagnosis was established in all 10 children by the characteristic increase in plasma renin and aldosterone levels, and in most children by the typical urinary corticosteroid findings.

Methods

PRA and PALdo concentration were measured using the methods of Dillon,²² and Dillon and Ryness.²³

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Abbreviations:

PHA: pseudohypoaldosteronism
PRA: plasma renin activity
PALdo: plasma aldosterone
GC: gas chromatography
GC/MS: gas chromatographic and mass spectrometric
17-OS: 17-oxosteroids
11-OI: 11-oxygenation index
17-OHP: 17-hydroxyprogesterone
ACTH: adrenocorticotrophic hormone
9FC: 9 α -fludrocortisone
DOCA: desoxycorticosterone
ATP: adenosine triphosphate

Urinary metabolites of cortisol and corticosterone were analysed by capillary GC.²⁴ Tetrahydroaldosterone and 18-hydroxytetrahydroCompound A were analysed simultaneously by a GC/MS analysis selected ion monitoring method.²⁵⁻²⁶ Plasma and urine electrolytes were measured simultaneously by flame photometry in a 5-channel autoanalyser. Standard methods were used to estimate urine 17-hydroxycorticoids,²⁷ 17-OS,²⁸ pregnanetriol,²⁹ and the 11-OI.³⁰ Competitive protein-binding methods were used to determine plasma cortisol,³¹ 17-OHP,³² and 11-deoxycortisol.³³ Plasma ACTH was determined by radioimmunoassay.³⁴

Case reports

Case 1. This boy was the second child of unrelated English parents. He was born normally at term weighing 2.75 kg and since birth he had had recurrent episodes of vomiting. At 9 weeks he was admitted to hospital because of a severe episode of vomiting associated with dehydration. Plasma sodium (Na) was 118 mmol/l and potassium (K) 5.0 mmol/l. A presumptive diagnosis of salt-losing congenital adrenal hyperplasia was made and he was treated with intravenous fluids and intramuscular hydrocortisone. After more vomiting associated with hyponatraemia, 9FC was given orally but his symptoms persisted.

Despite the treatment with mineralocorticoids the salt-losing state persisted; therefore 9FC was stopped and sodium chloride (NaCl) supplements (50 mmol/day) were started. He became hypertensive (140/110 mmHg) and remained so when the NaCl supplements were withdrawn, although he went into negative Na balance and plasma Na fell to 125 mmol/l. Plasma Na values were eventually stabilised above 130 mmol/l with Na supplements of 60 mmol/day, and the blood pressure slowly returned to normal. Because of the persistent hypertension, PRA, and PALdo concentration were measured. PRA was 81 000 ng A1/l per hour (reference range for age, 472-3130 ng A1/l per hour), and PALdo concentration was considerably greater than 3000 pmol/l (reference range for age, 160-3000 pmol/l) (Table).

Standard tests of renal function (including intravenous pyelography) all gave results that were within normal limits. Adrenal function tests including plasma 17-OHP, plasma cortisol, plasma 11-deoxycortisol, urine 17-OS, and urine 11-OI, before and after ACTH stimulation were essentially normal. GC/MS analyses of urinary corticosteroids were carried out on day 5 of the ACTH stimulation test. Cortisol metabolites were moderately raised

but extremely high excretions of *allo*-tetrahydrocorticosterone, tetrahydroaldosterone, and 18-hydroxytetrahydroCompound A were noted (Table).

It was possible gradually to reduce the treatment with corticosteroids without relapse, and later the salt supplements were tailed off. By age one year our patient was well and was receiving no treatment. He is now 5 years and is catching up in growth; he has a normal blood pressure, and can tolerate salt deprivation even when stressed by illness.

Case 2. This girl was the fifth child of unrelated English parents. Her birth was normal and she weighed 3.04 kg. At 7 days she had been found in a collapsed state and on admission to hospital was moribund. She was resuscitated with intravenous fluids, antibiotics, and hydrocortisone as the presumptive diagnosis was septicaemia. The initial response was satisfactory, but the next day her condition deteriorated with pronounced electrolyte imbalance despite intravenous fluids (plasma Na 125 mmol/l, K 8.4 mmol/l). Congenital adrenal hyperplasia was suspected although her genitalia were normal; she was treated with DOCA, hydrocortisone, salt supplements, and an ion-exchange resin. Several days later her condition again deteriorated, plasma Na falling to 125 mmol/l and K rising to 8.2 mmol/l. At this stage PRA was 107 300 ng A1/l per hour and PALdo concentration much greater than 3000 pmol/l (Table). Plasma electrolytes failed to improve until she was given 60 mmol/day NaCl in addition to hydrocortisone and DOCA. She developed pneumonia, superimposed cardiac failure, and generalised convulsions. With intensive treatment she recovered and was finally stabilised on 50 mmol/day NaCl.

Standard tests of renal function, including intravenous pyelography, gave results that were within normal limits. Adrenal function tests including plasma 17-OHP, plasma cortisol, plasma 11-deoxycortisol, urine 17-oxogenic steroids, urine 17-OS, and urine pregnanetriol were essentially normal before and after ACTH stimulation.

She has maintained satisfactory progress. Her blood pressure remained normal on treatment. She was discharged from hospital at 2 months on cortisone 10 mg twice daily, 9FC 0.1 mg daily, and 25 mmol/day of added NaCl. The 9FC was stopped at age 10 months and the cortisone withdrawn by 13 months. Aged 4½ years, although small, she has grown normally with height and weight following the 3rd centile. GS/MS analysis of urinary corticosteroids at 2½ years showed only moderately raised tetrahydroaldosterone and 18-hydroxytetrahydroCompound A. Secretion of cortisol metabolites was normal for age.

Table Plasma renin activity, plasma aldosterone concentration, and urinary corticosteroids in children with pseudohypoadosteronism

Case	1		2		3		4		5		6		7		8		9		10	
	4 months	5 months	9 months	10 days	33 months	38 months	6 weeks	2 months	6 months	28 months	1 month	3 months	5 months	3 months	8 months	3 months	9 months	3 months	2 months	2 months
PRA (ng A1/l per hour)*	81 000	41 000	2 160	107 300	12 300	10 400	24 900	59 100	49 300	2 128	13 000	43 900	43 800	18 500	11 500	30 300	11 500	11 500	11 200	11 200
PAldo (pmol/l)†	> 3000	> 3340	750	> 3000	1060	420	6 100	8 300	10 000	3 000	7 500	> 19 300	> 21 000	> 12 300	> 18 700	11 200	11 200	11 200	11 200	11 200
Tetrahydrocortisone (µg/24 h)	ND	623	873	ND	576	463	386	ND	250	567	ND	312	203	ND	208	ND	208	208	208	208
Tetrahydrocortisol (µg/24 h)	ND	424	86	ND	245	240	<25†	ND	16	404	ND	59	50	ND	69	ND	69	69	69	69
Allo-tetrahydrocortisol (µg/24 h)	ND	485	77	ND	588	757	<25†	ND	250	320	ND	85	91	ND	165	ND	165	165	165	165
Allo-tetrahydrocorticosterone (µg/24 h)	ND	1 477	249	ND	441	363	<25†	ND	277	382	ND	90	106	ND	86	ND	86	86	86	86
18-hydroxytetrahydrocorticosterone (µg/24 h)	ND	448	48	ND	132	282	266	ND	326	406	ND	279	883	ND	406	ND	406	406	406	406
Tetrahydroaldosterone (µg/24 h)	ND	1 299	69	ND	150	94	1 018	ND	354	320	ND	341	2 257	ND	320	ND	320	320	320	320

*Normal mean PRA from age 1 week to 1 year, 1460 ng A1/l per hour (range 470–3130), and from 1 to 4 years 760 ng A1/l per hour (range 110–2610).
†Normal mean PAldo from age 1 week to 1 year 790 pmol/l (range 165–2930), and from 1 to 4 years 295 pmol/l (range 70–950).
‡Apart from tetrahydrocortisone, the principal metabolite excreted at this age is 6α-hydroxytetrahydrocortisone (267 µg/24 h) and the major corticosterone metabolite is 6α-hydroxytetrahydrocorticosterone (250 µg/24 h).

ND = not done.
Conversion: SI to traditional units—PAldo: 1 pmol/l ≈ 0.036 ng/100 ml.

Case 3. This boy was the first child of unrelated English parents, born at term, weighing 2.98 kg. He had been admitted to hospital at age 4 weeks because he had gained no weight since birth and fed poorly with occasional episodes of vomiting. There were no abnormal features on examination, but plasma Na was 119 mmol/l and K 6.3 mmol/l. Urine 11-OI was 0.3, 17-OS 2.45 μ mol/24h (0.7 mg/24h), and plasma 17-OHP 18 nmol/l (0.6 μ g/100 ml). A specimen of urine collected by suprapubic aspiration contained a significant growth of *Enterobacter aerogens*. Intravenous pyelography was normal but a subsequent micturating cystogram showed bilateral ureteric reflux.

He was treated with added NaCl (15 mmol/day) and oral co-trimoxazole: plasma Na rapidly returned to normal but fell to 123 mmol/l when the additional salt was stopped. At this time PRA was 24 900 ng A1/l per hour and PAlDo concentration 6100 pmol/l (Table). Treatment with oral NaCl was restarted and the urinary infection treated with long-term co-trimoxazole. GC analysis of the urine (Figure) showed highly raised tetrahydroaldosterone and 18-hydroxytetrahydroCompound A (Table). Because of his age the infant exhibited the neonatal pattern of cortisol metabolites—levels of tetrahydrocortisol and *allo*-tetrahydrocortisol were extremely low, but 6 α -hydroxytetrahydrocortisone was raised. In addition, the major corticosterone metabolite identified was 6 α -hydroxytetrahydroCompound A (not *allo*-tetrahydrocorticosterone).

At age 6 months he was admitted for reassessment. By this time he was well and his growth was normal. On a Na intake of 35 mmol/day his plasma Na was 135 mmol/l, but PRA and PAlDo concentration were both raised (3460 ng A1/l per hour and >19 000 pmol/l respectively). Na intake was reduced to 10

mmol/day and plasma Na remained normal, but after 5 days of low Na intake, PRA rose further to 8450 ng A1/l per hour. A tetracosactrin test was normal with a rise in plasma cortisol from 248 to 670 nmol/l (8.9 to 24.3 μ g/100 ml) at 30 minutes. Additional NaCl supplements were then stopped and the child (now aged 3½ years) has remained well with normal plasma Na and sterile urine.

Case 4. This boy was the fifth child of unrelated English parents, born at term, weighing 4.08 kg. He had been admitted to hospital at age 3 weeks because he had gained no weight since birth, was feeding poorly, and had suffered several episodes of cyanosis and irritability. He was a clinically dehydrated infant with perioral cyanosis. Plasma Na was 119 mmol/l, K 7.2 mmol/l, and initially plasma total CO₂ was 4 mmol/l. He was treated at the referring hospital with intravenous fluids, sodium bicarbonate, and antibiotics. Despite these measures he continued to remain hyponatraemic and failed to thrive. Urinary Na excretion remained inappropriately high in view of the clinical and biochemical evidence of Na depletion. Transient generalised aminoaciduria and glycosuria were demonstrated, associated with an inability to acidify and concentrate the urine. These features disappeared by 6 weeks. PRA was 59 100 ng A1/l per hour and PAlDo concentration 8300 pmol/l when off salt supplements (Table). Apart from plasma creatinine of 78 μ mol/l (0.88 mg/100 ml) and ⁵¹Cr EDTA glomerular filtration rate of 12 ml/min per 1.73 m², renal function was normal, including intravenous pyelography and micturating cystourethrogram. Plasma creatinine and glomerular filtration rate returned to normal by 4 months.

Tests of adrenal function showed normal plasma

Figure (Case 3) Total urinary steroid profile at age 1 month. This chromatogram illustrates the typical neonatal pattern of corticosteroid metabolism—high excretion of 6 α -hydroxytetrahydroCompound A and 18-hydroxytetrahydroaldosterone and low excretions of the tetrahydrocortisols and *allo*-tetrahydrocorticosterone. The older infants exhibit the adult pattern of cortisol and corticosterone metabolites. The peaks marked AD (androstenediol), S (stigmastanol), and CB (cholesteryl butyrate) are internal standards.

cortisol, ACTH, 17-OHP and urine 17-ketosteroids, total 17-hydroxycorticoids, and 11-OI. GC/MS analysis of urinary corticosteroids at 6 months showed that cortisol metabolites were normal but metabolites of corticosterone, aldosterone, and 18-hydroxycorticosterone were greatly raised (Table).

He was treated with NaCl supplements and thrived. However, he intermittently became hyponatraemic and hyperkalaemic especially associated with intercurrent upper respiratory infections. PRA and PALdo concentration remain raised. He is now 3 years and still requires 3 mmol/kg per day additional NaCl. GC/MS analysis of urine collected at 2–3 years indicated that there were still very high excretions of tetrahydroaldosterone and 18-hydroxy-tetrahydroCompound A.

Case 5. This boy was the first child of unrelated English parents, born at 39 weeks' gestation, weighing 3.38 kg. He had been admitted to hospital at age 2 weeks because of vomiting and constipation, pyloric stenosis being suspected. Plasma Na was 123 mmol/l and K 5.7 mmol/l. There was evidence of inappropriate urinary Na loss in view of the clinical and biochemical evidence of Na depletion. PRA was 13 000 ng A1/1 per hour and PALdo concentration 7500 pmol/l (Table). There was no evidence of renal impairment. Adrenal function tests showed that plasma 17-OHP and urine 17-OS, 17-oxogenic steroids, and 11-OI were normal. Urinary corticosteroids were not analysed.

He was treated with NaCl and is now 11 months old. He is currently on 25 mmol NaCl/day in addition to dietary intake.

Other cases. Five other children (not described in detail) fulfil the criteria for a diagnosis of PHA. They were under the care of other units but measurements of PRA and PALdo concentration were undertaken at The Hospital for Sick Children and in most of them, GC/MS analysis of urine was undertaken at the Clinical Research Centre. These children's ages ranged from 2 to 5 months at time of investigation and there were 2 boys and 3 girls. Clinically they presented with urinary salt-wasting disease and failure to thrive. Investigations showed hyponatraemia and hyperkalaemia but no evidence of primary renal disease, glucocorticoid deficiency, or congenital adrenal hyperplasia. All cases had much increased values of PRA and PALdo concentration (Table) plus urinary GC/MS findings in the 3 children tested, similar to those seen in our other patients. All children responded to treatment with NaCl and they are now aged between 2½ and 3½ years.

Discussion

In 1958, Cheek and Perry¹ described a child with PHA—a 3-month-old boy who presented with failure to thrive and who had repeated episodes of hyponatraemia and dehydration. Adrenal and kidney function were normal. His clinical condition improved with oral NaCl supplements, but if these were stopped he deteriorated with hyponatraemia and a decrease in extracellular fluid volume. DOCA did not prevent salt loss and had no effect on the urinary Na/K ratio. It was suggested that the renal tubules were refractory to mineralocorticoids. Donnell *et al.*² also concluded that the renal tubule was unresponsive to aldosterone because urinary Na loss continued when their patient was salt-depleted but still had large quantities of aldosterone in the urine.

Not all patients are totally unresponsive to mineralocorticoids. Royer *et al.*⁶ demonstrated that spironolactone provoked an increase in urinary salt loss in one child. When the same child was studied 9 years later,³⁵ a low Na intake provoked a rise in urinary aldosterone and a decrease in Na excretion, so it was concluded that the child was partly responsive to aldosterone. Roy¹⁶ reported a family in which there were normal responses to spironolactone and DOCA, suggesting that there may be a spectrum of responsiveness of the renal tubules in this condition.

We view with suspicion the 7 children described by Rösler *et al.*²⁰ It was possible that their patients had defects of 18-oxidation in aldosterone biosynthesis. Increased PRA with normal, but inappropriately low, PALdo concentration is compatible with an 18-oxidation defect³⁶ and could have accounted for the response to mineralocorticoid. It is interesting that Rösler *et al.* subsequently wrote another paper which showed that there was in their patients a defect in the aldosterone biosynthetic pathway.²¹

The effect of aldosterone is mediated by the activation of sodium/potassium ATPase in the renal tubule.³⁷ Bierich and Schmidt¹⁴ showed that sodium/potassium ATPase activity was absent in a child with PHA. Their findings further support the suggestion that PHA is the result of lack of response of the renal tubule to aldosterone. The alternative suggestion of a disturbance of Na resorption in the proximal tubule and the loop of Henle is possible, but has been considered to be less likely.¹⁰ The secondary hyperaldosteronism due to Na loss resulting from the proximal tubular failure, would be associated with hypokalaemia rather than with the high or normal values that are observed. However, Roy¹⁶ has presented some evidence in favour of

impaired proximal tubular reabsorption of Na and has also reported some histological changes maximal in the proximal tubule. In addition, Rampini *et al.*¹⁹ demonstrated reversal of natriuresis with indomethacin which might imply that prostaglandin-induced proximal Na wastage could be playing a part. Proesmans *et al.*³⁸ showed that Na delivery to the distal nephron was excessive in patients with PHA, and Bierich and Schmidt¹⁴ showed that sodium/potassium ATPase was absent in the proximal and distal nephrons. These observations could account for the presence of proximal and distal salt loss with hyperkalaemia in PHA.

17 of the 30 patients so far reported have been boys, but the sex of the dizygotic twins described by Alvarez *et al.*¹³ was not given. In all but 3 of these, Na supplements have arrested the clinical and biochemical state. In 2 hyperkalaemia could not be reversed and proved fatal^{9 11}, and in the third¹⁴ the cause of death was uncertain.

PRA has been shown to be greatly increased in 11 typical examples of this condition.^{8 10 14-19} However, with the exceptions of Rampini *et al.*,¹⁹ Luras *et al.*,¹⁸ and Petersen *et al.*,¹⁷ the use of simultaneous PRA and PALdo measurements as a quick means of establishing the diagnosis of PHA has not been stressed. We previously reported the value of such measurements in discriminating between renal and adrenal causes of salt loss in childhood²³ and in demonstrating the presence of an aldosterone biosynthetic defect.³⁶ We have now shown that these estimations are of considerable diagnostic value in PHA. In the absence of gastrointestinal or overt renal disease, raised PRA and PALdo values in salt-losing hyperkalaemic infants are virtually diagnostic of PHA. The patients reported here clearly demonstrated this. In 2 patients the estimations quickly established the true nature of their illness when both were thought to have congenital adrenal hyperplasia. In the others the estimations distinguished between defects of aldosterone synthesis and PHA. The persistence of hyperaldosteronism even when Na balance is restored¹⁰ is interesting, although PALdo concentration can return to normal as happened in Case 2 and in the child described by Rampini *et al.*¹⁹

The hypertension in the presence of salt loss (Case 1), which led to the measurement of plasma renin and aldosterone, was probably caused by excess circulating angiotensin II due to renin stimulation. This has previously been described in children with congenital adrenal hyperplasia³⁹ and we have seen it in other salt-losing states. We did not feel that the degree of vesicoureteric reflux seen in Case 3 could account for the persisting biochemical findings although initially it caused some confusion. The

transient aminoaciduria and glycosuria seen in Case 4 on presentation also caused diagnostic difficulty and was initially thought to be associated with an episode of acute tubular necrosis. This might, indeed, still be the explanation, but since Luras *et al.*¹⁸ also reported similar findings in 2 of their patients it is possible that these observations may reflect a disturbance of proximal tubular function which is part of PHA.

In general, the children whose urine was examined by GC/MS analysis had a characteristic pattern of corticosteroid excretion, although this depended to some extent on age. For example, tetrahydrocortisol and *allo*-tetrahydrocorticosterone are not major metabolites of cortisol and corticosterone in infants less than 2 months. Instead, 6 α -hydroxy-tetrahydrocortisol and 6 α -hydroxytetrahydroCompound A are important metabolites. It was found that unless there was an extremely large tetrahydroaldosterone excretion, the condition was difficult to distinguish from hypoaldosteronism by capillary GC analysis alone, due to defect in 18-oxidation of corticosterone.²⁴ Common features of the profiles for the two conditions are high excretions of *allo*-tetrahydrocorticosterone and 18-hydroxytetrahydroCompound A and an excretion of *allo*-tetrahydrocortisol almost always greater than tetrahydrocortisol. In normal infants, children, and adults tetrahydrocortisol nearly always predominates. For this reason, definitive proof of the disorder was obtained by analysing tetrahydroaldosterone and 18-hydroxytetrahydroCompound A by a specific mass spectrometric method.

Although most reported cases are isolated examples, there are at least 5 reports of a familial incidence. Alvarez *et al.* described dizygotic twins,¹³ Bierich and Schmidt described 2 siblings,¹⁴ Roy described a family of 4 siblings and their father,¹⁶ Rösler *et al.* described 2 siblings,¹⁵ and Luras *et al.* described 2 siblings.¹⁸ In addition, several other reports^{3-4 8} imply that there might have been other cases within the families. Until Roy's paper¹⁶ it seemed likely that the condition was inherited on a recessive basis, but his study raises the possibility of a dominant inheritance and this is supported by studies undertaken by Luras *et al.*¹⁸ in 2 families of affected patients.

The apparently transient nature of the illness with spontaneous recovery is interesting, especially as it appears to occur despite sustained hyperaldosteronism.³⁵ This is similar to the age-dependent adaptation seen in children with 18-oxidation defects in aldosterone biosynthesis. We have speculated that this might be due to maturation of proximal tubular function associated with the development of a salt appetite,³⁶ which compensates

for the persistent defect in Na reabsorptive function. This spontaneous recovery between 1 and 2 years of age may well mask the true incidence of the disease, which we suspect is commoner than reports suggest.

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