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Type I Pseudohypoaldosteronism Includes Two Clinically and Genetically Distinct Entities with either Renal or Multiple Target Organ Defects

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ABSTRACT. Type I pseudohypoaldosteronism (PHA) is a hereditary disease characterized by salt wasting resulting from target organ unresponsiveness to mineralocorticoids. We have studied two kindreds including a total of nine patients with PHA. In kindred I, the propositus presented with renal salt wasting in infancy (vomiting, failure to thrive, short stature, hyponatremia, hyperkalemia) and responded dramatically to a high salt diet (2.5 g/day). Sodium supplementation was discontinued at the age of two. In seven additional family members from three generations, clinical expression of PHA varied from asymptomatic to moderate. In affected members (propositus, mother, and two brothers), hyperaldosteronism persisted over 13 yr; however, the PRA decreased gradually to near normal values. Persistent hyperaldosteronism in the face of a decrease in PRA indicated the development of tertiary hyperaldosteronism due to autonomously functioning zona glomerulosa. The pedigree was consistent with an autosomal dominant mode of transmission with variable expression.

In kindred II, the propositus, who was the product of a consanguineous marriage, developed severe renal salt losing at age 9 days. She had also increased salivary and sweat electrolytes consistent with PHA resulting from multiple organ unresponsiveness to mineralocorticoids. Life threatening episodes of salt wasting recurred beyond the age of 2 yr. At 5 yr of age she still requires high amounts of salt supplements (14 g/day). A sister died at 9 days of age with PHA symptoms. Six close relatives (parents, three siblings, maternal uncle) showed no biochemical abnormalities. This pedigree was consistent with an autosomal recessive mode of inheritance.

In view of the findings on these two kindreds and the analysis of those in the literature, we conclude that type I PHA includes two clinically and genetically distinct entities with either renal or multiple target organ defects. (*J Clin Endocrinol Metab* **73:** 936–944, 1991)

TYPE I pseudohypoaldosteronism (PHA) is a hereditary salt-wasting syndrome which usually starts in early infancy and is characterized by a diminished renal tubular responsiveness to aldosterone resulting in hyponatremia, hyperkalemia, markedly elevated plasma aldosterone, and hyperreninemia (1). The clinical expression of the disease varies significantly ranging from severely affected patients who may die in infancy (2–4) to those who are asymptomatic (5–7). Symptomatic patients are treated with sodium supplementation which becomes generally unnecessary by 2 yr of age (8–14). Serum electrolyte levels also normalize with increasing age (4), but aldosterone concentrations in both symptomatic and asymptomatic patients may remain elevated until adulthood (5–7, 15, 16). In a minority of patients with type I PHA, responsiveness to aldosterone is impaired in multiple organs including salivary and sweat glands, renal tubules, and colonic mucosal cells (12, 17–20). These patients exhibit a more protracted course of the disease with recurrent life-threatening episodes of salt losing.

In some families, PHA is inherited as an autosomal dominant trait with variable expression (5–7, 16). There are also a few reports suggesting an autosomal recessive mode of inheritance both in PHA with renal salt loss (2, 13, 21) and multiple target organ defect (18–20). However, in these reports the pedigree studies were based on a small number of family members and in many instances aldosterone and PRA levels in asymptomatic family members were not examined. Thus, the mode of inheritance of PHA in families with different clinical presentation has remained as a debated issue.

The clinical, biochemical, and genetic data I report here from 2 kindreds (with 18 family members) reveal major differences. While the propositus from kindred I had type I PHA with renal salt wasting, that from kindred II had features of PHA with multiple target organ unresponsiveness to mineralocorticoids. These two distinct clinical patterns are also associated with different modes of inheritance. We thus suggest that type I PHA includes two distinct forms with either renal or

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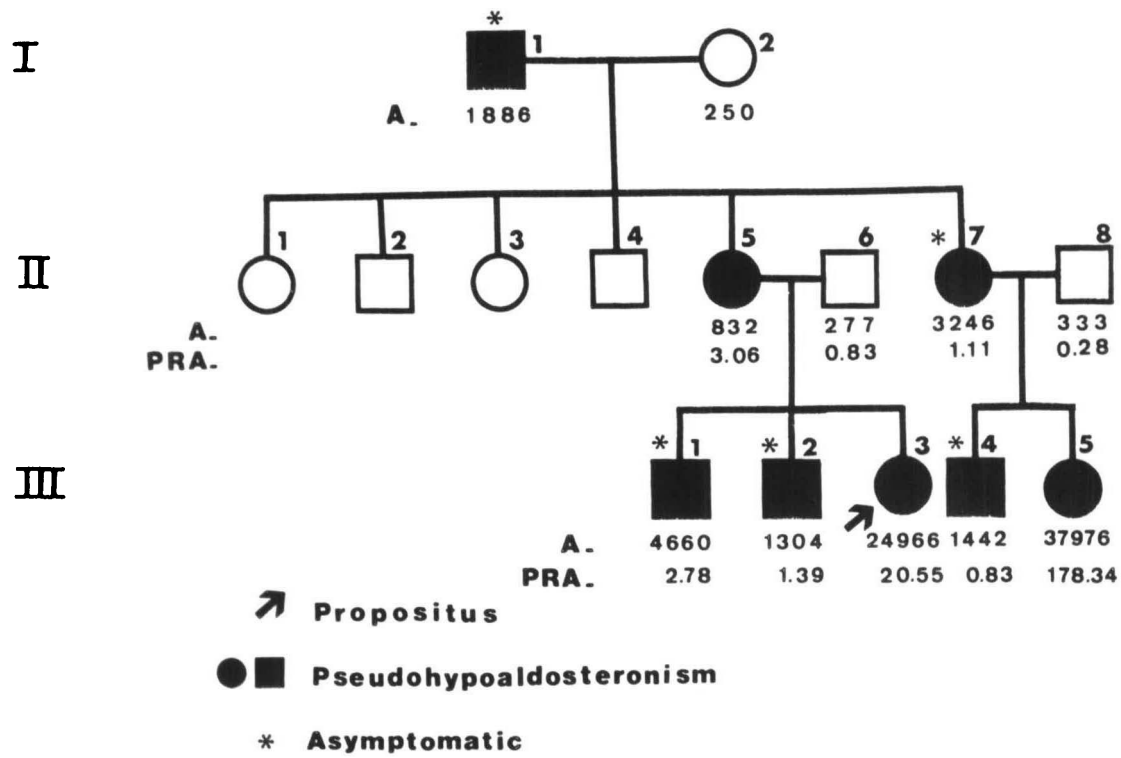

FIG. 1. The pedigree of a family with renal PHA. The results of the first determination of A, aldosterone (pmol/L) and PRA [ng/(L·s)] in propositus and family members are indicated below the symbols.

TABLE 1. The clinical and biochemical data of index case with renal PHA (kindred I)

	Hospital-ization	Follow-up		Last exam.
Age (months)	3–4.5	6	8.5–27	12 6/12 yr
Weight (kg)	3.6–4.1	5.1	10.6[a]	40
Percentile	<3	<3	10	25
Length/ht (cm)		61	86[a]	151
Percentile		≤3	25–50	25–50
Plasma/serum				
Sodium (mmol/L)	133–141	141	137–145	139
Potassium (mmol/L)	6.1–7.4	6.4	5.4–5.9	4.1
Aldosterone (pmol/L)	>16,640	24,970	1,720–6,990	2,275
18-OHB (pmol/L)				7,850
PRA [ng/(L·s)]		20.5	4.7	0.8
Urine				
Na/K	2.2–3[b]		1.3–3.1	
Therapy	iv NaCl	none	po NaCl 2.5 g/day	none

Serum/plasma ACTH, cortisol, 17-OH-P, renal function tests, IVP, sweat electrolytes were all normal. For normal reference values see *Subjects and Methods* and Table 2.

[a] Measured at age 25 months.

[b] Urinary Na repeatedly greater than 50 mmol/L.

multiple target organ unresponsiveness to mineralocorticoids.

Subjects and Methods

Nine affected and nine healthy individuals from two families were studied. Kindred I included eight affected family members with renal PHA who had been followed-up longitudinally over a period of up to 13 yr and three healthy individuals. Kindred II included an index case with multiple PHA and six healthy family members who have been followed-up over a period of 5 yr. The diagnosis of renal PHA was established according to classical features of the disease (1). The diagnosis of multiple form of PHA was made by elevated concentrations of sweat and saliva electrolytes in addition to the features of renal PHA.

Plasma aldosterone and PRA were determined by RIA kits (Aldosterone kit: International CIS, Compagnie Oris Industrie, France, and PRA kit: New England Nuclear, Boston, MA). The plasma aldosterone levels in healthy infants aged 7 days to 3 months were up to 3051 pmol/L (n = 7), and in those aged 4 months to 1 yr were up to 1110 pmol/L (n = 6). Beyond the age of 1 the aldosterone levels were not different from those of adults (55.5–388 pmol/L). The PRA in normal children aged 7 days to 1 yr was up to 2.78 ng/(L·s). These aldosterone and PRA values were generally consistent with normal values reported previously in infants and children (22, 23). Plasma 18-hydroxycorticosterone (18-OHB) was determined by RIA (4) in the laboratory of Dr. A. Rosler (Hebrew University-Hadassah Medical Center, Jerusalem, Israel). The levels of plasma 18-OHB in normal children older than 6 months of age were not different from the levels found in adults (1780 ± 980 pmol/L, Ref. 4).

Unless indicated otherwise, all blood samples for aldosterone, 18-OHB, and PRA were collected in the morning when the

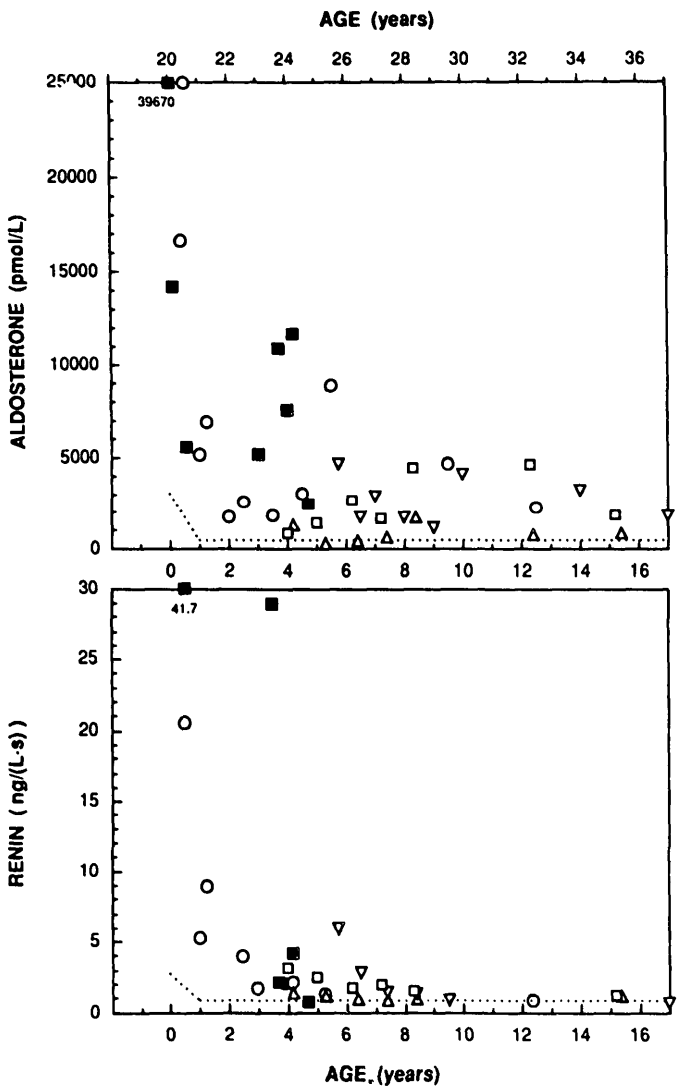

FIG. 2. Age-dependent changes in aldosterone and PRA in patients with PHA. Only the propositus from kindred II (■) was on sodium supplementation during the entire observation period. The other patients are from kindred I with renal PHA; propositus (○), two brothers (▽, △), and the mother (□). The values for the mother were determined between the ages of 24 to 35. The dotted lines: upper limit of the normal range.

patients became ambulatory and during normal sodium intake. Serum, urinary and sweat sodium and potassium concentrations were measured by flame photometry. Sweat was collected by pilocarpine iontophoresis. Saliva chloride concentrations were measured by a cystic fibrosis analyser (Advanced Instruments, Needham Heights, MA). Saliva was collected from the sublingual region.

Results

Kindred I

We investigated 11 people from 3 generations in this kindred of Iraqi-Jewish ancestry (Fig. 1). There was no history of consanguineous marriages.

Index case

This female infant was born at term after an uncomplicated pregnancy and normal delivery. Her birth weight was 2600 g. At the age of 3 months she was admitted because of failure to thrive. The clinical and laboratory findings indicated PHA with renal salt wasting (Table 1). Salt treatment (2.5 g/day) was started at 8.5 months of age and resulted in a dramatic increase in linear growth. The salt supplementation was discontinued at age 2 $^{3}/_{12}$ yr without any ill effects. The follow-up data are shown in Table 1.

Family members (Fig. 1)

The mother had been hospitalized several times during infancy because of vomiting and failure to thrive and had received parenteral fluid. Since the age of 1.5 yr she had gradually recovered. The biochemical screening of additional family members from three generations, disclosed PHA in seven of them (Fig. 1). A 33-yr-old maternal aunt and her 1-yr-old son who were asymptomatic, were diagnosed only recently (II-7, III-4). The maternal aunt's daughter (III-5) was born at 35 weeks of gestation. At the age of 19 days she developed hyperkalemia (6.4 mmol/L) and increased urinary Na/K ratio (2.2) in the face of hyponatremia (132 mmol/L) associated with poor feeding. She responded dramatically to oral salt supplements (0.6 g/day). Her electrolytes normalized after 2 days. In addition to high aldosterone levels, the affected family members had also increased concentrations of 18-OHB, precursor of aldosterone (5040 ± 1540 pmol/L, range = 3640–7850), but normal 18-OHB/aldosterone ratios (5.0 ± 4.6 Normal values were from Ref. 4). The pedigree of this kindred is consistent with autosomal dominant inheritance with variable expression.

The plasma aldosterone and PRA were determined periodically in four afflicted family members (propositus, mother, and two brothers) over 13 yr (Fig. 2). In the index case, both aldosterone and renin decreased notably during the first year. While aldosterone remained elevated, PRA decreased gradually towards normal levels with increasing age in all patients (Fig. 2).

The linear growth of patients appears to be correlated with the severity of biochemical abnormality not only in symptomatic patients (*i.e.* propositus), but also in asymptomatic patients (*i.e.* two brothers). The less severely affected brother (III-2) who had the lowest aldosterone and PRA also was the tallest member of the family: 170 cm (50th percentile) at the age of 15 $^{5}/_{12}$ yr. In contrast, the oldest brother (III-1) whose plasma aldosterone concentrations were much higher than his younger brother, was only 160 cm tall (just below the 3rd percentile) at the age of 17.

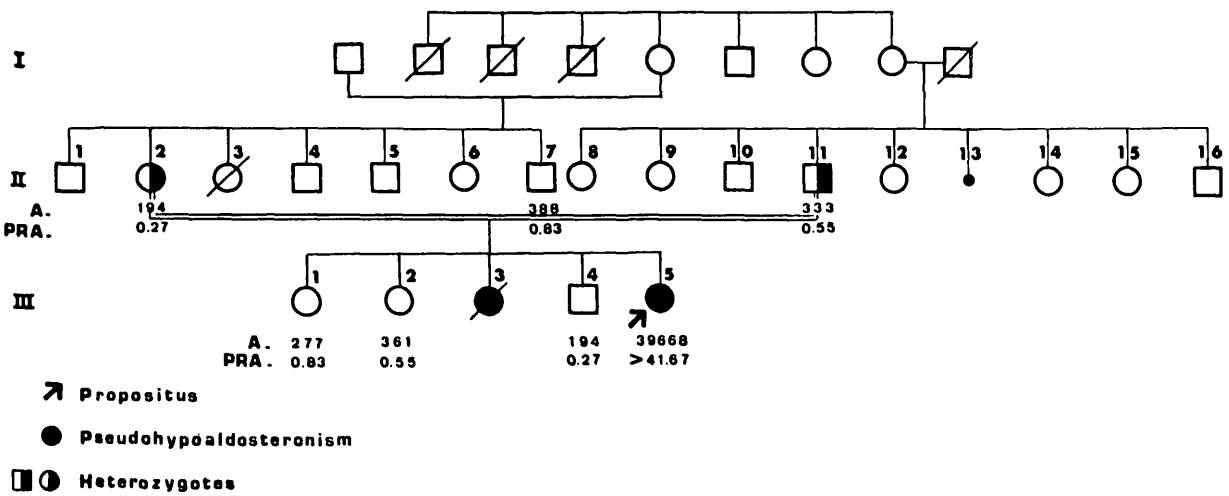

FIG. 3. Family pedigree of a patient with multiple PHA. The results of the first determination of A, aldosterone (pmol/L) and PRA [ng/(L·s)] in propositus and family members are indicated below the symbols.

TABLE 2. Biochemical data of index case with multiple PHA (kindred II)

	Admission		Follow-up		Normal
Age (months)	0.3	6–14	15–40	41–57	
Plasma/serum					
Sodium (mmol/L)	125	122[a]–142	126–140	135–140	136–146
Potassium (mmol/L)	10	4.6–10.5[a]	4.3–9.6	4.7–6.2	3.5–4.8
Aldosterone (pmol/L)	39,670	14,200	4,440–17,000	2,470–10,820	55–388
18-OHB (pmol/L)				37,570[b]	1,780 ± 980
PRA [ng/(L·s)]		>41.7	2.0–28.9	0.7–2.0	0.14–0.83
Sweat					
Sodium (mmol/L)		142	180		<60
Chloride (mmol/L)		120	140		<60
Saliva					
Chloride (mmol/L)		100	78		<30
Urine					
Na/K	18	13	8–18	9.5	~2
Therapy	iv NaCl 5 g/day, kayaxalate	po NaCl 6.5 g/day	po NaCl 9 g/day	po NaCl 14 g/day	

Serum 17-OH-P, pancreatic lipase, renal function tests, IVP, renal ultrasound, and chest x-rays were normal.

[a] Serum obtained during a severe salt losing crisis necessitating resuscitation at the age of 14 months.

[b] Determined at age 48 months.

Kindred II

We investigated seven members of this kindred over a period of 4 yr. Kindred II is of Iranian-Jewish ancestry and the parents of the index case are first cousins (Fig. 3).

Index case

A female infant presented at 9 days of age because of failure to thrive since birth. The pregnancy, labor, and delivery were uneventful and her birth weight was 3 kg. On admission she was severely dehydrated and weighed 2.5 kg. The laboratory data was consistent with PHA (Table 2). The patient remained dependent on high amounts of sodium (5 g/day) administered mainly iv. She was discharged at 4 months of age on sodium chloride and kayexalate, weighing 4.2 kg (< third percentile).

In follow-up there were recurrent episodes of severe salt wasting, necessitating hospitalizations (about six per year up to the age of 3). Her blood pressure was never elevated. Further laboratory work-up showed increased sweat and saliva electrolytes, indicating multiple end organ unresponsiveness to aldosterone (Table 2). The salt supplementation was gradually increased to 14 g/day resolving the salt losing episodes and normalizing the PRA. In contrast, hyperaldosteronism and high urinary Na/K ratio persisted (Table 2, Fig. 2). At the age of 4 yr she had a markedly increased 18-OHB level (Table 2), although the 18-OHB/aldosterone ratio was normal (6.7). During the 5 yr of follow-up her height and weight

TABLE 3. The cortisol, aldosterone, and electrolyte responses to ACTH and sodium depletion or repletion in a patient with multiple PHA

	iv ACTH test		No NaCl for 24 h		iv NaCl 300 ml/3 h	
Time (h)	0	1	0	24	0	3
Age (yr)	3	3	3 5/12	3 5/12	3 8/12	3 8/12
Weight (kg)			10.0	9.0	10.6	11.0
Plasma/serum						
Aldosterone (pmol/L)	5,190	13,010	17,005	34,120	8,960	2,940
PRA [ng/(L·s)]			31.4	50.8		
Cortisol (nmol/L)	276	938				
Sodium (mmol/L)	141		133.0	127.0	139.0	
Potassium (mmol/L)	5.7		6.4	6.6	5.0	
Urine						
Sodium (mmol/L)			223.0	101.0		
Potassium (mmol/L)			28.0	28.0		
Na/K			8.0	3.6		

remained below the third percentile and no catch-up growth was observed.

At 3 yr of age an ACTH stimulation (Cortrosyn, 0.25 mg iv) produced a 3- and 2.5-fold rise in cortisol and aldosterone respectively (Table 3). Discontinuation of sodium supplement for 24 h, while the patient remained on normal diet, resulted in weight loss, decreased serum sodium and urinary Na/K ratio, and elevated further serum potassium and aldosterone levels. In contrast, iv isotonic sodium loading suppressed aldosterone levels (Table 3). These results indicated an intact adrenal cortex (fasciculata) and renin-aldosterone system functions.

Family members (Fig. 3)

The parents of the propositus are first cousins. One sister (III-3) had died at 9 days of age, after a 1-day history of vomiting and shock that was strongly indicative of PHA. Family history did not reveal additional early neonatal deaths or symptoms suggestive of PHA in three generations. The repeated aldosterone and PRA determinations over 4 yr in parents (II-2, 11), three siblings (III-1, 2, 4), and maternal uncle (II-7) were normal. Similarly, their aldosterone and PRA response to salt depletion (iv furosemide) were also normal. This pedigree indicated an autosomal recessive mode of inheritance.

Discussion

The clinical, biochemical, and genetic data on the two kindreds presented here and the analysis of previous reports of PHA reveal two distinct forms of this disease (Table 4). I will refer to these as the Renal and Multiple forms of PHA.

Clinical and biochemical findings

In patients with both forms of PHA, hyperaldosteronism results from target organ resistance to mineralocorticoids and both renal and other adrenal functions appear normal (8–12, 16, 17). However the number of target organs involved, the severity of salt wasting, and the course of the disease vary significantly between these two forms of PHA (Table 4).

In patients with the renal form there does not appear to be a defect in other aldosterone responsive organs, since the sweat (index case of kindred I, 7–10, 16, 21–24) and salivary electrolytes (24, 25), and binding of aldosterone to colonic mucosal cells (15) appear normal. In contrast, in the multiple form of PHA, as in kindred II, unresponsiveness to aldosterone is observed not only in kidneys but also in sweat and salivary glands, and colon (Table 5).

Persistent hyperaldosteronism and age-dependent changes in aldosterone and PRA

Our longitudinal study of 13 yr revealed persistent hyperaldosteronism in all patients with renal form of PHA (both symptomatic and asymptomatic). In contrast, in the multiple form of PHA, hyperaldosteronism is limited to symptomatic patients only. Hyperaldosteronism was previously reported in children with renal PHA several years after spontaneous recovery (4, 15, 16, 21, 24) and in a few adults (5–7, 16, 30). However, in these studies periodic determinations of both aldosterone and PRA, were not carried out over a prolonged period.

In our index cases the aldosterone and PRA levels were highest in the first few months of life and decreased notably during the first 2 yr, but remained significantly elevated. Other patients with renal PHA show similar decreases in aldosterone in the first 2 yr of life (11, 25, 26). The urinary sodium excretion appears to remain constant during the same period indicating an increased renal conservation of sodium with age (26). It should be noted that tubular transport mechanisms in healthy children improve with increasing age (31). Moreover, plasma levels of aldosterone in healthy children is highest during the first months of life and decrease gradually toward normal values during the first year (22) in parallel with PRA (32). Overall, these data indicate that maturation of tubular functions with increasing age may play

TABLE 4. Characteristics of two major forms of type I PHA as seen in our patients and in the literature

	Renal (kindred I)	Ref.	Multiple (kindred II)	Ref.
Affected organs	Kidney	All refs. below	Kidney, sweat, colon, salivary glands	See Table 5
Salt wasting	Variable		Severe	12, 17–20, 44
	1. Asymptomatic	5–7, 16	(recurrent severe salt wasting, occasional early neonatal death)	
	2. Moderate (FTT[a], vomiting, short stature)	4, 6–11, 24–29, 36		
	3. Severe (dehydration shock, death)	2–4, 7, 11		
Urinary Na/K[b]	~2[c]	8–10, 25–27, 29, 36	Mostly >10[d]	12, 17, 19, 20, 44
Blood aldosterone and PRA in symptomatic pts.	Mostly very high, PRA decreases with age	4–7, 15, 16, 21, 24, 30	Very high	12, 17–20, 44
Improvement with age	Often	8–11, 13–15, 21, 24, 28	No?	12, 17–20, 44
High salt diet	1–3 yr	8–11, 13–15, 21, 24, 28	Lifelong?	12, 17–20, 44
Catch-up growth on NaCl	Often	4, 9–11, 24	Rare	12, 18, 19, 44
Mode of inheritance	Autosomal dominant	5–7, 12, 16, 35, 36	Autosomal recessive	12, 18–20, 44
Dx of asymptomatic pts.	Often (high aldosterone)	5–7, 16	No (normal aldosterone)	12, 20, 44
Receptor defect[e]	Most likely (MCR[f] defect?)	See *Discussion*	Most likely (type II GCR[f] defect?)	See *Discussion*

[a] FTT: failure to thrive.
[b] Na/K reflects mineralocorticoid effect on renal tubule.
[c] Inappropriately high value in the face of hyponatremia and hyperaldosteronism.
[d] In some patients as high as 500 due to very low urinary K (12).
[e] Receptor studies were not done in our patients.
[f] MCR, mineralocorticoid receptor; GCR, glucocorticoid receptor.

an important role in the amelioration of the disease in children with renal PHA, and to a lesser degree in multiple PHA.

In contrast to aldosterone levels, PRA decreased to normal levels in all patients with advancing age. These results are consistent with a few determinations reported in older patients (5, 7, 24, 30). We suggest the following explanation for the persistence of hyperaldosteronism in the face of normal renin in older patients with renal PHA. Chronic salt depletion and the resultant hyperreninemia over several years could stimulate zona glomerulosa leading to hypertrophy of the zone and secondary hyperaldosteronism. In animals with secondary hyperaldosteronism, the zona glomerulosa is indeed hypertrophied (33). In PHA, eventually tertiary hyperaldosteronism may develop with zona glomerulosa functioning at an enhanced capacity autonomously. In PHA 18-OHB originate predominantly from the zona glomerulosa (4). Thus, the increased 18-OHB levels in our older patients provide further evidence for enhanced function of zona glomerulosa. Additionally, the possibility that target organ defects may cause stimulation of aldosterone by yet unknown factors can not be eliminated.

The magnitude of PRA and aldosterone in patients may be affected by at least two additional factors: 1) The severity of salt losing: PRA and aldosterone levels are lower and may normalize earlier in life in some asymptomatic patients (*e.g.* patient III-3 from kindred I). Thus, once the renal form of PHA is identified in a patient, the other family members should be screened by measuring aldosterone and PRA at an as early age as possible for early diagnosis and treatment. 2) The amount of sodium supplements: The PRA normalized even in our index case with multiple PHA at a young age after administration of a sufficient amount of NaCl (see also case 2 in Ref. 12).

The elevated PRA in young asymptomatic patients probably reflects marginal salt loss and hence may impair growth. For these patients salt supplementation should be considered even in the absence of more severe signs of PHA.

The renin-angiotensin system and aldosterone biosynthesis

The renin-angiotensin system appears to be intact in both forms of PHA. Acute changes in sodium intake (sodium depletion or repletion) result in concomitant changes in aldosterone and PRA (our case with multiple PHA, 9, 12, 16, 25, 26, 34). Aldosterone biosynthetic capacity also appears to be normal in both forms of PHA (our cases, and Ref. 4).

TABLE 5. Major characteristics and family data of all reported patients with multiple PHA

Author (Ref.)	Age at onset (days)	Sex	End organ involved	Urinary Na/K	Total no. of sibs (affected)	Parental consanguinity	Origin	Parents' hormonal evaluation	Suggested inheritance	Age at last examination and outcome[a]
Oberfield (17)	7	M	Ki, Sw, Sa, Co	14–501	3 (2?)[b]	No				9 yr[c]
Savage (18)	8	M	Ki, Sw, Sa, Co		None	First cousins	Indian		Au. recessive	4 months
Savage (18)	6	M	Ki, Sw, Sa, Co		5 (2)[d]	First cousins	Indian		Au. recessive	6 months
Bosson (20)	14	M	Ki, Sw, Sa, Co	>32	2 (2)[e]	First cousins	Moroccan	Normal[f]	Au. recessive	Died
Speiser (12)	4	F	Ki, Sw	20	1 (1)	First cousins		Normal	Au. recessive	8 months
Speiser (12)	10	F	Ki, Sw, Sa, Co	5	1 (1)	No	Black	Normal		3 1/2 yr
Popow (19)	7	F	Ki, Sw, Sa, Co	64	2 (2)[e]			Normal	Au. recessive	7 yr
Bistritzer (44)[g]	7	M	Ki, Sw, Sa	20–30	5 (3)	First cousins	Iranian Jew	Normal	Au. recessive	9 mo
Present report	8	F	Ki, Sw, Sa	>8	5 (2)	First cousins	Iranian Jew	Normal	Au. recessive	5 yr

Ki, Kidney; Sw, sweat; Sa, saliva; Co, colon.

[a] Repeated episodes of salt depletion until last examination, despite high NaCl intake in all patients.

[b] Cause of death probably related to undiagnosed PHA in one sibling.

[c] Follow-up data from Ref. 12.

[d] A male sibling died of PHA at age 2 weeks.

[e] A female sibling with multiple PHA still on high NaCl beyond 2 yr of age.

[f] Diminished number of mineralocorticoid receptors in both parents (see also Ref. 38).

[g] Twin babies. The data are from both babies. A male sibling died of PHA at age 3 months.

Mode of inheritance

Previous investigators, ascribed conflicting modes of inheritance to PHA assuming that PHA is a unique entity. Our distinction resolves these conflicting reports as detailed below.

The pedigree of kindred I extends and further substantiates previous reports that the renal form of PHA is inherited as an autosomal dominant trait (5–7, 16). The study of four kindreds, including kindred I, from 3 consecutive generations indicate that renal PHA is transmitted by only one affected parent (5, 7, 36). The clinical spectrum in afflicted patients range from asymptomatic to severe PHA consistent with variable expression (Table 4). In addition to the kindreds noted above, *Kuhnle et al.* (37) proposed an autosomal dominant mode of inheritance for four families, but an autosomal recessive mode of inheritance for three other families with apparently renal PHA. The suggestion of a recessive mode of inheritance for these three families represents an exception in the literature. However, in a different study by the same group, an autosomal dominant inheritance was suggested for one of these three families and five additional families with renal PHA (35).

In contrast to kindred I, the pedigree of kindred II, and of other similar cases in the literature, indicate that the multiple form of PHA is inherited as an autosomal recessive disease (Table 5). In affected patients the expression of the disease appears to be remarkably uniform. Since serum aldosterone values appear normal in the parents of affected children, it can not be used to detect asymptomatic family members (heterozygotes) in multiple PHA.

Pathophysiology of PHA

In the pathogenesis of type I PHA several factors including deficient renal Na^+-K^+ ATPase activity (2), reduced number of mineralocorticoid (type I) receptors (30), and a qualitative receptor defect (35), have been implicated. However, some of these defects may be a secondary effect of hyperaldosteronism, or salt loss.

In one patient with renal PHA, renal Na^+-K^+ ATPase activity was almost undetectable in both proximal or distal nephron segments (2). This does not necessarily indicate a primary defect, since Na^+-K^+ ATPase activity can decrease as result of a reduction in renal sodium reabsorbtion (38, 39). A decrease in mineralocorticoid receptors have been reported in the mononuclear leucocytes of several patients with both renal and multiple forms of PHA (37) (patient 4 in Ref. 37 is a patient with multiple PHA as described in Ref. 20) and in some of

their family members. However, a similar decrease in mineralocorticoid (type I) receptors has been also reported in patients with primary aldosteronism (40). Thus, reduced number of receptors may reflect a down regulation of the receptor as a result of chronically elevated levels of aldosterone (35).

A qualitative receptor defect (a defective intracellular electrolyte response of mononuclear leucocytes to aldosterone) was shown to be inherited as an autosomal dominant trait in six families with renal form of PHA (35). Whether this is the primary cause of PHA remains to be seen by testing more patients and asymptomatic family members with both forms of PHA. Yet, this defect was also found in patients with primary aldosteronism (41).

Another approach to elucidate the biochemical basis of different subtypes of PHA would be to conduct receptor studies in major aldosterone target tissues. Obviously such studies can not be performed routinely. Tissue samples of rectal mucosa in two children with multiple PHA showed a decreased binding capacity for aldosterone in low affinity binding sites (type II receptor defect) (19). If this defect is the primary abnormality it should exist only in patients with multiple form of PHA. Indeed, the binding of aldosterone by colonic mucosa cells was found to be normal in a patient with renal PHA (15).

The gene for aldosterone receptor has been cloned (42). If the defect in the subtypes of PHA described here is in this receptor then, molecular biology techniques may be the ultimate means to identify this mutation in these forms and also in another much rarer form of PHA in which the salt loss is limited to salivary and sweat glands only (43).

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