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Plasma renin activity and mineralocorticoid replacement therapy in congenital adrenal hyperplasia

By

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Plasma renin activity and serum concentrations of sodium and potassium were repeatedly measured in seven children with congenital adrenal hyperplasia due to steroid-21-hydroxylase deficiency, to monitor the sodium balance during treatment. Infants with the salt-losing form had high plasma renin activity levels 5—11 months after subcutaneous implantation of a pellet containing 100 mg deoxycorticosterone acetate. These elevated plasma renin activity levels were suppressed to the normal range by repeated implantation of DOCA pellet. Moderately elevated values of plasma renin activity in older salt-losers normalized after increasing the dietary sodium intake. Plasma renin activity level has superiority over serum electrolyte concentrations as an index of mineralocorticoid deficiency.

The standard techniques for therapeutic monitoring of patients with congenital adrenal hyperplasia (CAH) due to steroid-21-hydroxylase deficiency include urinary 17-ketosteroids and serum sodium and potassium concentrations. The development of radioimmunoassay methods for the measurement of cortisol-precursors and adrenal androgens in serum has provided a new aid for the diagnosis and management of such patients. The 17-OH-progesterone value seems to be the most sensitive indicator of inadequate adrenal suppression [12, 13, 23]. In the salt-losing form of CAH a chronic depletion of sodium may develop due to insufficient mineralocorticoid treatment despite the presence of normal serum electrolyte concentrations.

As a sensitive index of mineralocorticoid deficiency, plasma renin activity (PRA) was measured in patients with CAH due to 21-hydroxylation deficiency. The main objective of this study was to determine the length of time for the effect of deoxycorticosterone-acetate (DOCA) pellets implanted subcutaneously in infants. In addition we wished to investigate PRA in older children who had discontinued treatment with salt-retaining hormone, in order to determine the amount of dietary sodium needed.

Materials and Methods

Seven girls aged 1—15 years with CAH due to steroid-21-hydroxylase deficiency were studied. Four were salt-losers and three were simple virilizers according to

clinical findings. The patients were treated with cortisone acetate (Adreson, Organon) 40—50 mg/m²/day. In the salt-losing infants, DOCA pellet (deoxycorticosterone-acetate tablet ad implantationem, 100 mg, Organon) was implanted subcutaneously.

The parameters used to monitor the efficacy of glucocorticoid suppression therapy included growth rate, skeletal age, urinary 17-ketosteroids and plasma 17-OH-progesterone determinations [20].

Children ranging in age from 6 months to 10 years after reconvalescence or before a minor surgical operation were studied as controls. All children were on a normal diet and showed no abnormalities of fluid-electrolyte balance.

Venipuncture was performed in the fasting state between 8—9 a.m. after the children had been in recumbent position for at least 3 hours. Ten ml blood was drawn into prechilled polyethylene tubes containing 0.5 ml of 1.5% sodium-EDTA for the determination of plasma renin activity. The plasma was separated immediately by centrifugation at 3000 r.p.m. at +4 °C. At the same time blood was collected in separate tubes for the determination of the serum concentrations of sodium and potassium.

Determination of plasma renin activity. The plasma was stored at +4°C overnight. After adjusting the pH to 5.5 and adding diisopropyl fluorophosphate and neomycin, incubation was performed at 37°C for 24 hr and the enzymatic reaction was stopped by boiling for 15 min. The supernatant was separated by centrifugation at 5000 r.p.m. for 10 min, followed by readjustment of the pH to 7.4 [8]. The pressor activity of the plasma was tested in pentolinium-pretreated rats, using angiotensin-amide (Hypertensin, Ciba) as standard and applying the four point assay. Plasma renin activity (PRA) was expressed as ng equivalent of angiotensin II per ml plasma per 24 hr of incubation. Reproducibility attained ±14.2% (intra-assay coefficient of variation, n = 16).

Serum concentrations of sodium and potassium were measured by flame photometry (Pye Unicam SP 191).

Results

Plasma renin activity in the control children ranged from 10 to 25 ng/ml/24 hr, with a mean value of 16.2 ± ± 4.7 ng/ml/24 hr (n = 15). The cal-

Table I

Plasma renin activity in control infants and children

Case No.	Sex	Age, years, months	Clinical situation	PRA (ng/ml)
1	M	6m	recovered from malnutrition	20
3	F	6m	recovered from pharyngitis	11
4	M	10m	recovered from bronchitis	15
5	M	10m	mental retardation	12
6	F	1y 4m	recovered from bronchitis	17
7	F	1y 4m	recovered from minor thermal injury	12
8	M	1y 9m	recovered from tonsillitis	10
9	M	2y	recovered from pneumonia	14
10	M	2y 6m	observation for megacolon congenitum	25
11	F	4y	before tonsillectomy	13
12	M	6y	before tonsillectomy	15
13	M	8y	before adenoidectomy	20
14	M	9y	before adenoidectomy	24
15	F	10y	chronic otitis media	14

mean ± S.D. = 16.2 ± 4.7

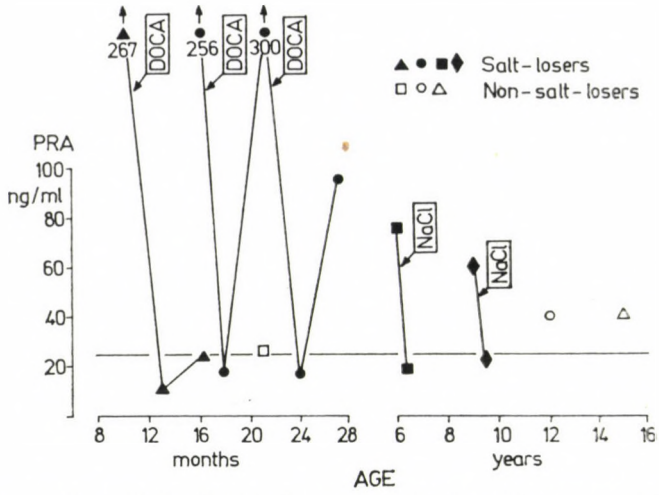

FIG. 1. Plasma renin activity (PRA) in seven patients with congenital adrenal hyperplasia due to steroid-21-hydroxylase deficiency. Each symbol identifies a separate patient. The shaded area indicates the upper limit of the normal range. DOCA = subcutaneous implantation of 100 mg deoxycorticosterone-acetate. NaCl = increase in dietary sodium intake

culated upper reference limit (mean + + 2 S.D.) in children from 6 months to 10 years of age is 25.6 ng/ml/24 hr. Individual data for the 15 normal infants and children are shown in Table I.

Plasma renin activity was extremely high in the two salt-loser infants 8.5 and 11 months after the implantation of DOCA, indicating an insufficient mineralocorticoid effect despite the normal blood pressure and serum electrolyte concentrations. These elevated PRA levels were suppressed to the normal range by repeated implantation of DOCA pellet. The second infant had again a high level of PRA after 5 months. At that time she also had an abnormally low sodium-potassium ratio in the serum.

Two salt-loser children, aged 6 and 9 years, who had discontinued treatment with salt-retaining hormone years before, showed moderately elevated values of plasma renin activity which were normalized after increasing their dietary sodium intake. During this time the serum sodium–potassium ratio remained in the normal range.

Two patients out of three simple virilizers had slightly elevated PRA values.

The results of the CAH patients are summarized in Fig. 1 and Table II.

Discussion

There is a progressive decrease of PRA as age increases from the newborn period to adulthood [1, 3, 18, 21]. In our study the PRA levels of normal children did not show age-related differences, presumably due to the limited number of subjects

TABLE II

Clinical data, serum concentrations of sodium and potassium, and plasma renin activity of patients with congenital adrenal hyperplasia due to 21-hydroxylase deficiency

Subjects	Sex	Age, years, months	Time elapsed from the last implantation of DOCA, months	Extra NaCl added, g/day	Serum			PRA ng/ml
					Na	K	Na/K ratio	
					mEq/l			
Patients								
*J. K.	F	1m	—	—	128	6.9	18.5	—
		10m	8.5	—	137	5.6	24.5	267
		1y 1m	2	—	138	5.3	26.0	11
		1y 4m	5	—	142	4.3	33.0	24
*L. T.	F	1m	—	—	122	6.0	20.3	—
		1y 4m	11	—	142	4.5	31.5	256
		1y 5m	1	—	144	4.4	32.7	18
		1y 9m	5	—	135	6.1	22.1	300
		2y	3	—	140	4.2	33.3	17
		2y 3m	6	—	137	5.2	26.3	95
L. A.	F	1y 7m	—	—	142	4.7	30.2	26
*M. G.	F	2m	—	—	125	6.0	20.8	—
		5y 8m	—	—	143	4.3	33.2	75
		6y	—	4	142	4.5	31.5	19
*R. T.	F	1m	—	—	123	7.1	17.3	—
		9y	—	2	142	3.7	38.4	60
		9y 6m	—	4	138	4.8	28.8	23
R. E.	F	12y	—	—	147	3.9	37.7	40
Z. E.	F	15y	—	—	148	4.5	32.9	40
Normal infants: mean ± S. D. (n)					140.5±3.5 (21)	4.70±0.55 (21)	30.3±3.6 (21)	16.2** ± 4.7 (15)
Normal children: mean ± S. D. (n)					142.2±4.6 (30)	4,18±0.38 (30)	34.3±3.1 (30)	

* salt-loser
** pooled value for infants and children

investigated. Therefore, we pooled the data of infants and children to calculate the upper reference limit for this age group.

Venipuncture was performed under standard conditions in the morning, after the patients had been recumbent overnight, because the PRA levels show a diurnal variation [9] and an elevation in the upright position [2, 5].

PRA has an inverse relationship to total body sodium and extracellular fluid volume [24, 25]. Dietary sodium restriction was shown to cause an elevation of PRA without a change in the serum concentration of electrolytes [19]. Our results indicate that PRA levels can be very high in infants with an early history of salt-wasting crisis even in the absence of symptoms of sodium loss. These findings are in agreement with the previously reported results in patients with CAH. Several authors have described elevated PRA levels

in salt-losing CAH [3, 11, 14, 17] and have shown that the levels return to normal on mineralocorticoid treatment [4, 7]. In contrast, Strickland and Kotchen [22] found the PRA level of a non-salt-loser to be in the range of salt-losers during dietary sodium restriction.

Nichols et al. [15] have implanted subcutaneously two 75 or 125 mg DOCA pellets repeatedly at intervals of 6 to 12 months. According to present data the implantation of 100 mg DOCA ensures an effective mineralocorticoid replacement for 5 to 11 months. The elevated level of PRA seems to be the most sensitive index for the determination of a salt-wasting tendency showing the need of a new implant.

Although salt-retaining hormone treatment may be stopped in late childhood, the salt-losing state in CAH persists and an increase in dietary sodium intake may be necessary in some cases. The amount of sodium needed cannot be determined by measurement of the serum sodium and potassium levels. It seems therefore useful to monitor the salt repletion therapy of children with salt-losing CAH by the level of plasma renin activity.

Our finding that PRA levels may be slightly elevated in some patients with CAH who have never shown clinical evidence of salt loss, agree with those of other authors [4, 11, 17] and suggest an impairment of salt homeostasis in these patients.

There is an interrelationship between the renin-angiotensin system and the pituitary-adrenal axis. Angiotensin II infusions produce ACTH release in normal subjects [16], and glucocorticoids stimulate the hepatic synthesis of angiotensinogen [10]. Rösler et al. [17] suggest the existence of this interrelationship in CAH patient, too. Thus, a rise in the ACTH level secondary to salt-loss may contribute to the hypersecretion of androgens.

The combination of serum 17-OH-progesterone and plasma renin assays can provide more exact and precise information and can indicate situations in which the patient does not require more glucocorticoid but rather a correction of mineralocorticoid replacement therapy or an increase in dietary salt intake [6, 11]. It is probable that in some CAH patients a reduction of the glucocorticoid dose will be possible when adequate sodium balance has been achieved.

In conclusion, we recommend the determination of PRA every three months in salt-losing infants and once yearly in childhood. Correction of a mild chronic sodium depletion can prevent unexpected salt-wasting crises and improve somatic development.

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