

## APPARENT MINERALOCORTICOID EXCESS IN THREE SIBLINGS

MARYAM RAZZAGHY-AZAR, M.D. AND JANOS HOMOKI, Ph.D. \*

*From the Dept. of Pediatrics, Hazrat Aliasghar Children's Hospital, Iran University of Medical Sciences,  
and the \*Dept. of Biochemistry, Ulm University, Ulm, Germany.*

### ABSTRACT

Three siblings (1 boy, 2 girls) with hypertension and hypokalemia are presented, two with low plasma aldosterone and suppressed renin activity and the eldest with a high renin and aldosterone level due to secondary changes in her kidneys. Urinary tetrahydrocortisol (THF) was increased relative to tetrahydrocortisone (THE). Cortisol ring A reduction constant was also lower than normal. These findings are suggestive of decreased cortisol-11  $\beta$ -hydroxysteroid dehydrogenase activity and ring A reduction defect which has previously been described in type 1 apparent mineralocorticoid excess.<sup>1</sup> The existence of this disease in three siblings from healthy parents with consanguineous marriage reveals the genetic (autosomal recessive) nature of the disease.

Spirolactone normalized serum potassium in all three patients and hypertension in two of them. Furosemide and captopril were required for lowering blood pressure in the eldest one. Treatment caused growth catch up in all three patients.

**Keywords:** Low renin hypertension, hypokalemia, cortisol metabolism, cortisol-11  $\beta$ -hydroxysteroid dehydrogenase.

*MJIRI, Vol. 10, No. 3, 249-254, 1996.*

### INTRODUCTION

The syndrome of apparent mineralocorticoid excess (AME) has thus far been reported only in children and young adults. Its clinical presentation is similar to primary aldosteronism with hypertension, hypokalemic alkalosis and suppressed plasma renin activity. The response of these clinical manifestations to spironolactone suggests the presence of a circulating mineralocorticoid. However, levels of aldosterone and all known mineralocorticoids are either very low or absent. It is very likely that the functioning mineralocorticoid in this disorder is cortisol, circulating in normal amounts but exerting a mineralocorticoid effect because of incomplete metabolism at target tissues.<sup>1</sup> This disorder has been detected in 18 children.<sup>3</sup> We report three children from one family in whom the pattern of urinary

steroid metabolite excretion suggests a similar metabolic defect as the cause of their hypertension.

### CASE REPORTS

#### Patient ND

A 11.6 year-old Iranian boy was referred to H. Aliasghar Hospital because of paralysis and vomiting. The parents gave a history of similar attacks following pharyngitis and fever in the past three to four winters. He had felt weakness and pain in his hands since the year before and was always very hypoactive and quiet. His parents are first cousins. There are six children (three boys and three girls) in the family. Two girls and one boy have AME. The other children and the parents are healthy (Fig. 1).

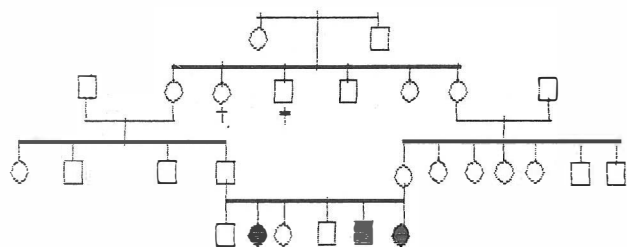
On physical examination, hypotonicity was noticed in

all his muscles, and foot drop and head drop were remarkable. The blood pressure in a recumbent position was 170/110 mmHg. His height and weight were under the 5th percentile of NHCS curves. The bone age was retarded according to the Atlas of Greulich and Pyle (G&P) (Table I). The genitalia were male phenotype with no sign of virilization. Electromyography and nerve conduction velocity showed polyneuropathy in the extremities. Brain CT scan was normal. In Doppler sonography and intravenous pyelography, the kidneys were a bit larger than normal with no stenosis in renal arteries. Serum potassium was 2 mEq/L, other laboratory tests are given in Tables II and III. The results of endocrine tests are on Table IV. Potassium supplementation with potassium chloride (10g/day by perfusion and orally) did not increase the serum potassium more than 2.6 mEq/L. Spironolactone with a dosage of 2 mg/kg/day normalized the serum potassium level and the blood pressure became 110/70 mmHg. After 1 year of treatment, creatinine clearance was 135.6 mL/min/1.73m<sup>2</sup>. The electrolytes and blood pressure remained normal.

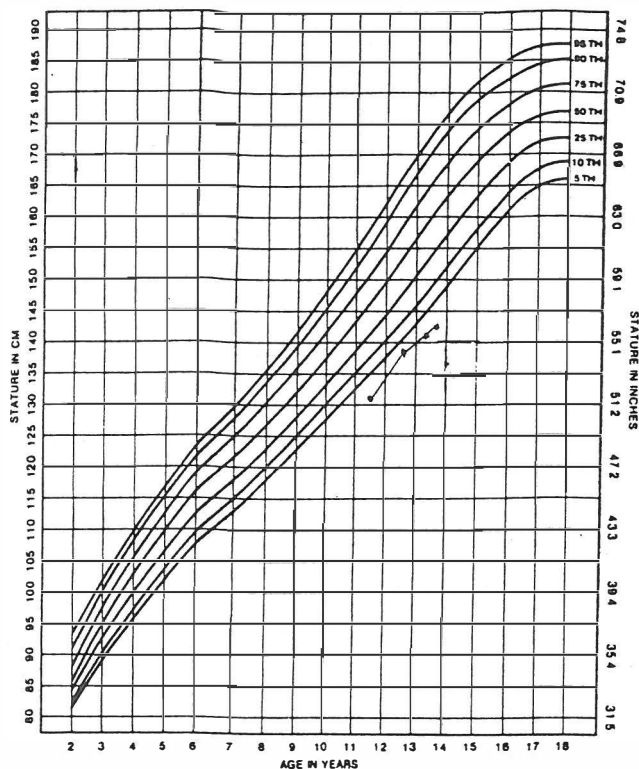
**Patient**

This sister of ND was 14.2 years old when she presented with polyuria, polydipsia and urinary incontinence since she was 5 years of age. She had suffered from umbilical and flank pain with radiation to the groin for about one year. She also complained of exertional dyspnea, palpitation, chest pain and anorexia. On physical examination her height and weight were under the 5th percentile. The blood pressure was 260/140 mmHg (Table I). Retinal examination showed grade 3 vasculopathies of hypertension (arteriolar narrowing, arteriovenous nicking, exudates and edema). On cardiac examination S<sub>1</sub> and S<sub>2</sub> were exaggerated. A functional systolic murmur was heard at the apex.

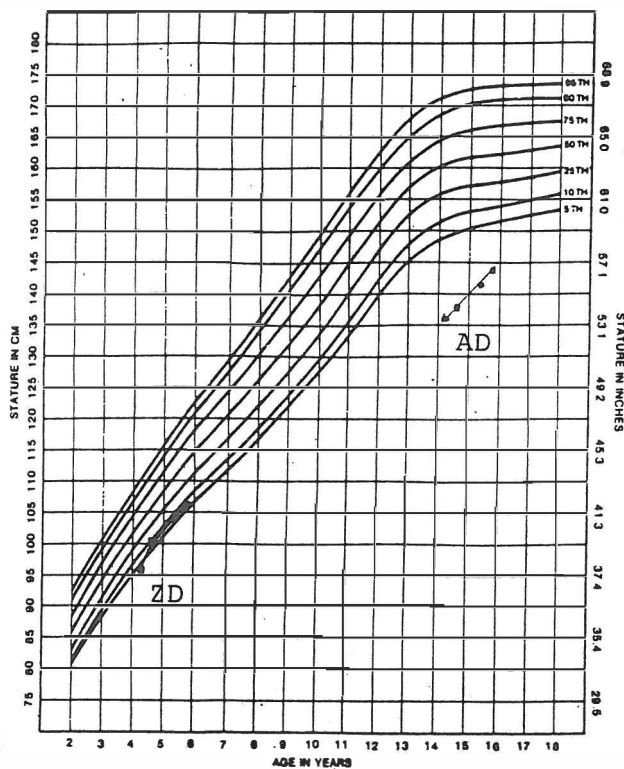
Her breast development was stage 3 and pubic hair stage 2 on the Tanner scale. The bone age was retarded according to the Atlas of G&P. The laboratory tests are given in Tables II-IV. Sonography of the kidneys showed the size of the right kidney to be 78×34mm and the left 84×29mm. Hyperechogenicity was detected in both kidneys and the border between the cortex and medulla was dull. Because of renal failure and hyperreninemia, we finally controlled



■, patients with AME  
 † dead in 3-4 years of age  
**Fig. 1.** The pedigree of patients with AME.



**Fig. 2.** The growth curve of the boy with AME (ND).



**Fig. 3.** The growth curves of the girls with AME (ZD, AD).

hypertension and hypokalemia with a combination of spironolactone 25 mg/day, furosemide 80 mg/day and

Table I. Anthropometric characteristics of the patients with AME in the first admission.

Patients	Age Year	Height Cm	HA year	Weight Kg	WA Year	BA Year	BP mmHg
ND	11.58	130.8	9	25	8	9	170/110
ZD	4	96	3	14	2.66	2.5	160/100
AD	14.2	135.5	9.33	29	9.33	9.5	220/160

HA, height age; WA, weight age; BA, bone age; BP, blood pressure

Table II. Laboratory tests of patients with AME at the first admission.

Patients	BUN mg/dL	Cre mg/dL	Cre.C mL/min	Na mEq/L	K mEq/L	Ca mg/dL	P mg/dL	MG mg/dL	Alk P units
ND	9	0.4	123.3	145	2.0	10.9	3.9	2.9	45
ZD	18	0.3	120	143	3.1	10.5	5.3	2.5	264
AD	22	1.5	19.6	134	2.8	9.8	5.6	2.0	163
Normal range	8- 23	0.3- 0.7	see* note	135- 148	3.5- 5.3	8.5- 10.5	4.5- 6.5	1.8- 2.9	88- 370

All the measurements are in the blood.

BUN, blood urea nitrogen; Cre, creatinine; Cre. C, creatinine clearance corrected with  $1.73\text{m}^2$ ; \*Normal range for 1.5 y to adolescence (male,  $124.0+25.8$ , female,  $108.8+13.5$  mL/min/ $1.73\text{m}^2$ ); Alk P, alkaline phosphatase.

captopril 75 mg/day in divided doses. The blood pressure decreased to 110/70 mmHg. Initially creatinine increased to 3.6 mg/dL, but after 3 months creatinine dropped to 1.5 mg/dL and creatinine clearance was 50 mL/min/ $1.73\text{m}^2$ .

#### Patients ZD

The sister of the two reported cases, she was 4.16 years old when examined for screening purposes due to the disease in her family. She had headache, occasional umbilical pain and enuresis. Her blood pressure was 160/100 mmHg and serum potassium was 3.2 mEq/L. Her anthropometric characteristics are given in Table I and the laboratory tests in Tables II-IV. Treatment with spironolactone 1.3 mg/kg/day corrected her blood pressure to 100/70 and the serum potassium to 4.5 mEq/L.

All three patients had compensated growth during the follow-up period as shown in Figs. 2,3.

All blood samples for renin and aldosterone were taken in cold tubes when the patients had been in supine position for at least 3 hours and upright for 2 hours. Plasma was immediately separated in a refrigerated centrifuge and kept frozen at  $-70^\circ\text{C}$  until time of assay. Plasma renin activity (PRA) was measured by radioimmunoassay (RIA) (INCSTAR, CA-1533 assay kit); its intra- and interassay coefficient of variations were 8% and 6.6%, respectively. Aldosterone was also measured by RIA (ALDOCTK-2, P2714, Sorin Biomedica), Intra- and interassay coefficient of variations were 9.7% and 11.5%, respectively.

Urine samples were collected from ND when he was 13 years old, from ZD at 5 years (on spironolactone and off spironolactone for 6 days), and from AD at 15 years of age on spironolactone, furosemide and captopril.

Urinary cortisol metabolites were measured by gas chromatography-mass spectrometry. Cortisol was isolated from urine by adsorption on C-18 Sep-Pak cartridges (Waters Co., Milford, MA) and elution with methanol and was kindly performed by Professor J. Homoki in Ulm University in Germany. The methodology of urinary steroid analysis was described by Shackleton in 1985.<sup>5</sup>

Cortisol/cortisone metabolite ratio as a measurement of the deficiency of  $11\beta$ -hydroxydehydrogenation is obtained by dividing the 24 hours urinary sum of tetrahydrocortisol and allotetrahydrocortisol by tetrahydrocortisone.<sup>1</sup>

Cortisol turnover quotient as a noninvasive measure of metabolic clearance was calculated by dividing the sum of the major urinary cortisol metabolites by urinary free cortisol in a 24-h collection, as described and justified previously.<sup>6</sup>

Since the procedure of cortisol ring A reduction constant is noninvasive, a steady state can be reasonably assumed throughout the study, in which adrenocortical secretion is balanced by inactivation and excretion. The reaction studied is the irreversible conversion of extracellular cortisol to tetrahydrocortisol and allotetrahydrocortisol ( $3\alpha$   $4\beta$ ). In the conversion, cortisol (F)  $\rightarrow$  tetrahydrocortisol (THF)+allotetrahydrocortisol (aTHF), the ring A reduction constant =  $\text{THF} + \text{aTHF}/\text{F}$ , where the steroids are F, mea-

## Mineralocorticoid Excess

Table III. Laboratory tests of patients with AME (continued).

Patients	HCO <sub>3</sub> <sup>-</sup> mmol/L	CL mEq/L	Blood pH	Minimum urine pH	Urine SG
ND	24	94	7.37	5	1012
ZD	22	98	7.38	5.8	1014
AD	24	95	7.39	6.6	1008

Cl, chloride; SG, specific gravity.

Table IV. Endocrine tests of patients with AME.

Patients	Cortisol 8 AM µg/dL	ACTH pg/mL	17OH-P ng/mL	Renin Upright ng/mL/hr	Renin Supine ng/mL/hr	Aldo Upright ng/dL	Aldo. Supine ng/dL
ND	22.4	54	1.4	0.7	—	3.2	—
ZD	19.9	34	0.3	0.04	0.03	1.0	0.07
AD	26.5	121	0.56	12.2	12.8	46.5	24.0
Normal range	5- 25	20- 90	0.1- 0.5	1.5- 5.7	0.2- 2.8	4.0- 31	1.0- 16

17OH-P, 17 Hydroxyprogesterone; Aldo., Aldosterone.

Table V. Urinary excretory rates of cortisol and its metabolites in three patients with type 1 variant of the AME syndrome.

Subject	Age (years)	Treatment	Urinary steroid, µg/day			
			F	THE	THF	Allo THF
ND	13	Y	NA	122	187	203
ND	13	N	7	60	112	137
AD	15	Y	NA	39	68	110
ZD	5	Y	10	46	56	118
ZD	5	N	15	76	12.6	197
Normal values						
Children (4-8yr)			20.5	1030	460	590
±SD (n= 5)			5.2	560	180	300
Adults			31.2	2590	1470	1370
±SD (n= 11)			8.6	1290	590	700

Y, on treatment; N, six days after discontinuing drug therapy; NA, not analyzed.  
Reference for normal range is (6).

sured in micrograms in 24-h urine collection. The constant in normal subjects is 101±23.

Table V shows the urinary steroid excretory rates of the patients. The very low excretion of cortisol metabolites is clearly demonstrated in all patients. Cortisol/cortisone metabolite ratio was 3.98±0.52 (3.2-4.6), so they have impairment of 11β-hydroxydehydrogenation (Table VII). Cortisol turnover quotient was markedly decreased in two patients which was 30.9±11.6 (range, 22.0-26.6). The mean was

one-seventh the normal value. In AD it was not analysed. Cortisol ring A reduction constant was decreased in all three patients and the mean value was 24.8±9.5, or approximately one-fourth of the normal value (Table VI).

## DISCUSSION

The abnormality in steroid metabolism in the syndrome of AME consists of decreased rate of metabolism of cortisol

Table VI. Cortisol metabolism dynamics in the patients with AME syndrome.

Subject	T	Cortisol/cortisone metabolite ratio (THF + aTHF/THE)	Cortisol turnover quotient (THF + aTHF + THE/F)	Ring A reduction constant (THF + aTHF/F)
ND13	Y	3.2	NA	NA
ND13	N	4.1	44.1	35.6
ZD5	Y	3.8	22.0	17.4
ZD	N	4.2	26.6	21.5
AD15	Y	4.6	NA	NA
Mean±SD		3.98±0.52	30.9±11.6	24.8±9.5
Normal (n= 10)				
Mean±SD		0.96±0.3	215±78	101±23

ND13, patient ND aged 13 years; ZD5, patient ZD aged 5 years; AD15, patient AD aged 15 years; T, treatment; Y, on treatment; N, six days after discontinuing drug therapy; NA, not analyzed; Reference for normal range is (1).

to cortisone. Cortisone itself is biologically inactive. Normally, a reversible 11 $\beta$ -hydroxy oxidoreduction leads to an equilibrium mixture of approximately equal amounts of cortisol and cortisone. This process converts administered cortisone to the biologically-active hormone and also inactivates cortisol by obligatory metabolism requiring resynthesis of a 2 mg pool of hormone about ten times per day.<sup>2</sup> The major sites of this terminal metabolism are the liver and kidney. 11 $\beta$ -hydroxysteroid dehydrogenase is the enzyme responsible for this oxidoreduction phenomenon. Classically, the enzyme has been considered to be bi-directional,<sup>7</sup> although it is well known that different body tissues favour one direction or the other.<sup>8</sup> What regulates the efficiency of reduction or oxidation was never determined. Ulick et al.<sup>9</sup> demonstrated that while no conversion of administered labeled cortisol to cortisone took place in one of the children with AME, labeled cortisone was effectively converted to metabolites of cortisol containing an 11 $\beta$ -hydroxyl group. It appeared therefore that the enzyme activity was only deficient in the oxidative direction. Thus the metabolic abnormality would be most easily explained by the existence of two enzyme activities, one catalyzing steroid oxidation and the other, 11-oxo-steroid reduction.<sup>5</sup> The disorder described in the children is therefore explained by deficiency of 11 $\beta$ -hydroxysteroid oxidase with normal activity of 11-oxo-steroid reductase. The defect in cortisol metabolism in the syndrome of AME is not limited to 11 $\beta$ -hydroxydehydrogenation. The ring A reduction is also much decreased, not only in the type 2 variant, but in the type 1 form as well.<sup>1</sup> In our patients, cortisol/cortisone metabolite ratio was decreased which shows the impaired 11 $\beta$ -hydroxydehydrogenation of cortisol to cortisone. Ring A reduction constant was also decreased compared to normal level.

Ulick et al.<sup>9</sup> reported in 1979 that the incomplete A ring reduction defect improved with time. 5 $\alpha$ -dihydrocortisol was no longer increased, but hypertension and hypokalemic

alkalosis still persisted. The difference between our patients and other reported cases<sup>4</sup> are:

- 1- Our patients and their family did not have alkalosis.
- 2- After 3 days of administering low doses of spironolactone, serum potassium increased and the blood pressure decreased. After 1.5 years of treatment, they still have normal blood pressure and electrolytes.
- 3- Our eldest patient had hyperreninemia which was definitely secondary to kidney changes, due to longstanding hypertension and hypokalemia. Her urinary steroid analysis and the existence of the syndrome in her siblings prove her disease. This hyperreninemia can be misleading in diagnosis of longstanding cases.

## CONCLUSION

Three patients with apparent mineralocorticoid excess syndrome are presented. The existence of the disorder in siblings of both sexes but not in the parents suggests an autosomal recessive mode of transmission. The emerging picture of the syndrome in this study is a disturbance in the peripheral metabolism of cortisol. The conclusion as to which activity (ring A reduction or 11 $\beta$ -hydroxydehydrogenation) is more important in the pathogenesis of this syndrome will become clear with more investigation in the future.

## REFERENCES

1. Ulick S, Tedde R, Wang JZ: Defective ring A reduction of cortisol as the major metabolic error in the syndrome of apparent mineralocorticoid excess. *J Clin Endocrinol Metab* 74: 593-99, 1992.
2. Ulick S: Two uncommon causes of mineralocorticoid excess. *Endocrinology and Metabolism Clinics of North America* 20: 269-75, 1991.

## Mineralocorticoid Excess

3. Di Gorge AM: Excess mineralcorticoid secretion. In: Behrman B (ed), Nelson Textbook of Pediatrics. W.B. Saunders, p. 1451, 1992.
4. de Man AJM, Hofman JA, Hendriks TH, et al: A direct radioimmunoassay for plasma aldosterone: significance of endogenous cortisol. *Neth J Med* 23: 79-83, 1980.
5. Shackleton CHL, Rodriguez J, Arteaga E, et al: Congenital 11-hydroxysteroid dehydrogenase deficiency associated with juvenile hypertension: corticosteroid metabolite profiles of four patients and their families. *Clin Endocrinol* 22: 701-10, 1985.
6. Ulick S, Tedde R, Mantero F: Pathogenesis of the type 2 variant of the syndrome of apparent mineralocorticoid excess. *J Clin Endocrinol Metab* 70: 200-6, 1990.
7. Bush IE, Hunter SA, Meigs RA: Metabolism of 11-oxygenated steroids – metabolism *in vitro* by preparation of liver. *Biochem J* 107: 239-58, 1968.
8. Murphy BEP: Ontogeny of cortisol-cortisone interconversion in human tissues: role for cortisone in human fetal development. *J Steroid Biochem* 14: 811-17, 1981.
9. Ulick S, Levine LS, Gunczler P, et al: A syndrome of apparent mineralocorticoid excess associated with defects in the peripheral metabolism of cortisol. *J Clin Endocrinol Metab* 49: 757-64, 1979.