Neonatal Transient Hyper- and Hypoaldosteronism

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Abstract: In spite of so-called hyperaldosteronism based on the laboratory measurement values, most healthy pregnant women, fetuses and newborn infants do not manifest the characteristic clinical signs corresponding to the disease. Such enhanced activity in the renin-angiotensin-aldosterone system has been considered to be a normal physical response in the mother-placenta-fetus or the mother-infant relationship, and its etiology, regulation and control mechanism have been studied by many authors. On the other hand, there have been few descriptions concerning the possibly reversible disorders in regulation or control of the enhanced renin-angiotensin-aldosterone system, and about the influence of the disorders on their clinical manifestations, which occur only throughout the pregnancy or during the so-called perinatal period. In this paper, two cases of newborn infants, under the headings of “neonatal transient hyperaldosteronism” and “neonatal transient hypoaldosteronism”, respectively, are presented and discussed.

Key words: neonate, hyperaldosteronism, hypoaldosteronism, renin-angiotensin-aldosterone system, mother-placenta-fetus or mother-infant relationship.

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Introduction

Recent studies have demonstrated several conditions of newborn infants born to mothers suffering from various endocrine disorders, including infants of diabetic mothers (IDM), infants of thyrotoxic mothers (neonatal thyrotoxicosis), and those of mothers who have received hormonal therapy. However, reports are poorly written on the clinical features in infants from mothers with disorders of the renin-angiotensin-aldosterone system, although there have been not a few reports on the physiological effect in both human and animal neonates as seen in the following paragraph.

Markedly enhanced activity in the renin-angiotensin-aldosterone system during the neonatal period has been well established by many authors (Hayduk *et al.*, 1972; Kotchen *et al.*, 1972; Katz *et al.*, 1974; Koshimizu *et al.*, 1974; Kowarski *et al.*, 1974; Pipkin & Smales, 1975; Dillon *et al.*, 1976; Koshimizu, 1977). Although the regulation or the control mechanisms are not yet clearly understood, it seems that only the renin-angiotensin system, but not the aldosterone level, may be responsive to acute change in blood volume (Dillon *et al.*, 1978) and to dehydration (Rosendahl & Hayduk, 1979). Also low salt feeding, used often in the early neonatal period, may have an effect on the renin

activity, but not on the aldosterone level. Thus, plasma renin activity (PRA) was found to be inversely correlated with sodium intake or with urinary sodium, and positively with urinary osmolality, while no correlation was found between PRA and systolic blood pressure, hematocrit, creatinine clearance, serum sodium, or serum potassium (Godard *et al.*, 1979). On the contrary, plasma or serum aldosterone concentration (PAC) was noticed not to be correlated with sodium intake and urinary excretion (Siegel *et al.*, 1974; Raux-Eurin *et al.*, 1977), despite the increased aldosterone production by a low salt diet in newborn rats (Dlouha *et al.*, 1973). Furthermore, there was no correlation between PAC and gestational age (Siegel *et al.*, 1974). However, it appears that the biologically active renin did not cross the placenta because there was no PRA in the cord blood of the anephric fetus (Symonds & Furler, 1973), and that the low PRA in the fetus rapidly increased during the last few days of gestation in rabbits (Pernollet *et al.*, 1979). Besides such physical circumstances, the specificity of renal function during the neonatal period was also emphasized (Koshimizu, 1977).

Recently, we treated two cases of newborn infants that became completely well, one of them received a regimen of fluid infusion and a low sodium formula feeding for secondary hyperaldosteronism-like disease, and the other a fluid restriction formula for the hypoaldosteronism-like disease as described below.

Case Reports

Case 1.

The male infant was delivered by cesarean section at 38 weeks of gestational age, weighing 2100 gm, in the maternity of a certain hospital. His Apgar score was 8, and, briefly, O₂ was supplied and warmth was administered to cyanosis in his peripheral parts.

According to the letter from the hospital, his mother, a 29-year-old woman, complained of fatigue, anorexia, thirst, nausea and vomiting at 22 days prior to delivery, and then was hospitalized in the department of internal medicine to be examined in detail. Secondary aldosteronism was diagnosed, based on the laboratory findings including persistent hyponatremia and hyperchloremia, and increased PRA and PAC as shown in Table 1. Soon after beginning 50 mg/day spironolactone, an anti-aldosterone preparation, her physical complaints ceased, but abnormal laboratory findings continued, in spite of increasing dosis of 150 mg/day spironolactone. At 38 weeks' gestation, the cesarean section was decided on because of cephalopelvic disproportion (CPD) and lowered creatinine clearance down to 10.9 ml/min.

During the delivery, the serum sodium measured 160 mEq/l, chloride 129 mEq/l, potassium 6.8 mEq/l, and calcium 4.0mEq/l in the cord venous blood as in Fig. 1.

The infant, on the second day of life, revealed irritability, tremor and coldness in the extremities as well as cyanosis, and was sent to our university hospital. As his laboratory data included serum sodium of 163 mEq/l, serum chloride of 121 mEq/l, and serum potassium of 5.3 mEq/l, care in an incubator, O₂ supply, fluid infussion and, later, low

Fig. 1. Serum electrolytes, plasma and/or urinary aldosterone, renin and angiotensin in Case 1, his mother and umbilical cord.

sodium formula feeding were started.

On the third day of life, his clinical signs reduced and suckling improved, whereas icterus appeared, and the total bilirubin in serum increased to 15.5 mg/dl and was subsequently decreased by means of phototherapy lasting for 22 hours.

On the 6th day of life, low salt milk was alternated with a normal formula. Since then, he has been doing well, showing always normal electrolyte values. At 57 days of age, weighing 3930 gm, and 53.8 cm in height, he was discharged from our hospital.

His mother's electrolyte values returned to normal 2 weeks after the delivery, and also her PRA and PAC one week later, as shown in Table 1 and Fig.1. Beside these, there were found many normal results as in BSP, Fishberg and renal scintigraphic tests. Surprisingly, renal signs including 42.7–43.7 ml/min creatinine clearance were measured on admission. Possible dilation of right pelvis and ureter diagnosed by intravenous pyelography on admission and lowered function in the renogram especially in the right kidney should be followed up for some time.

Table 1. Laboratory findings in the mother of Case 1 sent from Dr. Nonaka *et al.* at Moji City Hospital

	Aug. 13	18	30	Sep. 4	5	7	10	12	18	26
Blood pressure	126/100	130/84	120/90	130/90	130/80	126/50	116/86	120/80	110/84	110/60
Serum										
Na (mEq/l)	168	167	156	157	156	156	148	144	139	143
K (mEq/l)	4.0	3.8	3.8	4.4	3.7	4.1	5.0	4.1	4.2	4.2
Cl (mEq/l)	129	132	129	124	122	127	120	113	106	108
Ca (mg/dl)	4.4	4.2				4.1	4.4	4.2	3.9	4.3
BUN (mg/dl)	12.4		24.7	19.8				9.2		
Creatinin (mg/dl)	1.5		2.5	2.2				0.8		0.7
Blood										
Plasma renin activity (ng/ml/hr)	16.2	>32.0						12.0	3.6	1.7
Angiotensin I (pg/ml)								2320	520	
Angiotensin II (pg/ml)								246	31	
Plasma aldosterone (pg/ml)		410	590					113	100	40
PO ₂ (mmHg)		113.4						100.4	86.8	
PCO ₂ (mmHg)		30.9	(Aug. 24)					25.8	32.6	
pH		7.384						7.413	7.426	
Urine										
Volume (ml/day)	3800	1700	500	3000	3500	1400	1000	700		1200
Na (mEq/day)		39.1	22.4	37.8	102.0	102.0	154.5	25.9		
K (mEq/day)		16.7	18.2	24.8	81.6	16.6	45.9	15.1		
Cl (mEq/day)		35.7	21.6	29.4	102.0	88.0	175.5	40.6		
Diet: NaCl	←	↑	Delivery (Sep. 3)	about 15 g/day	→	Sep. 11	←	7 g/day	→	
Medication: Spironolactone	Aug. 13	←	Aug. 24	←	→	Sep. 11	→	Sep. 11		
		↑	50 mg/day		↑	150 mg/day			none	

Case 2.

The male infant was born from his healthy mother after a full-term uncomplicated pregnancy, labour and delivery, in the obstetric ward of our university hospital. His birth weight was 3168 gm, and Apgar score was 9.

13 hours after the delivery, his mother's breast milk was not yet secreting, and more than 5 hours later, breast feeding became possible, although yet weakly.

On the second day of life, the infant weighed 3118 gm, and suckled progressively, increasing his consumption rapidly.

On the third day of life, he gained 178 gm and reached 3296 gm, and edema was noticed in his eye lids, trunk and lower extremities. On entering our pediatric ward, he was begun on a regimen of fluid restriction or correction, based on the hypoaldosteronism-like laboratory findings including serum sodium of 118 mEq/l, serum chloride of 89 mEq/l, serum potassium of 5.2 mEq/l, PAC of 44 pg/ml, and urinary specific gravity of 1.001.

Fig. 2. Serum electrolytes, total protein, BUN, blood sugar, and blood and urinary osmolality in Case 2.

Fig. 2 shows the course of his chief measurement values.

At one week of age, edema disappeared and serum electrolyte values returned to normal.

At 2 weeks of age, his PAC also returned to normal.

17 days after birth, weighing 3200 gm, he left our hospital.

Discussion

In spite of having hyperaldosteronism, most pregnant women do not manifest the characteristic clinical signs such as edema, hypertension and the other complaints mentioned below. Marked stimulation of the renin-angiotensin-aldosterone system becomes maximal in the third trimester, increasing PRA by sevenfold, and PAC and urinary aldosterone excretion by eightfold or even more over nonpregnant levels, respectively (Wilson *et al.*, 1980). Progressive increases in these hormones as well as progesterone, estradiol and estriol in plasma are correlated closely with each other, and regarded as a normal physical response in the mother-placenta-fetus relationship. Also newborn infants do not usually manifest the clinical signs despite hyperaldosteronism.

On the contrary, both Case 1 and his mother revealed the features corresponding to secondary hyperaldosteronism, probably due to a disturbed response in the mother-infant relationship, which occurred throughout the pregnancy reversibly, and only during the course of the so-called perinatal period transiently. Concerning the clinical feature in such newborn infants and their mothers, it should be differentiated from all other kinds of hyper- or hypoaldosteronism presented in recent textbooks. The reasons for this are as follows.

First of all, primary aldosteronism originates most often in a functioning adrenocortical tumor (aldosteronoma), and sometimes in adrenal cancer and hyperplasia, which have been reported frequently in adults, but rarely in children. Acquired (juvenile) or congenital aldosteronism occurs in younger adults and children, following adrenal hyperplasia of unknown origin or a congenital defect in 17α -hydroxylase. Clinical and laboratory findings include low renin levels, hypertension, retinopathy, cardiomegaly, excess production of mineralocorticoids (manifesting polydipsia, polyuria, nocturia, paresthesias, visual disturbance, intermittent paralysis, tetany and fatigue), potassium depletion (manifesting muscle weakness and discomfort, and growth retardation), increasing in serum pH, carbon dioxide, and sodium and in urinary aldosterone, and decreasing in serum potassium, chloride and magnesium. For the diagnosis of such primary or congenital hyperaldosteronism, it is essential to demonstrate relative unresponsiveness to the restriction and administration of sodium. During a low salt diet, the renin-angiotensin system is suppressed in them, whereas PRA appears high or rises in secondary hyperaldosteronism as is seen below.

Secondary aldosteronism occurs in many common disorders such as the nephrotic syndrome, congestive cardiac failure, cirrhosis of the liver, and other edematous or renin-increasing diseases (ex. stenosis of the renal artery, and malignant or essential hyperten-

sion). Besides them, the fact that the secretion of aldosterone may be enhanced by normal homeostatic responses including the response to the decrease in body sodium and circulating plasma volume (due to bleeding, dehydration, etc.), and the increase in potassium accumulation all must be watched. Since the sodium level and the extracellular fluid volume are increased, the paradoxical enhancement of aldosterone excretion may also occur in some homeostatic conditions. Some authors regard the mother-placenta-fetus relationship as a kind of physical condition attributing it to the mother, the placenta or the fetus, and suggest that this relationship might need many homeostatic responses more than is used or able to be given individually. So the mother in the mother-placenta-fetus relationship needs a much larger volume of sodium and fluid than a nonpregnant woman does. The mother also reveals a relative hyponatremia, inducing an enhancement in the renin-angiotensin-aldosterone system. The newborn infant in the mother-infant relationship also shows similar signs.

Additionally, Bartter syndrome (Bartter *et al.*, 1962; Modlinger *et al.*, 1973; Littlewood *et al.*, 1978) and pseudohypoaldosteronism (Cheek & Perry, 1958; Dillon *et al.*, 1980) are included in the specific type of secondary hyperaldosteronism. The former is thought to be caused by inappropriate overproduction of prostaglandins in the kidney, and the latter by hyperactivity of the renin-angiotensin system.

In contrast, the deficient production of aldosterone and/or cortisol may result from a wide variety of congenital or acquired lesions of the hypothalamus, pituitary or adrenal cortex, and may manifest also a wide variety of symptoms depending upon the pathologic

Table 2. A male infant with possible isolated hypoaldosteronism associated with a defect in osmolality regulation due to 18-hydroxy steroid dehydrogenase deficiency

Age (month)	Food	Load test		Urinary		Plasma	Serum renin
		Salt (g/day)	Medication	Volume (ml/day)	Aldosterone (μ g/day)	Aldosterone (ng/dl)	Activity (ng/ml/h)
2	P. M.					8.7	6.12
3	Pre. M.	1.92					3.86
4	Pre. M.	1.92	2 mg DOCA (IM)	235	0.7		
4	Pre. M.	1.92				5.9	0.04
5	5th day in L. S. M.			170	0.6		>8.00
6	P. M.			440	1.6		
6	P. M.		0.5 mg synth. ACTH divided into 4 dosis (PO)	380	1.6		
7	P. M.		200 mEq/m ² potassium	700	3.2		<0.10
7	5th day in L. S. M.			380	5.3		>8.00
7	6th day in L. S. M.					17.2	

P. M. : Powder milk prepared in usual formula.

Pre. M. : Formula for premature infant.

L. S. M. : Low-salt milk.

Fig. 3. Plasma renin activity, serum and urinary osmolality, and urinary sodium excretion in Case 1, his mother and Case 2.

lesions, including various types of corticotropin deficiency, primary adrenal aplasia or hypoplasia, and inborn defects of steroidogenesis. Among them, the isolated defect of aldosterone synthesis, which is due to a defect either in the 18-hydroxylation of corticosterone or in the dehydrogenation of 18-hydroxycorticosterone, occurs very rarely. In Japan, only one case of a male infant with possible isolated hypoaldosteronism has been reported by our colleagues (Koshimizu *et al.*, 1974). It was associated with a defect in osmolality regulation due to 18-hydroxysteroid deficiency as shown in Table 2.

In comparison with these presentations, three types of secondary and reversible hyper- or hypoaldosteronism have been established: a secondary aldosteronism throughout pregnancy in the mother of Case 1, a neonatal transient hyperaldosteronism in Case 1, and a neonatal transient hypoaldosteronism in Case 2, respectively. Furthermore, the following observations also contribute toward the above three types.

Although the enhanced renin-angiotensin-aldosterone system in the mother of Case 1 did not regularly respond during the pregnancy, the elevated PRA decreased gradually after the delivery as shown in Fig. 3. Her urinary excretion of sodium was not parallel

with the PRA during pregnancy, increased rapidly after the delivery, and then decreased. The obstetrician's letter also reported that her blood level of estriol (E_3) remained always ≥ 5 mg/l till the delivery. Both infants of Case 1 and Case 2, despite the high versus low PRA, demonstrated similar courses of urinary sodium and osmolality as in Fig. 3, against the above presented results in literature (Godard *et al*, 1979).

Finally as in Fig. 4, the urinary Na/K ratio, which is an excellent parameter for the response to aldosterone in the distal tubulus in the kidney, indicated similar courses of an increase immediately after the delivery or the birth, and a few days later a decrease in all our three cases, although the degree of increase was dependent upon the PAC in individuals. It is possibly concluded that the enhanced renin-angiotensin-aldosterone system in Case 1 appeared much more intensely during the so-called perinatal period because of the mother's more enhanced renin-angiotensin-aldosterone system, her regimen (low salt diet and spironolactone administration) and her disturbed electrolyte balance (especially hyponatremia).

Fig. 4. Plasma aldosterone concentration, urinary Na/K ratio and feeding or diet in Case 1, his mother and Case 2.

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新生児一過性高および低アルドステロン血症

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要 旨: 正常の妊婦は、レニンーアンギオテンシンーアルドステロン系が亢進して2次性高アルドステロン血症となるにもかかわらず、症状（浮腫、高血圧など）は認めない。新生児では同系は更に一層亢進しているが、これも一種の生理的現象とみなされている。すなわち母体、胎盤、胎児、新生児は、それぞれが個別的に内分泌、代謝機能を営んでいるのではなく、いわば mother-placenta-fetus relationship または mother-infant relationship という特殊な内分泌、代謝的環境を形成し、たとえば循環血液量、ナトリウム量についてみても、その需要量は個別的のときと比べて遥かに増大し、そのため相対的な低 Na 血症をきたして細胞外液量が増加し、これがレニンーアンギオテンシンーアルドステロン系を亢進させる。かような周産期のホメオスターシスの失調した例として、最近経験した新生児一過性高および低アルドステロン血症の新生児各一例ずつを紹介し、かつ討論を加える。

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