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Original article

Severe pseudohypoaldosteronism in a pair of twins not associated with hydramnios

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Abstract. A pair of non-identical twins with severe pseudohypoaldosteronism (PHA) were followed over a period of 4 years. The diagnosis was based on dehydration, hyponatremia, hyperkalemia, high urine sodium/potassium ratios, and high serum concentrations of aldosterone and renin. Sweat and saliva electrolyte concentrations were high, suggesting multifocal target-organ unresponsiveness to mineralocorticoids. No hydramnios was observed during pregnancy. Despite continuous treatment with sodium chloride and sodium bicarbonate (≤20 g/day) and cation exchange resin (Kayexalate, sodium polystyrene sulfonate, ≤4 g/kg per day), the children had repeated episodes of dehydration, hyponatremia, and hyperkalemia. Growth velocity was normal in both twins. Catch-up growth was observed following infancy in the first twin. Normalization of plasma aldosterone, electrolytes, and renin concentrations was achieved at the age of 9 months.

Key words: Pseudohypoaldosteronism – Twins – Hydramnios

Introduction

Pseudohypoaldosteronism (PHA) is a rare familial disease usually occurring in early infancy and characterized by salt wasting, hyponatremia, and hyperkalemia, despite high levels of plasma aldosterone. The patients are insensitive to mineralocorticoids. Electrolyte abnormalities can be corrected only by sodium supplementation [1].

Since the first description of a patient with PHA in 1958 by Cheek and Perry [2], about 70 additional patients have been reported [3]. Clinically, the disease varies in severity, being self limited in most instances and spontaneous remission occurs within the first 2–3 years of life [4–6]. A minority of patients may exhibit a protracted course with recurrent, life-threatening episodes of salt loss [7, 8]. Hydramnios has been reported in premature infants with PHA [9, 10]. We report a pair of twins with severe PHA characterized by multifocal target-organ unresponsiveness to mineralocorticoids and not associated with hydramnios.

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Patients and methods

Methods

Hormone levels were determined by commercial radioimmunoassay kits: aldosterone, 17-hydroxyprogesterone (17-OHP), dehydroepiandrosterone sulfate (DHEA-S), and cortisol. Diagnostic Products (Los Angeles, Calif., USA); plasma renin activity (PRA), New England Nuclear (Boston, Mass., USA); testosterone, Zer Sci Based (Jerusalem, Israel). Sweat samples were collected by pilocarpine iontophoresis and saliva from the sublingual region.

Patients

The patients are a pair of male, non-identical twins born to Jewish parents – first cousins – of Iranian origin. Another male sibling with PHA died at 3 months of severe dehydration. The twins were born at 36 weeks' gestation after an uncomplicated pregnancy and normal delivery; birth weights were 3.3 kg (twin 1) and 2.5 kg (twin 2). Repeated ultrasound and fetal echocardiographic examinations during pregnancy were normal. At 5 days of age, they were hospitalized because of vomiting, anorexia, and severe weight loss. The results of laboratory investigations are shown in Table 1.

Increased sweat and saliva electrolyte concentrations suggested unresponsiveness to mineralocorticoids of the renal tubule, sweat and salivery glands. Congenital adrenal hyperplasia was excluded by normal plasma levels of 17-OHP, cortisol, testosterone, and DHEA-S. Ultrasonography of the adrenals and kidneys was normal in the first twin. Non-obstructive hydronephrosis was found in the second. The parents and two additional male siblings had normal values of PRA, aldosterone, and plasma and sweat electrolytes.

Clinical course. Treatment with high-dose intravenous sodium (≤20 g/day) as physiological saline and 7.5% sodium bicarbonate was initiated in both infants. Following normalization, both were switched to oral sodium chloride and

Table 1. Initial clinical and biochemical data in the twins with pseudohypoaldosteronism

Characteristic Boy	1st Twin	2nd Twin
Weight (kg)	2.8	2.1
Serum sodium/potassium (mmol/l)	116/9.2	118/8.8
Urinary sodium/potassium (mmol/l)	30/1	20/1
Sweat sodium/chloride[a] (mmol/l)	68	>100
Saliva chloride[b] (mmol/l)	80	>100
PRA ng/(l.s)[c]	308	47
Plasma aldosterone[d] (pmol/l)	126,910	69,012

PRA, Plasma renin activity
[a] Normal <40 mmol/l
[b] Normal <30 mmol/l
[c] Normal <2.8 ng/l.s)
[d] Normal <3,000 pmol/l

sodium bicarbonate therapy. Despite a high sodium intake similar to that administered intravenously, and the addition of cation exchange resin (Kayexalate, sodium polystyrene sulfonate, ≤4 g/kg per day), recurrent episodes of severe, life-threatening salt wasting with hyperkalemia, weight loss, and acidosis occurred throughout infancy. The amounts of sodium needed to maintain sodium balance were higher in the first twin than the second.

High doses (≤0.5 mg/day) of mineralocorticoids (9α-fludrocortisone) were administered, with no improvement in weight gain. A controlled trial of reduction of the oral sodium intake was unsuccessful. Plasma renin, electrolytes, and aldosterone levels remained unchanged. Fludrocortisone was discontinued after 8 weeks. Because of feeding difficulties and poor weight gain, feeding gastrostomy was performed in the second twin at the age of 8 months (weight 5.4 kg). During the 2nd year of life, a gradual improvement in appetite and weight gain was noted, but both twins continue to require high doses of sodium (the first twin 18.5 g/day and the second 17 g/day) and cation exchange resin (0.4 g/kg per day) at the age of 4 years. Sodium requirement was assessed by monitoring blood pressure, weight gain, renin and aldosterone concentrations.

From the age of 1 year, both twins had only three episodes of dehydration, hyperkalemia, and acidosis which were related to intercurrent respiratory infections and were more severe in the second twin. Both were treated intravenously with saline and sodium bicarbonate. When "healthy," adequate metabolic control was maintained with oral sodium chloride supplementation alone. Neither child suffered any skin infection.

During the 4 years of follow-up, there was a gradual improvement in height and weight of both children (Figs. 1, 2). Growth velocity was normal during the 1st year of life. However, both twins were below the 3rd percentile. Subsequently, catch-up growth was observed in twin 1, but twin 2 remained below the 3rd percentile (Figs. 1, 2). Psychomotor development is normal. PRA and plasma aldosterone levels decreased gradually reaching normal values at the age of 9 months in both children (Table 2). There was no deterioration of the hydronephrosis in the second twin during the 4-year follow-up period.

Discussion

Aldosterone unresponsiveness in PHA may be restricted to the renal tubule alone [4, 11–15] or may also affect sweat and salivary glands and colonic mucosa [16–19]. The clinical severity may reflect the degree to which mineralocorticoid receptors are affected as well as the number of organs involved. The severity of the disease in our patients is due, at least in part, to the involvement of multiple organs. The persistence of symptoms is also compatible with this form of PHA. Initial renin and aldosterone concentrations were markedly higher in the first twin. This difference most probably reflects the higher sodium loss, indicated by the larger amounts of sodium needed to maintain metabolic control.

The initially high plasma aldosterone levels reverted to normal in our patients at the age of 9 months and remained so during the 4-year follow-up period (Table 2). This is in contrast to previous studies [16, 17] reporting persistently high levels of aldosterone in children with PHA with multiple target-organ unresponsiveness. However, in these studies aldosterone levels were not followed over a long period, as in our patients. The parents of our patients had normal plasma aldosterone levels, as reported by others [16, 17]. PRA normalized in our patients with age (Table 2), which is consistent with a few determinations in older patients [4, 6, 13, 20].

The role of fetal polyuria in hydramnios is controversial. Several case reports have suggested that a primary defect in fetal renal function, such as Bartter syndrome or nephrogenic diabetes insipidus, may be associated with fetal polyuria, resulting in hydramnios. Several cases of premature babies with severe PHA associated with hydramnios have been reported [9, 10]. No hydramnios was found in our patients, despite repeated ultrasound examination during pregnancy. Therefore, the lack of hydramnios does not exclude the diagnosis of PHA.

The pedigree of the family described here, and of other similar cases in the literature, indicates that the form of PHA with multiple target-organ unresponsiveness is inherited as an autosomal recessive disease [16–19, 21]. As serum aldosterone levels are normal in the parents of affected children, aldosterone measurement can not be used to detect asymptomatic family members (heterozygotes) in this form of the disease. Our twins are the first to be reported with PHA with multifocal target-organ unresponsiveness to mineralocorticoids.

Spontaneous recovery has been reported in most cases of PHA with isolated renal salt wasting. This contrasts with the severity of salt loss observed in PHA with multiple organ involvement. Exogenous mineralocorticoid administration failed to improve the sodium balance in our patients. These features are typical of other cases of generalized PHA [17, 19, 21]. Our patients continue to require

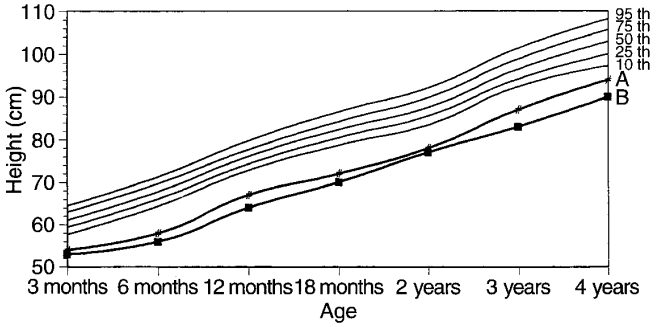

Fig. 1. Supine length of the first (A) and second (B) twin with age

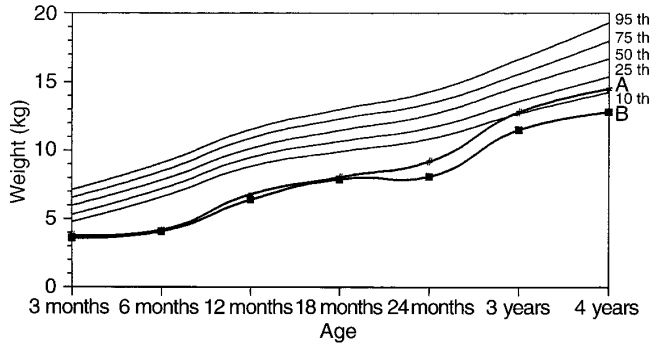

Fig. 2. Weight of the first (A) and second (B) twin with age

Table 2. PRA and plasma aldosterone concentrations in the twins[a, b]

Age (months)	1st Twin		2nd Twin	
	PRA [ng/(l.s)]	Aldosterone (pmol/l)	PRA [ng/(l.s)]	Aldosterone (pmol/l)
0.15	308	126,910	47	69,012
6	17.8	1,700	15.2	1,450
9	0.6	160	0.9	300
18	0.2	210	0.2	130
30	1.1	330	1.3	345
36	1.4	360	1.5	320
48	1.6	390	1.7	380

[a] The PRA in healthy children aged 7 days to 1 year is ≤2.8 ng/(l.s) and in children aged 1–4 years ≤1.8 ng/(l.s)

[b] Plasma aldosterone levels in healthy infants aged 7 days to 3 months are ≤3,000 pmol/l and in those aged 4 months to 1 year ≤900 pmol/l. Beyond the age of 1 year the aldosterone levels are in the same range as adults (55–388 pmol/l)

huge amounts of salt and cation exchange resin. With this therapy, a gradual improvement in height and weight was noted, as well as normalization of PRA, plasma aldosterone, and electrolyte levels.

The pathogenesis of PHA is still unclear. Several etiologies, such as deficient renal Na^+, $-K^+$-ATPase activity [22, 23], reduced number of mineralocorticoid (type I) receptors [20], and a qualitative receptor deficit [24], have been implicated. However, some of these defects may be secondary to the hyperaldosteronism or salt loss. The gene for the aldosterone receptor has been cloned [25]. Molecular biology techniques may provide a means of diagnosing this disease and distinguishing between the two clinical phenotypes.

In summary, our patients represent an extreme clinical and biochemical example of severe PHA. They survived only due to long-term supplementation with salt and cation exchange resin, which was tolerated without noticeable side effects.

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Literature abstracts

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‘Paradoxical’ rise in blood pressure during ultrafiltration in dialysis patients

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In some hypertensive haemodialysis (HD) patients, blood pressure rises further during ultrafiltration (UF). We investigated seven such patients, who were not responsive to hypotensive drugs, including converting enzyme inhibitors. All had marked cardiac dilatation, but most were non-oedematous. They were treated with repeated intense UF while monitoring cardiac function by echocardiography. After a variable time period they all became (near) normotensive without medication. Mean systolic and diastolic blood pressure decreased by 46 ± 18 and 22 ± 9 mmHg respectively while bodyweight decreased by a mean of 6.7 ± 3.0 kg. Plasma volume decreased by 22%, and mean albumin increased from 3.9 ± 0.3 to 4.2 ± 0.3 g/dl. Cardiothoracic index decreased from a 0.56 ± 0.02 to 0.45 ± 0.03. Mitral and tricuspid insufficiency was present in four patients and improved or disappeared in all of them. Diameters of the inferior vena cava, left atrium, and end systolic and diastolic left ventricle markedly decreased in all patients. Ejection fraction increased, but remained subnormal in some patients, while cardiac output increased in five and decreased in two patients. We conclude that paradoxical blood pressure rise with UF usually occurs in the presence overhydration and cardiac dilatation and should be treated by intensified UF. The explanation of this phenomenon remains speculative.

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Renal transplantation and osteoporosis

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A cross sectional study assessed the bone mineral density (BMD) of 20 young adult patients who received a renal transplantation in childhood. The BMD of the lumbar spine, mainly trabecular bone, and of the total body, mainly cortical bone, were measured and expressed as an SD score.

Fourteen patients (70%) had a BMD SD score of the lumbar spine below −1, of whom six patients were below −2. Fifteen patients (75%) had a BMD SD score of the total body below −1, of whom seven patients were below −2. Both trabecular and cortical bone appeared to be involved in the osteopenic process.

The cumulative dose of prednisone was inversely correlated to both lumbar spine and total body BMD SD score. In a multiple regression analysis the cumulative dose of prednisone appeared to be the only factor with a significant effect on BMD SD score.

Most young adult patients who had received a renal transplantation in childhood had moderate to severe osteopenia. Corticosteroid treatment played a major part in the development of osteopenia in these patients.