Pseudohypoaldosteronism : Mineralocorticoid Unresponsiveness Syndrome

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Abstract

We described a 10 day old boy who presented with hyponatremia, hyperkalemia, and metabolic acidosis. Therapeutic treatment with exogenous glucocorticoid and mineralocorticoid for 8 months failed to correct the electrolyte abnormalities. The elevated serum cortisol up to 44.34 μg/dl along with the absence of skin hyperpigmentation excluded defects in the glucocorticoid pathway. Pseudohypoaldosteronism was diagnosed on the basis of hyponatremia, severe urinary salt loss despite the markedly elevated serum aldosterone up to 6,500 pg/ml (normal range 50-800 pg/ml). The patient responded very well to oral salt supplementation and cation exchange resin therapy shown by normal physical growth and normal levels of serum electrolytes.

Key word : Hyponatremia, Mineralocorticoids, Mineralocorticoid Resistance, Mineralocorticoid Unresponsiveness, Pseudohypoaldosteronism

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Pseudohypoaldosteronism is a rare hereditary disorder characterized by target organ unresponsiveness to mineralocorticoids[1-3]. The affected patients usually present in early infancy with hyponatremia, hyperkalemia, metabolic acidosis, and high urinary sodium loss which mimicks patients with salt-wasting congenital adrenal hyperplasia. Therapy with exogenous mineralocorticoid fails to correct electrolyte abnormalities.

We described a case of a neonatal boy who presented with severe salt-wasting and severe hyperkalemia. The diagnosis was made on the basis of a very high serum aldosterone and unresponsiveness to exogenous mineralocorticoid.

CASE REPORT

The patient, a 10 day-old-boy, was the third child born at term to nonconsanguinous parents. His two elder brothers, aged 8 and 10 years, were in good health with their height and weight between 50th and 75th centile. The mother's pregnancy and delivery were uneventful. His birthweight was 3,800 g. He was well during the first week of life. At day 10, he was lethargic and fed poorly. His

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body weight decreased to 3,200 g. He was suspected to have neonatal sepsis. Antibiotics (Cefazolin and gentamicin) were given and intravenous fluid was started with 5 per cent D/NSS/5 at a rate 100 ml/kg/day. Laboratory investigation revealed blood glucose of 68 mg/dl, Na 120 mEq/L, K 14 mEq/L, HCO_3 6 mEq/L, and Cl 89 mEq/L. He was treated with 10 per cent calcium gluconate and 7.5 per cent $NaHCO_3$ intravenously and then referred to Songklanagarind Hospital. During transportation, he had cardiac arrest 4 times and was successfully resuscitated. At the emergency room, he was comatose. Physical examination revealed no skin hyperpigmentation (Fig. 1). Genitalia was normal male with well-formed scrotum, 3.5 cm penile length, and bilaterally descended testes. Blood glucose was 102 mg/dl, Na 118 mEq/L, K 15.6 mEq/L, HCO_3 8 mEq/L, Cl 87 mEq/L, BUN 25.6 mg/dl, creatinine 1.4 mg/dl, and calcium 8.9 mg/dl. Urine sodium was 68 mEq/L. The presumptive diagnosis was salt-wasting congenital adrenal hyperplasia. After serum cortisol was drawn, hydrocortisone was administered intravenously with 50 mg loading dose followed by a continuous drip of 150 mg/m^2/day. Initial fluid resuscitation was normal saline solution which was switched to 3 per cent NaCl for correction of severe hyponatremia. For severe hyperkalemia, he was given 10 per cent calcium gluconate, 7.5 per cent $NaHCO_3$, and Kayexalate. The patient's condition improved after 2 hours of treatment. He gained consciousness and could be extubated 10 hours later. Electrolyte disturbances slowly returned to normal levels within 2 days. Serum cortisol (RIA method) was high up to 44.34 ug/dl (serum 17-hydroxyprogesterone was not available at that time). However, we decided to continue hydrocortisone 5 mg twice daily. 9 α-Fluorocortisol (Florinef®) was started at a dosage of 0.2 mg/day. Despite therapy with hydrocortisone and 9 α-fluorocortisol, he still had frequent episodes of hyponatremia and hyperkalemia which required salt supplementation and Kayexalate therapy. The dosage of 9 α-fluorocortisol was gradually increased to 0.5 mg/day. However, the patient still had hyponatremia and hyperkalemia. At age 8 months, hydrocortisone and 9 α-fluorocortisol was discontinued due to the unresponsiveness to therapy. The electrolyte disturbances were very well controlled by oral NaCl supplementation 4 g/day and Kayexalate 0.6 g/kg/day. Serum aldosterone, performed at age 2.5 years, was markedly elevated at 6,500 pg/ml (normal range 50-800 pg/ml) which confirmed the end-organ resistance to aldosterone. At the time of this report, he was 4 years old and doing well with a body weight of 14.0 kg (50^{th} centile), height of 97 cm (25^{th} centile), and head circumference of 49.5 cm (25^{th} centile). Developmental milestones assessed by Denver Developmental Screening Test were appropriate for age. Laboratory evaluation revealed serum Na 134 mEq/L, K 4.2 mEq/L, HCO_3 24 mEq/L, Cl 102 mEq/L, Ca 10.4 mg/dl, albumin 4.5 g/dl. Urine Na was 45 mEq/L and urine calcium to creatinine ratio was 0.20. Twenty-four hour urine calcium excretion was 2.37 mg/kg/day.

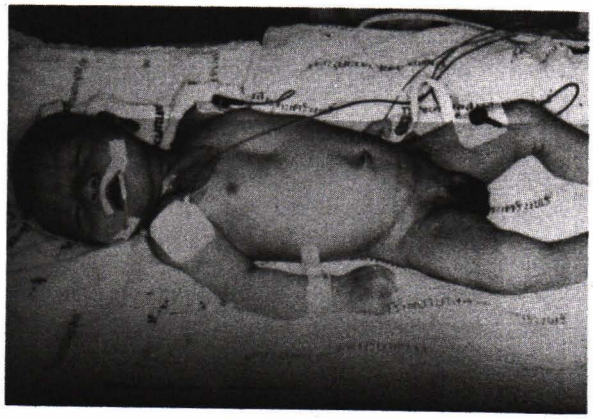

Fig. 1. The patient. Note the absence of skin hyperpigmentation. The scrotum is red due to irritation from the urine bag.

DISCUSSION

This patient presented with severe hyponatremia, hyperkalemia, and metabolic acidosis; the clinical characteristics of adrenal insufficiency. The most common etiology for this condition is congenital adrenal hyperplasia - P450c21 deficiency. Other differential diagnoses are congenital adrenal hyperplasia - 3 ß-hydroxysteroid dehydrogenase deficiency, congenital adrenal hypoplasia, and mineralocorticoid deficiency. The markedly elevated serum cortisol in this patient indicated that the glucocorticoid pathway was normal. Moreover, the absence of skin hyperpigmentation suggested that adrenocorticotrophic hormone was not excessive and hypothalamic-pituitary-adrenal axis was intact. At this point, congenital adrenal hyperplasia

was unlikely, and the differential diagnoses were switched to disorders involving only the mineralocorticoid pathway such as corticosterone methyl oxidase (CMO) -I deficiency, CMO-II deficiency, and pseudohypoaldosteronism. In disorders of CMO-I and CMO-II deficiency, the level of serum aldosterone is below normal and hyponatremia and hyperkalemia can be corrected by a therapeutic dose of exogenous mineralocorticoid. In our patient, hyponatremia and hyperkalemia persisted despite a very high dose therapy of exogenous mineralocorticoid. Furthermore, the serum aldosterone level was extremely high. All this evidence is compatible with end-organ unresponsiveness to mineralocorticoid or pseudohypoaldosteronism.

Pseudohypoaldosteronism was first described by Cheek and Perry in 1958[4]. Since then, over 100 cases have been reported. The clinical presentation is variable, ranging from severely salt wasting cases, who may die in the neonatal period, to those who presented with poor feeding and failure to thrive in infancy[1]. Urinary salt-wasting can present in utero with fetal polyuria resulting in polyhydramnios and premature labor[5,6]. Hyponatremia and hyperkalemia do not improve by exogenous mineralocorticoid but improve by salt supplementation and cation exchange resin therapy. The marked elevation of serum aldosterone up to 3,000-15,000 pg/ml with excessive salt loss in the urine is an important laboratory test for diagnosis of this disorder[2].

Pseudohypoaldosteronism has been distinguished into 3 types : type I, type II, and secondary form[1,2]. Type I pseudohypoaldosteronism is the salt wasting type. Type II or "Gordon syndrome" is the chloride shunt syndrome in which there is a partial unresponsiveness of the renal tubules to mineralocorticoid leading to inadequate potassium excretion, metabolic acidosis and hypertension, but no renal salt loss, and slightly elevated aldosterone. The decreased renal salt wasting in pseudohypoaldosteronism type II is proposed to be the increased reabsorption of chloride by renal tubule (leading to the name of "chloride shunt syndrome")[2]. For pseudohypoaldosteronism type I, there are two clinically distinct entities with different modes of inheritance : the isolated renal resistance which is inherited mostly by autosomal dominant trait, and the multiple target organs resistance (renal tubule, sweat gland, colon) which is inherited by autosomal recessive trait. However, sporadic cases have been described in both entities. Secondary pseudohypoaldosteronism is a transient renal tubular resistance secondary to other renal diseases such as obstructive uropathy[7], renal vein thrombosis[8], hydronephrosis[9], and urinary tract infection[10]. In our patient, the salt-wasting presented at early neonatal life and investigation revealed no renal disorder. Hence, secondary pseudohypoaldosteronism was excluded. The high urinary sodium loss suggested the renal tubule resistance to aldosterone or pseudohypoaldosteronism type I. The absence of other family members affected with the same disorder suggested that our patient was a sporadic case although the possibility of a dominant trait with new mutation or a recessive trait can not be excluded.

One of the characteristics of pseudohypoaldosteronism type I is that the urinary salt loss improves with advancing age[2]. Therapy with salt supplementation and cation exchange resin can be discontinued at age 4-6 years. However, during the time of high urinary salt loss, urinary calcium excretion should be monitored. As already known, tubular calcium reabsorption in patients with high urinary salt loss is decreased resulting in hypercalciuria. Recently, Shalev et al reported that 4 out of 5 patients with pseudohypoaldosteronism developed hypercalciuria and 3 of them had nephrolithiasis[11]. In our patient, urinary calcium excretion was 2.37 mg/kg/day which was not in the range to diagnose hypercalciuria (4 mg/kg/day).

The pathogenesis of tubular resistance to aldosterone remains unclear. Armanini et al demonstrated a decrease of aldosterone receptor in peripheral mononuclear leukocytes in affected patients [12]. However, subsequent studies found no abnormalities of gene encoding for mineralocorticoid receptor (chromosome 4q31.1 - q31.2), and no deletion or mutation of gene that could be the cause of aldosterone resistance[14-16]. Recently, Arai et al demonstrated point mutation $C^{944} \rightarrow T^{944}$, $Ala^{241} \rightarrow Val^{241}$ in 4 out of 5 patients with pseudohypoaldosteronism, but it was also found in 62 out of 100 normal subjects[16,17]. One of these 4 patients had an additional conservative heterozygous mutation $A^{760} \rightarrow G^{760}$, $Ileu^{180} \rightarrow Val^{180}$ which was also present in 11 out of 100 normal subjects. They concluded that the mutations in those 4 patients were polymorphisms which had no apparent pathological significance and was not the etiology of this disorder. They hypothesized that

the pathogenesis of this disorder might be the defect at the pre-receptor or post-receptor sites. At the pre-receptor, it could be interference by aldosterone binding competition for a binding site or the deficiency of a transport protein that is specific for carrying aldosterone to receptor molecules. For the post-receptor site, it could be a defect in signal transduction after aldosterone binding to the receptor or in the step of aldosterone action on water and ion transport at the distal renal tubules and collecting ducts. At present, the molecular basis of pseudohypoaldosteronism remains to be elucidated.

In summary, we described an infant boy with pseudohypoaldosteronism type I who had clinical symptoms of hyponatremia, hyperkalemia, and metabolic acidosis. The diagnosis was made on the basis of severe salt wasting despite markedly elevated serum aldosterone. As pseudohypoaldosteronism is a rare condition and difficult to differential diagnose from salt-losing congenital adrenal hyperplasia, it is recommended that both exogenous glucocorticoid and mineralocorticoid should be given until the definite diagnosis of pseudohypoaldosteronism is made.

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Pseudohypoaldosteronism : ภาวะที่ไตไม่ตอบสนองต่อ mineralocorticoid

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รายงานผู้ป่วยเด็กชายอายุ 10 วัน ที่มีภาวะโซเดียมในเลือดต่ำ โปแตสเซียมในเลือดสูง ร่วมกับภาวะ metabolic acidosis ผู้ป่วยได้รับการรักษาโดยการให้ยา hydrocortisone และ 9 α–fluorocortisol เป็นเวลา 8 เดือน โดยยังคงมีความผิดปกติของอิเล็กโตรลัยท์อยู่ตลอด ระดับ cortisol ในเลือดของผู้ป่วยที่สูงมากถึง 44.34 ไมโครกรัม/ดล. ร่วมกับการไม่มีสีผิวดำคล้ำมากกว่าปกติ เป็นสิ่งที่บ่งบอกว่าการสร้าง glucocorticoid จากต่อมหมวกไตเป็นปกติ การมีภาวะโซเดียมในเลือดต่ำ และมีการสูญเสียโซเดียมทางปัสสาวะเป็นปริมาณมาก ในขณะที่ระดับ aldosterone ในเลือดสูงมากถึง 6,500 พิโคกรัม/มล. (ค่าปกติ 50–800 พิโคกรัม/มล.) เป็นสิ่งที่บ่งบอกว่าไตไม่ตอบสนองต่อ aldosterone และนำไปสู่การวินิจฉัยภาวะ pseudohypoaldosteronism ผู้ป่วยรายนี้ตอบสนองดีต่อการรักษาด้วยการให้เกลือทดแทนทางปากร่วมกับการรักษาโดย cation exchange resin (Kayexalate) หลังการรักษาผู้ป่วยมีการเจริญเติบโตทางร่างกายปกติระดับอิเล็กโตรลัยท์อยู่ในเกณฑ์ปกติ

คำสำคัญ : ภาวะโซเดียมในเลือดต่ำ, ไตไม่ตอบสนองต่อ mineralocorticoid

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