Case report

A Case of pseudohypoaldosteronism type 1 with positive familial history

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BACKGROUND: Pseudohypoaldosteronism type 1 (PHA1) is a rare congenital disease of mineralocorticoid resistance which is characterized by neonatal renal salt wasting, vomiting, dehydration and failure to thrive. The clinical presentation of the disease represented mostly during neonatal period with a wide spectrum of symptoms regarding to autosomal recessive (systemic) or dominant (renal) inheritance mode. Biochemically, it is represented by high levels of plasma renin and aldosterone, hyponatremia and hyperkalemia. In this report, we present a case with clinical and biochemical findings of PHA1 and a positive familial history of the disease in her sister. **CASE REPORT:** A 3 months old girl infant was admitted to paediatrics emergency because of poor weight gain. At the time of admission, she was alert but dehydrated without history of vomiting or diarrhea for 1 week which had been deteriorated in last two days. **RESULTS:** Hyponatremia, hyperkalemia, metabolic acidosis and persistent electrolytes abnormalities were detected with dehydration in spite of adequate treatment, absence of hyperpigmentation, normal 17-OH-P values, high levels of plasma renin and aldosterone. No evidence of adrenal hyperplasia or renal anomalies was seen on ultrasonography. Acceptable response was achieved with high doses of fludrocortisone (0.5 mg/day) and oral NaCl. These findings in addition to positive familial history led to the diagnosis of pseudohypoaldosteronism type 1. **CONSLUSIONS:** In any infant who presents with hyponatremia, hyperkalemia and metabolic acidosis and non-specific symptoms such as growth retardation, some rare diagnosis such as PHA1 should be considered.

KEYWORDS: Pseudohypoaldosteronism Type 1, Hyponatremia, Hyperkalemia, Failure to Thrive, Familial

BACKGROUND

Pseudohypoaldosteronism type 1 (PHA1) is a rare congenital disease of mineralocorticoid resistance with estimated prevalence of < 1/1000000 which is characterized by neonatal renal salt wasting, vomiting, dehydration and failure to thrive.[1-3] It was first described by Cheek and Perry in 1958.[4]

PHA1 is caused by defective transepithelial sodium transport due to mutations in genes encoding the amiloride-sensitive epithelial sodium channel (ENaC) as autosomal recessive form or mineralocorticoid receptor (MR) as autosomal dominant form.[5] The clinical presentation of the disease represented mostly during neonatal period with a wide spectrum of symptoms regarding to its inheritance mode.[5]

The biochemical characteristics of the disease include high levels of plasma renin and aldosterone, hyponatremia and hyperkalemia resulting from systemic or renal resistance to aldosterone.[5]

Patients with autosomal dominant or renal form of the disease is characterized by renal salt loss, hyperkalemia, metabolic acidosis, failure to thrive, elevated PRA, and elevated aldosterone levels in infancy.. These patients can be treated with oral salt supplementation.[6] Patients with the autosomal dominant form of PHA1 typically show a gradual clinical improvement with regard to renal salt loss during childhood. Some individuals are clinically asymptomatic but may have elevated PRA and aldosterone levels.[6]

Those with autosomal recessive or systemic form of PHA1 are considered as the severe variant of the disease with multiple aldosterone target organ involvement such as colon, sweat glands and kidney. They may also represent with pulmonary symptoms such as cough, tachypnea, fever and wheezing but not neonatal respiratory distress syndromes. The symptoms of the disease in these patients are life long and recurrent and they need higher doses of salt supplementation and potassium-lowering agents in some cases.[7] In this report, we present a case of 3 months old girl with clinical and biochemical findings of PHA1 and a positive familial history of the disease in her sister.

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CASE REPORT

A 3 months old girl infant was admitted to paediatrics emergency unit of Al-Zahra hospital, affiliated to Isfahan University of Medical Sciences, because of poor weight gain in 2011.

She was a full term infant with a birth weight of 3400 gr (50th percentile), length of 53 cm (25th percentile) and head circumference of 35 cm (50th percentile). The patient had no perinatal problem. She was the 2nd child of consanguineous parents. In familial history, she had a 5.5 years old sister with PHA1 diagnosed at 3 months of age, with initial symptoms of dehydration and lethargy that was receiving fludrocortisones (2.5 tablets/day) and oral sodium chloride 5% (10 cc/day) as her treatment. She had no history of drug consumption except vitamins.

At the time of admission, she was alert but dehydrated without history of vomiting or diarrhea for 1 week which deteriorated in the last two days. On physical examination, her body weight, length and head circumference were 4 kg, 56.5 cm and 36.5 cm, respectively, all of them were beneath the 5th percentile.

She had depressed fontanels and sunken eyes. Her blood pressure was 60/40 mmHg, respiratory rate was 607/min (30-50), pulse rate was 160/min (up to 150), and body temperature was 37.2° C (36.5-37.2). She had no signs of skin pigmentation or virilization of external genitalia.

The initial biochemical examinations were as follows: serum sodium, 117 mEq/l (135-145); serum potassium, 7.4 mEq/l (3.5-5); blood sugar, 95 mg/dl (80-100); blood urea nitrogen, 19 mg/dl (10-20); serum creatinine, 0.5 mg/dL (0.3-0.7); C-reactive protein, negative; blood culture, negative. The results of venous blood gas were as follows: PH = 7.29 (7.35-7.45), Hco3 = 14.5 mmol/L (18-22), PCO2 = 35 mmHg (25-40), which represented metabolic acidosis.

Considering the hyponatremia, spot urine sodium and creatinine was examined. Urine sodium and FENa were elevated. Plasma renin and aldosterone levels were 615 IU/ml (upper limit = 40 IU/ML) and 468 pg/ml (upper limit = 180 pg/ml), respectively. The levels of 17-hydroxyprogestenone and DHEAS were normal. Renal ultrasonography was normal.

We hydrated her with normal saline but after 2 days, rise in serum sodium was not appropriate. The lack of clinical response and persistent biochemical abnormalities in addition to high levels of renin and aldosterone and history of her sister who had PHA1 prompted us to revise the diagnosis to PHA1. Therefore, we initiated fludrocortisone and oral sodium chloride.

Fludrocortisones doses increased up to 0.5 mg/day (5 tablets/day) gradually after that serum Na reached to normal levels in 4 days (serum Na = 137 mEq/l; serum K = 4.5 mEq/l). Finally we discharged her after three weeks of treatment with fludrocortisone (5 tablets/day), Shohl's solution (3 cc/6 hours) and oral sodium chloride 20% (32 cc/day). Her body weight was 4.8 kg at that time. We checked plasma renin and aldosterone level one more time; both of them were elevated again.

Now she is one year old and her body weight, length and head circumference are 8.5 kg (on the 10th percentile), 76 cm (on the 10th percentile) and 44 cm (on the 25th percentile). Her condition is satisfactory. She is now treated with fludrocortisone (4.5 tablets/day), Shohl's solution (5 cc/6 hours) and oral sodium chloride 20% (27 cc/day).

DISCUSSION

Absence of aldosterone, the main mineralocorticoid in humans, or an inappropriate response to it because of the mineralocorticoid receptor (MR) impairment results in renal salt loss, which is the main component of PHA1.[8] PHA1 which characterized by peripheral resistance to aldosterone may represent by autosomal recessive or dominant forms with wide spectrum of symptoms, mainly growth retardation and dehydration. After first description of the disease in 1958, about 100 cases of different type of the disease have been reported worldwide and the genetic origin of the disease is investigated too.[9,10] There was not any published case report of PHA1 from Iran in literature review.

In our reported patient, persistent electrolytes abnormalities with dehydration in spite of adequate treatment, absence of hyperpigmentation, normal 17-OH-P values, high levels of plasma renin and aldosterone, no evidence of adrenal hyperplasia or renal anomalies on ultrasonography and acceptable response to treatment with high doses of fludrocortisone (0.5 mg/day) and oral NaCl and positive familial history were clues to the diagnosis of PHA1.

According to previous studies, failure to thrive and

growth retardation are considered as one of the most common symptoms of PHA1 in infants and it is more prevalent in cases with autosomal dominant form of PHA1 (AD–PHA1) as was reported in our case too. Belot et al. have investigated a series of 10 patients with PHA1 from four paediatric departments in France. Four of them which were diagnosed as AD–PHA1 had referred at 15, 19, 22 and 30 days of life and failure to thrive was the most common initial symptom among them. They had appropriate outcome after salt supplementation. The parents of mentioned patients were all clinically normal without any symptoms likewise our reported case.[11] In a similar case report from Italy, a 2 month-old infant referred for failure to thrive and laboratory findings of hyponatremia, hyperkalemia and hypochloremia. At first step of treatment, assuming that origin of salt wasting syndrome could be aldosterone, rehydration and hydrocortisone were administrated but it failed, so oral NaCl supplementation was administrated which resulted in electrolyte balance in patient and supported the diagnosis of PHA1.[12]

Several studies have reported both familial and sporadic cases of the disease. Many studies have reported familial cases of PHA1. Nystrom and colleagues have reported 15 members of a Swedish five-generation family with the autosomal dominant form of PHA1 due to mutations of the MR gene.[13] In another study in Bahrain, a family with 3 children of PHA1 was reported, they presented by both severe and mild form of the disease and different symptoms.[14] Similarly, familial cases of PHA1 were reported in Germany and Turkey too.[15,16] In this report, we had two sister suffering PHA1 with the same initial complaint and clinically normal parents.

In milder form of PHA1, the parents may be asymptomatic or have only elevated plasma rennin and aldosterone levels on biochemical exams. Though elevated levels of aldosterone is considered the only laboratory marker of AD-PHA1 in adulthood type of the disease but there were evidences from many families indicated that adult carriers of MR or other causative mutations of the AD-PHA1 may have normal biochemical results even normal aldosterone.[16-18]

In this study the parents of the patient were not evaluated biochemically or genetically. In a case of PHA1 in a Japanese family, a novel mutation was reported in the father and older sister of the patients, both of them were clinically normal and it was assumed that the inheritance of the disease in the patient was AD.[19]

However, it seems that the AD-PHA1 cases are genetically heterogeneous and in families with the same genetic defect the symptoms may be different and phenotypic differences in families with more cases of PHA1 with the same mutation have been reported previously. Although we did not perform genetic study in two affected sister in this case report to determine the gene mutation, but the first presentation of disease in two sisters was similar. One of the factors that could predict the form of PHA1 is the course of the disease and patient's response to treatment during follow-up.

In renal form, the symptoms and electrolytes characteristics of the disease improves with age due to the maturation of the renal salt conservation abilities and amelioration of salt loss but in systematic form, the patients are represented by life-long and recurrent symptoms of the disease in addition to other organ involvement such as pulmonary manifestation and they need high doses of treatment.[11] During follow-up, the catch-up growths of the patient and clinical and biochemical condition was improved and the dose of drugs decreased during treatment. The dose of the drug in her sister was also reduced and it was tapered to discontinue.

The limitation of the study was that we had not the opportunity to perform genetic study in patient and her family. However, it would help us to determine the type of the PHA1 which consequently will help us to manage the disease favourably.

Nonetheless, the chief complaint of growth retardation and biochemical evidences of the disease, the symptoms of the disease which was renal and local, the mild presentation of them, the positive familial history of mild disease in her sister and clinically normal parents, all support the diagnosis of autosomal dominant form of the disease, though it would be confirmed by genetic study. It seems that there are some barriers which do not permit us to determine the genotype-phenotype correlation beyond the recessive or dominant forms of PHA1 such as the prevalence of the disease which is rare, less available research in this field and clinical descriptions. It seems that further studies by focusing on the clinical work-up of the disease are needed.[20]

In summary, several studies have indicated that even autosomal dominant form of the disease could be potentially fatal in infants and may be associated with high rate of mortality and proper management is essential for at risk neonates as reported by Geller et al.[18]

Therefore, in any infant who presents with hyponatremia, hyperkalemia and metabolic acidosis and non-specific symptoms such as growth retardation, some rare cases such as PHA1 should be considered.

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