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Pseudohypoaldosteronism type I in patient admitted with neonatal abstinence syndrome: A case report and review of literature

Arsalan Hashemiaghdam[1], Sayed Yousef Mojtahedi[2], Amirsina Sharifi[1], Reza Tavakolizadeh[2]

From [1]Department of Pediatrics, Faculty of Medicine, [2]Department of Pediatrics, Ziyaeian Hospital, School of Medicine, International Campus, Tehran University of Medical Sciences, Tehran, Iran

Correspondence to: Reza Tavakolizadeh, Department of Pediatrics, Ziyaeian Hospital, Abuzar Street, Qazvin Street, Tehran, PO: 1366736511, Tehran, Iran. Phone: 00989122256277. E-mail: Rezatavakolizadeh@yahoo.com

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ABSTRACT

Pseudohypoaldosteronism (PHA) type 1 is a rare genetic disorder affecting one in 47,000-80,000 newborns. An autosomal dominant type which is restricted to the kidney (also known as rPHA1) and an autosomal recessive type which is more severe and presents with systemic symptoms were reported. A 3-h-old male infant was admitted to the neonatology ward due to high pitch cries, jitteriness, mild tremors, and excessive sleep with a positive history of maternal addiction. For the 1st time, after 9 days, the infant developed hyperkalemia (7 mEq/L) with mixed respiratory alkalosis, and metabolic acidosis (PH: 7.42, Pco2: 22 mm-Hg, Hco3: 12 mmol/L) and blood pressures of 84/44 mm-Hg were recorded. Even after initial treatment, once again the patient developed hyperkalemia resistant to therapy. Hyponatremia was also noted. Hormonal assays were collected, and congenital adrenal hyperplasia (a common differential diagnosis in neonatal hyperkalemia) was ruled out. Elevated renin and aldosterone levels were reported. On the 20th day, hyperkalemia-induced cardiac arrhythmia was demonstrated in the 2nd lead (K^+ - 7.5 mEq/L). We report that this case as PHA type 1 is the rare but life-threatening cause of neonatal hyperkalemia. Initial therapy can prevent the possible occurrence of sudden death.

Key words: *Hyperkalemia, Hypernatremia, Neonate, Pseudohypoaldosteronism type 1*

Pseudohypoaldosteronism (PHA) type I is a rare genetic disorder affecting one in 47,000-80,000 newborns [1,2]. Cheek and Perry [3] have addressed PHA type 1 for the 1st time in 1958. In 1980, Dillon et al. [4] reported more cases, and later in 1991, Hanukoglu explained 2 different types of inheritance pattern after a clinical investigation in nine patients [5]: An autosomal dominant type which is restricted to the kidney (also known as rPHA1) and an autosomal recessive type mostly presenting with more severe systemic symptoms (also called sPHA1) [6]. The rPHA1 is caused by mutations in the NR3C2 gene on chromosome 4q31.1, which is responsible for encoding mineralocorticoid receptors (MR) [7,8]. Furthermore, genetic assessments in patients with an autosomal recessive type of disease have shown that SCNN1A, SCNN1B, and SCNN1G mutations occur in amiloride-sensitive epithelial sodium channels (ENaC) [1,9-11]. The ENaC channels are also present in all aldosterone-responsive target organs such as the kidneys, colon, lungs, and sweat glands. This permanent resistance to aldosterone in these organs can lead to severe sodium wasting, hypovolemia, hyperkalemia, metabolic acidosis, and failure to thrive [12,13]. Affected patients also suffer from recurrent pulmonary infections in a pattern that is not distinguishable from cystic fibrosis [14].

Neonatal-onset disease is more common in autosomal dominant type; it might present with a variety of symptoms and may lead to fatal cardiac arrhythmias due to hypoaldosteronism [15]. High renin and aldosterone levels are reported in serum hormonal assays of these patients. Sodium wasting distinguishes this condition from PHA type 2 (also called familial hyperkalemic hypertension or Gordon's syndrome) [16,17]. Urinary tract anomalies mostly cause secondary types in neonates [18,19]. Life-threatening consequences of this uncommon disease which can demonstrate itself with a broad spectrum of initial signs and symptoms made this unique case valuable to report to decrease the possibility of the under treatment or delayed treatment in a similar patient.

CASE REPORT

A 3-h-old male infant was admitted to the neonatology ward for high pitch cries, jitteriness, and mild tremors when disturbed and excessive sleep after formula-feeding. He was the product of the 2nd pregnancy of a non-consanguineous marriage. It was a full-term pregnancy, and the baby was delivered through cesarean section due to the previous history of the procedure. The 1st cesarean section was performed because of the couple's wish, without any medical indication. His birth weight was 3200 g with Apgar score of 9 and 10 at the 1st and 5th min, respectively.

Birth history indicated normal vital signs. No anatomical defects were mentioned. Genital organs included healthy

non-circumcised penis and descended testes. Mild bilateral hyperpigmentation of the nipples was noted. Maternal habitual history was positive for heroin addiction and methadone use as a rehabilitative medication. She continued heroin injections until delivery, and she passed away 36 h after giving birth due to a heroin overdose.

The infant was instantly hospitalized in the neonatology department. The modified Finnegan Neonatal Abstinence score of 6 was calculated [20]. Toxicology results were positive for morphine. Methamphetamine assessments on the 1st day and morphine on the 6th day were negative. The oncall pediatrician ordered loading and maintenance doses of intravenous phenobarbital with adequate hydration and continuous abstinence syndrome scoring. During admission, the patient had no seizure or epileptic signs, and his recorded abstinence scores never surpassed 3. There were no abnormal neurologic findings. Phenobarbital was changed to oral form.

Viral markers (antibodies and antigens) for Hepatitis B, Hepatitis C, and HIV were all negative. The patient had several episodes of post-feeding vomiting. Abdominopelvic ultrasonography revealed gastroesophageal reflux and did not yield any specific diagnosis. No whirlpool sign in midgut was reported. On the 3rd day of admission, a course of single surface phototherapy was started due to transient indirect hyperbilirubinemia with a total bilirubin of 6.2 mg/dl [0.1-1.2] and direct bilirubin of 0.28 mg/dl [0.0-0.4]. Normal ranges of laboratory data are shown inside the brackets after each respectively Table 1. On the 5th day, the infant had a hypoglycemic attack which was managed with the administration of dextrose saline serum.

On the day 9, laboratory data revealed hyperkalemia (K^+ = 7 mEq/L [normal 3.5-5.5]) with mixed respiratory alkalosis and metabolic acidosis (PH: 7.42, Pco2: 22 mmHg, Hco3: 12 mmol/L) and blood pressure of 84/44 mmHg were recorded. The infant had adequate urinary output with normal urinalysis. No changes in electrocardiography (ECG) occurred. Treatment of hyperkalemia immediately initiated by the following orders though it showed a slight resistance to the first-line steps. The entire potassium intake of the neonate was immediately cutoff. Calcium gluconate 10% (1 cc/kg) and bicarbonate were administered. After a slight response to treatment, once again on the day 10, potassium level was elevated (K^+ = 6.9 mEq/L) with an accompanying simultaneous hyponatremia (Na = 133 mEq/L [135-145]). Hormonal assays were collected (17-OH Progesterone: 19. 7 ng/ml [0.2-0.8 ng/ml], Cortisol 8 AM: 477.27 nmol/L [140-700 nmol/L]) and congenital adrenal hyperplasia, a common differential diagnosis in neonatal hyperkalemia, was ruled out Table 2 and 3. Elevated direct renin of 445 μIU/ml [2.8-39.9]) and aldosterone of 420 pg/ml [10-180] were noted. In addition to calcium gluconate, hydrochlorothiazide and furosemide were added to the medication list to overcome hyperkalemia.

Antibiotics were started after development of pneumonia and para-hilar haziness of the right lung on chest radiography. Potassium levels did not respond well to treatment and continuously fluctuated. In light of the laboratory (transtubular transient potassium gradient [TTKG >7, mild hyponatremia) and clinical findings (refractory hyperkalemia), PHA with a salt wasting pattern was the most probable diagnosis for this patient. No parental history of electrolyte disturbances was found. Hydrocortisone and fludrocortisone were added to his treatment regimen. The kidneys, bladder, and adjacent of urinary structures appeared normal finding on ultrasonography.

Table 1: Na (sodium) [135-145], K (potassium) [3.5-5.5], BS (Glucose) [<130], and Ca (Calcium)-[8.5-12.5] levels in blood samples of the patient

Days after birth	Na (mEq/L)	K (mEg/L)	BS (mg/dl)	Ca (mg/dl)
1	138	4	88	9.4
3	138	3.8	75	8.6
9	136	7	45	8.9
10	139	4.8	72	9.7
11	133	6.9	62	9.5
12	135	4.3	95	-
13	132	5.2	92	10.2
14	132	6.9	140	-
15	130	6	77	-
16	132	5.7	107	-
17	131	5	92	-
18	131	5.9	102	-
19	-	4.3	62	-
19.5	132	6.1	120	-
20	133	7.3	-	-
21	132	5.8	-	-
21.5	136-137	3.9-4.2	-	-
22	-	6.1	-	-
22.5	139	4.2	-	-
23	135	3.3	-	-

On the 20th day, hyperkalemia (K^+ = 7.5 m Eq/L)-induced cardiac arrhythmia was demonstrated in the 2nd lead ECG. Eventually, oral kayexalate 1 mg/kg in 2 doses was started which decreased the potassium and increased sodium levels successfully. Unfortunately, while the medical team was in the middle of the diagnostic and therapeutic process, the infant was discharged at his father's will, and therefore, genetic assessments could not be carried out. High sodium and low potassium diet were advised for the infant and family refused any other medical treatment.

DISCUSSION

In the past 50 years and since the 1st description of PHA type I, different inheritance patterns were discovered (autosomal dominant or autosomal recessive) [1,2,5]. Aldosterone is the principal mineralocorticoid for maintaining the hydration, essential fluid volume, and physiologic electrolyte balance. Hypovolemia or hyperkalemia provoke its secretion which leads mainly to reabsorption of sodium. Malfunctioning of ENaC or intracytoplasmic MR results in failure of aldosterone's effect on the renal cortex [7]. In contrast to the autosomal recessive type,

Table 2: Complete blood count of the patient during hospitalization

Days after birth	1	5	9	21	Reference ranges
White blood cells (1000 C/ml)	15.6	8.5	14.1	16.6	Birth: 9.0-30.0 1-7 days: 9.4-34.0 8-14 days: 5.0-21.0 15 days-1 month: 5.0-20.0
Neutrophils (%)	70.4	55.1	56	90.6	
Lymphocytes (%)	23.4	35.2	38	9.4	
Mixed cells (%)	6.2	-	15.1	-	
Band cells (%)	-	-	3	-	
Red blood cells (Mil C/ml)	5.05	4.24	4.06	2.67	Birth: 3.90-5.50×10 (12) 1-7 days: 3.90-6.00×10 (12) 8-14 days: 3.60-6.00 15 days-1 month: 3.00-5.50
Hematocrit (%)	55.20	45.2	42.1	26.8	Birth-7 days: 42.0-60.0 (%) 8-14 days: 39.0-60.0 (%) 15 days-1 month: 31.0-55.0 (%)
Hemoglobin (gr/dl)	19,7	15.5	15	9.1	birth-7 days: 13.5-22.0 8-14 days: 12.5-21.0 15 days-1 month: 10.0-20.0
Red blood cell distribution width (%)	23	21.6	19.8	17.5	<2 years: not established
Mean corpuscle volume (fl)	109.3	106	103	100.4	Birth: 98.0-120.0 1-7 days: 88.0-120.0 8-14 days: 86.0-120.0 15 days-1 month: 85.0-110.0
Platelets count (1000 C/ml)	323	348	622	398	150-350

Table 3: Additional laboratory data of patient during investigations

Days after birth	1	3	5	9	12	14	21	Reference range
ESR 1 h (mm/h)	-	-	-	3	-	-	10	Newborn: 0-2 neonatal: 3-13
Urea (mg/dl)	19	-	15	12	16	20	29	11-45
Creatinine (mg/dl)	1.1	-	0.6	0.62	0.67	0.61	0.5	0.4-1.4
T4/EIA (micg/dl)	-	-	-	8.9	-	-	-	4.7-12.6
TSH (micIU/mL)	-	-	-	1.1	-	-	-	0.3-6.5
Free T4 (ng/dl)	-	-	-	0.8	-	-	-	0.8-2.3
Total bilirubin (mg/dl)	-	6.2	-	-	-	-	-	0.1-1.2
Direct bilirubin (mg/dl)	-	0.28	-	-	-	-	-	0.0-0.4
CRP (Qual)	-	-	Negative	Negative	-	-	3+Positive	Negative

ESR: Erythrocyte sedimentation rate, T4: Thyroxine, EIA: Enzyme immunoassay, TSH: Thyroid-stimulating hormone, CRP: C-reactive protein

the autosomal dominant type results in less salt wasting and less systemic symptoms with more possibility of self-cure if the patient survives the critical first 6 months of life. This condition is mainly due to the development of proximal reabsorption of sodium in renal tubules [7]. Therefore, it is decisive to genetically prove the diagnosis of the autosomal recessive type to start the appropriate treatment and to inform the family about the prognosis.

In this case, TTKG levels were diagnostic for a malfunction in the mineralocorticoid system and the high aldosterone level in proof of resistance on the renal level. Initially, it was considered that secondary PHA which is more prevalent could describe the occurrence of symptoms. However, normal results of renal and pelvic sonography plus a lack of persistent hypoglycemia and hypertension along with no evidence of urinary tract infection ruled out this hypothesis.

As there were no clinical findings by high blood pressure, hyperchloremic metabolic acidosis, and volume expansion, PHA type II was excluded from the study. Obviously, there is no benefit to administering mineralocorticoids for patients with type 1 of the disease. Several medication regimens were used to control hyperkalemia in our patient and eventually hyperkalemia was maintained after adding oral kayexalate 1 g/kg in 2 doses per day. Patients with refractory hyperkalemia are always at great risk for arrhythmia and sudden death. However, our patient did not show any changes in ECG until day 20 when his ECG developed signs of hyperkalemia.

Properly adjusted doses of sodium chloride supplements, potassium-lowering treatments such as calcium gluconate, sodium bicarbonate, and potassium resin exchange, are the most relevant procedures to control the initial symptoms of PHA type I.

Close follow-up intervals with electrolyte monitoring should be considered in babies [21]. Previously, very few cases of PHA type I had been reported in Iran. No scientific manuscript confirmed the diagnosis by genetic assay and subtype classification was not performed in other studies [22].

CONCLUSION

PHA type 1 is one of the rare but life-threatening causes of neonatal hyperkalemia. Initial therapy can prevent the possible occurrence of sudden death. After ruling out more common etiologies, aforementioned clinical features (sodium wasting, hyperkalemia, and hypovolemia) along with elevated levels of aldosterone and plasma renin activity are sufficient for diagnosis and prompt treatment.

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