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Case Report

Pseudohypeoaldosteronism (Type 1) in a Neonate Presenting as Life-threatening Condition can Mimic CHA

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Abstract
Pseudohypeoaldosteronism (PHA) is a rare disease developing as a result of peripheral resistance to aldosterone and is characterized by salt loss. We present a 17-day old newborn who was admitted to NICU with poor enteral feeding and vomiting, with hyponatremia, hyperkalemia and elevated plasma aldosterone levels. Type 1 PHA was diagnosed due to resistance to the fluid replacement and steroid treatment. Genetic analysis showed homozygous SCNN1A mutation.

Introduction
Pseudohypeoaldosteronism (PHA) is a rare disorder of salt wasting results from resistance to the action of aldosterone [1]. Mainly characterized by hyperkalemia with high serum aldosterone and renin, and low or normal serum sodium according to the type of PHA.

Primary PHA is a genetic disorder, while Secondary PHA is a transient form of salt-losing states caused by various pathologies. Most frequently Urinary tract infections and obstructive uropathies [2].

Primary PHA has two types: type I PHA and type II (Gordon syndrome or chloride shunt syndrome) [1,3]. Type I PHA mainly presents in early infancy, it is subclassified into Renal and systemic type. PHA I Renal type is an AD, caused by mutation in mineralocorticoid receptor (MR), while PHA I systemic type is an AR, results from mutation in epithelial sodium channel (ENaC) and found has more severe clinical phenotype than AD and does not spontaneously improve during early childhood [3,4].

Patients with AR type have multisystem disease with sodium wasting in the kidney, lungs, colon, sweat, and salivary glands, as ENAC is found in these organs. ENAC allows the flow of sodium from the lumen into the epithelial cell and regulates the amount of sodium in the extracellular fluid [5,6]. Children with this type often develop pulmonary symptoms like congestion, wheezing, and recurrent pulmonary infections, in addition to skin lesions such as seborrheic dermatitis, folliculitis and miliaria like rush which developed due to high concentration of salt in sweat [4,7].

AD type is found milder than AR type, sodium will be waste only in the kidney [5]. Patients will be manifested with insufficient weight gain due to chronic dehydration with mild hyperkalemia [2].

Case Report
52 days old FT, SVD presented to ER at age of 17 days old with history of persistent vomiting decreased activity and intake for 2 days admitted to NICU R/o sepsis, found to have metabolic acidosis, hyponatremia Na: 122 and hyperkalemia K: 8.3. She is a product of Spontaneous vaginal delivery, Full term, with birth weight: 3 kg Positive consanguinity (first degree) positive Family history, 1 female sibling died at age of 10 days with unknown diagnosis and another female sibling died at age of 6 months due to Adrenal disorder (was on Nacl solution & Na resonium). Clinical examination: the patient was afebrile, severely jaundiced, and hypoactive with weight 3 kg (3rd%), not dysmorphic, normal systemic examination, normal female genitalia and no Clitormegly. She was managed with impression CAH vs Pseudohypeoaldosteronism as agreed by endocrinologist (with hydrocortisone, Nacl & Na resonium).

Initial Lab Workup
CBC was normal, Metabolic acidosis PH 7.25 HCO3 10, hyperkalemia K 8.3 mmol/L and hyponatremia Na 122 mmol/L. Bilirubin T 409 umol/L bilirubin D 15.9 umol/L. later Na 138 mmol/l, K+ 4.2 mmol/l (after correction & medication), LFT & renal profile were normal. The patient was admitted in neonatal intensive care unit (NICU) as neonatal jaundice to rule out sepsis. Intensive phototherapy was started to treat jaundice and IVF with sodium bicarbonate, sodium resonium were started in addition to salbutamol to correct the hyponatremia and hypokalemia. Despite to this treatment still sodium was in lower range of normal (124, 129) and potassium in higher side (6,7) so Further investigations were sent to rollout congenital adrenal hyperplasia or adrenal insufficiency as a deferential diagnosis Hormonal assay (cortisol was normal ACTH: 20.6 (n= 6-76) was normal, Aldosterone > 100 (high) repeated after one month therapy:

31.4), Plasma Renin high 500, 17- Hydroxyprogesrtone initially high 20 repeated was normal, Testosterone <0.13,VBG mild acidosis then normal, RBS maintained, Chromosomal analysis 46 XX. ECHO PFO with left pulmonary artery stenosis to be F/U after 1 month. US Abdomen uterus is normal, hepatic focal lesion, likely hemangioma reapted was normal. MRI brain was normal.

Hydrocortisone stress dose IV was given immediately then to maintenance dose and Fludrocortisone with sodium chloride 3% were started. PHA had also been considered due to elevated serum aldosterone. Blood samples for genetic analysis were obtained. In our patient systemic PHA was diagnosed after confirmation by molecular genetic analysis of whole exome sequencing (WES) Pathogenic variant in SCNN1A cause autosomal recessive type1 Pseudohypeoaldosteronism (PHA1B; OMIM: 264350) characterized by renal salt wasting and high concentration of sodium in sweat, stool, and salivs. The disorder involve multiple organ systems and is especially threatening in the neonatal period. Laboratory evaluation shows hyponatremia, hyperkalemia, increased plasma renin activity with high serum plasma aldosterone concentration, Respiratory tract infections are common in affected children and may be mistaken for cystic fibrosis. Aggressive salt replacement and control of hyperkalemia results in survival, and the disorder appears to become less sever with age. Based on the available information the patient's phenotype appears supportive for PHA1B.

Gene (Isoform)	Phenotype MIM number (Mode of Inheritance)	Variant	Zygosity	MAF GnomAD (%)	Classification
SCNN1A (NM_001038.6	264350 (AR)	c.1522>T p. (Arg508*) chr12: 6458147	hom	0.0033	Pathogenic

After normalization of the electrolyte the patient was discharged home on hydrocortisone, fludrocortisone, sodium chloride 3% and sodium resonium to be F/U by endocrinologist for genetic study. After the result hydrocortisone was weaned gradually the stopped with fludrocortisone.

Discussion

Salt–wasting syndromes in the neonatal period may present with different clinical features. While the clinical symptoms may be nonspecific such as feeding intolerance, loss of weight gain, vomiting and weakness, patients may admit to the emergency departments with shock symptoms due to hypoglycemia and/or severe dehydration.

This clinical situation may happen due to many causes in the newborn period and may be fatal. The differential diagnosis of salt wasting diseases includes primary and secondary causes. Primary adrenal insufficiencies include congenital adrenal hyperplasia, hypoplasia, adrenal bleeding, severe systemic infections and pseudohypoaldosteronism. Secondary adrenal insufficiencies, steroids passing from mother, hypothalamo-hypophysial defects, central nervous system tumors, trauma and associated bleeding. Other causes are renal sodium loss due to pyelonephritis, tubulopathy, inappropriate ADH secretion syndrome, central salt waste, pyloric stenosis, and congenital hypothyroidism [1,5].

Congenital adrenal hyperplasia must be considered in the first step in case of salt-loss clinical symptoms during the newborn period. The patients are generally admitted with salt-loss symptoms and sexual differentiation disorders. Although, salt-loss clinical symptoms may present early in the first week of life, generally the symptoms are expected to appear in the 2nd-3rd week of life. Therefore, the treatment should be aimed directly to correct the fluid and electrolyte imbalance, particularly hyperkalemia. Clinical and laboratory findings of patients should be closely monitored and the underlying causes of treatment failure should be considered. Aldosterone resistance should be considered and therefore plasma renin and aldosterone levels should be determined in case of resistance to fluid-electrolyte treatment and steroid replacement in patients with hyponatremia, hyperkalemia, and metabolic acidosis [1,5].

Our patient was admitted with severe vomiting and pathological weight loss. Genital examination was normal. Laboratory analysis showed metabolic acidosis, hypernatremia, hyperkalemia and increased sodium excretion in urine. There were no adrenal and intracranial bleeding, adrenal hyperplasia and renal structural anomaly on ultrasound. Infection criteria were negative. Cranial and hypophysial tomography and magnetic resonance imaging's were normal. Our patient was then diagnosed with pseudohypoaldosteronism with the resistance to fluid and steroid replacement treatment and the elevated plasma aldosterone level.

Aldosterone passively crosses the epithelial cell membrane and binds to the mineralocorticoid receptor. The ligand-bound receptor translocates into the nucleus and promotes or represses gene signaling. Transcription of signaling factors results in an accumulation of epithelial sodium channels at the plasma membrane and they increase sodium transport into the epithelial cell. Sodium is then actively given out of the cell by the sodium-potassium ATPase. Inactivating mutations in the mineralocorticoid receptor cause renal PHA type 1 whereas inactivating mutations in the epithelial sodium channel subunit genes cause the systemic form of the disease [1].

Pseudohypoaldosteronism may be primary due to a mutation in the mineralocorticoid receptor or amiloride-dependent epithelial sodium channel, or secondary to infection, uropathy or drugs. Type 1 pseudoaldosteronism (PHA1) may be inherited either autosomal dominant and autosomal recessively. Renal type PHA1 is transmitted autosomal dominantly. It is usually mild and may resolve spontaneously. The systemic form PHA1 is transmitted autosomal recessively and may be persistent until adulthood. SCNN1A gene mutations leading to Type 1 autosomal recessive PHA have been reported in the literature [4,6,7]. Mutation in the subunit genes (SCNN1A, SCNN1B, SCNN1G) of epithelial sodium channel and the NR3C2 gene encoding the mineralocorticoid receptor, result in systemic PHA1 and renal PHA1, respectively [7]. In our case, gene mutation was detected and the diagnosis of type 1 PHA was confirmed.

Conclusion

Early recognition and aggressive treatment. Both CAH and PHA1 present in the neonatal stage with a similar clinical picture (poor feeding, dehydration, and lethargy) and laboratory results suggestive of adrenal crisis (hyperkalemia, hyponatremia, and acidosis). Treatment with hydrocortisone should be considered in all patients with no index case of PHA, especially patients with ambiguous genitalia or male patients, because hydrocortisone results in an excellent response in the case of CAH. However, it is very important to send blood for 17-hydroxyprogesterone (17-OHP) aldosterone, renin, cortisol, and ACTH before starting hydrocortisone. When the patient is female with normal genitalia or the response to corticosteroids is poor, resistance to aldosterone should always be considered. Treatment of PHA1 should be considered as an emergency and life-saving measure. This comprises adequate rehydration, replacement of salt loss, and correction of hyperkalemia and acidosis in the acute phase. After initial stabilization, potassium exchange resins and salt supplementation are the mainstays of treatment

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