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Type IV Renal tubular acidosis – Pseudohypoaldosteronism

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I. Introduction

Renal tubular acidosis (RTA) is a group of transport defects secondary to reduced proximal tubular reabsorption of bicarbonate (HCO3-), the distal secretion of protons (hydrogen ion, H+) or both, resulting in impaired capacity for net acid excretion and persistent hyperchloremic metabolic acidosis. Based on pathophysiology, RTA has been classified into three types: type 1 (distal) RTA; type 2 (proximal) RTA; and type 4 RTA secondary to true or apparent hypoaldosteronism.

Type 4 RTA has metabolic acidosis with hyperkalemia that is disproportionately high for the degree of renal insufficency. Child presents with failure to thrive, polyuria, polydypsia, vomiting, listlessness, dehydration, hyponatremia, hyperkalemia & hyperchloremic acidosis; plasma rennin activity & urine and plasma aldosterone levels are greatly increased[1]. In children, aldosterone unresponsiveness is a more common cause of type IV RTA than aldosterone deficiency, and is commonly associated with obstructive uropathy.[2,11.]

We present an unusual case of type 4 RTA with sensorineural deafness that has not been reported. Although hearing loss associated with type 1 RTA has been reported [3,4.] , and one case of adult alport syndrome presenting with type 4 RTA has been reported [5].

II. Case report

A male infant 1st product of a nonconsanginous marriage, born at term with 2.5kg weight. No antenatal or perinatal complications, exclusively breast fed for 6 months & achieved 6kg. Apparently well till 6 months of age when he started having recurrent episodes of vomiting with diarrhea. He had a severe episode of sepsis and went into ARF at 9 months which was managed conservatively and discharged. On follow up he had failure to thrive with frequent vomiting and dehydration episodes, refusal to solid foods, preference for salt & liquids and suspected deaf mutism. Readmitted & polydypsia and polyuria (5.7ml/kg/hr) documented. On evaluation found to be normotensive with normal anion gap acidosis (pH 7.152), HCO_3^- – 10.3meq/l, hyperkalemia (6.7meq/l), blood urea – 243mg/dl, S.creatinine -1.3mg/dl. Urine Na^+ – 45meq/l, K^+- 12.1meq/l, pH < 5.5. S.Aldosterone raised (2103pg/ml), USG –KUB: no nephrocalcification, MCU – normal and on hearing assessment found to have b/l sensorineural deafness. Diagnosed as Type 4 RTA due to Pseudohypoaldosteronism and managed with potassium binder, sodabicarb and fludrocortisone with future plan for cochlear implant.

III. Discussion

The Cortical CT actively reabsorbs sodium via an aldosterone-dependent mechanism accompanied by passive chloride reabsorption and secretion of potassium. The negative intraluminal potential difference generated by sodium reabsorption facilitates active proton secretion by the H^+-ATPase.Impairment of CCT sodium transport suppresses secretion of potassium and hydrogen; if the H^+-ATPase is also inhibited in the MCT, hyperkalemic hyperchloremic metabolic acidosis will ensue. Such disorders include aldosterone deficiency or resistance known as type 4 RTA.

Aldosterone deficiency is the most frequently seen form of hyperkalemic metabolic acidosis in adults. Although originally described more than 40 years ago, the syndrome of isolated aldosterone deficiency has been recognized with regularity only during the past two decades.[6, 7]. Every endocrine deficiency disease has a corresponding resistance state. Aldosterone resistance is more common in children. The features of the aldosterone resistance are the same as those of aldosterone deficiency except aldosterone levels in the former are normal or increased. In patients with aldosterone deficiency or resistance, the ability to lower urine pH normally is present, as was found in our patient. There are at least two forms of aldosterone resistance: with or without salt wasting.

Aldosterone resistance or Pseudohypoaldosteronism in children is associated with profound salt wastage greatly in excess of that seen in adults.[8] The difference may be attributable, at least in part, to the normal GFR present in children. The disease results from hyporesponsiveness of the distal tubule to aldosterone. Therapy in this group includes salt supplement, $NaHCO_3$, and either potassium restriction or ion exchange resins.

Since primary PHA was first described, it has been further classified

Type I (PHA-I) - Renal type I (renal PHA-I)
- Multiple target organ defect type I (MTOD PHA-I)
- Early childhood hyperkalemia

Type II (PHA-II) - Gordon syndrome

- Adolescent hyperkalemic syndrome

Renal PHA-I, or early childhood hyperkalemia, is probably due to a maturation disorder in the number or function of aldosterone receptors. This autosomal dominant disorder has been associated with mutations in the human mineralocorticoid receptor gene (*MLR*) in numerous kindreds and also in sporadic cases. More than 70 cases of this salt-wasting syndrome have been reported in the literature since the first description in 1958.[9] Renal PHA-I, also called Cheek and Perry syndrome or classic PHA of infancy, represents the most common form of PHA-I. The early childhood hyperkalemia variant of renal PHA-I is the most common subtype of type 4 RTA in children and is found with equal frequency in males and females. Occasionally, several siblings are affected.

Renal PHA-I only occur in newborns and infants and usually improve with age. Early childhood hyperkalemia occurs in infants and young children. The clinical expression widely varies, even among members of the same family and with the same gene defect. Affected children may have severe symptoms in early infancy (first 2 wk of life) or may be essentially asymptomatic. Salt wasting and polyuria may be present in utero and result in polyhydramnios. Anorexia and vomiting generally develop immediately after birth Symptoms are similar to those observed in mineralocorticoid deficiency. Salt craving is observed in older children Vomiting is usually the only symptom in those with early childhood hyperkalemia. Symptomatic individuals have failure to thrive, weight loss, repeated episodes of dehydration and may appear to be in shock and comatose. Failure to thrive or growth retardation is the only physical finding in children with early childhood hyperkalemia. Hypertension is absent.

Sensorineural hearing loss (SNHL) occurs when there is damage to the inner ear (cochlea), or to the nerve pathways from the inner ear to the brain. Most of the time, SNHL cannot be medically or surgically corrected. This is the most common type of permanent hearing loss.

SNHL reduces the ability to hear faint sounds. Even when speech is loud enough to hear, it may still be unclear or sound muffled.

Some possible causes of SNHL:
- Illnesses
- Drugs that are toxic to hearing
- Hearing loss that runs in the family (genetic or hereditary)
- Aging
- Head trauma
- Malformation of the inner ear
- Exposure to loud noise

The fundamental abnormality in MTOD PHA-I is a loss-of-function mutation in the alpha or beta subunits of the epithelial sodium channel (ENaC), resulting in defective sodium transport in many organs containing the ENaC (e.g., kidney, lung, colon, sweat and salivary glands). This amiloride-sensitive member of the degenerin/epithelial sodium channel (Deg/ENaC) superfamily of ion channels is comprised of 3 homologous units (alpha, beta, gamma) and is expressed in the apical membrane of epithelial cells lining the airway, colon, and distal nephron. ENaC plays an essential role in transepithelial Na^+ and fluid balance. The state of hyper-reninism and hypoaldosteronism in these children is the result of sustained extracellular fluid (ECF) volume depletion and is not due to peripheral resistance to mineralocorticoid. Salt-wasting episodes develop soon after birth and usually are more severe than in renal PHA-I. These individuals have a high incidence of lower respiratory tract involvement secondary to impaired bacterial killing, resulting from increased sodium chloride concentration in airway surface fluid, which can mimic cystic fibrosis.

Management of PHA consists of correcting electrolyte & acid/base abnormalities. Ingestion of a high-sodium (10-15 mEq/kg/d) and low-potassium (0.6 mEq/kg/d) diet is generally effective in preventing both volume depletion and hyperkalemia. Alkalinizing agents are used for correcting acidosis in children with early childhood hyperkalemia during the first few years of life. Correction of acidosis does not correct the hyperkalemia. Sodium bicarbonate is a choice of alkali therapy because it is inexpensive, easy to prepare, and does not have to be metabolized by the liver. Citric acid and sodium citrate (Bicitra, Oracit) are metabolized by the liver to bicarbonate. Provides 1 mEq of sodium bicarbonate per mL. Potassium citrate solutions should be avoided. Dose is 3-6 mEq/kg/d PO divided tid/qid

Potassium-binding resins are used to successfully control hyperkalemia. Sodium polystyrene sulfate (Kayexalate) releases the sodium ions in the large intestine, and these are replaced mole for mole by potassium ions. 1 g/kg/dose PO/NG q6h alternatively, may administer PR as retention enema q6h.

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