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A Case of Primary Pseudohypoaldosteronism

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Abstract

Purpose: There is reported a case of a 5-month old boy diagnosed with Type I pseudohypoaldosteronism which is a rare salt-losing disease caused by resistance of the target organs to aldosterone. **Methods:** Diagnosis was based on clinical presentation with frequent admissions from a young age due recurrent episodes of vomiting and wheezing as well as relevant electrolyte and hormone disturbances. It is interesting that during hospitalizations, the baby showed recurrent episodes of wheezing not responding to b-blockers and corticosteroids and dependence from daily oxygen supplementation. **Molecular investigation of the ECa_v gene was normal.** **Conclusions:** The systemic form of type I pseudoaldosteronism involves pulmonary dysfunction in addition to increased levels of aldosterone.

Key words: Chronic wheezing, Pseudohypoaldosteronism.

Introduction

Type I pseudohypoaldosteronism is a salt-losing syndrome due to resistance of the target organs to aldosterone. Typical features of the disease include severe neonatal hyponatremia, hyperkalemia, metabolic acidosis and high serum aldosterone concentrations. Two forms are described. The systemic one, which is inherited as an autosomal recessive trait, is the more severe. Multi-organ aldosterone unresponsiveness affects kidneys, colon, sweat and salivary glands and the lung and has been associated with mutations encoding the amiloride-sensitive epithelial sodium channel (ENaC), a mineralocorticoid receptor gene [1]. In the lung ENaC regulates the quantity and composition of respiratory tract fluid. The condition could be fatal in infancy, but has an excellent prognosis later on. The classic form is autosomal dominant with renal involvement only and defects in tubular absorption of sodium [2].

Case Report

Our patient is a 5 month-old boy, the 4th child of unrelated normal, non-consanguineous Roma parents, born after an uneventful pregnancy with normal delivery and birth weight Bw=4.500gr. The 1st admission in the hospital was at the age of 2 months with bronchiolitis and failure to thrive (W=3.450<3rd PC). The last days, the mother mentioned frequent episodes of vomiting and insufficient feeding meals. During clinical examination no apparent malformations were noticed. At the age of 5 months, he was readmitted with the same

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symptoms. Apart from respiratory findings, mother referred a constant drip from his nose with clear, thin liquid. During his 2nd admission, the child's general condition deteriorated rapidly and he was transferred to the ICU unit with severe electrolyte disturbances (Na=111iu/ml, K=7.5iu/ml, pH=7.22, $\text{-HCO}_3=18.7\text{mM}$), pneumonia of the right lung and acute distress syndrome. He had a clinical presentation of septicemia and his overall condition was severe. He was intubated and delivered assisted ventilation for 9 days.

He remained in the hospital for 3 months in order not only to recover but also because of recurrent episodes of wheezing and oxygen supplementation requirements. It is interesting that our patient showed frequent unexplained episodes of rapid deterioration of lung function with decreased oxygen saturation and poor response to bronchodilators and corticosteroids.

Laboratory Investigation

Extensive laboratory investigation was negative for bacterial infection, apart from positive RSV antibodies. The blood examination revealed an increased number of leucocytes, but the acute reaction proteins were almost normal. In detail, the total leucocyte number was 18.800mm^3 (neutrophils=29%, lymphocytes=56%, monocytes=11%, eosinophils=7%), CRP=1mg/L, TKE=59mm. Extended investigations for infectious diseases were negative, including antibodies for *Meningitidococcus*, *Pneumococcus*, *Haemophilus influenza*, *Staphylococcus*, *Pseudomonas* and viruses including CMV, EBV, HSV, H1N1.

The immunological profile with immunoglobulins (IgG=394 mg/dl, IgA=38 mg/dl, IgM=112 mg/dl, IgE<2U/L) and lymphocyte immune-phenotyping was normal. Heart investigation was also normal. Lung investigation showed hyperventilation on X-ray and the CT scan revealed infiltrations type ground glass in the right and left upper and medium lobe. Infiltration did not clear up one month later despite appropriate treatment. Furthermore, he had a normal sweat test and DNA test excluding cystic fibrosis. Gastroesophageal reflux was ruled out by PH measurements. Renal function was normal, as was ultrasonography and the urine electrolytes detected increased sodium excrete (K=130 $\mu\text{M/L}$, Na=40 $\mu\text{M/L}$, Cl=23 $\mu\text{M/L}$).

Hormone profile revealed secondary adrenal insufficiency. Increased titers of renin >310pg/ml (normal 3.6-20.1), and aldosterone >5547pmolL (normal 55.5-3051.4) were detected. Although ACTH was increased (ACTH=10.43pg/ml), the cortisol pathway was normal (DHEA-S<15ug/dl, $\Delta 4$ -androstendion<0.30ng/ml, 17OH progesterone=1.37ng/ml, testosterone=62.0ng/dl, cortisol=9.62 $\mu\text{g/dl}$). Diagnosis of primary hypo-aldosteronism was confirmed. Pulmonary participation advocated for the systemic form. However, DNA analysis of ECaN gene did not reveal any mutations.

Treatment

The treatment during the acute phase in the ICU consisted of antibiotics and high doses of dexamethasone due to unresponsiveness to bronchodilators. However, those high doses were the cause of secondary adrenal insufficiency

detected on the laboratory investigation and the rapid restoration protocol was applied. His primary disease management consisted of high doses of sodium chloride (800 mg/kg) orally to stabilize salt loss. The diet was a formula with low potassium. According to literature, he was treated for pulmonary dysfunction with adrenaline and Ibuprofen 20mg/kg with excellent results. He gained weight and had normal development, but oxygen saturation remained at 92-94%. He was under permanent oxygen supplementation and saturation rate remained 90-92% throughout the day.

Discussion

The case described is a rare one and few reports are found in the literature. The patient presented with symptoms of recurrent vomiting and failure to thrive since the age of 2 months. Furthermore, he developed symptoms from the lungs also presenting with recurrent wheezing. However, diagnosis was established at the age of 5 months due to severe electrolyte disturbances and acute distress syndrome.

The diagnosis of primary hypo-aldosteronism type I was suspected from the hormone profile, hyperkalemia and the high titers of renin and aldosterone. In addition, suppression of the adrenal axis was noted due to high doses of corticosteroids provided at the acute phase and the unresponsiveness of the patient to bronchodilators. During his long hospitalization, it was interesting to find that the patient had also recurrent episodes of lung involvement unresponsive to common medications. He responded to high salt and oxygen supplementation as well as per os Ibuprofen.

The systemic form of primary hypoaldosteronism is a rare disease [3,4] and is associated with a distinct respiratory syndrome [5]. The clinical presentation resembles that of asthma and cystic fibrosis. The disease presents during early infancy and is characterized by severe salt wasting displaying with hyponatremia, hyperkalemia, dehydration and metabolic acidosis despite high levels of plasma aldosterone.

Pulmonary involvement due to water and salt homeostasis disturbance leads to decreased sodium absorption and increased volume of an exudate [6]. This liquid that is more than twice the normal value, narrows the airway diameter and predisposes to wheezing. Active sodium absorption is the dominant mechanism of ion transport in airway epithelium, but its role in pulmonary physiology and airway host defense is unknown. The osmolality of the liquid inhibits antimicrobial activities of the salt-sensitive defense mechanisms and it is implicated in mucus clearance. Defect of these mechanisms predisposes to severe lung infections in early life from bacteria such as *Pseudomonas aeruginosa* and *staphylococcus aureus* [7]. These children have a persistent rhinorrhea and recurrent respiratory illness characterized by congestion, tachypnea, wheezing suggesting asthma as it was first described in 1958 [8]. It is difficult to predict the phenotype and pathophysiology of lung disease in patients in whom airway epithelial sodium transport may be affected [9].

Although the clinical presentation of our patient was

typical, there were found no mutations in the ECaN gene [9]. According to the literature, the epithelial Na⁺ channel (ENaC) protein is composed by three subunits (α-β-γ) and it is known to play a critical role in salt and fluid homeostasis. The homozygous mutations in the gene are lethal due to inability to clear fluids from the lungs after birth [1]. Different diseases are generated from mutations in the different units of the gene, including pseudohypoaldosteronism type 1 and Liddle syndrome, an inherited autosomal dominant form of human hypertension [10]. Liddle syndrome is an autosomal dominant form of hypokalemic hypertension due to mutations in the β- or γ-subunit of the epithelial sodium channel (ENaC) [11]. Abnormally high ENaC activity has been demonstrated in cystic fibrosis patients [1].

Other authors have described patients where mutations were not identified, suggesting that probable promoter or intronic mutations or mutations in other genes could be responsible for the function of sodium channels [12,13]. Recently, other genes implicated to the sodium transportation have been suggested for a combined cystic fibrosis phenotype and hypokalemia such as CFTR, SCNN1A, SCNN1B, SCNN1G and SERPINA1 that increase the ENaC activity [14].

Our case is reported because of its rarity. Endocrinology genetic syndromes are frequently the cause of failure to thrive and hospitalizations with electrolyte disturbances. However, the entity of hormonal dysfunction and pulmonary manifestations is only presented in the systemic form of primary hyperaldosteronism. The genetic profile of the condition is still under investigation and in our case no mutations were detected in the ENaC gene.

Declaration

The authors have nothing to declare.

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