Transient Pseudohypoaldosteronism: A Rare Cause of Severe Hyponatremia in a Baby

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Abstract: Hyponatremia and dehydration in children represent a medical emergency due to a variety of underlying illness. Other than an evidence of gastroenteritis with diarrhea and vomiting (which is the major cause of hypoosmolar hyponatremia in pediatric age), other causes should be considered, especially if there is evidence of hyperkalemia and high sodium fraction excretion (FENa), like iatrogenic causes (diuretic excess), transient or genetic abnormalities of the renal mineralocorticoid pathway, syndrome of inappropriate anti-diuretic hormone secretion (SIADH), acute renal failure, congenital adrenal hyperplasia (CAH).

Here we present a case of transient pseudohypoaldosteronism in a 2 months old baby secondary to urinary tract infection, who presented with a history of poor sucking, fever and dehydration.

Keywords: Pseudohypoaldosteronism, Hyponatremia, Infant.

INTRODUCTION

Hyponatremia and hyperkalemia are often observed in the first months of life, commonly associated with conditions like gastroenteritis. However, it's important to recognize some significant life-threatening conditions as Congenital Adrenal Hyperplasia (CAH), the most worrying of all, followed by isolated aldosterone deficiency, drugs and Pseudohypoaldosteronism (PHA) [1].

PHA is a rare pathology due to mineralcorticoid resistance, caused by deficiency in sodium transport in distal tubule of the kidney. Clinical manifestations are life-threatening dehydration, hyperkalemia, acidosis and failure to thrive [2].

We report a 2-month-old baby with hyponatremic-hyperkalemic dehydration and clinical and biochemical signs of Urinary Tract Infection (UTI). Despite PHA being a rare condition, it was considered in the differential diagnosis, together with CAH and Hypertrophic Pyloric Stenosis (HPC).

CASE PRESENTATION

A 2 months-old male, born at term, previously healthy, was brought to our department with progressive lethargy. He was born at full term with a birth weight of 4075 g. He was transferred to our Centre from a provincial Hospital, in which he was admitted a week before, for fever and intense vomiting. There, for the high inflammation indices on his screening investigations, an empiric antibiotic therapy was commenced, and the baby was discharged at home. For the persistence of symptoms and the onset of diarrhea, the patient was re-admitted to the same hospital. Then, for the worsening conditions, the evidence of severe hyponatremia and failure to thrive, he was referred to our Centre for further management. On presentation he was suffering in appearance, pale and dehydrated. Initial investigations revealed; Na 127 mmol/L, K 6 mmol/L and increased RCP. A fluid resuscitation was commenced, and we decided to continue the antibiotic therapy started before the admission. For the evidence of bacteriuria at the urinalysis, a urine culture was performed, which resulted negative for pathogenic bacteria. To investigate kidneys and urinary tract, an ultrasound was performed, with no evidence of malformations or other abnormalities. Moreover, to exclude other important and potentially life-threatening causes of neonatal hyponatremia (CAH, hypoaldosteronism), specific hormone levels were dosed (17-OHP, Cortisol) which resulted to be normal. Then we considered other possible causes of hyponatremic hyperkalemic metabolic acidosis, therefore we obtained serum aldosterone level which resulted to be elevated at 1177 pg/ml (reference range < 300 pg/ml), implying tubular unresponsiveness. Simultaneously also renin levels resulted to be high (105 pg/ml). For this reason, a diagnosis of transient PHA was considered. During the hospitalization the child's health conditions have progressively improved. Once appropriately treated hyponatremia with infusion of sodium chloride, our little

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patient exhibited improved weight gain and normalization of laboratory tests. Indeed, examinations performed in pre-discharge (electrolytes, renal function, CPR) appeared to be normal. In particular the values of renin and aldosterone were normalized, confirming the transient nature of the disease. The child returned to outpatient control after one month and after four months. At both visits the baby showed to grow well and other blood samples were taken to check electrolytes, aldosterone and renin, which appeared to be normal (Table **1**).

DISCUSSION

Hyponatremia is a well recognized cause of "near miss" sudden infant death syndrome. A combination of hyponatremia and hyperkaliemia with metabolic acidosis is very much suggestive of adrenal insufficiency and hydrocortisone treatment gives excellent response.

However, when the clinical picture is peculiar and atypical and/or the response to corticosteroids is poor, peripheral resistence to aldosterone should always be considered as possible diagnosis.

As the last effector of the Renin-Angiotesin-Aldosterone pathway, Aldosterone has the important function of sodium reabsorption and regulation of potassium secretion through the distal renal tubule. It is released in response to hypotension or hyperkalemia with the aim of regulating blood pressure and potassium homeostasis [3]. For this reason, the renal resistance to the action of aldosterone is expressed with increased sodium loss, hyperkalemia, acidosis, hyperreninemia and elevated plasma aldosterone levels [4].

Resistance to the aldosterone effects could be due to alteration of renal mineralcorticoid receptor or of tubular ion channels which were implicated in the sodium-potassium balance [5].

Particularly, transient PHA is a rare cause of hyponatremia in pediatric age. It can occur at any age, but most of the times affects neonates or young infants in whom an immaturity of the renal tubules can be detected [6]. It mimics hypoaldosteronism and is characterized by tubular resistance of the collector duct to the action of aldosterone. This renal unresponsiveness results in electrolyte disorders, such as hyponatremia, hyperkalemia, metabolic acidosis and dehydration which can also be life-threatening for the patient and lead to cardiac arrhythmias like ventricular flutter [7].

PHA may be primary or secondary. Primary form has a genetic etiology and includes a wide group of diseases with heterogeneous manifestations, due to different types of mutation of the mineralcorticoid receptor, while in the secondary or transient form no genes mutations are found [8]. On the contrary in these patients other underlying conditions can be observed frequently, first of all Urinary Tract Malformations (UTM), obstructive uropathy (valves of the posterior urethra) or bowel abnormalities [9]. PHA is also described in absence of these malformations. The severe inflammatory response during UTI seems to produce distal tubular aldosterone resistance, in addition to renal tubular immaturity of the first months of life [10].

Furthermore, the heterogeneous and nonspecific presentation of symptoms sometimes makes this condition really challenging for the clinician to deal with and it can lead consequently to a delay in the diagnosis. In literature, in fact, emerges how in the clinical practice is not rare to mistake this condition with other diseases, like HPC or CAH [8, 11].

Table 1: Biochemical Evaluation

	1st Day of Hospitalization	Last Day of Hospitalization	1 Month after Hospitalization	4 Months after Hospitalization
Sodium	127 mmol/L	134 mmol/L	131 mmol/L	134 mmol/L
Potassium	6 mmol/L	4,6 mmol/L	6,4 mmol/L	5,1 mmol/L
17-OHP	5.20 ng/ml			
Cortisol	43.60 mcg/dl			
Aldosterone	1077 pg/ml	518 pg/ml	578 pg/ml	140 pg/ml
Renin	-----	43.7 pg/ml	21.2 pg/ml	26.3 pg/ml

In addition to hypothalamic-pituitary-adrenal axis hormones (aldosterone, cortisol, ACTH) and serum electrolytes, other exams like kidney-urinary tract ultrasound could be useful in order to an UTM diagnosis but can't support the suspicion of transient PHA in patients with UTI [12].

Reporting this case, our aim is to support the possibility, already described in literature, of a renal resistance to aldosterone due to a UTI [13-15], and the importance of recognize it correctly in order to avoid a delay in diagnosis as well as unnecessary exams or inappropriate therapies (*e.g*. hydrocortisone in the suspicion of CAH). The lack of response to corticosteroid therapy increases the suspicion of PHA, particularly in case of clinical improvement after rehydration. In this case, a renal cause must be sought, despite the absence of clinical signs of pyelonephritis or fever [16].

However, in case of alteration of electrolysis and acid-base balance, firstly it is necessary to think about other more common pathologies, according to epidemiology and clinical manifestations (for example: meningitis, gastroenteritis, respiratory tract infections) [17]. But transient PHA is an important life-threatening pathology not always well recognized and it may be more common than we know. Some authors speculate that some confounding factors could contribute to its low incidence [18].

CONCLUSION

PHA remains an important cause of dehydration in infants which cannot be excluded and should be considered in children younger than 6 months with hyponatremia, hyperkalemia, lethargy, vomit and elevated aldosterone levels [19]. It is apparently rare but also underdiagnosed, according to some speculations. In clinical practice, in fact, symptomatic UTI or UTM are commonly associated with hyponatremia, hyperkalemia and metabolic acidosis [20]. For this reasons, secondary or transient PHA must be considered and known to avoid inappropriate practices.

AUTHORSHIP CONTRIBUTION

CU, DAF, VM wrote the paper, LPA, BN, Z G, SG followed the patient, CCM and VGF searched references.

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