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## Pseudohypoaldosteronism type 1 secondary to vesicoureteral reflux: An endocrinologic emergency<sup>☆</sup>



## Pseudohypoaldosteronismo tipo 1 secundario a reflujo vesicoureteral: una urgencia endocrinológica

Hypoaldosteronism is an endocrine disease characterized by hyperkalemia and mild hyperchloremic metabolic acidosis with normal anion gap (type 4 renal tubular acidosis).

Causes of hypoaldosteronism include acquired disorders (hyporeninemic hypoaldosteronism, drug-induced angiotensin II inhibition, heparin therapy and primary adrenal insufficiency) and, less commonly, hereditary disorders. Adrenal aldosterone synthesis or renin release is affected in all these conditions.<sup>1</sup>

Aldosterone is a mineralocorticoid mainly acting in the kidney and, secondarily, in other organs (colon, lung, and sweat, lacrimal, and salivary glands). Aldosterone action, which requires a mineralocorticoid receptor and a sodium transporter protein, called sodium epithelial channel (SEC), regulates plasma sodium reabsorption and urinary potassium excretion.<sup>2</sup> It is essential to differentiate decreased aldosterone production from aldosterone resistance.

The most commonly reported causes of the aldosterone resistance syndrome include treatment with potassium-sparing diuretics and antibiotic therapy with co-trimoxazole and pentamidine. A particularly uncommon condition is pseudohypoaldosteronism type 1 (PHA1).

PHA1 may have a genetic basis and be inherited as a recessive autosomal disorder which affects SEC, impacting on all target organs (multiple form), or a dominant autosomal form, characterized by mutations in the gene encoding for the renal aldosterone receptor (renal form).<sup>3,4</sup> Among secondary or acquired forms, special mention should be made of those derived from obstructive (organic or functional) and/or infectious uropathy, tubular interstitial disease, and side effects of drugs<sup>4</sup> (Table 1).

PHA1 is characterized by aldosterone resistance, associated to hyponatremia, hypovolemia, hyperkalemia, and hyperchloremic metabolic acidosis. Plasma renin and aldosterone levels are markedly increased.

Although the syndrome has an insidious course, it may exceptionally lead to water and electrolyte emergencies. We therefore report the clinical case of a patient with severe dehydration, critical hyperkalemia, and urine output excessively high for the degree of dehydration. This was a 19-day-old male infant who was admitted to the pediatric ICU for dehydration and 19% weight loss (birth weight 3090 g [10th–25th percentiles] after vaginal eutocic delivery at 41 weeks of pregnancy). The infant had not had clinical signs or symptoms of infection or fever.

Family history included grade 1 left vesicoureteral reflux (VUR), complicated with pyelonephritis at 15 days of life and requiring hospital admission, in a 6-year-old sister.

Laboratory tests showed leukocytosis (27,100 WBC/mm<sup>3</sup>), with presence of band cells (9%). Chemistry showed greatly impaired renal and electrolyte profiles (urea, 234.9 mg/dL; creatinine, 1.67 mg/dL; sodium, 122.6 mEq/L; chlorine, 90.4 mEq/L; potassium, 11.25 mEq/L; and calcium, 11.6 mg/dL). Because of this critical potassium level, factitious hyperkalemia or preanalytical error (hemolyzed serum, EDTA-K<sup>3</sup> contamination, excess compression or tourniquet time, and a drug-induced effect) were ruled out. Arterial blood gases showed metabolic acidosis (pH, 7.17; pCO<sub>2</sub>, 15 mmHg; pO<sub>2</sub>, 105 mmHg; HCO<sub>3</sub><sup>-</sup>, 5.5 mmol/L, and SBE, -20.1 mmol/L). Analysis of urine collected by suprapubic puncture showed microscopic hematuria, pyuria, negative nitrites, proteinuria (150 mg/dL), pH 6, specific gravity 1010, sodium 21 mEq/L, and potassium 27.3 mEq/L, with an osmolarity of 228 mOsmol/kg. Blood, urine, and rectal swab samples for culture showed urinary tract infection (UTI) by *E. coli* susceptible to aminoglycosides, third-generation cephalosporins, and fosfonates. The patient is a rectal carrier of ESBL-producing *K. pneumoniae*, with negative blood cultures. Lumbar puncture provided no findings of interest, including cultures.

ECG showed characteristic signs of hyperkalemia (spiking T waves and PR in the upper limit of normal).

The etiological study was completed by abdominal ultrasonography, which showed bilateral ureterohydronephrosis, winding ureters, and hyperechogenic contents related to turbid urine. Based on these findings, voiding cystoureterography was performed, which ruled out structural obstruction and showed enlarged bladder, grade IV right and grade V left VUR, and incoordination of urinary detrusor/sphincter muscles consistent with functional obstruction, valve-like syndrome, uncoordinated voiding in the male infant, or Hinman–Allen syndrome.<sup>5</sup> A renal scan with dimercaptosuccinic acid (DMSA) showed kidney function impairment (60% in the right and 40% in the left).

Adrenal function tests showed aldosterone levels higher than 2000 pg/mL (17–130), plasma renin activity (PRA) of

<sup>☆</sup> Please cite this article as: Ruiz Ginés MÁ, Ruiz Ginés JA, Saura Montalbán J, Fontelles Alcover R, Piqueras Martínez AN. Pseudohypoaldosteronismo tipo 1 secundario a reflujo vesicoureteral: una urgencia endocrinológica. *Endocrinol Nutr.* 2014;61:495-497.

**Table 1** Types of pseudohypoaldosteronism.

Pseudohypoaldosteronism type 1 (aldosterone resistance)	
<i>Primary (hereditary or sporadic)</i>	
RAH (multiple form)	Inactivating mutations in genes encoding for SEC: SCNN1A (chromosome 12p13) SCNN1B (chromosome 16p12) SCNN1G (chromosome 16p12)
DAH or sporadic (renal form)	Inactivating mutation in the gene encoding for MR: NR3C2 (chromosome 4q31) Significant genetic variability (sporadic cases with or without mutation)
<i>Secondary or acquired</i>	
Uropathies/UTI	Bacterial toxins, inflammatory cytokines (TGF- $\beta$ ), obstruction with increased intrarenal pressure, blood flow reduction
Tubular interstitial disease (lupus, transplant rejection, sickle cell anemia, diabetes mellitus)	Immunological tubular lesion, inflammatory cytokines, medullary ischemia
Drugs: ACEIs, ARBs, heparin, ketoconazole, cyclosporin, tacrolimus, trimethoprim, pentamidine, NSAIDs, betablockers, spironolactone, potassium-sparing diuretics, ketoconazole	SEC, MR, and RAAS
<i>Pseudohypoaldosteronism type 2, Gordon syndrome, or familial hypertension and hyperkalemia syndrome (decreased aldosterone production)</i>	
DAH	Mutations and deletions in WNK: WNK 4: Inhibition of Na/Cl co-transporter (NCC) and apical potassium channels (ROMK), inhibiting sodium reabsorption and potassium secretion respectively WNK1: caused by increased activity of both SEC and NCC

SEC: sodium epithelial channel; DAH: dominant autosomal heredity; RAH: recessive autosomal heredity; NCC: Na/Cl co-transporter; MR: mineralocorticoid receptor; ROMK: epithelial potassium channel; RAAS: renin-angiotensin-aldosterone system; WNK: with no lysine kinase.

27.9 ng/mL/h (0.2–2.3), an aldosterone/PRA ratio higher than 72 (1.5–11). Free cortisol level in 24-h urine (16.7 g/dL; 4.2–38.4) and ACTH (18 pg/mL; 9–52), DHEA-S (375.2 g/dL; 108–406), and 17- $\alpha$ -hydroxyprogesterone (1.46 ng/mL;  $\leq$ 4.5) levels were normal.

In conclusion, Hinman–Allen syndrome may result in a significant impact on kidney function, specifically on water and electrolyte homeostasis. The most important consequence is acquired PHA1<sup>6</sup> or renal aldosterone resistance syndrome. The main characteristics of PHA1 include hyponatremia, hyperkalemia and metabolic acidosis with abnormally high aldosterone levels. PHA1 has exceptionally been reported in children with obstructive uropathy or VUR and concomitant urinary infection. It has been postulated that PHA1 is caused by release of prostaglandins, thromboxane A<sub>2</sub>, leukotrienes, endothelin, angiotensin II, TNF- $\alpha$ , TGF- $\beta$ 1, and interleukins 1 and 6, associated to the renal parenchyma inflammatory process, mediated by bacterial endotoxins. As a result, vasoconstriction, decreased glomerular filtration rate, and natriuresis occur, related to transient damage to aldosterone receptors.<sup>7</sup>

During the first months of life, because of tubule immaturity, high aldosterone levels are required for adequate maintenance of water and electrolyte balance, which could

be affected by uropathy, with or without an added infectious process.

Our patient had multiple risk factors involved in development of secondary PHA1, such as age, male sex, severe VUR, and UTI. The genetic basis of the condition was ruled out when hormone levels normalized after treatment. Otherwise, mutation in the *NR3C2* gene (overlapping phenomenon) should have been evaluated.<sup>8</sup>

The initial symptomatic treatment consisted of rehydration, pH normalization, and correction of hyperkalemia (provision of sodium bicarbonate and calcium gluconate),<sup>9</sup> together with implementation of a low pressure urinary system (urinary catheterization or vesicostomy), which reduces aggression of VUR on the upper urinary tract.<sup>10</sup> Surgery was subsequently performed, consisting of bladder augmentation cystoplasty, which prevent progression to chronic renal failure.

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## Primary thyroid lymphoma<sup>☆</sup>



## Linfoma primario del tiroides

Primary thyroid lymphoma (PTL) is an uncommon condition which, to be categorized as such, must only affect the thyroid gland and, eventually, the locoregional lymph nodes. Primary disease in other location should be ruled out.<sup>1,2</sup> Diagnosis of PTL is complex, and surgery is often required to make a definitive diagnosis. Therapeutic management has greatly changed over time, and chemotherapy, with or without radiotherapy, is the current treatment of choice.<sup>1,2</sup> We report our experience in PTL management since introduction of the new chemotherapy protocols in order to analyze: (1) the need for surgery; (2) recurrences; and (3) changes over time.

Patients treated at our hospital in the past 10 years with histological diagnosis of any of the pathological variants of PTL were selected for the study. Epidemiological, diagnostic, therapeutic, histological, and evolutionary variables were analyzed.

Seven patients, a majority of them women with a mean age of 64 years, met the diagnostic criteria for PTL. PTL occurred in all cases as a rapidly growing neck tumor, associated to compression symptoms in six of them (86%) (Table 1). Ultrasonography showed diffuse thyroid enlargement in 3 patients (43%) and a thyroid nodule occupying a great part of the corresponding half of the thyroid gland in the other 4 patients. Surgery was indicated in all

patients, in 4 (57%) due to suspected malignancy and in the other 3 for compression symptoms. Five patients (71%) underwent total thyroidectomy, and the other 2, hemithyroidectomy. There were no postoperative complications. Four patients (57%) had a diffuse B lymphoma, and 3 patients a low grade MALT lymphoma. B lymphomas were associated to Hashimoto thyroiditis. A stage IE tumor was found in 6 patients (86%), and the remaining patient had a stage IIE tumor. All patients were given adjuvant CHOP chemotherapy (cyclophosphamide, adriamycin, vincristine, and prednisone), associated to radiotherapy with 50 Gy in 5 patients (71%). Six patients are currently alive and free of disease, and one patient died at 8 years for a cause unrelated to the disease.

PTL is an uncommon disease with a greater incidence in women over 60 years of age. Risk of PTL development is 80-fold higher in lymphocytic Hashimoto thyroiditis, but evolution from this condition to lymphoma is uncommon (0.1%).<sup>1</sup> In our series, B lymphoma was universally associated to Hashimoto thyroiditis, but in no case to MALT lymphomas.

The most common clinical presentation is a rapidly growing mass that causes symptoms due to compression or tissue infiltration, as seen in our patients. Some authors suggest that patients often experience neck adenopathies, but these did not occur in most of our patients. It should be noted that B symptoms only occur in 10% of thyroid lymphomas.<sup>1,2</sup>

Diagnosis of certainty usually requires a surgical biopsy, because most examinations have a low sensitivity for diagnosis of lymphoma.<sup>2</sup> However, although surgical biopsy appears to be the gold standard for diagnosis, fine needle aspiration (FNA) should be the initial test of choice. Conventional cytological examination will probably be insufficient, and should therefore be supplemented with immunohistochemistry, molecular techniques, flow cytometry, and detection

<sup>☆</sup> Please cite this article as: Ríos A, Rodríguez JM, Febrero B, Parrilla P. Linfoma primario del tiroides. *Endocrinol Nutr.* 2014;61:497–499.