American Journal of Hypertension Research, 2013, Vol. 1, No. 1, 13-16
Available online at http://pubs.sciepub.com/ajhr/1/1/3

DOI:10.12691/ajhr-1-1-3

Refractory Hypokalemia, Endocrine Hypertension, and the Role of Primary Hyperaldosteronism: A Case Report

Luljeta Çakërri[1], Elira Myrtaj[2], Florian Toti[2], Gentian Vyshka[1,*]

[1]Biomedical and Experimental Department, Faculty of Medicine, University of Medicine in Tirana, Albania
[2]Service of Endocrinology, University Hospital Center "Mother Theresa", Tirana, Albania
*Corresponding author: gvyshka@yahoo.com

Received September 27, 2013; Revised October 21, 2013; Accepted October 22, 2013

Abstract The case of an Albanian patient is reported, with bilateral adrenal hyperplasia diagnosed after a condition of persistent hypokalemia, in spite of continuous and adequate potassium administration. The patient, a Caucasian male of middle age, was suffering from diabetes, hypertension and angina pectoris, and admitted in a University Hospital Facility due to an unexplained confusional state. U waves were registered in the electrocardiography, and abdominal imaging was suggestive of adrenal hyperplasia. His plasmatic levels of potassium started to improve and became normal only after a therapy with potassium sparing diuretic, in our case with spironolactone. The administration of this type of drug has been widely advocated even for diagnostic purposes, when an unexplained condition of hypokalemia persists. Our case suggests that in lack of obvious causes of hypokalemia, suspicions on the existence of a primary hyperaldosteronism should be formulated, and investigations or therapeutic interventions have to be purposefully shaped.

Keywords: *primary hyperaldosteronism, hypokalemia, spironolactone, adrenal gland hyperplasia*

Cite This Article: Luljeta Çakërri, Elira Myrtaj, Florian Toti, and Gentian Vyshka, "Refractory Hypokalemia, Endocrine Hypertension, and the Role of Primary Hyperaldosteronism: A Case Report." *American Journal of Hypertension Research* 1, no. 1 (2013): 13-16. doi: 10.12691/ajhr-1-1-3.

1. Introduction

Primary hyperaldosteronism (PH) was initially described from Conn in the early 1950s. His are three papers, published during the same year of 1955, when to the medical community was reported a new clinical syndrome [1,2,3]. The most frequent findings of the PH are arterial hypertension, hypokalemia, metabolic alkalosis, suppression of plasma renin activity and high plasmatic levels of aldosterone; probably much of the long-term changes in patients with refractory hypertension might to some extent be related to pro-inflammatory and pro-fibrotic effects of aldosterone itself, or through angiotensin mediation [4]. Aldosterone is recently more and more implied as a cause of hypertension, thus considering suspicions toward an adrenal dysfunction not merely as a search for an orphan disorder, whose prevalence should be higher than it was believed some decades before [5].

PH in most of cases is related to a bilateral adrenal hyperplasia, the so-called idiopathic hyperaldosteronism (IHA); more rarely the condition is caused from an aldosterone-producing adenoma (aldosteronoma). There are divergent opinions regarding the relative frequencies of both over-mentioned diagnosis toward their etiological role in the appearance of PH, with some surgeons considering aldosteronomas to account for approximately 60% of all cases with PH [6]. Authors dealing with the endocrine hypertension emphasize the fact that arterial hypertensive values might persist even after the removal, when feasible, of an adrenal adenoma; thus the need for a better understanding and classification of PH subtypes is obvious [7,8]. However, when adrenal glands are implied, the disorder generally seems to involve those bilaterally; a unilateral adrenal hyperplasia seems uncommon, probably due to the diagnostic difficulty it presents [9].

2. Case Report

A Caucasian male aged 68 years old, hypertensive since ten years, was emergently transferred from a district facility into the University Hospital Center of Tirana, due to a confusional state of unclear origin.

Under treatment for a diversity of internal disorders, he was receiving Insulin Rapid 14 IU at morning and at noon, as well as Insulin NPH (intermediate-acting) 14 IU in the evening, for relatively unstable diabetes. In spite of such a continuous treatment abnormally high values of glycemia (522 mg/dl) were registered upon admission. Mildly obese (BMI index 33 kg per meter square) he was as well receiving Nitrosorbide for chest angina (10 milligrams thrice daily) as well as a beta-blocker (Carvedilol in a daily dosage 6.25 milligram). Hypertension was satisfactorily controlled through an angiotensin receptor blocker (Losartan 50 milligrams half a tablet twice daily), with a systolic blood pressure (BP) value 145 mmHg and a diastolic BP value of 90 mmHg upon admission. BP values remained without any substantial changes throughout the hospitalization period.

A neurological consultancy and imaging (head CT) ruled out CNS involvement; a thorough blood biochemical analysis suggested a hypokalemia and a severe metabolic alkalosis (values summarized in Table 1 and Table 2). Meanwhile, although a normal sinus heart rhythm was registered, electrocardiography showed consistently U-waves in precordial lead derivations (Figure 1).

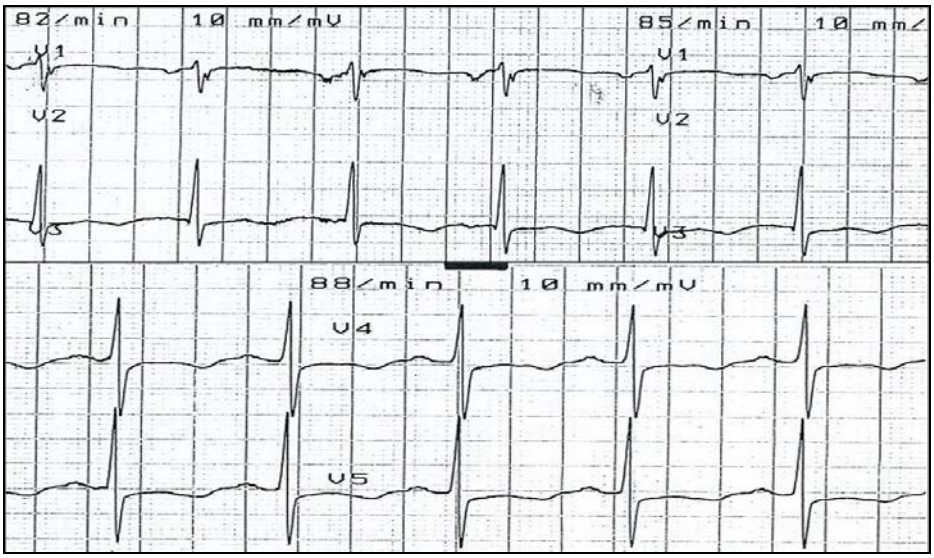

Figure 1. U Waves in precordial ECG leads

Table 1. Blood electrolytes

Plasmatic level of sodium and potassium	Upon admission	6th day (starting treatment with Spironolactone)	7th day (second day of treatment with Spironolactone)	8th day	15th day
Na^+ (mEq/l) [Normal range: 135-147 mEq/L]	146	139	133	129	152
K+ (mEq/l) [Normal range: 3.5-5.1 mEq/L]	2.1	2.0	2.6	2.6	4.8

Table 2. Blood bicarbonates, gas analysis and pH values

Parameter	3rd day after admission	5th day	6th day (starting treatment with Spironolactone)	7th day	8th day	15th day
Arterial pH [Normal range: 7.34-7.45]	7.629	7.640	7.630	7.607	7.544	7.520
Arterial pCO2 (mmHg) [Normal range: 33-45 mmHg]	59.1	49.6	51.5	45.6	46.2	44.3
Arterial pO2 (mmHg) [Normal range: 75-100 mmHg]	49	55	54	61	70	74
HCO3- levels (mmol/L) [Normal range: 18-23 mmol/L]	62.8	54	54.9	46.1	40.3	40.1

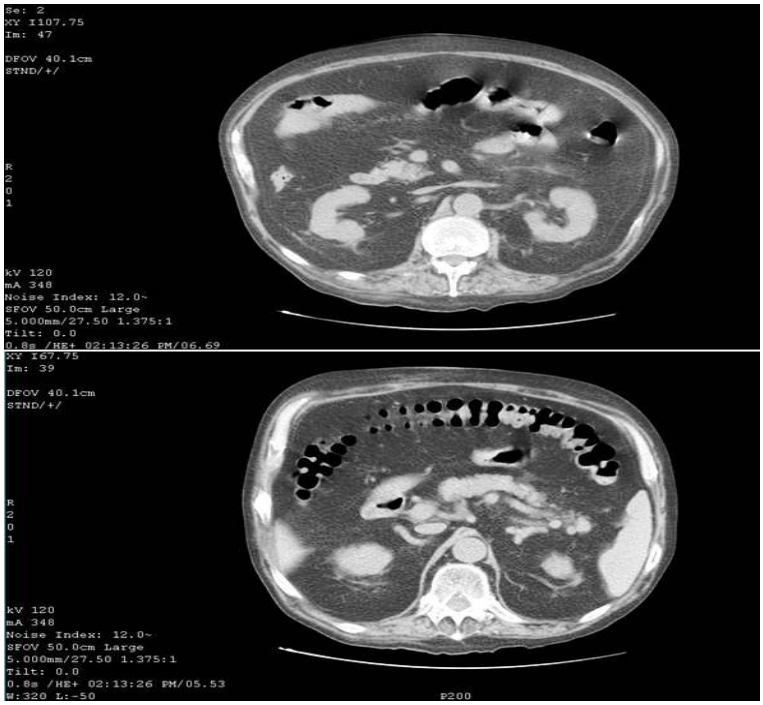

Figure 2. Upper part, abdominal CT showing normal renal structure. **Lower part,** abdominal CT images acquired rostrally to the previous slice. Bilateral hyperplasia of adrenal glands was suggested, with a slight predominance of the right side

Table 3. Plasmatic levels of potassium and electrolyte quantities administered before and after the initiation of the therapy with Spironolactone

	1st day	2nd day	3rd day	4th day	5th day	6th day (starting treatment with Spironolactone)	7th day	8th day	15th day
Quantity of administered potassium (mEq)	60	280	320	120	160	160	160	40	---
Plasmatic levels of potassium (mEq/L)	2.1	2.0	1.9	2.6	2.3	2.0	2.6	2.6	4.8

Since hypokalemia was unresponsive to the treatment with intravenous potassium, the patient was put under combined treatment with a potassium-sparing diuretic (Spironolactone). The treatment with Spironolactone started the 6th day of hospitalization, after that potassium values remained persistently low. At the same time, the clinical suspicion of a hyperaldosteronism was raised, after the first days of ineffective treatment with potassium, and the persistence of a clinically severe confusion.

The suspicion of PH was supported from the laboratory data, with the patient showing a plasma aldosterone level in supine position of 320 pmol/L (normal range: 55-250 pmol/L); meanwhile he was having a normal to a slightly restricted diet sodium.

A computerized tomography of adrenal glands resulted in bilateral hyperplasia of the structure, without concomitant renal involvement (Figure 2).

Potassium therapy was stopped the fifteenth day, after the patient showed for three consecutive days normal plasmatic levels of electrolytes. The patient was discharged on the eighteenth day in a stable condition, with Spironolactone thereafter being part of its normal therapy, in a pro daily dose of 100 milligrams.

3. Discussion

PH represents the most frequent cause of secondary hypertension, although other causes have to be taken into account, such as pheochromocytoma and stenosis of renal artery [10]. In middle-aged adults aldosteronism might prevail, and the recommended initial diagnostic test is an aldosterone/ renin ratio [10]. If several decades it was rarely considered, aldosteronism (which for several authors is considered as equivalent term to PH) now is on the 'top of the list' regarding secondary hypertension related to endocrine pathologies [11]. Hypokalemia, nevertheless, should orientate clinicians toward a probable PH; albeit a considerable percentage of patients with aldosteronism initially present potassium levels within norm, or at least variable [11]. Unprovoked hypokalemia with renin-producing tumors, PH or renin-mediated renovascular hypertension should normally be a part of differential diagnosis [12].

There are specific tests confirming the diagnosis of PH, but those tests optimally should be performed when the patients is abstaining from antihypertensive drugs. Aldosterone-Renin-Ratio (ARR) is a useful screening option, but the saline infusion test and the adrenal vein sampling have been proposed; the latter mainly when there is a suspicion of a unilateral abnormally high aldosterone production [13].

We based our diagnosis on the presence of refractory hypokalemia, on the plasma aldosterone level (patient in supine position), and on the abdominal CT imaging; on the other hand Spironolactone itself has been initially suggested as a therapeutic proof, and its clinical efficacy might lead further therapeutic and diagnostic steps [14].

Our patient was since years under insulin therapy and the dosage of the latter was sustained (14 UI thrice daily) thus there were no reasons to suggest any connection between this therapy with the refractory hypokalemia. However, a meticulous differential diagnosis needs to be done regarding the metabolic alkalosis, whose presence might be related to panoply of other reasons and pathological processes [15,16]. In the table below we summarize the main pathologies that might lead to metabolic alkalosis.

Table 4. Major causes of metabolic alkalosis (*adapted from 15, 16, and 17*)

Related to gastrointestinal pathologies or processes	Vomiting Villous adenoma of colon Congenital chloride-losing diarrhea Gastric suction Milk-alkali syndrome Infectious diarrhea Enteric fistula
Related to urinary pathologies or processes	Impaired chloride associated sodium transport: Gitelman's syndrome, Bartter's syndrome Renovascular hypertension
Mineralocorticoid excess	Primary hyperaldosteronism Adrenal hyperplasia Renin secreting tumors Cushing's syndrome Liddle's syndrome 17α-hydroxylase deficiency 11β –hydroxysteroid dehydrogenase deficiency
Drug-induced	Carbenicillin therapy Rapid bicarbonate or citrate administration (in blood) in renal failure Diuretics Fludrocortisone Aminoglycosides High dose glucocorticoids Ingestion of licorice or derivatives
Situations related to internal or tumoral pathologies	Heart failure Hypoalbuminemia Calcium carbonate release from bone in malignancy Tumors (for example, VIPoma) Cancer therapy (for example, radiation enteropathy)

The diagnosis of adrenal gland hyperplasia or of an incidental adrenal adenoma remains still controversial; CT imaging might offer information, but its sensitivity as a diagnostic option is questionable; moreover incidental adenomas might be non-secretory thus functionally non important [18].

Although a relatively old medication, spironolactone has been accused for several side effects, but has not yet been considered obsolete [19]. Other aldosterone antagonists have been uncovered, with eplerenone presumably showing less side effects, and being the drug of choice where available [20]. In fact, spironolactone has an affinity for androgen and estrogen receptors, causing hereby gynecomastia in men and menstrual disorders in women [21].

The list of probable causes leading to hypokalemia is a long one, but three major factors have been accused: a- reduced oral intake; b- real loss of potassium (through gastrointestinal or renal routes) and c- intracellular shift of potassium (due to rare disorders such as familial hypokalemic paralysis or alkalemia) [22]. To our opinion, when there is lack of a clear loss of potassium due to clinically evident disorders, or related to specific drugs (loop diuretics in first order) a therapeutic proof of spironolactone seems logical [23]. This will be a helpful diagnostic step, in view of persistent low plasmatic levels of potassium even after adequate administration, when the suspicion of aldosteronism will be raised, and appropriate diagnostic tests or imaging will follow to confirm such a suspicion.

References

[1] Conn JW. Primary aldosteronism. J Lab Clin Med. 1955 Apr; 45(4):661-4.

[2] Conn JW. Presidential address. I. Painting background. II. Primary aldosteronism, a new clinical syndrome. J Lab Clin Med. 1955 Jan; 45(1):3-17.

[3] Conn JW, Louis LH. Primary aldosteronism: a new clinical entity. Trans Assoc Am Physicians. 1955; 68:215-31; discussion, 231-3.

[4] Brown NJ. This is not Dr. Conn's aldosterone anymore. Trans Am Clin Climatol Assoc. 2011; 122:229-43.

[5] Foo R, O'Shaughnessy KM, Brown MJ. Hyperaldosteronism: recent concepts, diagnosis, and management. Postgrad Med J. 2001 Oct; 77(912):639-44.

[6] Carter Y, Roy M, Sippel RS, Chen H. Persistent hypertension after adrenalectomy for an aldosterone-producing adenoma: weight as a critical prognostic factor for aldosterone's lasting effect on the cardiac and vascular systems. J Surg Res. 2012 Oct; 177(2):241-7.

[7] Young WF Jr. Endocrine hypertension: then and now. Endocr Pract. 2010 Sep-Oct; 16(5):888-902.

[8] Layden BT, Hahr AJ, Elaraj DM. Primary hyperaldosteronism: challenges in subtype classification. BMC Res Notes. 2012 Oct 30; 5:602.

[9] Shigematsu K, Yamaguchi N, Nakagaki T, Sakai H. A case of unilateral adrenal hyperplasia being difficult to distinguish from aldosterone-producing adenoma. Exp Clin Endocrinol Diabetes. 2008; 117(3):124-128.

[10] Viera AJ, Neutze DM. Diagnosis of secondary hypertension: an age-based approach. Am Fam Physician. 2010 Dec 15; 82(12):1471-8.

[11] Sica DA. Endocrine causes of secondary hypertension. J Clin Hypertens (Greenwich). 2008 Jul; 10(7):534-40.

[12] Akpunonu BE, Mulrow PJ, Hoffman EA. Secondary hypertension: evaluation and treatment. Dis Mon. 1996 Oct; 42(10):609-722.

[13] Potthoff SA, Beuschlein F, Vonend O. [Primary hyperaldosteronism--diagnostic and treatment]. [Article in German] Dtsch Med Wochenschr. 2012 Nov; 137(48):2480-4.

[14] North JD, Sims FH, Sayers EG. Primary aldosteronism. The value of spironolactone in diagnosis. Lancet. 1961 Sep 16; 2(7203):618-21.

[15] Bear RA. A clinical approach to the diagnosis of acid-base disorders. Can Fam Physician. 1986 Apr; 32:823-7.

[16] Devendra D, Rowe PA. Unexplained hypokalaemia and metabolic alkalosis. Postgrad Med J. 2001 Oct; 77(912):E4.

[17] Mráz L, Rusavý Z, Zdeněk P, Heidenreichová M, Kozeluhová J, Steinigerová J, Těsínský P. [A vasoactive-intestinal-polypeptide producing tumor (VIPoma) as an uncommon cause of life-threatening hypokalemia]. Vnitr Lek. 1995 Aug; 41(8):535-7.

[18] Orme NM, Hart PA, Mauck KF. 46-year-old man with treatment-resistant hypertension. Mayo Clin Proc. 2010 Oct; 85(10):e70-3.

[19] Delyani JA. Mineralocorticoid receptor antagonists: the evolution of utility and pharmacology. Kidney Int. 2000 Apr; 57(4):1408-11.

[20] Spence JD. Physiologic tailoring of treatment in resistant hypertension. Curr Cardiol Rev. 2010 May; 6(2):119-23.

[21] Jeunemaitre X, Chatellier G, Kreft-Jais C, Charru A, DeVries C, Plouin PF, Corvol P, Menard J. Efficacy and tolerance of spironolactone in essential hypertension. Am J Cardiol. 1987 Oct 1; 60(10):820-5.

[22] Rastegar A, Soleimani M. Hypokalaemia and hyperkalaemia. Postgrad Med J. 2001 Dec; 77 (914):759-64.

[23] Kokot F, Hyla-Klekot L. Drug-induced abnormalities of potassium metabolism. Pol Arch Med Wewn. 2008 Jul-Aug; 118(7-8):431-4.