Primary Aldosteronism with Concurrent Primary Hyperparathyroidism in a Patient with Arrhythmic Disorders

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Abstract

A 25-year-old Caucasian woman was admitted to our department with severe hypokalemia that was associated with hypercalcemia. An endocrinological investigation showed the coexistence of primary hyperparathyroidism (PHPT) and primary aldosteronism (PA), arising from an adenoma of the left cortical adrenal gland. The patient underwent left laparoscopic adrenalectomy, but refused the surgical neck exploration that would be required for parathyroidectomy. The post-operative course was uneventful, and the patient realized a normalization of her potassium serum level and a reduction of her blood pressure values. We herein report the important issues regarding the management of a severe electrolyte imbalance, in view of the reciprocal interaction between aldosterone and parathyroid hormone, and their combined potential for causing cardiovascular damage.

Key words: hyperaldosteronism, hyperparathyroidism, arrhythmic disorders, electrolyte disorders

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Introduction

Primary aldosteronism (PA) is major cause of secondary hypertension, accounting for 5-11% of all hypertensive subjects (1). The metabolic effects of this disease and its association with parathyroid and calcium metabolism have so far been poorly described in the literature. Recently, research group of Rossi GP has hypothesized the existence of a bidirectional link between the adrenocortical glomerulosa zona and parathyroid gland in patient with PA due to adrenal adenoma concurrent with primary hyperparathyroidism [PHPT, (2)]. We herein report the findings of a case of PA with concurrent PHPT showing arrhythmic disorders.

Case Report

A 25-year-old Caucasian woman was admitted to our Emergency Department (ED), with palpitations, abdominal pain and worsening dyspnea. Her medical history included a recent admission to another hospital for acute flaccid paralysis and severe hypokalemia (K⁺ 1.2 mEq/L, normal range: 3.4-5.5 mEq/L) that was complicated by cardiopulmonary arrest due to ventricular fibrillation that was successfully treated with resuscitation. At the time of admission, the patient was taking potassium chloride supplements and β-blockers (bisoprolol). No other metabolic or endocrine disorders were reported at that time. A physical examination was completed with the following results: respiratory rate, 35 breaths/min; heart rate, 160 beats/min; blood pressure, 120/70 mmHg and temperature, 36.7°C. Auscultation of the chest revealed basal crackles on both lungs. An abdominal examination revealed a generalized defensive contraction without any palpable mass and labeled reduction of peristaltic tone.

The laboratory data showed severe hypokalemia (K⁺ 1.8 mEq/L), hypochloremia (95 mEq/L; normal range, 98-105 mEq/L), hypercalcemia (ionized calcium 1.52 mmol/L; nor-
normal range, 1.18-1.33 mmol/L) and metabolic alkalosis (pH, 7.50; pCO₂, 25 mmHg and HCO₃⁻, 35 mmol/L).

The electrocardiogram (EKG) showed an atrial flutter with a 2:1 fixed atrium-ventricular (AV) conduction and a mean ventricular rate of 150 beats/min (Fig. 1a). An X-ray revealed signs of pleural suffusion and basal stasis of the chest. Echocardiography showed an increased left ventricular end diastolic diameter (LVEDD) of 60-mm, a left atrial volume (LA) of 53-mm, an interventricular septum (IVS) wall thickness of 10-mm and a posterior wall (PW) thickness of 10-mm with normal left ventricular performance (EF, 60%). There were no signs of myocardial fibrosis by echocardiography.

The patient was given intravenous potassium chloride, amiodarone (a bolus of 300 mg and a 900 mg infusion in 5% glucose over 24 hours) and unfractionated heparin (8,000 UI). She experienced a quick restoration of her sinus rhythm, a few coupled ventricular polymorph extrasystoles and relevant QT prolongation (QT, 0.64 sec; QTc, 0.76 sec) (Fig. 1b). The patient was then referred to our Department of Internal Medicine and Medical Specialties.

A laboratory analysis confirmed the diagnoses of hypokalemia (2.7 mEq/L), hypercalcemia (total calcium, 11.2 mg/dL; normal range, 8.4-10 mg/dL) and an elevated urinary excretion of potassium (138 mEq/24 h; normal range, 25-125 mEq/24 h), sodium (318 mEq/24 h; normal range, 40-220 mEq/24 h) and calcium (352 mg/24 h, normal range, 50-300 mg/24 h), with a normal creatinine clearance (108 mL/min).

An endocrinological investigation revealed a suppressed plasma renin activity (PRA) (0.21 ng/mL/h; normal range, 0.3-2.7 ng/mL/h), a high plasma aldosterone concentration (PAC) (40.1 ng/dL; normal range 0.75-15 ng/dL) and a high PAC/PRA ratio (190.9 ng/dL: ng/mL/h; normal range, ≤30 ng/dL: ng/mL/h). In order to confirm the diagnosis of primary aldosteronism (PA), a captopril test was performed with a captopril dosage of 50 mg. After 60 minutes, the PAC/PRA ratio was elevated beyond the normal physiological limits. Magnetic resonance imaging (MRI) of the superior abdomen revealed the presence of a 20-mm nodule in the left cortical adrenal gland.

Moreover, the PTH concentration was elevated to 148 pg/mL (normal range, 10-54 pg/mL), suggesting a diagnosis of PHPT. The diagnosis was confirmed by ultrasonography and scintigraphy which revealed the presence of two parathyroid adenomas (left lower and upper) (Fig. 2). On the basis of these results, we concluded that she had PA accompanied with PHPT. The patient received an appropriate level of potassium chloride supplementation, antihypertensive therapy (felodipine) and antagonist aldosterone receptor treatment (spironolactone). She underwent left laparoscopic adrenalectomy, but refused the neck exploration required for parathyroidectomy. A histopathological exam confirmed the presence of an adenocortical adenoma.

A 2-month follow-up after adrenalectomy showed a blood pressure of 130/80 mmHg, a heart rate of 76 beats/min and a normal QT interval of 0.42 seconds (Fig. 1c). Her potassium concentration was 4.5 mEq/L, her sodium level was 138 mEq/L and she displayed normalized results for PRA, PAC and the PAC/PRA ratio as well as urinary aldosterone

Figure 1. a. Atrial flutter with 2:1 conduction. b. Sinus rhythm with couple ventricular extrasystole. c. Sinus rhythm.
excretion. However, the patient remained hypercalcemic (total calcium 11.3 mg/dL; ionized calcium 1.51 mmol/L) and maintained a high plasma PTH level (146 pg/mL). The patient remains well to date, and she has been followed up periodically in our department.

**Discussion**

We herein report the important issues regarding the management of a severe electrolyte imbalance. The development of symptomatic arrhythmia was closely associated with the identification of electrolyte disorders (hypokalemia and hypocalcemia) in a patient with concurrent PA and PHPT. Ventricular arrhythmia in association with PA is an uncommon presentation that has reported previously in the literature. A prolongation of the QT interval due to hypokalemia and an aldosterone excess may result in the development of life-threatening arrhythmias such as ventricular fibrillation (3). Our patient demonstrated that hypercalcemia can simultaneously decrease the ventricular conduction velocity and shorten the effective refractory period. Moreover, aldosterone and the PTH itself can cause a positive result in the stimulation of the heart cells. Potassium is predominantly an intracellular cation as only 2% of the total body potassium can be found in the extracellular space. The homeostatic serum potassium concentration is maintained by the terminal nephron segments of the kidney. Insulin, β-adrenergic agonists, aldosterone and a change in blood pH may all independently affect the serum potassium levels (4).

As many as 10% to 40% of the patients on thiazide diuretics, and almost 50% of patients who are resuscitated following out-of-hospital ventricular fibrillations have low potassium levels (5). In our patient, her severe hypokalemia was due to the presence of an inappropriate adrenal-aldosterone secretion. PA is the most common form of endocrine hypertension, and is commonly caused by the autonomous production of aldosterone by the adrenal cortex. The prevalence of PA increases with the severity of the hypertension and is currently estimated to be around 10% of the referred patients and 4% of those under primary care (1, 6), but it could be as high as 20% in those patients with resistant hypertension (7). The two main causes of PA are aldosterone-producing adenomas (APA) and bilateral adrenal hyperplasia, so-called idiopathic adrenal aldosteronism (IAH). Patients with PA typically present with hypertension, the high plasma aldosterone levels that are typically associated with a low PRA and varying degrees of hypokalemia and metabolic alkalosis.

Potassium plays an important role in maintaining the electrical potential across the cellular membrane, as well as in the depolarization and the repolarization of the myocytes. In particular, hypokalemia can have dramatic effects on the cardiac cell conduction and many lead to observable changes on the EKG. Moreover, as the serum potassium levels decline, the transmembrane potassium gradient decreases. The effect on the cell membrane is an elevation in the resting membrane potential and a prolongation of the action potential (particularly in phase 3 repolarization) and the refractory periods (8). As a result of the increased duration of the activation potential and the refractory period, patients with hyp-
pokalemia are at increased risk for arrhythmias. The prolongation of the QT interval can precipitate a ventricular arrhythmia. It has been reported that patients with hypokalemia are at increased risk of arrhythmias (9). PA patients also display unfavourable cardiovascular profiles, suggesting that aldosterone may play an additional role beyond its well-known hypertensive effects. Extensive experiments using animal models have demonstrated that aldosterone can stimulate an abnormal accumulation of collagene (type I and type II), which can be partially reversed by treatment with spironolactone. In particular, a study by Brilla et al. demonstrated that an aldosterone infusion with a high salt intake induces both cardiac hypertrophy and myocardial interstitial fibrosis (10). In clinical studies, Rossi et al. reported that PA patients exhibit significant changes in the myocardial tissue as compared to essential hypertensive patients, and, secondary to cardiac fibrosis, can serve as an important determinant of myocardial remodeling and impaired tissue stiffness (11). Moreover, in a retrospective study, a twelve-fold increase in the relative risk of atrial flutter or fibrillation was seen in PA patients, as compared to essential hypertensive patients (12). There are at least three possible mechanisms for the development of atrial fibrillation in patients who have been diagnosed with PA but have no evidence of coronary artery disease. These mechanisms include hypertension with consequent left ventricular hypertrophy (LVH), hypokalemia and high circulating levels of aldosterone. In particular, an excess of aldosterone has been shown to induce cardiac fibrosis (13). In the context of PA, cardiac fibrosis is a plausible mechanism for promoting the development of arrhythmias, likely due to the disruption of the hormonal intracardiac conduction system.

The human body has a nearly inexhaustible reservoir of calcium that is stored as hydroxyapatite in the skeletal bone. Calcium is important in several physiological mechanisms, including skeletal muscle contractions, enzymatic reactions and the electrical activity of myocytes and myocardial contractions (14).

The effect of hypercalcemia on the EKG is evidenced by the shortening of the QTc interval, the decrease of ventricular conduction velocity and the decrease of the effective refractory period. The appearance of any clinically significant rhythm disturbances that could associated with hypercalcemia is rare because the elevation of the extracellular calcium level is generally not associated with triggered dysrhythmias. Cardiac conduction abnormalities may occur, especially those that are associated with hypomagnesemia. In fact, it is well known that both supraventricular and ventricular dysrhythmias can be triggered by hypomagnesemia (15). We recently identified high QT dispersions and a lack of a physiological adaptation of the QT length to R-R intervals in patients with PTHT and secondary hypercalcemia (16). These alterations were restored after a successful parathyroidectomy (17).

Our patient was diagnosed with two simultaneous endocrinological diseases: PA and PHPT (18-20). There are several possible explanations for the association of these two rare diseases, including the possibility that the combination was a random finding, that PA induces PHPT or vice versa. Recently, in a relative cohort of patients with unequivocally confirmed PA due to APA, Maniero et al. showed a highly significant 31% increase in the number of cases of PTH (2), thus suggesting that there is a bi-directional functional link between the adrenocortical zona glomerulosa and the parathyroid gland. Moreover, Pilz et al. showed that patients with PA are prone to secondary hyperparathyroidism that can be successfully treated with either MR antagonists or adrenal surgery (20).

In conclusion, in view of the reciprocal interaction between aldosterone and PTH, and the potentially ensuing cardiovascular damage, further studies are needed to evaluate the diagnostic and therapeutic strategies that can address the interaction between these two hormones.

The authors state that they have no Conflict of Interest (COI).

References


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