Primary Aldosteronism Presented with Hypokalemic Paralysis: Two Case Reports

Hipokalemik Paralizi ile Prezente Olan Primer Aldosteronizm: İki Olgu Sunumu

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ABSTRACT Primary aldosteronism may appear with various clinical presentations. Primary aldosteronism presented with hypokalemic paralysis is a very rare condition. Case 1; a 33-year-old male was admitted to the emergency department with the complaint of muscle weakness affecting all four extremities (quadriparesis). The patient had a history of hypertension and despite triple antihypertensive therapy his blood pressure was around 160/100 mmHg in follow-up evaluations. In physical examination, upper and lower ekstremity motor strength was 1/5 and deep tendon reflexes were absent. Case 2; a 39-year-old female were admitted to the hospital with the complaint of muscle weakness and pain, difficulty in stair climbing. She had no history of hypertension. In her physical examination; blood pressure was 150/80 mmHg. There was weakness in muscle strength especially in the lower extremities, and decrease in deep tendon reflexes. Hypokalemia (1.4 and 1.7 mEq/L, respectively) and hyporeninemic hyperaldosteronism were determined in both of the patients' laboratory examination. Adrenal adenoma was detected in the magnetic resonance images of both cases and improvements in hypokalemia and hypertension were observed following laparoscopic adrenalectomy for aldosterone producing adenoma. We believe that primary aldosteronism should be kept in mind in differential diagnoses of patients having muscle weakness, hypertension, and hypokalemia.

Key Words: Hypokalemia; muscle weakness; hyperaldosteronism

ÖZET Primer aldosteronizm birçok klinik durumla prezente olabilir. Hipokalemik paralizi ile prezente olan primer hiperaldosteronizm çok nadir bir durumdur. İlk olgu; 33 yaşında erkek, acil servise dört ekstremitede yaygın kas güçsüzlüğü (quadriparezi) şikâyeti ile başvurdu. Hastanın hipertansiyon öyküsü vardı ve üçlü antihipertansif tedaviye rağmen kan basıncı 160/100 mmHg idi. Fizik muayenede üst ve alt ekstremite motor gücü 1/5 olarak değerlendirildi ve derin tendon refleksleri alınamadı. İkinci olgu; 39 yaşında kadın, kas güçsüzlüğü, merdiven çıkamama ve ağrı şikayeti ile başvurdu. Hipertansiyon öyküsü olmayan hastanın başvurusunda kan basıncı 150/80 mmHg idi. Fizik muayenede özellikle alt ekstremitede daha belirgin olmak üzere dört ekstremitede de motor gücü ve derin tendon reflekslerinde azalma mevcuttu. Her iki olgunun laboratuvar incelemesinde, hipopotasemi (1,4 ve 1,7 mEq/L, sırasıyla) ve hiporeninemik hiperaldosteronizm saptandı. Bunun üzerine çekilen sürrenal manyetik rezonans görüntülemede her iki olguda da adrenal adenoma tespit edildi ve aldosteron üreten adenoma nedeniyle yapılan laparoskopik adrenalektomi sonrası hipopotasemi ve hipertansiyonun düzeldiği görüldü. Bu iki olgu ışığında biz, kas güçsüzlüğü, hipertansiyon ve hipopotasemi saptananlarda, primer aldosteronizmin ayırıcı tanıda akılda bulundurulması gerektiğini düşünmekteyiz.

Anahtar Kelimeler: Hipokalemi; kas güçsüzlüğü; hiperaldosteronizm

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Aldosterone is the principal mineralocorticoid in human. It's classical functions include regulation of extracellular volume and potassium homeostasis through its effects on the renal distal convoluted

tubule. Hyperaldosteronism can result from autonomous secretion of aldosterone from one or both adrenal glands, which is referred to as primary aldosteronism (PA). Primary aldosteronism is a common cause of secondary hypertension. Resistant hypertension and hypokalemia with suppressed plasma renin activity (PRA) and increased plasma aldosterone concentration (PAC) are observed classically.[1] Additionally, normokalemia is observed more frequently than hypokalemia.[2,3] Hypokalemia is a chronic condition in PA and symptoms are mostly tolerated by the patients. Hypokalemia rarely cause muscle weakness, paresthesia, and tetany. Rhabdomyolysis, rarely quadriplegia, and hypokalemic periodic paralysis have been reported in severe hypokalemia.[4-10] Here we present two cases with PA accompanying with hypokalemic periodic paralysis.

CASE REPORTS

CASE 1

A 33-year-old male was admitted to the emergency department with the complaint of muscle weakness affecting all four extremities (quadriparesis). Upon detection of low serum potassium levels, the patient was referred to the neurology clinic with the suspicion of hypokalemic periodic paralysis or Guillain Barré Syndrome. The patient, who had history of intermittent pain and tingling in arms and legs for 3-4 years, had visited the physical therapy outpatient clinic 2 months ago when these complaints increased. No reduce was seen in his complaints with analgesics and the patient was admitted the neurology outpatient clinic due to continuing complaints and additional inability to climb stairs and weakness, where he was given steroid therapy considering polymyositis. But, his complaints were increased with the steroid therapy. Electromyography (EMG) was performed and the diagnosis of polymyositis was excluded. Despite antihypertensive therapy (amlodipin, perindopril and carvedilol) for 8 years, his blood pressure was around 160/100 mmHg in follow-up evaluations. He had no history of trauma, infection, or intoxication. In physical examination, his blood pressure was 140/90 mmHg, pupils were isochoric with normal light reflex, upper and lower extremity motor strength was 1/5, deep tendon reflexes were absent, and sensory examination results were normal. In laboratory examination, serum potassium level was 1.4mEq/L (normal range: 3.5-5.5 mEq/L), creatine phosphokinase (CPK) level was 1465 IU/L (normal range:21-232) IU/L (Table 1). U wave was observed in his electrocardiogram (ECG). Guillain Barré Syndrome was excluded by lumber puncture. After that, patient was transferred to Endocrinology Clinic with the initial diagnosis of PA. The symptoms of the patient were improved after potassium replacement therapy. PA screening tests were done to the patient. PAC was 60 (normal range: 7-30) ng/dL, PRA was 0.6 (normal range: 0.7-3.3) ng/ml/h, and PAC/PRA ratio was 100 (normal range: <20). Saline infusion was done as a confirmation test. The antihypertensive therapy of patient was discontinued prior to the tests and switched to calcium channel blocker. Additionally, the 24 hour

TABLE 1: Biochemical data of our cases and the normal reference ranges.

	Case 1	Case 2	Normal reference range
Potassium	**1.4**	**1.7**	3.5-5.5 mEq/L
Sodium	140	**147**	136-145 mEq//L
Glucose	**155**	**105**	74-106 mg/dL
ALT	**83**	51	7-45 IU/L
AST	**98**	62	13-40 IU/L
CPK	**1465**	**1825**	21-232 IU/L
Calcium	8.8	8.7	8.6-10 mg/dL
Magnesium	1.8	2.0	1.3-2.7 mg/dL
Phosphorus	**5.5**	5.1	2.4-5.4 mg/dL
Chlorine	102	100	98-107 mEq/dL
Creatinine	**1.4**	**1.3**	0.2-1.3 mg/dL
BUN	**40**	**41**	6-20 mg/dL
Urine sodium	104	88	20-110 mmol/L
Urine potassium	59.5	55	12-62 mmol/L
Arterial blood gases			
pH	**7.45**	**7.48**	7.35-7.45
HCO_3	**26.6**	**29.6**	22-26 mmol/L
pCO_2	44.2	**45.5**	35-45 mm Hg
pO_2	78.3	82.6	80-100 mmHg

CPK: Creatine phosphokinase; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; LDL: Low-density lipoprotein; BUN: Blood urea nitrogen; HCO_3: Bicarbonate; pCO_2: Partial carbon dioxide pressure; pO_2: Partial oxygen pressure.

urine catecholamine metabolites and 1 mg overnight dexamethasone suppression test (DST) were normal (Table 2). An adrenal adenoma of 12 mm in size was detected in the left adrenal gland in a magnetic resonance imaging (MRI) (Figure 1A). Therefore, aldosterone producing adenoma (APA) was believed to be the cause of PA. The patient's blood pressure was controlled with an aldosterone antagonist and then, a laparoscopic left adrenalectomy was performed. Postoperative pathology was reported as an adrenal cortical adenoma (Figure 1B). All antihypertensive medications were discontinued, as the postoperative serum potassium level and blood pressure of the patient returned to normal values. In the first postoperative year, the patient is on follow-up with continuously normal potassium levels and without a need for any antihypertensive medication.

CASE 2

A 39-year-old female patient was admitted to the physical therapy outpatient clinic with the complaints of fatigue, muscle pain, difficulty in stair climbing, and weakness over the past 6 months. The complaints of the patient had not relieved with analgesics. In laboratory examination; low potassium levels were detected and the patient was referred to our Endocrionology outpatient clinic. She had no history of hypertension. In her physical examination; blood pressure was 150/80 mmHg. There was weakness in muscle strength especially in the lower extremities, and decrease in deep tendon reflexes. In laboratory examination; serum potassium level was 1.7 mEq/L, CPK was 1825 IU/L, and metabolic alkalosis (pH 7.498, bicarbonate 29.6 mEq/L) was determined (Table 1). U wave was observed in her ECG. The patient, having hypertension and hypokalemia, was hospitalized for etiologic investigation. Following potassium replacement therapy, PA screening tests were performed. PAC, PRA, and PAC/PRA ratio were 46 ng/dL, 0.3 ng/mL/h, and 153.3, respectively; and saline infusion test was performed and also this test confirmed diagnosis of PA. The other endocrine test results were within the normal reference ranges (Table 2). MRI performed for subtype analysis detected an adrenal adenoma of 12 mm in size that was confined to the inferior lobule of the left adrenal gland. APA was believed to be the cause of PA. Aldosterone antagonist therapy was started and then a laparoscopic left adrenalectomy was performed. Postoperative pathology was reported as adrenal cortical adenoma. Postoperative potassium and blood pressure follow-ups were within normal limits. At the 6-month follow-up visit, the patient had normal potassium levels and blood pressure.

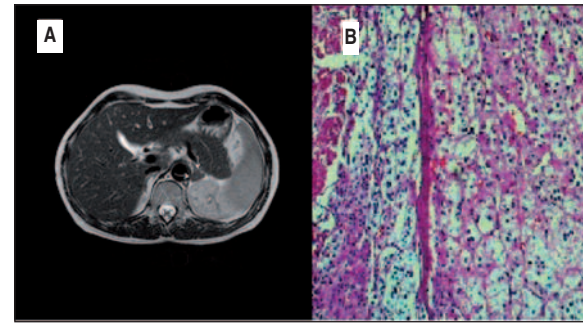

FIGURE 1: MRI revealed a 15x9 mm adenoma in left adrenal **(A)** and histopathological diagnosis was adrenocortical adenoma **(B).**
(See color figure at
http://www.turkiyeklinikleri.com/journal/ic-hastaliklari-dergisi/500/tr-index.html)

TABLE 2: Endocrine test results of our cases and the normal reference ranges.

	Case 1	Case 2	Normal reference range
Basal endocrine tests			
PRA	**0.6**	**0.3**	0.7-3.3 ng/mL/h
PAC	**60**	**46**	7-30 ng/dL
PAC/PRA	**100**	**153.3**	< 20
Normetanephrine (urine)	207	398	88-444 µg/day
Metanephine (urine)	90.90	155	52-341 µg/day
Cortisol	14.5	21.7	5-25 µg/dL
TSH	0.7	1.95	0.4-4 IU/mL
DHEAS	180	75.8	35-560 ug/dL
Intravenous saline infusion test			
PRA	**0.5**	**0.2**	<1 ng/mL/h
PAC	**55.5**	**69**	<5 ng/dL
PAC/PRA	**111**	**345**	<20
1 mg overnight DST			
Cortisol	1.1	0.9	<1.8 µg/dL

PRA: Plasma renin activity; PAC: Plasma aldosterone concentration; TSH: Thyroid stimulating hormone; DHEAS: Dehydroepiandrosterone sulfate; DST: Dexamethasone suppression test.

DISCUSSION

Aldosterone plays an important role in the regulation of blood pressure, sodium, and potassium balance. In PA, serum sodium levels and fluid volume increase, renin/angiotensin II levels are suppressed, and hypertension develops due to increased aldosterone production in the adrenal cortex. In response to sodium retention, potassium and hydrogen ions are excreted. If this condition continues severely and for a long time, hypokalemia and metabolic alkalosis may develop.[11] However, most PA patients are normokalemic. Hypokalemia is usually observed in 9-37% of the patients.[12] Severe hypokalemia and associated hypokalemic paralysis are observed rarely. Hypertension, severe hypokalemia, hypokalemic paralysis, and hyporeninemic hyperaldosteronism were present in both of our cases.

PA cases may appear with various clinical presentations. Proximal muscle weakness, muscle cramps, rhabdomyolysis, and hypokalemic paralysis may develop due to hypokalemia. With increased muscle enzymes, it may be misdiagnosed as polymyositis and Guillain Barré Syndrome as it can lead to quadriparesis.[13,14] The first case presented here, in accordance with the literature, was misdiagnosed as polymyositis due to high CPK levels and clinical symptoms. The patient, who had severe hypokalemia following steroid therapy, had later developed quadriparesis. Differential diagnosis was therefore needed to exclude Guillain Barré Syndrome. Both patients had admitted with hypokalemic periodic paralysis, which is rarely observed among PA cases.[8-10] Acute hypokalemic paralysis is a rare clinical syndrome that is characterized with acute systematic muscle weakness and low serum potassium (<2.5 mEq/L) levels. Severe neuromuscular disorders are associated with the development speed and ratio of hypokalemia. Development of acute and severe potassium deficiency may lead to rhabdomyolysis, and even paralysis. In cases of severe hypokalemia, generalized muscle weakness is observed especially in the lower extremities. Very severe hypokalemia (<2mEq/L) on the other hand, may lead to total paralysis including respiratory, bulbar, and cranial muscles. Physical examination demonstrates reduced or lost deep tendon reflexes in addition to reduced motor strength. Symptoms often regress with potassium replacement. Hypokalemic paralysis develops due to either the changes in the distribution of potassium across cells or the actual low levels of potassium that is associated with renal or extrarenal loss.[15,16] Being more significant in the first case presented here, we observed weak or absent deep tendon reflexes and paralysis in all four extremities due to severe hypokalemia. CPK levels were increased in relation to rhabdomyolysis. Additionally, the symptoms had regressed in both cases with potassium replacement.

PA used to be known as a rare cause of hypertension. Recently, its prevalence increased with the screenings using PAC/PRA ratio and is reported to be responsible for 5-13% of the hypertension cases.[17,18] High prevalence rates of around 17-22% are reported among cases with resistant hypertension.[19] PA should be investigated in cases of moderate or resistant hypertension; hypokalemia that is spontaneous or induced with diuretic therapy associated with hypertension; hypertension that accompanies adrenal incidentaloma; hypertension with positive family history of early-onset hypertension or with history of cerebrovascular events occurred below the age of 40; and among first degree relatives of hypertensive patients.[20] PA was considered in the differential diagnosis of both cases presented here due to observation of resistant hypertension in the first case and newly diagnosed hypertension accompanied by spontaneous hypokalemia in the second case.

The first line screening tests for cases where PA is suspected are PAC, PRA, and PAC/PRA ratio. Potassium levels should be normalized prior to the testing; and can be performed while the patient is on antihypertensive medications. However, ideally, the angiotensin receptor blockers (ARBs), angiotensin converting enzyme (ACE) inhibitors, dihydropyridine calcium channel blockers, and aldosterone antagonists (at least for 2 weeks), and beta-blockers (at least for 6 weeks) should be discontinued prior to the test.[20] We used the PAC and PRA levels and PAC/PRA ratio as the screening

tests for both of our cases. Prior to the testing, we discontinued the antihypertensive therapy of the first case; the second case was not on antihypertensive medication. Additionally, hypokalemia was normalized prior to the test. Values of PAC >15 ng/dL, PRA <1 ng/mL/h, PAC/PRA >20 indicate that the screening result is positive, at which point the confirmation test should be administered for PA. Oral sodium loading or saline infusion tests are the most commonly used confirmation tests. Neither one of the tests is superior to the other. In both of our cases, PAC was high, PRA was low, and PAC/PRA ratio was >20. Saline infusion test was used for confirmation since it is easier to apply. Computerized tomography (CT), MRI, or adrenal venous sampling can be used for subtype analysis.[20,21] We used MRI for subtype analyses. Adrenal venous sampling is not recommended in cases under the age of 40, when the adrenal adenoma is larger than 1 cm in size, and in case of normal contralateral glands.[22] Therefore, adrenal venous sampling was not performed in our cases.

Aldosterone producing adenoma is the cause of about 35% of the primary aldosteronism cases. Size of the adenoma is often <2 cm, hypokalemia is more frequent and severe, resistant hypertension is more frequent, the patients are mostly <40 years of age, and PAC is higher.[21] Our cases had adrenal adenomas < 2 cm in MRI, severe hypokalemia, and high PAC. The first case additionally had resistant hypertension. Therefore, the diagnoses of both cases were evaluated as APA.

Adrenalectomy is the first treatment of choice in treating APA treatment. Symptoms associated with hypertension and hypokalemia regress following surgery. If it is not possible to operate, aldosterone antagonist treatment may be an alternative.[11] Postoperative histopathology was adrenocortical adenoma in both of our cases and the symptoms of both patients were observed to regress with adrenalectomy.

Various clinical presentations are seen in cases with PA. Severe hypokalemia and associated hypokalemic paralysis are rare conditions. We believe that the potassium level of all patients that have fatigue, muscle weakness, and hypertension should be checked and those with low potassium levels should be evaluated for PA.

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