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Hypokalemic rhabdomyolysis: a rare manifestation of primary aldosteronism

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Abstract. – Rhabdomyolysis is a rare presentation of hypokalemia, although muscle weakness is a well-known manifestation of hypokalemia. Primary aldosteronism is characterized by hypertension, suppressed plasma renin activity, increased aldosterone excretion and hypokalemia with metabolic alkalosis. Rhabdomyolysis is not common in primary aldosteronism.

We present here a 40-year-old woman presenting with rhabdomyolysis accompanied by severe hypokalemia as heralding symptom of primary aldosteronism.

Key Words:
Hypokalemia, Rhabdomyolysis, Primary aldosteronism.

Introduction

Primary aldosteronism (PA) was initially considered a rare disease affecting 1% of hypertensive patients. Studies published in the last years revealed that PA is the most frequent cause of secondary arterial hypertension[1]. The main causes of PA included aldosterone producing adenoma (APA), unilateral and bilateral adrenal cortex hyperplasia (IHA), the familial types of the disease and aldosterone secreting adrenal carcinoma[2,3]. APA and unilateral adrenal hyperplasia (UAH) are treated by adrenalectomy, whereas IHA is treated with aldosterone receptor antagonists[4].

Patients with PA typically present hypertension, and the uncontrolled synthesis of aldosterone leads to increased sodium reabsorption, kaliuresis, varying degrees of hypokalemia and metabolic alkalosis. The hypokalemia is usually mild[5]. Nevertheless it could become extremely severe and even life threatening. In particular serious complication of hypokalemia is the rhabdomyolysis[6] which may be the first manifestation of the PA. At today few cases have been reported in the English literature[7-26].

Here, we present a new case of PA presenting with rhabdomyolysis due to severe hypokalemia.

Case Report

A 40-year-old woman was referred to our Hospital with severe myalgia involving legs, stiffness and muscle weakness of the upper arms, lasting 4 days. She had a previous history of arterial hypertension diagnosed two years previously and treated with irbesartan plus hydrochlorothiazide. The family history was negative for PA and history of hypokalemic disorder. She did not take liquorice and herbs.

At the Emergency Department, laboratory findings showed severe hypokalemia (K^+ 1.64 mEq/L; normal range 3.4-5.5 mEq/L), metabolic alkalosis (pH 7.58, pCO_2 54 mmHg, HCO_3^- 44.3 mmol/L), increase of creatine phosphokinase (CPK) 12.085 U/L (normal range 90-140 U/L) and myoglobinemia 1714 ng/ml (normal range: 25-58 ng/ml). Based on these data and clinical picture hypokalemic rhabdomyolysis was diagnosed. Fluid intravenous (IV) hydration and IV potassium supplementation were administered, and the patient was referred to Department of Clinical Medicine, Nephrology and Dialysis. At admission, her physical examination was unremarkable, apart from extreme muscular weakness, especially of the arms and the legs, rendering elevation above the shoulder level almost impossible. No edema or rash was detected. Blood pressure was 130/80 mmHg. Electrocardiogram revealed flattered T waves and prolongation of QT interval (QTc 597

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msec). The chest x-ray was normal, and 2-dimensional Doppler echocardiogram revealed a mitral prolapse.

Laboratory findings confirmed severe hypokalemia (1.66 mEq/L), extreme elevation of the serum CPK level (9122 U/L), high serum myoglobin level (911 ng/ml) and metabolic alkalosis (Table I). The patient was treated with IV administration of potassium rich solutions followed by reduction of hypokalemia and reversal

Table I. Laboratory data at admission and follow-up.

Variables	At admission	3 weeks during recovery	At discharge	6 months after recovery
Blood chemistry				
WBC ($\times 10^3/\mu L$)	6.4	6.5	4.98	4.72
RBC ($\times 10^3/\mu L$)	441	420	413	428
HB (g/dL)	12.7	12.1	11.9	12.1
HCT (%)	36	34.4	33.6	39
PLT ($\times 10^3/\mu L$)	26.3	25.2	19.6	22.1
BUN (mg/dL)	8	7	6.3	6.4
CREAT (mg/dL)	0.6	0.5	0.9	0.8
GOT (IU/L)	262	178	25	30
GPT (IU/L)	118	114	49	50
LDH (IU/L)	445	426	204	200
γGT (IU/L)	39	30	25	24
T-BIL (mg/dL)	0.48	0.46	0.52	0.48
Na (mEq/L)	142	141	138	139
K (mEq/L)	1.66	2.76	4.2	4.1
Cl (mEq/L)	90	101	102	103
Ca (mg/dL)	9.2	8.5	9.3	9.8
P (mg/dL)	2.3	2.9	3.1	3.5
Glucose (mg/dL)	84	81	74	85
T-chol (mg/dL)	128	-	158	168
TG (mg/dL)	117	-	127	81
HDL-C (mg/dL)	48	-	51	65
CPK (U/L)	9122	5273	124	77
CPK-MB (U/L)	16	10	4.1	0.8
Myoglobin (ng/ml)	911	631	55	14.6
Alb (g/dl)	4	4.2	4.1	4.2
Uric Acid (mg/dL)	1.6	1.8	1.7	2.5
Arterial blood gas analysis				
pH	7.58	7.48	7.42	7.4
pO_2 (mmHg)	61	69	88	92
pCO_2 (mmHg)	52	47	33	32
HCO_3- (mmHg)	48.8	35	21.4	20.4
B.E. (mmHg)	23.7	10.1	2.4	1.1
Urine excretion				
Ca^+ (mg/24h)	242	238	201	—
P^+ (mg/24h)	837	821	805	—
K^+ (mEq/24h)	88	53	35	—
Cl^- (mg/24h)	161	158	140	—
Na^+ (mEq/24h)	190	147	130	—
Mg^+ (mg/24h)	141	138	132	—

Table II. Endocrine tests results.

Hormones	At diagnosis	Follow up with eplerenone treatment	Normal range
Plasma renin activity (PRA) (ng/ml/h)	0.2	0.2	(0.3-2.7)
Plasma aldosterone (PAC) (ng/dl)	28.67	58.8	(3-16)
Plasma cortisol (PC) (µl/dl)	524.9	628.6	(266-720)
Plasma ACTH (pg/ml)	58.8	48.3	(10-90)
PAC/PRA ratio (ng/dl:ng/ml/h)	143	294	(< 30)
Urinary excretion			
Urinary free cortisol (UFC) (nmol/24 h)	233.5	185.9	(38-208)
Urinary aldosterone (UA) (µg/24 h)	39.8	55.2	(2,84-34)

of muscular weakness (Table I). The combination of hypokalemia, hyperkaluria, metabolic alkalosis with hypertension raised the suspicion of inappropriate secretion of mineralcorticoids, and, we performed hormonal analysis.

Plasma renin activity (PRA) was suppressed (0.20 ng/ml/h) with an increase of plasma (PAC) and urine aldosterone (UA) concentrations (28.67 ng/dl and 39.8 ng/24h, respectively), with a high PAC/PRA ratio (143 ng/dl:ng/ml/h) (Table II).

Suspecting an APA, we conducted further evaluation. Abdominal magnetic resonance (MR) showed multiple nodules in the bilaterally adrenal glands (Figure 1A). Subsequently, adrenal venous sampling (AVS) was performed (Figure 1B). Proper placement of the catheter tip was confirmed using a small amount of contrast medium. The PAC levels in the left and the right adrenal veins were 87.35 ng/dl and 100.62 ng/dl, respectively. Based on the plasma cortisol (PC) levels in the left and the right adrenal veins (554 mmol/l and 577.8 nmol/l, respectively), we consider that the catheters had been correctly inserted into the adrenal vein.

All these results suggest no lateralization of PAC from the adrenal glands and excluding the possibility of surgical procedure in this case. The patient was treated with an anti-aldosterone receptors drugs (spironolactone) and oral potassium supplement with restoration of electrolytes balance and good control of blood pressure (130/80 mmHg) (Table I).

Six months after discharge the patient was asymptomatic, and followed in our Specialized

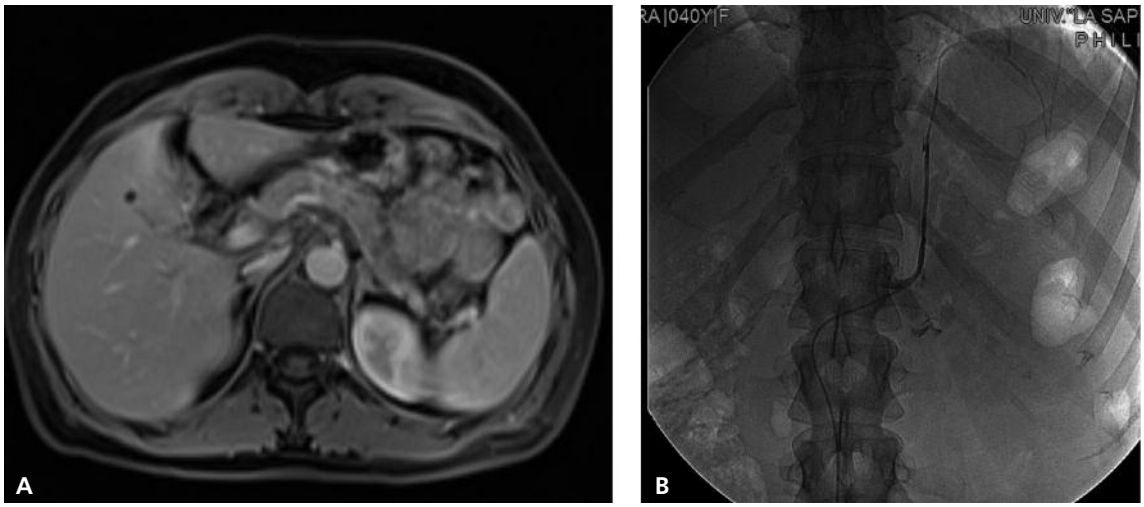

Figure 1. Abdominal magnetic resonance scan ***(A)*** showed a bilateral adrenal nodules; ***(B)*** selective catheterism of adrenal veins for adrenal venous sampling (AVS).

Center of Secondary Hypertension. Physical examination was normal, her average blood pressure was 130/85 mmHg, and 24-h-ambulatory blood pressure monitoring (ABPM) showed mean normal values (125/80 mmHg) with dipping-profile. Electrocardiogram was normal. General laboratory test did not reveal any remarkable abnormalities, with normalization of potassium, CPK and myoglobinemia values (Table I). The patient continued receiving treatment with an anti-aldosterone receptors drug (eplerenone).

Discussion

Rhabdomyolysis is the destruction of a significant amount of striated muscle, leading to disruptions in fluid balance, electrolytes and renal function. Diagnosis is typically made though the timely determination of the serum CPK in a patient with a suggestive history or clinical features[27,28]. The most frequent symptoms of rhabdomyolysis are fatigue, weakness, muscular pain and swelling, although it is possible that some patients are completely asymptomatic[29]. The common and well known causes of rhabdomyolysis include excessive physical exertion trauma, alcoholism, drugs (such as statins), liquorice, certain genetic disorders and electrolytes disorders such as hypokalemia.

The presented patient showed severe hypokalemia of 1.6 mEq/l associated with generalized weakness and rhabdomyolysis. Severe hypokalemia was attributed to PA due to bilateral nodular adrenal glands. At today few complete cases have been reported of PA excess being related to hypokalemic rhabdomyolysis in the English literature[7-26] (Table III).

The severity of neuromuscular disorders, in the rhabdomyolysis, tends to be proportionate to the rate at which hypokalemia develops. Muscle destruction due to rhabdomyolysis causes the release of large amounts of potassium in the circulation. Consequently, where the clinical syndrome of hypokalemia and rhabdomyolysis develops, the absolute concentration of potassium is for below the normal limits. Large amounts of potassium supplementation are necessary associated with generous intravenous hydratation[29]. Frank rhabdomyolysis usually occurs only when serum potassium values are below 2.0 mEq/L[30].

PA is characterized by the autonomous overproduction of aldosterone by the adrenal glands, and only a minority of patients (less than one half) presented with hypokalemia; the majority of patients showing normokalemic hypertension, especially in IHA[1,31].

Potassium is predominantly an intracellular cation, as only 2% of the total body potassium can be found 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 is blood pH may all independently affect the serum potassium levels[32].

Severe hypokalemia might play an important role in muscle damage, secondary to: (1) contraction of capillaries with reduction muscle blood supply and resulting in lysing muscle cells; (2) suppression of synthesis and storage of glycogen, and (3) deranged ion transport across the cell membrane[33,34].

Conclusions

We report an unusual case of PA due to multiple bilateral nodules, presenting with rhabdomyolysis secondary to severe hypokalemia and not associated with the devolpment of acute kidney injury. The prompt volume expansion and correction of hypokalemia resolved the rhabdomyolysis. It is possible that metabolic alkalosis associated to hypokalemia may have contribute to the good outcome of kidney function.

This case underline the risk of hypokalemia-induced rhabdomyolysis in patients with PA, in particular when diuretic treatment for hypertension is associated.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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Table III. Clinical and main laboratory characteristics of patients with rhabdomyolysis and primary aldosteronism including the present case.

No.	Age (years)	Sex (m/f)	Anti-HTN drugs	BP at admission (mmHg)	Muscular weakness	Renal failure	K+ (mmol/l)	Na (mmol/L)	Metabolic alkalosis	CK (U/L)	PAC (ng/dL)	ARR (ng/dL: ng/mL/h)	Image investigation	AVS	Subtype	References
1	68	M	HCT	UN	Yes	No	0.6	138	UN	3.250	34.7	UN	UN	UN	UN	Crawhall JC. et al. 1976[20]
2	49	M	HCT	150/100	Yes	Yes	2.5	142	Yes	12.030	81	300	UN	Yes	Adenoma	Dominic JA et al. 1978[16]
3	55	M	Furosemide	UN	Yes	No	1.8	141	Yes	2.000	33.3	UN	UN	UN	Adenoma	Atsumi T. et al. 1979[21]
4	60	M	Metoprolol,	185/100	Yes	UN	1.4	144	UN	36.000	22	0.23	CT	UN	UN	Schady W. et al. 1981[22]
5	32	F	B-blocker, HCT	170/110	Yes	No	2.0	UN	UN	10.000	60	58	CT, Scintigraphy	UN	Adenoma	Mahdyoon H et al. 1990[15]
6	70	M	B-blocker, Calcium channel blocker	UN	Yes	Yes	1.8	138	UN	2.800	117.2	UN	CT	No	Adenoma	Chow CP. et al. 1997[14]
7	30	F	Fosinopril, Calcium channel blocker, HCT, Furosemide	170/100	Yes	No	1.3	146	Yes	1.751	97.1	UN	Ultrasound, CT	UN	Adenoma	Ozgür B et al. 2002[13]
8	44	F	ACEI, Verapamil	160/90	Yes	No	1.2	137	UN	6.133	46	153.3	CT	UN	Adenoma	Ka ifo lu T. et al. 2005[23]
9	36	F	Atenolol, Chlorthalidone	152/108	Yes	Yes	2.2	UN	Yes	2.860	17.4	87	CT	UN	Adenoma	Petidis K. et al. 2007[18]
10	50	F	Amlodipine	180/70	Yes	No	1.95	UN	UN	9.546	62.2	UN	Ultrasound, CT	UN	Nodular hyperplasia	Gonerska -Szadkowska A. et al. 2007[24]
11	28	F	None	174/111	Yes	No	1.8	143	Yes	12.147	19.8	141	CT	UN	Adenoma	Chuang T. et al. 2008[25]
12	42	F	None	166/108	Yes	UN	1.3	138	Yes	21.000	96.6	>241.5	CT	UN	Adenoma	Martínez JJ et al. 2009[10]
13	14	F	None	160/120	No	UN	1.7	145	Yes	3.375	29.5	147.5	CT,MR	UN	Adenoma	Karagüzel G. et al. 2009[9]
14	55	M	Amlodipine, Valsartan, HCT	138/68	Yes	No	1.4	152	Yes	15.760	26.6	266	CT	UN	Adenoma	Goto A. et al. 2009[12]
15	73	M	Amlodipine	140/80	Yes	No	1.6	UN	Yes	7.463	49.8	71.14	CT	UN	Unilateral hyperplasia	Kotsaftis P. et al. 2009[11]
16	49	F	Amlodipine, Valsartan	130/80	Yes	No	1.8	UN	Yes	1.753	64.89	67.7	CT	UN	Bilateral adenomas	Tsai WT. et al. 2012[8]

Table continued

Table III. *(Continued).* Clinical and main laboratory characteristics of patients with rhabdomyolysis and primary aldosteronism including the present case.

No.	Age (years)	Sex (m/f)	Anti-HTN drugs	BP at admission (mmHg)	Muscular weakness	Renal failure	K^+ (mmol/l)	Na (mmol/L)	Metabolic alkalosis	CK (U/L)	PAC (ng/dL)	ARR (ng/dL: ng/mL/h)	Image investigation	AVS	Subtype	References
17	45	F	Nitrendipine, Captopril	143/80	Yes	No	1.38	142	No	4.907	63.93	76.12	CT	UN	Adenoma	Wen Z. et al. 2013[17]
18	44	F	UN	UN	Yes	No	1.98	146	Yes	8.531	44.97	642.43	CT	UN	Adenoma	Wen Z. et al. 2013[17]
19	42	F	Nifedipine, Atenolol, Losartan	160/100	Yes	No	2.0	145	Yes	11.347	22.6	113	CT	UN	Adenoma	Cooray MS. et al. 2013[7]
20	60	M	None	UN	Yes	No	1.7	142	UN	1.522	UN	UN	MR	Yes	Adenoma	Finsterer J et al. 2013[19]
21	38	M	Metoprolol, Felodipine	165/102	Yes	No	2.8	145	No	2.974	13	130	CT	No	Adenoma	Yao B et al. 2015[26]
22	40	F	Irbesartan, HCT	130/80	Yes	No	1.66	142	Yes	9.122	28.67	143	MR	Yes	Bilateral nodular hyperplasia	Present Case

Abbreviations: ACEI = angiotensin-converting enzyme inhibitor; ARR = aldosterone to renin ratio; AVS = adrenal venous sampling; BP = blood pressure; CK = creatine kinase; CT = computed tomography; F = female; HCT = hydrochlorothiazide; HTN = hypertension; M = male; MR = magnetic resonance; UN = unavailable; PAC = plasma aldosterone concentration

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