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CASE REPORT

SEVERE HYPOKALEMIC MYOPATHY WITH VERY HIGH CREATINE KINASE AS THE FIRST MANIFESTATION OF PRIMARY HYPERALDOSTERONISM - AN UNUSUAL PRESENTATION OF A RARE DISORDER

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Abstract

Hypokalemia is one of the most common electrolyte imbalances to be encountered in clinical practice. The kidney is the primary actor that maintains long term potassium homeostasis and regulates serum level around a narrow range of 3.5-5.5mmol/L. There is a long list of common causes for hypokalemia; apart from these, rare diseases should not slip our mind while treating such a case. Regarding clinical features, muscular weakness accounts for a common one; however occasionally, severe hypokalemia can cause myopathy and/or rhabdomyolysis. Here, we present the case of a middle-aged man, who brought up to us with severe muscular weakness owing tohypokalemia; which was later found to be the rare clinical entity of a rare disorder - primary hyperaldosteronism (PH). In this article, we as well focused on the pathophysiological basis ofPH and hypokalemia leading to myopathy.

Key words: *Hypokalemia, Myopathy, Creatine kinase, Primary hyperaldosteronism*

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Introduction

Myopathy is a general term that refers to the diseases that affect the skeletal muscles. It can be categorised into – i) Inherited as congenital, mitochondrial, metabolic or as muscular dystrophies, Or, ii) Acquired as autoimmune, toxic, infectious, critical illness myopathy, hypo/hyperthyroidism, hyperparathyroidism, electrolyte imbalances, Addison's disease, Cushing's syndrome. In addition to these, very rarely primary hyperaldosteronismleading to severe hypokalemia can cause myopathy and/or rhabdomyolysis[1].

The syndromeof primary hyperaldosteronism (PH) resulting from the autonomous hypersecretion of aldosterone produces a few signs or symptoms. PH is a secondary form of hypertension and it is estimated to be 4.6%–16.6% in unselected hypertensive populations and 17%–23% in patients with resistant hypertensiont .The diagnosis is suspected when a hypertensive patient is having either spontaneous hypokalemia or easily provoked hypokalemia, and the age of diagnosis is usually between 20-60 years[2].

Primary hyperaldosteronism may exist in several forms and the most common forms are idiopathic hyperaldosteronism (IHA) (60%–66%) and aldosterone-producing adenoma (APA) (30%–35%). The remaining forms are extremely rare including primary adrenal hyperplasia, familial hyperaldosteronism syndrome type 1 or 2, adrenocortical carcinoma, or ectopic aldosterone productiont.

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Hypokalemia in association with inappropriate kaliuresis, suppressed plasma renin activity (PRA), high plasma aldosterone concentration (PAC) and a highPAC/PRA ratio are the usual findings on initial screening tests that suggestsPH. The diagnosis can be confirmed by demonstrating non-suppressible aldosterone excretion along with normal cortisol excretionu. Radiological imaging (CT/MRI of abdomen) seldom helps to the diagnosis if itis adrenal macroadenoma; but in most cases of microadenoma, imaging appears to be normal.

The choice of therapy is based on distinguishing unilateral from bilateral adrenal disease. With a unilateral adrenal adenoma, surgical removal has an excellent outcome that reverses the hypokalemia and frequently cures the hypertension. In most patients with bilateral adrenal hyperplasia who are treated surgically, however, hypertension persists; thus, the initial treatment in these patientsis preferably pharmacologicu.

Case report:

A 48-year-old male, asthmatic from childhood, known to have essential hypertension for 12 years, and newly diagnosed diabetic patient presented to the emergency department with the complaints of gradually progressive muscular weakness of all four limbs for last 2 months.Thisweakness started like proximal myopathyof upper limbs described as facing difficulty in raising his hands up; later involved all four limbs andprogressed upto a level whenhe couldn't walk without any aid for 4days prior to the admission. He had no history of diarrhea or vomiting, no toxin exposure, that could precipitate the muscular weakness. Also,no known genetic muscular dystrophies run in his family.

His hypertension was not well controlled despite being treated with combination of three anti-hypertensive medications as beta-blocker, ACEi and a thiazide like diuretic. Rather, 8 months back, he had been diagnosed as a case of CKD, based on his persistently raised serum creatinine, reduced eGFR and radiologicalchanges involving his both kidneys.

On admission, his BP was 160/100 mmHg, pulse was 100 bpm, absent pedal edema. Muscle power was 3/5 in all four limbs both proximally and distally. Knee jerks were bilaterally diminished. Planters were flexor, no sensory loss was present. And other neurological and systemic examinations were normal as well.

Investigations on admission:

Serum Level	Na+ (mmol/L)	K+ (mmol/L)	Cl^- (mmol/L)	HCO_3^- (mmol/L)	Mg** (mg/dl)	Ca++ (mg/dl)	Creatinine (mg/dl)
	137	1.50	96	25	2.17	10.43	2.36
Arterial blood gas analysis	pH: 7.48		pCO2: 29.3		HCO3: 21.7 mmol/L		

ECG on admission:

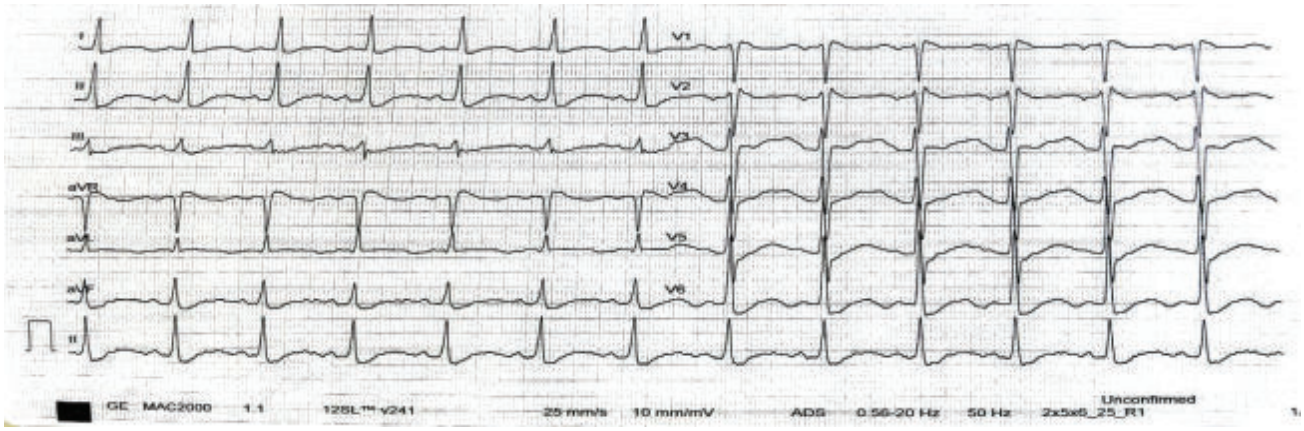

Fig.-1: *ECG showed sinus rhythm, mild ST depression, flat T wave, and presence of U wave as features of severe hypokalemia*

As thiazide like diureticis a potential cause of hypokalemia, Indapamide was kept on hold; and he received I/V potassium supplement at a dose of 100mmol/L/day for 3 consecutive days. Despite all effective measures, his serum potassium level failed to reach the optimum level and raised only up to 2.35 mmol/L.

On 3rd day of admission, he noticed a new symptom of persistent generalized muscle ache, which was moderate to severe in intensity. Increased with movement.As per lab tests, his serum CPK and Aldolase levelcame out markedly elevated.

Muscle enzymes:

	3rd day of admission	4th day of admission
S. CPK (U/L)	12,345	22,314
[Normal range: 55-170]		
S. Aldolase (U/L)		56.30
[Normal range: up to 7.60]		

Urine R/M/E revealed no abnormality. His thyroid function test was normal.

Severe hypokalemic myopathy once in a while can be the first clinical manifestation of primary hyperaldosteronism, keeping that on mind relevant tests were done; that showed - very high plasma aldosterone concentration (PAC) level with suppressedplasma renin activity (PRA), and markedly elevated PAC/PRA ratio.

Plasma Aldosterone Concentration	Plasma Renin Activity	PAC/PRA ratio
[Early morning range: 20-180 pg/ml]	[Range: 4.0-37.52 pg/ml/h]	[Normal ratio: <30]
363.90	6.81	53.44

24 hours Urinary Electrolytes: (Urine volume: 5,500ml/24hrs)

Na+ (mmol/24h)	K+ (mmol/24h)	Cl^- (mmol/24h)
[Normal range: 40-220]	[Normal range: 25-125]	[Normal range: 110-250]
423	80.57	355.30

Urinary potassium excretion >40 mEq/L is significant for renal loss. In his treatment adjustment, he was switched over from I/V to oral potassium supplementation and Kz -sparing diuretic (Spironolactone).Within the next 3 days, he was physically improved, myalgia and muscle weakness were much less severe.

Repeat tests showed improvement too:

Serum Level	Na+ (mmol/L)	K+ (mmol/L)	Cl^- (mmol/L)	HCO_3^- (mmol/L)	Creatinine (mg/dl)	CPK (U/L)
	137	3.49	104	20	1.81	5,725

Repeat ECG before discharge:

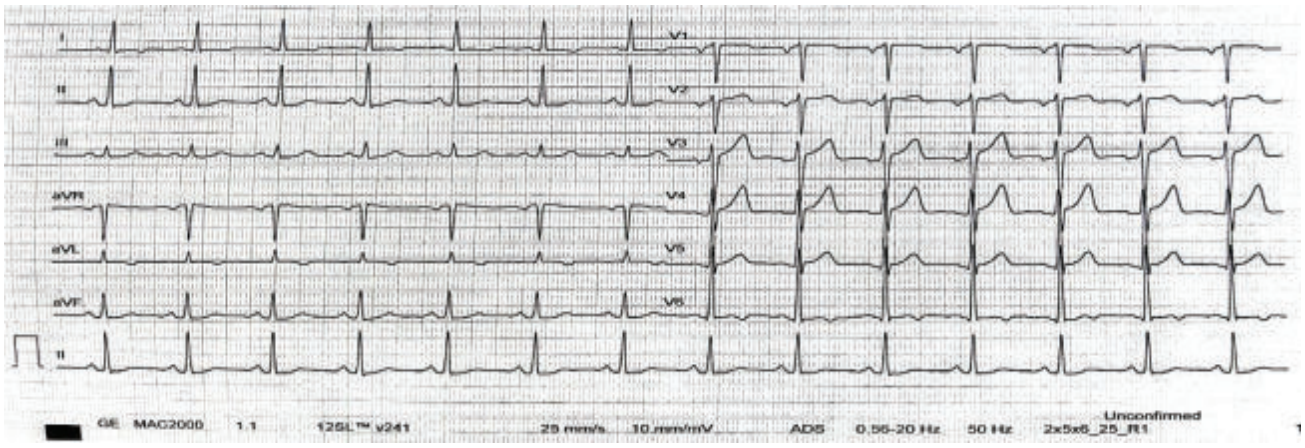

Fig.-2: *Normal T wave, no U wave, no ST depression.*

For further evaluation, imaging studies were done. USG of whole abdomen appeared normal for suprarenal glands.While contrast CT scan of abdomen revealed, a small (18mm × 11mm) homogenous right adrenal mass with 6 HU in pre-contrast scan and 74.0% absolute washout. Left adrenal gland appeared normal.

This patient had been finally diagnosed as a case of primary hyperaldosteronism due to unilateral right adrenal microadenoma with secondary hypertension with new-onset DM and CKD. He was discharged with pharmacological management. And came for his follow up visit after 14 days with no new complaints and his BP also came within normal limit. Follow up tests revealed resolving of hypokalemia associated with normal serum CPK level. Although his PAC remained high and renal loss of potassium persisted at a low level.

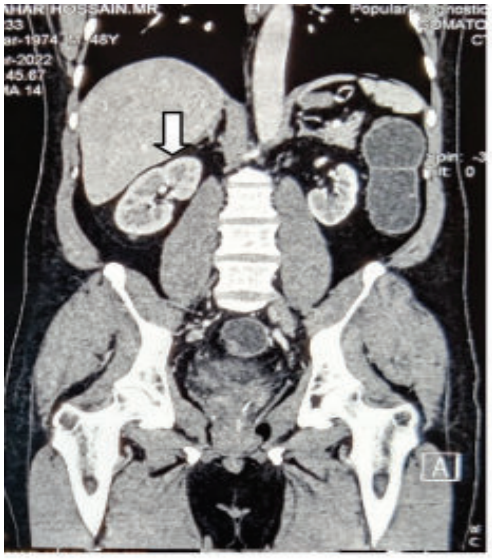

Fig.-3: *Contrast CT scan of abdomen shows homogenous right adrenal mass (arrow)*

Follow up tests after 14 days:

Serum Level	Na+ (mmol/L)	K+ (mmol/L)	Cl^- (mmol/L)	HCO_3^- (mmol/L)	Creatinine (mg/dl)	CPK (U/L)	Morning PAC (pg/ml)
	137	5.4	108	20	2.32	82	274.50

24 hours Urinary Electrolytes (Urine volume: 2,600ml/24hrs)	Na+ (mmol/24h) [Range: 40-220]	K+ (mmol/24h) [Range: 25-125]	Cl^- (mmol/24h) [Range: 110-250]
	158.6	61.88	195

Discussion:

American endocrinologist Jerome W. Conn first labelled Primary hyperaldosteronism (PH) or Conn's disease in 1955 in a 34-year-old woman[2]; which results from excess production of mineralocorticoid hormone - aldosterone by the adrenal cortex. It is normally caused either by unilateral aldosterone-producing adenoma (APA) or by bilateral adrenal hyperplasia. ClassicallyPH presents as -hypokalemia (>50%), arterial hypertension, intermittent paralysis, and metabolic alkalosis. Severe muscle weakness in PHis usually related to coexistent hypokalemia. A review study of PH due to UAH showed, myopathy is not reported as a characteristic manifestation. In the majority of cases presenting with myopathy, paralysis commonly affects the limb muscles. It has been reported that PH associated with hypokalemic paralysis or hypokalemia-induced rhabdomyolysis are more common in Asian populations[1]. In another study on patients with PH, plasma potassium was lower in patients with paralytic myopathy compared to those without (1.8 ± 0.3 mmol/L Kz vs. 2.3 ± 0.4 mmol/L Kz respectively)[2]. Among hypertensive patients with PH, hypokalemia can present many years after the appearance of arterial hypertension, with a median serum potassium level of 2.8 mmol/L. There is also increased risk of hypokalemia-induced-rhabdo-myolysis in patients with PH, particularly when diuretic treatment for hypertension is associated[3].

The cause of hypokalemia-induced-myopathy in PH is obscure, but studies suggestthatin PH there is enhanced muscle Naz -Kz pump activity that results in an increased potassium influx into the cells. The potassium ion is considered to be a major factor mediating the rise of muscle blood flow. Severe hypokalemiaplays an important role in muscle damage, secondary to: (i) Contraction of capillaries with reduction muscle blood supply and resulting in lysing muscle cells; (ii) Suppression of synthesis and storage of glycogen, and (iii) Deranged ion transport

across the cell membrane[3].PH accompanied with hypokalemic myopathymay have elevated CPK directly related to pre-existing hypokalemia[2].

24 h urinary potassium excretion may be found at some degree confusing. Usually, low urinary potassium concentrations <20 mEq/L favour extrarenal fluid losses such as diarrhoea, vomiting. Besides, concentrations >40 mEq/L are considered compatible with urinary losses such as mineralocorticoid excess (i.e: PH), Bartter's syndrome. The concentration of urinary potassium can be lower than expected in PH as a compensatory effect of kidneys,if extrarenal fluid lossesco-existt .

Along with other relevant tests, in most cases, the imaging control (CT/MRI of abdomen or scintigraphy) contributes to the diagnosis and helps in deciding the appropriate mode of treatment. A unilateral adrenal macroadenoma (>1 cm) detected by CT is highly suggestive of APA. On the contrary, many cases of small size APA (microadenomas <1 cm) are undetectable by classical imaging tests for a long period and it demands further investigation with specific tests. The prevalence of APA, IHA and UAH is 4.9%, 1.2% and 0.1% respectively. UAH constitutes a rare cause of PH, which usually mimics an adrenal adenoma and is difficult to diagnose because imaging results are often unreliable[2].

Muscle biopsy for hypokalemic myopathy and/or rhabdomyolysis is not a routine test and is rarely done. Histopathological findings include, under light microscopy - diffuse necrosis and vacuolization of muscle fibres in damaged muscle, and under electron microscopy - complete dissolution of myofilaments with the disappearance of sarcoplasmic reticulum and T-tubules in the necrotic muscle fibres[1].

It is interesting to note that, hypokalemia can be related to glucose intolerance also, though exact mechanism is not wellknown yet - possibly related to defectsin insulin release or insulin sensitivity. ACEi and ARB drugs that results in an increase in serum K^+, has the lowest rates of new-onset diabetes and improve insulin sensitivity. Data from studies over the past 40 years suggest that K^+ replacement minimizes the occurrence of new-onset diabetes observed with thiazide diuretics. With our patient who was being treated with thiazide like diuretic for a long time, it would not be completely wrong to speculate a triggering effect of hypokalemia in newly onset hyperglycaemiat .

The recognition of PH has an important impact on clinical management, since the choice of therapy is different - surgical for adenoma and medical for hyperplasia. The treatment of choice for PH secondary to UAH is unilateral total adrenalectomy, which has a worthy outcome after surgical treatment. Postoperative complication includes hyperkalemia due to secondary hypoaldosteronism; thus, serum potassium levels should be monitored weekly for 4 weeks. Typically, arterial hypertension decreases substantially within 1 to 3 months without antihypertensive treatment[2].

Conclusion:

In our day-to-daypractice, we should not overlook PHwhile treating hypertensive patients with unexplained hypokalemia ensuing recent or episodicmyopathy; as PH is a very much treatable rare disorder.

Conflict of Interest:

The authors stated that there is no conflict of interest in this study.

Abbreviations:

PH: Primary hyperaldoteronism
CK/CPK: Creatine kinase/ Creatine phosphokinase
APA: Aldosterone-producing adenoma
IHA: Idiopathic hyperaldosteronism
PRA: Plasma renin activity
PAC: Plasma aldosterone concentration
BP: Blood pressure
ACEi: Angiotensin-converting enzyme inhibitor
ARB: Angiotensin II receptor blocker
CKD: Chronic kidney disease

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