Triple Electrolyte Disorder (Hypokalemia, Hypophosphatemia and Hypomagnesemia) - A Rare Cause of Rhabdomyolysis!

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Abstract

The spectrum of rhabdomyolysis ranges from an asymptomatic illness with mild elevation in the creatine kinase level to a life-threatening condition associated with extreme elevations in creatine kinase, electrolyte imbalances, acute renal failure and disseminated intravascular coagulation. Acute kidney injury (AKI) occurs in 33-50% of patients with rhabdomyolysis. Muscular trauma is the most common cause of rhabdomyolysis. Less common causes include muscle enzyme deficiencies, electrolyte abnormalities, infectious causes, drugs, toxins and endocrinopathies. Weakness, myalgia and tea-coloured urine are the main clinical manifestations. The most sensitive laboratory finding of muscle injury is an elevated plasma creatine kinase level. The management of patients with rhabdomyolysis includes early vigorous hydration to prevent renal failure. During rhabdomyolysis the injured muscle leaks potassium leading to hyperkalemia. Hyperkalemia also occurs due to renal failure and hence hypokalemia as a cause of rhabdomyolysis is usually missed. We report a rare case of rhabdomyolysis due to combined hypokalemia, hypophosphatemia and hypomagnesemia, who despite high elevations of creatine kinase escaped renal injury.

Keywords — *hypokalemia, hypophosphatemia, muscle pain, creatine kinase, rhabdomyolysis.*

I. INTRODUCTION

Rhabdomyolysis means destruction or disintegration of striated muscle. This syndrome is chcharacterized by muscle breakdown and necrosis resulting in the leakage of the intracellular muscle constituents into the circulation and extracellular fluid [1]. One of the key compounds released is myoglobin, an 18,800-Dalton oxygen carrier. The cause of rhabdomyolysis is usually easily identified; however, in some instances the etiology is elusive. Muscular trauma is the most common cause of rhabdomyolysis. Other causes include muscle enzyme deficiencies, infections, drugs, toxins, endocrinopathies and electrolyte abnormalities like hypocalcemia, hyponatremia, hypokalemia etc [2]. As rhabdomyolysis develops, the injured muscles leak potassium. When combined with renal failure, this can lead to hyperkalemia. Thus, hyperkalemia.is a consequence of rhabdomyolysis, while hypokalemia as a rare cause of rhabdomyolysis, is often overlooked. We report, an unusual case of rhabdomyolysis caused by severe hypokalemia and concomitant hypophosphatemia and hypomagnesemia.

II. CASE REPORT

A 50 years old lady was admitted to our hospital with complaints of generalized body aches, cramping sensation of forearms and calves, followed in a day by weakness in all limbs and difficulty in walking and carrying out daily activities seven days prior to hospital admission. There was no preceding history of trauma, intensive physical exercise, medicinal or illicit drug abuse, fever, seizures, loose stools, nausea, vomiting or decreased urine output. She used to take hadia (local country liquor) on social occasions for 3 years and had consumed about 150 ml to 200 ml of hadia about 7 days before her symptoms started. She was hypertensive but had stopped taking anti hypertensives 6 months prior to the admission without doctor's advice. There was no history of similar weakness in other family members. On admission, she was lean, coherent, afebrile, had mild pallor, no lymphadenopathy, clubbing, cyanosis, icterus, no muscle tenderness, erythema, pulse rate was 82/minute, regular, adequate volume, BP was 130/80 mm Hg and respiratory rate was 18/minute. Examination of central nervous system revealed normal higher mental functions, normal cranial nerves, power of 3/5 in all four limbs, hypotonia, absent deep tendon reflexes in both upper and lower limbs, and downgoing plantars. Sensory system examination was normal. Examination of other systems was normal. Blood parameters on admission showed hemoglobin of 9.9gm/dl, MCV 66.5 fl, PDW 20.7fq, total leucocyte count of 8,800/cu mm with 71% neutrophils, 5% monocytes and 17% lymphocytes, 6% esoinophils, platelet count 2.5 lakhs/cu mm. Her biochemical tests showed blood urea, 30.5 mg/dl, serum creatinine 1.1 mg/dl, serum sodium 137mmol/L, serum potassium 4.1mmol/L, serum calcium 8.0 mg/dl, serum magnesium 1.2 mg/dl, TSH 3.16 µIU/ml, serum amylase 64.6U/L, and serum LDH 3486.4U/L. Her liver function test revealed serum bilirubin 1.5mg/dl, ALT 369.4U/L,

AST 1113.4U/L, ALP 145.3U/L, total proteins 6.47g/dl, serum albumin 3.4g/dl, serum globulin 3.07g/dl, INR 1.1, serum TSH 4.2mIU/L, serum iron 10.3mcg/dl, serum ferritin 45µg/L, 25-hydroxy D3 11.4 ng/ml (normal range:50-70 ng/ml) and PTH 112 pg/ml (normal range:12-88pg/ml). Her RA factor and ANA were negative. Urine examination was positive for occult blood and negative for red blood cells and white blood cells suggesting myoglobinuria. Arterial blood gas (ABG) on admission revealed PH of 7.61, PCO_2 24 mm Hg, PO_2 – 112 mm Hg, HCO_3^- 29 mmol/L, lactate-3.2 mmol/L suggestive of metabolic alkalosis. Her ECG showed sinus rhythm with diffuse ST depression, and prolonged cQT interval (**figure 1**).

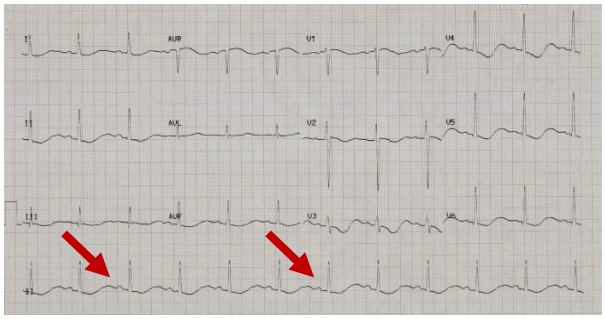

Figure 1: ECG on Admission, Showing Evidence of Hypokalemia (Diffuse ST Depression, QTc Prolongation)

Ultrasound examination of whole abdomen was normal. A provisional diagnosis of electrolyte imbalance (hypokalemia, hypophosphatemia and hypomagnesemia) induced severe rhabdomyolysis, hypovitaminosis D and iron deficiency anaemia was made. She was treated with intravenous fluids - isotonic saline 4litres/day for 3 days, intravenous potassium in form of KCl 120 mmol/day, magnesium sulphate 1g tid intravenously for 3 days in addition to oral supplementation of potassium and calcium. She also received spironolactone 50 mg twice a day and ferrous fumarate 200 mg twice a day. Her serial biochemical investigations from admission to discharge are tabulated in **table 1**. She responded to the above treatment with full recovery of muscle power and was discharged on 6th day against medical advice due to financial constraints.

III. DISCUSSION

Rhabdomyolysis is a potentially life-threatening condition characterized by the breakdown of skeletal muscle and the release of intracellular contents into the circulation. There are varied presentations of rhabdomyolysis which range from an asymptomatic illness with mild elevation in the creatine kinase (CK) level to a life threatening condition associated with extreme elevations in CK, muscle edema, electrolyte imbalances, pigment-induced acute renal failure (ARF) and disseminated intravascular coagulation [2],[4]. The diagnosis of rhabdomyolysis can be easily overlooked.

Hereditary conditions which can set off rhabdomyolysis include; enzyme deficiencies affecting carbohydrate metabolism and mitochondrial lipid metabolism, malignant hyperthermia and the neuroleptic malignant syndrome [2],[3]. Acquired causes of rhabdomyolysis include toxins (alcohol, drugs, other toxins), excessive muscle exercise (military training, epileptic state, asthmatic state, prolonged convulsions acute dystonia), direct muscle injury (crush, freezing), ischemic injury (compression, vascular occlusion), metabolic and endocrine disorders (diabetic ketoacidosis, nonketototic hyperosmolar coma, hypothyroidism, thyrotoxicosis), electrolyte disorders (hypophosphatemia, hyponatremia, hypokalemia), infections (bacterial, viral, plasmodium), heat stroke and inflammatory myopathies (polymyositis, dermatomyositis) [2]. In our case the cause was most probably severe hypokalemia with concomitant hypophosphatemia and hypomagnesemia, as patient did not have any muscle trauma, convulsions, preceding fever, coma and was not on any drugs like statins, fibrates which are known to cause myopathy. She was a social drinker and had consumed alcohol about 2 weeks prior to the development of her symptoms. Acute alcohol-induced rhabdomyolysis can occur after binge drinking or a sustained period of alcohol abuse, and is associated with pain and swelling of muscles, particularly the quadriceps [5], which was not found in her case. The mechanism of hypokalemia induced rhabdomyolysis is not exactly clear. Severe hypokalemia (serum potassium < 2.5mmol/L) can precipitate in muscle injury. It has been postulated that potassium release from contracting skeletal muscle cells into interstitial fluid of the muscle directly dilates adjoining arterioles, and thus, potassium plays a major role in regulating the increase in skeletal muscle blood flow which normally occurs with exercise. Accordingly, if potassium release from potassium - deficient skeletal muscle is impaired during intense exercise, muscle injury or frank necrosis could occur as a consequence of relative ischemia. In addition to hypoperfusion, hypokalemia-induced impairment in muscle glycogen synthesis also may contribute to muscle dysfunction [10]. Thus, a combination of diminished glycogen reserves and impaired oxygen delivery/aerobic energy production may induce energy depletion which then initiates myocyte necrosis [9],[10]. Potassium-depleted animals showed elevated creatine phosphokinase (CPK) activity in serum, suggesting a loss of skeletal muscle integrity.

Hypokalemia is a common clinical problem. It can result from reduced potassium intake, increased translocation from extracellular spaces into the cells (as a transient condition) or, most commonly, from increased gastrointestinal, skin or urinary losses [12]. Increased potassium secretion in the distal nephron may account for such losses, for example,

with the intake of diuretics, liqorice or because of mineralocorticoid excess. The exact cause of hypokalemia could not be ascertained in our patient. There was no overt loss of potassium through GI tract and skin. Clinically, the combination of hypokalemia, hypertension and metabolic alkalosis should make one suspect hyperaldosteronism either primary or secondary. Ultrasound abdomen did not reveal any adrenal lesion. We could not do plasma renin activity (PRA), serum aldosterone, Angiotensin II levels and urinary calcium, potassium and osmolality as these facilities are not available in our hospital. Patient refused CT scan of the abdomen.

Our patient also had hypophosphatemia, which could be a co-existent risk factor for hypokalemia induced rhabdomyolysis. Intracellular inorganic phosphate deficiency possibly limits ATP production, potentially imposing an energy deficient state [11]. The latter then predisposes to intracellular Ca^{2+} loading, ultimately triggering myocyte death. While chronic phosphate depletion can induce myopathy [11], it rarely produces overt rhabdomyolysis in the absence of pre-existent muscle damage, in this case produced by hypokalemia. Her hypophophatemia was probably due to combined nutritional vitamin D deficiency, alkalosis resulting in transcelullar shift of phosphate and impaired renal phosphate reabsorption due to combined hypokalemia and hypomagnesemia. Magnesium deficiency is frequently associated with hypokalemia. Concomitant magnesium deficiency aggravates hypokalemia due to potassium wasting by increasing distal potassium secretion. A decrease in intracellular magnesium, caused by magnesium deficiency, releases the magnesium-mediated inhibition of ROMK channels and increases potassium secretion [12].

Although the causes of rhabdomyolysis are diverse, they ultimately lead to muscle necrosis which regardless of mechanism, results in a cascade of events that leads to leakage of extracellular calcium ions into the intracellular space [2],[4]. The excess of calcium activates cellular proteases causing muscle destruction and fiber necrosis. With muscle injury, large quantities of potassium, phosphate, myoglobin, CK and urate leak into the circulation. Myoglobin in the renal glomerular filtrate can precipitate and cause renal tubular obstruction, leading to renal damage [4],[6],[8],[11].

There is a wide variation in the clinical presentation of rhabdomyolysis. The ‘classic’ triad of symptoms includes muscle pain, weakness and dark urine [6]. The clinical manifestations can be classified as musculo-skeletal signs, general manifestations and complications. The muscle pain, weakness, tenderness may involve specific groups of muscles or may be generalized [7]. The most frequently involved muscle groups are the calves and the lower back. The muscles can be tender and swollen, and there can be skin changes indicating pressure necrosis. However, these classic features are seen in less than 10% of the patients. The condition may also remain asymptomatic or may cause minimal symptoms as in our patient. The general manifestations of rhabdomyolysis include malaise, fever, tachycardia, nausea and vomiting [8]. The complications can be classified as early or late complications. The complications include hyperkalemia, hypocalcemia, elevated liver enzymes, cardiac dysrhythmias and cardiac arrest, while the late complications include ARF and disseminated intravascular coagulation. The main pathophysiologic mechanisms of myoglobinuric ARF are renal vasoconstriction, intraluminal cast formation, and direct heme-protein induced cytotoxicity [11]. Indeed, it has been suggested by some authors that rhabdomyolysis from all causes leads to 5–25% of cases of ARF [11]. Mortality is higher in patients with multiorgan dysfunction syndrome. CK levels are the most sensitive indicator of myocyte injury in rhabdomyolysis [2]. The classic laboratory finding is an elevated serum CK of at least five times the normal value, where the creatinine kinase isoenzyme found predominately in striated muscle (CK-MM) predominates. Normal CK enzyme levels are 45–260 U/l. CK rises in rhabdomyolysis within 12 hours of the onset of muscle injury, peaks in 1–3 days, and declines 3–5 days after the cessation of muscle injury. The peak CK level may be predictive of the development of renal failure and a level of 5000 U/l or greater is related to renal failure [11]. The half-life of CK is 1.5 days and so it remains elevated longer than serum myoglobin levels. Myoglobin is filtered by the kidney and produces pigmenturia which imparts a dark red–brown colour to urine when its urine concentration exceeds 100 mg/dl. Our patient did not complain of change of urinary colour, probably due to lack of myoglobinuria. Myoglobin has a short half-life (2–3 hours) and is rapidly cleared by renal excretion and metabolism to bilirubin [2],[4],[7]. Serum myoglobin levels may return to normal within 6–8 hours. Hence, estimation of myoglobin in serum and urine is useful, only in the early phases of the disease. Thus, many workers do not recommend measurement of myoglobin for diagnosis of rhabdomyolysis [7]. In the present report rhabdomyolysis was diagnosed on the basis of serum CK levels and its serial measurements.

Other muscle markers like carbonic anhydrase III present in skeletal muscles but not in myocardium can be used to detect muscle injury and an increase in its levels is more specific for skeletal muscle injury than are CK levels [2],[4]. Other findings include electrolyte abnormalities like hyperkalemia, hypocalcemia, hyperphosphatemia and hyperuricemia along with elevated levels of other muscle enzymes like lactate dehydrogenase, aldolase,

and aminotransferases [8]. Urinalysis in patients with rhabdomyolysis will reveal the presence of protein, WBCs, brown casts and uric acid crystals. A urine dipstick is a quick way to screen for myoglobinuria, as the reagent on the dipstick that reacts with hemoglobin also reacts with myoglobin. Thus, the presence of occult blood in urine in the absence of RBCs should make one suspect rhabdomyolysis.

The treatment of rhabdomyolysis includes initial stabilization and resuscitation of the patient while concomitantly attempting to preserve renal function. Retrospective analysis demonstrates that early aggressive fluid replacement with saline is beneficial in minimizing the occurrence of renal failure [16]. Other supportive measures include alkalinisation of urine with bicarbonate, mannitol, free-radical scavengers and antioxidants but these are not found to be of any proven benefit in clinical studies. Despite optimal treatment, some patients will develop ARF, often with severe acidosis and hyperkalemia. These patients will require renal replacement therapy to correct fluid, electrolyte and acid–base abnormalities [16]. Daily hemodialysis or continuous hemofiltration may be required. In our case, vigorous hydration probably prevented the patient from going into renal failure, though her CPK levels were enormously high on presentation.

There are few published case reports on hypokalemia induced rhabdomyolysis in the literature [13],[14],[16]. An extensive literature search did not reveal any case report describing combined hypokalemia, hypophosphaemia and hypomagnesemia as a cause of rhabdomyolysis. This article is meant to make the clinicians aware of this rare entity which carries a good prognosis if properly managed. Early diagnosis, along with aggressive treatment, decreases the morbidity and mortality.

IV. CONCLUSION

Rhabdomyolysis is a potentially life-threatening condition that must be suspected in all patients with a history of any condition that can result in damage of skeletal muscle. The classic presentation of rhabdomyolysis includes localizing myalgias, muscle stiffness, cramping, swelling, tenderness, and tea-colored urine. Laboratory tests such as an elevated serum CK level more than 5 times the upper limit of normal and a urine analysis that reveasl pigment casts and is positive for hemoglobin, without red blood cells on microscopic examination, are diagnostic of this condition. Aggressive hydration may prevent the complication of ARF. Mannitol and bicarbonate, although commonly recommended, are of unproven benefit. Electrolyte disorders, especially combined one is a rare cause of rhabdomyolysis and should be borne in mind while evaluating the causes of rhabdomyolysis.

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Table 1: Serial Parameters from Admission to Discharge

Parameters	Normal reference values	Day1	Day 2	Day 3	Day 4	Day 5
Hemoglobin	12 – 15.5	9.9 g/dl		10g /dl		
ALT	7 – 56 U/L	369 U/L	312.4 U/L		281.1 U/L	
AST	10 - 40	1113 4 U/L	1138 U/L		290 U/L	
ALP	45 - 147	145 U/L			145 U/L	
CPK	60 - 190	54,165 U/L	45,185.9U/L	35,048.1	7,819 U/L	5,100 U/L
CKMB	5 - 25	562 U/L	489 U/L			63.4U/L
LDH	140 – 280	2212 U/L	1978 U/L	1515.5 U/l		1125U/L
Serum Calcium	8.5 – 10.2	8.4 mg/dl		8.9 mg/dl		9.4mg/dl
Serum Potassium	3.5 – 5	1.4 mEq/L	2.5	2.8 mEq/L	3.8	4.2 mEq/L
Serum Phosphorus	2.5 – 4.5	2.5 mg/dl		3.6 mmol/L		
Serum Magnesium	1.5 – 2.5	1.2 mEq/L			2.2mEq/L	
Sodium	135 - 145	137mmol/L		134 mmol/L		132mmol/L
Serum Creatinine	0.6 – 1.2	1 mg/d			0.9 mg/dl	

ALT – Alanine transaminase, AST – Aspartate transaminase, ALP – Alkaline phosphatase, CPK – Creatine Kinase, LDH – Lactate dehydrogenase

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