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Causes, Clinical Features and Treatment of Rhabdomyolysis: A Retrospective Analysis

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Abstract: Abstract: Background: RM is a condition of skeletal muscle breakdown which ranges from an asymptomatic illness with elevation in CK level to a life-threatening condition associated with extreme elevation in CK, electrolyte imbalance, AKI, and disseminated intravascular coagulation. In this study, the author analyzed the causes, clinical features, and treatments of RM. Methods: The study collected the records of 48 patients in the First Affiliated Hospital of Jinan University who were diagnosed RM from June 2012 to August 2016. By using SPSS to analyse the data, the study draw a clear chart about the distribution of patients' age, etiologies and clinical symptoms respectively. The statistic analysis also reveals dramatically change on CK and other indicators after treatment. Results: A total of 48 patients were eligible for the study (mean age = 29.7 ± 12.3 years; 36 males and 12 females). Strenuous exercises and infections took the greatest percent amount the causes of RM. Muscular weakness and muscle aches were the two most common symptoms. Among the patients, 42 received intravenous (IV) fluid therapy, and none developed acute kidney injury (AKI). The other six patients accepted CRRT, five of whom had an alleviation of their symptoms. One patient was transferred to another hospital for further treatment since the primary disease was dermatomyositis and it was non-responsive to immunotherapy. Discussion and conclusions: RM is treatable if early diagnosis, comprehensive therapy, active prevention, and the timely elimination of complications are put into effect. Its main symptoms such as muscle aches, muscular weakness, and dark urine may not presented at the same time. In this study, Strenuous exercise is the most common cause of RM and IV fluid therapy is the cornerstone of RM treatment. CRRT should also be considered when life-threatening electrolyte abnormalities emerge as complications of AKI, or when the RM is non-responsive to initial therapy.

Keywords: Rhabdomyolysis, Acute Kidney Injury, Muscle Aches, Muscular Weakness

1. Introduction

RM is a condition of skeletal muscle breakdown where muscle injury causes a release of myoglobin and the muscle enzymes creatine phosphokinase (CPK), lactate dehydrogenase (LDH), and the transaminases [1]. The classic presentation of this condition is muscle aches, weakness, and tea-colored urine. RM can range from an asymptomatic illness with elevation in CK levels to a life-threatening condition associated with extreme elevations in CK, electrolyte imbalances, AKI, and disseminated intravascular coagulation [2]. The common link is the presence of CK levels that are five-times the upper limit of normal levels in circulation (>1000 U/L). RM is commonly associated with myoglobinuria, and if sufficiently severe, this can result in AKI [3]. Since a systematic review of RM is currently lacking

in the literature, The author undertook this study of the causes, clinical features, and treatments of RM.

2. Methods

2.1. Study Design and Data Sources

This is a single-center, retrospective chart review of the patients diagnosed with RM in the First Affiliated Hospital of Jinan University. The author screened patients who had a confirmed diagnosis of RM (creatine kinase [CK] level higher than 1000 U/L; urinary dipstick test for blood is positive in absence of red blood cells; and significantly increased serum or urine myoglobin) in the discharge diagnosis by searching the First Affiliated Hospital of Jinan University electronic medical records system. The search covered all patients from June 2012 to August 2016. In total, 48 of the 205,147 patients who met the criterion were included in the study (three foreign patients were excluded). Clinical data, including patient age, gender, history of allergies, medication history, diet history, associated symptoms and signs (potentially causative), impairment of renal function, initial, peak and discharge serum CPK, LDH, and aspartate and alanine aminotransferase (AST and ALT), was retrieved and abstracted from the electronic medical records system and laboratory databases. Other data, including intravenous fluid therapy and need for CRRT, was from the computerized physician order entry (CPOE). The study was approved by the medical ethics committee of the First Affiliated Hospital of Jinan University, Guangzhou, China.

2.2. Identification of AKI

AKI was defined according to the KDIGO [4] criteria as: an increase in SCR by ≥0.3 mg/dl within 48 hours, or an increase in SCR by ≥1.5 baseline within 7 days, or urine volume ＜0.5 ml/kg/h for 6 hours.

2.3. Statistical Analysis

The data for the categorical variables was summarized as number and percentage, and continuous variables were expressed as mean ± standard deviation. The analysis was performed with the paired samples t-test using SPSS software (version 17.0), with the statistical significance set at P＜0.05.

3. Results

3.1. Patient Demographics

A total of 48 patients met the criteria for being included in the study (mean age = 29.7 ± 12.3 years; 36 males and 12 females; male: female ratio of RM was 3:1). Of the total, 43 patients were 44 years old or younger, 4 patients were 45-59 years old, and 1 patient was over 60 years old. Six patients needed continuous renal replacement therapy (Table 1).

Table 1. *Patient demographics by age category.*

Variables	Subclass	Non-CRRT N=42		CRRT N=6		Total N=48	
		n	%	n	%	n	%
Gender	Male	32	76.19	4	66.67	36	75.00
	Female	10	23.81	2	33.33	12	25.00
Age (year)	Young (≤44)	39	92.86	4	66.67	43	89.58
	Middle-aged (45-59)	2	4.76	2	33.33	4	8.33
	Elderly (≥60)	1	2.38	0	0.00	1	2.08

3.2. Causes

In this study, the most common causes of RM were strenuous exercises and infection, with other causes, in descending order, being: unknown, drug and alcohol abuse, dermatomyositis, and surgery. In this study, RM was due to viral infections in nine patients (six patients had upper respiratory tract infections, and three patients had pneumonia), and to bacterial infections in three patients (one was suppurative tonsillitis and the others were acute pyelonephritis) (Table 2).

Table 2. *Etiologies of rhabdomyolysis.*

Cause	Non-CRRT N=42		CRRT N=6		Total N=48	
	n	%	n	%	n	%
exercise	22	52.38	2	33.33	24	50.00
infection	11	26.19	1	16.6	12	25.00
drug	2	4.76	1	16.6	3	6.25
alcohol abuse	2	4.76	0	0.00	2	4.17
dermatomyositis	1	2.38	1	16.6	2	4.17
surgery	1	2.38	0	0.00	1	2.08
unknown	3	7.14	1	16.6	4	8.33

3.3. Clinical Symptoms

Two of the most common symptoms were muscular weakness and muscle aches. The other symptoms were fever, tea-colored urine, emesis, and oliguria (Table 3).

Table 3. *Clinical symptoms of patients with rhabdomyolysis.*

Symptom	Non-CRRT N=42		CRRT N=6		Total N=48	
	n	%	n	%	n	%
muscular weakness	30	71.43	5	83.33	35	72.92
muscle aches	27	64.28	4	66.67	31	64.58
tea-colored urine	17	40.48	2	33.33	19	39.58
fever	9	21.42	0	0	9	18.75
emesis	5	11.90	0	0	5	10.42
oliguria	0	0.00	2	33.33	2	4.17

3.4. Treatment and Outcome

All of the patients received a large amount of fluid administration once the symptoms were identified. Forty-two of the patients received intravenous fluid therapy alone, which significantly decreased their serum CPK, LDH, AST, and ALT after treatment ($P < 0.05$); none developed AKI (Table 4). Among six patients who received CRRT, two patients also received AKI treatment, two patients had multiple organ failure (MOF) and uremia, and the others were non-responsiveness to intravenous fluid therapy. Five patients had alleviated symptoms, one patient was transferred to another hospital for further treatment, because the primary disease was dermatomyositis and the patient was non-responsive to glucocorticoid and immune globulin therapy (Table 5). During their hospital stay, the patients' serum CK gradually declined to a normal level, after 12 to 15 days, except for patient 2 and patient 6.

Table 4. *Comparison of laboratory results, before and after treatment (42 patients).*

Variables	CK (U/L)	LDH (U/L)	AST (U/L)	ALT (U/L)
Before	5755.0±4912.3	364.3±166.5	123.2±93.4	52.1±31.5
After	307.5±400.4	195.0±66.1	34.5±26.6	29.7±12.0
P-value	0.000	0.000	0.000	0.000

Table 5. *Details of the patients received Continuous renal replacement therapy.*

Case	1	2[a]	3	4	5	6[b]
Cause	unknown	strenuous exercise	strenuous exercise	pneumonia	statins	dermatomyositis
Cardinal symptom	muscular weakness, fever, oliguria	muscular weakness, pain	fuscular weakness, pain	fever, oliguria	muscular weakness, pain	muscular weakness, pain
Cause of received CRRT	AKI	MOF	non-responsive to fluid therapy	AKI	uremia, cannot tolerate fluid	non-responsive to fluid therapy
Peck CK level (U/L)	25156	220100	34696	52855	7311	22533
CK level (posttreatment)	195	6381	109	238	72	6948
Peck Cr level (μmol/L)	916	486	/	406	/	/
Cr level (posttreatment)	106	179	/	101	/	/

Cr creatinine

a Associated with malignant neurinoma, transferred to Cancer hospital after alleviated

b The primary disease was dermatomyositis, CK elevate again after stop CRRT.

4. Discussion

The causes of RM are often complex and variable, and typically classified as physical/non-physical, exertional/non-exertional, and acquired/inherited. In this study, the major causes of RM were reported to be exertion during exercise, trauma, alcohol abuse, and cocaine. The literature is filled with RM case reports due to a range of causes like animal bites (i.e., spider and snake) to drug abuse (i.e., cocaine) [1-3]. The study found the most common cause of RM to be exercise, which is consistent with two other studies that report a close association between RM and exercise[5, 6], especially since exercise is increasingly popular in modern society. Although RM mainly occurs from high-intensity exercise, the disease can also occur from low-intensity exercise. Generally, to avoid triggering RM, people should be encouraged to warm up sufficiently before exercise at any level of intensity [1]. In this study, two patients had RM that resulted from dermatomyositis. Although the cause of RM is usually easily identified, dermatomyositis is a chronic autoimmune condition that only rarely progresses to RM. If inflammatory muscle disease is suspected, patients should undergo a muscle biopsy [7]. In this study, the two patients with dermatomyositis were diagnosed by muscle biopsy.

The classic presentation of RM is muscle aches, weakness, and tea-colored urine, which are highly suggestive of the diagnosis. Nevertheless, the classic triad of symptoms does not present in all patients [2]. Clinical symptoms might also include nonspecific symptoms, such as fever, nausea, dyspepsia, and vomiting [1]. The study found muscular weakness and muscle aches to be two of the most commonly presenting symptoms, and tea-colored urine was reported in only 39.58% of the patients. Nonspecific symptoms included fever, emesis, and oliguria. For patients with mild and sub-clinical RM, clinicians are usually only able to diagnose RM through a careful history and measurements of elevated serum CK.

Comprehensive treatment of RM includes etiological therapy, RM therapy, and the prevention of associated complications. Once the syndrome is identified, the first measure is to remove the underlying source of muscle injury, by stopping a potentially harmful drug, treating the underlying infection, and by using other means [9]. Fluid replacement is the keystone of RM treatment, and in this study, all of the patients received early and aggressive fluid therapy. As the main intervention for preventing and treating AKI, early and aggressive fluid therapy increases the urine flow rate and secretion of nephrotoxic compounds that may lead to AKI [9, 10]. In this study, the symptoms of muscular aches and lack of strength among patients who received early and aggressive fluid therapy, significantly improved, and their CPK level also gradually decreased without an electrolyte imbalance or AKI. No specific recommendations were made for the type of fluid. According to the literature, mannitol, bicarbonate, and saline have been commonly used for urine alkalization, forced diuresis, and to preserve renal function. In this study, the type of IV fluid varied from a combination of 5% dextrose and normal saline (NS), lactated Ringer's solution, and NS with or without bicarbonate. Cervellin and coworkers were cited in a review [11] as recommending maintaining a urine output of 200 ml/h, urine pH above 6.5 and plasma pH below 7.50, using 500 ml of sterile saline solution alternating with 500 ml of 5% glucose solution and the addition of 200-300 mmol sodium bicarbonate. While aggressive fluid resuscitation may preserve cardiac output and renal perfusion pressure, hemodynamic parameters and urine output should be monitored closely to prevent complications such as fluid overload or metabolic acidosis. Furosemide at 40-120 mg per day may also be added if necessary [8, 11]. Remarkably, these therapeutic measures are not useful in the context of severe oliguria or anuria and may lead to interstitial and pulmonary edema [12]. In short, the selection, timing, and doses of IV fluids should be evaluated carefully with the aim of maximizing their efficacy and minimizing the side-effects.

AKI is one of the most severe complications of RM. The incidence of RM-induced AKI was 4% in this study, which is considerably lower than the incidence (13%-50%) reported by Petejova et al. [8]. AKI is well accepted to result from myoglobin deposition in the kidney and it may also be associated with other mechanisms, including hypovolemia and metabolic acidosis. Myoglobin cytotoxicity affects the kidney by lipid peroxidation and the production of reactive oxygen species, and tubular obstruction by myoglobin is also associated with AKI [8, 9, 13]. Renal biopsy revealed heavy deposits of myoglobin in RM-induced AKI individual [14]. Generally, renal replacement therapies are efficient in cases of RM-induced AKI. In this study, six patients with RM received continuous renal replacement therapy; three of the patients had impaired renal function, two patients were resistant to IV fluid therapy and had consistently elevated CK levels, and one patient had uremia. Myoglobin is a small globular protein (molecular weight 17 kDa) that is expressed in the skeletal muscles and heart of vertebrates. It is poorly removed from the circulation using conventional extracorporeal techniques, and intermittent hemodialysis is not recommended [8]. Sorrentino et al. [15] reported a significant clearance of myoglobin by extended dialysis with a high flux dialyzer (effective surface area 1.8 m^2), allowing for the elimination of substances with molecular weights up to 30 kDa The effect of high cut-off renal replacement therapy on myoglobin removal was investigated in 11 patients with RM-associated AKI using a 45 kDa cut-off hemofilter with a surface area of 1.1 m^2. [16] The result was a 20-fold higher mean myoglobin clearance, compared to standard high-flux filters [16]. Moreover, long session, high-flux hemodialysis appears to be more suitable for the treatment of RM. In this study, of the patients who received continuous renal replacement therapy, five patients had alleviated symptoms. One patient was transferred to another hospital for further treatment, because the primary disease was dermatomyositis and the patient was non-responsive to immunotherapy. Renal replacement

therapies are generally regarded to be efficient in cases of RM-induced AKI; however, the extracorporeal circuits may lead to additional complications. In addition, since the kidney is the greatest filter for removing myoglobin, a specific perfusion pressure and fluid volume is required to help the kidneys eliminate the toxin [8]. So, What is the best optimal management of RM-induced AKI ? The mainstays of efforts to prevent AKI in patients with rhabdomyolysis are saline solutions to expand intravascular volume and treatment of the underlying cause of rhabdomyolysis, [17] Renal replacement therapy should not be initiated on the basis of the myoglobin or CK serum concentration, but on the basis of the status of renal impairment. Continuous renal replacement therapy should only be considered when life-threatening electrolyte abnormalities emerge as complications of AKI, and they are not responsive to the initial therapy.

5. Conclusion

RM is a complex condition with non-specific symptoms that can develop from various causes. The syndrome is treatable and has good outcomes. Early and aggressive fluid has been the main intervention for preventing and treating AKI. Renal replacement methods can also play a supportive role, though they are not the first line of treatment for RM-induced AKI. The study indicate that the most effective treatments are early diagnosis, comprehensive therapy, active prevention, and the timely elimination of complications. However, This was a single-center study, further study is still needed because of the limited cases alloted.

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