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CLINICAL EVALUATION OF NON-TRAUMATIC RHABDOMYOLYSIS PATIENTS FOLLOWED IN THE INTERNAL DISEASES CLINIC

İÇ HASTALIKLARI KLİNİĞİNDE TAKİP EDİLEN NON-TRAVMATİK RABDOMİYOLİZ HASTALARININ KLİNİK DEĞERLENDİRİLMESİ

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Öz

Amaç: Rabdomiyoliz, çizgili kas liflerinin yıkımı sonucu hücre içindeki toksik potansiyeli olan maddelerin sistemik dolaşıma katılmasıyla oluşan klinik ve biyokimyasal bir durumdur. Bu çalışmada, non-travmatik rabdomiyoliz tanısı ile takip edilen semptomatik hastaların epidemiyolojik verileri morbidite, mortalite ve hastanede kalış süreleri açısından değerlendirildi.

Materyal ve Metot: Hastanemizde non-travmatik rabdomiyoliz tanısı konduktan sonra iç hastalıkları kliniğine yatırılan ve takip edilen 18 yaş üzeri 95 hastanın serum kreatin kinaz (CK), miyoglobin ve kreatinin (CR) seviyeleri retrospektif olarak değerlendirildi (retrospektif kohort çalışması).

Bulgular: Bu çalışmamızda, hasta grubumuzda, hastalık etiyolojisi ile hastanede yatış süresi arasında istatistiksel olarak anlamlı bir fark saptanmadı. Hastaların kreatinin değerleri ile hastanede yatış süresi arasında pozitif bir korelasyon vardı. Hastanede yatış süresi ile başvuru anında ve yatıştan sonra 24. saatteki kreatinin değerleri arasında istatistiksel olarak anlamlı fark saptandı (p=0,043). Başvuru anındaki CK değerleri ile takip ve taburculuktaki CR değerleri arasında istatistiksel olarak anlamlı fark bulunmadı (p=0,594). Non-travmatik rabdomyoliz tanısı ile yatırılan hastaların başlangıç CK değerinden bağımsız olarak uygun takip ve tedavi ile böbrek fonksiyonlarının izlemde olumsuz etkilenmediği saptanmıştır.

Sonuç: Travmatik olmayan rabdomiyoliz yaygın olmakla birlikte olası komplikasyonlar erken tanı, uygun tedavi ve takip ile en aza indirilebilir. Serum CK ve kreatinin değerleri hastaların takibinde önemli bir prognostik değere sahip olmasına rağmen birçok parametrenin birlikte değerlendirilmesi ve hastalık prognozunun değerlendirilmesini standardize etmek için daha fazla çalışmaya ihtiyaç vardır.

Anahtar Kelimeler: Rabdomiyoliz, kreatin kinaz, yatış süresi, böbrek yetmezliği.

Abstract

Objectives: Rhabdomyolysis is a clinical and biochemical condition that occurs when substances that have a toxic potential inside of cells enter systemic circulation as a result of the destruction of striated muscle fibers. In this study, the epidemiological data of patients who were symptomatic and followed-up with a diagnosis of non-traumatic rhabdomyolysis were evaluated in terms of morbidity, mortality, and length of hospitalization.

Materials and Methods: The serum creatinine kinase(CK), myoglobin, and creatinine(CR) levels of 95 patients who were over 18 years of age and had been hospitalized and followed up in the Internal Diseases ward after being diagnosed with non-traumatic rhabdomyolysis at the hospital were evaluated retrospectively.

Results: In this study, no statistically significant difference was found between disease etiology and the duration of hospitalization. There was a positive correlation between the CR values and the duration of hospitalization. A statistically significant difference was found between the length of hospitalization and the CR values on admission and at 24h following admission(p=0.043). No statistically significant difference was found between the CK values on admission and the CR values at follow-up and hospital discharge (p=0.594). It was found that patients admitted with a diagnosis of non-traumatic rhabdomyolysis did not negatively affect kidney function with appropriate follow-up and treatment, regardless of the initial CK value.

Conclusion: Although non-traumatic rhabdomyolysis is common, possible complications can be minimized with early diagnosis, appropriate treatment, and follow-up. Although serum CK and creatinine values have an important prognostic value in the follow-up of patients, many parameters need to be evaluated together, and more studies are needed to standardize the evaluation of disease prognosis.

Keywords: Rhabdomyolysis, creatine kinase, length of stay, renal insufficiency.

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Introduction

Rhabdomyolysis is a complex medical condition that occurs when substances that have a toxic potential inside of cells enter systemic circulation as a result of the destruction of striated muscle fibers. The clinical spectrum of rhabdomyolysis can range from the asymptomatic elevation of muscle enzymes to the development of life-threatening acute renal failure and severe electrolyte disturbance. Rhabdomyolysis is classified according to traumatic or non-traumatic causes. Although rhabdomyolysis is mostly due to traumatic causes, there are a significant number of non-traumatic rhabdomyolysis cases among admissions to internal medicine clinics. Infections, drugs, muscle diseases, and rheumatic diseases are among the causes of non-traumatic rhabdomyolysis.[1–4] The classic symptoms of rhabdomyolysis are myalgia, weakness, and tea-colored urine. Although there are no consensus diagnostic criteria for rhabdomyolysis, an increase in serum creatinine kinase (CK) levels five times above the normal level is sufficient for diagnosis. In some studies, a 10-fold increase is the desired reference value for diagnosis.[5] In this study, the epidemiological data of patients who were symptomatic and followed-up with a diagnosis of non-traumatic rhabdomyolysis were evaluated in terms of morbidity, mortality, and length of hospitalization.

Materials and Methods

The serum CK and myoglobin levels of 95 patients who were over 18 years of age and had been hospitalized and followed up in the Internal Diseases ward after being diagnosed with non-traumatic rhabdomyolysis at the hospital, between January 2016 and December 2018, were evaluated retrospectively (retrospective cohort study). Patients with test values five times the normal value or higher were included in the study. Patients with kidney disease, hypertension, diabetes mellitus, muscular dystrophy, neuromuscular disorder, and those with creatine kinase elevation who were using statin class drugs were excluded from the study. Demographic data, laboratory test values, organ failure, and prognosis of the patients were evaluated. For all of the patients, age, gender, creatine kinase levels, complaints, etiology, development of acute renal failure, hospitalization and discharge status, and patient clinic were evaluated.

Statistical Analysis

The IBM SPSS 21.0 statistical software package for Windows was used for the statistical analysis of the data. For all data, the normality assumption was evaluated via the Shapiro-Wilk test. Numerical data are indicated by median (minimum-maximum), and categorical data are indicated by numbers (percentage). The Mann-Whitney U test was used to compare numerical data between two groups, and the Kruskal-Wallis test was used to compare more than two groups. Values of $p<0.05$ were considered statistically significant.

Results

Included in the study were 95 patients who had been hospitalized with the diagnosis of non-traumatic rhabdomyolysis. The demographic data and laboratory findings of the patients are shown in Tables 1 and 2. Of the patients, 63 (66,31%) had proteinuria. The number of patients with myoglobinuria was 38 (40%). Muscle biopsy was performed in 9 patients (9,47%) (Table 3). The patients with the longest hospitalization according to etiology were those with bleeding/disseminated intravascular coagulation (DIC). In these patients, the median hospital stay was 6,50 days. The patients requiring the shortest hospitalization were those with a drug/herbal/alcohol etiology (Table 4). However, no statistically significant difference was found between disease etiology and the duration of hospitalization (p=0,053). There was a positive correlation between the creatinine values and the duration of hospitalization (Table 4). A statistically significant difference was found between the length of hospitalization and the creatinine values on admission and at 24 h following admission (p=0,043). No statistically significant difference was found between the CK values on admission and the CR values at follow-up and hospital discharge (Table 5). It was found that the renal function of patients hospitalized with a diagnosis of rhabdomyolysis was not affected by appropriate follow-up and treatment, regardless of the CK value on admission. According to the CR values on admission, there was no difference between patients with a CR value >1,45 and those with a CR value <1,45 (Table 6).

Table 1. Demographic, etiological, treatment, and length of stay data of the patients.

		n	(%)
Gender	Women	34	35.78
	Men	61	64.21
Age [Median(Min-Max)]		52 (17 - 72)	
Complaint on Application	Pain	40	42.10
	Nausea and vomiting	10	10.52
	Change of consciousness	14	14.73
	Decrease in urine	8	8.42
	Shortness of breath	21	22.10
	No	2	2.10
Etiology	Pharmaceuticals/herbal/alcohol/poison	20	21.05
	Infection	34	35.78
	Ischemia/Convulsion	15	15.78
	Exercise	18	18.94
	Bleeding/DIC	8	8.42
Treatment	Oral hydration	8	8.42
	IV hydration	72	75.78
	Dialysis	15	15.78

Table 2. Laboratory findings of the patients.

	Median (Min-Max)
AST (U/L)	98 (19 - 198)
ALT (U/L)	41 (19 - 82)
Ca (mg/dL)	8.80 (4.50 – 11.10)
P (mg/dL)	4.20 (1.30 – 14.80)
K (mEq/L)	4.60 (2.10 – 7.50)
pH	7.33 (7.26 – 7.38)
GFR (CKD-EPI) (ml/dk/1.73m²)	88 (15 - 123)
Uric acid (mg/dL)	6.90 (4 – 9.20)
Myoglobin (mcg/L)	1106 (95 - 8751)
CK1 (U/L)	2352 (647 - 203766)
Creatine kinase MB (mcg/L)	10.50 (1.70 - 903)
CR (mg/dL)	1.20 (0.40 – 9.00)
LDH (U/L)	422 (192 - 6521)
Troponin (ng/L)	5 (1.50 - 18)
Urea (mg/dL)	63 (6 - 225)

(AST: aspartat aminotransferaz, ALT: alanin aminotransferaz, Ca: calcium, P: phosphorus, K: potassium, pH: Power of Hydrogen, GFR: Glomerular Filtration Rate, CK: creatine kinase, CR: Creatinine, LDH: Lactate dehydrogenase, CKMB: Creatine Kinase MB Isoenzyme)

Table 3. Evaluation of the urine findings and muscle biopsies of the patients

Variables		**n**	**%**
Myoglobinuria	**Yes**	38	40
	No	57	60
Proteinuria	**Yes**	63	66.31
	No	32	33.68
Muscle Biopsy	**No**	86	90.52
	Yes	9	9.47

Table 4. Hospitalization according to the etiology and creatinine levels of the patients

Variables		Duration of hospitalization (Day)	p
		Median (Min-Max)	
Etiology	Pharmaceuticals/herbal/alcohol/poisoning	2.50 (0 - 63)	0.053
	Infection	5 (0 - 40)	
	Ischemia/Convulsion	3 (0 - 98)	
	Exercise	3 (0 - 20)	
	Bleeding/DIC	6.50 (3 - 19)	
CR		1.20 (0.40 - 9)[a]	0.043
CR 24		1.10 (0.30 – 8.60)[b]	
CR 48		1.10 (0.30 - 9)	
CR 72		1.10 (0.30 - 9)	

(CR: Creatinine; a-b: groups that make the difference)

Table 5. CK and CR values on admission, follow-up, and hospital discharge

Variables		CK1	CR	CR24	CR48	CR72	CR at discharge
CK1	Correlation Coefficient	1.000	-0.018	-0.105	-0.068	-0.100	-0.063
	p-value	-	0.863	0.313	0.515	0.337	0.594

Table 6. Follow-up and discharge CR values according to the basal CR values

	CR 24th hour		CR 72nd hour		CR at discharge	
CR Baseline	<1.45	>1.45	<1.45	>1.45	<1.45	>1.45
<1.45	60	2	61	0	57	4
>1.45	1	32	2	31	1	32
p-value	1		0.5		0.375	

(CR: Creatinine)

Discussion

Similar to the literature in this study, rhabdomyolysis frequency was higher in males than in females.[6,7] The frequency of etiological causes varies according to age. Similar to the current study, the most common non-traumatic causes in adults are infections and drugs.[8] In a study with 8610 patients in which drug-related rhabdomyolysis cases were evaluated, it was reported that statin-associated rhabdomyolysis constituted 45% of all cases.[9] Atorvastatin, one of the commonly used statins in Turkey, is metabolized through CYP3A4 and is relatively risky in terms of drug-related rhabdomyolysis. Rosuvastatin metabolized via CYP2A9 seems to have a lower risk of rhabdomyolysis, and the risk of statin-related severe CK elevation is less than 1%.[10,11] Among the drug-related rhabdomyolysis patients in the current study, there were no patients who used a statin. It was believed that this was caused by these patients being admitted to the emergency department mostly due to symptomatic cases. Statin-associated rhabdomyolysis may be more asymptomatic and diagnosed in outpatient settings. Due to etiological reasons, it was seen that the patients with the longest hospitalization were those with DIC/bleeding-induced-rhabdomyolysis. The reason for this may have been the need for additional treatment other than hydration and a tendency towards hypovolemia, hypoperfusion, and ischemia.

The most common symptoms in rhabdomyolysis patients are pain, especially in the proximal muscles, darkening of the urine color, and weakness.[12] In this study, the most common symptom on presentation was muscle pain, followed by shortness of breath. The reason for this may have been the involvement of the proximal muscle group, which is the most commonly involved muscle group, and the presence of severe pain. The most basic laboratory test for the diagnosis of rhabdomyolysis is the serum CK level. The CK level can be between 1500–100,000 IU/L. In a study in which rhabdomyolysis cases with different etiologies were evaluated, the mean CK peak level was reported to be between 10,000–25,000 IU/L.[13] In the current study, there was an increase in serum aminotransferase levels, especially the aspartate transaminase (AST) level, due to muscle cells. In a study in which rhabdomyolysis patients with serum CK levels above 1000 IU/L were evaluated, it was reported that 93,10% of the patients had elevated AST levels.[14] Myoglobin is a heme-containing monomer that is released from damaged muscle cells. When the plasma concentration exceeds 1,50 mg/dL, it passes into the urine, and the urine concentration must be 100–300 mg/dL in order to give the urine its characteristic color.[15,16] In this study, proteinuria was detected in 66,31% of the patients, but myoglobinuria was found in only 40%. The myoglobin half-life is much shorter than that of CK, and it can regress to normal serum levels within 6–8 h. For this reason, myoglobinuria may not be seen in rhabdomyolysis patients, even though the CK level is high.[16] In more than half of rhabdomyolysis patients, myoglobinuria cannot be detected by a dip-stick test in urine.[12] In this study, the difference between the frequency of myoglobinuria and proteinuria may have been caused by this fact. Hemoglobinuria may be detected in rhabdomyolysis patients. Hemoglobinuria may be the cause of this condition in patients with proteinuria detected independent of myoglobinuria.

Acute kidney injury (AKI) is a common complication in rhabdomyolysis patients, with a rate of 10%–50%.[17,18] Patients with a CK level below 15,000–20,000 IU/L on admission have a low risk of AKI, and dehydration, sepsis, and acidosis increase the risk of AKI in these patients.[19] In a study in which patients with serum CK levels above 5000 IU/L were evaluated, a scoring system was created for the risk of developing AKI in rhabdomyolysis patients. The patients were evaluated in terms of serum creatinine, CK, calcium, phosphate, bicarbonate values on admission, age, gender, and underlying predisposing factors. Patients with scores of 5 or less were considered to be at low risk for developing AKI.[20] According to this scoring, patients with a serum CK level above 40,000 IU/L on admission were given 2 points, while those with a serum creatinine level of 1,40–2,20 mg/dL were given 1,5 points, and those with a serum creatinine level of 2,20 or above were given 3 points. In this study, no correlation was found between the serum CK levels on admission and serum creatinine levels at follow-up and discharge. Patients with serum CK levels below 5000–10,000 IU/L have been reported to have a low risk of developing AKI.[21] In a meta-analysis by Safari et al., it was stated that the importance of the serum CK level in predicting the risk of AKI changed, and there was a correlation between the serum CK value and the risk of developing AKI in traumatic rhabdomyolysis patients.[22] When evaluated in this respect, serum CK values alone could not predict the risk of developing AKI in non-traumatic rhabdomyolysis patients and should be evaluated together with other factors. Considering the serum creatinine values on admission, there was no significant difference in the risk of developing AKI between the patients with a serum creatinine value >1,45 and those with a serum creatinine value <1,45. In this respect, it is suggested that the serum creatinine value alone cannot predict the risk of AKI and should be evaluated together with other factors. There was a positive correlation between the serum creatinine levels of the patients on admission and the duration of hospitalization. When the serum creatinine levels on admission were compared with the serum creatinine levels 24 h following admission, a significant difference was found in terms of the duration of hospitalization, which revealed the importance of appropriate treatment and follow-up of the patients.

Of the patients, 9 had muscle biopsy indications. Muscle biopsy was performed on patients whose etiology was unclear. Muscle biopsies of 2 patients were found to be compatible with dermatomyositis. No enzyme deficiency or pathology was found to suggest rhabdomyolysis in the muscle biopsies of 7 patients. It was believed that the herbs used by these patients may have played a role in the etiology.[23]

Rhabdomyolysis has a wide spectrum, from mild increases in serum CK levels to a severe, life-threatening syndrome. Although non-traumatic rhabdomyolysis is common, possible complications can be minimized with early diagnosis, appropriate treatment, and follow-up. Although serum CK and creatinine values have an important prognostic value in the follow-up of patients, many parameters need to be evaluated together, and more studies are needed to standardize the evaluation of disease prognosis.

Ethical Considerations

The study was approved by the ethics committee of the local hospital on 25.11.2020 with number E1-20-1311. The authors declared that this study is in accordance with the Helsinki Declaration. In addition, informed consent was obtained from patients during their application to the hospital.

Conflict of Interest

The authors declare no conflict of interest.

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