Iranian Journal of Toxicology
ARAK UNIVERSITY OF MEDICAL SCIENCES
January 2023, Volume 17, Number 1

Research Paper

Rhabdomyolysis and Aminotransferase Activity Due to Acute Intoxication With Psychotropic and Chemical Substances

Aleksandra Babulovska[1*], Daniela Chparoska[1], Vesna Velikj-Stefanovska[2], Natasha Simonovska[1], Zanina Pereska[1], Afrodita Berat-Huseini[1], Kristin Kostadinoski[1], Kiril Naumoski[1]

1. Faculty of Medicine, University Clinic for Toxicology, Skopje, Republic of North Macedonia.
2. Institute of Epidemiology and Biostatistics, Faculty of Medicine, Skopje, Republic of North Macedonia.

Use your device to scan and read the article online

How to cite this paper Babulovska A, Chparoska D, Velikj-Stefanovska V, Simonovska N, Pereska Z, Berat-Huseini A, et al. Rhabdomyolysis and Aminotransferase Activity Due to Acute Intoxication With Psychotropic and Chemical Substances. Iranian Journal of Toxicology. 2023; 17(1):63-70. http://dx.doi.org/10.32598/IJT.17.1.1031.1

http://dx.doi.org/10.32598/IJT.17.1.1031.1

Article info:
Received: 01 Sep 2022
Accepted: 11 Dec 2022
Online Published: 01 Jan 2023

*** Corresponding author:**
Aleksandra Babulovska, PhD.
Address: *University Clinic for Toxicology, Faculty of Medicine, University Clinic for Toxicology, Skopje, Republic of North Macedonia.*
E-mail: *ababulovska@yahoo.com*

ABSTRACT

Background: Rhabdomyolysis is caused by the release of enzymes from skeletal muscles into the blood, which leads to systemic complications with diverse etiologies. This study evaluated the serum aminotransferases in patients with rhabdomyolysis following acute intoxication with either psychotropic drugs or other chemical agents.

Methods: This study randomly recruited 140 patients suffering from rhabdomyolysis. They were divided into two groups affected by either psychotropic drugs or chemical agents. Rhabdomyolysis was defined as having serum creatine kinase (CK) levels greater than 250 U/L, based on the poisoning severity score.

Results: On day 1, the CK/AST correlation was significantly stronger in the psychotropic than the chemical group (P=0.0009). On day 5, patients in the psychotropic group had significantly higher AST (P=0.0138) and ALT (P=0.0129) than those poisoned with other chemicals. The difference in the strength of the CK/ALT correlation between the two groups was insignificant. Between the two groups, the differences between the CK levels and the following serum parameters were insignificant: Alkaline phosphatase; gamma-glutamyl transferase; prothrombin time; total bilirubin; and albumin.

Conclusion: The elevated aminotransferases in patients with rhabdomyolysis due to acute psychotropic toxicity might have resulted from the skeletal muscle injury rather than hepatotoxicity. In rhabdomyolysis patients poisoned with other chemicals, the elevated serum aminotransferases are likely due to liver toxicity arising from the consumed substances. These patients are likely to manifest clinically severe long-term multi-organ failure. Intoxications with typical agents, such as herbicides, petroleum distillates, and corrosives were responsible for the rhabdomyolysis in the second group.

Keywords: Aminotransferases, Chemical toxicity, Creatine kinase, Psychotropic drugs, Rhabdomyolysis

Introduction

Rhabdomyolysis is a clinical entity characterized by the release of intracellular enzymes from skeletal muscles into the bloodstream that leads to systemic complications [1, 2]. The etiology of skeletal muscle injury is quite diverse, including excessive muscle stress and ischemia, genetic defects, and direct toxic or physical damages [3]. In the past, the common causes of acute rhabdomyolysis were crush injuries during wartime and natural disasters [4]. More recently, as reported by

a published series, drugs and alcohol have become the frequent causative agents in over 80% of rhabdomyolysis cases [5]. The clinical manifestations of this condition include muscle pain, weakness, dark, tea-colored urine (pigmenturia), and biochemical serum finding with marked elevation of serum creatine kinase (CK), 5-10 times greater than its upper level in normal sera [6]. The most severe complications of rhabdomyolysis are compartment syndrome, electrolyte disturbance which may cause arrhythmia or cardiac instability, acute kidney injury, and disseminated intravascular coagulation [7, 8].

Serum aminotransferases, such as aspartate aminotransferase (AST) and alanine aminotransferase (ALT), are considered the representative markers of liver cells necrosis in patients with acute or chronic hepatitis. When hepatotoxic events occur, the damage to hepatocytes and their increased cell membranes permeability may contribute to the intravascular spread of the enzymes released from hepatocytes, which reflects a liver inflammatory condition [9].

Aim of the study: Given the absence of published literature similar to this article, we planned to compare and contrast the serum aminotransferase levels in patients with rhabdomyolysis secondary to acute intoxication with either psychotropic or chemical substances.

Materials and Methods

This clinical trial was conducted in 2019 at the University Clinic for Toxicology in Skopje, Republic of North Macedonia. As a prospective study, we recruited 140 patients with rhabdomyolysis, and divided them into two groups, depending on the toxic substance consumed by them.

Patients grouping and inclusion criteria: Patients were divided into two groups based on the following inclusion criteria:

• Group 1: Patients poisoned with psychotropic agents, e.g. heroin and methadone.

• Group 2: Patients intoxicated with other chemical agents.

Rhabdomyolysis was defined as a creatine kinase (CK)>250 U/L according to the poisoning severity score (PSS). We included adult patients at ages of 18 and older with rhabdomyolysis in the study. They had been acutely intoxicated with either psychotropic or chemical substances within the 48 hours prior to admission into the hospital.

Exclusion criteria: We excluded patients with myocardial infarction, acute and chronic hepatitis B and C, and other hepatic impairments, based on the medical history. The study was approved by the Ethics Commission of the Faculty of Medicine, Ss. Cyril and Methodius at the University of Skopje, Republic of North Macedonia.

Statistical analyses: The study data were analyzed with SPSS software, version 22. The quantitative data were analyzed in series, using central tendency (mean and median) and dispersion measures (standard deviation and IQR). Mann Whitney U test was used to compare the averaged values, based on the data distribution. Spearman's correlation coefficients were used to determine the relationship among the numerical variables. The statistical significance was set at $P<0.05$.

Results

A total of 1446 patients with diagnoses of acute intoxications were treated during the study period at the University Clinic for Toxicology in Skopje, Republic of North Macedonia. Of the total number, 140 patients had developed rhabdomyolysis. Ninety-six (68.6%) patients with rhabdomyolysis had been poisoned with psychotropic drugs (Group 1), while the other 44 individuals (31.4%) had consumed chemical agents (Group 2). Intoxications with psychotropic substances were significantly more frequently seen among the patients than those poisoned with chemical substances.

On average, the male patients were about four years younger than the female ones (40.8 Vs 44.1); however, the age difference between the two groups was statistically insignificant based on Mann-Whitney U test. In total, 60% of the patients had increased AST levels. In Group 1, 43% had increased AST levels, while in Group 2, the corresponding number was 17%.

AST levels in group 1: The highest AST levels in Group 1 were as follows:

a) Heroin (N=5/4/4) with the median IQR being 823 (226-1052) vs. 415 (130.5-797.5) vs. 93.5 (68-232.5) U/L; and, b) Methadone (N=15/11/8) with the median IQR being 242 (76-845) vs. 420 (98-830) vs. 285 (128-531) U/L.

AST levels in group 2: The highest AST levels in Group 2 were:

Table 1. Patients with rhabdomyolysis by type of intoxication and AST level at three times

	AST	N	Mean±SD	Min	Max	Percentiles		
						25th	50th (Median)	75th
Day 1	Psychotropic	96	210.16±428.12	13.30	2761.00	27.10	41.30	98.95
	Chemical	44	123.69±272.90	16.90	1427.00	25.91	35.80	66.55
	Total	140	182.98±387.21	13.30	2761.00	26.94	38.81	83.00
	Mann-Whitney U Test: Z=1.0212; P=0.3072							
Day 3	Psychotropic	60	242.05±349.17	16.00	1939.00	39.00	84.50	301.50
	Chemical	30	201.65±459.97	27.34	2380.00	38.00	49.76	93.00
	Total	90	228.58±387.47	16.00	2380.00	39.00	70.50	221.00
	Mann-Whitney U Test: Z=1.5877; P=0.1123							
Day 5	Psychotropic	39	156.74±169.16	17.00	678.00	41.00	84.00	187.00
	Chemical	23	71.68±71.05	13.00	325.00	28.00	49.88	88.00
	Total	62	125.18±146.16	13.00	678.00	35.47	71.50	145.00
	Mann-Whitney U Test: Z=2.4629; P=0.0138*							

Days 1/3/5: Friedman test: N=62, Chi-Square=43.538, d_f=2, P=0.0001*; Days 3/5: Wilcoxon Signed ranks test: Z=-5.283, P=0.0001*; Days 3/1: Wilcoxon signed ranks test: Z=1.036, P=0.300; Days 5/1: Wilcoxon signed ranks test: Z=1.872, P=0.061.

*Statistical significance at P<0.05, AST reference: 10-34 U/L

a) Herbicides (N=3/2/1) with the median IQR being 71.7 (30-1427) vs. 1216.3 (52-2380) vs. 41 U/L; and, b) petroleum distillate (N=1/1/1) with the median IQR being 907 U/L vs. 973 vs. 194 U/L. Further, we consistently found high values for these agents over the three measurements taken on days 1, 3 and 5 (Tables 1 and 2).

ALT levels in group 1: The highest ALT levels in Group 1 were as follows:

a) Heroin (N=5/4/4) with the median IQR being 276 (66-385) Vs. 433 (141-1411) Vs. 204.5 (99.5-638) U/L; and, b) Methadone (N=15/11/8) with the median IQR being 176.8 (33-632) Vs. 157 (50-529) Vs. 172 (122-563) U/L.

ALT levels in group 2: The highest ALT levels in Group 2 were:

a) Herbicides (N=3/2/1) with the median IQR being 540.8 (21-5229.8) Vs. 2108 (357-3858.9) Vs. 280 U/L; and, b) Petroleum distillate (N=1/1/1) with the median IQR being 277 U/L. Further, we consistently found high values for these agents over the three measurements taken on days 1, 3 and 5.

Other lab parameters: In groups 1 and 2, 75% of the patients' serum levels for the following laboratory parameters: Alkaline phosphatase-AP (pNPP), Gamma-glutamyltransferase-GGT (IFCC), total bilirubin, albumin, and prothrombin time were within the normal reference ranges. Also, we found no significant differences between the two groups on the first day for their lab values of AP, GGT, total bilirubin, albumin, and prothrombin time (Tables 3 and 4).

Correlations of CK, AST & ALT: The correlations between the levels of CK and AST on the first day were as follow:

a) Group 1: Significantly positive (R=0.798; P=0.0001). With an increase in the CK levels, that of AST also increased significantly.

b) Group 2: Significantly positive (R=0.438; P=0.003). With an increase in the CK levels, that of AST also increased significantly. The CK/AST correlation was significantly stronger in Group 1 than in Group 2 on the first day (P=0.0009) (Table 5).

Table 2. AST levels in patients with rhabdomyolysis according to etiological agents

	Etiological Agents	Day 1					Day 3					Day 5				
		N	Mean±SD	Percentiles			N	Mean±SD	Percentiles			N	Mean±SD	Percentiles		
				25th	50th	75th			25th	50th	75th			25th	50th	75th
1	Benzodiazepines	20	54.0±78.8	22.7	37.5	46.5	9	49.8±22.0	37.0	42.0	60.0	5	50.5±23.1	35.5	41.0	64.0
2	Neuroleptics	12	234.6±327.8	17.0	55.0	467.5	12	243.1±194.4	78.0	163.0	443.5	7	200.3±105.7	135.4	187.0	206.0
3	Anticonvulsants	6	46.7±27.3	29.0	35.0	79.0	4	223.8±245.8	73.5	137.5	374.0	4	174.3±207.9	55.0	90.5	293.5
4	Antidepressants	12	160.2±334.1	17.9	30.0	100.0	11	116.2±125.4	33.0	46.0	209.0	7	60.0±25.3	33.0	67.0	80.0
5	Antiparkinsonian	2	42.2±24.3	25.0	42.2	59.3	2	74.0±1.4	73.0	74.0	75.0	1	38.0±0.0	38.0	38.0	38.0
6	Other medications	2	25.7±12.5	16.9	25.7	34.6	0	--	-	-	-	0	--	-	-	-
7	Insecticides	15	31.8±15.1	20.6	27.2	37.1	13	73.3±68.0	37.0	47.0	64.0	12	53.5±29.3	28.6	47.4	77.0
8	Corrosive agents	12	160.5±242.3	27.7	39.1	167.0	6	210.7±252.1	42.1	69.0	409.8	6	110.4±116.9	28.0	70.0	156.3
9	Heroin	5	786.0±704.8	226.0	823.0	1052.0	4	464.0±399.2	130.5	415.5	797.5	4	150.3±140.1	68.0	93.5	232.5
10	Methadone	15	575.0±743.8	76.0	242.0	845.0	11	598.5±594.1	98.0	420.0	830.0	8	325.5±239.0	128.0	285.0	531.0
11	Amphetamines	4	39.9±4.1	37.1	39.8	42.8	0	--	-	-	-	0	--	-	-	-
12	Cocaine	1	42.0±0.0	42.0	42.0	42.0	1	28.0±0.0	28.0	28.0	28.0	0	--	-	-	-
13	Ecstasy	-	--	-	-	-	-	--	-	-	-	-	--	-	-	-
14	Tramadol	3	24.1±7.8	16.3	23.9	32.0	2	20.5±6.4	16.0	20.5	25.0	1	17.0±0.0	17.0	17.0	17.0
15	Ethyl alcohol	15	76.2±118.6	29.3	46.0	68.0	4	81.8±84.5	29.0	48.5	134.5	2	40.5±29.0	20.0	40.5	61.0
16	Herbicides	3	509.6±794.8	30.0	71.7	1427.0	2	1216.3±1645.8	52.5	1216.3	2380.0	1	41.0±0.0	41.0	41.0	41.0
17	Carbon monoxide	7	54.6±34.0	30.0	34.0	69.0	5	59.6±47.4	30.0	38.0	61.0	1	58.0±0.0	58.0	58.0	58.0
18	Petroleum distillate	1	907.0±0.0	907.0	907.0	907.0	1	973.0±0.0	973.0	973.0	973.0	1	194.0±0.0	194.0	194.0	194.0
19	Gasoline	2	46.5±10.7	38.9	46.5	54.0	1	42.0±0.0	42.0	42.0	42.0	1	31.0±0.0	31.0	31.0	31.0
20	Ethylen glycol	1	52.0±0.0	52.0	52.0	52.0	1	53.0±0.0	53.0	53.0	53.0	1	20.3±0.0	20.3	20.3	20,3
21	Other	1	25.5±0.0	25.5	25.5	25.5	1	34.0±0.0	34.0	34.0	34.0	0	--	-	-	-
22	Cannabis	1	20.0±0.0	20.0	20.0	20.0	0	--	-	-	-	0	--	-	-	-
	Total	140	183.0±387.2	26.9	38.8	83	90	228.6±387.5	39.0	70.5	221.0	62	125.2±146.2	35.5	71.5	145.0

AST reference values: 10-34 U/L

Iranian Journal of Toxicology
ARAK UNIVERSITY OF MEDICAL SCIENCES

Table 3. Patients with rhabdomyolysis by type of intoxication and ALT levels at three times

	ALT	N	Mean±SD	Min	Max	Percentiles		
						25th	50th (Median)	75th
Day 1	Psychotropic	96	155.17±452.09	8.08	3426.00	19.32	27.00	63.00
	Chemical	44	187.04±786.06	10.75	5229.84	19.29	26.00	60.40
	Total	140	165.18±575.37	8.08	5229.84	19.29	26.00	62.40
	Mann-Whitney U Test: Z= -0.1908; P=0.8487							
Day 3	Psychotropic	60	239.95±786.31	13.00	5698.54	28.00	46.00	128.00
	Chemical	30	216.27±700.82	11.49	3858.90	23.00	39.50	68.00
	Total	90	232.06±755.01	11.49	5698.54	27.00	43.50	113.00
	Mann-Whitney U Test: Z=1.0699; P=0.2847							
Day 5	Psychotropic	39	230.04±633.72	12.00	3911.00	32.00	79.00	150.00
	Chemical	22	71.80±85.66	20.00	280.00	24.17	30.50	60.00
	Total	61	172.97±512.63	12.00	3911.00	30.00	51.00	141.00
	Mann-Whitney U Test: Z=2.4857; P=0.0129*							

Days 1/3/5: Friedman test: N=62, Chi-Square=43.538, d_f=2; P=0.0001*; Days 3/5: Wilcoxon signed ranks test: Z=-3.125, P=0.002*; Days 3/1: Wilcoxon signed ranks test: Z=-0.467, P=0.641; Days 5/1: Wilcoxon signed ranks test: Z=0.839, P=0.401.

*Significantly for P<0.05; ALT reference: 10-45 U/L

In Group 1, there was a moderate but significant correlation between the CK and ALT levels on the first day (R=0.355; P=0.0001). With an increase in the CK level, that of ALT also increased significantly.

In Group 2, we found no significant correlation for these variable (R=0.091; P=0.003). With an increase in the CK levels, the ALT increased insignificantly, and there was an insignificant correlation for the differences between the CK and ALT levels in the two groups (P>0.05) (Table 5). Also, there were insignificant correlations for the differences among the CK/AP, CK/GGT, CK/prothrombin time, CK/total bilirubin, and CK/albumin between the two groups (P>0.05) (Table 5).

Discussion

In this study, 60% of the intoxicated patients with rhabdomyolysis had increased serum AST levels. The percentage consisted of 43% in Group 1 and 17% in Group 2. A retrospective study by Weibrecht et al. reported elevated AST in 93.1% of the patients with rhabdomyolysis and elevated ALT in 75.0% of the patients with serum creatine kinase ≥1000 U/L [10]. The discrepancy might be associated with different etiology responsible for the rhabdomyolysis. We found that AST and ALT were significantly higher on day 5 compared to those on day 3 but insignificantly higher than those documented on day 1.

Alanine aminotransferase (ALT) is normally found in greater concentrations in the liver than in the heart and skeletal muscles, and kidneys. Therefore, it is useful in the diagnosis of liver disease. The activity of aspartate aminotransferase (AST) in men is usually the highest in cardiac muscles followed by liver and skeletal muscles, while it is also detectable in the brain and kidneys [11]. The serum ALT level is used as an early marker in the assessment of various liver diseases [12]. However, the exact mechanism of hepatocellular damage in this syndrome is not well understood. To differentiate whether elevated AST and ALT are only attributed to muscle injury or to a concomitant liver damage, we analyzed the prothrombin time, the serum bilirubin and albumin levels. Our results demonstrated that in 75% of the patients intoxicated with psychotropic and chemical substances, such as AP, GGT, TB, AL, and PT, the values were within the normal reference limits.

Table 4. Patients with rhabdomyolysis by type of intoxication and the levels of selected parameters

	Type of Intoxication	Day 1 (N)	Mean±SD	Min	Max	Percentile 25th	Percentile 50th (Median)	Percentile 75th
AP	Psychotropic	96	65.20±21.07	31.00	140.00	50.48	62.00	77.50
	Chemical	44	72.95±33.56	33.00	190.95	48.66	67.05	85.50
	Total	140	67.63±25.78	31.00	190.95	50.48	65.00	78.85
			Z=-0.9785; P=0.3278					
GGT	Psychotropic	96	35.69±26.41	5.29	186.00	17.50	28.00	44.37
	Chemical	44	50.63±56.35	8.80	284.85	19.50	28.00	54.00
	Total	140	40.38±38.82	5.29	284.85	18.00	28.00	47.29
			Z=-0.6576; P=0.5108					
TB	Psychotropic	96	12.41±11.33	3.00	86.00	6.84	10.60	14.00
	Chemical	44	17.13±20.67	3.58	123.60	7.38	11.00	17.50
	Total	140	13.91±15.02	3.00	123.60	6.90	11.00	14.04
			Z=-1.0687; P=0.2852					
DB	Psychotropic	95	5.83±5.12	0.09	39.80	3.00	4.70	7.00
	Chemical	44	8.49±15.77	1.40	97.39	3.00	4.28	8.00
	Total	139	6.67±9.84	0.09	97.39	3.00	4.66	7.32
			Z=-0.1449; P=0.8848					
TP	Psychotropic	95	5.83±5.12	0.09	39.80	3.00	4.70	7.00
	Chemical	44	8.49±15.77	1.40	97.39	3.00	4.28	8.00
	Total	139	6.67±9.84	0.09	97.39	3.00	4.66	7.32
			Z=-0.3999; P=0.6899					
Al	Psychotropic	95	42.76±5.15	26.00	54.55	40.00	43.00	46.00
	Chemical	43	43.01±6.50	25.65	56.85	40.00	43.19	48.00
	Total	138	42.83±5.58	25.65	56.85	40.00	43.00	46.72
			Z=-0.2873; P=0.2877					
PT	Psychotropic	22	13.66±3.34	9.00	24.00	11.90	12.61	14.05
	Chemical	16	13.94±4.35	9.81	24.70	11.60	12.05	14.35
	Total	38	13.78±3.75	9.00	24.70	11.76	12.56	14.20
			Z=0.5469; P=0.5844					

Abbreviations: AP (pNPP):Alkaline phosphatase –ref. values: 38-126 U/L; GGT: Gamma-glutamyl transferase –ref. values: 9-64U/L; TB: Total bilirubin – ref. values: 6.8-20.5 µmol/L; DB: Direct bilirubin – ref. values:1.5-6.8 µmol/L; TP: Total protein – ref. values: 63-83 g/L; Al : Albumin - ref. values: 35-50 gl/L; PT: Prothrombin time–ref. value 9.8-14.2 sec; Mann-Whitney U Test: Z.

*Significance at P<0.05.

Table 5. Correlation between CK and select laboratory parameters

Parameters	CK–Spearman's Rank Order Correlations			P[1]
	Psychotropic Agent	Chemical Agent	Total	
AST	R (96)=0.798; P=0.0001*	R (44)=0.438; P=0.003*	R (140)=0.756; P=0.0001*	P=0.0009*
ALT	R (96)=0.355; P=0.0001*	R (44)=0.091; P=0.559	R (140)=0.2351; P=0.005*	P=0.1354
AP (pNPP)	R (96)=0.277; P=0.064	R (44)=0.054; P=0.726	R (140)=0.169; P=0.065	P=0.2191
GGT	R (96)=0.305; P=0.279	R (44)=0.147; P=0.342	R (140)=0.278; P=0.271	P=0.1296
Prothrombin time	R (22)=-0.197; P=0.379	R (16)=-0.12; P=0.655	R (38)=-0.156; P=0.343	P=0.8471
Total bilirubin	R (95)=0.051; P=0.630	R (44)=0.053; P=0.732	R (139)=0.021; P=0.810	P=0.9915
Albumin	R (95)=-0.144; P=0.163	R (43)=-0.052; P=0.742	R (138)=-0.117; P=0.172	P=0.6235

Abbreviations: AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; AP (pNPP): Alkaline phosphatase; GGT: Gamma-glutamyl transferase. P[1]: Z-statistics, *Significance at P<0.05.

Based on our results, the CK/AST correlation on day 1 was significantly stronger in Group 1 than Group 2 patients. The difference in the strength of the CK/ALT correlation between the two groups was not significant. Patients with elevated aminotransferases had moderately to severely developed rhabdomyolysis if they had been intoxicated with psychotropic substances. In these patients, the serum aminotransferases were elevated if they did not suffer a severe liver disease, and the serum AST values were usually higher than those of ALT levels. This suggests that extra-hepatic causes (i.e. skeletal muscle damage) may be a significant source of elevated AST and ALT in patients with rhabdomyolysis, secondary to acute intoxication with psychotropic agents. Despite these findings, concurrent liver injury as an additional source of AST or ALT elevation could not be ruled out.

There are scarce studies addressing rhabdomyolysis and the association with the serum levels of CK, AST and ALT. A study addressing this topic followed 44 boys and girls who performed exercises on treadmill [13]. In that study, the serum ALT and AST significantly increased at 24 and 48 hr along with increases in CK and LDH. The effects were more pronounced in boys than in girls. It has been demonstrated that prospective clinical studies provide stronger evidence than case reports since they include otherwise healthy individuals with normal data for their baseline biochemical variables. Based on the findings reported by another study [10], AST concentrations paralleled the decline of CK levels during the first six days of hospitalization due to acute rhabdomyolysis. It was assumed that ALT concentrations dropped slower because of its longer serum half-life (47 Vs. 17 hours for AST) [10].

In rhabdomyolysis, isolated elevations of alanine aminotransferase may occur, and it may be expected that the increased level is linked to the peak creatine kinase [14]. Aminotransferases return to normal levels when the CK level is also normalized after treatment in 85% of patients [15]. In the current study, most of the patients in Group 2 showed elevated serum aminotransferases, but they manifested mild to moderate rhabdomyolysis, depending on their serum CK levels. In certain chemical intoxications, elevated aminotransferases are primarily due to hepatotoxic effects of the consumed toxins, or intoxication with herbicides, corrosive agents, and toxic gases usually develop manifestations of severe multiorgan syndromes, including liver failure.

The extent of hepatotoxicity in herbicides poisoning is not clear as increases in serum aspartate, alanine aminotransferase and lactic dehydrogenase have not been characterized based on specific isoenzymes. Such toxicities may instead reflect skeletal or cardiac muscle injuries [16, 17]. In severe poisonings with corrosive agents, the reason for the elevated transaminases is probably due to poor perfusion and ischemic hepatitis, i.e. liver shock. Elevated liver enzymes have also been reported following ingestion and intravenous injection of petroleum distillates [18]. The exact mechanism of hepatotoxicity after such intoxications is poorly understood.

Conclusions

Elevated aminotransferases in rhabdomyolysis due to acute intoxication with psychotropic substances might be indicative of skeletal muscle injury rather than damage to hepatocytes. In patients with rhabdomyolysis who are

acutely intoxicated with chemical substances, elevated aminotransferases are either due to hepatotoxic effects of the substances or may accompany a severe clinical presentation with multiorgan failure. Intoxications with herbicides, petroleum distillates and corrosive agents are the typical etiologic agents.

Ethical Considerations

Compliance with ethical guidelines

This study was approved by the Ethics Committee of the Faculty of Medicine, Ss. Cyril and Methodius, University in Skopje, 1000 Skopje, Republic of North Macedonia (Ethics Code: 03-1864/4; dated 19.04.2019).

Funding

This research did not receive any grant from funding agencies in the public, commercial, or non-profit sectors.

Authors' contributions

Conceptualization and supervision: Aleksandra Babulovska and Daniela Chaparoska; Methodology: Natasha Simonovska and Zanina Pereska; Investigation, writing – original draft, review & editing: All authors;

Conflict of interest

The authors declared no conflict of interest.

Acknowledgements

The authors are grateful to the University Clinic for Toxicology for facilitating this work and to Lenche Danevska for English proofreading of the manuscript.

References

[1] Huerta-Alardín AL, Varon J, Marik PE. Bench-to-bedside review: Rhabdomyolysis-an overview for clinicians. Critical Care. 2005; 9(2):158-69. [PMID] [PMCID]

[2] Giannoglou GD, Chatzizisis YS, Misirli G. The syndrome of rhabdomyolysis: Pathophysiology and diagnosis. European Journal of Internal Medicine. 2007; 18(2):90-100. [DOI:10.1016/j.ejim.2006.09.020] [PMID]

[3] Cervellin G, Comelli I, Lippi G. Rhabdomyolysis: Historical background, clinical, diagnostic and therapeutic features. Clinical Chemistry and Laboratory Medicine. 2010; 48(6):749-56. [DOI:10.1515/CCLM.2010.151] [PMID]

[4] Vanholder R, Sever MS, Erek E, Lameire N. Rhabdomyolysis. Journal of The American Society of Nephrology. 2000; 11(8):1553-61. [DOI:10.1681/ASN.V1181553] [PMID]

[5] Prendergast BD, George CF. Drug-induced rhabdomyolysis--mechanisms and management. Postgraduate Medical Journal. 1993; 69(811):333-36. [PMID] [PMCID]

[6] Bagley WH, Yang H, Shah KH. Rhabdomyolysis. Internal and Emergency Medicine. 2007; 2(3):210-8. [PMID]

[7] Chavez LO, Leon M, Einav S, Varon J. Beyond muscle destruction: A systematic review of rhabdomyolysis for clinical practice. Critical Care. 2016; 20(1):135. [PMID] [PMCID]

[8] Zutt R, van der Kooi AJ, Linthorst GE, Wanders RJ, de Visser M. Rhabdomyolysis: Review of the literature. Neuromuscular Disorders. 2014; 24(8):651-9. [DOI:10.1016/j.nmd.2014.05.005] [PMID]

[9] Pratt DS. Liver chemistry and function tests. In: Feldman M, Friedman LS, Brandt LJ, editors. Sleisenger and fordtran's gastrointestinal and liver disease. Amsterdam: Elsevier; 2015. [Link]

[10] Weibrecht K, Dayno M, Darling C, Bird SB. Liver aminotransferases are elevated with rhabdomyolysis in the absence of significant liver injury. Journal of Medical Toxicology. 2010; 6(3):294-300. [PMID] [PMCID]

[11] Cuccherini B, Nussbaum SJ, Seeff LB, Lukacs L, Zimmerman HJ. Stability of aspartate aminotransferase and alanine aminotransferase activities. The Journal of Laboratory and Clinical Medicine. 1983; 102(3):370-6. [PMID]

[12] Prati D, Taioli E, Zanella A, Della Torre E, Butelli S, Del Vecchio E, et al. Updated definitions of healthy ranges for serum alanine aminotransferase levels. Annals of Internal Medicine. 2002; 137(1):1-10. [DOI:10.7326/0003-4819-137-1-200207020-00006] [PMID]

[13] Pal S, Chaki B, Chattopadhyay S, Bandyopadhyay A. High-intensity exercise induced oxidative stress and skeletal muscle damage in postpubertal boys and girls: A comparative study. Journal of Strength and Conditioning Research. 2018; 32(4):1045-52. [PMID]

[14] Lim AKH, Arumugananthan C, Lau Hing Yim C, Jellie LJ, Wong EWW, Junckerstorff RK. A cross-sectional study of the relationship between serum creatine kinase and liver biochemistry in patients with rhabdomyolysis. Journal of Clinical Medicine. 2019; 9(1):81. [PMID] [PMCID]

[15] Mathur T, Manadan AM, Thiagarajan S, Hota B, Block JA. Serum transaminases are frequently elevated at time of diagnosis of idiopathic inflammatory myopathy and normalize with creatine kinase. Journal of Clinical Rheumatology : Practical Reports on Rheumatic & Musculoskeletal Diseases. 2014; 20(3):130-2. [DOI:10.1097/RHU.0000000000000038] [PMID]

[16] Braberry SM, Watt BE, Proudfoot AT, Vale JA. Mehanisms of toxicity, clinical features, and management of acute chlorophenoxy herbicide poisoning: A review. Journal of Toxicology. Clinical Toxicology. 2000; 38(2):111-22. [DOI:10.1081/CLT-100100925] [PMID]

[17] Brahmi N, Mokhtar HB, Thabet H, Bouselmi K, Amamou M. 2,4-D(chlorophenoxy) herbicide poisoning. Veterinary and Human Toxicology. 2003; 45(6):321-2. [PMID]

[18] Domej W, Mitterhammer H, Stauber R, Kaufmann P, Smolle KH. Successful outcome after intravenous gasoline injection. Journal of Medical Toxicology. 2007; 3(4):173-7. [PMID] [PMCID]