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The evaluation of inherited metabolic diseases presenting with rhabdomyolysis from Turkey: Single center experience

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A R T I C L E I N F O

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A B S T R A C T

Aim: It was aimed to identify markers that would indicate which cases presenting with rhabdomyolysis are more likely to be associated with inherited metabolic diseases.

Methods: We analyzed 327 children who applied to our Hospital Pediatric Nutrition and Metabolic Diseases Clinic with rhabdomyolysis. The diagnosis of rhabdomyolysis was made by measuring the serum creatinine kinase level in cases presenting with muscle pain, weakness and dark urine.

Results: Metabolic disease was detected in 29 (16/13, M/F) patients from 26 different families. 298 patients (165/133, M/F) had normal metabolic work-up. We detected glutaric aciduria type 2 in 13 patients (44,6%), glycogen storage disease type 5 in three patients (10,3%), MCAD deficiency in three patients(10,3%), mitochondrial disease in three patients (10,3%), glycogen storage disease type 9 in one patient (3,5%), VLCAD deficiency in one patient (3,5%), LCHAD deficiency in one patient (3,5%), CPT2 deficiency in one patient(3,5%), Tango2 deficiency in one patient (3,5%), lipin-1 deficiency in one patient (3,5%) and primary carnitine deficiency in one patient (3,5%).

Conclusion: In our study, consanguineous marriage, developmental delay, and intellectual disability were found more frequently in patients with metabolic disease. In addition, CK levels above 2610 U/L was found to be significantly correlated with metabolic disease.

1. Introduction

Rhabdomyolysis is a clinical condition resulting from skeletal muscle damage due to various causes. As a result of damage to skeletal muscle cells, intracytoplasmic proteins such as creatine kinase and myoglobin are released into the plasma. Inherited enzyme deficiencies associated with myoglobinuria were described by Penn and Rowland in 1972 [1]. The most common causes of rhabdomyolysis are viral myositis, drug overdose, vigorous exercise, trauma and connective tissue diseases [2]. In addition, many metabolic diseases such as glutaric aciduria type 2, lipin-1 deficiency, McArdle disease, fatty acid oxidation defects, mitochondrial diseases, CPT2 deficiency, Tango2 deficiency can also cause rhabdomyolysis.

Common clinical symptoms of rhabdomyolysis include muscle pain, muscle weakness, and dark urine. Nonspecific findings such as nausea, vomiting, fever, tachycardia, weakness, malaise can be seen. The definitive diagnosis of rhabdomyolysis is made by laboratory tests. However, its clinical symptoms should not be overlooked. Muscle pain and muscle weakness may not be seen in mild rhabdomyolysis. In severe forms of rhabdomyolysis, pain, tenderness, swelling, and weakness are observed in the affected muscles. The presence of myoglobin in the urine causes the urine to appear dark in color. Rhabdomyolysis can cause life-threatening complications such as electrolyte disturbances, disseminated intravascular coagulation, and acute kidney injury.

Although the etiology is extensive, CK levels higher than five times the upper limit of normal, or higher than 1.000 U/L, is frequently used for rhabdomyolysis diagnosis. It is essential to diagnose and treat rhabdomyolysis as soon as possible due to the numerous causes that can result in a high mortality and morbidity rate. There are only few studies in the literature examining patients who presented with rhabdomyolysis and diagnosed with inherited metabolic disease.

In this study, it was aimed to identify markers that would indicate which cases presenting with rhabdomyolysis are more likely to be associated with inherited metabolic diseases. In addition, we aimed to determine the incidence of inherited metabolic diseases in patients presenting with rhabdomyolysis.

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2. Methods

2.1. Study design

This retrospective investigation examined the medical records of children and adolescents diagnosed with rhabdomyolysis and treated at our hospitals between January 2017 and June 2022. Our study was approved by the Ethics Committee of the Gazi Yasargil Training and Research Hospital under decision number 2022–6/127. Due to the retrospective nature of the study, informed consent was waived.

2.2. Study population

The diagnosis of rhabdomyolysis was made by measuring the serum creatine kinase level in cases presenting with muscle pain, weakness and dark urine. Rhabdomyolysis was accepted as serum CK levels >1000 U/L (reference range:30–200 U/L) or above 5 times of the normal levels. Patients who met the definition of rhabdomyolysis and were aged between one month and eighteen years ($n = 327$) were eligible for inclusion. Individuals were excluded from this study if they had known metabolic or genetic diseases, or had insufficient medical records. The patients were divided into two groups according to the etiology: Metabolic disease (MD) group and Non-metabolic disease (Non-MD) group.

2.3. Data collection

The following information was taken into consideration during the evaluation of the patient's medical records: anthropometric data, history of consanguinity, gender, age at diagnosis, current age, clinical findings, complications of rhabdomyolysis, laboratory results, physical examination findings and outcomes. Acute kidney injury was defined as a rise in serum creatinine of at least 0.3 mg/dL (26.5 mol/L) within 48 h or a 50% rise in serum creatinine from baseline during hospitalisation. Oliguria was defined as a urine discharge of <0.5 mL/kg/h for 12 h.

Complete blood count, electrolytes, blood sugar, liver enzymes, urea, creatinine, creatine kinase, lactate dehydrogenase, total cholesterol, triglyceride, HDL cholesterol, LDL cholesterol, blood gas, ammonia and lactate levels were measured in all patients. Plasma amino acid analysis, plasma acylcarnitine analysis and urine organic acid analysis were performed for specific metabolic screening. Abdominal ultrasonography, brain MRI examination, fundus examination and echocardiography were performed in selected cases. The diagnosis was confirmed by molecular analysis in cases with suspected metabolic disease based on clinical and laboratory findings. Sanger sequencing was used to validate all detected variants. The databases Varsome, mutation taster, and ensembl were utilized to ascertain the pathogenicity of the variants identified by genetic analysis.

2.4. Statistical analysis

All statistical analyses were performed using the SPSS software (SPSS Ver. 16.0; SPSS Inc., Chicago IL, USA). As descriptive statistics, numbers, and percentages for categorical variables, mean ± standard deviation or median (minimum-maximum) were used for numerical variables. For the comparison of MD and non-MD subgroups, continuous variables were compared using the Student *t*-test or Mann-Whitney *U* test, and categorical variables were compared using the chi-squared test or Fisher exact test. Threshold values were determined by a ROC curve. *P* values <0.05 were considered statistically significant.

3. Results

327 patients admitted to our pediatric metabolism outpatient clinic due to rhabdomyolysis were examined. 326 patients were alive and one patient died at the time of examination. Metabolic disease was detected in 29 (16/13, M/F) patients from 26 different families (Fig. 1). 298 patients (165/133, M/F) had normal metabolic work-up. We detected glutaric aciduria type 2 in 13 patients (44,6%), glycogen storage disease type 5 in three patients (10,3%), MCAD deficiency in three patients (10,3%), mitochondrial disease in three patients (10,3%), glycogen storage disease type 9 in one patient (3,5%), VLCAD deficiency in one patient (3,5%), LCHAD deficiency in one patient (3,5%), CPT2 deficiency in one patient(3,5%), Tango2 deficiency in one patient (3,5%), lipin-1 deficiency in one patient (3,5%) and primary carnitine deficiency in one patient (3,5%) (Table 1). The definitive diagnosis was confirmed by molecular analysis (single-gene analysis or Whole Exome Sequencing).

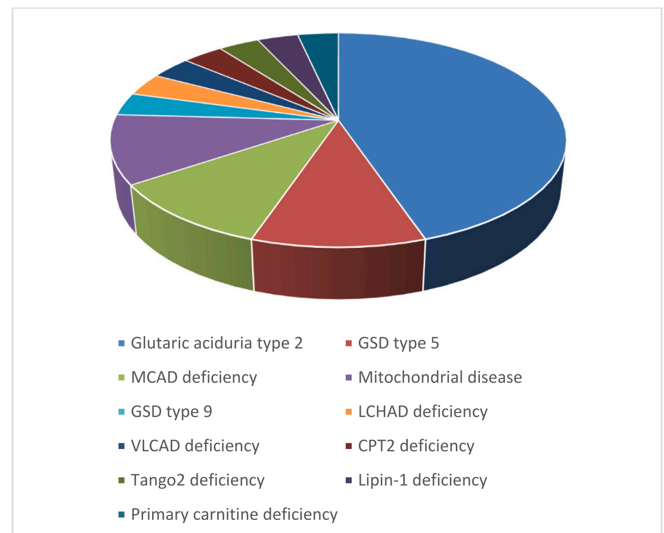

Fig. 1. Pie-chart showing the distribution of metabolic diseases.

WES analysis identified GSD V in our three patients who experienced rhabdomyolysis episodes induced by persistent skeletal muscle activity. The patient who diagnosed with lipin-1 deficiency exhibited a CK level of 9870 U/L (Table 1). Cardiomyopathy was not observed in the case of primary carnitine deficiency, which was identified and treated at a young age. In the deceased patient, metabolic disease was not identified. A diet and riboflavin supplement were administered to patients who were diagnosed with Glutaric aciduria type 2.

The patients were divided into two groups according to the etiology: Metabolic disease (MD) group and Non-metabolic disease (Non-MD) group. 16 (55.1%) individuals in MD group and 34 (11.4%) individuals in Non-MD group were born to consanguineous marriage (Table 2). Three patients (10.3%) had death sibling history in MD group.

The mean age at diagnosis of the patients with MD was 42.48 ± 49.05 months ($n = 29$, min:2-max:156). The mean age at diagnosis of the patients with Non-MD was 37.46 ± 45.80 months ($n = 298$, min:2-max:162). The current age of the MD patients was 8.27 ± 4.02 years (n = 29, min: 2, max:15). The current age of the Non-MD patients was 8.97 ± 3.86 years (n:297, min: 2, max:15). The mean onset time for clinical symptoms in the MD group was 38.27 ± 47.80 months (n = 29, min: 1, max:151). The mean onset time for clinical symptoms in the Non-MD group was 29.92 ± 35.24 months ($n = 298$, min:2, max:156). There was no statistically significant difference between the groups in terms of age at diagnosis, current age and onset time for clinical symptoms.

The median initial creatine kinase (CK), AST, ALT levels were 3250 (IQR 2475–5275) U/L, 273 (IQR 175–589) U/L, 125 (IQR 85–341) U/L in MD group, respectively (Table 2). The median initial CK, AST, ALT levels were 2300 (IQR 1780–3250) U/L, 225 (IQR 155–313) U/L, 125 (IQR 85–159) U/L in Non-MD group, respectively (Table 2). CK, AST and ALT levels were significantly higher in the patients with metabolic disease compared to the patients without metabolic disease ($p = 0.001$, p =

Table 1
Clinical and laboratory findings of the patients with inherited metabolic diseases.

Patient no	Gender	Age at diagnsosis (months)	Current age (years)	Presentation findings	CK levels	Consanguinity	Genotype	Diagnosis
1	F	24	13	Rhabdomyolysis, muscle pain, muscle weakness	1500	Yes	ETFB gene c.382G > A (p.D128N) homozygous mutation*	Glutaric aciduria type 2
2	F	12	8	Rhabdomyolysis, muscle pain, muscle weakness	3000	Yes	ETFB gene c.382G > A (p.D128N) homozygous mutation*	Glutaric aciduria type 2
3	F	15	4	Rhabdomyolysis, muscle pain, muscle weakness	3250	No	ETFB gene c.382G > A (p.D128N) homozygous mutation*	Glutaric aciduria type 2
4	F	24	6	Rhabdomyolysis, muscle pain, muscle weakness	5700	Yes	ETFB gene c.382G > A (p.D128N) homozygous mutation*	Glutaric aciduria type 2
5	M	36	7	Rhabdomyolysis, muscle pain, muscle weakness	8500	Yes	ETFDH gene c.1130 T > C (p. L377P) homozygous mutation*	Glutaric aciduria type 2
6	M	36	8	Rhabdomyolysis, muscle pain, muscle weakness	1700	No	ETFB gene c.382G > A (p.D128N) homozygous mutation*	Glutaric aciduria type 2
7	M	48	6	Rhabdomyolysis, muscle pain, muscle weakness	1100	No	ETFDH gene c.1130 T > C (p. L377P) homozygous mutation*	Glutaric aciduria type 2
8	M	156	19	Rhabdomyolysis, muscle pain, muscle weakness	2850	No	ETFB gene c.382G > A (p.D128N) homozygous mutation*	Glutaric aciduria type 2
9	M	9	9	Rhabdomyolysis, muscle pain, muscle weakness	2970	Yes	ETFDH gene c.1130 T > C (p. L377P) homozygous mutation*	Glutaric aciduria type 2
10	F	12	3	Rhabdomyolysis, muscle pain, muscle weakness	3250	No	ETFDH gene c.1130 T > C (p. L377P) homozygous mutation*	Glutaric aciduria type 2
11	M	12	11	Rhabdomyolysis, muscle pain, muscle weakness	3300	No	ETFDH gene c.1130 T > C (p. L377P) homozygous mutation*	Glutaric aciduria type 2
12	M	48	12	Rhabdomyolysis, muscle pain, muscle weakness	4850	No	ETFB gene c.382G > A (p.D128N) homozygous mutation*	Glutaric aciduria type 2
13	M	9	4	Rhabdomyolysis, muscle pain, muscle weakness	4150	Yes	ETFDH gene c.1130 T > C (p. L377P) homozygous mutation*	Glutaric aciduria type 2
14	F	144	13	Rhabdomyolysis, muscle weakness	8540	Yes	PYGM gene c.1094C > T (p. A365V) homozygous mutation**	GSD type 5
15	M	156	14	Rhabdomyolysis, muscle weakness	7840	Yes	PYGM gene c.1 A > G (p. Met1Val) homozygous mutation**	GSD type 5
16	F	144	13	Rhabdomyolysis, muscle weakness	4320	Yes	PYGM gene c.1094C > T (p. A365V) homozygous mutation**	GSD type 5
17	F	18	8	Rhabdomyolysis, hypoglycemia	2810	Yes	PHKG2 gene c.433delC (p. h145fs*10) homozygous mutation**	GSD type 9
18	M	108	11	Rhabdomyolysis, hypoglycemia	2850	No	ACADM gene c.157C > T (p. Arg53Cys) homozygous mutation*	MCAD deficiency
19	M	24	7	Rhabdomyolysis, weakness	2150	Yes	ACADM gene c.985 A > G (p. Lys329Glu) homozygous mutation*	MCAD deficiency
20	M	12	15	Rhabdomyolysis, hypoglycemia	4280	Yes	ACADM gene c.157C > T (p. Arg53Cys) homozygous mutation*	MCAD deficiency
21	F	6	2	Rhabdomyolysis, fever	2710	Yes	HADHA gene c.1528G > C (P. Glu510Gln) homozygous mutation*	LCHAD deficiency
22	F	2	14	Rhabdomyolysis, hypoglycemia	3450	No	ACADVL gene c.1406G > A (p. Arg469Gln) homozygous mutation**	VLCAD deficiency
23	M	48	6	Rhabdomyolysis, muscle pain	8520	No	CPT2 gene c.137 A > G (p. Gln46Arg) homozygous mutation*	CPT2 deficiency
24	F	24	3	Rhabdomyolysis, developmental delay	7810	No	TANGO2 gene c.670 T > G (p. Y224D) homozygous mutation***	Tango2 deficiency
25	F	12	5	Rhabdomyolysis, fever	9870	Yes	LPIN1 gene c.1684G > *T* (p. Glu562*) homozygous mutation**	Lipin-1 deficiency
26	M	12	7	Rhabdomyolysis, weakness	3510	No	*SLC22A5 gene* c.844C > T (p. R282*) homozygous mutation*	Primary carnitine deficiency
27	F	8	3	Rhabdomyolysis, developmental delay	1350	Yes	NSUN3 gene c.465dupA (p. Gly156fs) homozygous mutation*	Mitochondrial disease
28	M	66	8	Rhabdomyolysis, developmental delay	1780	Yes	SCO2 gene c.418G > A (p. Glu140Lys) homozygous mutation*	Mitochondrial disease
29	M	10	5	Rhabdomyolysis, developmental delay	2240	No	NDUFS4 gene c.44G > A (p. Trp15Ter) homozygous mutation*	Mitochondrial disease

* pathogenic mutation.
** likely pathogenic mutation.

*** VUS.

Table 2
Comparison of clinical and laboratory findings between groups.

	MD Group n:29	Non-MD Group n:298	P value
Gender (M/F)	16/13	165/133	0.98
Consanguineous marriage	55.1%	11.4%	0.001
Developmental delay	13.7%	1.6%	0.001
Intellectual disability	20.6%	2.6%	0.001
Hospitalisation time (day)	6 (5–6.5)	6 (5–7)	0.94
CK (U/L)	3250 (2475–5275)	2300 (1780–3250)	0.001
AST (U/L)	273 (175–589)	225 (155–313)	0.001
ALT (U/L)	125 (85–341)	125 (85–159)	0.001

0.001, p = 0.001, respectively). A comparison between the patients with and without metabolic diseases showed that the cut-off value for CK levels was 2610 U/L, with a sensitivity of 75% and a specificity of 63% (Table 3).

None of our patients needed dialysis during the rhabdomyolysis attack. In MD group, 13.7% developmental delay and 20.6% intellectual disability were detected. In Non-MD group, 1.6% developmental delay and 2.6% intellectual disability were detected. The median hospitalisation time was similar between the MD group and Non-MD group [6 (IQR 5–6.5) days and 6 (IQR 5–7) days, respectively, $p = 0.94$] (Table 2). Patients with inherited metabolic diseases exhibited a higher likelihood of consanguineous marriage (OR 9.55, 95% CI 4.23–21.57), developmental delay (OR 9.37, 95% CI 2.36–37.14), intellectual disability (OR 9.45, 95% CI 3.02–29.58), and CK levels>2610 U/L (OR 5.21, 95% CI 2.16–12.61).

4. Discussion

Pediatricians must identify rhabdomyolysis as soon as possible because it can occur often in the course of pediatric practice due to a variety of etiologies and can be fatal if treatment is delayed. One of the major subjects in the etiology of rhabdomyolysis is inborn errors of metabolism (IEM). When symptoms are persistent, recurrent, unexplained, and unresponsive to conventional therapy, pediatricians should take IEMs into consideration. In addition, the presence of individuals with similar clinical findings and symptoms in the family history should suggest an inherited metabolic disease. In this study, the frequency of metabolic disease in patients admitted for rhabdomyolysis was investigated. Metabolic disease was detected in 8.8% of the cases who applied to our pediatric metabolism outpatient clinic due to rhabdomyolysis. Glutaric aciduria type 2 was found in 44.8% of our patients. In this study, the most common cause of rhabdomyolysis was glutaric aciduria type 2 (Multiple AcilCoa Dehidrogenase deficiency, MADD). Patients with normal metabolic screening were excluded from genetic analysis in our study as a result of financial limitations. Therefore, certain patients with inherited metabolic diseases might have been overlooked.

In our study, consanguineous marriage, developmental delay and intellectual disability were found more frequently in patients with metabolic disease compared to the patients without metabolic disease. Neurodevelopmental assessment test was not performed in patients with normal neurological examination. In addition, the CK level was found to be significantly higher in cases with IEM. In this study, we found that the cut-off value for CK levels is 2610 U/L. If the CK levels is above 2610 U/L, IEM should be considered. Due to the unbalanced distribution of case numbers in the inherited metabolic disorders patient cohort, no comparison was made between metabolic disease groups.

Acute renal failure is a frequent complication of patients with rhabdomyolysis.[3] However, acute renal failure was not detected in our patients. Our study's demographic distribution was, in general, comparable to those previously reported, with males predominantly affected.

Several studies have previously explored the prevalence of IEM in conjunction with rhabdomyolysis. Our results was not compared with previous studies because of the different design of our study. Melli et al. examined 475 hospitalized patients with rhabdomyolysis and analyzed the incidence of different etiologies [3]. They described the characteristics of 17 etiologic categories associated with rhabdomyolysis. Myotoxins were the most common cause of rhabdomyolysis. They reported 2 cases of mitochondrial myopathies and 3 dystrophinopathies presenting with rhabdomyolysis [3]. Vivante et al. examined a group of 21 unrelated individuals with rhabdomyolysis for the presence of disease-causing mutations [4]. They identified 8 different causative mutated genes in 9 out of 21 individuals studied. They detected carnitine palmitoyltransferase II deficiency in one patient,paramyotonia congenita in one patient, malignant hyperthermia susceptibility 1 in one patient, freeman-sheldon syndrome in one patient, malignant hyperthermia susceptibility 5 in one patient, s-adenosylhomocysteine hydrolase deficiency in one patient, glycogen storage disease type X in one patient and glycogen storage disease type VII in one patient [4]. In the study conducted by Vivante et al., metabolic screening of the patients were not evaluated. Kruijt et al. examined 1302 patients with rhabdomyolysis [5]. Ischemia/anoxia was the most frequent trigger, followed by trauma. They determined rhabdomyolysis-associated gene in 72 patients [5]. Alaygut et al. investigated different etiologies and management of the rhabdomyolysis in 8 children [6]. In this case series; two cases had carnitine palmitoyltransferase II deficiency-associated rhabdomyolysis and one case was diagnosed as very long chain acyl-CoA dehydrogenase deficiency. Limited information regarding genetic and metabolic testing was included in previous studies, probably reflecting the minimal availability of genetic and metabolic testing.

Glutaric aciduria type 2 is an autosomal recessive metabolic disease caused by the deficiency or absence of multiple acyl-CoA dehydrogenase enzyme [7,8]. ETFA, ETFB and ETFDH genes encode the multiple acyl-CoA dehydrogenase enzyme. In glutaric aciduria type 2, a large number of organic acids accumulate in the blood and urine. There are a few case reports in the literature presenting with rhabdomyolysis and diagnosed as glutaric aciduria type 2 [9–11]. In this study, glutaric aciduria type 2 was the most common metabolic disease in patients presenting with rhabdomyolysis.

After glycogen stores are depleted during prolonged fasting and times of higher energy needs, fatty acid β-oxidation fuels hepatic ketogenesis, a key source of energy for peripheral tissues. The most common fatty acid β-oxidation disorder is medium-chain acyl-coenzyme A dehydrogenase (MCAD) deficiency. There was only one case report of MCAD deficiency presenting with rhabdomyolysis. Ruitenbeek et al. reported 30 year old man presented with rhabdomyolysis, muscle weakness, and acute encephalopathy after strenuous exertion [12]. This patient was diagnosed as MCAD deficiency by DNA analysis. In our study, 3 cases of MCAD deficiency presenting with rhabdomyolysis were identified. Rhabdomyolysis was accompanied by metabolic acidosis and hypoglycemia.

Specific mutations in the HADHA gene lead to long-chain

Table 3
Cut-off value, sensitivity and specificity for CK levels.

	AUC (95%CI)	Cut off	*P*-value	Sensitivity (%)	Specificity (%)
CK levels	0.670 (0.565–0.776)	2610	0.002	75	63

hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency which is a disorder of fatty acid oxidation. There were no case reports of LCHAD deficiency presenting with rhabdomyolysis. In our study, LCHAD deficiency was detected in a case who presented with rhabdomyolysis at the age of 6 months.

Very Long-Chain Acyl-CoA Dehydrogenase (VLCAD) deficiency is an autosomal recessive, clinically heterogeneous disease with a wide range of age at onset. VLCAD catalyzes the first step of mitochondrial long-chain fatty acid β-oxidation. There are case reports of VLCAD deficiency presenting with rhabdomyolysis in the literature [13–15]. Rhabdomyolysis as a presenting finding is also seen in rare metabolic diseases such as CPT2 deficiency, primary carnitine deficiency, TANGO2 deficiency and LPIN1 deficiency [16–19]. In our study, 1 CPT2 deficiency, 1 primary carnitine deficiency, 1 TANGO2 deficiency and 1 LPIN1 deficiency were detected in patients presenting with rhabdomyolysis.

Glycogen storage diseases develop as a result of deficiencies of various enzymes involved in the catabolism or anabolism of glycogen or, more rarely, of carrier proteins. It is classified as muscle, liver and mixed type glycogenoses according to clinical findings and organ involvement. There are >12 subtypes of glycogen storage diseases. Among them, glycogen storage disease type V, glycogen storage disease type VII, glycogen storage disease type IX, glycogen storage disease type X, glycogen storage disease type XI and glycogen storage disease type XIII cause rhabdomyolysis [20,21]. In this study, glycogen storage disease type V was detected in 3 patients and glycogen storage disease type IX was detected in one patient.

Mitochondria is an organelle that plays an important role in meeting the energy needs of the cell. Mitochondria have many functions such as intracellular energy production, phospholipid synthesis, heme biosynthesis, maintaining calcium homeostasis, and apoptosis [22,23]. Defects in genes encoding enzymes in mitochondria cause mitochondrial diseases. Clinical findings vary according to the energy requirement of the tissues. Although it affects all tissues, clinical findings are more severe in tissues with high energy requirements such as skeletal muscle, heart muscle, and central nervous system. Mitochondrial diseases do not present with isolated rhabdomyolysis. In this study, mitochondrial disease was detected in 3 of our patients who presented with rhabdomyolysis and neuromotor retardation.

We conducted this study so that patients would not be overlooked and would guide centers where metabolic tests cannot be performed. In our study, consanguineous marriage, developmental delay, and intellectual disability were found more frequently in patients with metabolic disease. The presence of consanguineous marriage, developmental delay, and intellectual disability should suggest an inherited metabolic disease. In addition, one of the laboratory parameters, CK levels above 2610 U/L, was found to be significantly correlated with metabolic disease. Although the most common causes of rhabdomyolysis are viral myositis, drug overdose, and trauma, we recommend metabolic screening in patients in the cases mentioned above.

Ethics committee approval

Our study was approved by the Ethics Committee of the Gazi Yasargil Training and Research Hospital under decision number 2022–6/127. The study was conducted in accordance with the Helsinki Declaration of Ethical Principles for Medical Research Involving Human Subjects.

Author's contributions

H.B. designed the study, collected and analyzed data, wrote the manuscript. A.E.B. collected and analyzed data, wrote the manuscript. All authors read and approved the final manuscript.

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The authors declare that they do not have any financial and personal relationships with other people or organizations.

CRediT authorship contribution statement

Huseyin Bilgin: Writing – original draft, Validation, Supervision, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Ayse Ergul Bozaci:** Writing – original draft, Validation, Supervision, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

There are no conflicts of interest.

Data availability

Data will be made available on request.

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