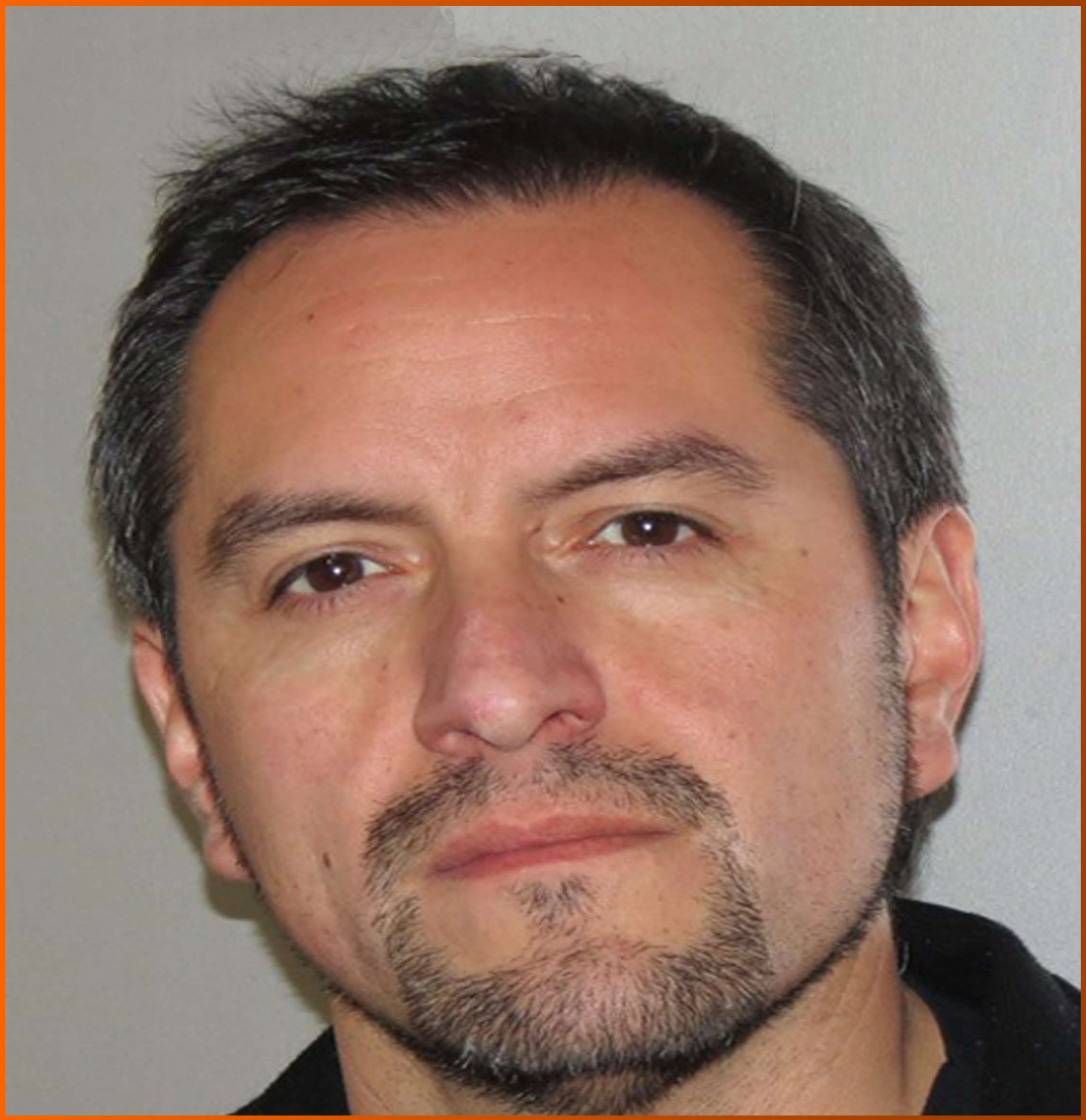
ISSN 2219-2808 (online)

World Journal of *Clinical Pediatrics*

World J Clin Pediatr 2017 November 8; 6(4): 161-179



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WJCP

World Journal of Clinical Pediatrics

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INDEXING/ABSTRACTING

World Journal of Clinical Pediatrics is now indexed in PubMed, PubMed Central.

FLYLEAF **I-III** Editorial Board

NAME OF JOURNAL
World Journal of Clinical Pediatrics

ISSN
ISSN 2219-2808 (online)

LAUNCH DATE
June 8, 2012

FREQUENCY
Quarterly

EDITORIAL OFFICE
Xiu-Xia Song, Director
World Journal of Clinical Pediatrics
Baishideng Publishing Group Inc
7901 Stoneridge Drive, Suite 501, Pleasanton, CA 94588, USA
Telephone: +1-925-2238242
Fax: +1-925-2238243
E-mail: editorialoffice@wjgnet.com
Help Desk: http://www.f6publishing.com/helpdesk
http://www.wjgnet.com

PUBLISHER
Baishideng Publishing Group Inc
7901 Stoneridge Drive,
Suite 501, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.f6publishing.com/helpdesk
http://www.wjgnet.com

PUBLICATION DATE
November 8, 2017

INSTRUCTIONS TO AUTHORS
http://www.wjgnet.com/bpg/gerinfo/204

ONLINE SUBMISSION
http://www.f6publishing.com

World Journal of Clinical Pediatrics

Submit a Manuscript: http://www.f6publishing.com

World J Clin Pediatr 2017 November 8; 6(4): 161-168

DOI: 10.5409/wjcp.v6.i4.161

ISSN 2219-2808 (online)

ORIGINAL ARTICLE

Retrospective Study

Rhabdomyolysis with different etiologies in childhood

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Author contributions: Alaygut D and Torun Bayram M contrubuted equally to this work; Alaygut D wrote the paper; Kasap B contributed new analytic tools; Soylu A and Türkmen M analyzed the data; Kavukcu S designed the research.

Institutional review board statement: The study was reviewed and approved by the Ethics Committee of the Dokuz Eylul University Hospital.

Informed consent statement: Patients were not required to give informed consent tot he study because the analysis used anonymous clinical data that were obtained after each patient agreed to tratment by written consent. For full disclosure, the datails oft the study are published on the home page of Dokuz Eylul Medical University.

Conflict-of-interest statement: We have no financial relationships to disclose.

Data sharing statement: No additional data are available.

Manuscript source: Invited manuscript

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Received: November 11, 2016
Peer-review started: November 13, 2016
First decision: March 8, 2017
Revised: July 11, 2017
Accepted: July 21, 2017
Article in press: July 22, 2017
Published online: November 8, 2017

Abstract

AIM

To investigate different etiologies and management of the rhabdomyolysis in children.

METHODS

Eight pediatric rhabdomyolysis cases who applied to the Dokuz Eylul University Faculty of Medicine Department of Pediatric Nephrology with different etiologies between January 2004 and January 2012 were evaluated in terms of age, gender, admission symptoms, physical examination findings, factors provoking rhabdomyolysis, number of rhabdomyolysis attacks, laboratory results, family history and the final diagnosis received after the treatment.

RESULTS

Average diagnosis ages of eight cases were 129 (24-192) ± 75.5 mo and five of them were girls. All of them had applied with the complaint of muscle pain, calf pain, and dark color urination. Infection (pneumonia) and excessive physical activity were the most important provocative factors and excessive licorice consumption was observed in one case. In 5 cases, acute kidney injury was determined and two cases needed hemodialysis. As a result of the further examinations; the cases had received diagnoses of rhabdomyolysis associated with mycoplasma pneumoniae, sepsis associated rhabdomyolysis, licorice-induced hypokalemic rhabdomyolysis, carnitine palmitoyltransferase Ⅱ deficiency, very long-chain acyl-CoA dehydrogenase deficiency, congenital muscular dystrophy and idiopathic paroxysmal rhabdomyolysis (Meyer-Betz syndrome).

CONCLUSION

It is important to distinguish the sporadic and recurrent

rhabdomyolysis cases from each other. Recurrent rhabdomyolysis cases should follow up more regardful and attentive.

Key words: Rhabdomyolysis; Children; Etiology; Acute kidney injury; Treatment; Hemodialysis

Core tip: This is a retrospective study to evaluate rhabdomyolysis in childhood. Rhabdomyolysis could be caused by a number of reasons, which could be classified as sporadic and hereditary/recurrent. The initial point that is to attract attention in this manuscript is the importance of the rhabdomyolysis type (recurrent/sporadic). Even though rhabdomyolysis is not routinely involved in textbooks concerning neuromuscular diseases, it is an integral part of these diseases. It should be taken into consideration in the first diagnosis and clinical follow-up of patients. It is possible to encounter with a rhabdomyolysis attack in every case. But its treatment is different from that of a primary disease.

Alaygut D, Torun Bayram M, Kasap B, Soylu A, Türkmen M, Kavukcu S. Rhabdomyolysis with different etiologies in childhood. *World J Clin Pediatr* 2017; 6(4): 161-168 Available from: URL: http://www.wjgnet.com/2219-2808/full/v6/i4/161.htm DOI: http://dx.doi.org/10.5409/wjcp.v6.i4.161

INTRODUCTION

Rhabdomyolysis is a pathological condition that occurs as a result of musculoskeletal damage. Substances such as creatine kinase (CK), myoglobin, aspartate aminotransferase, alanine aminotransferase, and potassium pass from cells into circulation as a result of this damage[1]. Among them, particularly myoglobin is substantially toxic for kidneys and causes acute kidney injury (AKI)[2]. The syndrome generally presents with the triad muscle pain, weakness and dark urin[3] Nearly half of patients with rhabdomyolysis have these symptoms[4]. For the clinician, suspicion starts with increase of creatinine kinase level. This suspicion is verified by measuring serum or urine myoglobin level[4]. Rhabdomyolysis can result from a wide range of disorders. While 80% of the cause of rhabdomyolysis in adults is trauma and drugs, it is infections and congenital disorders in children[4,5]. If rhabdomyolysis is recurrent, it is recommended to carry out some further examinations (muscle biopsy, metabolic and genetic tests). Early diagnosis is crucial to prevent AKI. Prevention is important in patients with inherited forms[4]. The purpose of this article is to present eight pediatric cases with rhabdomyolysis diagnosis depending upon different etiologies.

MATERIALS AND METHODS

The study consisted of eight patients with rhabdomyolysis. Medical files of cases, who were referred to Pediatric Nephrology of Medicine Faculty of Dokuz Eylul University, were retrospectively examined between the years of 2004 and 2012. The following parameters were recorded as age, gender, presenting symptoms, provocative factors, attacks number, positive physical examination findings, background and family history, laboratory results on admission, management, and final diagnosis. All cases were inquired at the admission time in terms of drug usage, infections, excessive physical activity, alcohol usage and herbal treatments. Family history was evaluated in terms of the individuals diagnosed with rhabdomyolysis in his/her family and neuromuscular diseases. In terms of etiology; further examinations were performed other than basic laboratory evaluation especially for the cases with recurrent rhabdomyolysis attacks. These consisted of serologic screening (Hepatitis, TORCH, EBV, Mycoplasma, Trichinella) in terms of infection parameters, bleeding profile and sepsis screenings, toxic screening, thyroid function test, ANA and ENA panels, lactic acid, ammonia, pyruvic acid levels, organic acid profile, acylcarnitine, total and free carnitine levels, metabolic screening (in terms of glucose and fat metabolism defects), electrography and echocardiography, electromyography (EMG), muscle biopsy and genetic studies. SPSS 18.0 - software package program was used to conduct statistical analysis.

RESULTS

Average diagnosis ages of eight cases, five of them being female, in the patient series was 129 (24-192 mo) ± 75.5. Examining the admission symptoms; all the patients in older age group had specified muscle pain, myalgia, calf pain, fatigue, and dark urination complaints. In two younger cases (case 1 and 7); dark color urination finding was the most remarkable finding. Cases 4 and 5 were also presented with muscle weakness. Additionally, first, second and seventh cases had cough and fever and third case had vomiting complaints. Examining the factors provoking rhabdomyolysis attack; infection (pneumonia) in three cases (case 1, 2, 7), excessive physical activity in three cases (case 4, 5, 8), both infection and excessive physical activity in one case (case 6), and excessive licorice consumption in one case (case 3) were observed. Assessing their physical examination findings on admission; three patients had fever over 38 degrees and bilateral crepitation in their pulmonary examination (case 1, 2, 7). Muscle strength loss was determined in upper and lower extremities in 2 cases (case 4, 5). Findings of volume loss were present in the third case but blood pressure was normal and the physical examinations of sixth and eighth cases were normal except for their muscle sensitivities. In the evaluation of personal backgrounds; case 7 was followed for epilepsy due to microcephaly. In cases 4, 5, 6 and 8, recurrent rhabdomyolysis attack was present. Also hemodialysis (HD) treatment was applied to case 6 at a different center due to a rhabdomyolysis attack 10 mo ago. Parents of cases 4, 5 and 6 were relatives. Cases 4 and 5 were siblings. In 4 of the cases;

Table 1 General characteristics of patients

Case no	Age (mo)	Gender	Presenting symptoms	Provacative factors	Positive physical examination findings	Past/family history	Attacs number
1	24	F	Dark colored urine, fever, cough	Infection	Fever, bilateral crepitationsin chest examination	Unremarkable	1
2	84	F	Fever, cough,myalgia, calf pain, fatigue, dark colored urine	Infection	Fever, bilateral crepitationsin chest examination	Unremarkable	1
3	192	M	Myalgia, calf pain, fatigue, dark colored urine, vomiting	Excess licorice use	Volume depletion signs, normal blood pressure	Unremarkable	1
4	132	F	Myalgia, calf pain, fatigue, muscle weakness, dark colored urine	Prolonged physical exercise	Muscle strengths 3-4/5 bilateral in upper and lower extremities	Recurrent rhabdomyolysis, parents are consanguineous	7
5	192	M	Myalgia, calf pain, fatigue, muscle weakness dark colored urine	Prolonged physical exercise	Muscle strengths 3-4/5 bilateral in upper and lower extremities	Recurrent rhabdomyolysis, parents are consanguineous	6
6	192	F	Myalgia, calf pain, fatigue dark colored urine	Infection, prolonged physical exercise	Muscle pain	Recurrent rhabdomyolysis, hemodialysis treatment 10 mo ago due to attack, parents are consanguineous	6
7	24	M	Dark colored urine, fever, cough	Infection	Fever, bilateral crepitationsin chest examination	Epilepsy, micocephalia	1
8	192	F	Myalgia, calf pain, fatigue dark colored urine	Prolonged physical exercise	Muscle pain	Recurrent rhabdomyolysis	3

M: Male; F: Female.

rhabdomyolysis attack was seen for the first time (case 1, 2, 3, 7), but it was the seventh rhabdomyolysis attack for the forth case, sixth rhabdomyolysis attack for the fifth and sixth cases and third rhabdomyolysis attack of the eighth case. Table 1 illustrates general characteristics of the patients. In line with rhabdomyolysis; CK values of all the patients was > 1000 U/L, and their blood and urine myoglobin levels were additionally high. In none of the patients; hypoglycemia and cardiac enzyme increase were observed. In five cases, AKI was present (case 1, 2, 3, 4, 7). Table 2 illustrates laboratory results at the time of admission.

Hydration, alkalinization, electrolyte replacement if needed, antibiotics treatment and allopurinol were applied to all the patients. HD was applied to cases three and four. Examining in terms of etiology; the patients were diagnosed with rhabdomyolysis associated with mycoplasma pneumoniae, sepsis associated rhabdomyolysis, licorice-induced hypokalemic rhabdomyolysis, carnitine palmitoyltransferase Ⅱ deficiency, very long-chain acyl-CoA dehydrogenase deficiency, congenital muscular dystrophy and idiopathic paroxysmal rhabdomyolysis (Meyer- Betz syndrome) (Table 3).

DISCUSSION

Rhabdomyolysis is a clinical result that may appear in numerous situations. In this article, eight cases with developed rhabdomyolysis related to different etiologies were assessed. Rhabdomyolysis is diagnosed when serum CK level exceeds 1000 U/L in case of absence of myocardial infarction[5].

Some studies accept that serum myoglobin level of > 300 ng/mL and urine myoglobin level of > 10 ng/mL are diagnostic[6].

Presence of myoglobin in serum and its infiltration to urine turns the color of urine into red. While heme reaction occurs in urine sticks, it is typical not to observe erythrocyte in microscopy[7]. Compared to CK, myoglobin is eliminated more quickly and if there is no myoglobinuria at high CK level, the diagnosis of rhabdomyolysis is not excluded[8]. CK levels of all the patients was > 1000 and their concurrent blood and urine myoglobin levels were over the reference values. All of them had red or brown urine findings and no erythrocyte was observed in microscopy. Common symptoms include myalgia, muscle tenderness, and weakness. While numerous patients experience lower-leg pain, some patients may have nonspecific symptoms such as fever, fatigue, vomiting, and nausea[8]. All the patients had applied with the above-mentioned common symptoms. Only the diagnosis of the 24-mo-old first and seventh cases was established with the red urine and laboratory values.

AKI is the most significant complication of rhabdomyolysis. It is defined as creatinine level above 97 percentile with respect to age and gender[5]. Previous studies identified that rhabdomyolysis-related AKI was 17%-35% in adults and 42%-50% in children[6,7,9]. If AKI is also comorbid in the cases with CK level above 100000 U/L, mortality rates reach up to 80%[4]. In five of the cases in this series, AKI was determined at the time of admission.

We stated that infections were more critical in etiology of rhabdomyolysis in children compared to adults. Several causes of infection may be associated with rhabdomyolysis. Viral infections are responsible for one

Table 2 Laboratory results of patients on admission

Case No.	Hb g/dL	WBC /mm^3	Plt /mm^3	Glu mg/dL	BUN mg/dL	Creat mg/dL	CPK U/L	AST IU/L	ALT IU/L	LDH U/L	Uric acid mg/dL	Na mmol/L	K mmol/L	Cl mmol/L	Ca mg/dL	P mg/dL	Urine myog.	Blood myog.
1	8.6	17.5	225	86	36	2.3	1158	451	3903	1227	6.1	139	4.2	110	8.6	4.5	193	155
2	12.9	6.5	93	102	65	4.7	12976	788	215	933	6.8	149	4.8	114	7.8	8.3	679	274
3	15.2	20.6	307	95	150	3.7	8379	780	250	1100	10	125	2.2	65	8.2	8.8	1370	3740
4	12.6	3.6	163	90	57	7	42670	998	249	1303	2.6	136	3.9	107	8.7	4.3	1200	1200
5	13.2	10.6	213	75	12	0.5	3012	210	664	1466	3.5	141	4.9	104	9.9	4.3	1200	1200
6	12.4	17.5	127	119	10	0.7	25983	338	87	1797	5	136	3.9	105	9.4	3.5	1200	1200
7	9.3	9.6	146	85	38	1.1	31119	683	235	1853	6.9	144	2.9	115	8.4	3.7	767	800
8	14.2	18.6	332	90	12.5	0.8	51228	1108	341	2381	2.3	135	3.7	107	10.1	3.6	800	1200

Hb: Hemoglobin; WBC: White blood cell; Plt: Platelet; Glu: Glucose in urine; CPK: Creatine phospho kinase; BUN: Blood urea nitrogen; AST: Aspartate aminotransferase; LDH: Lactate dehydrogenase; ALT: Alanine aminotransferase.

Table 3 Management and final diagnosis of patients

Case	Management	Renal replacement therapy	Final diagnosis
1	Antibiotic treatment, hydration, alkalinization	No	Rhabdomyolysis associated with Mycoplasma pneumoniae pneumonia
2	Antibiotic treatment, hydration, alkalinization, fresh frozen plasma	No	Sepsis, pneumoniae, rhabdomyolysis
3	Hydration, alkalinization, antiemetic, hemodialysis	Yes, HD	Licorice-induced hypokalemic rhabdomyolysis
4	Hydration, alkalinization, hemodiyalysis	Yes, HD	Rhabdomyolysis with carnitine palmitoyltransferase II deficiency
5	Hydration, alkalinization	No	Rhabdomyolysis with carnitine palmitoyltransferase II deficiecy ?
6	Hydration, alkalinization	No	Rhabdomyolysis with very long-chain acyl-CoA dehydrogenase deficiency
7	Hydration,alkalinization	No	Rhabdomyolysis due to congenital muscular dystrophy
8	Hydration, alkalinization	No	İdiopathic paroxysmal rhabdomyolysis "Meyer- Betz Syndrome

HD: Hemodialysis.

third of the cases[5,10] (Many infections are associated with rhabdomyolysis. While influenza takes place on the top among viral infection agents, Epstein-Barr virus (EBV), cytomegalovirus (CMV), and human immunodeficiency virus (HIV) are the other causes[4]. Although the pathophysiology is not presently clear, bacterial infections have also been associated with rhabdomyolysis. In a review in which 60 cases were reported, Legionella spp, Francisella spp, Streptococcus spp, Salmonella spp, and Staphylococcus aureus were determined as the most frequent factors[11]. Rhabdomyolysis was also reported with Enterococcus species, Pseudomonas aeruginosa[12], Neisseria meningitidis[13], *Escheria coli*[14], and Haemophilus influenzae[15], Mycoplasma pneumoniae[16], leptospirosis[17], and Coxiella burnetii (Q fever)[18]. In this case series; two cases (case 1, 2) had infection-associated rhabdomyolysis. Case 1 had applied with cough and high fever complaints and anemia (Hb 8.6 g/dL) reticulocytosis (8.5%), leukocytosis (17500) and acute renal insufficiency (BUN 36, creatinine 2, 3) were found in the laboratory examinations. Blood gas and urine analysis were normal. Concurrently AST, ALT, LDH, CPK and uric acid values were also found high. Empirical antibiotics treatment (Ⅳ clarithromycin), hydration and alkalinization were started to be given. Hemolysis findings were found in the peripheral smear which was examined due to anemia, and direct combs test was found as + 2 positive. In the tests sent in terms of the infection agents; mycoplasma pneumoniae IgM was positive. The outcome was rapidly favorable, and she did not experience another attack. The family history was negative for the rhabdomyolysis. Mycoplasma pneumonia infection may lead to multiple organ involvement as well as it may be asymptomatic. 25% of the patients develop extrapulmonary complications (cardiovascular, gastrointestinal, hematologic, and central nervous system). These complications may occur before, during, and after the infection. Sometimes, they appear with autoimmune events without pulmonary findings[19]. Formation of cold agglutinin which is observed in 10% of the patients also occur with this infection agent and is responsible for antibody-induced hemolysis[20].

It has not been understood exactly yet why rhabdomyolysis develops during mycoplasma infections, however direct invasion of muscles by the organism or muscular damage resulting from immune reactions are considered as responsible[16]. Although it is rare, rhabdomyolysis-induced AKI or glomerulonephritis, interstitial nephritis and nephrotic syndrome may develop with this infection[20,21].

Renal biopsy was not administered to patient due

to normal complement levels, absence of nephrotic syndrome, and existence of an AKI that does not require dialysis. Diagnosis of the patient was supported with positive serum mycoplasma IgM titration, antibody-induced hemolysis, and rapid response to anti-mycoplasma antibiotic treatment. Second case was a 84-mo-old girl. While she was being followed up for pneumonia; sepsis chart (thrombocytopenia, hypotension, bradycardia and disseminated intravascular coagulation) was developed. Then, diagnosis of rhabdomyolysis was made due to acute renal insufficiency and high CK, LDH, AST, ALT values. The patient had recovered without the need of appropriate antibiotherapy, hydration and alkalinization treatments and renal replacement treatment. Rhabdomyolysis attack of this patient did not repeat, and her family history was also negative. Sepsis-associated rhabdomyolysis was reported in numerous case reports[22-25]. In this case, we could not show any specific agent in the blood culture that may cause sepsis. Also no causative agent was reported in some studies about sepsis and rhabdomyolysis[26]. But specific causes such as blood pressure, electrolyte abnormalities, tissue hypoperfusion, hyperthermia, hypoxia, dehydration, and acidosis are known to induce rhabdomyolysis in any patient with a critical condition[27]. However, sepsis-associated microorganisms were identified in very few original studies. Even though these studies reported that bacterial sepsis-induced rhabdomyolysis can develop with numerous types of microorganisms, Betrosian *et al*[11] stated that it may occur mostly with gram positive organisms and Kumar *et al*[27] indicated that they may develop mostly with gram negative organisms[12,28].

Drugs, toxins and foods are other important causative factors for rhabdomyolysis. There are many drugs associated with development of rhabdomyolysis[8]. Drugs cause rhabdomyolysis due to direct or indirect muscle damage. Toxin poisoning related rhabdomyolysis has been reported by using honeybees[29], rattlesnakes[30], and brown recluse spider bites[31]. Carbon monoxide poisoning is another reason[32]. All the patients were examined during the anamnesis in terms of drug and toxin exposure and there were no patients with positive findings. Foods may also be a triggering factor. The most remarkable example about this issue is consumption of licorice root which may lead to hyperaldosteronism, hypokalemia, and rhabdomyolysis[33-35]. Third case was a 16-year-old male patient with chronic heavy cola consumption-associated rhabdomyolysis and AKI that were reported previously by Kasap *et al*[32] Due to the laboratory results that are concordant to hypokalemia, metabolic alcalosis, acute kidney insufficiency; diagnosis of hypokalemia associated metabolic alkalosis was made.

It was then learned from the history of patient that he/she was drinking about 1 lt of cola every day for 2-3 years. A substance was suspected causing the aldosterone effect with low serum plasma renin activity, normal aldosterone, and existence of hypokalemia. Licorice root in the cola consumed by the patient daily was emphasized. The patient was diagnosed with hypokalemic rhabdomyolysis induced by the use of licorice root. HD was applied because of volume load and oliguria developing when the patient was treated with intravenous fluid therapy. Acute tubular damage was determined in the renal biopsy performed in order to exclude the underlying chronic renal disease.

Hereditary diseases, most of which are metabolic diseases, develop another group that cause rhabdomyolysis. It should be especially considered in the cases with positive rhabdomyolysis in the family history and with recurrent rhabdomyolysis attacks[8]. Some individuals tend to have muscle damages especially after exercise. This low exercise tolerance is tried to be explained by CK-MM gene polymorphism and angiotensin-converting enzyme (ACE) polymorphism. C49T and C3788A genotypes of myosin light chain kinase cause CK level increased in response to exercise[36]. When 114 asymptomatic patients varying between ages of 3 and 70 and with incidental CK level increase were evaluated; 18% metabolic or neuromuscular diseases were determined.

The most frequent diagnoses were carnitine palmitoyltransferase deficiency and malignant hyperthermia[37]. Carnitine palmitoyltransferase deficiency was the most frequently observed disease in 36-patient series of idiopathic rhabdomyolysis[38].

Long chain fatty acids (LCFA) are the major source of energy for muscles in case of prolonged exercise. These fatty acids which cannot passively pass into mitochondria move inside actively *via* carnitine palmitoyltransferase pathway in the outer membrane of mitochondria. This pathway consists of enzymes of carnitine palmitoyltransferase Ⅰ located in the outer membrane and carnitine palmitoyltransferase Ⅱ located in the inner membrane.

Autosomal recessive carnitine palmitoyltransferase Ⅱ deficiency is the most frequent disorder in LCFA metabolism[39]. Clinic of rhabdomyolysis accompanying this condition is considerably variable. CK levels are normal or slightly high between attacks of rhabdomyolysis induced by this enzyme deficiency, increase between attacks, and muscle pains occurring after exercise start as from the childhood[40].

Enzyme analysis and mutation scanning should be performed for the diagnosis. Forth case in this article was an 11-year-old girl and we have learnt that she had complaints of not walking for a long distance, generalized muscle weakness from time to time, muscle cramps and dark colored urination problems from her early childhood ages. Her parents were relatives and her two brothers also had similar complaints. One of these brothers was the case five in our patient group. In CPT 2 gene; homozygote mutation was determined for SI13L. Genetic analysis was planned for his brother and possible CPT Ⅱ deficiency was accepted.

Case six was a 16-year-old female patient who had applied with sixth rhabdomyolysis attack and was within acyl-CoA dehydrogenase (ACAD) family and taken the diagnosis of very long chain acyl-CoA dehydrogenase

(VLCAD) deficiency. Very long chain acyl-CoA dehydrogenase deficiency is an autosomal recessive disorder progressing with inability for beta oxidation of fatty acids in the mitochondria. Its three phenotypes that are associated with different mutations were identified. The first one is the most critical phenotype starting in newborn period and having high mortality progressing with hypertrophic cardiomyopathy and hypoketotic hypoglycemia. The second one is observed during infancy period. There is no cardiomyopathy. Hypoketotic or nonketotic hypoglycemia develops. Rhabdomyolysis occurring in case of hunger or after exercise in preadolescence period, like in our patient, exists in the muscle type with late onset[41]. In the fibroblast culture of the case; very long chain acyl-CoA dehydrogenase activity was 4.3 nmol/min per milligram protein (controls: 5.1-21.7) (n = 28) and heterozygote carrier was found. Case seven was a patient who was followed up due to epilepsy, microcephaly and hypotonia and who had been diagnosed with infection-induced rhabdomyolysis. Myopathic findings were found in the electromyography and dystrophic changes were specified in the muscle biopsy. Visual examination and hearing test of the patient were normal. Congenital muscular dystrophies are a disease group which is clinically and genetically heterogeneous and is evident with early-onset and progressive muscle weakness. It has numerous genetic types that have been defined till now[42]. Thus, it was decided to conduct a genetic study on the patient in order to determine the sub type.

Despite all the further examinations; it cannot be possible to find the reason of recurrent rhabdomyolysis in some patients and idiopathic recurrent rhabdomyolysis is known as "Meyer Betz Syndrome". In fact, this is an exclusion diagnosis. Case eight was reported by Kasap *et al*[43] previously. The patient was applied with rhabdomyolysis finding that was induced by excessive physical activity at the first attack and after two months, he had applied again with a moderate CK increase. Metabolic screening of the patient (blood acylcarnitine analysis, total and free serum carnitine levels, and blood lactic acid level were normal, or tests conducted in terms of fatty acid oxidation defect -) was normal. EMG was normal. Ischemic effort test was applied in order to exclude McArdle's disease. Blood lactate and ammonia levels examined before and after exercise were above the normal. This picture is not expected in McArdle disease. Thus, muscle biopsy was applied to the patient and no glycogen deposit was observed.

If rhabdomyolysis is suspected in terms of the history and laboratory independently from underlying etiology, aggressive fluid treatment should be immediately started with isotonic saline[8]. Electrolyte abnormalities should be closely monitored and treated[8]. After urine output was observed, the urine may be alkalized with sodium bicarbonate. Many authors suggest a high hydration value, like 200 mL/h, until CK level decreases below 1000 U/L. Of course, this should be performed in a more controlled manner in pediatric cases. The indications for HD were severe hyperkalemia and prolonged oligo-anuric renal failure[4]. Two patients in this series were applied with HD treatment because of prolonged oligoanuric phase and hypertension in case three and high creatinine level and also hypertension in case four.

As a consequence; although the rhabdomyolysis picture is basically presented to us together with the same clinical and laboratory results, clarification of the etiology should be the primary factor. Especially it is very important to distinguish the sporadic and hereditary cases from each other. It should be considered that the primary organ to be rescued in the acute period is the kidney and aggressive fluid therapy, alkalinization and when needed, HD should be taken into consideration.

COMMENTS

Background

Rhabdomyolysis could be caused by a number of reasons, which could be classified as sporadic and hereditary/recurrent. All of the diseases causing rhabdomyolysis lead formation of cell membrane damage, hypoxia and lytic enzymes such as phospholipase A2, and decrease of energy source ATP as a result of cell's exposure to mechanical stress. Final outcome is disruption of intracellular ion balance, Ca concentration occurring within cell, hyperactivity in Ca-dependent proteolytic enzymes, and formation of oxidative free radicals. In the next periods, on the other hand, cell death occurs as a result of free radicals and proteases. It was intended to convey clinical and laboratory outcomes of rhabdomyolysis to reader and to identify extreme conditions within the scope of basic information. In this study, the authors evaluated clinical differences and etiologies of rhabdomyolysis in childhood.

Research frontiers

Rhabdomyolysis is an important clinical process in childhood. Clinicians must be keep in mind that sporadic and recurrent cases have different clinical properties.

Innovations and breakthroughs

Rhabdomyolysis is an important clinical situation. Clinician must be investigate it carefully. Unless a convenient treatment is performed, it will result in an acute kidney injury.

Terminology

Although the rhabdomyolysis picture is basically presented to us together with the same clinical and laboratory results, clarification of the etiology should be the primary factor. Especially it is very important to distinguish the sporadic and hereditary cases from each other. To concisely and accurately describe, define or explain the specific, unique terms that are not familiar to majority of the readers, but are essential for the readers to understand the article. AKI: Acute kidney injury; ACAD: Acyl-CoA dehydrogenase; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BM: Blood myoglobin levels; BUN: Blood urea nitrogen; Ca: calcium; CPT II: Carnitinepalmitoyltrans ferase II enzyme; Ch: Chlor; CMV: Cytomegalovirus; Creat: Creatinine; CK: Creatinine kinase; EMG: Electromyography; EBV: Epstein-Barr virus; FDA: Food and Drug Administration; HD: Hemodialysis; Hb: Hemoglobin; HIV: Human immuno deficiency virus; K: Potassium; LDH: Lactate dehydrogenase; LCFA: Long-chain fatty acids; Na: Sodium; P: Phosphorus; PRA: Plasma renin activity; Plt: Platelet; UM: Urine myoglobin levels; VLCAD: Very long chaiin acyl-coA dehydrogenase; WBC: White blood cell.

Peer-review

The manuscript is a series of 8 case-reports occurring in children. I would thank the authors for these clinical cases that remembers us that rhabdomyolysis also occurs in children and that the etiologies are quite different from adults.

REFERENCES

1 **Singh D**, Chander V, Chopra K. Rhabdomyolysis. *Methods Find Exp Clin Pharmacol* 2005; **27**: 39-48 [PMID: 15834458]
2 **Al-Ismaili Z**, Piccioni M, Zappitelli M. Rhabdomyolysis: pathogenesis of renal injury and management. *Pediatr Nephrol* 2011; **26**: 1781-1788 [PMID: 21249398 DOI: 10.1007/s00467-010-1727-3]
3 **Warren JD**, Blumbergs PC, Thompson PD. Rhabdomyolysis: a review. *Muscle Nerve* 2002; **25**: 332-347 [PMID: 11870710]
4 **Elsayed EF**, Reilly RF. Rhabdomyolysis: a review, with emphasis on the pediatric population. *Pediatr Nephrol* 2010; **25**: 7-18 [PMID: 19529963 DOI: 10.1007/s00467-009-1223-9]
5 **Mannix R**, Tan ML, Wright R, Baskin M. Acute pediatric rhabdomyolysis: causes and rates of renal failure. *Pediatrics* 2006; **118**: 2119-2125 [PMID: 17079586 DOI: 10.1542/peds.2006-1352]
6 **Watanabe T**. Rhabdomyolysis and acute renal failure in children. *Pediatr Nephrol* 2001; **16**: 1072-1075 [PMID: 11793103 DOI: 10.1007/s004670100030]
7 **Luck RP**, Verbin S. Rhabdomyolysis: a review of clinical presentation, etiology, diagnosis, and management. *Pediatr Emerg Care* 2008; **24**: 262-268 [PMID: 18418269 DOI: 10.1097/PEC.0b013e31816bc7b7]
8 **Gabow PA**, Kaehny WD, Kelleher SP. The spectrum of rhabdomyolysis. *Medicine* (Baltimore) 1982; **61**: 141-152 [PMID: 7078398 DOI: 10.1097/00005792-198205000-00002]
9 **Dell KM**, Schulman SL. Rhabdomyolysis and acute renal failure in a child with influenza A infection. *Pediatr Nephrol* 1997; **11**: 363-365 [PMID: 9203195 DOI: 10.1007/s004670050299]
10 **Singh U**, Scheld WM. Infectious etiologies of rhabdomyolysis: three case reports and review. *Clin Infect Dis* 1996; **22**: 642-649 [PMID: 8729203 DOI: 10.1093/clinids/22.4.642]
11 **Betrosian A**, Thireos E, Kofinas G, Balla M, Papanikolaou M, Georgiadis G. Bacterial sepsis-induced rhabdomyolysis. *Intensive Care Med* 1999; **25**: 469-474 [PMID: 10401940 DOI: 10.1007/s001340050882]
12 **van Deuren M**, Neeleman C, Assmann KJ, Wetzels JF, van der Meer JW. Rhabdomyolysis during the subacute stage of meningococcal sepsis. *Clin Infect Dis* 1998; **26**: 214-215 [PMID: 9455554 DOI: 10.1086/517026]
13 **Henrich WL**, Prophet D, Knochel JP. Rhabdomyolysis associated with Escherichia coli septicemia. *South Med J* 1980; **73**: 936-937 [PMID: 6992286 DOI: 10.1097/00007611-198007000-00032]
14 **Benedetti P**, Nicolin R, Pellizzer G, Scagnelli M, de Lalla F. Rhabdomyolysis and acute renal failure associated with meningitis and sepsis due to Haemophilus influenzae: case report. *Clin Infect Dis* 1997; **24**: 533-534 [PMID: 9114226 DOI: 10.1093/clinids/24.3.533]
15 **Minami K**, Maeda H, Yanagawa T, Suzuki H, Izumi G, Yoshikawa N. Rhabdomyolysis associated with Mycoplasma pneumoniae infection. *Pediatr Infect Dis J* 2003; **22**: 291-293 [PMID: 12664885 DOI: 10.1097/00006454-200303000-00023]
16 **Turhan V**, Atasoyu EM, Kucukardali Y, Polat E, Cesur T, Cavuslu S. Leptospirosis presenting as severe rhabdomyolysis and pulmonary haemorrhage. *J Infect* 2006; **52**: e1-e2 [PMID: 16051370 DOI: 10.1016/j.jinf.2005.05.001]
17 **Hervás JA**, de la Fuente MA, García F, Reynés J, de Carlos JC, Salvá F. Coxiella burnetii myopericarditis and rhabdomyolysis in a child. *Pediatr Infect Dis J* 2000; **19**: 1104-1106 [PMID: 11099098 DOI: 10.1097/00006454-200011000-00019]
18 **Waites KB**, Talkington DF. Mycoplasma pneumoniae and its role as a human pathogen. *Clin Microbiol Rev* 2004; **17**: 697-728, table of contents [PMID: 15489344 DOI: 10.1128/CMR.17.4.697-728.2004]
19 **Khan FY**, A yassin M. Mycoplasma pneumoniae associated with severe autoimmune hemolytic anemia: case report and literature review. *Braz J Infect Dis* 2009; **13**: 77-79 [PMID: 19578637 DOI: 10.1590/S1413-86702009000100018]
20 **Campbell JH**, Warwick G, Boulton-Jones M, McLay A, Jackson B, Stevenson RD. Rapidly progressive glomerulonephritis and nephrotic syndrome associated with Mycoplasma pneumoniae pneumonia. *Nephrol Dial Transplant* 1991; **6**: 518-520 [PMID: 1922914 DOI: 10.1093/ndt/6.7.518]
21 **Ojukwu IC**, Newton DW, Luque AE, Kotb MY, Menegus M. Invasive Group C Streptococcus infection associated with rhabdomyolysis and disseminated intravascular coagulation in a previously healthy adult. *Scand J Infect Dis* 2001; **33**: 227-229 [PMID: 11303816 DOI: 10.1080/00365540151060969]
22 **Shih KY**, Chu TS, Hung CC, Wu MS. Rhabdomyolysis associated with Streptococcus pneumoniae bacteremia in a splenectomized patient. *J Formos Med Assoc* 2002; **101**: 429-431 [PMID: 12189650]
23 **Teramoto S**, Fukuchi Y, Matsuse T, Sasahira N, Eto M, Sudo E, Katayama H, Ohga E, Toba K, Ouchi Y. [Two elderly patients with Rhabdomyolysis and respiratory infection with Streptococcus pneumoniae]. *Nihon Ronen Igakkai Zasshi* 1997; **34**: 49-53 [PMID: 9077105 DOI: 10.3143/geriatrics.34.49]
24 **Turner MC**, Naumburg EG. Acute renal failure in the neonate. Two fatal cases due to group B streptococci with rhabdomyolysis. *Clin Pediatr* (Phila) 1987; **26**: 189-190 [PMID: 3549109 DOI: 10.1177/000992288702600408]
25 **Veenstra J**, Smit WM, Krediet RT, Arisz L. Relationship between elevated creatine phosphokinase and the clinical spectrum of rhabdomyolysis. *Nephrol Dial Transplant* 1994; **9**: 637-641 [PMID: 7970089 DOI: 10.1093/ndt/9.6.637]
26 **Lewis TH**, Hall JB. Rhabdomyolysis and myoglobinuria. In: Hall JB, Schmidt GA, Wood LDH (eds) Principles of Critical Care. New York: Mc Graw-Hill, 1992: 1913-1919
27 **Kumar AA**, Bhaskar E, Palamaner Subash Shantha G, Swaminathan P, Abraham G. Rhabdomyolysis in community acquired bacterial sepsis--a retrospective cohort study. *PLoS One* 2009; **4**: e7182 [PMID: 19787056 DOI: 10.1371/journal.pone.0007182]
28 **Betten DP**, Richardson WH, Tong TC, Clark RF. Massive honey bee envenomation-induced rhabdomyolysis in an adolescent. *Pediatrics* 2006; **117**: 231-235 [PMID: 16396886 DOI: 10.1542/peds.2005-1075]
29 **Bush SP**, Jansen PW. Severe rattlesnake envenomation with anaphylaxis and rhabdomyolysis. *Ann Emerg Med* 1995; **25**: 845-848 [PMID: 7755213 DOI: 10.1016/S0196-0644(95)70218-0]
30 **Elbahlawan LM**, Stidham GL, Bugnitz MC, Storgion SA, Quasney MW. Severe systemic reaction to Loxosceles reclusa spider bites in a pediatric population. *Pediatr Emerg Care* 2005; **21**: 177-180 [PMID: 15744197]
31 **Melli G**, Chaudhry V, Cornblath DR. Rhabdomyolysis: an evaluation of 475 hospitalized patients. *Medicine* (Baltimore) 2005; **84**: 377-385 [PMID: 16267412 DOI: 10.1097/01.md.0000188565.48918.41]
32 **Kasap B**, Soylu A, Cetin BS, Camlar SA, Türkmen MA, Kavukçu S. Acute kidney injury following hypokalemic rhabdomyolysis: complication of chronic heavy cola consumption in an adolescent boy. *Eur J Pediatr* 2010; **169**: 107-111 [PMID: 19330351 DOI: 10.1007/s00431-009-0975-3]
33 **van den Bosch AE**, van der Klooster JM, Zuidgeest DM, Ouwendijk RJ, Dees A. Severe hypokalaemic paralysis and rhabdomyolysis due to ingestion of liquorice. *Neth J Med* 2005; **63**: 146-148 [PMID: 15869043]
34 **Sorokin AV**, Duncan B, Panetta R, Thompson PD. Rhabdomyolysis associated with pomegranate juice consumption. *Am J Cardiol* 2006; **98**: 705-706 [PMID: 16923466 DOI: 10.1016/j.amjcard.2006.03.057]
35 **Heled Y**, Bloom MS, Wu TJ, Stephens Q, Deuster PA. CK-MM and ACE genotypes and physiological prediction of the creatine kinase response to exercise. *J Appl Physiol* (1985) 2007; **103**: 504-510 [PMID: 17478608 DOI: 10.1152/japplphysiol.00081.2007]
36 **Prelle A**, Tancredi L, Sciacco M, Chiveri L, Comi GP, Battistel A, Bazzi P, Martinelli Boneschi F, Bagnardi V, Ciscato P, Bordoni A, Fortunato F, Strazzer S, Bresolin N, Scarlato G, Moggio M. Retrospective study of a large population of patients with asymptomatic or minimally symptomatic raised serum creatine kinase levels. *J Neurol* 2002; **249**: 305-311 [PMID: 11993531 DOI: 10.1007/s004150200010]
37 **Tonin P**, Lewis P, Servidei S, DiMauro S. Metabolic causes of myoglobinuria. *Ann Neurol* 1990; **27**: 181-185 [PMID: 2156480 DOI: 10.1002/ana.22248]
38 **Anichini A**, Fanin M, Vianey-Saban C, Cassandrini D, Fiorillo C, Bruno C, Angelini C. Genotype-phenotype correlations in a large series of patients with muscle type CPT II deficiency. *Neurol Res* 2011; **33**: 24-32 [PMID: 20810031 DOI: 10.1179/016164110X12767

786356390]
39 **Fidan K**, Kandur Y, Tumer L, Hasanoglu A, Soylemezoglu O. Rhabdomyolysis and acute kidney injury in two children: questions. *Pediatr Nephrol* 2013; **28**: 899-900, 901-902 [PMID: 22923202 DOI: 10.1007/s00467-012-2261-2]
40 **Voermans NC**, van Engelen BG, Kluijtmans LA, Stikkelbroeck NM, Hermus AR. Rhabdomyolysis caused by an inherited metabolic disease: very long-chain acyl-CoA dehydrogenase deficiency. *Am J Med* 2006; **119**: 176-179 [PMID: 16443431 DOI: 10.1016/j.amjmed.2005.07.064]
41 **Andresen BS**, Olpin S, Poorthuis BJ, Scholte HR, Vianey-Saban C, Wanders R, Ijlst L, Morris A, Pourfarzam M, Bartlett K, Baumgartner ER, deKlerk JB, Schroeder LD, Corydon TJ, Lund H, Winter V, Bross P, Bolund L, Gregersen N. Clear correlation of genotype with disease phenotype in very-long-chain acyl-CoA dehydrogenase deficiency. *Am J Hum Genet* 1999; **64**: 479-494 [PMID: 9973285 DOI: 10.1086/302261]
42 **Mercuri E**, Muntoni F. Muscular dystrophy: new challenges and review of the current clinical trials. *Curr Opin Pediatr* 2013; **25**: 701-707 [PMID: 24240289 DOI: 10.1097/MOP.0b013e328365ace5]
43 **Kasap B**, Soylu A, Türkmen M, Kavukcu S. An adolescent girl with Meyer-Betz syndrome. *Clin Rheumatol* 2006; **25**: 904-906 [PMID: 16328090 DOI: 10.1097/MOP.0b013e328365ace5]

P- Reviewer: Jullian-Desayes I **S- Editor**: Ji FF **L- Editor**: A
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