Clinical features of acute rhabdomyolysis in 55 pediatric patients

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Abstract

OBJECTIVE This study was designed to compare the clinical manifestations, laboratory tests, etiology, and prognosis of children with acute rhabdomyolysis (RM) at various ages. This study was designed to analyze the risk factors for acute kidney injury (AKI) in children with RM and to identify the role of neuromuscular and immunological disorders in children with RM.

PATIENTS AND METHODS Clinical data for 55 children with RM were collected and statistically analyzed. Patients were stratified to an infant group (G1) (age <1 yr), preschool group (G2) (age 1-6 yr), school-age group (G3) (age 7-11 yr), and an adolescent group (G4) (age 12-16 yr).

RESULTS The most common clinical features were dark urine (53%), myalgia (38%), and fever (24%). Patients in G1 had fever (71%), vomiting (78%), and abnormal urinalysis (14%), without triad clinical manifestations (myalgia, muscle weakness, and dark urine). 55% of patients in G4 group had myalgia; 71% had dark urine; 75% had abnormal urinalysis. The most common cause in each age group was as follows: sepsis (57%) in G1; hereditary neuromuscular diseases (44%) in G2; immunological disorders (40%) in G3; strenuous exercise (50%) in G4. Logistic regression analysis showed that AKI was not correlated with age, gender, or peak creatine phosphokinase. AKI was, however, associated with presence of an electrolyte disorder.

CONCLUSION The clinical manifestations and laboratory findings in infants with acute RM are not typical and need to be taken seriously. The presence of an electrolyte disorder is a risk factor for AKI in children with RM. The most common pathogenesis of RM varies among age groups. Congenital hereditary disease and immunological disorders should not be ignored as a cause of RM in children.

Introduction

Rhabdomyolysis (RM) is a group of clinical syndromes that cause skeletal muscle damage. A lapse in the integrity of the cellular membrane allows a large amount of cellular contents (such as enzymes, proteins, ions, etc.), especially myoglobin, to rapidly enter the circulation and urine. Typical manifestations of RM are myalgia and muscle weakness with dark urine\textsuperscript{1}. However, sometimes the occurrence of RM in children is easily missed or overlooked clinically due to atypical clinical manifestations, resulting in serious complications including acute renal failure. With the development
of new genetic detection technologies as next generation sequencing and whole exome sequencing in recent years, the etiology spectrum of RM in children has been greatly expanded. More than 60 oligogenic diseases have been found to associate with RM\(^2\). In addition, various immunological disorders have been identified as important causes of RM\(^3, 4\).

Because the bodies of children are in various stages of organ development and functional maturity, they respond differently to the large number of cytolysates in blood and urine, making it difficult to unify the clinical characteristics of RM. To better understand the characteristics of RM in children at different ages, in order to improve diagnosis and treatment, we compared clinical manifestations, laboratory tests, etiology, and prognosis. We focused on the etiology of hereditary neuromuscular and immunological disorders, which are less common but important. We also try to analysis the risk factors for AKI in these patients.

Materials And Methods

Patients and groups

This study was a retrospective single-center medical chart review of patients with a diagnosis of RM. The patients were included because of their histories and elevated serum creatine phosphokinase (CK) levels (> 1000 IU/L, at first presentation). They were admitted to the department of neurology of Children's Hospital of Chongqing Medical University from January 2010 to August 2019. Patients were excluded if they had: (1) a documented history of muscular dystrophy or other metabolic muscle disorders with stable condition and CK value; (2) a history of myocardial damage with a documented creatine kinase isoenzyme (CK-MB) fraction above 5%. The clinical data for 55 children with RM were collected. A standardized form was applied to review the medical records. All charts were reviewed by at least two authors. This project was authorized by the Ethics Committee of Chongqing Medical University.

Cases were divided into four age groups at the time of the first visit: (1) infant group (G1) (age < 1 year); (2) preschool group (G2) (age 1-6 year); (3) school-age group (G3) (age 7-11 year); (4) adolescent group (G4) (age 12-16 year).

Data Collection

Information on history and laboratory tests was collected. The history information included age,
gender, complaints, symptoms of infection (fever, cough, nasal obstruction, sore throat, vomiting, diarrhea, etc.), myalgia, muscle weakness, dark urine, oliguria, convulsions or disturbance of consciousness, multiple-organ dysfunction, history of exercise or trauma, past history (developmental milestones and history of RM), treatment plan, and outcome. The laboratory data analyzed included initial CK, peak CK, CK-MB, myoglobin (Mb), lactate dehydrogenase (LDH), aspartate aminotransferase (AST), alanine aminotransferase (ALT), urea nitrogen, blood electrolytes, serum creatinine, and urine routine. Cause classification was based on the patient's discharge diagnosis or follow-up assessment by specialists.

AKI is defined according to the KDIGO criteria as: (1) Serum creatinine (Scr) increases ≥ 26.5umol / L within 48 hours; (2) Scr increases above 1.5 times of the basic value within 7 days; (3) urine output decreases (< 0.5 ml / kg / h) and the duration is above 6 h.

**Statistical Analysis**

Statistical processing was performed using SPSS 17.0 software (IBM-SPSS; Chicago, IL, USA). The count data are expressed as percentages; the laboratory parameters (such as CK, ALT, AST, CK-MB, and LDH) were expressed as mean ± standard deviation (x ± s). Statistical comparisons were performed using the chi-square test or one-way ANOVA, and logistic regression was used to analyze risk factors for AKI. A p-value (P) < 0.05 was considered as indicative of a significant difference”.

**Results**

**Clinical Manifestations**

55 patients with RM (37 males and 18 females) were included in this study. Median age was 11 yr (inter-quartile range : 5.5-11 yr). 23 cases (41.8%) had fever; 13 cases (24%) had vomiting; 21 cases (38%) had myalgia; 15 cases (27%) had muscle weakness; 29 cases (53%) had dark urine; 16 cases (29%) had convulsions and/or consciousness disorder (Table 1). Significant differences were found among the groups in the clinical manifestations of fever, vomiting, and dark urine. 6 cases (78%) in the infant (G1) group were admitted because of vomiting. No signs of myalgia, muscle weakness, or dark urine were found in G1. However, in the adolescent (G4) group, 12 cases (50%) had myalgia; 8 cases (33%) had muscle weakness; 17 cases (71%) had dark urine.
Etiology

The most prevalent causes of RM were exercise (24%), infection (16%), immunological disorders (16%), and myopathy (15%), respectively. The most common etiologies among age groups were as follows: sepsis (57%) in the infant (G1) group; hereditary neuromuscular disease (44%) in the preschool (G2) group; immunological disorders (40%) in the school-age (G3) group; strenuous exercise (50%) in the adolescent (G4) group (Table 2).

Notably, 8 patients (15%) were diagnosed with hereditary neuromuscular disease. 2 of them were admitted with RM at the time of their first visit to the hospital. In 5 cases previously diagnosed with hereditary neuromuscular disease (4 with Duchenne muscular dystrophy, 1 with mitochondrial myopathy), RM was recurrent and induced by either infection or strenuous exercise. There was a 22 months old male with RM who was admitted because of vomiting and diarrhea. He had language development retardation, occasional walking instability, and mildly impaired coordination. His siblings died of vomiting, diarrhea, and coma at 3 years of age. His muscle biopsy did not show any specific changes. However, whole-exon sequencing revealed a heterozygous mutation in the TANGO2 gene. The patient was therefore diagnosed with TANGO2 variant-related metabolic encephalopathy with RM.

In addition, 9 patients (16%) in this study had immunological disorders. Among them, 4 cases had autoimmune encephalitis with RM during treatment. 2 of them were anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis; one was voltage-gated potassium channel complex (VGKC) antibody-mediated encephalitis; another case was anti-NMDA antibody combined with myelin oligodendrocyte glycoprotein (MOG) antibody encephalitis. Dark urine appeared after treatment with gamma globulin and/or glucocorticoids in these 4 cases. Moreover, vomiting and myalgia with muscle weakness happened in one patient with neuromyelitis optica after long-term use of prednisone.

Laboratory Tests

No significant differences between groups were found in CK, CK-MB, Mb, LDH, ALT, or AST (Table 3), indicating that there was no age-related difference in levels of these markers among children with
RM. However, abnormal urinalysis differed significantly among groups \( (P=0.039) \); urine abnormalities were significantly less common in the infant (G1) group (14%), compared with the other groups. Twenty patients had electrolyte disorders, including 17 cases with hypokalemia (3.5 mmol/L) and 12 cases with hypocalcemia (2.23 mmol/L). However, there was no significant difference among groups \( (p =0.863) \). 27 patients (49.1%) had AKI; nevertheless, the incident rate of AKI was not different among the groups.

To explore the factors involved in AKI, logistic regression was then applied to analyze the relationship between AKI and patient gender, age, peak CK, and presence of an electrolyte disorder (Table 4). The results indicated that AKI had no relationship with gender, age, or peak CK levels, but AKI was significantly associated with the presence of an electrolyte disorder. 18 of the 27 patients (67%) with AKI had an electrolyte disorder, while only two of 28 patients without AKI had an electrolyte disorder, suggesting that the presence of an electrolyte disorder was a risk factor for AKI among patients with RM.

**Outcomes**

In the G1 group, an infant with very long-chain acyl-CoA dehydrogenase deficiency died after 8 days in the intensive care unit. The remaining 6 patients improved after hydration and alkalinization and 2 of them had renal replacement therapy (RRT). 2 cases in the G2 group diagnosed with severe sepsis and 1 patient with febrile infection-related epilepsy syndrome (FIRES) was discharged abnormally. These patients died shortly afterwards. All of the remaining 7 cases in G2 were discharged with recovery. One case in G3 received RRT, and 3 cases (diagnosed as anti-NMDAR encephalitis, sepsis, and car accident, respectively) died shortly after abnormal discharge. The remaining 11 cases were fully recovered. 11 cases in G4 were treated with RRT. All cases in G4 recovered after discharge. The condition of the child with RM combined with TANGO2 variant-related metabolic encephalopathy improved after treatment with hydration and alkalinization. His CK levels returned to normal at the time of discharge. We adjusted mealtime and increased the amount of raw corn starch in his diet. No RM recurrence was observed at the one-year follow-up visit. All patients were followed by telephone.
The median follow-up time was 21 months. No patient had a recurrence of RM. There was no difference in outcomes among the four groups.

Discussion

RM is typically characterized by a clinical triad: myalgia, muscle weakness, and dark urine. However, < 10% of children with RM in this study had such typical signs. Indeed, more than 50% of patients only have dark urine without myalgia or muscle weakness\[^{5, 6}\]. The most common manifestation in this study was dark urine (53%), followed by fever (42%). Our data indicate that the clinical manifestations in children with RM are age related, which is similar to Chen’s findings\[^{7}\]. The younger the age is, the more atypical are the clinical manifestations. In the infant (G1) group, the common clinical manifestations were fever and vomiting with convulsions or disturbance of consciousness. The infants were not able to describe their feelings of myalgia and had negative urine test results. They did not have the typical triad of clinical manifestations. In this condition, they are easily misdiagnosed with other diseases such as encephalitis. The differential diagnosis requires careful attention. However, for older children with RM, especially adolescents (G4), the clinical triad was more common, and the incidence of positive urine test results was higher.

AKI is a common serious complication of RM that may be induced by myoglobinuria, hypovolemia, and/or metabolic acidosis, the probability of which is 10–60\[^{8}\]. Studies have reported that the factors affecting AKI in patients with RM are serum concentrations of potassium, creatinine, and albumin\[^{9}\]. Other studies have shown that serum calcium, phosphorus, potassium, and uric acid levels are independent predictors of AKI\[^{10}\]. A high CK level has been reported as a risk factor for AKI\[^{11}\]. However, other studies have shown no correlation between peak CK levels and AKI development\[^{12}\]. Our data showed that the overall incidence rate of AKI among patients with RM was 49%. No significant difference between age groups was found in peak CK or Mb. Complications of AKI were not found to correlate with age, gender, or peak CK levels. Our data showed AKI is associated with the presence of an electrolyte disorder. The pathophysiological mechanisms of AKI caused by electrolyte disorder may be as follows\[^{13}\]: Electrolyte disorders may cause abnormalities in Na + / K
+ ATPase on the proximal tubule cytoskeleton and lead renal tubular to damage. An increase in dense plaque-like calcium ions will activate phosphatase A2, leading to the release of arachidonic acid, which may eventually lead to the contraction of the arteriolar arteries and insufficient renal perfusion. In addition, increased free calcium ion concentration can cause increased activity of calpain and caspase-1, leading to increased release of interleukin-18, which may also cause renal tubular damage.

RM can result from various disorders including trauma, infection, excessive exercise, inflammation, drugs, metabolism, and heredity [14]. It has previously been reported that the most common causes of adult RM are trauma and drugs (up to 80% of cases). However, the top pathogens in pediatric RM are infections and congenital diseases [15, 16]. In this study, the most common cause of pediatric RM was strenuous exercise (24%), followed by infection (16%) and immunological disorders (16%). The most common cause of RM among babies is infection. Nevertheless, excessive exercise is an important cause among children with RM, especially adolescents. Studies have reported that pre-exercise factors, such as poor physical condition, high humidity, restrictive clothing, use of anticholinergics, hypokalemia caused by excessive sweating, and the use of drugs that enhance strength, may be associated with RM after exercise[17]. In addition, muscle tension (such as running downhill) causes eccentric contractions, which are more likely to induce muscle injury than concentric contractions[18].

With the development of new genetic detection technologies as next generation sequencing and whole exome sequencing in recent years, more hereditary causes including metabolic myopathies, structural myopathies, channel-related gene mutations, and other congenital hereditary metabolic diseases have been found to be associated with RM. Exome sequencing has revealed that 43% of RM cases have single-gene mutations[19]. It has been reported that 36% of limb-girdle muscular dystrophy 2I (LMGD2I) cases may experience recurrent RM[8]. Chan also reported an increased risk of RM in patients with Duchenne muscular dystrophy (DMD)/Becker muscular dystrophy (BMD), fukutin-related protein, dysferlin, γ-sarcoglycans, and anoctamin 5 deficiency-associated muscular
atrophy\textsuperscript{[20]}. In this study, the most common hereditary neuromuscular disease associated with recurrent RM was DMD, which may be unique to this Chinese population. It should be noted that some patients with myopathy have no clinical manifestations during the interval, and recurrent RM may be induced by certain triggers, such as strenuous activity, fasting, fever, infection, cold exposure, anesthesia, and drugs\textsuperscript{[21]}. The presence of hereditary myopathy should be investigated in any RM patient with any of the following conditions: recurrent RM, exercise intolerance, ptosis, eye muscle paralysis, dystonia, exercise-induced muscle spasm or muscle weakness, dark urine and myalgia induced by minimal exercise, family history of myopathy\textsuperscript{[21]}. RM could also happen in patients with immune encephalitis\textsuperscript{[22, 23]}. 9 patients included in the study had immunological disorders, 3 of whom had anti-NMDAR encephalitis. An important hypothesis is that the recovery of NMDA receptors after immunotherapy can suppress the dopaminergic system, leading to hypersensitivity to dopamine receptor blockers, which is likely to cause RM and neuroleptic malignant syndrome\textsuperscript{[22]}. However, in our study, only one case with VGKC antibody-mediated encephalitis was treated with chlorpromazine, haloperidol, and risperidone in succession. One patient with anti NMDAR encephalitis was treated with haloperidol. Another 2 patients with anti-NMDAR encephalitis were never treated with a dopamine receptor blocker. The reason for their RM could not be explained by this hypothesis. Notably, one study reported treatment with short-term high-dose steroid therapy in one RM patient who could not take intravenous fluids\textsuperscript{[24]}. We suspect that RM may be related to the special immune status in those patients. The specific pathogenesis is still unclear. More cases and further research are needed urgently.

**Conclusion**

The clinical features of 55 children with RM were analyzed in different age groups. The results indicated that clinical manifestations and laboratory findings in infants with acute RM are not typical and need to be taken seriously. Electrolyte disorder was a risk factor for AKI in the children with RM. In contrast to the etiology observed in adult cases, the most common cause of RM in children was strenuous exercise, followed by infection and immunological disorders. Also, congenital hereditary
disease should not be ignored as a cause of RM in children.

Declarations

Author Contribution: Ping Yuan designed the study. Ping Yuan and Zhengxiong collected and analyzed the data. Ping Yuan wrote the paper. Siqi Hong, Mei Li and Li Jiang helped to analyze the data.

Conflict of interest: On behalf of all authors, the corresponding author states that there is no conflict of interest.

Ethical approval: It was authorized by the Ethics Committee of Chongqing Medical University, Chongqing, China. Written informed consent was obtained from patients’ parents / caregivers.

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Tables

Table 1. Classification of clinical manifestations of RM among groups

|                | Total | G1 | G2 | G3 | G4 | P   |
|----------------|-------|----|----|----|----|-----|
| N              | 55    | 7  | 9  | 15 | 24 |     |
| Gender M:F     | 37:18 | 3:4| 6:3| 9:6| 19:5| 0.278|
| Fever n(%)     | 23(42)| 5(71)|7(86)|7(47)|4(17)| 0.002|
| Vomiting n(%)  | 13(24)| 6(78)|2(22)|2(13)|3(13)| 0.001|
| Myalgia n(%)   | 21(38)| 0  | 3(33)|6(40)|12(50)| 0.106|
| Muscle weakness n(%) | 15(27)| 0  | 4(57)|3(20)|8(33)| 0.198|
| Dark urine n(%)| 29(53)| 0  | 6(67)|6(40)|17(71)| 0.004|
| C/C n(%)       | 16(29)| 4(57)|3(33)|5(33)|4(17)| 0.191|
G1: age <1 yr; G2: age 1-6 yr; G3: age 7-11 yr; G4: age 12-16 yr; N: number of patients; M: male; F: female; C/C: convulsions and/or consciousness disorder.

Table 2. Etiology of RM among groups

|                  | G1   | G2   | G3   | G4   | Total n (%) |
|------------------|------|------|------|------|-------------|
| N                | 7    | 9    | 15   | 24   | 55          |
| Infection        | 4    | 1    | 4    | 0    | 9(16)       |
| Exercise         | 0    | 0    | 1    | 12   | 13(24)      |
| Immunological    | 0    | 2    | 6    | 1    | 9(16)       |
| Genetic          | 0    | 4    | 2    | 2    | 8(15)       |
| Metabolism       | 1    | 0    | 0    | 1    | 2(4)        |
| Poison/drug      | 0    | 1    | 0    | 3    | 4(7)        |
| Trauma           | 1    | 0    | 2    | 1    | 4(7)        |
| Unknown          | 1    | 1    | 0    | 4    | 6(11)       |

N: number of patients. Metabolism in this table means diabetic ketoacidosis. The situation of poison or drug is as follows: one patient had organophosphate poisoning, one took haloperidol 80 tablets by mistake, and another 2 cases got bee sting.

Table 3. Laboratory results for all groups

|                  | G1   | G2   | G3   | G4   | P       |
|------------------|------|------|------|------|---------|
| N                | 7    | 9    | 15   | 24   |         |
| CK(U/L)          | 1677.1 | 60475.3 | 64130.2 | 39622.3 | 0.271   |
| Mb(U/L)          | 3744.0 | 5052.0 | 5175.0 | 5998.0 | 0.893   |
| CK-MB(U/L)       | 280.8  | 568.1  | 246.7  | 277.0  | 0.270   |
| LDH(U/L)         | 2967.2 | 4244.2 | 4396.8 | 3434  | 0.743   |
| ALT(U/L)         | 921.7  | 891.6  | 657.8  | 374.6  | 0.341   |
| AST(U/L)         | 1200.0 | 1766.0 | 1751.0 | 1369.0 | 0.696   |
| Electrolyte disorder n(%) | 2(29) | 3(33) | 7(47) | 8(33) | 0.863   |
| Abnormal urinalysis n(%) | 1(14) | 6(67) | 10(67) | 18(75) | 0.039   |
| AKI n(%)         | 3(43) | 4(44) | 8(53) | 12(50) | 1.000   |

N: number of patients; CK: creatine phosphokinase; CK-MB: creatine kinase isoenzymes; LDH: lactate dehydrogenase; ALT: alanine aminotransferase; AST: aminotransferase; AKI: acute kidney injury.
Table 4. Logistic regression analysis for risk factors for AKI in children with RM

|                | OR (95%CI)                  | P       |
|----------------|----------------------------|---------|
| Gender         | 8.675(0.567-132.681)        | 0.121   |
| Age            | 0.899(0.700-1.142)          | 0.382   |
| CK             | 1.154(0.975-1.390)          | 0.133   |
| Electrolyte disorder | 92.526(5.704-1500.862) | 0.001   |

OR: odds ratio; CK: creatine phosphokinase