CASE REPORT

Three Cases of Rhabdomyolysis Induced by Viral Infections in Children and Literature Review

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Abstract The clinical data of 3 patients with rhabdomyolysis (RM) caused by different viral infections were retrospectively reviewed. The diagnoses were established according to the clinical symptoms, physical signs, myocardial enzymes, and muscle biopsy. Case 1 was a 11-year-old boy with influenza A virus infection, whose major symptoms were fever, cough and myalgia. After the treatment of active anti-virus, hydration, and alkalization, the patient completely recovered. Case 2 was a 10-year-old girl with Epstein-Barr (EB) virus infection who had significant musculoskeletal pain and muscle weakness symptoms with significantly elevated serum creatine kinase. After active hydration and anti-infective treatment, the patient's condition returned to normal. Case 3 was a 15-year-old boy with human cytomegalovirus infection, whose symptoms were mainly repeated fever, accompanied by myalgia and facial edema. Antibacterial therapy was ineffective, and the disease progressed with respiratory muscle weakness and multiple organ injuries. After antiviral treatment, respiratory support and hemofiltration, the symptoms relieved and patient recovered without sequela. With literature review, we believe that although influenza virus, Epstein-Barr virus and cytomegalovirus rarely cause RM in children, it should be attached attention to. With early diagnosis and treatment, the prognosis is favorable.

RHABDOMYOLYSIS (RM) refers to the damage of striated muscle cell membrane caused by trauma, ischemia, inflammation, metabolic abnormalities, or systemic poisoning, which results in leakage of cell contents, including myoglobin (Mb), enzymes, such as creatine kinase (CK), and ions, into blood circulation and consequently causes a group of clinical syndromes of tissue and organ damage. The clinical manifestations include myalgia, muscle weak-

ness, tawny urine, Mb urine, and elevation of serum CK and Mb.

The causes of RM are generally physical and non-physical.^[1] Physical factors include crush and trauma, exercise and excessive muscle activity, electric shock, and high fever, etc. Non-physical causes include drugs, poisons, infections, electrolyte disorders, autoimmune diseases, endocrine and genetic metabolic diseases. Infection is the most common cause in children with RM. It was reported that viral myositis were the etiology of more than a third of all RM cases among pediatric patients, especially in their first decade of life.^[2] Common pathogenic virus include influenza A/B virus, parainfluenza virus, adenovirus, Epstein-Barr virus, Coxsackie virus, Echo virus, herpes simplex virus,

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cytomegalovirus, HIV virus. Due to the low incidence of this disease in children and the diversity of its clinical manifestations, it is easy to be misdiagnosed, missed, or delayed for the treatment, and even leads to acute renal failure and other complications. In this study, we present 3 cases of RM in children who were infected with influenza virus, Epstein-Barr virus, and human cytomegalovirus respectively with comprehensive review of literature on this disease.

CASE DESCRIPTION

Case 1

A 11-year-old boy was hospitalized for intermittent fever, cough for 6 days, and myalgia for 2 days. Six days before admission, the child had fever, with a maximum body temperature of 40.2°C. He was referred to a local hospital and given intravenous infusion of "cephalosporin antibiotics" for 4 days, and his condition regressed. Two days before admission, the boy developed myalgia in the upper and lower extremities, with difficulty in walking. No rash, no dyspnea, normal urine volume and color, and normal defecation. He had been healthy with no special medication history and no recent strenuous exercise. Physical examination: normal vital signs, heart, lungs and abdomen were unremarkable. The tenderness of limbs was positive, with normal muscle strength, muscle tone of limbs, and normal sensory. The urine became tawny on the third day of admission. Blood routine examination: white blood cell (WBC) $3.63 \times 10^9/L$; urine routine examination: occult blood +++, protein ++, 5-8 red blood cells per high power field. On the second day of admission, the serum CK elevated to 12594 U/L, CK-MB was 322.6 U/L, and serum myoglobin (sMb) reached 497.6 ng/mL on the fourth day of admission. No abnormality in renal function. RT-PCR for the pharynx test strips revealed positive for *influenza A* virus. Clinical diagnosis: acute upper respiratory tract infection, RM.

The patient received oral oseltamivir for antiviral therapy, with symptomatic and supportive treatments, e.g., intensive infusion, alkalinized urine, etc. On the 6th day of admission, the patient could walk freely, myalgia was completely relieved, urine volume and color were normal. Recheck on the 8th day revealed CK 338U/L, CK-MB 18.7U/L, and sMb 49.3 µg/L. The patient recovered and was discharged from hospital. Follow up two weeks after discharge

showed normal myocardial enzymes, liver function, renal function, and urine routine, with no discomfort and symptoms.

Case 2

A 10-year-old girl was hospitalized due to intermittent fever and vomiting for 5 days, myalgia and tawny urine for 1 day. She was given oral antipyretic drugs as symptomatic treatment. One day before admission, she developed myalgia, most prominently on the inner side of the thighs, which was too severe to walk, accompanied with tawny urine. There was no rash, and defecation was normal. Personal history was unremarkable. Physical examination on admission: normal vital signs, heart, lungs and abdomen were unremarkable. Her consciousness was clear, but was dysphoria and complaining about the pain. The tenderness of the lower limbs was obvious, and prominent in the proximal end. Muscle strength was grade II, with increased muscle tension. Pathological reflex was negative.

After the admission, both her thighs began to swell, and the urine color continued to be tawny. Laboratory examinations showed elevation of WBC ($14.2 \times 10^9/L$), Urine occult blood +++, protein +++, urobilinogen +; significant increases in serum CK (549600 U/L), CK-MB (10530 U/L), AST (5080 U/L), ALT (1825.3 U/L), and sMb (896.4 µg/L). Etiological detection: Epstein-Barr virus (EBV) capsid antigen IgG +, EBV capsid antigen IgM +, EBV early antigen IgM +; EBV-DNA 3.21×10^5 copies/mL; other pathogens tested were negative. Electromyography revealed myogenic disorder. Pathology of muscle biopsy demonstrated multiple fibrous zone necrosis, regeneration, and striated muscle structure with no normal myofiber observed; the ragged red fiber was not found in Gomori's trichome staining, and no abnormalities were found in glycogen fatty staining; microangiogenesis in muscular mesenchyma and mild infiltration of inflammatory cells were observed around the vessels, which was consistent to the diagnosis of RM.

After anti-viral therapy (intravenous administration of ganciclovir) and supportive treatment, patient's swelling subsided and the pain was completely relieved on the 8th day of hospitalization. On the 14th day of hospitalization, the patient could walk independently, with muscle strength of grade IV and no swelling of the lower limbs. Rechecks of urine routine, liver function and myocardial enzymes were normal. The patient was

discharged from hospital. Nothing abnormal at the 1 month follow-up.

Case 3

A 15-year-old boy was admitted to the hospital due to fever for 15 days, myalgia and facial edema for 4 days. Urine color and urine volume were normal before admission. His medication history was unremarkable, and no recent strenuous exercise. Physical examination: body temperature 38.2°C, blood pressure 14/11 kPa. Facial edema accompanied with obvious bilateral eyelid swelling was observed; liver swelling 3 cm under the ribs. Laboratory examination: WBC $3.68 \times 10^9/L$, lymphocyte 0.35%; CRP 17.1 mg/L; CK 6730 U/L, CK-MB 114.4 U/L; AST 228.9 U/L, ALT 82.5 U/L; Urine routine: occult blood +++, protein +++, urobilinogen +.

As elevation of neutrophils and CRP indicated a possibility of bacterial infection, antibacterial treatment was given (cefuroxime, 60 mg/d, iv). Three days later, fever persisted, and both myalgia and face edema worsened. The patient developed limb weakness, difficulty in breath, tawny urine and reduced urine volume. Peripheral WBC $1.57 \times 10^9/L$; CK 42020 U/L, CK-MB 642.0 U/L, sMb 1114.0 $\mu g/L$; AST 982.5 U/L, ALT 281.2 U/L; kidney function was normal. Cytomegalovirus antibodies test: cytomegalovirus IgG antibody 4.794 S/CO, cytomegalovirus IgM antibody 2.324 S/CO, human cytomegalovirus pp65 antigen ++; other pathogens tested were negative. Muscle biopsy revealed muscle fibers varied in size, atrophic muscle fibers and nuclear shift were occasionally seen; muscle fiber cytoplasm partially dissolved with visible cavitation, supporting the diagnosis of RM.

The patient's condition worsened with respiratory failure and multiple organ injuries. Consequently, we conducted tracheal intubation and respiratory support, anti-human CMV virus treatment with ganciclovir, continuous renal replacement therapy (CRRT), and methylprednisolone sodium succinate (4 mg/kg/d). Three days later, the edema was relieved, fever was alleviated, and patient's condition improved gradually. The CRRT was discontinued after 7 consecutive days, and the mechanical ventilation was discontinued after 9 days. On the 22nd day of admission, recheck of blood routine, urine routine, liver function, renal function, and myocardial enzyme, were all normal. The patient was discharged with no discomfort. At one month follow-up, the patient was in good condition, walking well, with normal muscle strength, muscle tone, sMb,

serum myocardium enzymes, and liver function.

DISCUSSION

In children, infection is the most common cause of RM apart from trauma. Previous studies reported that viral myositis accounted for more than half of all pediatric RM cases, and physical exertion and seizure disorder were the second and third most frequent reasons, respectively.^[3-5] All three children in this study had no history of trauma, strenuous exercises, or taking special drugs or toxicants. Therefore, the etiologies were mainly referred to infectious aspects, and the relevant virus was clearly confirmed by the etiological examination. Pratt *et al.*^[6] detected varicella zoster virus DNA by PCR in muscle specimens from patients with RM, indicating direct viral invasion of muscle tissue. In Case 2 and Case 3 of this study, damages of muscle tissue were demonstrated pathologically by muscle biopsy, but no virus inclusion bodies were detected.

It was reported that clinically, typical symptoms, e.g. myalgia, muscle weakness, and tawny urine, were found in less than 10% RM patients.^[7] In this study, all three cases had myalgia, muscle weakness, and fever. However, one developed tawny urine before hospitalization and two developed tawny urine after the hospitalization. Therefore, even if there is no tawny urine, the symptoms of fever and myalgia should raise alert to the RM, a disease that early diagnosis can prevent serious consequences, such as acute renal failure. In the Case 3, as a 15-year-old boy was not considered being susceptible to human cytomegalovirus generally, he was treated for bacterial infection. The failure in diagnosis might delay the disease and lead to respiratory failure and multiple organ injuries. Therefore, strengthening awareness of the disease and timely diagnosis are important to reduce patient's suffering and economic burden. In addition, both the Case 1 and Case 3 had medication history of cephalosporin, and therefore need to be differentiated from drug-induced hematuria. Mostly, the drug induced hematuria is asymptomatic with no myalgia or muscle weakness, no abnormality in CK and Mb, and usually recover after drug withdrawal, which is not consistent with the three cases reported.

The management of RM generally focuses on treating the cause, preventing renal failure, and

reducing complications. For Case 1 and Case 2, antiviral and supportive treatments were effective, and the symptoms of the two children were quickly controlled with no complications. However, as pathogen in the Case 3 was not clear at the beginning of the disease, multiple organ injury and respiratory failure developed, but were controlled with the treatment of ganciclovir, mechanical ventilation, and CRRT which enable continuous removal of solutes and gradual correction of fluid overload. Previous studies have shown that CRRT may be beneficial for patients with RM for it removing circulating Mb and other nephrotoxic metabolites.^[8,9] Although the Case 3 presented oliguria and multiple organs injures with no kidney failure, we actively performed CRRT to remove macromolecular inflammatory mediators, stabilized the internal environment, and provided intravenous nutritional support, which was demonstrated effective.

In general, acute renal failure and electrolyte disturbances (hyperkalemia) are common life-threatening complications of RM. It has been reported that acute renal failure occurs in 13% to 46% of RM patients.^[10-12] The incidence of acute renal failure is much lower in children than in adults.^[2,13] In this study, the highest CK value in 3 cases was up to 549600 U/L, but none of 3 children had acute renal failure, although there were transient ion disorders. Regarding to the prognosis, patient with early diagnosis and treatment of the disease has a good prognosis. The three virus infections in the current report are common in children, and the manifestations can be various. Influenza viruses mainly lead to respiratory infections; Epstein-Barr virus and cytomegalovirus mainly cause children's pneumonia, blood system disorders and liver damage; muscle invading as in the reported 3 cases is relatively rare. According to our literature searching on viral infections in children with RM, studies were mainly on a single pathogen, or a single case, or on a single pathogen and multiple cases. The current article describes 3 cases of RM caused by 3 different pathogenic infections, by which we hope to provide readers a deeper understanding about this disease.

Conflict of interests disclosed

None.

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