CASE REPORT

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Rhabdomyolysis and coronavirus disease-2019 in children: A case report and review of the literature

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ABSTRACT

Introduction: Coronavirus disease-2019 (COVID-19) presents with a variety of symptoms, but rhabdomyolysis has rarely been reported in children.

Case presentation: We report a 10-year-old girl who presented with fever, myalgia, and limping. The patient was tested positive for severe acute respiratory syndrome coronavirus-2. On admission, creatine kinase (CK) level was 13 147 units per liter and the patient was diagnosed with rhabdomyolysis. She was treated with intravenous fluids, which resulted in CK levels decrease. There are currently seven case reports of children with rhabdomyolysis associated with acute COVID-19 infection and two reports with the multisystemic inflammatory syndrome.

Conclusion: Children presenting with muscle pain and weakness in the acute phase or following COVID-19 infection, should alert physicians of the possibility of rhabdomyolysis.

KEYWORDS

Adolescents, Children, COVID-19, MIS-C, Rhabdomyolysis, SARS-CoV-2

INTRODUCTION

Coronavirus disease-2019 (COVID-19) affects all age groups worldwide. COVID-19 infection can present in children with symptoms from the upper and lower respiratory tract, the gastrointestinal system, the skin, and cardiovascular system.[1] Rhabdomyolysis has been previously reported in adults and is attributed to direct toxicity from severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) or to an increased inflammatory response.[2]

SARS-CoV-2 associated rhabdomyolysis has rarely been reported in children.[3] Rhabdomyolysis is defined as an acute muscle breakdown that can lead to muscle weakness, myalgia, and occasionally brownish urine. We present a case of rhabdomyolysis in a child with COVID-19 infection and concomitantly review all literature data related to rhabdomyolysis in children diagnosed with acute COVID-19 infection or multisystem inflammatory syndrome.

CASE REPORT

A 10-year-old girl who was previously healthy attended the pediatric emergency department with a 2-day history of pain in the lower extremities and limping. She was febrile (up to 39.1°C twice daily) and was complaining of

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headache 5 days prior to admission, but symptoms subsided within 3 days. The patient developed mild diarrhea but did not report cough, breathlessness, vomiting, or decreased sense of smell or taste. Antipyretics were utilized by the patient. She denied any history of dark urine. From the previous history, she was participating in sports and had no history of recent trauma or changes in the training schedule. The patient had a nonsignificant previous medical history.

On the initial examination, she was afebrile with normal vital signs. The respiratory examination and chest X-ray were normal. Initial laboratory investigations revealed lymphopenia (absolute lymphocyte count: 1×10^9/L), normal C-reactive protein (1.4 mg/L, normal range 0–3 mg/L), and marked elevation of creatine kinase (CK) at 13 147 U/L (normal range: < 140 U/L). Lactate dehydrogenase was 631 U/L (normal range: 120–300 U/L). Liver function tests were abnormal with aspartate aminotransferase at 288 U/L (normal range: < 60 U/L) and alanine aminotransferase at 67 U/L (normal range: < 45 U/L).

The renal function was normal, without evidence of red blood cells or hemoglobin in the urine. The patient had a normal electrocardiogram and echocardiogram. The SARS-CoV-2 polymerase chain reaction (PCR) test was performed on the nasopharyngeal swab and was positive with a low cycle threshold (ORF 16/N 15). The upper respiratory panel was positive only for SARS-CoV-2. The serology for Epstein–Barr virus and cytomegalovirus were negative. She started to receive intravenous fluids (1.5 times the daily fluid requirement appropriate for the patient's weight), which resulted in significant improvement of myalgia and decrease in CK to 9107 U/L 12 h later. The following day, CK further decreased to 3824 U/L and the myalgia had resolved. The intravenous fluids were then stopped and the patient was discharged the day after. During the follow-up visit, the child was normal and CK was further decreased to 120 U/L.

The research team has conducted a search on PubMed and Google Scholar using the following search terms COVID-19, a multisystem inflammatory syndrome in children (MIS-C), rhabdomyolysis, children, and adolescents. Our search has retrieved seven case reports of children-adolescents with rhabdomyolysis after acute COVID-19 infection and two reports associated with the multisystem inflammatory syndrome (see Table 1).

In all seven cases of acute COVID-19 infection with rhabdomyolysis, the patients were males with a mean age of 15 years old in contrast to the two female patients with MIS-C and a mean age of 9 years.

CK values ranged from 3392 to 427 656 U/L. Obesity was reported in three out of seven cases of acute COVID-19 infection. Among the seven reported cases of acute COVID-19 infection, one presented with acute renal failure and the need for renal replacement therapy, whereas the two MIS-C associated cases presented with acute renal failure, one of them required renal replacement therapy. One out of the seven reported cases of acute COVID-19 infection had initial symptoms of abdominal pain, vomiting, and diarrhea whereas all two MIS-C-associated cases reported abdominal pain and diarrhea. In terms of management, hyperhydration was used in 5/9 cases, whereas sodium bicarbonate was additionally prescribed in 4/9 cases. Three children out of seven with acute COVID-19 infection were prescribed drugs (1/3 received azithromycin and paracetamol, 2/3 paracetamol, 3/3 chlorothiazide, lisinopril, and metformin). A computed chest radiograph was performed in two cases of rhabdomyolysis associated with acute COVID-19 infection and in both cases there were no abnormal radiological findings. Intravenous immunoglobulins (IVIG) and steroid therapy were administered in the two cases of MIS-C with subsequent improvement of myalgia and CK levels. In all reported cases, a SARS-CoV-2 PCR test was used to confirm SARS-CoV-2 infection, except for one case for whom a Rapid Antigen SARS-CoV-2 test was applied.

DISCUSSION

Herein, we present a pediatric patient with rhabdomyolysis and intact renal function as the initial manifestation of COVID-19 infection. Interestingly, myalgias of the legs and weakness with a history of fever were the only symptoms of acute COVID-19 infection. In our patient, there was no history of recurrent episodes of muscle pain, exercise intolerance, or a positive family history of myopathies; hence the possibility of metabolic myopathy was excluded.

The diagnosis of rhabdomyolysis was based on clinical symptoms and the raised CK level. Most studies support the use of CK as the most reliable biochemical marker for the diagnosis and monitoring of rhabdomyolysis severity.[12] Aldolase is another enzyme of the glycolytic pathway which can be found in the brain, liver, and skeletal muscles. However, it is not specific nor sensitive for muscle injury. Nevertheless, when the diagnosis is not clear then raised aldolase along with high CK levels is suggestive of muscle injury.[13] The diagnosis was clear in our patient based on the clinical history, examination, and raised levels of CK, hence aldolase test was not performed.

Acute childhood myositis manifestations can range from benign myalgia to rhabdomyolysis and may be associated with myoglobinuric renal failure.[14] The differential diagnosis includes metabolic inherited diseases, muscle overexertion, toxins, or inflammation. Various triggers may result in rhabdomyolysis including traumatic causes such as multiple trauma, crush injury, surgery, immobilization, and nontraumatic reasons such as extreme exertion,

TABLE 1 Published reports of rhabdomyolysis in children and adolescents associated with coronavirus disease-2019 (COVID-19) acute infection or multisystem inflammatory syndrome

Reference	Age (year)	Sex	Coexisting conditions	Fever (>38°C)	Respiratory symptoms	Muscle pain	CK (U/L)	Survived
Acute COVID-19 infection								
Tram et al.[3]	15	Male	No	No	No	Proximal muscle pain	21 876	Yes
Gilpin et al.[4]	16	Male	Asthma	Yes	No	Shoulders and thighs	116 640	Yes
Gefen et al.[5]	16	Male	Autism, morbid obesity	Yes	Yes	Arms, legs, and back	427 656	Yes
Anwar et al.[6]	16	Male	No	Yes	Yes	Myalgia and leg weakness	Not available	Died
Armanpoor et al.[7]	10	Male	No	Yes	Yes	Myalgia and leg weakness	8000	Yes
Samies et al.[8]	16	Male	Obesity, hypertension, type 2 diabetes mellitus, and obstructive sleep apnea	Yes	Yes	Upper and lower extremities	274 664	Yes
Bach et al.[9]	16	Male	Morbid obesity, anaphylaxis	No	Yes	Myalgias exacerbated by ambulation	64 560	Yes
Multisystem inflammatory syndrome								
Fabi et al.[10]	6	Female	No	Yes	Yes	Lower extremities	3392	Yes
Cassim et al.[11]	12	Female	No	Yes	Yes	Myalgia and leg weakness	22 000	Yes

Abbreviation: CK, creatine kinase.

environmental heat illness, seizures, metabolic and mitochondrial myopathies as well as drugs, toxins, infections, endocrinopathies, and inflammatory myopathies. In some patients, no etiology is identified.[13] In a study by a pediatric tertiary care hospital that included 191 children with rhabdomyolysis, viral myositis, trauma, and connective tissue disorders were found to be the most common causes of rhabdomyolysis.[13] The frequency of acute renal failure in this study (5%) was much lower than that reported in adult studies. In a large study of children with recurrent rhabdomyolysis, a metabolic cause was detected in 24% of cases.[15] The most common metabolic cause of recurrent myoglobinuria in both adults and children is carnitine palmitoyltransferase 2 deficiency.

Rhabdomyolysis can also be a feature of a group of conditions, called autoimmune myopathies. These disorders include dermatomyositis and polymyositis and present mainly with muscle weakness, raised levels of CK, and lymphocytic infiltration of the muscle. The presence of these conditions is usually subacute and is associated with other systemic manifestations of autoimmunity, such as heliotrope rash and Gottron papules in dermatomyositis and arthritis, interstitial lung disease, and fever in polymyositis. Systemic lupus erythematosus and autoimmune hepatitis have also been reported to be associated with rhabdomyolysis mainly in adult patients.[16] The patient we present did not fulfill any other criteria of a coexistent autoimmune condition and rhabdomyolysis responded to the treatment, hence our team did not perform further investigations with the autoimmune panel.

Possible mechanisms of rhabdomyolysis in SARS-CoV-2 infection include direct viral destruction of the muscle cells or collateral muscle damage precipitated by an excessive immune response.[6,9] Dalakas describes that SARS-CoV-2 connects to the angiotensin-converting enzyme 2 receptor, which is expressed in skeletal muscle cells and leads to down-regulation of renin-angiotensin, directly changing muscle integrity.[17] Interestingly, a recent case report of a child with severe rhabdomyolysis associated with MIS-C has demonstrated clinical improvement after IVIG suggesting an immune-mediated mechanism comparable to the pathogenesis of necrotizing autoimmune myositis described in up to 10% of adults with COVID-19 infection.[10,18] In a recent cohort multicenter study from the Americas and Europe on 17 children with critical COVID-19 requiring intensive care, no cases of myositis or rhabdomyolysis were observed.[19]

Children with COVID-19 may present with a wide range of clinical manifestations which are nonspecific and severe, such as immune thrombocytopenia, multisystem inflammatory syndrome, respiratory failure, severe thrombocytopenia, and myocarditis, especially in patients presenting with primarily gastrointestinal symptoms.[4,19] In our study, three out of seven children with acute COVID-19 infection reported obesity, which is a known risk factor for severe illness with SARS-CoV-2.[20]

The fluid management of severe rhabdomyolysis and COVID-19 infection can be challenging. Patients diagnosed with rhabdomyolysis should receive careful fluid administration to prevent acute kidney injury from myoglobinemia. However, patients with COVID-19 may suffer from acute respiratory distress syndrome and the excessive administration of fluids could result in volume overload, deterioration of lung function, and respiratory failure, which could further compromise renal function.[21] Therefore, it would be advisable to implement prudent fluid use while monitoring urine output, creatinine and CK trend, oxygen requirement, as well as a frequent physical examination to detect early signs of fluid overload. There is no evidence that bicarbonate therapy is more effective than saline in preventing acute kidney injury.[22]

The prompt identification of rare manifestations of SARS-CoV-2 is important for the appropriate testing and management. Furthermore, continuous monitoring of novel presentations will be helpful for clinicians as SARS-CoV-2 presents with a very wide range of clinical symptoms.[23]

In summary, COVID-19 in children can present with nonspecific symptoms, without respiratory system involvement and clinicians should have high vigilance in such cases. Rhabdomyolysis should be ruled out in COVID-19 patients presenting with muscle pain of the extremities with or without associated weakness and dark urine. Judicious use of fluids is mandatory to avoid fluid overload and compromise of respiratory function.

CONSENT FOR PUBLICATION

Written consent was obtained from the patient's parents.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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