Archives of the Balkan Medical Union
vol. 57, no. 2, pp. 191-196
June 2022
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CASE REPORT

MELTING MUSCLES: PARAINFLUENZA-INDUCED RHABDOMYOLYSIS

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Received 15 March 2022, Accepted 26 April 2022
https://doi.org/10.31688/ABMU.2022.57.2.09

Abstract

Rhabdomyolysis (RML) is a potentially life-threatening condition with diverse etiology. Infections, and less frequently metabolic diseases, are most often responsible in young children. The classical clinical triad includes myalgia, muscle weakness, and dark urine, combined with a rapid increase in creatine kinase concentration. Timely administered, aggressive hydration is important to preserve renal function and prevent acute kidney injury (AKI). We reported the cases of two children with muscle damage caused by parainfluenza viruses 2 and 3. One of the patients had benign myositis and the other pneumonia and RML, complicated by AKI. The presence of one obvious cause of RML such as

Résumé

Destruction des muscles: rhabdomyolyse induite par le virus para-influenza

La rhabdomyolyse (RML) est une maladie potentiellement mortelle d'étiologie diverse. Les infections, et moins fréquemment les maladies métaboliques, en sont le plus souvent responsables chez les jeunes enfants. La triade clinique classique comprend des myalgies, une faiblesse musculaire et des urines foncées, associées à une augmentation rapide de la concentration de la créatine-kinase. Une hydratation agressive administrée en temps opportun est importante pour préserver la fonction rénale et prévenir les lésions rénales aiguës

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respiratory infection did not preclude us to search for another, especially in the absence of a clear diagnosis. Nevertheless, in our case, it was parainfluenza virus 3 that caused RML, complicated with AKI. The final and accurate microbiological diagnosis, based on multiplex PCR, is needed for better management of the patients.

Keywords: rhabdomyolysis, acute kidney injury, parainfluenza viruses, children, multiplex polymerase chain reaction.

List of abbreviations:
RML – rhabdomyolysis
AKI – acute kidney injury
mPCT – multiplex polymerase chain reaction
HPIV- human parainfluenza viruses
CP – creatine kinase
CK-MB – creatine kinase MB

(AKI). Nous avons rapporté les cas de deux enfants atteints de lésions musculaires causées par les virus para-influenza 2 et 3. L'un des patients avait une myosite bénigne et l'autre – une pneumonie et un RML, compliqués par AKI. La présence d'une cause évidente de RML telle qu'une infection respiratoire, ne nous a pas empêchés d'en rechercher une autre, surtout en l'absence d'un diagnostic clair. Néanmoins, dans notre cas, c'est le virus para-influenza 3 qui a causé le RML, compliqué d'IRA. Le diagnostic microbiologique définitif et précis, basé sur la PCR multiplex, peut aider à une meilleure prise en charge du patient.

Mots-clés: rhabdomyolyse, insuffisance rénale aiguë, virus para-influenza, enfants, amplification en chaîne par polymérase multiplex

Introduction

Human parainfluenza viruses (HPIVs) are important respiratory pathogens in the pediatric and immunocompromised population. There are four HPIV serotypes (HPIV-1, HPIV-2, HPIV-3, and HPIV-4) with a seasonal specific for each of them[1]. HPIV-1 and HPIV-2 account for approximately 60-75% of croup in young children[2]. HPIV-3 is the most virulent and is second only to the respiratory syncytial virus as a cause of pneumonia and bronchiolitis in the first year of life[3]. With the more widespread use of multiplex molecular testing, HPIV is being recognized as a relevant pathogen in other patient groups, such as hospitalized adults[4]. In addition, there are increasing reports about extrapulmonary manifestations of HPIVs, including the central nervous system, myocardium, or skeletal muscles. However, this has probably been overlooked, mainly due to their substantial association with respiratory diseases[5].

We reported two cases with HPIV-induced muscle damage with a different clinical spectrum: a 5-year-old boy with benign myositis and a 12- year-old boy with rhabdomyolysis (RML), complicated with acute kidney injury (AKI).

Case presentations

The first case presentation

A previously healthy 5-year-old male was admitted to hospital with a 3-day history of mild fever and pain in both legs. He was treated by his physician with ibuprofen. The fever resolved and the pain reduced. On the day of admission, he woke up with excruciating pain in his legs and refused to bear weight. His vitals were within normal limits. The exam was remarkable for exquisite tenderness to palpation over both his calf muscles, without redness and warmth. Tendon reflexes were normal. Joint swelling and tenderness were absent. A provisional diagnosis of myositis was made. Blood investigations revealed normal renal and liver function tests, full blood count, calcium, potassium, and sodium. The only abnormal blood results were a high creatine-kinase (CK) level of 4829 U/L (reference range, 20-200 U/L) and mildly elevated aspartate aminotransferase and lactate dehydrogenase. CK gradually decreased over the next days to 1587 U/L on discharge. The urinalysis showed protein 3+, pH of 6.9, ketone 3+, on microscopy – no cells. He was treated with intravenous fluids and analgesics. A nasopharyngeal specimen was tested for various respiratory pathogens by a multiplex polymerase chain reaction (mPCR) (Film Array, bioMerieux, France) and it was found positive for human parainfluenza virus type 2. Electrocardiogram, abdominal ultrasonography, and chest X-ray found no abnormalities. He was closely monitored for urine output and myoglobinuria (risk for RML). The pain settled over the next 3 days, and he started to gradually bear weight on his legs. He was discharged completely recovered after 4 days.

The second case presentation

A 12-year-old male with psychomotor retardation and spastic quadriplegia presented with high fever, dyspnea, tachycardia, and reduced urine output for one day. The child (of Russian descent) and his family were visiting relatives in a neighbouring city.

His past medical history was remarkable for cerebral palsy because of perinatal asphyxia, and symptomatic epilepsy with severe mental retardation. His pharmacological-resistant epilepsy has been controlled only after being put on a ketogenic diet a year ago. At the time, the metabolic panel was negative. His sister had rhinorrhea and cough.

The boy was admitted to a local hospital in the city because of deterioration of his general condition, difficult eating, and reduced urine output for one day. On presentation, he was febrile with tachypnea, tachycardia, and crackles in the left lung base. Laboratory studies were remarkable for electrolyte abnormalities and elevated levels of creatinine and blood urea nitrogen. After stabilization, he was transferred to another hospital on the same day and admitted to the pediatric intensive care unit for additional evaluation and treatment.

Upon admission, he was severely dehydrated, dyspneic, and unresponsive, with occasional cough. Vital signs were as follows: temperature of 39°C, tachypnea (40 breaths/minute), tachycardia (140 beats/minute) with normal heart sounds, and oxygen saturation of 95% in room air. Auscultation revealed bibasilar crackles in both lungs. Spastic quadriplegia was present, without meningeal signs.

The initial complete blood count disclosed severe hemoconcentration. Biochemical analysis revealed very high creatine kinase (CK) of 68125 U/L (20-200) and creatine kinase MB (CK-MB) of 322 U/L (<25). Aspartate aminotransferase, alanine aminotransferase, and lactate dehydrogenase were also markedly increased, consistent with skeletal muscle necrosis (Table 1). Serial troponin results were normal. Creatinine and blood urea nitrogen levels were increased, 352 mmol/L (74-134) and 36 μmol/L (3.2-8.2), respectively. The electrolyte profile was notable for elevated sodium and reduced levels of potassium and calcium in the serum. The diagnosis of acute RML with AKI was made.

Triglycerides and cholesterol levels were within normal range. The initial serum glucose concentration was 14.2 mmol/L and on the second day 23.3 mmo/L, but spontaneously returned to normal. Hemoglobin A1 was 5.53% (4-5.6%) and oral glucose tolerance test 8.9 mmol/L after 180 minutes, planned to be repeated after a month. Thus, his elevated serum glucose level probably represented a stress response. The coagulation parameters and ammonia were normal. Arterial blood gases revealed metabolic acidosis.

The urine analysis with a dipstick revealed a pH of 5.0, protein 2+ and blood+, microscopy showed 3 red blood cells /high-power field (0-5). Myoglobin in the urine was not assessed. A metabolic panel was submitted to the national genetic laboratory in Sofia, but the results were not received until the discharge.

Aggressive hydration with normal saline, sodium bicarbonate and empiric intravenous ceftriaxone was administered after a blood culture set was obtained. On the second day, local seizures developed. Phenobarbital and midazolam were initially administered and later replaced by levetiracetam.

A nasopharyngeal specimen was tested by mPCR (Film Array, bioMerieux, France) and it was found positive for HPIV type 3. On admission, chest X-ray was unremarkable. As the high fever continued, the repeated X-ray after four days showed bilateral infiltrates. Antibiotic coverage was broadened to include intravenous cefepime and levofloxacin. Abdominal ultrasonography demonstrated normal kidney size and echogenic structure. Blood and urine cultures remained negative.

Over the next days, the patient's general condition slowly improved, his urine output increased, and

Table 1. Laboratory parameters of interest over time.

Date	*Creatinine* μmol/L	*BUN* mmol/L	*CK* U/L	*AST* U/L	*LDH* U/L	*AST* U/L
Day 1*	352	35.6	62 126	234	6067	24.7
	321	35.2	90533	404	6896	1406.2
Day 2	292	31.3	212 897	807.1	20449	2735.8
Day 3	120	16.4	181 859	731.8	13074	222.5
Day 4	55	4.2	77 729	669.9	4737	1456.6
Day 6	55	4.9	61853	665	4629	723.6
Day 9	46	4.0	25 910	481	1945	233.8
Day 12	39	2.9	8942	339		
Day 14	35	2,2	-	-	-	-

Abbreviations: AST, Aspartate aminotransferase (0-50 U/L); ALT, Alanine aminotransferase (0-45 U/L); CK, Creatine kinase (20-200 U/L); Creatinine (74-134 μmol/L); BUN, Blood urea nitrogen (3.2-8.2 mmol/L); LDH, Lactate dehydrogenase (230-460 U/L). Reference ranges are given in parenthesis.
*On day 1 the patient was tested twice

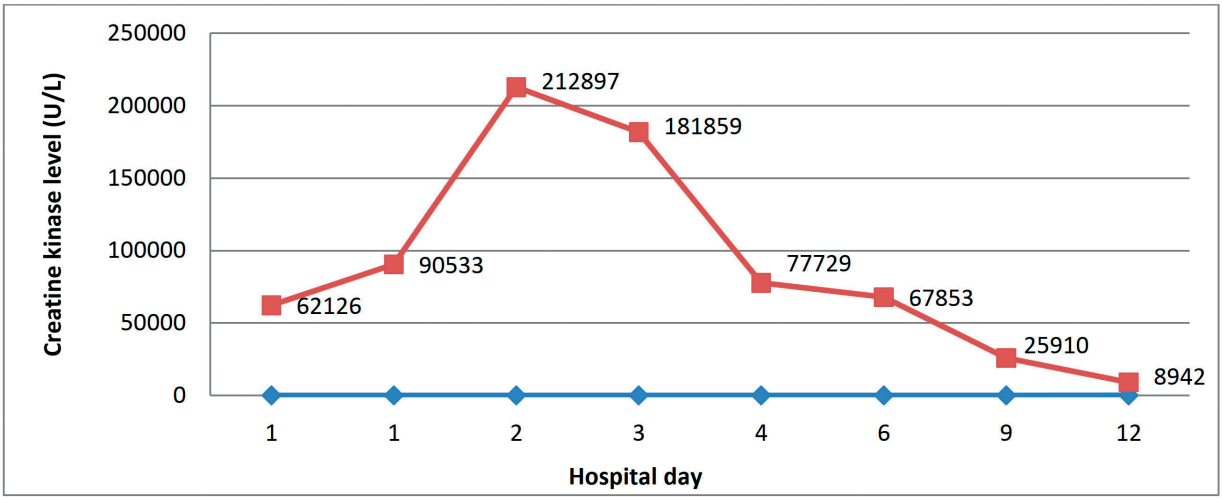


Figure 1. Creatinine kinase concentration overtime.

creatinine and blood urea nitrogen levels decreased. However, CK and CK-MB continued to rise on day 2, with a peak of 212 897 U/L and 1300.5 U/L, respectively, and CK gradually trended down (Figure 1). Respiratory symptoms also improved. Blood and urine cultures were repeatedly negative.

The patient was discharged on day 19, with restored renal function, a CK level of 8000 U/L, and a prescription for levofloxacin and levetiracetam. A follow-up visit was scheduled after five days. However, his parents had never returned to the hospital. Two months later, the results of the metabolic panel in our premorbid impaired child returned negative.

Discussion

We reported two children with HPIV-induced muscle damage in both extremes of severity – ranging from benign self-limiting myositis to RML, complicated by AKI.

Benign myositis after an acute viral illness is a clinical condition that typically presents with sudden onset of leg pain and difficult walking and is mostly self-limiting. RML is a rare but severe complication, particularly after influenza A virus infections[6].

RML is a potentially life-threatening condition due to skeletal muscle injury. It is followed by the release of cell components, such as myoglobin and CK, into circulation[7]. The classical clinical triad includes myalgia, muscle weakness, and dark urine, combined with a rapid increase in CK level. Although there is no formal consensus, RML is usually defined by a serum CK concentration of > 1000 U/L, which is five times the upper limit of normal. This is the standard definition for a mild RML. In addition, other causes of CK elevation such as myocardial, cerebrovascular, and renal events and neuromuscular disorders, should be ruled out[7]. Acute kidney injury is the most recognizable delayed complication. The etiological list of RML is extensive and variable. Drugs and trauma are the most common causes in adults, while infections and less frequently metabolic disorders are responsible for pediatric RML[8]. Some pathogens, mainly respiratory viruses, have been reported to induce RML[9], including SARS-CoV-2[10].

Following the first pediatric case of HPIV-induced viral myositis, published in 1976, nine more cases in children have been reported in the PubMed database in the English literature[11-13]. Three of them have developed RML and AKI. The 12-year-old boy we presented is the fourth case of HPIV-3-induced RML, diagnosed by mPCR, complicated by AKI.

The typical clinical picture consists of myalgia, muscle weakness, and dark urine, but not all symptoms are present at the same time. Less than 10% of patients show these characteristics simultaneously and only 3.6% have dark urine[14]. This points to a potentially insidious beginning of RML. Myalgias are the main and often the only symptoms in pediatric patients. In young children, due to lack of cooperation, it is difficult to distinguish muscle weakness from uncoordinated walking. Regarding myalgia, it is not always possible to decide whether muscle tenderness or pain are related to the presence of RML or another underlying chronic condition. The diagnosis can be more challenging, as in our older patient. Due to delayed psychomotor development and spasticity, he was not able to complain of muscle soreness or weakness.

Given the non-specificity and variability of the symptoms, the clinical diagnosis is difficult. Therefore, two laboratory parameters have diagnostic importance: CK, the most sensitive enzyme marker

for muscle breakdown, and myoglobin, pathognomonic for RML.

The acute elevation in CK concentration and its chronological sequence is mostly used for diagnosis[7]. Serum CK begins to increase within 2 to 12 hours after the initial muscle insult, peaks at approximately 2 to 5 days, then decreases at a relatively constant rate, and returns to normal in most patients 6 to 10 days later[15]. The concentration of CK is directly proportional to the degree of muscle injury. If CK does not decline as expected, there may be ongoing muscle injury or the development of compartment syndrome, another serious RML complication. Like the high level of CK in our case, severe forms of RML are characterized by CK concentration > 5000-10 000 U/L. It is not yet clear whether higher CK levels possess a greater risk for AKI, as CK is only a surrogate marker of myoglobin nephrotoxicity[16].

Myoglobin may be evident by the passing dark (reddish-brown) urine, which, however, is short-lived. Thus, it can be easily overlooked by patients and clinicians. The myoglobin level, which rises before CK level, can be detected in urine or serum but only if examined within the first 24 hours. Its half-life of only 1 to 3 hours often leads to false-negative results. Nevertheless, lack of myoglobin due to the timing of measurement does not rule out the diagnosis. As in our case, urinary dipstick positive for blood in the absence of red blood cells is suspicious for myoglobinuria and supports the diagnosis[17].

At admission, this patient was diagnosed not only with RML, but also with AKI. We suppose that his severe dehydration was a contributing factor to the early onset of this otherwise delayed complication. The exact mechanism is not yet known, but kidney vasoconstriction, hypovolemia, direct myoglobin toxicity, and tubular obstruction may contribute to the development of kidney injury[18]. According to the largest study of pediatric RML[19], the risk of AKI in children is 5-8%, lower than in adults. Contrary to expectations, viral rhabdomyolysis does not cause AKI less frequently than the nonviral etiology of RML[20]. Notably, the initial degree of CK elevation is not a reliable predictor for AKI[20,21].

The overall goal in the treatment of RML is to preserve the renal function and prevent AKI. Regardless of the underlying etiology when RML is suspected, it is important to initiate aggressive intravenous rehydration and correct electrolyte abnormalities. The treatment is most effective if administered early, ideally within the first 6 hours after a muscle insult[22]. The addition of sodium bicarbonate to alkalize the urine aims to reduce the intra-tubular precipitation of myoglobin. However, the current guidelines do not support its routine use[23]. Bicarbonate should be mainly used for the treatment of acidosis. When hydration therapy fails and overt renal failure develops, continuous renal replacement therapy must be administered. Conventional hemodialysis does not effectively remove myoglobin due to its size. However, the benefits of the former are still controversial[24]. Our patient responded to the therapy and was discharged with resolved AKI, down-trending CK level, and normalized electrolyte levels.

Other potential serious pathologies should be considered. We excluded the presence of endocarditis by normal serial troponin tests and transthoracic echocardiography in our case. However, without an accurate reason for RML and given the CK elevation higher than expected, we hypothesized the existence of a metabolic disorder even in the presence of HPIV-3 infection. It is not uncommon for the infection to trigger the acute decompensation of a metabolic disorder. Although the initial assessment often begins in the hospital, the final diagnosis is made only after discharge, as test results are obtained weeks later[25]. Fortunately, the metabolic results of our patient were negative again.

Conclusions

RML is a potentially life-threatening condition with a non-specific clinical presentation. This requires a high index of suspicion and timely testing for CK, and myoglobin. Infections, and less frequently metabolic diseases, are most often responsible in young children, necessitating rapid microbiological diagnostic techniques. The presence of an obvious viral cause of RML should not preclude unveiling the other. HPIV has not triggered the acute decompensation of an underlying metabolic disease in our case. However, it was HPIV-3 that caused RML, complicated with AKI. The final and accurate microbiological diagnosis, based on mPCR, could be useful for better management of the patient.

Authors' contributions:

A.A. was the principal investigator responsible for the microbiological examination, writing the manuscript, and reviewing the literature. M.A. was responsible for the design of the study, data review, and reviewed the manuscript. R.K. was responsible for writing the manuscript, reviewing the literature and the review editing. K.K. and I.P. were responsible for the data acquisition and data review. G.L. and Y.K. were responsible for the microbiological investigations and data review. M.M. was responsible for the microbiological investigations, and the review editing. All authors have seen and approved the final version of the manuscript

Compliance with Ethics Requirements:

„The authors declare no conflict of interest regarding this article"

„The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law. Informed consent was obtained from the children's parents included in the study."

Acknowledgments:

This article was funded by the Intra-university project „DPDP-02/2020" Medical University of Plovdiv, Bulgaria, and the Project „National University Complex for Biomedical and Applied Research, linked to participation in BBMRI-ERIC (NUCCI-BBMRI. BG), Contracts D01-285 / 17.12.2019 and D01395/ 18.12.2020, within the National Roadmap for Research Infrastructure (2020 – 2027).

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