

Case Report

Rhabdomyolysis following influenza A infection in children: case report and literature review

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Abstract: Influenza A infection is commonly associated with respiratory illness, ranging from mild upper respiratory infection to severe pneumonia and acute respiratory distress syndrome. Rhabdomyolysis is an uncommon but potentially fatal extrapulmonary complication of influenza A infection. Here, we report a rare case of rhabdomyolysis in a pediatric patient with influenza A infection. An 11-year-old girl had a tight cough and severe myalgia. It was noted she had contact with a classmate suffering from influenza-like syndrome. A rapid antigen test for influenza A was positive. Laboratory data showed a remarkably high level of creatine kinase (CK) level at 2,866 U/L. Based on these examinations, the girl was diagnosed with rhabdomyolysis as a complication from the influenza A infection. With treatment of aggressive hydration, her conditions improved steadily, and renal function remained normal throughout the entire disease course. The patient had no residual weakness or myalgia, and laboratory tests of CK and aspartate aminotransferase (AST) values returned to normal 3 and 11 days after discharge, respectively. As pediatric physicians, it should be noted that rhabdomyolysis maybe a complication of influenza A infection in pediatric patients with severe myalgia or muscle weakness, and appropriate treatment addressing rhabdomyolysis may reduce the risk of renal failure. Also, it is important to check the CK levels in hospitalized patients with influenza infection.

Keywords: Rhabdomyolysis, influenza, pediatric patients

Introduction

The typical symptoms of influenza infection in children can differ from those in adults [1, 2]. Children can present with higher maximum temperatures than adults, and infants can have an undifferentiated fever or febrile seizures. Chills, running nose, cough, sore throat, laryngotracheobronchitis, bronchiolitis, and bronchitis, malaise, and headache may also occur [2, 3]. Gastrointestinal symptoms, such as abdominal pain, vomiting, diarrhea, are more commonly seen in children than in adults [2]. Common complications of influenza in children are acute otitis media, sinusitis and pneumonia which may be a primary viral process or a secondary bacterial infection [3]. Myositis is a common presentation in influenza [4]; however, there are only a few reports of pediatric patients experiencing severe myalgia and rhabdomyolysis [5-7]. The common causes of rhabdomyolysis are crush injuries, medications, seizures and electrolyte disorders; however, virus-

associated rhabdomyolysis is very rarely seen [6]. Rhabdomyolysis is a syndrome characterized by the leakage of muscle cell contents, such as electrolytes, myoglobin, and other proteins (e.g. creatine kinase (CK), lactate dehydrogenase (LDH), aspartate aminotransferase (AST), and alanine aminotransferase (ALT)) into the circulation [8, 9]. Rhabdomyolysis can occur after a viral infection especially in children [10]. The manifestations of rhabdomyolysis can range from asymptomatic conditions with the elevated levels of muscle enzymes in serum to potentially fatal conditions, such as compartment syndrome and acute renal failure [8, 9].

Here, we report a rare case of rhabdomyolysis in a pediatric patient with the influenza A infection, and review the literature for similar cases. After treatment, the patient had no residual weakness or myalgia, and the laboratory tests of CK and AST values returned to normal 3 and 11 days after discharge, respectively. Therefore, pediatric physicians should keep in mind

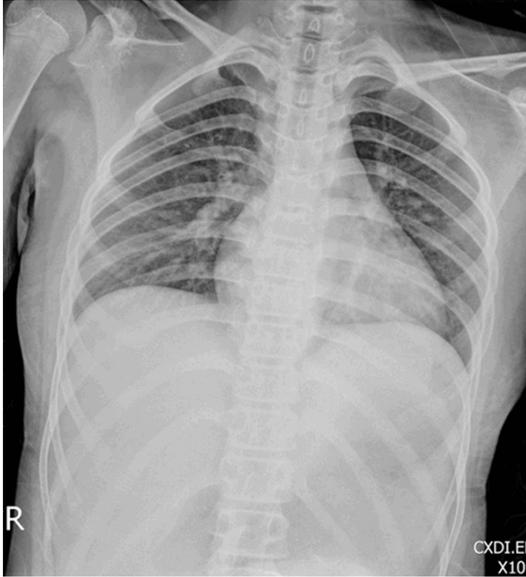


Figure 1. The chest X-ray did not reveal any remarkable findings.

that rhabdomyolysis maybe a complication of influenza A infection in pediatric patients with severe myalgia, and proper treatment of rhabdomyolysis may reduce the risk of renal failure.

Case presentation

An 11-year-old girl suffered from fever and soreness of the lower legs for 6 days. Three days before these symptoms, she had loose stool passage four times which resolved that day after temporary NPO (nothing per oral). She had visited the local medical department twice, but fever persisted after medication. One day before admission, she had a tight cough and severe myalgia, without significant improvement. It was noted that she had contact with a classmate suffering from influenza-like syndrome. She had no other symptoms, recent travel, intensive exercise, injuries or previous myalgia. Physical examination revealed that she was febrile but had normal blood pressure. The functions of her organs, such as heart, lung and skin were normal. Chest radiograph revealed unremarkable findings (**Figure 1**). However, the rapid antigen test for influenza A showed positive indicating influenza infection. Laboratory data showed a remarkably high level of CK at 2,866 U/L (normal: 45 to 163 U/L) and CK-MB at 13.05 ng/mL (normal: < 4.88 ng/mL), increased AST at 90 U/L (nor-

mal: 8 to 38 U/L), normal ALT at 26 U/L (normal: 4 to 44 U/L), elevated LDH at 406 U/L (normal: 106 to 211 U/L), and normal complete blood counts, blood urea nitrogen (BUN) and creatinine. C-reactive protein level was within normal range (0.029 mg/dL) (**Tables 1** and **2**). Blood culture was negative for bacteria, and urine myoglobin was negative. Based on these examinations, the girl was diagnosed with rhabdomyolysis, a complication from the influenza A infection.

After admission, the patient was treated with regular oral mefenamic acid and oseltamivir (75 mg twice daily for five days), her fever declined and subsided one day later. Further treatment with aggressive hydration, improved her renal function and electrolytes recovered and values of muscle enzymes gradually decreased. Upon hospital day 3, the follow up laboratory data revealed the decline of AST (90→72 U/L), LDH (406→287 U/L), and CK level (2,886→1,003 U/L) (**Table 2**). Subsequently, the girl was discharged on next day. Follow up in the outpatient department 3 days and 11 days after discharge, she had no residual muscle weakness or myalgia. Laboratory levels of CK and AST returned to normal (CK: 1003→113 U/L; AST: 72→18 U/L) at 3 and 11 days after discharge, respectively (**Table 2**).

Discussion

Myalgia is a common presentation in influenza; however, there are only a few reports of pediatric patients experiencing severe myalgia and developing rhabdomyolysis, including two recently reported cases [11-18] (**Table 3**). Viral myositis progressing to rhabdomyolysis is uncommon, and it can be life-threatening. In the present case, the previously healthy patient did not present with severe pulmonary complications from the virus. However, this case highlighted the importance of recognizing severe rhabdomyolysis as a complication of influenza A infection. Pediatricians, do not neglect such complications as it could be potentially life-threatening. Also, our case highlighted the significance of checking the CK levels in hospitalized patients with influenza infection.

Rhabdomyolysis is a clinical condition characterized by injury to myocytes and the release of intracellular contents into the extracellular space. There are a number of etiologies for

Rhabdomyolysis following influenza A

Table 1. The routine blood examination data of the patient during the time of the admission to our hospital and the follow-up in outpatient department

	HcT (%)	Hgb (g/dL)	MCH (/pg)	MCHC (g/dL)	MCV (/fL)	RBC (/μL)	WBC (/μL)	Platelet (/μL)	Basophil (%)	Eosinophil (%)	Lymphocyte (%)	Monocyte (%)	Neutrophil Band (%)	Neutrophil Segment (%)
Reference range	37.0-47.0	12.0-16.0	27.0-31.0	33.0-37.0	80.0-99.0	4,200,000-5,400,000	4,500-10,000	130,000-400,000	0-1	0.0-4.0	19-48	0-9	0-6	40-74
Examination date														
Hospital day 1	38.9	12.3	20.3	31.6	64.2	6,060,000	6,180	332,000	0	1	50	7	0	42
Hospital day 3	40.5	12.5	19.9	30.9	64.4	6,290,000	4,500	255,000	1	1	50	7	0	41
11 days after discharge	33.1	10.2	19.7	30.8	64.0	5,170,000	7,710	347,000	0	1	40	6	0	53

HcT: Hematocrite; Hgb: Hemoglobin; MCH: Mean corpuscular hemoglobin; MCHC: Mean corpuscular hemoglobin concentration; MCV: Mean corpuscular volume; RBC: Red blood cell; WBC: White blood cell.

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Table 2. The biochemical examination data of the patient during the time of admission to our hospital and the follow-up in outpatient clinic

	BUN (mg/dL)	CK-MB (ng/mL)	CK (U/L)	CREA (mg/dL)	CRP (mg/dL)	AST/GOT (U/L)	ALT/GPT (U/L)	LDH (U/L)	eGFR (mL/ min/1.73)
Reference range	8-20	< 4.88	45-163	0.5-1.2	< 0.3	8-38	4-44	106-211	>90
Examination date									
Hospital Day 1	9	13.05	2,866	0.42	0.029	90	26	402	235
Hospital Day 3	-	6.09	1,003	-	0.026	72	37	287	-
3 days after discharge	-	-	113	0.42	-	-	-	-	235
11 days after discharge	-	-	-	-	-	18	-	222	-

BUN: blood urea nitrogen; CK-MB: Creatine kinase MB; CK: Creatine kinase; CREA: Creatinine; CRP: C-reactive protein; AST/GOT: aspartate aminotransferase/glutamic oxaloacetic transaminase; ALT/GPT: Alanine aminotransferase/glutamate pyruvate transaminase; LDH: Lactate dehydrogenase; eGFR: estimated glomerular filtration rate.

rhabdomyolysis, such as extraordinary exercise, viral infection, trauma, drugs, genetic mutations, and metabolic and neuromuscular disorders [10]. The cause of acute pediatric rhabdomyolysis is different from that of adult rhabdomyolysis; common causes of pediatric rhabdomyolysis are viral myositis, trauma, and connective tissue disease [10].

In a retrospective series from a pediatric emergency department, 38% of rhabdomyolysis cases were caused by viral myositis [4, 10]. Among viral etiology, influenza has been reported to be the predominant cause of infection-induced rhabdomyolysis [19]. Myositis are more frequently seen in patients with influenza B infection than those with influenza A. On the other hand, influenza A virus is more frequently recognized in the cases of rhabdomyolysis than influenza B [14, 16], but there are some reports of pediatric influenza B-associated rhabdomyolysis [16, 20] (**Table 3**).

The mechanisms of developing rhabdomyolysis by influenza virus are still elusive. There are some hypothetical mechanisms proposed in which muscle damage was caused by viral invasion directly or indirectly through induction of an immune-mediated action [6]. Desdouts et al provided evidence of influenza A viral replication and budding, and subsequent muscle cell lysis in their experiments indicating that influenza A virus can infect primary human muscle cells *in vitro* [21]. Genetically, *LPIN1* mutations have been reported as a cause of rhabdomyolysis; it demonstrated a high incidence (59%) of *LPIN1* mutations in young patients with severe rhabdomyolysis [22]. *Lipin1* has a dual role; as a phosphatidate phosphatase 1 for triacylglycerol and phospholipid

biosynthesis, and as a transcriptional co-activator regulating the genes encoding mitochondrial fatty acid β -oxidation defects and mitochondrial respiratory chain enzymes [22]. These mutations appeared to be associated with acute and severe rhabdomyolysis exacerbated by febrile disease [22].

In the pediatric patient, influenza associated myositis and rhabdomyolysis appears to occur often during the early convalescent phase of the disease [10]. Clinical presentations of rhabdomyolysis vary from an asymptomatic increase in CK to severe complications of acute renal failure (**Table 3**). The classic triad of rhabdomyolysis represents as muscle weakness, myalgia, and dark urine; however, it was reported that < 10% of pediatric patients had all three symptoms [8, 9]. The typical laboratory diagnostic criteria of rhabdomyolysis is based on raised serum CK of ≥ 5 times the normal level [8]. In our case, the patient had a remarkably high level of CK and CK-MB, but her urine myoglobin was absent. Although myoglobinuria is usually detected in the cases of rhabdomyolysis, the absence of myoglobinuria in the presence of elevated CK could not exclude the diagnosis of rhabdomyolysis, because myoglobin has a short half-life of about 2-3 hours and could be rapidly metabolized and excreted by the liver and kidney [8, 9].

Acute renal failure is the most common complication of rhabdomyolysis, it has been reported in 13 to 50% of adult patients, but only about 2.5-5% occurred in children [10]. It has been suggested that the critical factors for developing renal failure are hypovolemia or dehydration and aciduria (i.e. pH of urine < 6.5) [8, 9]. Consequently, the standard treatment for acute renal failure is prompt and vigorous fluid

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Table 3. Rhabdomyolysis following influenza infection in children: review of the case reports

No.	Year	Influenza Serotype	Age	Gender	Initial Symptoms	Creatine kinase (U/L)	Other Complications	Treatments	Death	References
1	2009	A/H1N1 2009	16	boy	fever, cough, sore throat, and mild headache	164,149	-	Intravenous 0.9% normal saline to achieve urine output of 2 mL/kg/h and morphine for controlled analgesia. Empiric intravenous cefotaxime, oral roxithromycin, and oral oseltamivir (75 mg twice daily)	No	[11]
2	2010	A/H1N1 2009	17	girl	cough, myalgia and weakness	192,372	-	acetaminophen and oseltamivir (75 mg twice daily for five days); aggressive hydration for rhabdomyolysis	No	[12]
3	2011	A/H1N1 2009	8	girl	fever, chills, cough, body aches, vomiting, and increasing bilateral thigh pain; anuric for approximately 12 hours	11,922	compartment syndrome; acute renal failure	clindamycin, cefotaxime, vancomycin; bilateral thigh fasciotomies; continuous renal replacement therapy for 1 week, followed by hemodialysis for 2 weeks	No	[13]
4	2012	A/H1N1 2009	11	girl	has Crigler-Najjar syndrome; fever, coughing, difficulty breathing, vomiting, anxiety, and increased jerking movements	101,237	-	cefotaxime and oseltamivir; intense hydration and sodium bicarbonate for rhabdomyolysis	Yes	[14]
5	2012	A/H1N1 2009	8	boy	severe leg pain, hypotension and hypothermia	78,420	cardiac dysfunction and compartment syndrome	intense hydration and intravenous sodium bicarbonate; calcium gluconate hydrate, olprinone hydrochloride hydrate, dobutamine hydrochloride, prednisolone, intravenous immunoglobulin and furosemide; decompression fasciotomies; continuous hemodiafiltration to control hyperkalemia	No	[15]
6	2013	B	15	boy	has cerebral palsy; fever, decreased activity, productive cough and yellow sputum	407,421	acute renal failure; developed disseminated intravascular coagulation, and had hematuria and bleeding from the gastrointestinal tract	oseltamivir 60 mg bid and ampicillin and sulbactam 1.5 g every 6 hours were prescribed; administration of sodium bicarbonate; hemodialysis. The oseltamivir treatment was shifted to peramivir because of poor GI absorption	No	[16]
7	2019	B	6	girl	febrile illness and profound pain in lower extremities	5,169	asystolic cardiac arrest; coagulopathy	intravenous hydration and oral paracetamol; sodium bicarbonate infusion; intermittent hemodialysis; renal replacement therapy; Cytosorb filter was added to remove myoglobin and CK	No	[17]
8	2019	A/H1N1	15	boy	stabbing pain in the left flank, fever with cold shivers and a one-time voiding of dark urine	565,644	-	aggressive fluid therapy with isotonic saline and alkalinization of urine	No	[18]
9	2019	A	11	girl	fever and soreness of lower legs	2,866	-	oral mefenamic acid and oseltamivir (75 mg twice daily for five days), aggressive hydration	No	Our case

repletion and bicarbonate therapy [9, 17] (**Table 3**). Other complications include cardiac dysfunction, compartment syndrome, hematuria, and bleeding from the gastrointestinal tract [8, 9] (**Table 3**).

Conclusion

Although influenza A infection is commonly associated with respiratory illness ranging from mild upper respiratory infection to severe pneumonia and acute respiratory distress syndrome [9], pediatric physicians can be warned that rhabdomyolysis maybe the complication of influenza A infection in pediatric patients with severe myalgia or muscle weakness, and proper treatment addressing rhabdomyolysis may highly reduce the risk of renal failure. Also, it is important to check the CK levels in hospitalized patients with influenza infection.

Disclosure of conflict of interest

None.

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