Evaluation of the prevalence and clinical and laboratory features of acute viral myositis in children with influenza referred to the emergency department of Ali Asghar Tehran Hospital in 2019 and 2020

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ABSTRACT

Introduction: Influenza-related viral myositis is observed mostly in children with influenza, and the disease is more common in influenza type B. The aim of the present study was to evaluate the prevalence, and clinical and laboratory features of acute viral myositis in children with influenza in 2019 and 2020. Methods: This retrospective cross-sectional study was performed in Ali Asghar Hospital, from December 2019 to February 2020. Children aged 2–14 years with symptoms of acute onset of fever, along with the symptoms of influenza with or without muscle pain who referred to the emergency department of Hazrat Ali Asghar Children’s Hospital, were included in the study. The data were collected and analyzed by Statistical Package for the Social Sciences (SPSS) version 22. Results: Out of the 105 participants in this study, 62 (59%) were male and the rest were female. The average age of the patients was 5.34 years (SD = 2.63). Clinical signs of lower limb pain, myalgia, lameness, weakness, and lethargy were significantly more common in patients with myositis (P-value < 0.05). In-vitro examination demonstrated that creatine phosphokinase (CPK), aspartate aminotransferase (AST), and aAlanine aminotransferase (ALT) levels were significantly higher in patients with myositis. Conclusion: Based on the present results, the clinical symptoms in patients are quite clear, and based on the symptoms, it is possible to diagnose and treat myositis without relying on laboratory findings; due to the self-limitation of this complication and lack of the need for complex treatments in case of early diagnosis, physicians can diagnose and treat many cases, depending on the clinical symptoms and the accuracy of the examination.

Keywords: Acute viral myositis, clinical symptoms, influenza

Introduction

Influenza is a common viral respiratory infection caused by the influenza virus, and annual flu outbreak occurs worldwide during the cold season. Influenza is associated with a variety of complications that primarily affect the respiratory system and central nervous system.[11] Influenza-associated myositis (IAM),
another complication of the infection, has only been reported sporadically since its first description in 1957. Although the frequency of IAM is higher in children than in adults, the age of onset during the influenza outbreak is unknown. IAM is a benign and self-limiting disease that mostly affects boys and presents as muscle pain and a sudden onset of difficulty in walking after a flu infection. However, IAM is not easily distinguishable from other diseases and therefore children may undergo unnecessary diagnostic tests. In addition, several cases of severe IAM and life-threatening complications have been reported. The clinical range of muscle involvement associated with viral infections varies from more common benign myalgias to less common rhabdomyolysis (in some cases with myoglobinuric renal failure). Signs and symptoms include primary viral infection such as fever, anorexia, and a history of upper respiratory tract infection or gastrointestinal symptoms. Acute childhood myositis is a predominantly benign disease. For patients with myositis-associated rhabdomyolysis, viral symptoms may manifest 4–14 days before the onset. Moderate myalgias and muscle tenderness occur frequently in the early stages of many acute viral infections, the back and legs are most affected. These symptoms are often self-limiting. Weakness may be proportional to the severity of the muscle involvement, and eventually pigmenturia is reported as dark urine in patients with rhabdomyolysis. Laboratory values depend on the severity of the disease. In mild cases, myalgia and muscle tenderness have been reported without laboratory abnormalities that show muscle inflammation or necrosis. However, a sharp increase in creatine kinase (CK) can be observed in more severe cases of acute viral myositis leading to rhabdomyolysis, with levels ranging from <10,000 to >500,000 international units per liter (IU/L).

As myositis in children often occurs as a result of a lack of weight on the limbs or legs, differential diagnosis of infection and joint involvement is required for them, which may be more expensive and sometimes complicated, such as x-ray and ultrasound and even invasive procedures such as joint fluid aspiration.

Therefore, early diagnosis of acute viral myositis, based on the history of the patient, findings of clinical examination, and laboratory values of creatine phosphokinase (CPK), is of great importance and can prevent invasive procedures, long-term hospitalization of the child, and psychological and financial burden of the family and the treatment system, and perhaps based on serum CPK range, high-risk individuals can be distinguished from low-risk individuals (in the cases of rhabdomyolysis), and thus fewer individuals can be followed-up for disease progression and the need for supportive care.

Materials and Methods

The present research is a retrospective cross-sectional study and the collection of information was performed without applying any intervention in the current situation of the subjects. All stages of this research have been done with the approval of the ethics committee (IR.IUMS.FMD.REC.1399.772) Vice Chancellor for Research, School of Medicine, Iran University of Medical Sciences, and written permission has been obtained from the hospital management to access the files. A total of 105 children with influenza, who were referred to the emergency department of Ali Asghar Hospital from December 2019 to February 2020, were studied. All children were in the range of 2–14 years and had the symptoms of acute onset of fever along with the symptoms of influenza with or without muscle pain (especially lower extremities, with or without gait disturbance, and during the flu season). Common symptoms of the cases were complaints of lameness, lack of weight, or muscle pain, which were recorded in the hospital records of the emergency department.

Inclusion criteria included: children of 2–14 years who were referred to Ali Asghar Hospital with one of the symptoms of fever in addition to acute onset of respiratory disease; fever in addition to exacerbating chronic lung disease; people with community-acquired pneumonia; central fever with >38°C with or without cough and sore throat; without a known cause other than influenza that can justify symptoms; and availability of the patient’s records and test results. Exclusion criteria were symptoms of vomiting; decreased level of consciousness; lack of deep tendon reflexes (DTR); history of metabolic, musculoskeletal, and thyroid diseases; and also history of consuming drugs such as colchicine, hydroxychloroquine, and alpha interferon in the last 24 h; and heavy exercise or trauma, as well as signs of arthritis, positive blood or urine culture, evidence of bacterial pneumonia on the x-ray findings, or signs and symptoms of a patient with a disease other than influenza.

Clinical suspicion and diagnosis of influenza were based on clinical signs and symptoms of fever with one or more other accompanying symptoms including headache, myalgia, upper respiratory tract symptoms, cough, and gastrointestinal symptoms during the flu season and no polymerase chain reaction (PCR) test was required. Complete clinical examinations were performed including evaluation of vital signs, physical condition (whether the child is happy or ill), otolaryngology, cardiopulmonary and neurological examinations, and complete joint examination in terms of swelling, erythema, tenderness, and limitations in walking or standing. Also, complete paraclinical examination of blood cells (complete blood count [CBC]) and acute phase factors including erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) and serum electrolytes, muscle enzymes including CPK and lactate dehydrogenase (LDH), blood culture, urine analysis and culture, and, in case of symptoms of lower respiratory infection, chest x-ray was performed.

In addition, the number of days of incapacity or difficulty in walking was recorded, and some of these individuals who had the signs of rhabdomyolysis were isolated as high-risk cases and were assessed with other patients in terms of laboratory factors to determine the significance of these criteria.
We also examined the association between increased CPK and the onset of symptoms of pain and muscle tenderness in children with influenza as a sub-objective.

Finally, the effect of oseltamivir was measured by comparing the number of days the children were symptomatic in the two study groups; one of which receiving the drug and the other was the control group.

If a person had been infected with influenza more than once during this period (from December 2019 to February 2020), he/she could have entered the study each time.

A data collection form (checklist) designed by the researcher was used for each patient. This form included a demographic information section (such as age, sex, and contact information) and the main information about the disease at the time of arrival to the emergency department (e.g., fever, number of days on the onset of the symptoms, patient’s main complaint, and patient's test results including CBC-AST-ALT – blood urea nitrogen (BUN)-Cr-LDH-CPK-U/A-Cx-ray, and the result of throat PCR for influenza if sent). At the end of data collection, the data were entered and analyzed in Statistical Package for the Social Sciences (SPSS) version 22.

## Results

In this study, a total of 105 children diagnosed with influenza, which were referred to the emergency department of Ali Asghar Hospital from December 2019 to February 2020, were studied. Of the patients studied 59% were boys and 41% of them were girls. Most of the patients had no underlying diseases. The result of the pharyngeal examination was 50.5% with no positive points. As 37.1% was with erythema. The prevalence of myositis in patients with influenza was 17.1%. None of the patients had evidence of rhabdomyolysis, and no mortality was observed. According to Table 1, the most common symptoms and initial findings were cough, fever, lethargy and anorexia, respectively.

Three patients had RBC evidence of urinary incontinence and two had proteinuria, all in the non-viral myositis group.

As seen in Table 1, the most common symptoms and initial findings were cough, fever, lethargy, and anorexia, respectively.

In laboratory studies, the levels of CPK, aspartate aminotransferase (AST), and alanine transaminase (ALT) in patients with a diagnosis of myositis were significantly higher both at the beginning and at the end of hospitalization [Table 2].

According to Table 3, symptoms of lower extremity pain, myalgia, lameness, and weakness and lethargy were significantly more common in patients with influenza-induced myositis than in others.

| Symptoms                  | Abundance | Percentage |
|---------------------------|-----------|------------|
| Cough                     | 87        | 82.9       |
| Fever                     | 78        | 74.3       |
| Weakness and lethargy     | 76        | 72.4       |
| Anorexia                  | 74        | 70.5       |
| Corisa                    | 46        | 43.8       |
| Myalgia                   | 42        | 40         |
| Myalgia                   | 34        | 32.4       |
| Lower limb pain           | 34        | 23.8       |
| Diarrhea                  | 25        | 21.9       |
| Otitis                    | 23        | 21.9       |
| Headache                  | 23        | 16.2       |
| Sore throat               | 17        | 16.2       |
| Pene taki                 | 15        | 14.3       |
| Muscle tenderness         | 12        | 11.4       |
| Tachycardia               | 11        | 10.5       |
| Respiratory distress      | 11        | 10.5       |
| Maleness                  | 7         | 6.7        |
| Convulsion                | 4         | 3.8        |
| Skin lesion               | 4         | 3.8        |
| Decreased urination       | 2         | 1.9        |

### Discussion

The aim of this study was to evaluate the prevalence, and clinical and laboratory features of acute viral myositis in children aged 2–14 years with influenza. Clinical signs of lower limb pain, myalgia, lameness, weakness, and lethargy were significantly more common in patients with myositis (P-value < 0.05). In-vitro examination demonstrated that CPK, AST and ALT levels were significantly higher in patients with myositis. During our study, none of the patients had evidence of rhabdomyolysis, and no mortality was observed. According to Table 1, the most common symptoms and initial findings were cough, fever, lethargy and anorexia, respectively.

Clinical manifestations can be significant, but in most cases, IAM usually follows a benign and self-limiting period. Diagnosis of rhabdomyolysis is made when myoglobinuria is also present.\(^9\) In our study, the prevalence of IAM was 17.1%. None of the patients diagnosed with myositis had myoglobinuria or hematuria/RBC in the urine.

IAM appears to be the more frequent in children than in adults, but the age of onset during the flu season is unknown. Because IAM is typically associated with influenza B virus, its occurrence may depend on the nature of circulating strains during a particular epidemic.\(^10\) Most of the patients with influenza in our study were boys (59%). Also, in comparison between boys and girls, the prevalence of viral myositis in boys (22.58%) was significantly higher than girls (9.3%) (P-value < 0.05). In a study by Agyeman et al.,\(^11\) the prevalence of myositis due to influenza was twice as high in boys than in girls. Physicians treating with emergency cases should be aware of the signs and symptoms...
of influenza-related infectious myositis in children, especially during the flu season.\[^{15}\] Other studies have also reported that viral myositis is more common in boys. This predominance of male may be due to genetic predisposition or unknown metabolic defects in males.\[^{13,14}\] Understanding the clinical and laboratory features of IAM, as stated in our study, provides a cost-effective and appropriate therapeutic approach.\[^{15}\] In a study by Dr. Sharad Ghatag, which was performed on benign acute myositis in children, patients recovered significantly on day 4. All the patients were able to walk on the seventh day after admission without any complication, and all patients were satisfied with the treatment.\[^{14}\] In a study by Sunil Pradhan, 32 patients that were present in the outpatient clinic or hospital emergency department with severe myalgia were evaluated. The mean age of patients was (14.3 ± 7.8) years, and most cases (53.1%) had myalgia after febrile disease. Symptoms resolved after an average of 5.7 days (1.6 days); myalgia was present in 21 cases (65%), while proximal myopathy was prominent in 14 cases (43%). Also, electrolyte abnormalities (hypokalemia) were present in four cases (12.5%). In all patients, muscle enzymes (CPK, serum glutamic oxaloacetic transaminase, serum glutamic pyruvic transaminase, and lactate dehydrogenase) were elevated, and electromyography showed a myopathic pattern. Significant improvements were observed within 5–7 days. Acute childhood myositis in cases of severe proximal myopathy in adolescents should be further evaluated.\[^{17}\]

The mean age of patients with myositis was 5.58 (SD = 1.16) and the mean age of other patients was 5.29 (SD = 2.84) and there was no significant difference between the ages of the two groups. In a study by Lundberg, the mean age of patients was 9 years, while Mackay et al., and Agyeman et al. reported the mean age of patients with myositis to be 8.1 years, 7 years, and 8.5 years, respectively.\[^{11,18,19}\] The mean age in our study group was lower than the studies mentioned. Also, there was no difference in the treatment plan and the drugs of choice between the two groups, and the number of hospitalization days of patients with IAM was not different from the other patients with influenza. IAM is characterized by the rapid and spontaneous resolution of clinical symptoms within a week of the onset of symptoms, and its main treatment is supportive therapy, while antiviral drugs are not considerably effective.\[^{15}\] However, in the overall study of patients, 86.7% received oseltamivir and antiviral drugs at the time of admission. Also, 42.85% of patients were prescribed oral oseltamivir at home after discharge, since previous studies have shown satisfactory results for non-hospitalized patients that received antiviral treatment.\[^{20}\]

Oseltamivir treatment has been associated with reduced disease duration, influenza-related complications, and subsequent hospitalization among children.\[^{21}\] On the other hand, in our study, 62.9% of patients received antibiotics during hospitalization. Given that antibiotics have no place in the treatment of influenza itself, this high rate of antibiotic prescribing in a medical center should be considered and diagnosed. However, it should be noted that although bacterial pneumonia may occur only in a minority of patients, it can be difficult to diagnose viral pneumonia from bacterial pneumonia in severe cases, especially in hospitalized patients; therefore, administration of antibiotics may be rational.\[^{21}\] Another important point is that antibiotic treatment should only be used to treat bacterial pneumonia and should not be prescribed by doctors in any way to prevent this complication. Educating physicians and assistants to prescribe

| Variable | Number (percentage of frequency) | P  |
|----------|---------------------------------|----|
| Pain in the lower extremities | 13 (72.22%) | 0.00 |
| Lameness | 6 (33.3%) | 0.00 |
| Myalgia | 15 (83.33%) | 0.00 |
| Weakness and lethargy | 15 (83.33%) | 0.01 |

The mean age in our study group was 8.1 years, 7 years, and 8.5 years, respectively.\[^{19}\] In a study by Lundberg, the mean age of patients was 9 years, while Mackay et al., and Agyeman et al. reported the mean age of patients with myositis to be 8.1 years, 7 years, and 8.5 years, respectively.\[^{11,18,19}\] The mean age in our study group was lower than the studies mentioned. Also, there was no difference in the treatment plan and the drugs of choice between the two groups, and the number of hospitalization days of patients with IAM was not different from the other patients with influenza. IAM is characterized by the rapid and spontaneous resolution of clinical symptoms within a week of the onset of symptoms, and its main treatment is supportive therapy, while antiviral drugs are not considerably effective.\[^{15}\] However, in the overall study of patients, 86.7% received oseltamivir and antiviral drugs at the time of admission. Also, 42.85% of patients were prescribed oral oseltamivir at home after discharge, since previous studies have shown satisfactory results for non-hospitalized patients that received antiviral treatment.\[^{20}\]
antibiotics rationally and adhere to guidelines, and prescribing only in cases with indications, can reduce the unnecessary administration of antibiotics and the risk of antibiotic resistance and drug side effects in children.

According to Table 3, symptoms of lower limb pain, myalgia, lameness, and weakness and lethargy were significantly more common in patients with IAM. In a five-year study, the majority of patients with myositis had lower limb pain and myalgia.[23] Diagnosis based on early clinical symptoms may facilitate treatment management, and physicians can avoid misdiagnosis and unnecessary treatment by considering clinical symptoms. However, the limitation of the present study was the limited number of patients and also the unavailability of patient records in different time periods and different hospitals in the country.

The prognosis is excellent and management may include rest and pain relief.[24] Symptomatic and supportive management, along with explanation and reassurance, is the only thing needed to manage the disease.[25] Finally, children are more vulnerable to influenza virus and may experience harsher symptoms.[26]

According to Table 2, in laboratory examination, the levels of CPK, AST, and ALT in patients with myositis were significantly higher both at the beginning and at the end of hospitalization. In a study by Yoon et al.,[27] a significant increase in blood CPK, AST, and LDH levels was shown in patients with myositis. Leukopenia is one of the laboratory findings that was reported in the studies. In our study, it was observed that the mean level of leukocytes in patients with IAM was lower than in other patients, although this difference was not statistically significant. Also, the prevalence of leukopenia in patients with myositis was higher compared to other patients.[13]

**Conclusion**

In general, according to the results of the present study, the prevalence of viral myositis in patients with seasonal flu referred to the Ali Asghar Hospital was relatively high. In laboratory examination, the levels of CPK, AST, and ALT in patients with myositis were significantly higher both at the beginning and at the end of hospitalization. Clinical symptoms in patients are well defined and based on them, it is possible to diagnose and treat myositis without relying on laboratory findings. Considering the self-limiting nature of this complication and the lack of the need for complex treatments in case of early diagnosis, physicians can diagnose and treat many cases, depending on the clinical symptoms and the accuracy of the examination. Prevention of overprescription of drugs, especially antibiotics, and regular monitoring of patients reduces the costs of the health care system and families, as well as drug resistance, and benefits public health. Therefore, training and monitoring of doctors and assistants are highly important.

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**Conflicts of interest**

There are no conflicts of interest.

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