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Predictors of influenza A and influenza B in children 3 - 18 years in epidemic seasons 2017 - 2018 and 2018 - 2019

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ABSTRACT

The aim of the study is to optimize the early diagnosis of influenza A and influenza B, by careful analysis of the clinical and laboratory features of the disease course in children aged 3 to 18 years in the epidemic seasons of 2017-2018 and 2018-2019 in Ukraine. 209 children with influenza who were treated in hospital were taken to consideration. Based on the results of the examination, two groups were formed. The first (I) group consisted of 122 children with influenza A, the second (II) group included 87 patients with influenza B. The result of the study is the delineation of clinical symptoms characteristic of influenza A and influenza B. It may allow to suspect a specific disease caused by a certain type of virus, especially in several strains of influenza circulation. Detection of clinical predictors of a particular type of influenza virus in a patient allows us to predict the course of the disease, possible complications and their nature.

Keywords: influenza A (H3N2), influenza B, predictor symptoms, children.

1. INTRODUCTION

Influenza occupies a leading position among the whole group of acute respiratory viral infections (ARVI) and belongs to socially associated diseases. In Ukraine, during the period of epidemics lasting 4-6 weeks, 5-6 million people get sick in a short time. During the 2018-2019 season in Ukraine, 5.4 million people became ill with influenza and ARVI, 65.3% of whom were children under the age

of 17, 64 people died, including 12 children under the age of 17. It is a challenge to determine the real incidence of influenza due to the lack of full coverage of the population by diagnostic methods. Children play an important role in the spread of influenza (Nejad et al. 2020); incidence among them has significant socioeconomic consequences due to the high rate of disease transmission to family members, high levels of hospitalization during the outbreak, increased outpatient workload for the family doctor. In a season, 2 or 3 viruses can participate simultaneously or sequentially with the dominance of one of the subtypes of influenza A virus or influenza virus type B (McCullers et al., 2012). Of special attention is that in recent seasons (since 2015) the proportion of influenza B has increased. Our experience shows the possibility of infection and consequently, the disease of children with clinically manifest forms of seasonal influenza, both A and B during one season.

There are conflicting data in the literature on possible differences in the clinical manifestations of influenza A and B in children (Daley et al., 2010; Su et al., 2014; Mosnier et al., 2015). The basic clinical symptoms of influenza A and B are similar due to the only pathomorphological processes occurring in the body under the action of the virus. But along with the common features, there are significant differences in the clinic, depending on the type and serovar of the pathogen (McCullers et al., 2012; Su et al., 2014). In an epidemic, the diagnosis of influenza can be established on the basis of a typical clinic in a patient without laboratory confirmation. It is important to outline the indicator predictor symptoms characteristic of influenza caused by a particular type of virus. With the help of these symptoms you can predict the course of the disease, probability of development and nature of complications, to address the use of antiviral drugs and reduce the irrational antibiotic therapy.

The aim of the study is to analyze the clinical manifestations of influenza A and B in children, to study the dominance and duration of the leading symptoms and the nature of probable complications.

2. MATERIAL AND METHODS

The study was conducted in the municipal medical institution "Lviv Clinical Regional Infectious Diseases Hospital" (Ukraine) and included 209 children with influenza aged 3 to 18 years in epidemiological seasons of 2017-2018 and 2018-2019. Informed consent was obtained from the parents of all study participants. The exclusion criteria were the presence of chronic diseases in children, which can change the clinical manifestations of influenza and increase the risk of complications. Influenza was established on the basis of epidemiological history, complaints of patients, characteristic clinical symptoms, changes in complete blood count (CBC)

To verify the diagnosis, the Polymerase Chain Reaction (PCR) method was used to detect specific influenza virus RNA in nasopharyngeal mucus, as well as the method of qualitative immunochromatographic analysis in the form of rapid tests of a commercial kit from CerTest Biotec S.L., Spain. Determined the level of a specific "muscle" enzyme - creatine phosphokinase (CPK) (analyzer and test system Cobas 6000; Roche Diagnostics, Switzerland), and the instrumental method of examination - electromyography.

Statistical processing of the results was performed using the software package "STATISTICA FOR WINDOWS 6.0" (Statsoft, USA). Data were presented as arithmetic mean values with standard deviation. Verification of the normality of the distribution was performed according to the Shapiro-Wilk test. To identify a statistically significant difference between the groups a pairwise comparison using the nonparametric Mann-Whitney test was used, $p < 0.05$ was considered statistically significant.

3. RESULTS

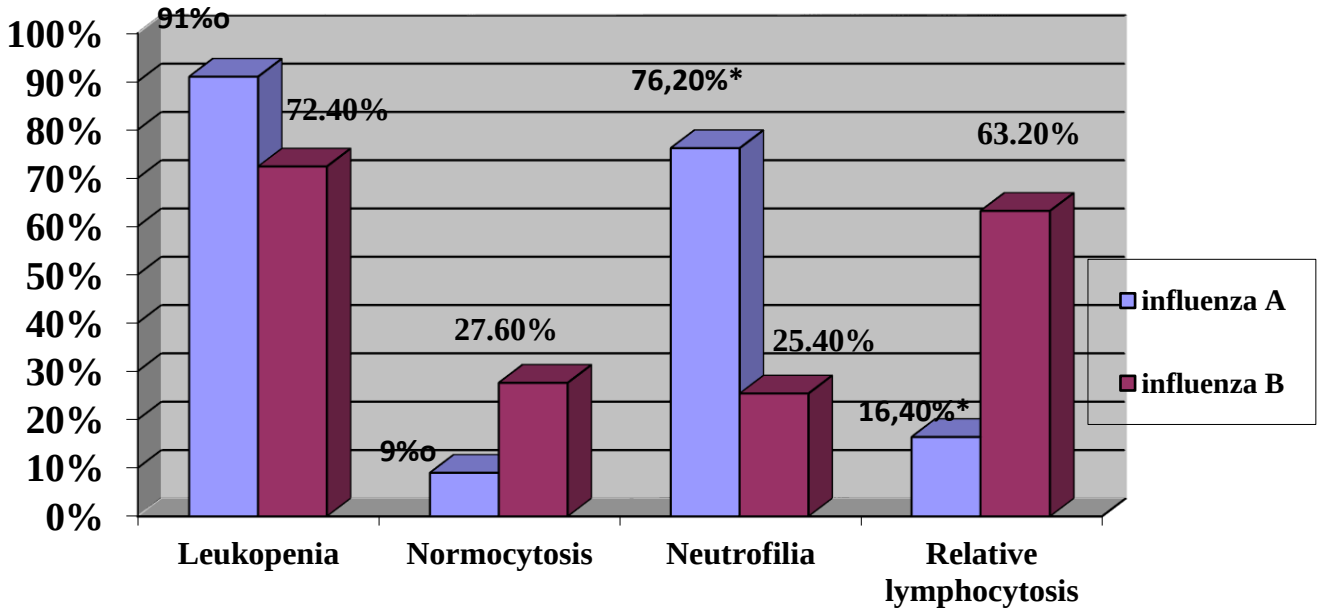
The study involved 426 children with influenza symptoms during epidemic increases in morbidity. The comparison group included 209 children with a confirmed diagnosis of influenza by immunochromatographic method. Group I consisted of 122 children with influenza A (41 children in the epidemiological season 2017 - 2018, 81 children in the epidemiological season 2018 - 2019). Group II included 87 patients with influenza B (65 children in the epidemiological season 2017 - 2018, 22 children in the epidemiological season 2018 - 2019). In 32 (26.2%) patients out of 122 with influenza A and in 24 (27.6%) out of 87 children are with influenza. The diagnosis was verified by detection of influenza virus RNA in nasopharyngeal mucus by PCR. In 13 patients with confirmation of the diagnosis by immunochromatographic method, PCR was negative, so these children were not included in the study group. PCR study was not performed in other patients.

According to the Public Health Center of Ukraine, identical types of influenza A and B viruses were circulating during both epidemic seasons, although they may have differed slightly in intensity in different regions. Gender characteristics, clinical manifestations and laboratory parameters in selected children were similar for two seasons. The average age of children with influenza A (group I) was 4.9 ± 0.4 years, female- 55 (45.1%), male- 67 (54.9%). The onset of the disease was acute in 97 (79.5%) patients. In 25 (20.5%) patients, the rise in temperature was preceded by a short (4-5 hours) prodromal period. The fever lasted 3.9 ± 0.6 days. The intoxication syndrome lasted 4.1 ± 0.4 days.

Table 1 Leading syndromes / symptoms of influenza A and influenza B

Syndromes/Symptoms		Group I (influenza A) n = 122	Duration (days)	Group II (influenza B) n = 87	Duration (days)
Acute onset		79,5%^		90,8%	
Body temperature	Febrile	63,9%	3,9± 0,6	75,9%	5,2± 0,5
	Hyperthermia	36,1% º		16,1%	
	Relative subfebrile			48,3%	3,4± 0,6
Respiratory syndrome	Present at the first day of the disease	4,9%*	7,8± 0,6*	79,3%	2,7± 0,3
	Nasal congestion, sneezing	44,3%		34,5%	
	Runny nose	87,7%*		9,2%	
	Dry cough	51,6%		62,1%	
	Wet cough	37,7%*		4,6%	
	Throat pain	39,3%*		10,3%	
	Conjunctivitis	72,1%	4,2± 0,4		
Intoxication syndrome	Weakness	100%	4,1 ± 0,4	100%	5,3 ± 0,5
	Headache	51,6% ^		24,1%	
	Decreased appetite	88,5%		89,7%	
	Nausea	32,8% *		11,5%	
	Vomiting	27,0% *		8,0%	

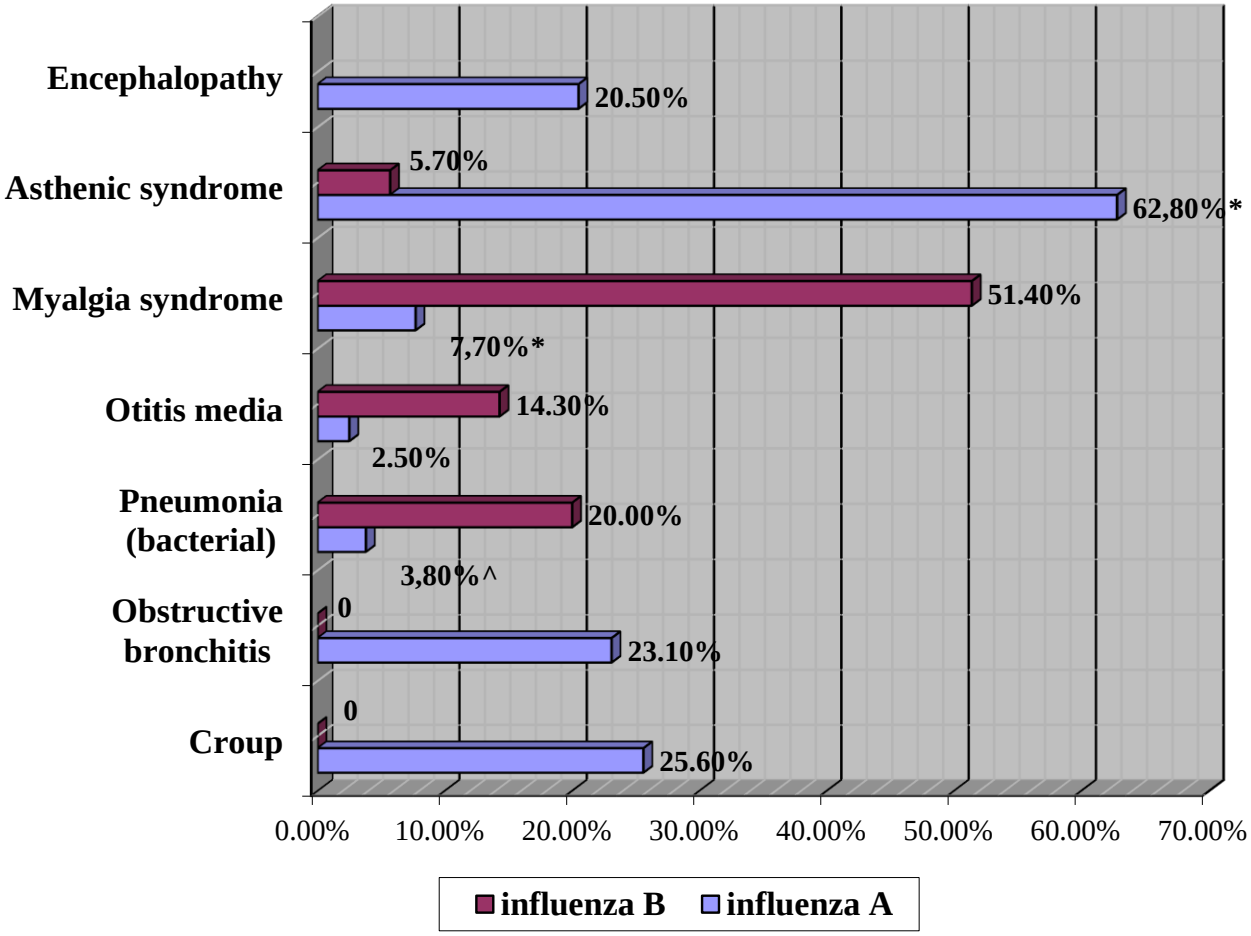
Notes: ^ - p <0.02 compared with group II;
º - p <0.002 compared with group II;
* - p <0.001 compared with group II.



Notes: º - p <0.002 compared with group II;
* - p <0.001 compared with group II.

Chart 1 CBC in patients with influenza A and influenza B

Respiratory syndrome was pronounced since the first day in 76(62.3%), since the second - in 46 (37.7%) patients (Table 1). The duration of catarrhal symptoms was 7.8 ± 0.6 days. In 88 (72.1%) patients since the first day of the disease exudative conjunctivitis was observed, this lasted for 4.2 ± 0.4 days (Table 1). Leukopenia was prominent in 111 (91.0%) children within (2.9 ± 0.5) x 10^9 / l, normocytosis - in 11 (9.0%) patients, neutrophilia - in 93 (76.2%) patients. The dynamics of the disease was characterized by prolonged leukopenia up to 10.4 ± 0.2 days with relative lymphocytosis in the recovery period (Chart 1). Complications developed in 63.9% of patients (Chart 2).



Notes: ^ - p <0.05 compared with group II;
* - p <0.001 compared with group II.

Chart 2 Complications in influenza A and influenza B

In 100 patients (82.0%) influenza A was severe, in 22 (18.0%) - moderate. The mean age of patients in group II with influenza B was 6.0 ± 1.2 years. This group was dominated by female patients - 49 (56.3%). The onset of the disease was acute in 79 (90.8%) patients with a sudden rise in body temperature to a febrile level with a cold. The fever lasted 5.2 ± 0.5 days and decreased gradually, after which 42 (48.3%) patients without complications maintained subfebrile at 37.1 ° C - 37.4 ° C for 3.4 ± 0, 6 days (Table 1). The intoxication syndrome was accompanied by fever and lasted: 5.3 ± 0.5 days. Clinical signs of toxicosis were lethargy, weakness in 100% of patients, headache, decreased appetite, or anorexia, nausea, vomiting. Respiratory syndrome in the first 3.3 ± 0.3 days was absent in most 69 (79.3%) patients. In the midst of the disease manifested itself moderately in the form of sneezing, nasal congestion and sore throat, dry cough, loose serous discharge from the nose. CBC of patients with influenza B was dominated by leukopenia in 63 patients (72.4%) with relative lymphocytosis. Changes in CBC were determined for 6.2 ± 0.5 days in 77 (88.5%) patients (chart 1). Complications developed in 40.2% of patients (chart 2). In 22 (25.3%) patients, influenza B was severe, in 65 (74.7%) - moderate.

4. DISCUSSION

The paper reveals differences in the clinical course of influenza caused by different types of virus: A and B. The average age of patients with influenza A was lower - 4.9 ± 0.4 years against 6.0 ± 1.2 years with influenza B. Common to both groups was acute onset of fever, manifestations of general toxicosis, moderate damage to the mucous membrane of the upper respiratory tract. In 90.8% of cases, influenza B began acutely against 79.5% in influenza A ($p < 0.02$), in 20.5% of children with influenza A prodrome was observed. In a comparative study of the clinic of influenza A and B, it was found that hyperthermia is significantly more common ($p < 0,002$) in influenza A, although the duration of fever in the uncomplicated course of the disease is significantly longer in influenza B (5.2 ± 0.5 vs. 3.9 ± 0 , 6 days, $p < 0,05$) with the subsequent long (to 3,4 ± 0,6 days) subfebrile which is not present at Influenza A. Manifestations of an infectious toxicosis were at 100% in both groups of patients and on duration corresponded to fever.

Influenza A was characterized by a significantly shorter duration of fever (3.9 ± 0.6 days; $p < 0.05$); severe intoxication syndrome with nausea ($p < 0.001$), headache ($p < 0.02$), vomiting ($p < 0.001$); early onset of catarrhal manifestations from 1-2 days of the disease with a predominance of wet cough in 37.7% of children ($p < 0.001$), sore throat (39.3%; $p < 0.001$). Rhinitis and exudative conjunctivitis were observed in these seasons for the first time. Influenza B was observed: significantly more often acute onset ($p < 0.02$); longer duration of fever with uncomplicated course (5.2 ± 0.5; $p < 0.05$); subfebrile without complications occurred in 48.3% of children, almost no catarrhal manifestations in 79.3% of patients in the first days of the disease ($p < 0.001$). In the comparative analysis of the CBC, leukopenia was significantly more often observed in patients with influenza A ($p < 0.002$) and neutrofilia ($p < 0.001$), in contrast to influenza B. Complications occurred significantly more often with influenza A (63.9%) than with influenza B ($p < 0.01$). Croup syndrome (25.6%), obstructive bronchitis (23.1%), encephalopathy (20.5%) were observed only in influenza A. Influenza B significantly more often developed community-acquired bacterial pneumonia and otitis media ($p < 0.05$). Complications in the form of myalgic and asthenic syndromes in the period of early convalescence and their duration, frequency of occurrence, intensity, depending on the type of pathogen, attract special attention. In both groups of patients with myalgic syndrome, the pain was localized symmetrically, exclusively in the calf muscles, especially caused by dorsiflexion of the legs or vigorous compression of the calf muscles, which made it difficult or impossible to move. All children have diffuse pain and swelling of the muscles on palpation, painful tendon attachments. Muscle strength, tone, tendon reflexes and all kinds of sensitivity of the lower extremities were evenly preserved, symmetrical. In all patients with myalgic syndrome, the level of creatine phosphokinase (CPK) in the serum exceeded the reference values by 8-14 times (1273.0 IU / l - 2332.4 IU / l) (Pokrovska and Hnatiuk, 2016).

Myalgic syndrome in influenza B (which we first met in the epidemiological season of 2014-2015) developed on day 6 ± 0.7 of the disease, occurred in 51.4% of patients (Hnatiuk and Pokrovska, 2016). In the 2017-2018 season, we first encountered a similar syndrome with influenza A (7.7%; $p < 0.001$), which is significantly less common than with influenza B, but the duration of myalgic syndrome was significantly longer with influenza A, compared with influenza B (7.2 ± 0.3 vs. 3.01 ± 1.17; $p < 0.001$). The age group for the development of this complication in both influenza A and influenza B is the same: children 4-8 years. It is interesting to note that 4 of our male patients had a new episode of myalgia of the same localization a year later, also associated with influenza. In the dynamics of these children there were changes in electromyography. Influenza-associated myositis usually occurs in children (Mall et al., 2011) and is more often associated with influenza type B, possibly due to the presence of a glycoprotein unique to strains B, which makes the virus more myotropic (Ferrarini et al., 2014). Cases of acute benign myositis due to a new strain of H1N1 have been reported (Koliou et al., 2010). The exact cause of influenza-associated myositis is unclear (direct viral invasion along with the immunological mechanism); however, the influenza virus was isolated from muscle tissue, indicating a direct viral invasion of muscle fibers, their necrosis, leading to to elevated CPK (Brook, 2008). Other biopsy results include edema and focal infiltration of polymorphonuclear and mononuclear cells.

Asthenic syndrome was manifested by an astheno-apathetic state in the form of apathy, lethargy, lethargy, drowsiness, loss of interest in the environment and developed at 6 ± 0.4 days from the onset of the disease in influenza A and B. But in group I, compared with group II, the frequency of asthenia (62.8% vs. 5.7%; $p < 0.001$), intensity and duration (6.1 ± 0.8 vs. 2.3 ± 0.3 days; $p < 0.001$) were significantly higher in influenza A. Prolonged asthenic syndrome in the absence of clinical and laboratory signs of intoxication syndrome, complications in the period of recovery. Post-influenza asthenia is associated with a violation of the regulation of the use of energy reserves, not with their depletion. An important role is played by metabolic disorders that lead to acidosis, hypoxia and, as a consequence, the aerobic pathway of glucose oxidation changes to non-aerobic, reduced levels of ATP, creatine phosphate in cells, which, in turn, disrupts the formation and use of energy. Acidosis induces oxidative stress due to depression of glycolysis enzymes, reduced lactate utilization. Mitochondrial activity also decreases, protein catabolism increases, and hyperammonemia develops. At asthenia at patients mechanisms of disturbance of the immune status which is shown by decrease in level of T-lymphocytes and T-suppressors, activation of system of phagocytosis, development are described. That's why the proper treatment is necessary (Sinchuk, 2017).

In general, the results obtained on the clinical features of influenza A and B indicate a more severe course of influenza caused by virus type A and confirm the data of other researchers (Maltsev et al., 2013; Popov et al., 2015; Dat Tran et al., 2016).

5. CONCLUSION

Influenza A is characterized by a gradual onset of the disease, with a pronounced intoxication; significant catarrhal manifestations from the first day of illness in the form of runny nose, wet cough, sore throat and conjunctivitis; in the hemogram - leukopenia with neutrophilia; complicated by severe asthenic syndrome, croup syndrome, obstructive bronchitis. Influenza B is characterized by an acute onset of moderate intoxication, fever, which can last a long time without complications; minor catarrhal phenomena that appear on 2 - 3 days of illness; in the CBC - leukopenia with lymphocytosis; complicated by myalgia in the calf muscles, bacterial pneumonia, otitis. The predictors outlined above allow, in the absence of specific laboratory diagnosis, to suspect the patient of a disease caused by a certain type of virus. On the other hand, under the condition of laboratory verification of the etiology of influenza, knowledge of clinical predictors inherent in different types of influenza virus allows to predict the course of the disease, to predict the occurrence of possible complications and their nature.

Abbreviations

ARVI – Acute respiratory viral infections; PCR – Polymerase chain reaction; CPK – Creatinine phosphokinase; CBC – Complete blood count

Participation of authors

Concept and research plan – Hnatyuk Vira, Pokrovska Tetyana;
Collection of materials – Pokrovska Tetyana, Hnatyuk Vira, Lytvyn Halyna;
Material editing – Pokrovska Natalia, Pokrovska Tetyana;
Text writing – Pokrovska Tetyana, Hnatyuk Vira, Lytvyn Halyna;
Statistical data analysis – Pokrovska Tetyana;
Text Editing – Hnatyk Vira, Lytvyn Halyna, Pokrovska Natalia.

Conflict of Interest

The authors declare no conflict of interest or financial support. All authors contributed to the research and/or preparation of the manuscript.

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Informed consent

Lviv Regional Infectious Diseases Clinical Hospital is the clinical base of the Pediatric Infectious Diseases Department of Danylo Halytsky Lviv National Medical University. All patients and their parents upon admission to the hospital sign an informed consent for treatment and the possibility of using their data for scientific work (form №003-6/o approved by Order of the Ministry of Health of Ukraine 08.08.2014 №549).

Ethical approval

The study was approved by the Medical Ethics Committee of Danylo Halytskyi Lviv National Medical University (ethical approval code: 171/20).

REFERENCES AND NOTES

1. Brook I. Microbiology and management of soft tissue and muscle infections. Int J Surg 2008;6(4): 328-38.
2. Daley AJ, Nallusamy R, Isaacs D. Comparison of influenza A and influenza B virus infection in hospitalized children. J Paediatr Child Health 2000;36(4):332–4.

3. Ferrarini A, Lava SA, Simonetti GD, et al. Influenza Virus B-associated acute benign myalgia cruris: an outbreak report and review of the literature. Neuromuscul Disord 2014;24(4):342-6.
4. Hnatiuk V, Pokrovska T. Myalgic syndrome associated with influenza B. Ukr neurolog Zh 2016;3:46 -9.
5. Koliou M, Hadjiloizou S, Ourani S, et al. A case of benign acute childhood myositis associated with influenza A (H1N1) virus infection. Clin Microbiol Infect 2010;16(2):193-5.
6. Mall S, Buchholz U, Tibussek D, et al. A large outbreak of influenza B-associated benign acute childhood myositis in Germany, 2007/2008. Pediatr Infect Dis J 2011;30(8):142-6.
7. Maltsev OV, Grishin IS, Peredelsky EV, et al. Influenza B Virus: Some Features of Clinical Findings and Etiotropic Treatment. J Infect 2013;5(3):28-34.
8. McCullers JA, Hayden FG. Fatal influenza B infections: time to reexamine influenza research priorities. J Infect Dis 2012;205(6):870–2.
9. Mosnier A, Caini S, Daviaud I, et al. Clinical Characteristics Are Similar across Type A and B Influenza Virus Infections. PLoS One 2015;10(9):e0136186. Published 2015 Sep 1.
10. Nejad MA, Hashemian M, Ganjalikhani H, Ahmadipour M. Evaluation of prevalence and severity of acute respiratory distress syndrome in hospitalized patients due to H1N1 outbreak in Kerman, Iran. Medical Science, 2020, 24(101), 135-142
11. Pokrovska T, Hnatyuk V. Influenza B in Children in Epidemic Season 2014-2015. Infect Dis J 2016;3 (85):51-4.
12. Popov A F, Simakova AI, Dmitrenko KA, et al. Clinical picture of influenza caused by different virus serotypes. Epidemiologiya i Infektsionnye Bolezni 2015; 20(6): 39-43.
13. Sinchuk NO. Asthenia in children in the modern practice of the pediatrician. Medical newspaper "Health of Ukraine" 2017;15–6.
14. Su S, Chaves SS, Perez A, et al. Comparing clinical characteristics between hospitalized adults with laboratory-confirmed influenza A and B virus infection. Clin Infect Dis 2014;59(2):252–5.
15. Tran D, Vaudry W, Moore D, Bettinger J A, et al. Hospitalization for Influenza A Versus B. Pediatric 2016;138(3): e20154643.

Data and materials Availability
All data associated with this study are present in the paper.

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