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ORIGINAL ARTICLE

INFECTIOUS MONONUCLEOSIS DURING THE WAR AND COVID INFECTION PANDEMIC IN UKRAINE

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Kateryna Pikul, Valentina Ilchenko, Liudmyla Syzova, Oksana Muravlova, Iryna Dvornyk

POLTAVA STATE MEDICAL UNIVERSITY, POLTAVA, UKRAINE

ABSTRACT

The aim: To analyze the current views on diagnosis and management of infectious mononucleosis in children. The purpose of our work is also a comparative characteristic of the incidence of infectious mononucleosis in Ukraine and the city of Poltava (2006-2022).

Materials and methods: The data of scientific literature have been analyzed, using the bibliosemantic method of study. We used a retrospective analysis of statistical data on the incidence of infectious mononucleosis 2006-2022 and the most frequent cases of infectious pathology in children in the period 2019-2022, and also conducted an analysis of the percentage of those vaccinated according to the vaccination calendar.

Results: We had an increase in the incidence in 2009, but in subsequent years it was in the range of 23-25.2 per 100.000 children. The incidence of patients diagnosed with infectious mononucleosis per 100.000 of the children population in the Poltava region is one of the lowest in Ukraine, accounting for 8.1 - 10.1% over the past 3 years, which can be explained by the decrease in visits by parents and their children to the hospital to avoid contact with patients with the coronavirus disease and the fact that our region also had rather lower rates of children with Covid-19 compared in Ukraine.

Conclusions: the situation with the spread of infectious mononucleosis in children in Ukraine is such that it causes concern, and when comparing the incidence in 2009 and 2022, the authors noted an increase in the overall incidence of this nosology by 5%.

KEY WORDS: children, management, prophylaxis, infectious mononucleosis

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INTRODUCTION

Currently, the issue of infectious mononucleosis is relevant due to the following main factors: the rising incidence of morbidity in Ukraine over the past 3 years, the great variability of the clinical course of the disease and the complexity of specific diagnostics, which leads to a large percentage of diagnostic errors, the general infection with the Epstein-Barr virus (EBV), which can affect the immune system. Antibodies to EBV are detected in 15% of children under 1 year of age and 90% of adults.

All this is caused by a large number of risk factors: migration of the population from temporarily occupied territories, overcrowding of people in places of refuge from the war, changes in the quality of food, humanitarian difficulties, the action of chemicals, stress and immunosuppression. The war led to an increase in viral etiology and an increase in the share of children with secondary bacterial complications, a decrease in the percentage of vaccinated persons according to the vaccination calendar. We know that after such childhood infections as measles and chicken pox there is lifelong immunity, then infectious mononucleosis is a

rather serious disease that affects the immune system, epitheliocytes of blood vessels, can turn into a chronic course and complicate the quality of life, causing concern to doctors.

THE AIM

The aim of the paper is to analyze the current views on diagnosis and management of infectious mononucleosis in children. The purpose of our work is also a comparative characterization of the incidence of infectious mononucleosis in Ukraine and the city of Poltava (2006-2022) against the background of an increase in infectious pathology in children and a decrease in the percentage of mandatory preventive vaccinations during the Covid-19 pandemic and martial law, as mediated factors affecting the increase of patients with the indicated nosology.

MATERIALS AND METHODS

We used a retrospective analysis of statistical data on the incidence of infectious mononucleosis 2006-2022

and the most frequent cases of infectious pathology in children in the period 2019–2022, as well as an analysis of the percentage of people vaccinated according to the vaccination calendar. The authors, as children's infectious disease specialists, cite one of the examples of a case from the history of the disease, which recently occurred in the children's infectious disease department of Poltava. The data of scientific literature have been analyzed, using the bibliosemantic method of study.

RESULTS

The disease was first described by N.F. Filatov in 1885 under the name "idiopathic lymphadenitis with fever". The causative agent of infectious mononucleosis is the Epstein-Barr virus (EBV), isolated in 1964 by Epstein and Barr from Burkitt lymphoma cells. It has been proven that EBV is widely disseminated and antibodies to the virus have been detected in all studied populations with the incidence rate of infection 80% to 90% of the population worldwide. The studies revealed great diversity in the time of primary infection and the stages of infection dissemination. Wealthy population of highly developed countries are most often infected at the age of 14–15 years, while the lower socioeconomic groups of population of developing countries is already infected in 70%–100% of cases by the age of 3–5 years. However, despite the general prevalence and contagion, there is a clinical diversity of diseases caused by the virus in different regions: infectious mononucleosis, nasopharyngeal carcinoma and Burkitt lymphoma predominate in Europe, Asian countries, and Africa, respectively. A detailed description of the symptoms of the disease and their combination refers to 1970–1975. Treatment of infectious mononucleosis remains symptomatic until now. Acyclovir, which has been successfully used for the treatment of other herpes infections, is ineffective. The appropriateness of antibiotic therapy is denied by a number of contemporary domestic and foreign authors.

EBV belongs to the herpesvirus family, genus γ -herpesvirus type 4. It is a DNA-containing virus. A mature virus has a spherical shape, contains a double-stranded DNA genome, a capsid, a protein, and a lipid outer shell. EBV has specific antigens: capsid (VCA), nuclear (EBNA), early (diffuse EAD and localized EAR), membrane (MA). During the acute infection, first, antibodies to early antigens (EA, VCA) appear, and then to nuclear ones (EBNA). Detection of antibodies to capsid (VCA) and nuclear (EBNA) antigens in the absence of antibodies to early antigens (EA) is the marker of persistent infection: latent infection. The spectrum of antibodies differs significantly in different diseases associated with EBV. Thus, patients with IM develop antibodies that belong

to three classes of immunoglobulins, to various virus-specific antigens. Patients with Burkitt lymphoma have increased titers of IgG antibodies to EAR. Patients with nasopharyngeal carcinoma have increased titers of IgA antibodies to EAD and VCA. Antibody titers correlate with enlargement of the neoplasm and decrease in case of successful treatment.

The virus produces proteins that are analogs of interleukins that alter the immune response and suppress cellular immunity. There is a marker of the lymphoproliferative process on the X-chromosome, and the Epstein-Barr virus has a tropism for lymphoid tissue. An incorrect immune response due to abnormal genetic recombination can provoke an oncological process, Burkitt lymphoma, lymphogranulomatosis, etc. The DNA virus enters the cell, where the proliferation of lymphocytes occurs; this process is called immortalization (immortality of lymphocytes). In the acute phase, up to 20% of B-lymphocytes are affected. When the process is generalized and chronic, disturbances occur in T-lymphocytes, killer cells, and epitheliocytes of the vessels.

Ways of penetration into the child's body: airborne, sexual, vertical – from mother to child, hematogenous. The incubation period can range from several days to 1–2 months.

The following are the features of infectious mononucleosis in children:

- activation of the Epstein-Barr virus (EBV) can be caused by frequent acute respiratory infections, convulsive syndrome, neurological diseases, childhood infections [1];
- after the primary reaction, the diseases may not manifest itself and become chronic; it can be determined only by the markers;
- in the primary regional infection, lymphadenopathy, more often cervical and submandibular, is noted, and tonsillitis phenomena (from catarrhal to purulent inflammation) are apparent. Notably, tonsillitis without lymphadenopathy can be confused with infectious mononucleosis, although such cases could be possible;
- parenchymal dissemination is noted at the end of the 1st week: splenomegaly is less prominent compared to liver enlargement, as well as possible alterations in the myocardium, blood vessels, kidneys, lungs, and nervous system. Timing is crucial only for 30% of children;
- in young children, the disease may proceed as a respiratory disease;
- when the clinical picture is similar, but there is no serological confirmation, then infectious mononucleosis syndrome is possible, the causative agent of which can be measles, rubella, toxoplasmosis,

Table I. Incidence of infectious mononucleosis in children of the Poltava region.

No.	Year	Number of cases	Morbidity per 100.000 of children population
1.	2006	50	23.71
2.	2007	58	28.39
3.	2008	54	27.18
4.	2009	69	35.17
5.	2010	63	28.47

Table II. Vaccination coverage 2020-2022 in the Poltava Region and Ukraine

The name of the vaccination (revaccination)	2020 year		2021 year		9 months 2022 year	
	Region %	Ukraine %	Region %	Ukraine %	Region %	Ukraine %
Tuberculosis up to 1 year	95,6	88,8	88,7	88,8	71,4	43,0
Whooping cough, diphtheria, tetanus under 1 year	89,8	80,1	90,6	80,1	72,5	46,9
Whooping cough, diphtheria, tetanus in 18 months	92,1	78,1	91,6	78,1	72,7	46,1
Diphtheria, tetanus of children in 6 year	58,7	59,7	83,8	59,7	69,3	46,6
Diphtheria, tetanus of children in 16 year	90,4	73,6	92,2	73,6	65,8	43,4
Diphtheria, tetanus in adults	76,6	47,0	75,0	47,0	52,3	24,2
Poliomyelitis up to 1 year	92,0	83,0	89,7	83,0	89,7	83,0
Poliomyelitis at 18m.	92,7	83,0	91,5	83,0	91,5	83,0
Poliomyelitis at 6 years	92,2	81,7	89,1	81,7	89,1	81,7
Poliomyelitis at 14 years	92,5	81,8	91,2	81,8	91,2	81,8
Measles, mumps, rubella 1 year	94,8	83,3	96,6	83,3	96,6	83,3
Measles, mumps, rubella at the age of 6m.	92,0	83,4	92,8	83,4	92,8	83,4
Hepatitis B-3 up to 1 year	91,8	79,8	91,0	79,8	91,0	79,8
Hemophilic infection of children up to 1 year	91,2	85,1	93,1	85,1	93,1	85,1

hepatitis B virus, HIV infection, adenovirus infection, cytomegalovirus infection;

- it is also necessary to take into account the possibility of simultaneous human infection with several causative agents of the family of herpesviruses: co- and superinfection. Among patients, in 2% of cases, the clinical course of the disease takes the form of combined EBV- and CMV-infectious mononucleosis.

Children with severe immune deficiency may develop generalized forms of EBV-infection with damage to the central and peripheral nervous system in the form of meningitis, encephalitis, and polyradiculoneuritis. Duncan syndrome belongs to a group of hereditary diseases that appear in men after EBV infection. The prognosis of the disease is very unfavorable, more than 70% of patients die before reaching 10 years of age. Survivors often develop severe hypogammaglobulinemia, lymphoblastic lymphoma, less commonly aplastic anemia, and necrotizing vasculitis with damage to arteries and large vessels [2].

Our attention was drawn to the problem of the increasing tendency of infectious mononucleosis among

children in 2020-2022 in Ukraine. There are many scientific works and studies on the coronavirus disease, but the authors did not find publications about how often children get sick with infectious mononucleosis after suffering from Covid-19, so we share observations from our own experience of working as a pediatric infectious disease specialist.

Under the Covid-19 pandemic, coronavirus infection (pneumonia of a new type) was first diagnosed on March 3, 2020 in Chernivtsi. On March 13, the first death associated with coronavirus infection was recorded. As of October 24, 2022, there were 5,279,346 (12.8%) sick people in Ukraine, of which 109,819 (2.1%) died. Distribution of those infected with COVID-19 in Ukraine by the age of 0-17 years is 5.00%, 18-29 years is 11%, 30-49 years is 37%, 50-69 years is 38%, 70 years and older is 9%.

In April 2020, several European countries reported an increase in cases of Kawasaki-like syndrome among children. Kawasaki syndrome is a disease that is diagnosed mainly in infants and children under the age of five. However, the new multisystem inflammatory syn-

drome, which the experts have linked to COVID-19, also occurs in older children, accompanied by high fever, rash, swelling, inflammation affecting the eyes, blood vessels and heart, as well as infectious-toxic shock [3].

A recent study of 186 children with multisystem inflammatory syndrome showed that the average age of patients was 8.3 years; 73% of children were previously healthy, the rest had laboratory evidence of SARS-CoV-2 infection (PCR and/or antibodies). Gastrointestinal (92%), cardiovascular (80%), hematological (76%), skin-mucosal (74%) and respiratory (70%) symptoms were observed in children [4]. But these complications are minor in Ukraine. The coronavirus in children most often occurs in a mild form or without symptoms, but it still leads to a decrease in the body's resistance to other infections for a certain time [5].

According to the authors, this can be material for further research by scientists on the incidence of infectious mononucleosis after a history of coronavirus disease, as a pathological chain is observed - "virus-immune system-vascular epitheliocytes-cells-RNA".

Scientists have investigated: gene polymorphism, coding the host proteases, which are involved in the virus entry into the cells can influence the susceptibility to and mortality from coronavirus disease 19 (COVID-19). Our study indicated the presence of an association between the *tmprss2* rs12329760 polymorphism and the severity of COVID-19 in the Ukrainian population [6].

Activation of the infection, infectious mononucleosis, is facilitated by the factors that reduce general and local immunity. The authors drew attention to statistical data on the incidence of infectious mononucleosis among children in previous years (Table I).

We had an increase in the incidence in 2009, but in subsequent years it was in the range of 23-25.2 per 100.000 children (Table I). In January 2021, the incidence was 28.1 per 100.000, and in January 2022 it was 29.2. We noted an increase by 5% in the incidence of infectious mononucleosis in Ukraine. The findings can be useful for further research on the relationship of the activation of the above infection in individuals who were sick or had an asymptomatic course of Covid-19. The incidence of patients diagnosed with infectious mononucleosis per 100.000 of the children population in the Poltava region is one of the lowest in Ukraine, accounting for 8.1 - 10.1% over the past 3 years, which can be explained by the decrease in visits by parents and their children to the hospital to avoid contact with patients with the coronavirus disease and the fact that our region also had rather lower rates of children with Covid-19 compared to other regions of the country.

The authors noted that 8 children in 2022, who had a previous diagnosis of infectious mononucleosis, were

transferred to other specialized departments with multiple complications, pneumonia, coronavirus disease, diabetes, which can be explained by a decrease in immunity due to the stressful situation in the population in the last year. In 2022, the number of refusals from hospitalization for 1-3 days increased due to the complications of the war and the fear of parents for the life of the child when staying in institutions with increased crowding. The number of children discharged with improvement due to parents' desire to continue treatment in outpatient settings has increased. Scientists know that an increase in the incidence of infectious mononucleosis can also be caused by other commonly transmitted infectious diseases. In 2018, we had a measles outbreak due to a decrease in the number of people vaccinated.

The authors state that children whose parents refused vaccinations according to the calendar had a history of measles, chicken pox, and frequent colds. They were more often infected with infectious mononucleosis due to triggered immunity.

According to official data, that the increase in the incidence of measles in the Poltava region [7] and in Ukraine as a whole was preceded by years with a rather low coverage of the population with vaccination against this disease.

So, a relatively high percentage of vaccinated children in the Poltava region was observed only in 2012 and had a constant downward trend in subsequent years. During the period from 2013 to 2018, the absolute number of cases of measles registered in this region among children under 17 years old increased 13.6 times, and among adults – 24 times [8].

New challenges have arisen today due to stress, nutritional disorders during military operations. The authors are concerned that we are observing a tendency towards a decrease in preventive vaccinations during 2020-2022, in particular against diphtheria, poliomyelitis, and tuberculosis [9].

We have come across reports of a fiery outbreak of diphtheria in September 2022 in one of the western regions of Ukraine. The authors indicate these data to emphasize that even among controlled infections with the help of vaccinations, fiery outbreaks were observed in Ukraine during the specified period. But serious concern is caused by adverse trends in the health of children among the incidence of uncontrolled infection - infectious mononucleosis.

Specific prevention has not been developed against infectious mononucleosis, but we have a decrease in the percentage of vaccinations in Ukraine due to the war, covid disease (Table II).

It is known that, in most cases, the disease is caused

by specific causes (causing agents) independent of the person, but a certain proportion of this disease occurs due to non-compliance with the correct lifestyle and neglect of the principles of hygiene (after all, this is also a disease of kisses), vaccination, as a way of protection against controlled infections and prevention of immunodeficiency and probable infection of this not highly contagious infectious mononucleosis. In this regard, special attention should be paid to the problem of preventive measures and recommendations for indirect prevention of the development of this pathology. The authors present the data in Table II, where we clearly observe a decrease in the percentage of vaccinations among the child population during the last 2 years, which may cause an increase in the incidence of these diseases, according to immunodeficiency and the mediated occurrence of infectious mononucleosis. Scientists know that up to 90% of people become infected with viruses of the herpes family (which includes the Epstein-Barr virus) during their lifetime, but 15%, who probably have reduced immune resistance, get sick (Table II). So, this is another reason for concern and further study of the trend towards an indirect increase in the incidence of infectious mononucleosis in 2020-22 by 5% in Ukraine.

DISCUSSION

We present a clinical case of a young female patient with a diagnosis of infectious mononucleosis who received treatment at the children's infectious unit in Poltava city. On August 17, 2022, the 15-year-old female patient S. was admitted to the First City Clinical Hospital with complaints of an increase in body temperature to 37.8, sore throat, difficulty breathing through the nose, general weakness, and loss of appetite. From the past medical history, it is known that she has been ill since 08/12/22, when the fever and sore throat appeared and nasal breathing became difficult. It is also known that it grew and developed according to age. The child had infectious diseases often. It is known that the parents have had coronavirus infection six months ago. Vaccinations according to the calendar were carried out only at 1 year of life, the parents refused the following ones.

The girl received outpatient treatment (symptomatically) that was not successful. During the examination, the child's condition was moderate due to intoxication syndrome. Body temperature was 37.8, clear consciousness, moderately lethargic. Bed status was active. Normosthenic physique. Nutrition was satisfactory. Soft tissue turgor was preserved. The skin was pale, clean. Visible mucous membranes were clean, normal color. The mucous membrane of the oropharynx was

hyperemic, the tonsils were enlarged, purulent masses in the lacunae were removed with a spatula, no bleeding. No swellings were noted. Swallowing was not impaired. Enlarged lymph nodes: submandibular – 2.0 x 1.5 cm, painless, mobile, not fused to the skin and surrounding tissues; posterior-cervical – 1.0 cm, in the form of a "chain", the rest were small. The skin over them was not changed. Breathing through the nose was difficult. The respiration rate was 18 breaths per minute. Over the lungs: percussion-pulmonary sound; auscultatory: breathing was vesicular, no wheezes. The boundaries of the heart were not changed. Auscultation revealed clear heart sounds, the rhythm was normal. The heart rate was 90 beats per minute. The tongue was wet with a white coating. The abdomen was soft, painless on palpation, involved in the act of breathing. Liver +1.0 cm, spleen -. Feces were normal. Urination was painless, diuresis was sufficient. Pasternatsky's symptom was negative on both sides. Meningeal signs were negative. No focal neurological symptoms were detected. Laboratory tests (made on 17/08/22) showed: CBC: RBC=4.42x10¹²/L, Hb=129g/L, WBC=9.2x10⁹/L, ESR=40mm/h, eosinophils=1%, stab=2%, segmental=26%, lymphocytes=49%, monocytes=7%, atypical mononuclear cells=14%, platelets= 328x10³/L. Blood biochemical tests (made on 18/08/22) showed: total bilirubin=10.1µmol/L, direct bilirubin=3.110¹²/L, indirect bilirubin=7.0x10¹²/L, AlAT=265 units, AsAT=145 units, urea= 3.1g/L, total nitrogen=20g/L, creatinine=20 µg/l, glucose=5.0 mmol/l. Urinalysis (made on 17/08/22) showed: light yellow color, clear, density=1020, acid reaction, RBC= 2-6 FOV, WBC= 0-1 FOV, few epithelia, mucus, no salt; Tests for viruses of the herpes-group (made on 18/08/22) showed: ELISA IgM VCA EBV: positive. Nasal smear for eteobiosis (made on 17/08/22): not detected. Fecal worm egg counts (made on 17/08/22): not detected. Nasal and oropharynx smear for BL No.73-74 (made on 17/08/22): negative. Oropharynx smear for microflora and sensitivity to antibiotics No. 948 (made on 17/08/22): *Citrobacter freundii*. ECG (made on 19/08/22) showed: sinus arrhythmia, heart rate was 57-100 beats per minute. Vertical position of the electrical axis of the heart. Violation of the processes of repolarization of the apical-lateral area of the left ventricle. The treatment was provided: 1000 mg ceftriaxone twice a day No. 7, herpevir, probiz, loratadine, chlorophyllipt, nasal irrigation with saline solutions, intravenous drip: 0.9% sodium chloride solution, dexamethasone, 4% glutargin solution, 5% glucose solution. She was discharged with improvement on 08/25/2022 at her mother's insistence with the follow-up treatment recommendations: supervision of a pediatrician for 12 months; adherence to the diet No.5 for 6 months,

exclusion of the physical activity and insolation for 12 months; home stay for 1 month; continue treatment with: probiz 1c twice No.15, 400 mg lipster 4 times for 7 days, 500 mg/day ukrliv for 1 month. Blood biochemistry test, blood test (liver and kidney tests) after 1 month and if necessary. PCR blood DNA EBV after 1 month, once in 3 months up to 12 months. Scheduled abdominal ultrasound and ECG. Examination by a pediatrician (infectiologist) after 1 month, once in 3 months up to 12 months. Scheduled examination by a cardiologist.

CONCLUSIONS

Therefore, there are many indirect risks that increase the possibility of contracting infectious mononucleosis - frequent infectious diseases, due to refusal of vaccination, stress, immunodeficient state, which will reduce the resistance of the body against the Epstein-Barr virus.

The situation with the spread of infectious mononucleosis in children in Ukraine is such that it causes concern, and when comparing the incidence in 2009 and 2022, the authors noted an increase in the overall incidence of this nosology by 5%. Preventive measures are very important to prevent the development of this category of disease. Vaccination against other viral diseases refers to secondary prevention factors that can be influenced by preventing immunosuppression and reducing the risk of infection with the Epstein-Barr virus.

The development of a vaccine against infectious mononucleosis is a promising direction to overcome this problem as a necessary motivator to maintain health at a young age. Thus, pediatricians, family doctors, infectiologists should carry out prophylaxis among the population regarding infectious mononucleosis, coronavirus infection as it is a reliable measure of preventing morbidity and reduction.

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ORCID and contributionship:

Kateryna Pikul: 0000-0002-5724-4343^{A-F}

Valentina Ilchenko: 0000-0002-1451-442X^{D-F}

Ljudmyla Syzova: 0000-0002-8335-3295^{D-F}

Oksana Muravlova: 0000-0002-1202-7206^{D,F}

Iryna Dvornyk: 0000-0002-3660-3239^{D,F}

Conflict of interest:

The Authors declare no conflict of interest.

CORRESPONDING AUTHOR

Kateryna Pikul

Poltava State Medical University

24 Shevchenko st., 36000 Poltava, Ukraine

tel: +380992697785

e-mail: ekateryna.pikul@gmail.com

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