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METAPNEUMOVIRUS INFECTION IN CHILDREN

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Objective: to study the clinical features of metapneumovirus infection in children of different ages in a hospital.

Materials and methods. A retrospective analysis of medical records of 142 patients aged 1 month to 14 years inclusive who were hospitalized in the period from January 2012 to April 2019. Metapneumovirus infection was confirmed by hMPV nucleic acid isolation by PCR in nasopharyngeal smears.

Results. Metapneumovirus infection is detected among hospitalized children with acute respiratory viral infections in 4,4% of cases. In the age structure, 72,2% are children under 4 years old, and the maximum incidence rate is among children aged 3 years of life. The leading clinical symptoms are cough in 93,0% of cases and rhinitis in 96,5% of cases. In 88,2% of children, the disease proceeds with an increase in temperature >38 °C, including in 34,6% – 39,5 °C and above. Symptoms of gastrointestinal dysfunction in the form of vomiting and diarrhea develop in 26,1% and 22,5% of children, respectively. 78,2% of patients requiring hospitalization suffer hMPV infection with damage to the lower respiratory tract, including in the form of bronchitis in 85,6% of cases and pneumonia in 14,4% of cases. The disease is complicated by the development of bronchial obstructive syndrome in 38,7% and acute respiratory failure in 22,3% of cases. ARF and BOS are significantly more likely to develop in children of the first 3 years of life – 71,0% versus 29,0% in children of the older age group ($p = 0.038$) and 69,8% against 30,2% ($p = 0.007$), respectively. In a clinical blood test for hMPV infection, leukopenia and leukocytosis are detected only in 3,5% and 12,7% of cases, respectively, as well as an increase in ESR in 23,9% of children. The level of CRP in the 93,0% of children was less than 20 mg/l.

Conclusions. Virological confirmation of metapneumovirus infection in hospitalized children with lower respiratory tract infections contributes to the formation of an adequate therapeutic tactic.

Keywords: metapneumovirus infection; acute respiratory viral infection; children; PCR.

МЕТАПНЕВМОВИРУСНАЯ ИНФЕКЦИЯ У ДЕТЕЙ

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Цель: изучить клинические особенности метапневмовирусной инфекции у госпитализированных детей разного возраста.

Материалы и методы. Ретроспективный анализ медицинских карт 142 пациентов в возрасте от 1 месяца до 14 лет включительно, находившихся на стационарном лечении в период с января 2012 по апрель 2019 г. Метапневмовирусная инфекция подтверждена на основании выделения рибонуклеиновой кислоты hMPV методом полимеразной цепной реакции в назофарингеальных мазках.

Результаты. Метапневмовирусная инфекция выявляется среди госпитализированных детей с острыми респираторными вирусными инфекциями в 4,4 % случаев. В возрастной структуре 72,2 % составляют дети до 4 лет, причем максимальная заболеваемость приходится на детей в возрасте трех лет. Ведущие клинические проявления: кашель в 93,0 % и ринит в 96,5 % случаев. У 88,2 % детей заболевание протекает с повышением температуры >38 °C, в том числе у 34,6 % — 39,5 °C и выше. Симптомы желудочно-кишечной дисфункции в виде рвоты и диареи развиваются

у 26,1 и 22,5 % детей соответственно. 78,2 % пациентов, требующих госпитализации, переносит hMPV-инфекцию с поражением нижних дыхательных путей, в том числе в виде бронхита в 85,6 % и пневмонии в 14,4 % случаев. Заболевание осложняется развитием бронхообструктивного синдрома в 38,7 % и острой дыхательной недостаточности в 22,3 % случаев. Острая дыхательная недостаточность и бронхообструктивный синдром достоверно чаще развиваются у детей первых трех лет жизни — 71,0 против 29,0 % у детей старшей возрастной группы (p = 0,038) и 69,8 против 30,2 % (p = 0,007) соответственно. В клиническом анализе крови при hMPV-инфекции лейкопения и лейкоцитоз выявляются только в 3,5 и 12,7 % случаев соответственно, повышение СОЭ — у 23,9 % детей. Уровень С-реактивного белка у 93,0 % детей составлял менее 20 мг/л.

Выводы. Вирусологическое подтверждение метапневмовирусной инфекции у госпитализированных детей с поражением нижних дыхательных путей способствует формированию адекватной терапевтической тактики.

Ключевые слова: метапневмовирусная инфекция; острая респираторная вирусная инфекция; дети; полимеразная цепная реакция; ПЦР.

INTRODUCTION

Acute respiratory viral infections (ARVI) are an urgent problem because of their significant annual worldwide prevalence, including the Russian Federation (RF). According to Rospotrebnadzor, in 2018, more than 30 million acute upper respiratory tract infection cases were registered in the RF. In contrast, the incidence rate among children is 2.4–2.9 times higher than among adults. Regarding their economic importance, respiratory viral infections have been consistently leading among other infectious diseases over the past 10 years. In 2018, the economic damage from ARVI amounted to more than 500 billion rubles [*].

Various viruses have tropism for the respiratory tract epithelium, but not every known respiratory virus affects the lower respiratory tract [4]. One of the most studied is the respiratory syncytial virus that causes bronchitis and bronchiolitis in children [14]. Other viruses, such as human metapneumovirus (hMPV) and bocavirus, are classified as "new," with insufficiently specified clinical and pathogenetic aspects.

Metapneumovirus was discovered relatively recently; in 2001, however, a serological study of archived sera showed antibodies to it in previously collected samples (in 1958) [15]. The data of phylogenetic data analyses showed that the virus is related to the avian pneumovirus and deviated from the genetic line of its ancestor approximately 200 years ago [7, 12]. hMPV is now found in most of the world [12]. According to the modern classification, the virus is referred to as the Pneumoviridae family, the Metapneumovirus genus [5]. The viral genome is represented by single-stranded non-segmented RNA encoding nine structural and non-structural proteins, covered with a thick lipid envelope with surface glycoproteins [13]. The virus has two genotypes, A and B, subdivided into subgroups A1, A2, B1, and B2 based on the variability of surface glycoproteins F and G [8].

Virus prevalence data differ significantly across studies and range from 0% to 36.4%, averaging 6.24% [10]. Predominantly, hMPV infection is specific to children and rarely causes illness in adults, but its frequency increases among the elderly and those with immunodeficiency [11]. Clinical manifestations of metapneumovirus infection range from mild upper respiratory tract infection to severe lower respiratory tract infection, making it relevant to study [1–3, 6, 9].

The aim of work: this investigation studies the clinical features of metapneumovirus infection in hospitalized children of different ages.

MATERIALS AND METHODS

A retrospective analysis of the medical records of 142 patients with confirmed metapneumovirus infection and hospitalized at the clinic of the Children's Research and Clinical Center for Infectious Diseases of the Federal Medical and Biological Agency from January 2012 to April 2019 was conducted. The patients' ages ranged from 1 month to 14 years old inclusive.

The diagnosis confirmation was performed based on the isolation of ribonucleic acid (RNA) from metapneumovirus in nasopharyngeal smears. The diagnosis was confirmed using multiplex polymerase chain reaction with hybridization-fluorescence detection of amplification products with the AmpliSens® ORViskrin-FL reagent (Central Research Institute of Epidemiology, Rospotrebnadzor, Russia). It provides the detection of specific nucleic acid fragments: ARVI pathogens human respiratory syncytial virus, parainfluenza viruses type 1–4, human coronaviruses, human metapneumovirus, human rhinoviruses, and DNA from human adenoviruses of groups B, C, E, and bocaviruses.

[*] On the sanitary and epidemiological well-being of the population in the Russian Federation in 2018. State report. Moscow: Federal Service for Supervision of Consumer Rights Protection and Human Well-being, 2019. P. 114.

The following studies' data were analyzed: clinical blood count with white blood cell count (WBC) differential, ESR, C-reactive protein level, chest X-ray, and culture of secretions from the oropharynx and nose. All children were consulted by an otorhinolaryngologist.

The patients were divided into age groups: children under one-year-old included patients from 1 to 11 months and 29 days; 1 year, up to 1 year 11 months 29 days; 2 years, up to 2 years 11 months 29 days; 3 years, up to 3 years 11 months 29 days; 4 years, up to 4 years 11 months 29 days; 5 years, up to 5 years 11 months 29 days; 6 years, up to 6 years 11 months 29 days; 7 years, up to 7 years 11 months 29 days; 8 years, up to 8 years 11 months 29 days; 9 years, up to 9 years 11 months 29 days; and 10–14 years, up to 14 years 11 months and 29 days old.

Mathematical and statistical processing of the research data was performed using the Data Analysis and Chart Wizard modules of the Excel spreadsheet editor and the Basic Statistics/Tables modules of the Statistica for Windows software package for statistical data processing. The assessment of the significant difference in the sign manifestation frequency in different patient groups was performed using a nonparametric method for evaluating the hypotheses of the Pearson χ^2 goodness-of-fit test.

RESULTS AND DISCUSSION

From 2012 to 2019, 11,671 hospitalized patients with clinical manifestations of acute respiratory infection were examined for respiratory viruses at the Children's Research and Clinical Center for Infectious Diseases of the Federal Medical and Biological Agency. Nucleic acids of various respiratory viruses were isolated from 3253 people (27.9%). Among them, metapneumovirus infection was confirmed in 142 patients that constituted 4.4% of the total confirmed ARVI cases. A retrospective analysis of these medical records was conducted.

In the studied time interval, the maximum detection rate of hMPV was noted in 2012, when 39 (27.5%) cases of this infection in hospitalized children were confirmed, with a more than a 2-fold decrease in the subsequent 2013 and a minimum indicator in 2014 – 6.3% of cases. In subsequent years, metapneumovirus infection showed a gradual increase from 7.7% to 15.5% by 2019 (Fig. 1).

When analyzing the seasonal characteristics of metapneumovirus infection epidemiology, the increase in the incidence usually occurred at the end of autumn and continued in winter. In winter, children with ARVI of metapneumoviral etiology were hospitalized significantly more often compared with the autumn period – 55.6 ($n = 79$) versus 23.2% ($n = 33$) of cases, respectively ($p < 0.05$). Most hospitalizations during autumn were in November. In the spring, there was a gradual decrease in registered cases – only 32 (22.5%), with 20 (14.1%) in March, 11 (7.7%) in April, and one case (0.7%) in May. However, in 2014 and 2019, metapneumovirus infection in hospitalized children was diagnosed more often in the spring months. In the summer, hMPV infection cases were practically not recorded.

When analyzing the age structure of hospitalized children, children under four years of age are most susceptible to hMPV. One hundred four children belonged to the age group under four years old, amounting to 72.2% of patients, with the maximum morbidity in children aged three years (Fig. 2).

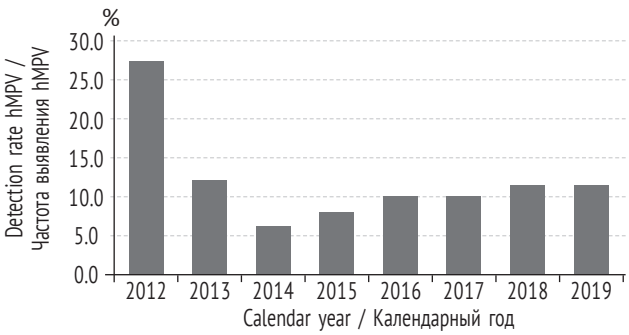

Fig. 1. Dynamics of detection by years of metapneumovirus (hMPV) infection in hospitalized children in the period 2012–2019

Рис. 1. Динамика выявления по годам метапневмовирусной (hMPV) инфекции у госпитализированных детей в период с 2012 по 2019 год

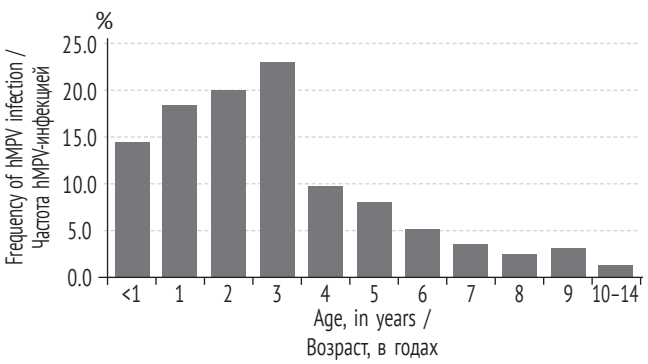

Fig. 2. Age structure of children admitted to hospital with metapneumovirus (hMPV) infection

Рис. 2. Возрастная структура детей, госпитализированных в стационар с метапневмовирусной (hMPV) инфекцией

Table 1 / Таблица 1

Features of the clinical picture of metapneumovirus infection in children

Особенности клинической картины метапневмовирусной инфекции у детей

Clinical manifestations / Клинические проявления	Patients / Пациенты (n = 142)	
	abs.	%
Rhinitis / Ринит	137	96.5
Cough / Кашель	132	93.0
Fever / Лихорадка	136	95.8
Lymphadenopathy / Лимфоаденопатия	71	49.3
Hepatomegaly / Гепатомегалия	38	26.8
Vomiting / Рвота	37	26.1
Diarrhea / Диарея	32	22.5
Lethargy, weakness / Вялость, слабость	30	21.1
Dyspnea / Одышка	26	18.3
Conjunctivitis / Конъюнктивит	16	11.3
Tonsillitis / Тонзиллит	13	9.2
Sore throat / Боль в горле	12	8.5
Exanthema / Экзантема	12	8.5
Cyanosis / Цианоз	8	5.6
Splenomegaly / Спленомегалия	7	4.9

In children over four years old, there was a gradual decrease in the metapneumovirus infection detection frequency. In the age group of children over 14 years old, no disease cases were recorded.

Patients with metapneumovirus infection were characterized by an acute onset of the disease. Among clinical manifestations, catarrhal symptoms, and increased body temperature were primarily identified, and intoxication and dyspeptic syndromes were also expressed. The main clinical manifestations of metapneumovirus infection in hospitalized children are presented in Table 1.

The dominant symptoms were cough in 93.0% (n = 132) of cases and rhinitis in 96.5% (n = 137) of cases. Sore throat was much less common – in 8.5% (n = 12) of children, tonsillitis: 9.2% (n = 13), conjunctivitis: 11.3% (n = 16). An increase in body temperature of varying severity was typical for most patients: 95.8% (n = 136). 88.2% (n = 120) of them had an increase in temperature >38°C including 34.6% (n = 47), the temperature reached 39.5°C and higher. In 21.1% (n = 30) of children, the disease was accompanied by intoxication syndrome manifestations in the form of weakness and lethargy. Dyspnea was observed in 18.3% (n = 26) of children, less often auxiliary muscles participation in the act of breathing and skin cyanosis were recorded-8.5% (n = 12) and 5.6% (n = 8), respectively. In 12 (8.5%) patients, exanthema appeared in the form of petechial eruptions on the skin of the face, chest, and back. An increase in lymph nodes was detected in half of the patients – 49.3% (n = 70), mainly in the submandibular or anterior cervical group. Approximately a quarter of patients had gastrointestinal dysfunction symptoms in the form of vomiting and diarrhea – 26.1% (n = 37) and 22.5% (n = 32), respectively.

When analyzing the nature of the respiratory system lesion, the lower respiratory tract was most often involved in the pathological process – in 78.2% (n = 111) of cases. Bronchitis was recorded in 85.6% (n = 95) of children, and pneumonia was radiographically confirmed in 14.4% (n = 16) of patients (Fig. 3).

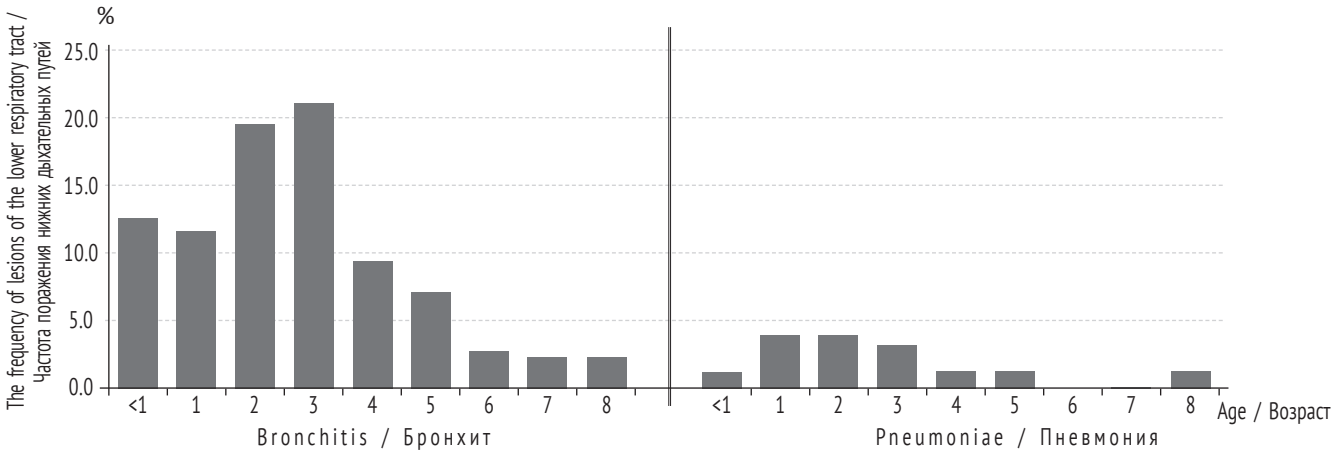

Fig. 3. The frequency of lesions of the lower respiratory tract with metapneumovirus infection, depending on age
Рис. 3. Частота поражения нижних дыхательных путей при метапневмовирусной инфекции в зависимости от возраста

Metapneumovirus infection was manifested only in the upper respiratory tract in 21.8% ($n = 31$) of hospitalized children in the form of isolated rhinopharyngitis or combination with laryngotracheitis in eight children. Laryngotracheitis was more common in children over seven years of age. Bronchitis was the dominant nosological form at the age of seven, with the maximum frequency of registration in children two (18.9%) and three years (20.7%). During the first two years of a child's life, bronchitis was detected with almost the same frequency from 11.7% to 12.6% of hMPV infection cases. In patients four and five years old, bronchitis was diagnosed less often – 9.0% and 6.3%, respectively. Pneumonia was most often confirmed between one and four years [87.5% ($n = 14$) of all reported cases].

In hMPV infection with lower respiratory tract involvement, 38.7% ($n = 43$) of patients developed broncho-obstructive syndrome (BOS). In the age group from one month to three years, biofeedback was recorded significantly more often than at an older age: 69.8% ($n = 30$) versus 30.2% ($n = 13$), respectively ($p = 0.007$). In children under one year of age, biofeedback was noted in 20.9% ($n = 9$) of hMPV infection cases, at the age of 1–2 and 2–3 years: 23.3 ($n = 10$) and 25.6% ($n = 11$), respectively. It was found that in children over three years old, the incidence of biofeedback decreases with increasing age of patients: in children 3–4 years old: in 18.6% ($n = 8$), at 5–6 years old: in 9.3% ($n = 4$) and 7–8 years old: in 2.3% ($n = 1$).

Complications in the form of acute respiratory failure (ARF) were observed in 31 patients, which is 22.3% of all children with lower respiratory tract involvement (Fig. 4). ARF of varying degrees was detected in patients under the age of nine years, and significantly more often in children during the first three years of life compared with children of older age groups – 71.0 ($n = 22$) versus 29.0% ($n = 9$), respectively ($p = 0.038$). ARF Degree 2 developed exclusively in children under three years of age, and the frequency of manifestations of respiratory failure decreased with increasing age of the observed patients. So, in children during the first year of life, three (9.7%) ARF cases were recorded: two of Degree 2 and one of Degree 1 at the age of 1 year, only nine (29%) cases; two of Degree 2 and seven of Degree 1 at the age of 2 years, 10 cases (32.3%); one of Degree 2 and nine of Degree 1 at the age of 3–4 years; and Degree 1 in seven (22.6%) people; 5–6 and 7–8 years old with one observation each.

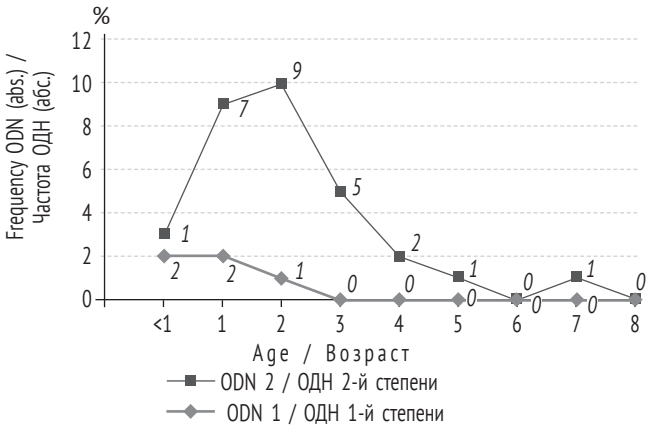

Fig. 4. Frequency and severity of acute respiratory failure in etapneumovirus infection ($n = 31$)

Рис. 4. Частота и степень выраженности острой дыхательной недостаточности (ОДН) при метапневмовирусной инфекции ($n = 31$)

In 93 (83.8%) cases, children with lower respiratory tract involvement underwent X-ray examination, based on which the features of infiltrative changes in the lung tissue were revealed in 16 patients. When analyzing the examined children's chest radiograph data, the right lung was more often affected: in 68.8% ($n = 11$) of cases, the left lung: in 25% ($n = 4$), and in one case (6.2%) the pathological process was bilateral. The most frequently infiltrative changes were found in the VIII and IX segments of the right lung – six (37.5%) cases each and another four (25%) cases – in the VIII segment of the left lung. The defeat of other segments was noted in single observations.

The patients' laboratory examinations on the first day of hospitalization revealed that 30.3% ($n = 43$) had clinical blood count values within the age norm, and 69.7% ($n = 99$) showed various inflammatory changes. The WBC >10.9 · 109/L was detected only in 18 (12.7%) children and <4.1 · 109/L in 5 (3.5%) patients. There was an increase in segmented neutrophils of more than 50% in 12.7% ($n = 18$) of patients in the WBC formula, a stab shift of more than 10% in 4, monocytosis of more than 12% in six (4.2%) patients. In 23.9% of cases ($n = 34$), an ESR acceleration of more than 15 mm/h was observed. The C-reactive protein (CRP) level was determined in 71 patients, whereas an increase in CRP level <20 mg/L was observed in the vast majority of children (93.0%, $n = 66$). Only five people (7.0%) had CRP values >45 mg/L, whereas all five patients had concomitant foci of bacterial infection (acute purulent otitis media, tonsillitis, or urinary tract infection).

CONCLUSION

Thus, metapneumovirus infection from 2012 to 2019 amounted to 4.4% in the structure of ARVI in children treated at the clinic of the Children's Research and Clinical Center for Infectious Diseases of the Federal Medical and Biological Agency. During the first four years of life, 72.2% of hMPV infection cases were observed in hospitalized patients. Along with the leading clinical manifestations in the form of catarrhal syndrome and febrile fever, a quarter of patients had a dyspeptic syndrome. The defeat of the lower respiratory tract was detected in 78.2% of patients with metapneumovirus infection: bronchitis in 85.6% of cases and 14.4% pneumonia, which was complicated by the development of BOS in 38.7% and ARF in 22.3% of cases. In hemograms with hMPV infection, minimal changes were revealed: leukopenia and leukocytosis in 3.5% and 12.7% of cases, respectively, increased ESR in 23.9% of children. The CRP level in the vast majority of children (93.0%) was less than 20 mg/L. The revealed clinical and laboratory features of metapneumovirus infection in children make it possible to expand our knowledge of lower respiratory tract viral diseases, optimizing etiotropic therapy and reducing the antibacterial load on patients.

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