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CLINICAL CHARACTERISTICS OF COVID-19 IN CHILDREN OF DIFFERENT AGE GROUPS

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The study is devoted to accessing the clinical and epidemiological features of the coronavirus infection in children of different ages who were hospitalized during the 2020–2021 outbreaks of the epidemic. A retrospective analysis of 530 case histories of children under the age of 18 with coronavirus infection was conducted. The study revealed the predominance of general infectious symptoms and manifestations of upper respiratory tract lesions in children of all ages. A more severe course of the disease was registered in older children and was associated with the lower respiratory tract involvement. Children aged 1 month had relatively lower risks of lower respiratory tract injury compared to other age groups. We also found relatively higher levels of leukocytes, platelets and procalcitonin in children of this age.

Key words: coronavirus infection, children, clinical picture, epidemic.

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КЛІНІЧНА ХАРАКТЕРИСТИКА COVID-19 У ДІТЕЙ РІЗНИХ ВІКОВИХ ГРУП

Дослідження присвячене вивченню клініко-епідеміологічних особливостей перебігу коронавірусної інфекції у дітей різного віку, які перебували на стаціонарному лікуванні в період спалахів епідемії 2020–2021 років. Проведений ретроспективний аналіз 530 історій хвороб дітей з коронавірусною інфекцію віком до 18 років. В ході дослідження виявлено переважання загальноінфекційних симптомів та проявів ураження верхніх дихальних шляхів у дітей всіх вікових груп. Більш тяжкий перебіг захворювання був притаманний дітям старшого віку та асоціювався з ураженням нижніх дихальних шляхів. Діти у віці 1 місяця мали відносно нижчі ризики ураження нижніх дихальних шляхів порівняно з іншими віковими категоріями. Також ми виявили відносно вищі показники лейкоцитів, тромбоцитів та прокальцитоніну у дітей цього віку.

Ключові слова: коронавірусна інфекція, діти, клінічна картина, епідемія.

The work is a fragment of the research project "Modern features of acute neuroinfections in children", state registration No. 0119U103914.

Coronavirus disease (COVID-19) continues to be a problem for the pediatric population. From autumn 2020 to 2021, the share of children in the structure of patients with coronavirus disease in Ukraine is significantly increasing. The frequency of children hospitalized with severe and complicated cases is also increasing. According to reports from different countries, the proportion of children with COVID-19 is relatively small and ranges from 0.8 to 5 % of all cases [2, 8, 11, 12]. However, severe forms and complications can also occur. According to the epidemiological study by Dong et al. 13 % (n=94) of patients were asymptomatic from 731 laboratory-confirmed cases of SARS-CoV-2, 43.1 % had mild disease with upper respiratory tract involvement, and 41 % (n=300) of children had symptoms of the lower respiratory tract damage [5].

Systematized data on the clinical characteristics of COVID-19 in the pediatric population are still quite limited, especially about children of early age, such as newborns and children in the first year of life. The results of the separate studies show that infants and adolescents have a relatively more severe course, and it is also believed that the presence of concomitant chronic pathology is a risk factor for a severe course [6, 13].

The purpose of the study was to determine the clinical features of COVID-19 in hospitalized children of different ages.

Materials and methods. The work was carried out in the Kyiv City Children's Clinical Infectious Disease Hospital, Kyiv, Ukraine. We analyzed 530 cases of COVID-19 in children who were hospitalized during the first two waves of the outbreak from June 2020 to May 2021.

The hospital's bioethics commission accepted conducting of the research. Obtaining informed consent was not intended, as it was a retrospective analysis of routine medical information.

We divided children according to age categories for age-related clinical and epidemiological features identifying: from the birth to the first month of age, from 1th to 12th months, from 1st year to 5th year, from 6th to 9th years and adolescents. The comorbid condition of patients was also considered, according to which it was divided into groups with comorbidities and without them.

The research is single-center, cohort and retrospective. We performed statistical processing of the results using the statistical package EZR v. 1.54 (graphical user interface for R statistical software version 4.0.3, R Foundation for Statistical Computing, Vienna, Austria) and used descriptive statistics methods.

Results of the study and their discussion. The main epidemiological characteristics of the patients of certain age groups are presented in Table 1.

Table 1

Epidemiological characteristics of the patients of different age groups

Parameters	Age group				
	0–1 months (n=45)	1–12 months (n=109)	1–5 years (n=187)	6–9 years (n=74)	10–18 years (n=115)
Boys n(%)	27 (60)	54 (49.5)	107 (57.2)	39 (52.7)	53 (46)
Girls n(%)	18 (40)	55 (50.5)	80 (42.8)	35 (47.3)	62 (54)
Contact with patients n(%):					
Family members	34 (75.5)	94 (86.2)	126 (67.4)	43 (58.1)	49 (42.6)
Children's team	0	0	3 (1.6)	4 (5.4)	14 (12.2)
Unknown	11 (24.5)	15 (13.8)	58 (31)	27 (36.5)	52 (45.2)
Hospitalization Day, M (IQR)	1 (1–2.75)	2 (1–4)	3 (1–4.25)	4 (2.25–6)	5 (2–8)
Bed–days, M (IQR)	4 (1–5.75)	5 (3–7)	5 (3–8)	7.5 (4.75–11)	8 (4–12)
Concomitant pathology n:					
Allergological		1	2	4	2
Endocrine		1	1	2	3
Hematological		3	2	1	1
Nephrological		2	1		
Neurological		1	2	3	3
Oncological			2		
Adiposity				3	5

According to the data of the epidemiological anamnesis, the likely source of infection for the majority of patients in this cohort was the family members. Postnatal infection was observed among the neonates in all cases; there were no cases of vertical transmission among the patients from this cohort. Most of the children were hospitalized during the first five days of illness (M (IQR) – 3 days (1–5)). An increase in the age category was associated with an increase in hospitalization days: it was the shortest in children during the first month of life and the longest in the group of teenagers. We observed the same trend during hospital stays.

Among the analyzed cohort of children, 45 (8.5 %) comorbidities were registered. Most often we observed the following pathology: 8 cases of adiposity, endocrine (Itsenko-Cushing syndrome, aplasia of the thyroid gland, rickets, type I diabetes mellitus); haematological (iron deficiency anemia and Minkowski-Shofar anemia); allergological (bronchial asthma, allergic and atopic dermatitis); nephrological (hypoplasia); neurological (cerebral palsy, congenital malformation of the brain, mental retardation, Down syndrome, epilepsy); oncological (cerebellum`s metastatic medulloblastoma), and there were observed two cases with meningococcemia.

The main clinical symptoms in patients of different age groups are presented in Table 2.

In the clinical picture, we most often observed general symptoms, including fever and general weakness, as well as symptoms of respiratory tract involvement, such as a runny nose. These symptoms were observed in all age categories with almost the same frequency. Cough was also a frequent symptom and was present in most patients of all ages except children in the first month of life, among whom cough was observed in 46.6 % of cases. The duration of fever ranged from 1-16 days (M (IQR) – 3 days (2-4)), and general weakness – within 1–14 days (M (IQR) – 5 days (3–6)). When comparing the duration of general symptoms between different age groups, we noted a relatively longer duration of general symptoms in patients of older age groups than in younger children. We observed a similar trend in the duration of respiratory symptoms such as cough and runny nose. Defecation disorders in the form of diarrhea were observed in 50 (9.4 %) patients. Cases of diarrhea were observed with approximately the same frequency in all age groups. In all cases, the diarrhea had a secretory nature. The median duration of diarrhea in the cohort was 2 days (1 to 6 days). In all cases of diarrhea, no alternative infectious cause of this syndrome was identified. Skin rash was observed in 31 (5.8 %) patients during the acute period of the disease. A relatively higher frequency of exanthema was in the age group of children from 6 to 9 years (10.8 %).

Among these cases, two patients were diagnosed with meningococcal disease, which occurred on the background of COVID-19 and was accompanied by a classic hemorrhagic rash. Another two children had an acute period of chicken pox (according to clinical and epidemiological data) with a typical pseudopolymorphic rash. In other cases, the exanthema was nonspecific in the form of maculopapular rash.

All patients underwent general clinical examinations, laboratory and instrumental methods, such as general blood tests, biochemical blood tests, coagulation tests, markers of inflammation and X-ray examination.

Table 2

Frequency and duration of the clinical symptoms in patients of different ages

Symptoms	0–1 months (n=45)	1–12 months (n=109)	1–5 years (n=187)	6–9 years (n=74)	10–18 years (n=115)
Fever, n (%)	33 (73.3)	102 (93.6)	177 (94.7)	71 (95.9)	113 (98.2)
Duration of fever (days), M (IQR)	2 (2–3)	3 (2–5)	3 (2–5)	5 (3–7)	5 (3–6)
Weakness, n (%)	37 (82.2)	100 (91.7)	170 (90.9)	71 (95.9)	107 (93)
Duration of weakness (days), M (IQR)	3 (2–5.5)	4 (3–5.8)	5 (3–6)	6 (4–8)	6 (4–9)
Cough, n (%)	21 (46.6)	89 (81.7)	141 (75.4)	53 (71.6)	83 (72.1)
Duration of cough (days), M (IQR)	5 (4–6)	6 (4–8)	7 (5–9)	6 (5–8)	7 (6–9)
Rhinitis, n (%)	31 (68.8)	82 (75.2)	132 (70.6)	41 (55.4)	47 (40.9)
Duration of rhinitis (days), M (IQR)	4 (2–5)	5 (3–6)	5 (3–6)	6 (4–7)	7 (4.75–9)
Sore throat, n (%)	ND	ND	37 (19.8)	29 (39.2)	57 (49.6)
Duration of sore throat (days), M (IQR)	ND	ND	5 (4–7)	6 (4.75–8)	7 (6–9)
Diarrhea, n (%)	2 (4.4)	13 (11.9)	17 (9)	7 (9.5)	11 (9.6)
Duration of diarrhea (days), M (IQR)	3 (3–3)	2 (1.75–2)	2 (1–3.5)	4.5 (4–5)	3 (1–3.5)
Headache, n (%)	ND	ND	7 (3.7)	14 (18.9)	36 (31.3)
Duration of headache (days), M (IQR)	ND	ND	2 (1.5–3)	2.5 (2–3.8)	2 (1–4)
Shortness of breath, n (%)	0	0	16 (8.6)	8 (10.8)	4 (3.5)
Duration of shortness of breath (days), M (IQR)	0	0	3 (3–4.3)	3 (3–6.5)	2.5 (2–3.5)
Myalgia/arthralgia, n (%)	ND	ND	2 (1.06)	4 (5.4)	25 (21.7)
Duration of myalgia/arthralgia (days), M (IQR)	ND	ND	8.5 (5.25–11.8)	5.5 (4.5–7.5)	4 (2.75–5)
Anosmia/ageusia, n (%)	ND	ND	1 (0.5)	0	41 (35.7)
Duration of anosmia/ageusia (days), M (IQR)	ND	ND	8 (8–8)	0	7 (5–9)
Rash, n (%)	2 (4.4)	5 (4.6)	14 (7.4)	8 (10.8)	2 (1.7)
Duration of rash, (days), M (IQR)	2 (2–2)	1.5 (1–2)	5.5 (2–8.8)	6.5 (4.5–8.3)	5.5 (5.25–5.8)

ND – the parameter was not determined.

The results of the general clinical blood analysis in most of patients at the initial examination were within the normal range. The median number of leukocytes was 8.1×10^9/l (from 2.2 to 31.3×10^9/l). Leukopenia ($<4\times10^9$/l) was observed in 19 (4.4 %) patients, leukocytosis ($> 10\times10^9$/l) - in 131 (30.5 %). The level of platelets in this cohort of patients ranged from 34 to 878×10^9/l (median - 249×10^9/l). Thrombocytopenia ($<150\times10^9$/l) was observed in 29 (6.8 %) patients, and elevated platelet count ($>420\times10^9$/l) was observed in 33 (7.7 %). In most of children (389 / 90.7 %) An erythrocyte sedimentation rate (ESR) was within normal limits. Just in 40 (9.3 %) patients it was higher than 10 mm/h. Among this cohort of patients, the C-reactive protein (CRP) study was performed in 245 cases. Simultaneously, in most of results (163/66.5 %) it prevailed 6 mg/l. Procalcitonin was investigated in 85 patients. It was found to vary from 0.011 to 0.4 ng/ml. An alanine transaminase (ALT) was determined in 383 children and ranged from 10 to 180 U/l. In 325 (84.9 %) the level of ALT was within the norm; the increased level was registered in 58 (15.1 %). The level of aspartate aminotransferase (AST) among the 379 studies ranged from 16 to 265 IU/l and was within the norm in 221 (58.3 %) children, an increased level was observed in 158 (41.7 %) children. We noticed higher transaminases rates in the youngest children under 1 year of age. International normalized

ratio (INR) was estimated in 146 patients. We determined fluctuations from 1 to 1.12 (median 1.05). 302 children were evaluated for fibrinogen levels. This figure was 1.6-7.88 g/l (median 3.4 g/l).

Radiological examination was performed in 407 (76.8 %) patients. According to the results, in 323 from 407 (79.4 %) cases changes from the lung parenchyma were registered, and in 84 (20.6 %) patients the picture without radiological changes was described. Among radiological changes, interstitial lesions were most often registered, which were described in 261 (80.8 %) out of 323 patients, peribronchial infiltration in 50 (15.5 %), and the share of lesions in 12 (3.7 %) patients. In 240 (74.3 %) cases the radiological changes were bilateral and in 83 (25.7 %) they were unilateral. The frequency of radiological changes detection during the initial examination was the lowest in the group of children of the first month of life, and the highest in the patients of the older age category (p=0.011).

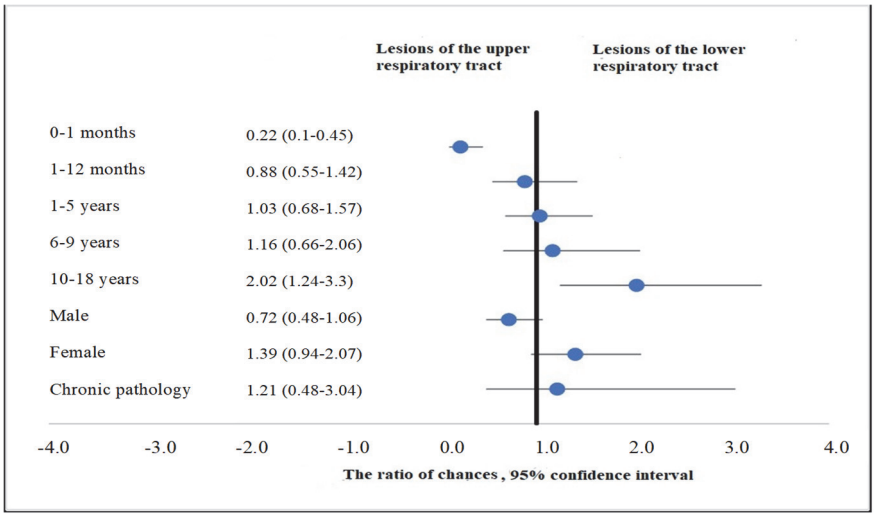

Fig. 1. Adjusted odds of the upper and lower airway injury in COVID-19 among hospitalized patients

Mild cases of COVID-19 are usually characterized by a predominant lesion of the upper respiratory tract, a more severe course of the disease, on the contrary, is associated with an infection of the lower respiratory tract [7]. We analyzed the relationship between demographic factors, the presence of chronic pathology the probability of the course of the disease with a predominant lesion of the upper or lower respiratory tract (fig. 1).

According to the indices of the adjusted odds ratio, children of the first month of life had a significantly higher probability of the course of the disease affecting only the upper respiratory tract ($p<0.05$). At the same time, the analysis showed, that patients of the older age group (10–18 years) had a significantly higher probability of the lower respiratory tract lesions than children of the younger age groups ($p<0.05$).

The course of the disease was moderate in most of children. In this cohort of patients 25 (4.7 %) children were treated in the intensive care unit (fig. 2). The main causes of the severity were 1–2-degree respiratory failure, septic shock and neurological disorders. The oxygen support was provided to 25 patients with signs of respiratory failure. Patients received oxygen through a face mask or nasal cannulas. Invasive lung ventilation was not performed among this cohort of patients.

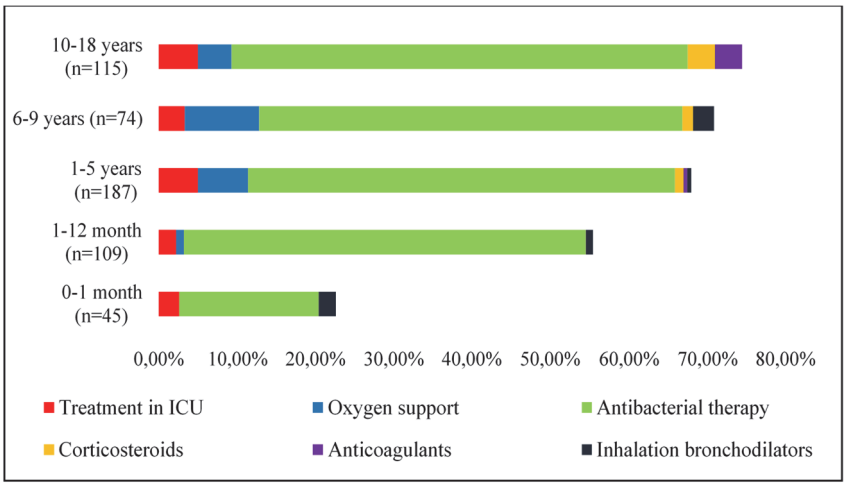

Fig. 2. The main characteristics of inpatient treatment in patients of different ages

Antiviral therapy for SARS-CoV-2 has not been used in these children. Antibacterial therapy was performed in 273 (51.5 %) patients. Antithrombotic drugs were prescribed in 5 cases. Corticosteroids (dexamethasone, methylprednisolone) were administered intravenously in 7 patients. Five patients in this cohort were given inhaled beta-agonists corticosteroids. All children were discharged from the hospital with clinical improvement. There were no fatalities. According to the duration of inpatient treatment, the shortest average terms were observed in children aged 0 to 1 month, and the longest – in patients aged 10 to 18 years.

This study was performed in a specialized infectious children's clinic, which from the first days of the pandemic became a main hospital for children with COVID-19 in Kyiv. This makes it possible to consider this study as sufficiently representative of the description of the characteristics of the disease among the children's population of the largest city in Ukraine. The diagnosis was made by PCR examination of a nasopharyngeal swab, or by determination of IgM and IgG antibodies to the SARS-CoV-2 by immunoenzymatic analysis, which correlates with the study of Avetikov D.S. et al. Also, the researchers pointed to the predominance of autumn-winter seasonality, which is likewise common to our study, as many of the confirmed cases of COVID-19 in our research were recorded during the cold season [1].

We divided patients by age categories and focused on the clinical characteristics of the disease in each age group. According to the results of our study, we found that although the clinical symptoms of the disease in patients of different ages are similar, but children in the first month of life had a relatively lower risk of lower respiratory tract damage. In this age group, we also observed a lower frequency of such symptom as cough, the absence of respiratory distress syndrome, less frequent radiological signs of lung damage, and the shortest length of hospital stay. These data are somewhat inconsistent with the results of individual studies. In particular, according to a multicenter European study, the category of children under 1 month of age was identified as a risk factor for hospitalization to intensive care units [6]. However, the published material did not provide information on the clinical causes of this hospitalization. This aspect is considered in more depth in a recent systematic review of 176 confirmed cases of SARS-CoV-2 infection in newborns [10]. There authors note that, although children of this age group do often become patients in intensive care units, this is mainly due to other factors not related to the severity of COVID-19. They note that, although indeed the incidence of neonatal hospitalization is relatively higher in neonates, than in older children, in none of the 176 cases there were no conditions that would require critical care assistance. Another study, examining the clinical features of COVID-19 in inpatients, also noted, that among the 19 hospitalized children in the first 60 days of life, there was no case of a severe course of the disease [7].

Regarding the source of infection and the route of transmission of the virus, data from studies of the virus transmission route to newborns from pregnant women and breast milk analysis, indicate the possibility of vertical transmission, although in our studies it was not established. In addition, violation of the placental barrier during the placental abruption or hemorrhage of the mother and fetus can potentially transmit the virus and/or IgM antibodies to the fetal circulation [3]. According to the aforementioned meta-analysis [10], among the 176 confirmed cases of SARS-CoV-2 infection, in 30 % of newborns was confirmed the vertical route of transmission.

In our study, we also found, that older children (from 10 to 18 years) have a relatively higher risk of lower respiratory tract injury during COVID-19 than younger children. Patients in this age group also have a longer duration of symptoms such as fever, general weakness, cough and runny nose, as well as the longest length of hospital stay. More often than in other age groups, teenagers needed the use of corticosteroids and antithrombotic agents. Among the published previous studies describing the course of COVID-19 in this age group, we found that there are some differences. According to a study in the United States, which showed 20,714 cases of COVID-19 in children, half of the severe forms were patients from 12 to 18 years. [9]. In a systematic review by Yasuhara J. was found that in children older than 10 years more often than in younger age categories, X-ray changes typical for COVID-19 are detected (55.6 %). The highest frequency of hospitalization in the intensive care units also was noticed in this age group [14]. Another study examined factors associated with an increased risk of fatal COVID-19 in Indonesia. According to the authors, the age over 10 years was also one of such factors [4]. However, in some studies, this age group of children is not associated with an increased risk of severe course. In particular, in a European multicenter study, there were not found a significant increase in the risk of hospitalization to intensive care units of teens with COVID-19, compared to younger patients [6, 9].

Conclusions

1. Consequently, based on the results of this research, we can determine that the most frequent symptoms in children of all age groups undergoing inpatient treatment for COVID-19 were fever, general weakness, upper respiratory tract symptoms, and cough. We noted a more severe course of the disease, which was associated with damage to the lower respiratory tract, in older children (10–18 years).

2. We observed high levels of leukocytes, platelets and procalcitonin in children under 1 month of life.

3. A higher frequency of neutrophilic shift and CRP was registered in children of 1–5 years old.

4. The frequency of general infectious and respiratory symptoms manifestation was almost the same in all age groups, slightly prevailing in the age group of 1–5 years, but their duration in older patients was longer than in younger ones.

5. Anosmia/ageusia was observed only in the older age group of 10–18 years (35.7 %)

6. Relatively higher frequency of exanthema occurred in the age group of children from 6 to 9 years (10.8 %)

7. Limitations of this study include the fact that it is retrospective, based on single-center data, and does not include information about late complications of COVID-19, such as multisystem inflammatory syndrome. Our study is an intermediate and currently serves to highlight certain trends in the clinical picture of COVID-19 in children of different ages. In the future, we plan to increase the volume of the inpatients sample and collect information on the long-term consequences of the disease.

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