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Prognostic factors of nervous system damage in children with COVID-19

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Abstract: *this work is devoted to the study of the features of the structure of symptoms related to the nervous system in children with coronavirus disease (COVID-19). During the COVID-19 pandemic, there is a rapid increase frequency of neurological lesions. The share of neurological manifestations in COVID-19 among adult patients is up to 82%, in children it ranges from 3% to 47%. The aim of the work was to study the frequency and structure of neurological symptoms in children who were hospitalized in an infectious disease hospital with a laboratory-confirmed diagnosis of COVID-19 during 2020-2022 and to determine prognostic factors of nervous system damage. Materials and methods: We retrospectively investigated 945 medical histories of children aged from birth to 18 years who were hospitalized at the Kyiv City Children's Infectious Disease Hospital ("KCCIDH") in Kyiv, Ukraine during the pandemic. Among them, we analyzed cases accompanied by neurological symptoms. Features of the clinical picture, laboratory and demographic-epidemiological data were determined. The statistical calculation of the obtained results was carried out by using the statistical package Statistical software EZR v. 1.54. Results: Neurological symptoms were detected in 142 (15%) children, the majority of them were adolescents (55.6%). The leading symptoms of nervous system involvement were headache, ageusia/anosmia, convulsive syndrome, acute polyneuropathy, and myalgia/arthralgia. According to the analysis of odds ratio developing of neurological symptoms among patients in our cohort, children of the older age group (10-18 years) had statistically greater chances developing of neurological manifestations. Odds ratio developing of the aforementioned symptoms depending on clinical syndromes were also analyzed. Among respiratory syndromes, the presence of cough (5.53; 95%CI 3.53-8.65) and signs of lower respiratory tract inflammation (1.8; 95%CI 1.21-2.67) were associated with a higher risk of nervous system symptoms damage. According to the study of laboratory indicators, an increased level of leukocytes (2.01; 95%CI 1.2-3.38) was associated with an increase frequency of neurological manifestations, and in groups of patients with an increased level of C-reactive protein (0.39; 95%CI 0.23-0.68) or procalcitonin (0.21; 95% CI 0.11-0.43), on the contrary, a lower frequency of neurological symptoms was observed. Conclusions: Neurological symptoms occur in 15% of children with COVID-19. According to the results of our work, the older age of the child, cough and symptoms of inflammation of the lower respiratory tract are the prognostic factors of the occurrence of neurological symptoms in children with COVID-19. In addition, our study demonstrated the prognostic value of the appearance of neurological symptoms with an increase in the leukocyte index, as well as the absence of a correlation of neurological symptoms with an increase in CRP and procalcitonin.*

Key words: [children](#), [neurological manifestations](#), [central nervous system](#), [COVID-19](#), [cerebro-spinal axis](#).

Introduction

COVID-19 continues to pose a challenge to the pediatric population. Since the fall of 2020 and over the course of three years, the share of children in the structure of patients with COVID-19 in Ukraine has been increasing significantly. According to the data from Ministry of Health of Ukraine, since the beginning of 2022 the number of children hospitalized with or suspected of having COVID-19 has increased almost fourfold. The frequency of hospitalization of children with serious and complicated cases also continues to rise (Cloete H., et al., 2022; Khandia R., et al., 2022). Although, in general, published data from various countries indicate that the share of children among patients with COVID-19 is relatively small and amounts to 5%, there are also risks of developing severe and complicated forms of the disease (Moreira A., et al., 2021).

A rapid increase quantity of reports about neurological complications in patients with COVID-19 has been observed increasingly during the pandemic. The spectrum of COVID-19 neurological manifestations among adult patients is, according to various data, up to 82% and is represented in the acute period by delusions and convulsions (34 %), fatigue (32%), myalgia (20%), impaired smell or taste and headache (13%). Patients are also diagnosed with stroke in 2% of cases, meningoencephalitis and Guillain-Barré syndrome in 10% of cases (Misra S., et al., 2021). Anosmia was observed in patients with a mild course with a frequency from 34% to 89% (Giacomelli A., et al., 2020; Lechien J.R., et al., 2020). According to the description of neurological manifestations published by the Ministry of Health of Ukraine, in the post-covid period was registered such clinical symptoms in patients, as fatigue (63%), myalgia (63%), sleep disturbances (26%), anxiety disorders and depression (23%), difficulty concentrating (24%), headaches (13%), dizziness (12%), confusion (11%), nervous excitement (45%) and cognitive impairment (15%). Numerous neurological and psychiatric disorders can be observed even during six months after COVID-19. According to published studies, where more than

230,000 patients were analyzed, the frequency of neurological and psychiatric diagnoses in patients after COVID-19 in the next six months amounted to more than 33%, and in almost 13% of cases the diagnosis was established for the first time. In patients who were treated in the intensive care unit, this frequency was 46.42%, and was represented by ischemic stroke, dementia, intracranial hemorrhages, parkinsonism, psychotic and anxiety disorders (Taquet M., et al., 2021).

This aspect remains understudied among children. From 3% to 47% of children with COVID-19 may have symptoms of nervous system damage according to available meta-analyses and literature data (Garazzino S., et al., 2020; Frank C.H., et al., 2020; Sandoval F., et al., 2021). The most common symptoms are headache (61%), encephalopathy (15.3%) and pyramidal signs (7.6%). Symptoms of peripheral nervous system damage include muscle weakness (61.5%), hypo/areflexia (23%), ageusia (15.3%) and anosmia (7.6%). The frequency of the peripheral nervous system damage in children is 7-15%, according to a study in Great Britain (Abdel-Mannan O., et al., 2020). Guillain-Barre syndrome in children is described with a frequency of 15 cases per 100,000 of population, and convulsions in 20-30%. Common symptoms of Guillain-Barre in children included weakness of the lower and upper extremities, paresthesia, and ataxia. (Panda P.K., et al., 2021; Kurd M., et al., 2021).

There is information about the association between severe neurological complications in children and multisystem inflammatory syndrome (MIS-C). In particular, according to American scientists, 31–47% of children diagnosed with MIS-C had neurological symptoms, including headache, encephalopathy, and altered mental status (Cheung E.W., et al., 2020; Dufort E.M., et al., 2020). According to the results of a multicenter study in the United States, 5% of children diagnosed with MIS-C had serious neurological complications such as seizures, coma, encephalitis, demyelinating disorders, and serous meningitis (Feldstein L.R., et al., 2020). Another study in the United Kingdom demonstrated the presence

of neurological symptoms in 4 of 27 patients with MIS-C, including dysarthria, dysphagia, encephalopathy, cerebellar ataxia, and peripheral neuropathy. Neuropathy was characterized by general weakness of proximal muscles and decreased reflexes (Abdel-Mannan O., et al., 2020).

Aim

To investigate the frequency and structure of neurological symptoms in children who were hospitalized in an infectious disease hospital with a laboratory-confirmed diagnosis of COVID-19 during 2020-2022 and to determine prognostic factors of the nervous system damage.

Materials and methods

There was a retrospective, single-center and cohort research. The exploration of 945 medical histories of children who were hospitalized to the Kyiv City Children's Clinical Infectious Diseases Hospital (KCCCIDH) (Kyiv, Ukraine) with COVID-19 in the period from June 2020 to February 2022 was conducted.

The study is part of the research work "Modern features of acute neuroinfectious in children" which is performed by Pediatric infectious diseases department of the Bogomolets National Medical University, state registration number №0119U103914.

Among 945 medical histories, 142 cases with neurological symptoms were analyzed. The main inclusion criteria for the study were children with PCR-confirmed COVID-19 who had symptoms of headache, ageusia/anosmia, myalgia/arthralgia, convulsions, polyneuropathy without any organic causes in the anamnesis. Among the exclusion criteria, it should be noted that the study did not include cases of refuted COVID-19, congen-

ital malformations of the central nervous system, oncological diseases of the nervous system, perinatal brain lesions, and any neurological diagnoses in the anamnesis. The conduct of this study was agreed with the hospital's bioethics committee. A retrospective evaluation of routine medical information did not involve obtaining patients informed agreement.

Due to the International Classification of Diseases (ICD) we determined the diagnostic code U07.1. In accordance with the current protocol, laboratory confirmation was carried out using a one-time PCR study of a nasopharyngeal swab. The PCR study was conducted in the hospital's local laboratory. In the presence of a positive PCR test for SARS-Cov-2, the case was confirmed.

We analyzed the medical records regarding the anamnesis of the disease, clinical-epidemiological and laboratory data of the patients.

If the children had symptoms of cough, nasal congestion, rhinorrhea or runny nose than an upper respiratory tract infection (URTI) was diagnosed. Indicators of lower respiratory tract infection (LRTI) included cough, dyspnea, auscultatory changes or parenchymal changes on chest X-ray examination.

With the aim to study the age-related clinical and epidemiological characteristics of all patients, we divided them into four age categories: less than 12 months, 1-5 years, 6-9 years and 9-18 years.

The statistical analysis results of the research provided by the statistical package Statistical software EZR v.1.54 and performed point, interval distribution estimates and used the D'Agostino-Pearson test.

Figure 1. Age structure of patients with COVID-19 and neurological manifestations

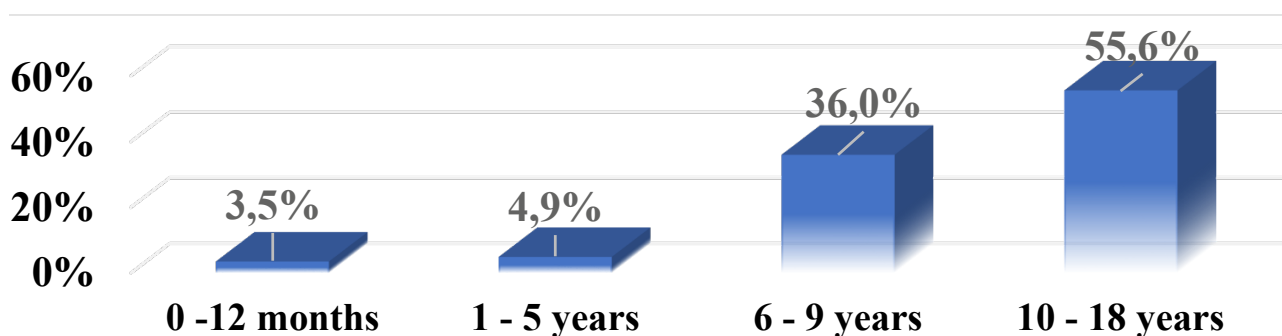


Table 1. Interval assessment of the frequency of neurological symptoms in children

Symptoms	The number of patients with this manifestation, n	Frequency of neurological manifestations, % (95% CI)
Headache	45	31,7 (24,3-39,6)
Ageusia/anosmia	34	23,9 (17,3-31,3)
Seizure syndrome	3	2,1 (0,4-5,1)
Polyneuropathy	12	8,5 (4,4-13,6)
Myalgia/arthritis	18	12,7 (7,7-18,7)

Results

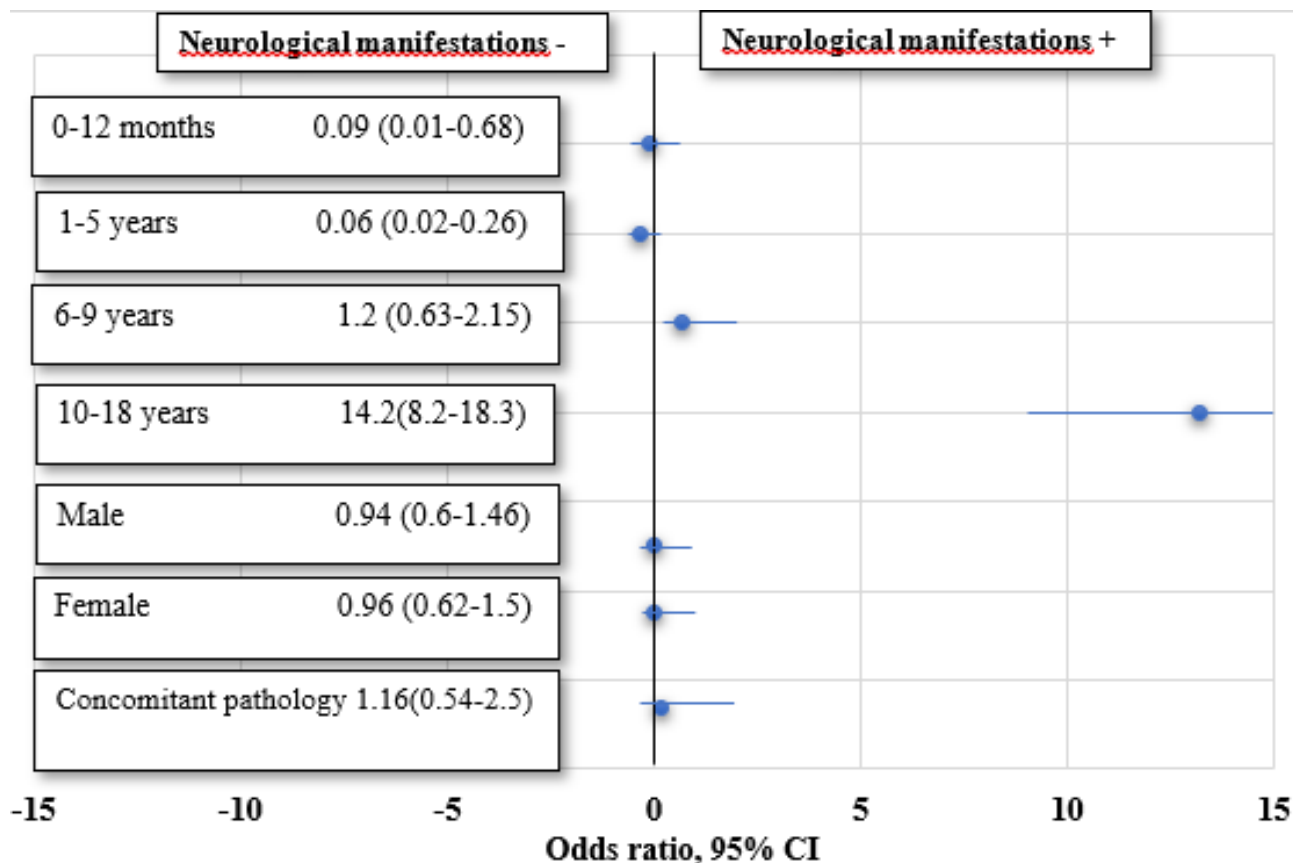
Among this cohort of children, neurological symptoms were noted in 142 (15%) patients. The age structure of the patients is shown in Figure 1.

According to the age distribution, adolescents from 10 to 18 years of age prevailed, 55.6%, (79/142), p=0.058. The next largest number was the group of children aged from 6 to 9 years, 36%, (51/142), p<0.001. Patients from birth to 12 months were 3.5%, (5/142) and children aged 1 to 5 years - 4.9%, (7/142), p<0.001. No significant difference was observed in the gender structure.

The leading neurological symptoms in children were headache, ageusia/anosmia, convulsive syndrome, acute polyneuropathy and myalgia/arthritis. Interval assessment of the frequency of the above-mentioned symptoms is presented in Table 1.

Headache was observed in 31.7%, (45/142) of cases and its duration was from 1 to 14 days (median - 2 days). Symptoms of ageusia and anosmia were observed in 23.9%, (34/142), of which 97% (33) of patients were children over 10 years old. The average age of patients with anosmia/ageusia

Figure 2. Adjusted odds ratio for neurological symptoms among hospitalized patients with COVID-19.



was 14.9 years. The duration of these symptoms was from 2 to 14 days (median - 7 days). Convulsive syndrome was observed in 2.1%, (3/142) of children, the duration varied from 1 to 4 days (median – 1 day). Acute polyneuropathy was observed in 8.5% (12/142) of patients, with an average duration from 5 to 10 days (median–7 days), myalgia/arthritis in 12.7%, (18/142) of children with an average duration from 1 to 15 days (median – 4 days). It should be noted that the symptoms of headache, anosmia and ageusia were not determined in children under the age of 1 year. In all these cases, there was a rapid recovery of neurological dysfunction with complete clinical recovery at the time of discharge.

We analyzed the relationship between neurological symptoms (presence of at least one neurological symptom) and other factors, in particular, demographic data (age, gender, comorbidities), respiratory symptoms (cough, LRTI), shortness of breath, the presence of anemia (hemoglobin level <110 mg/l), severity of inflammatory re-

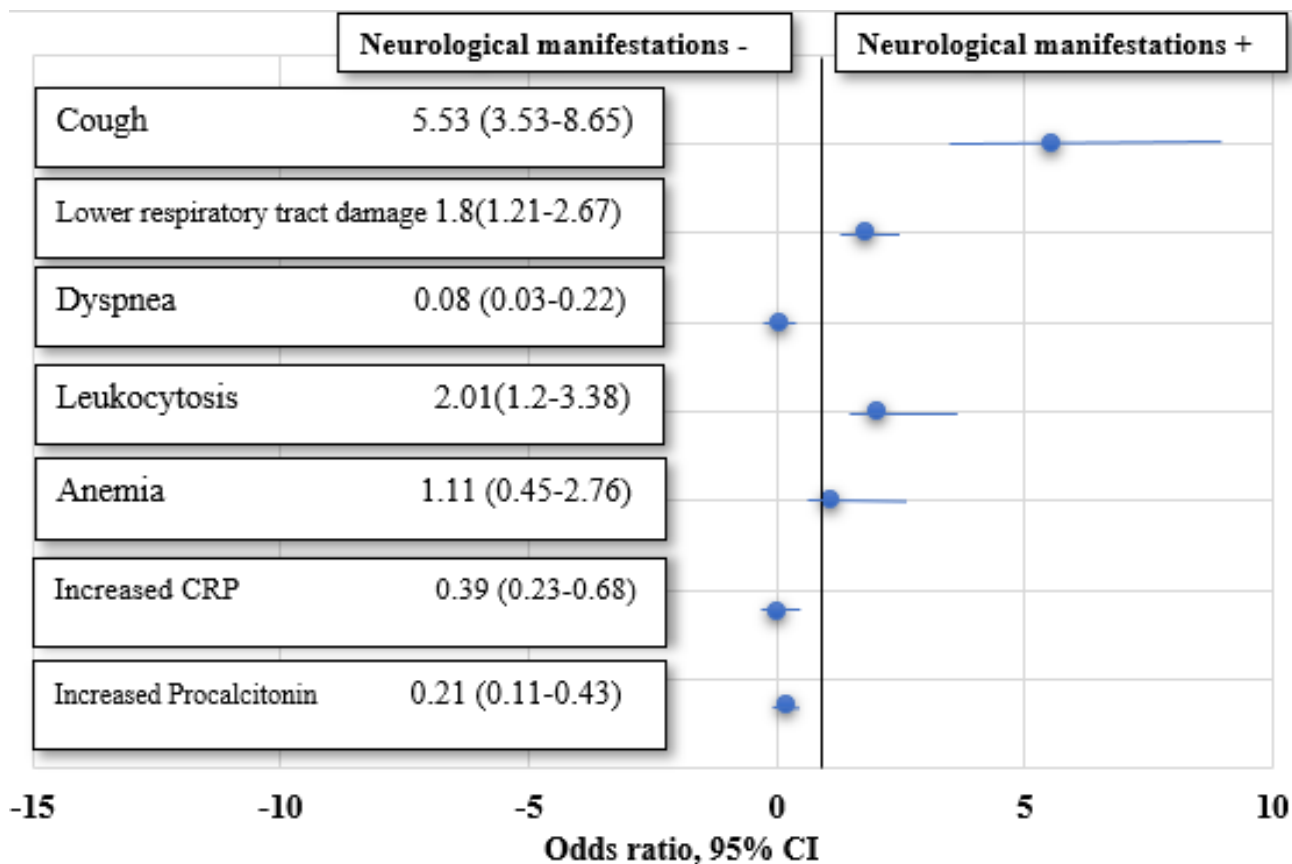
action (increased level of leukocytes (>9 G/l), increased C-reactive protein (CRP>6 mg/l) and increased level of procalcitonin (PCT>0.05 ng/ml)).

Figure 2 shows the adjusted odds ratio for the development of neurological symptoms in children with COVID-19.

According to the results of the data analysis among the patients of our cohort (Fig. 2), children of the older age group (10-18 years) had a statistically higher chance of developing neurological symptoms (14.2; 95%CI 8.2-18.3). At the same time, other age categories and gender did not have a significant relationship with the frequency of neurological symptoms.

We found concomitant pathology in 6% (9/142) of patients, which was presented in the form of allergic dermatitis, obesity, bronchial asthma, and Minkowski-Shofar anemia. There was no reliable connection with the frequency of neurological symptoms in children with existing concomitant pathology.

Figure 3. Adjusted odds ratio for neurological symptoms in COVID-19 depending on clinical syndromes and laboratory parameters



Odds ratio of the development of neurological symptoms depending on clinical syndromes and laboratory parameters were also analyzed, shown in Figure 3.

Cough (5.53; 95% CI 3.53-8.65) and signs of lower respiratory tract inflammation (1.8; 95% CI 1.21-2.67) were associated with a higher risk of neurological manifestations (Fig. 3). At the same time, shortness of breath (0.08; 95% CI 0.03-0.22) was accompanied by a lower frequency of neurological symptoms.

Indicators levels of leukocytes (2.01; 95% CI 1.2-3.38), C-reactive protein (0.39; 95% CI 0.23-0.68) and procalcitonin (0.21; 95% CI 0.11-0.43) had prognostic value for the appearance of neurological symptoms. But, if an increased level of leukocytes in the peripheral blood was associated with an increase frequency of neurological symptoms, then in groups of patients with an increased level of C-reactive protein or procalcitonin, on the contrary, a lower frequency of neurological symptoms was observed.

Discussion

This study was carried out in a specialized children's infectious hospital in Kyiv, which from the first days of the pandemic became a specialized hospital for patients with COVID-19. It's determining the representativeness of this research from the point of studying view of the disease characteristics among the children's population of the largest city in Ukraine.

Having analyzed the relationship of neurological manifestations with such factors, as age, sex, concomitant pathology, respiratory symptoms and laboratory indicators, we found statistically greater chances of developing neurological symptoms in adolescents, compared to other age groups of patients. In addition, the older age group of children (10-18 years) prevailed in the age distribution of the studied cohort, $p=0.058$. Numerous studies also indicate the predominance of adolescents in the structure of neurological complications of COVID-19 (Siracusa L., et al., 2021; Siddique R., et al., 2022). Most of older pediatric patients have neurological manifestations, mainly represented by symptoms of headache, anosmia, ageusia. Manifestations are mild and usually do not complicate the course of the disease. However, in some cases, severe complications associated with changes in neuroimaging and electroencephalography

may develop. Encephalopathy, encephalitis, central or peripheral acute flaccid paralysis, acute disseminated encephalomyelitis, convulsions, and stroke are found in children with laboratory-confirmed SARS-CoV-2 infection (Singer T.G., et al., 2021; Principi N., et al., 2021).

However, symptoms such as headache, ageusia, and anosmia are difficult to assess in young children, so the dependence of such manifestations on age has certain limitations here is a need to pay attention to other important signs. Overall, there is little published data on neurological symptoms in infants with COVID-19. Available case reports have limited generalizability, and many lack sufficient detail to establish a causal relationship between SARS-CoV-2 and neurological symptoms (Stafstrom C.E. et al., 2020). In published studies, the authors describe neurological symptoms in infants in the form of hypotension, drowsiness, upward deviation of the eyes, stiffness, lethargy, encephalopathy, stiff legs, convulsions, irritability, and hypertonia (Nathan N. et al., 2020; Chacon-Aguilar R. et al., 2020; Lorenz9999N. et al., 2020; Dugue R. et al., 2020; Vivanti A.J. et al., 2020).

According to the literature, severe neurological manifestations in children with COVID-19 are associated with a complicated course of the disease, accompanied by MIS-C and concomitant chronic pathology. The frequency of nervous system damage in case of MIS-C can reach 55% (Lin J.E., et al., 2021; Esposito S., Principi N., 2021). In a study by Chen TH., et al., 2020, 34% of children with MIS-C had meningitis, encephalitis, manifested by headache, positive meningeal signs and changes in mental status.

When we evaluated the odds ratio development of symptoms as a signs of nervous system damage depending on the existing respiratory manifestations, cough and signs of lower respiratory tract inflammation were correlated with a higher risk of the study complications.

There are no similar comparisons in the data of published sources, but numerous authors also emphasize the development of neurological symptoms against the background of acute respiratory symptoms (Whittaker A., et al., 2020; Berlitz P., et al., 2020; Harapan B.N., et al., 2021).

We singled out such a symptom as cough in the evaluation of the relationship with neurological

symptoms, because this respiratory sign can be associated with lesions of nervous system. Cough is a reflex that is modulated by the cerebral cortex and mediated by control centers in the respiratory regions of the brainstem. Researcher Al-Biltagi M et al., 2022, described a wide range of neurological disorders in which the sensitivity of the cough reflex may be increased. These include, in particular, brainstem lesions, secondary bone marrow lesions, ties, somatic cough, cerebellar neurodegenerative diseases, and neuropathies. Cough sensitivity may also decrease in multiple sclerosis, cerebral hypoxia, cerebral-hemispheric stroke with brainstem shock, peripheral neuropathy, and hereditary sensory and autonomic neuropathy type IV. In the case of our study, the cough is directly related to the underlying respiratory disease, but it is worth remembering the importance of assessing the cough reflex during the cranial nerves examination in order to timely identify lesions of the nervous system.

Among the laboratory data, we found a prognostic value for the appearance of neurological symptoms in the leukocyte index, CRP and procalcitonin. An increase level of leukocytes was correlated with an increase frequency of neurological symptoms. However, a lower frequency of detection of neurological manifestations was observed in patients with elevated levels of procalcitonin and CRP. The obtained data correlate with the results of published studies of a relatively easy and uncomplicated course of COVID-19 (Li Y., et al., 2020). Severe and complicated cases are accompanied by a high level of inflammatory markers (CRP, ESR, fibrinogen, D-dimer, procalcitonin) (Cheung E.W., et al., 2020; Dufort E.M., et al., 2020; Carter M.J., et al., 2020). The main reason for these changes, which is explained in the literature, is the hyperreactivity of the immune system, which leads to a violation of the hematoencephalic barrier due to the action of pro-inflammatory cytokines IL-1 β , IL-6, TNF α and IL-17. Cytokines activate glial cells and stimulate neuroinflammation, leading to increased neuronal excitability, seizures and main manifestations (Dantzer R., 2018; Helms J., et al., 2020).

Our research has certain limitations. In particular, the retrospective nature and limitation of the sample to one clinical center. In addition, there is a problem of terminology, since the concept of

neurological symptoms currently does not have a clear, generally recognized spectrum. The quality of statistical processing and the determination of statistical relationships could also be affected by the analysis of data from patients of different age groups, which covered the period of infancy, younger and older childhood. In particular, this concerned subjective symptoms, the assessment of which is difficult in younger children. Further research in this direction is needed to clarify the frequency and spectrum of neurological disorders in children with coronavirus disease. It is advisable to expand the collection of medical data also due to the post-infection period.

Conclusions

Neurological symptoms occur in 15% of children with COVID-19. According to the results of our work, the older age of the child, cough and symptoms of inflammation of the lower respiratory tract are the prognostic factors of the occurrence of neurological symptoms in children with COVID-19. In addition, our study demonstrated the prognostic value of the appearance of neurological symptoms with an increase in the leukocyte index, as well as the absence of a correlation of neurological symptoms with an increase in CRP and procalcitonin. Further observations and conducted studies will include a larger patient cohort, the acute onset of neurologic symptoms, rates of progression, and long-term outcomes of neurological disorders in children with COVID-19.

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Conflict of interests

The authors declare no conflict of interests.

Consent to publication

Consent was obtained from participants included in the study.

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A – Research concept and design, B – Collection and/or assembly of data, C – Data analysis and interpretation, D – Writing the article, E – Critical revision of the article, F – Final approval of article

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Прогностичні фактори ураження нервової системи у дітей з COVID-19

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Анотація: ця робота присвячена вивченню особливостей структури симптомів пов'язаних з нервовою системою у дітей з коронавірусною хворобою (COVID-19). За час пандемії COVID-19 спостерігалось стрімке збільшення частоти уражень неврологічного характеру. Частота неврологічних проявів при COVID-19 серед дорослих пацієнтів становить до 82%, у дітей коливається від 3% до 47%. Метою роботи було дослідження частоти та структури неврологічних симптомів у дітей, які перебували на стаціонарному лікуванні в дитячій інфекційній лікарні з лабораторно підтвердженим діагнозом COVID-19 впродовж 2020-2022 років та визначення прогностичних факторів ураження нервової системи. Матеріали і методи: Було проведено ретроспективний аналіз 945 історій хвороб дітей віком від народження до 18 років, які

були госпіталізовані до Київської міської дитячої інфекційної лікарні (КНП «КМДКІЛ») міста Києва, Україна в період пандемії. Серед них було проаналізовано випадки, що супроводжувались неврологічними симптомами. Визначались особливості клінічної картини, лабораторні та демографічно-епідеміологічні дані. Статистичний аналіз отриманих результатів проводився із використанням статистичного пакету Statistical software EZR v. 1,54. Результати: Неврологічні симптоми були виявлені у 142 (15%) дітей, з них переважну кількість становили підлітки (55,6%). Провідними симптомами ураження нервової системи були головний біль, агевзія/аносмія, судомний синдром, гостра полінейропатія та міалгія/артралгія. За результатами аналізу даних відношення шансів розвитку неврологічних симптомів серед пацієнтів нашої когорти, статистично більші шанси розвитку неврологічних проявів мали діти старшої вікової групи (10-18 років). Також були проаналізовані коефіцієнти відношення шансів розвитку вищезгаданих симптомів залежно від клінічних синдромів. Серед респіраторних синдромів наявність кашлю (5.53; 95%ВІ 3.53-8.65) та ознаки ураження нижніх дихальних шляхів (1.8; 95%ВІ 1.21-2,67) асоціювались із вищим ризиком появи симптомів ураження нервової системи. За даними дослідження лабораторних показників, збільшений рівень лейкоцитів (2.01; 95%ВІ 1.2-3.38) асоціювався із зростанням частоти неврологічних проявів, а в групах пацієнтів із підвищеним показником С-реактивного білку (0.39; 95%ВІ 0.23-0.68) або прокальцитоніну (0,21; 95%ВІ 0,11-0,43), навпаки, спостерігалась менша частота виявлення неврологічної симптоматики. Висновки: Неврологічні симптоми виникають у 15% дітей з COVID-19. За результатами нашої роботи прогностичними факторами виникнення неврологічної симптоматики у дітей із COVID-19 є старший вік дитини, кашель та симптоми ураження нижніх дихальних шляхів. Крім того, наше дослідження продемонструвало прогностичну цінність появи неврологічної симптоматики з підвищенням лейкоцитів, а також відсутність кореляції неврологічних проявів з підвищенням СРБ і прокальцитоніну.

Ключові слова: діти, неврологічні прояви, центральна нервова система, COVID-19.



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