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PECULIARITIES OF THE COURSE OF COVID-19 IN SCHOOL-AGE CHILDREN AS A FUNCTION OF HUMORAL IMMUNITY AGAINST PERTUSSIS

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Summary

Coronavirus disease remains one of the most serious diseases in the world. The percentage of severe and fatal cases in children is lower than in adults. The search for biomarkers of disease severity continues. There is evidence of heterologous immunity between the causative agent of coronavirus infection and some other infectious agents. Both Bordetella pertussis and SARS-CoV-2 cause damage to the respiratory system. It should be noted that the incubation period and transmission mechanism are similar for these two microorganisms. Pertussis vaccinations are given in childhood.

***The purpose of the study** is to find the charcteristics of the course of COVID-19 in school-aged children depending on the state of humoral immunity against pertussis toxin, assessing their level of immunoglobulin G against pertussis.*

***Material and methods.** 92 pediatric patients aged 6 to 17 years were studied, including 30 children without signs of the disease in the control group and 62 children with manifestations of laboratory-confirmed COVID-19. The clinical features of the disease and laboratory indicators (C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), white blood cells, D-dimer) were evaluated, as well as the levels of free salivary cortisol and vitamin D. According to the severity of the disease, 3 groups were formed: the first – 20 children with a mild course of COVID-19, the second – 33 patients with a moderate course of the disease, the third – 9 with a severe course of the disease.*

All children were tested for immunoglobulin G (Ig G) to pertussis toxin by enzyme-linked immunosorbent assay (VIROTECH B. pertussis PT Ig G ELISA, Rüsselsheim, Germany). The result was considered negative (no increase in the titer of specific class G antibodies to pertussis toxin), borderline, and positive (there is an increase in the titer of immunoglobulin G to pertussis toxin).

Statistical analysis was performed using the program «Stat Plus» (Shapiro-Wilk test, mean ± SD (standard deviation) with correct distribution of characteristics; median, upper and lower quartiles with incorrect distribution, Chi-square test, Man-Whitney test, Fisher's test).

The study was conducted in accordance with the rules of patient safety and ethical principles of scientific medical research involving human subjects (2000). The permission to conduct this study was given by the Bioethics Commission (Protocol No. 61 of 13.11.2020). The parents (legal representatives) of the patients gave their written consent to the conduct of this study.

This study is a fragment of research work «An Integrated Approach to Symptom Control, Long-Term Prognosis in the Context of Comorbid Pathology in the Clinic of Internal Diseases and Family Doctor Practice» (state registration No. 0118U000361).

***Results.** The mean age of the patients was 11.57±3.82 years. The study groups did not differ in sex (x2=4.97, p=0.174) and age (p=0.490) composition.*

The level of humoral immunity against pertussis toxin differed significantly between the study groups. A positive and borderline result for the presence of specific immunoglobulin G to tetanus toxin was found in 75.86 % of children without signs of disease. At the same time, only 41.51 % of children with COVID-19 manifestations had a positive and borderline result (p=0.005). A positive and borderline result for the presence of specific immunoglobulin G to tetanus toxin was seen in 66.67 % of children with mild infection, 33.33 % of patients with moderate disease, and only 12.50 % of patients with severe disease (X^2=16.91, P=<0.001).

Children with a negative result for immunoglobulin G to pertussis toxin have significantly higher WBC count (1.3-fold), ESR (2.4-fold), D-dimer (3.4-fold), and CRP (1.5-fold) compared to patients with positive and borderline levels of these antibodies. In children with a negative result, there was a 6.25-fold increase in salivary free cortisol (p<0.001) and a 2.0-fold decrease in vitamin D levels (p<0.001).

***Conclusions.** In children with COVID-19 manifestations, there was a significantly higher percentage of negative test results for the presence of IgG to pertussis toxin compared to the control group, indicating a lower level of humoral immunity to tetanus in this group of patients. In children with mild disease, there was a significantly higher percentage of positive and borderline test results for the presence of IgG to pertussis toxin (indicating a higher level of humoral immunity against this pathogen) compared to the groups of children with moderate and severe disease. The absence of specific immunoglobulins G to pertussis toxin is associated with an increase in the level of pro-inflammatory markers (leukocyte count, ESR, CRP) and D-dimer, which also indicates a more severe course of COVID-19. Patients who are negative for pertussis toxin antibodies have elevated cortisol levels as a marker of stress and decreased vitamin D levels. Both biologically active substances are involved in the immune response to infectious agents and may serve as additional non-specific markers of COVID-19 severity. Therefore, low humoral immunity to pertussis contributes to the increase in COVID-19 severity in childhood.*

***Key words:** Children; COVID-19; Pertussis; Humoral Immunity.*

Introduction

Coronavirus disease remains one of the most serious diseases of mankind with a high percentage of complications and mortality. The pediatric population has a lower percentage of complications and mortality compared to adults [1, 2]. Some microorganisms are cross-immune to coronaviruses. Such data exist for Bordetella pertussis, the causative agent of pertussis, which was a formidable disease in childhood before the advent of specific vaccine prophylaxis. Pertussis, like coronaviruses, is a respiratory disease. Common epidemiologic features are the length of the incubation period, the mode of transmission and

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the possibility of asymptomatic carriage. In the world literature there is information about a milder course of influenza, respiratory syncytial infection associated with the formed post-vaccination immunity against pertussis [3, 4]. Since pertussis vaccinations are mainly administered in childhood, studying the course of COVID-19 in relation to the state of humoral immunity against pertussis may be of great importance for predicting the severity of disease caused by COVID-19 and the risk of its recurrence.

The purpose of the study was to find the features of the course of COVID-19 in children depending on the state of post-vaccination immunity against pertussis toxin, assessing their level of humoral immunity against pertussis.

Material and methods

A total of 92 children aged 6 to 17 years were examined, including 30 children without signs of the disease (the control group) and 62 children with manifestations of laboratory-confirmed COVID-19. Clinical features of the disease, laboratory indicators (C-reactive protein, ESR, D-dimer, leukocytes), and levels of free salivary cortisol and serum vitamin D were assessed. Criteria for mild COVID-19 course were subfebrile fever, diarrheal syndrome without signs of dehydration, catarrhal syndrome without lower respiratory tract involvement, and changes in taste or smell. Moderate course criteria were hyperthermia above subfebrile, signs of dehydration, and signs of pneumonia without disturbing saturation. Patients with severe disease were treated in the intensive care unit, had signs of severe respiratory failure, and required supplemental oxygen; no patients died.

Qualitative determination of immunoglobulin G levels against pertussis toxin was performed by enzyme immunoassay (VIROTECH B. pertussis PT Ig G ELISA, Rüsselsheim, Germany). According to this semi-quantitative method, the result is evaluated as negative (no increase in the titer of specific class G antibodies against pertussis toxin), borderline (there is an increase in the titer of immunoglobulin G against pertussis toxin), positive (very high titer of G antibodies against pertussis toxin). This technique is based on the determination of the antibody index [5, 6].

Statistical analysis was performed using Stat Plus [7,8] (Shapiro-Wilk tests, mean ± SD in case of correct distribution of measurements, median, upper and lower quartiles in case of incorrect distribution, Chi-square test, Mann-Whitney test, Fisher test).

The study was conducted in accordance with the rules of patient safety and ethical principles of scientific medical research involving human subjects (2000). The permission to conduct this study was given by the Bioethics Commission (Protocol No. 61 of 13.11.2020). The parents (legal representatives) of the patients gave their written consent to the conduct of this study.

This study is a fragment of research work «An Integrated Approach to Symptom Control, Long-Term Prognosis in the Context of Comorbid Pathology in the Clinic of Internal Diseases and Family Doctor Practice» (state registration No. 0118U000361).

Results and discussion

The mean age of the patients was 11.57±3.82 years. The mean age of patients in the control group was 11.57 ± 3.27 [95 % CI 10.18; 12.95] years, the first group (children with mild disease) – 12.00 ± 3.92 [95 % CI 10.31; 13.69] years, the second group (moderate disease) – 11.55 ± 4.05 [95 % CI 10.19; 12.91] years, the third group (patients with severe disease) – 9.67 ± 4.39 [95 % CI 7.14; 12.19] years (p=0.490). There was no significant difference in gender composition (x^2=4.97, p=0.174) between the study groups.

The status of humoral immunity against pertussis toxin in patients in the control group and in children with manifestations of SARS-CoV-2 infection is shown in Table 1.

Table 1

Presence of immunoglobulins G against pertussis toxin in children of the control group and in patients with manifestations of SARS-CoV-2 infection

Presence of immunoglobulin G to pertussis toxin	Control group, n=30	Children with manifestations of SARS-CoV-2 infection, n=62	P=0.005*
Negative result	24.14 %	58.49 %	
Borderline and positive result	75.86 %	41.51 %	* – A statistically significant difference

In the control group, positive and borderline results for antibodies to pertussis toxin are 1.8 times more frequent than in the group of children with manifestations of COVID-19.

The state of humoral immunity against pertussis toxin in patients with different courses of COVID-19 is shown in Table 2.

Table 2

Presence of immunoglobulins G against pertussis toxin in children with manifestations of COVID-19

Presence of immunoglobulin G to tetanus toxin	The first group (mild course of COVID-19), n=20	The second group (moderate course COVID-19), n=33	The third group (severe COVID-19), n=9	X^2=16.91 P=<0.001*
Negative result	33.33 %	66.67 %	87.50 %	
Borderline and positive result	66.67 %	33.33 %	12.50 %	* – Statistically significant difference

As the severity of the disease increases, the number of children with borderline and positive results of specific immunoglobulin G against pertussis toxin decreases.

The number of leukocytes, ESR, D-dimer and CRP depending on the presence (absence) of specific immunoglobulins G against pertussis toxin are shown in Table 3.

Table 3

WBC (white blood cell) count, ESR and D-dimer, and CRP depending on the results of specific immunoglobulins G against pertussis toxin

Immunoglobulins G to pertussis toxin	White blood cell count, 10^9/l	ESR, mm/hour	D-dimer, ng/ml	CRP, mg/l
Negative result	7.80 [4.65; 12.67]	12.00 [4.00; 17.00]	259.00 [103.70; 444.55]	5.20 [3.00; 13.97]
Borderline and positive result	5.80 [4.60; 7.40]	5.00 [3.00; 7.50]	76.00 [45.30;98.00]	3.40 [2.60; 4.30]
	P=0.008*	P<0.001*	P<0.001*	P=0.004*

*Note: * – Statistically significant difference*

In children with a negative result of specific immunoglobulin G against pertussis toxin, the values of leukocyte count (1.3 times), ESR (2.4 times), D-dimer (3.4 times) and CRP (1.5 times) are significantly higher than in borderline and positive patients, which indicates a more severe course of the disease.

Increased cortisol levels [9-16] and decreased vitamin D levels [17-18] have been found in children with more severe disease.

The mean levels of salivary free cortisol and serum vitamin D in children with different results of specific class G antibodies to pertussis toxin are shown in Table 4.

Table 4

Mean levels of free salivary cortisol and vitamin D in children with the different result of specific class G antibodies to pertussis toxin

	Negative result	Borderline and positive result	
Free salivary cortisol, mcg/dl	1.00 [0.70; 1.05]	0.16 [0.11; 0.35]	P<0.001*
25-OHvitamin D, ng/ml	13.59 [11.00; 17.42]	27.49 [22.05; 31.59]	P<0.001*

*Note: * – Statistically significant difference*

In children with negative results for specific G-antibodies to pertussis toxin, there was a 6.25-fold increase in salivary free cortisol and a 2.0-fold decrease in vitamin D levels.

The number of severe and fatal cases in children with COVID-19 is significantly lower than in adults [19]. There is also evidence that some vaccines received by children may provide cross-protection against the causative agent of coronavirus disease [8, 20]. In the world, there is a term «heterologous non-specific effects of vaccines» (in other words, «off-target effects») – this is their effect on the body's immune response, which is different from their direct purpose. In 2015, the conference «Off-target effects of vaccination» was held in Annecy, France. There is growing evidence that vaccines can affect diseases other than those for which they were designed [21]. Such data are available for BCG, measles, mumps, rubella, diphtheria and tetanus vaccines [22]. Children are better protected against COVID-19 in countries with higher indicators of vaccination against so-called childhood infections [23]. The world scientific community has not yet been able to fully explain this phenomenon. Some peptides of the acellular pertussis vaccine are similar to SARS-CoV-2 peptides, i.e. it is possible to develop a cross-immune response against these two infections simultaneously [24, 25]. Another study [26] demonstrated a milder course of SARS-CoV-2 infection in mice vaccinated with pertussis vaccine. There are also data on the activity of this vaccine against adenovirus and herpes viruses in mice [22-24]. These preliminary findings provide much hope for future research to eliminate large-scale outbreaks of COVID-19 and predict the course of this disease.

The study of the possible protective role of antitoxic immunity against pertussis can be done in several steps: The first step is the study of epidemiological data (collection of information on previous vaccinations against pertussis, comparison of the incidence of COVID-19 in countries with different levels of non-specific vaccination); the second step is the determination of the level of specific immunoglobulins G against pertussis in patients with different courses of coronavirus disease, which was the case in our study; The next steps are molecular and cellular studies [27, 28], testing of cross-reactivity between antibodies and T cells induced by SARS-CoV-2 and pertussis, in vivo experiments in animals that first develop immunity against pertussis by specific vaccination, followed by infection with SARS-CoV-2 and study of its course, clinical trials (independent clinical trials are currently underway to assess the course of COVID-19 in vaccinated and unvaccinated health care workers against pertussis [29].

Low vitamin D levels and elevated cortisol levels are also seen in more severe COVID-19 [30, 31] and may

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serve as additional non-specific prognostic biomarkers of disease severity.

Conclusions

1. The number of children with specific antibodies to pertussis toxin was 1.8 times higher in the control group than in the group of children infected with COVID-19.

2. In children with different courses of coronavirus disease, an increase in its severity is associated with an increase in the percentage of negative results for pertussis toxin in children. Children with negative results for specific pertussis immunoglobulin G have a more severe course of COVID-19.

3. The negative results for specific pertussis immunoglobulins G are also associated with elevated levels of pro-inflammatory markers (leukocyte count, ESR, CRP) and D-dimer, which also indicates a more severe course [7] of disease caused by COVID-19.

4. Pediatric patients with negative results for pertussis antibodies have elevated levels of cortisol as a marker of stress and decreased levels of vitamin D. Both biologically active substances are involved in the immune response to infectious agents and may act as additional non-specific markers of COVID-19 severity.

Conflict of Interests. The authors have no conflicts of interest to declare.

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ОСОБЛИВОСТІ ПЕРЕБІГУ COVID-19 У ДІТЕЙ ШКІЛЬНОГО ВІКУ ЗАЛЕЖНО ВІД ГУМОРАЛЬНОГО ІМУНІТЕТУ ПРОТИ КАШЛЮКУ

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Резюме.

Коронавірусна хвороба залишається однією з найважчих у світі. Відсоток важких і летальних випадків серед дітей нижчий, ніж у дорослих. Триває пошук біомаркерів, які вказують на тяжкість перебігу захворювання. Є дані про наявність гетерологічного імунітету між збудником коронавірусної інфекції та деякими іншими інфекційними агентами. І Bordetella pertussis, і SARS-CoV-2 призводять до ураження дихальної системи. Слід зазначити, що інкубаційний період і механізм передачі подібні для цих двох мікроорганізмів. У дитячому віці проводять щеплення проти кашлюку.

Мета дослідження: з'ясувати особливості перебігу COVID-19 у дітей залежно від стану поствакцинального імунітету проти кашлюкового токсину, оцінюючи у них рівень гуморального імунітету проти кашлюка.

Матеріал та методи дослідження. Обстежено 92 дитини віком від 6 до 17 років, з них 30 дітей без ознак захворювання становили контрольну групу, 62 дитини були з проявами лабораторно підтвердженого COVID-19. Оцінювався клінічний перебіг захворювання та деякі лабораторні показники (С-реактивний білок (СРБ), швидкість осідання еритроцитів (ШОЕ), кількість лейкоцитів, Д-димер), а також рівень вільного кортизолу слини та вітаміну Д. За важкістю перебігу захворювання сформовано 3 групи: перша – 20 дітей з легким перебігом COVID-19, друга група – 33 пацієнтів з середньо-тяжким перебігом захворювання, третя – 9 із важким перебігом.

Усім дітям проведено визначення рівня імуноглобуліну G (Ig G) проти кашлюкового токсину методом імуноферментного аналізу (VIROTECH B. pertussis PT Ig G ELISA, Russelsheim, Germany). Результат оцінювався як negative (відсутнє підвищення титру специфічних антитіл класу G до кашлюкового токсину), borderline (наявне підвищення титру імуноглобулінів G до кашлюкового токсину), positive (дуже високий титр антитіл G до кашлюкового токсину).

Статистичний аналіз здійснювався за допомогою програми «Stat Plus» (критерій Шапіро-Вілка, Mean ± SD при правильному розподілі ознак; медіана, верхній та нижній квартилі при неправильному розподілі, критерій x^2, критерій Мана-Уітні, точний критерій Фішера).

Під час проведення роботи дотримані правила безпеки пацієнтів та етичних принципів проведення наукових медичних досліджень за участю людини (2000 р.). Комісія з біоетики надала дозвіл на проведення цього дослідження (протокол No 61 від 13.11.2020). Батьки (законні представники) пацієнтів надали письмову згоду на проведення даного дослідження.

Дане дослідження є фрагментом науково- дослідної роботи «Комплексний підхід до контролю симптомів, віддаленого прогнозу в умовах коморбідної патології в клініці внутрішніх хвороб та практиці сімейного лікаря» (державна реєстрація № 0118U000361).

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Результати дослідження. Середній вік пацієнтів становив 11,57±3,82 роки. Середній вік пацієнтів контрольної групи був 11,57±3,27 [95 % CI 10,18;12,95], першої групи (діти з легким перебігом захворювання) – 12,00±3,92 [95 % CI 10,31;13,69], другої групи (середньоважкий перебіг захворювання) – 11,55±4,05 [95 % CI 10,19;12,91], третьої групи (пацієнти з важким перебігом) – 9,67±4,39 [95 % CI 7,14;12,19] років (p=0,490). Не було достовірної відмінності між статевим (x^2=4,97, p=0,174) складом у групах даного дослідження.

Рівень гуморального імунітету проти токсину кашлюка достовірно відрізнявся у групах порівняння. У контрольній групі (діти без ознак захворювання) у 75,86 % випадків був borderline and positive результат на наявність специфічних імуноглобулінів G до правцевого токсину, тоді як у дітей з проявами COVID-19 лише у 41,51 % (p=0,005). При порівнянні трьох груп пацієнтів з COVID-19 у першій групі (діти з легким перебігом інфекції) positive and borderline результат на наявність специфічних імуноглобулінів G до правцевого токсину був у 66,67 %, у другій групі (діти із середньоважким перебігом захворювання) – у 33,33 % пацієнтів, у третій групі (важкий перебіг хвороби) – 12,5 % (X^2=16,91, p<0,001). У дітей з негативним результатом на наявність імуноглобулінів G проти токсину кашлюка достовірно відмічаються вищі показники кількості лейкоцитів (в 1,3 рази), ШОЕ (в 2,4 рази), Д-димеру (в 3,4 рази) та СРБ (в 1,5 рази) порівняно із пацієнтами positive and borderline рівнем цих антитіл. У дітей з відсутністю специфічних антитіл G до кашлюкового токсину достовірно в 6,25 разів відмічається збільшення показника вільного кортизолу слини (p<0,001) та у 2 рази зменшення рівня вітаміну Д (p<0,001).

Висновки. У групі дітей з проявами COVID-19 спостерігався достовірно більший відсоток негативного результату тесту на наявність IgG проти токсину кашлюка порівняно з контрольною групою, що вказує на нижчий рівень гуморального імунітету проти кашлюка у даної групи пацієнтів. У дітей з легким перебігом захворювання відмічався достовірно більший відсоток позитивного результату тесту на наявність IgG проти токсину кашлюка, що свідчить про вищий рівень гуморального імунітету проти даного збудника, порівняно з групами дітей із середньоважким та важким перебігом захворювання. На фоні відсутності специфічних імуноглобулінів G до кашлюкового токсину відмічається зростання рівня прозапальних маркерів (кількості лейкоцитів, ШОЕ, СРБ) та Д-димеру, що свідчить про більш важкий перебіг захворювання, викликаного COVID-19. У пацієнтів дитячого віку з негативним результатом на наявність антитіл спостерігається підвищений рівень кортизолу, як маркера стресу, та зменшення рівня вітаміну Д. Обидві біологічно активні речовини беруть участь в імунній відповіді на інфекційні агенти та можуть виступати додатковими неспецифічними маркерами важкості COVID-19. Тобто на фоні нижчого рівня гуморального імунітету проти кашлюка спостерігається зростання важкості захворювання, спричиненого COVID-19.

Ключові слова: діти; COVID-19; кашлюк; гуморальний імунітет.

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