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ASSESSMENT OF THE STATE OF POST-VACCINATION IMMUNITY TO MEASLES IN CHILDREN WITH POST-CAVID LONG SYNDROME AND OPTIMIZATION OF PREVENTIVE MEASURES TO REDUCE THE INCIDENCE OF MEASLES

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Abstract: Patients with juvenile idiopathic arthritis (JIA) may have low protective levels of antibodies to vaccine antigens due to the immunologic features of the disease, disrupted vaccination schedules, and use of immunosuppressive medications. The purpose of the study was to study the state of post-vaccination immunity and determine the factors associated with the preservation of the protective level of antibodies in patients with JIA.

Key words: children, juvenile idiopathic arthritis, vaccine prevention, antibody titer, measles, rubella, mumps, hepatitis B, diphtheria, risk factors.

Juvenile idiopathic arthritis (JIA) is one of the most common rheumatic diseases of childhood, with a prevalence of approximately 1 in 1000 children [1]. For the treatment of JIA, drugs that suppress the activity of the immune system are used: methotrexate, cyclosporine A, systemic glucocorticosteroids, genetically engineered biological drugs (GEBPs) [2]. For this reason, as well as due to dysfunction of the immune system associated with the pathogenesis of the disease itself, patients with JIA are highly susceptible to pathogens of infectious diseases [3–5].

Intercurrent infections can cause exacerbations of JIA and require discontinuation of ongoing immunosuppressive therapy, which negatively affects the achievement or maintenance of an inactive disease state [6]. Patients receiving immunosuppressive drugs are characterized by more severe infections, the need for prolonged antibacterial therapy, the use of “reserve” antibiotics and intravenous immunoglobulin [3–5]. For viral infections, such as mumps and measles, there is no specific therapy, and the presence of a background immunosuppressive state leads to an increased risk of complications and death in children with immunopathological diseases [7].

The most effective way to prevent the development of vaccine-preventable infections in patients with JIA is vaccination [8]. However, such patients may have an inadequate immune response to vaccination, including due to a low antibody titer compared to healthy peers or their rapid loss during therapy [9]. In approximately 40% of children with JIA, the onset of the disease occurs in the second year of life [2]. As a result, in such patients, primary vaccination is often not carried out, and not only parents, but also rheumatologists who observe the child refuse revaccination [2].

The purpose of the study was to study the state of post-vaccination immunity and determine the factors associated with the preservation of the protective level of antibodies in patients with JIA.

Eligibility criteria Inclusion criteria:

• patients with JIA aged 2–17 years, routinely vaccinated before the age of 2 years of life (before the development of JIA) against measles, rubella, mumps, hepatitis B and diphtheria. Non-inclusion criteria: •

routine vaccination within 6 months prior to inclusion in the study;

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• administration of intravenous immunoglobulin or blood plasma preparations during the 12 months preceding inclusion in the study;

• taking cytotoxic drugs (except methotrexate) in the past or at the time of inclusion in the study.

The diagnosis of JIA was made (N.A. Lyubimova, M.M. Kostik) according to the criteria of the International League of Associations for Rheumatology (ILAR) [10]. Information on past routine vaccinations against measles, rubella, mumps, hepatitis B and diphtheria was obtained from vaccination cards (Form 63) stored with each patient's medical records.

Information on vaccination in the last 6 months and the administration of intravenous immunoglobulin or blood plasma preparations in the last 12 months was obtained from preventive vaccination cards, as well as by interviewing the patient's legal representatives. Data on the use of cytotoxic drugs (except methotrexate) were obtained by studying the patient's medical documentation (discharge certificates, child development chart) and by interviewing patients or their parents.

Venous blood samples (4 ml) were taken on an empty stomach on the day the child was admitted to the hospital. Samples were centrifuged at 1200 rpm for 15 min. The serum was collected in separate tubes, frozen at -20°C and then transported to the laboratory of virological and molecular biological research methods of the Federal State Budgetary Institution "Children's Scientific and Clinical Center for Infectious Diseases of the Federal Medical and Biological Agency" (Moscow) in compliance with the cold chain.

Immunoglobulin (Ig) G levels were determined by enzyme immunoassay [11] using an open-type Lasurit device (Dynex Technologies Inc., USA). For measles, rubella, mumps, and hepatitis B, commercial kits "Vector-Best" (Russia) were used, for diphtheria – IBL International GMBH (Germany). IgG concentrations were determined from calibration curves generated using Dynex Technologies Inc. software. (USA). The minimum protective level of antibodies was established in accordance with the criteria specified in the manufacturer's instructions: for anti-measles IgG - 0.18 IU/ml (coefficient of variation, CV, 8%; analytical sensitivity 0.07 IU/ml), for antibodies to the rubella virus - 10 IU/ml (8%; 2 IU/ml), for hepatitis B (anti-HBs antibodies) - 10 mIU/ml (8%; 2 mIU/ml), for diphtheria toxoid - 0.09 IU/ml (7, 5%; 0.004 IU/ml). The minimum protective concentration of IgG to the mumps virus was established at a positivity rate of > 1.0. The positivity rate was calculated as the ratio of the optical density (OD) obtained in dual-wavelength (450/620 nm) mode in the well with the patient sample to the critical OD (OPcrit), calculated by the formula:

$$OPcrit = OPsr(K-) + 0.3,$$

where OPsr(K-) is the arithmetic mean value of OD in wells with a negative control sample.

Among the predictors of the preservation of post-vaccination immunity (the minimum protective level of antibodies), we considered the characteristics of therapy (use in the past or at the time of inclusion in the study of glucocorticosteroids, methotrexate, biologically active drugs), the number of vaccinations (1 each against measles, rubella and mumps, > 1 against hepatitis B and diphtheria), duration of JIA, age of the child.

The preservation of post-vaccination immunity was studied in three age groups: up to 7 years, 8–12 years and 13–17 years. The choice of age periods is determined by the timing of vaccinations in accordance with the national calendar of preventive vaccinations.

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The study sample size was not pre-calculated. The analysis of the obtained data was carried out using the statistical software package STATISTICA, version 10.0 (StatSoft Inc., USA).

The description of quantitative indicators is carried out with the indication of the median (25th; 75th percentile). Comparison of qualitative indicators was carried out using the Pearson test 2. Independent predictors of maintaining the minimum protective level of antibodies were established using binary logistic regression by including in the analysis quantitative and qualitative indicators associated with the dependent variable (patients with a minimum protective level of antibodies to the corresponding infection) according to the results of univariate regression analysis. The multivariate statistical model took into account age at the time of inclusion in the study, the number of vaccinations, the fact of treatment with glucocorticosteroids, methotrexate, biological medications, and the duration of JIA. The results of the regression analysis are described with the indication of the slope ( ) and standard error (SE). The coefficient of determination (R2) was taken into account from the parameters of the multivariate regression model. Differences or relationships were considered statistically significant at $p < 0.05$.

The study included 90 patients (64 girls) with JIA at the age of 11.3 (7.5; 14.9) years, 438Original article age of onset of the disease - 6.0 (4.0; 8.0) years, duration of JIA before inclusion in the study - 4.0 (2.0; 7.3) years. Oligoarticular variant of JIA was present in 38 (42%) patients, polyarticular - in 36 (40%), systemic arthritis - in 7 (8%), enthesitis-associated arthritis - in 9 (10%) patients. Uveitis was diagnosed in 11/89 (12%). In 1 patient, data on the results of examination by an ophthalmologist were missing. 24 patients (27%) out of 88 received glucocorticosteroid therapy in the past or at the time of inclusion in the study, 81/88 (92%) received methotrexate, 54/89 (61%) received GEBD, of which 31 (57%) received factor inhibitors. tumor necrosis alpha; 11/54 (20%) people were receiving more than one steroid. 52 (58%) children received revaccination against the measles, rubella, and mumps virus.

Less often (50–54% of children in the study sample), the minimum protective level of antibodies was detected to measles viruses, hepatitis B and diphtheria toxoid, in 2/3 of patients - to the mumps virus, in the majority of children with JIA - to the rubella virus (Table 1). No differences were found in age groups in the frequency of children with minimal protective levels of antibodies.

According to univariate regression analysis, the following predictors of preservation of post-vaccination immunity were identified:

• to the measles virus: duration of JIA, age at the time of inclusion in the study, number of vaccinations, therapy with biologically active drugs;

• to diphtheria toxoid: age at the time of inclusion, use of glucocorticosteroids.

According to the results of multivariate regression analysis, predictors of maintaining the minimum protective level of antibodies to the measles virus were the number of vaccinations against measles, and to diphtheria toxoid - the duration of JIA and glucocorticosteroid therapy (Table 3). No statistically significant predictors of the preservation of post-vaccination immunity against mumps and hepatitis B were identified.

A significant number of patients with JIA (from 32 to 50%) have insufficient protective levels of antibodies to measles, mumps, hepatitis B viruses and diphtheria toxoid. However, the majority of patients with JIA retain post-vaccination immunity to the rubella virus. Predictors of

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preservation of post-vaccination immunity were booster vaccinations and shorter disease duration.

The main limitations of the study are related to the small sample size, different ages of the included patients, different duration of the disease, as well as differences in the number of previous vaccinations. The small sample size did not allow risk factor analysis to fully assess immunity against rubella and hepatitis B. It should be noted that the study did not have a control group, which did not allow us to fully assess the dynamics of the decrease in antibody formation in healthy children without risk factors. The presence of a control group would allow us to evaluate whether the studied predictors actually influence the decrease in antibody production or not. Limitations of the study could affect the correctness of determining the predictors of preservation of post-vaccination immunity, i.e. the studied factors could be erroneously regarded as possible predictors (lack of a control group), and the role of other factors, for example, the combination of drugs with the duration of JIA, the age of prescription of certain drugs drugs and duration of therapy that were important could not be identified. How each of the risk factors separately (medicines, number of vaccinations, disease duration, arthritis subtype) could influence it is impossible to determine unambiguously due to the fact that some patients received combination therapy, and the groups were not stratified by age of onset and/or disease duration. Perhaps a larger sample size would have allowed for more detailed subgroup analyses. We also did not take into account factors such as duration of therapy, cumulative doses, and combination of treatment methods. One patient could receive several types of therapy, as well as other concomitant pathology, which could affect the rate of drug elimination and, indirectly, the characteristics of the immune response. An error in the study is allowed due to the accuracy of the measurement methods (CV of the methods used to determine the level of antibodies was in the range of 7.5–8%).

JIA is an immunopathological disease that requires the use of immunosuppressive drugs to achieve remission [2]. The immune mechanisms underlying the genesis of this disease, as well as the use of drugs that affect the function of memory B cells and plasma cells, can lead to the loss of the protective titer of measles post-vaccination antibodies in a shorter period of time than in the population [12, 13]. According to a population study, the protective titer of anti-measles antibodies was determined in 85% of healthy children aged 3–6 and 7–14 years [14]. In another study, the proportion of healthy children who do not have a minimum protective titer of anti-measles antibodies in the period from 2 months to 5 years after a single vaccination is 10-12%, in the period from 4 months to 9 years after revaccination - 13-17% [15] . After vaccination against the mumps virus in the period from 2 months to 5 years, from 5 to 9% of healthy children did not have a minimum protective titer of antibodies; in the period from 4 months to 9 years after revaccination - from 2 to 13%. After vaccination against rubella, 6.9% of healthy children did not have the minimum protective antibody titer [15]. In our sample, the proportion of children who did not have a minimum protective titer of antibodies to these infections was lower than that found in population studies, with the exception of immunity against rubella. The latter can be explained by the high proportion of children who had rubella in an erased form due to primary vaccination.

According to seromonitoring data, the proportion of people with a protective antibody titer against the hepatitis B virus 3 months after vaccination is 99%, and 77% after 7 years. In case of violation of the vaccination schedule, the proportion of healthy people with a minimum

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protective antibody titer is 53% [16]. In our study, despite the absence of patients with a disrupted vaccination schedule against hepatitis B, the proportion of children with JIA with a minimal protective titer of antibodies against the hepatitis B virus was 54%. A protective titer of antibodies against diphtheria toxoid was detected in 95–97% of the child population, of which 96% aged 3–4 years, 98% aged 15–17 years, 93% of adults with high immunity (85, 91 and 81%, respectively) [17, 18].

An early age at the onset of JIA, after which vaccine prevention is stopped in real clinical practice, leads to a lower level of antibodies in older children [9]. In our study, only 52% of children received revaccination against measles, while the coverage of revaccination against measles, according to the Moscow Government Health Committee, reaches 99% [14]. An incomplete vaccination complex is an independent predictor of the absence of a protective antibody titer in our sample.

Previously published studies assessed the effect of drugs on the quality of antibody formation after vaccination. It was shown that methotrexate did not have a significant effect on the short-term and long-term effectiveness of antibody formation when administered various vaccines, such as measles, rubella, mumps, tetanus, diphtheria, hepatitis B [9, 19]. Regression models also did not show a significant effect of methotrexate on the protective level of antibodies against measles, rubella, mumps, diphtheria and tetanus toxoid viruses [9]. In our study, when comparing patients who received and did not receive methotrexate therapy, there were also no statistically significant differences in antibody levels. However, given the fact that it is impossible to assess the role of methotrexate alone without taking into account other risk factors, it can be assumed that methotrexate does not have a significant effect on the process of antibody formation.

When studying the effect of biologically active drugs, it was shown that in the majority of patients with JIA who received biologically active drugs, post-vaccination antibodies were preserved. However, a number of studies have shown that the average level of anti-measles antibodies, antibodies to meningococcus type C and pneumococcus in patients using biological drugs was lower or decreased more rapidly over time than in patients not receiving biologic drugs [20–22]. GEBD therapy is usually prescribed to patients with a longer duration of the disease. Our study found that among patients receiving biological therapy, the proportion of patients who had a protective titer of measles antibodies was lower (48%) compared to those who did not receive biological therapy (73%): $p = 0.013$; odds ratio 3.0; 95% confidence interval 1.2–7.3. These differences were not confirmed by the results of multivariate analysis.

Children with JIA treated with systemic glucocorticosteroids generally maintained minimal protective antibody titers after vaccination, but their geometric mean levels may have been lower compared to patients who did not receive such treatment [23]. In general, there was no significant effect of glucocorticosteroids on the levels of post-vaccination antibodies against mumps, measles and rubella, tetanus and diphtheria [9, 24, 25], however, it is important to consider the duration of this therapy and the cumulative doses of drugs. Children with JIA who received therapy with glucocorticosteroids and methotrexate and were vaccinated against hepatitis B had an adequate immune response [9, 19].

JIA is an example of an immunocompromised disease in which the effectiveness of vaccination against childhood infections may be reduced due to the duration and form of JIA, immunosuppressive therapy, and violations of the revaccination schedule. Subsequent studies are

needed to study in more detail the dynamics of the preservation of the specific immune response in patients with JIA in order to develop individual revaccination algorithms.

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