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SPECIAL ISSUE ARTICLE

How do the characteristics of juvenile idiopathic arthritis affect the continuation or refusal of vaccination against diphtheria? A cross-sectional study data

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ABSTRACT

Introduction: Patients with juvenile idiopathic arthritis (JIA) often stop being vaccinated after the onset of the disease due to fear of disease flare, although the effectiveness and safety of vaccination in immune compromised patients have been demonstrated.
Aim: The objective of this study was to evaluate the JIA characteristics associated with the refusal to continue to be vaccinated against diphtheria.
Methods: In a cross-sectional study, we included data about patients who continued (n = 25) or refused (n = 51) vaccination against diphtheria after the development of JIA. In all patients, the levels of anti-diphtheria vaccine antibodies (immunoglobulin G) were determined with the enzyme-linked immunosorbent assay. The data are presented with a median and 25 – 75%.
Results: The age of disease onset, JIA duration, and JIA categories were similar between groups. Patients who declined the following vaccination often received methotrexate and biologics and switched at least one biologic. Methotrexate (odds ratio [OR] = 9.5 [95% confidence interval (CI): 1,004; 90.3]) and biologics (OR = 4.4 [95% CI: 1.6; 12.1]) were predictors of refusal of revaccination against diphtheria. Vaccination against diphtheria was effective, as evidenced by the almost two-fold prevalence of patients with a protective antibody titer compared to those who refused revaccination. Serious adverse events, as well as JIA flares in 3 months after vaccination were not observed.
Conclusion: The continuation of vaccination against diphtheria in children with JIA was effective and safe. The treatment with methotrexate and biologics was a predictor of refusal of revaccination against diphtheria. Further studies are needed to confirm the safety and efficacy of vaccination against diphtheria in children with JIA and can increase the level of confidence of physicians in the vaccination of children with rheumatic diseases.
Relevance for Patients: Patients with JIA should know the necessity, efficacy, and safety of vaccination against diphtheria. There are no contraindications from the disease side to vaccination against diphtheria. Health-care providers should discuss and encourage any vaccination in immune-mediated children.

1. Introduction

Vaccination is an important tool for infection prevention, especially for immunocompromised patients [1]. Immunocompromised patients are at risk for frequent and severe infections due to immune system dysfunction, treatment with immunosuppressive medications, and incomplete vaccination [2-6]. High-risk groups include patients with rheumatic diseases who may have vaccinations according to national schedules but do not

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have protective levels of post-vaccination antibodies [7]. It is known that younger children (≤4 years) with juvenile idiopathic arthritis (JIA) and patients with higher disease activity have an increased incidence of infection [8,9]. The majority of vaccinations against vaccine-controlled infections occur at the age of 4 years. Immune-mediated disease and immunosuppressive treatment (corticosteroids, tumor necrosis factor-alpha (TNF-α) inhibitors, and anti-B cell therapy) may influence the protective level of anti-vaccine antibodies, and memory B-cell function [10-12]. Many national and international professional associations are calling for the commitment of physicians and patients to the vaccination process [10]. However, despite this, many patients, parents, and physicians are opposed to vaccinations due to fear of flare of the disease or low efficacy of the vaccination [9,13,14]. In the Russian Federation, the vaccination coverage of children with JIA in the last decade against major vaccine-controlled infections remains at a low level and amounts to 50 – 58% [9].

In recent years, the number of cases of diphtheria reported worldwide has been gradually increasing. In 2018, 16,651 cases were registered, which is more than twice the annual average for 1996 – 2017 (8105 cases) [15]. The coronavirus disease 2019 pandemic caused the largest decline in vaccination in the past three decades [16,17]. In 2021, according to the World Health Organization, 25 million children did not receive a vaccine against measles, diphtheria, and tetanus [18]. It is known that diphtheria is a life-threatening disease, with high mortality associated with asphyxia due to obstruction of the respiratory tract by edema and patches, as well as myocardial and nervous system involvement resulting from exposure to bacterial toxins [19]. In the early stages, anti-diphtheria serum and antibacterial therapy are used for treatment, which may eventually become ineffective due to the development of resistance of C. diphtheriae to antibiotics [15]. The schedule of primary vaccinations against diphtheria and tetanus is the same in different countries, with differences mainly in the number and timing of booster doses [20]. In the Russian Federation, vaccination against diphtheria is carried out from the age of 3 months. The primary vaccination consists of three doses, starting from 3 months, performed at intervals of 45 days. Revaccination is carried out 1 year after the initial vaccination, then at 7 and 14 years, for adults – every 10 years throughout life [21]. Vaccination with three doses of diphtheria toxoid vaccine is highly (87%) effective against symptomatic disease and reduces transmission by 60% [19].

Despite the developed immunization schedules, the global suboptimal vaccination coverage is typical for many countries. It may lead to outbreaks of vaccine-controlled infections, including diphtheria, due to a lack of collective immunity. To reduce morbidity, it is necessary to achieve high vaccination coverage and introduce recommended booster doses, and it is also important to identify persons, who require routine assessment of the level of anti-vaccine antibody over the safety of post-vaccination immunity. The study aimed to evaluate the characteristics of JIA associated with the refusal of the following vaccinations against diphtheria.

2. Methods

In the cross-sectional study, we included information about patients, who continued (n = 25) or declined (n = 51) vaccination against diphtheria due to the onset of JIA. Study inclusion lasted from 2019 to 2020 years and was conducted in the Department of Pediatric Rheumatology of Saint-Petersburg State Pediatric Medical University.

Inclusion criteria were as follows: (i) Diagnosis of JIA was established according to International League of Associations for Rheumatology criteria [21]; (ii) age <18 years; (iii) done initial vaccination against diphtheria in the 1st year of life; and (iv) similar demographic characteristics of the patients with a similar number of vaccines before the onset of the JIA.

Exclusion criteria were as follows: (i) Incomplete initial vaccination in the 1st year of life and (ii) patients, whose demographic characteristics and number of vaccines differed between groups.

We evaluated demography, JIA category, treatment, vaccination status, and levels of antibodies against the diphtheria vaccine.

The data about the JIA course and treatment were obtained from the patient's charts. We selected the oligoarticular course (<5 active joints), polyarticular course (extended oligoarthritis, rheumatoid factor [RF]-positive, and RF-negative polyarthritis), and systemic arthritis. The following classes of immunosuppressive medications, which were used by the patients during study recruitment, were taken into account: corticosteroids, methotrexate, and biologics.

2.1. National vaccine schedule

Russian national vaccine schedule supposes diphtheria-tetanus-pertussis vaccination in 3, 4½, 6, and 18 months and further diphtheria-tetanus vaccination in 6 – 7 and 14 years. Vaccination is mandatory in the Russian Federation. According to national recommendations, immunosuppressive drugs were not discontinued before/during diphtheria vaccination.

2.2. Assessment of the levels of antibodies against diphtheria

In all patients, the levels of post-vaccination antibodies (immunoglobulin G [IgG]) for diphtheria were measured with enzyme-linked immunosorbent assay during study inclusion. IgG concentrations were determined from calibration curves constructed using Dynex Technologies Inc. Software (USA). The protective level of antibodies was established by the criteria specified in the manufacturer's instructions for diphtheria – 0.09 IU/ml (7, 5%; 0.004 IU/ml). To detect diphtheria antibodies, we used the commercial kit, created by IBL International GMBH (Germany). Information about the scheduled vaccination against diphtheria was obtained from the personal vaccine certificates.

2.3. Statistical analysis

Statistical analysis was performed with the software STATISTICA, version 10.0 (StatSoft Inc., USA) and MedCalc (MedCalc Software, Belgium). The sample size was not calculated, the power was 0.409. All continuous variables were checked by the

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Kolmogorov–Smirnov test, with no normal distribution identified. Description of quantitative variables was done with median and interquartile range (25%; 75%) for continuous variables and in terms of absolute meanings and percentages for categorical variables. For comparison, the categorical variables Pearson's χ^2 test or Fisher's exact test in case of expected frequencies <5 were used, and a comparison of two quantitative variables was carried out using the Mann–Whitney test. $P < 0.05$ was considered statistically significant.

2.4. Ethics

Written consent was obtained according to the Declaration of Helsinki. The Ethics Committee of Saint Petersburg State Pediatric Medical University (protocol number 9/2 from September 2, 2019) approved this retrospective study's protocol. All patients or patients' representatives (for patients under the age of 15) gave their consent in their case report forms authorizing the anonymous use of their medical information. All patients were appropriately anonymized.

3. Results

3.1. Patients' demography

The studied population was presented with girl predominance (n = 48; 63%), oligoarticular (n = 31; 41%), and polyarticular (n = 30; 40%) predominance. Treatment modalities included corticosteroids (n = 33; 43%), methotrexate (n = 71; 93%), and biologics (n = 48; 63%). Ten patients (13%) received two biologics and more, consequently.

3.1.1. The predictors of the refused vaccination against diphtheria

The protective level against diphtheria was in 33 (%) of patients. The following differences were found among patients with JIA who continued to be vaccinated against diphtheria. Patients with a less severe course of JIA, who received methotrexate less often, who needed less both primary administration of biologics and switching between biologics more often continued to be vaccinated. We did not observe the association of vaccination refusal, depending on the type of biologic. Vaccination against diphtheria was effective, as evidenced by the almost two-fold prevalence of patients with a protective antibody titer compared to those who refused revaccination. Data are in Table 1.

4. Discussion

Many children with rheumatic diseases in the Russian Federation stop being vaccinated after diagnosis [21]. A lot of practicing pediatricians and pediatric rheumatologists are unreasonably afraid of post-vaccination complications, and flares of rheumatic disease, and also consider vaccination ineffective when using immunosuppressive therapy. Often they do not take into account the fact that prolonged use of immunosuppressive drugs, escalation of treatment regimens, and the presence of signs of immune dysfunction leads to an altered "protective"

Table 1. Patients demography and post-vaccination immunity against diphtheria in children with JIA

Parameter	Vaccination against diphtheria		*P*
	Continued (n=25)	Declined (n=51)	
Demography			
Sex, males, n (%)	12 (48)	16 (31)	0.158
JIA onset age, years, Me (25%; 75%)	5.0 (4.1; 6.5)	5.1 (3.0; 11.4)	0.820
Age of inclusion in the study, years, Me (25%; 75%)	11.6 (9.8; 16.0)	13.8 (11.0; 15.8)	0.670
JIA duration, years, Me (25%; 75%)	6.5 (4.9; 8.2)	6.2 (3.6; 9.5)	0.699
JIA courses			
Oligoarthritis, n (%)	11 (44)	20 (39)	0.678
Polyarthritis, n (%)	8 (32)	22 (43)	
Systemic arthritis, n (%)	1 (4)	3 (6)	
Vaccine diphtheria status			
Antibodies against diphtheria, IgG, IU/ml, Me (25%; 75%)	0.14 (0.07; 0.34)	0.06 (0.02; 0.22)	0.695
Patients with protective levels of antibodies against diphtheria, n (%)	15 (60)	18 (35)	0.041
Time since the last diphtheria vaccination, years, Me (25%; 75%)	5.6 (3.6; 10.3)	6.7 (4.0; 10.7)	0.025
Treatment			
Corticosteroids, n (%)	4 (16)	16 (31)	0.153
Methotrexate, n (%)	21 (84)	50 (98)	0.020
Methotrexate duration treatment, years, Me (25%; 75%)	3.1 (1.6; 5.8)	5.1 (2.6; 8.7)	0.027
Biologics, n (%)	10 (40)	38 (75)	0.003
Biologics duration treatment, years, Me (25%; 75%)	1.9 (1.0; 4.1)	3.4 (2.6; 8.7)	0.674
Using > one biologics, sequentially, n (%)	1/9 (11)	9/29 (31)	0.009

Abbreviations: JIA: Juvenile idiopathic arthritis; Me: Median

Serious adverse events, as well as JIA flares in 3 months after vaccination were not observed. We found that methotrexate odds ratio [OR]=9.5 (95% confidence interval [CI]: 1,004; 90.3) and biologics OR=4.4 (95% CI: 1.6; 12.1) were predictors of refusal of revaccination against diphtheria.

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immune response and an increase in the risk of infectious diseases [13,22].

Intercurrent infections not only lead to flares of JIA but also require treatment discontinuation, which negatively affects the achievement or maintenance of the inactive status of the disease and significantly increases the financial costs associated with treatment [2]. The disrupted vaccination schedule in patients with rheumatological diseases is typical even for developed countries, the share of missed vaccines from the national calendar, for example, in Slovenia is 35%, and in Canada 39% [23,24]. It was found that the proportion of missed vaccines is proportional to age, as well as the severity of arthritis (polyarthritis, systemic arthritis), and depends on the type of vaccines. In the above-described studies, revaccinations against measles, hepatitis B, diphtheria, rubella, and mumps were most often missed [23-25].

According to research, the fear of parents and physicians was often the reason for the refusal of subsequent vaccinations in children with rheumatic diseases [23,26-29]. Many physicians postpone vaccination until the inactive stage of the disease is reached or long-term remission of JIA, which affects the presence of a protective antibody titer [23,26].

4.1. Is vaccination against diphtheria safe and effective?

There is little international experience in the safety and efficacy of vaccination of children with rheumatic diseases against diphtheria. In a cohort of 29 patients previously vaccinated against diphtheria and tetanus, aged 2 – 5 years, with polyarticular JIA, who received subcutaneous abatacept, the protective level of antibodies against diphtheria was detected in 26 (89.7%) children. Methotrexate and low doses of corticosteroids did not affect the level of antibodies [30].

In our study, the protective level of antibodies against diphtheria was detected in 51.8% of patients with JIA. However, it should be borne in mind that in the study by Brunner *et al.*, children at the time of inclusion were younger or preschool age [30]. It should be noted that the more time passes since the last vaccination, the more likely it is to have a low level of antibody. According to the study of Heijstek *et al.*, patients with different JIA categories had equal levels of antibodies against diphtheria similar to the results of the previous study [30,31]. In this study, incomplete vaccination, methotrexate treatment duration, and biologics affected the level of antibodies against diphtheria, which is also observed in our study [31]. Methotrexate disturbed the production of antibodies against diphtheria in a prospective multicenter study by Bühler *et al.* There were no flares of rheumatic disease after vaccination. These data also coincide with our results [32]. In a multicenter study on the duration of antibody persistence after vaccination against diphtheria/tetanus in patients with rheumatic diseases undergoing immunosuppressive therapy after vaccination, median concentrations of antibodies against diphtheria were lower in patients with rheumatic diseases than in the control group (0.05 vs. 0.22; $P = 0.002$). Patients with rheumatic diseases had lower proportions of short-term tetanus and diphtheria protection as demonstrated by crude OR of 0.30 ($P = 0.017$) and OR: 0.52 ($P = 0.004$), respectively [33].

Recently, the European League Against Rheumatism published updated recommendations on the vaccination of children with rheumatic diseases. This update takes into account new studies on the safety of live attenuated vaccines and the immunogenicity of vaccines in patients receiving new anti-rheumatic drugs. This update addresses three important aspects of vaccine safety: no serious side effects, no flare of the underlying disease, and no triggering of infections in the case of live attenuated vaccines [10].

According to these recommendations, non-live vaccines can be prescribed to children receiving glucocorticosteroids, disease-modifying anti-rheumatic drugs. Patients with rheumatic diseases may have lower antibody titers compared to healthy peers, but in general, vaccination is effective and safe [31,34-37]. Several studies confirmed the safety of vaccines in pediatric rheumatic diseases [35,38,39].

No increased frequency of JIA flares after vaccination against chickenpox, PCP, diphtheria, or poliovirus (inactivated) was observed [35,38,39].

The group of patients who need to monitor antibodies against vaccines includes patients who also receive any biological drugs, as well as those who have an incomplete set of vaccines [40]. Personalized vaccination is recommended for patients suffering from rheumatic diseases based on the presence of risk factors, as well as determining the level of the protective titer of antibodies [10].

Educational work with physicians and health-care providers reduces fears of vaccination and encourages vaccination in children with immunocompromised conditions [41,42].

Our study is not without the limitations. JIA is a rare disease and a small sample size, specific selection of the patients, and different times between and after vaccination could affect the study results.

5. Conclusion

Treatment with methotrexate and biological drugs is a predictor of refusal of subsequent vaccination against diphtheria after the onset of JIA. Vaccination against diphtheria in children with JIA is a safe and effective tool for controlling incidence in this group of patients. It is necessary to increase the level of confidence of doctors in the vaccination of children with rheumatic diseases.

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Conflicts of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Ethics Approval and Consent to Participate

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Consent for Publication

All participants and/or their legal representatives had given their consents for publication of the materials. The consents were obtained in the patients' case histories.

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