ORIGINAL RESEARCH

F.V. Vinokurova, V.M. Argunova, P.A. Sleptsova, V.M. Nikolaev, E.K. Rumyantsev, T.E. Burtseva, V.G. Chasnyk, M.M. Kostik

PREVALENCE AND STRUCTURE OF JUVENILE IDIOPATHIC ARTHRITIS IN CHILDREN IN THE REPUBLIC OF SAKHA (YAKUTIA)

DOI 10.25789/YMJ.2020.72.01

Juvenile idiopathic arthritis is the most common type of childhood arthritis. The prevalence and structure of this disease has pronounced geographical and ethnic characteristics. One of the factors that determines the prevalence of JIA and its subtypes is the prevalence of the HLAB27 antigen in the population.

Summary: the article presents the results of analysis of the structure and prevalence of juvenile idiopathic arthritis in children in the Republic of Sakha (Yakutia). Differences in the structure of the JIA are determined by different frequencies of the JIA variants. Our study showed that the high prevalence of the HLA B27 antigen affects the structure of JIA in the region.

The purpose of the study is to elucidate the prevalence and structure of JIA in children in the Republic of Sakha (Yakutia).

Methods and objects of research: The retrospective study included 170 sick children with juvenile idiopathic arthritis (ILAR, 2001), hospitalized in the cardio-rheumatology department of the Pediatric Center of the Republic of Sakha (Yakutia) "RB #1-NCM" from 2009 to 2017.

Results: the prevalence of JIA in children under 18 years of age in Yakutia was 64.3 per 100,000 population (0-17 years); the prevalence in children under 14 was 67.2; among teenagers - 47.3 per 100,000 population. Among the JIA cases, the indigenous population accounted for 30.9% of cases, while the Caucasians accounted for 7.4%. The average prevalence of JIA in the Republic of Sakha (Yakutia) is comparable to the all-Russian indicator, but there are significant differences across regions. In 14 districts and the city of Yakutsk, the prevalence of JIA is higher than the nationwide indicator. In 9 districts of Yakutia, no children with JIA were found. In the indigenous population, JIA was more often diagnosed among boys; they were characterized by a later age of JIA onset. In children of the indigenous population of Yakutia, the structure of JIA was significantly dominated by patients with enthesitis-associated JIA. The population of indigenous children was characterized by a rare incidence of systemic arthritis, RF (+) polyarthritis, and psoriatic arthritis. The prevalence of HLA B27 antigen in juvenile idiopathic arthritis was 57%.

Conclusions: the peculiarities of the structure of JIA in Yakutia are due to the high frequency of occurrence of the HLAB27 antigen in the population as a whole and in JIA.

Keywords: juvenile idiopathic arthritis, enthesitis-associated variant of JIA, HLA B27 antigen, frequency.

VINOKUROVA Fekla Vasilievna - Researcher, Yakutsk Scientific Center for Complex Medical Problems (YSC CMP), vfekla@gmail.com, **ARGUNOVA Vera Maichna** - Head of the Cardio-Rheumatology Department of the Pediatric Center of the State Autonomous Institution of the Republic of Sakha (Yakutia) "Republican Hospital No. 1 - National Center of Medicine (GAU RS (Y)" RB No. 1-NCM "), **SLEPTSOVA Polina Andreevna** - Candidate of Medical Sciences, cardio-rheumatologist of the Pediatric Center of the State Autonomous Institution of the Republic of Sakha (Yakutia) "Republican Hospital No. 1 - National Center of Medicine (GAU RS (Y)" RB No. 1-NCM"), **NIKOLAEV Vyacheslav Mikhailovich** - Candidate of Biological Sciences, Chief Researcher, Head of the Department for the Study of Adaptation Mechanisms, Yakutsk Scientific Center for Complex Medical Problems (YSC CMP), Nikolaev1126@mail.ru, **RUMYANTSEV Egor Konstantinovich** - Junior Researcher, Yakutsk Scientific Center for Complex Medical Problems (YSC CMP), **BURTSEVA Tatyana Egorovna** - Doctor of Medical Sciences, Professor of the Department of Pediatrics and Pediatric Surgery of the Medical Institute, Federal State Autonomous Educational Institution of Higher Education "North-Eastern Federal University named after M.K. Ammosov", Head of the Laboratory of the Yakutsk Scientific Center for Complex Medical Problems (YSC CMP) , tel. 8 (914) 2943244, e-mail: bourtsevat@yandex.ru/, **CHASNYK Vyacheslav Grigorievich** - Doctor of Medical Sciences, Head. Department of Hospital Pediatrics, St. Petersburg State Pediatric Medical University (SPbGPMU), **KOSTIK Mikhail Mikhailovich** - Doctor of Medical Sciences, Professor of the Department of Hospital Pediatrics, St. Petersburg State Pediatric Medical University (SPbGPMU).

Relevance. Juvenile idiopathic arthritis is the most common type of childhood arthritis. [1; 4]. The prevalence of juvenile idiopathic arthritis ranges from 2 to 19 cases per year per 100,000 population, and in recent decades this pathology has been increasing [3]. There are significant ethnic and geographical differences in the prevalence of JIA and its categories, so the prevalence of all juvenile arthritis in different countries ranges from 0.05% to 0.6%. In the Russian Federation, the prevalence of JIA in children under 18 reaches 62.3 per 100 thousand population [2]. The prevalence of JIA in Moscow in 2016 was 52.2 per 100 thousand children (0-14 years old) and 99.8 per 100 thousand adolescents (15-17 years old) [6]. In Bashkortostan, according to 2006 data, the prevalence of JIA is 83.8; high prevalence is in the Kushnarevsky district - 132.3; low - in Ufa - 57.6 cases per 100,000 child population [5].

As a rule, the main differences in the structure of JIA are determined by different frequencies of the oligoarticular variant, enthesitis-associated variant and systemic variants of JIA. Therefore, in Europe and North America, the predominant variant is the oligoarticular variant of JIA, in Japan the systemic variant, and in Asian populations (China, India, South Korea), the enthesitis-associated variant of JIA is predominant. One of the risk factors for the implementation of enthesitis-associated arthritis is the HLAB27 antigen, and its frequency in a healthy population determines the frequency of this subtype of arthritis and the prevalence of JIA itself in the population. Previous studies have shown high frequency of the prevalence of the HLAB27 antigen among the indigenous population of the Republic of Sakha (Yakutia), which could have influenced the structure of JIA in the region.

The purpose of study is to elucidate the prevalence and structure of JIA in children in the Republic of Sakha (Yakutia).

Materials and methods: the retrospective study included data from the case histories of 170 pediatric patients (under 18 years of age) who were treated in the department of cardio-rheumatology Pediatric Center of the Republic of Sakha (Yakutia) "RB #1-NCM" from 2010 to 2019. The diagnosis of JIA was established based on the criteria of ILAR, 1997 [16]. The information was taken from the case histories about the demographic characteristics of patients, the type of

arthritis, the provoking factor, characteristics of arthritis, such as indicators of inflammatory activity, the presence of the HLAB27 antigen, seropositivity for antinuclear and rheumatoid factors, the number of active joints, the presence of comorbid pathology, the therapy and the region of residence the patient. The ethnicity was determined by the parents' self-identification method. The study included children of the indigenous population (Sakha, small indigenous peoples of the North) and Caucasians (Russians, Ukrainians) living in the Republic of Sakha (Yakutia). The prevalence of JIA was calculated using the following formula:

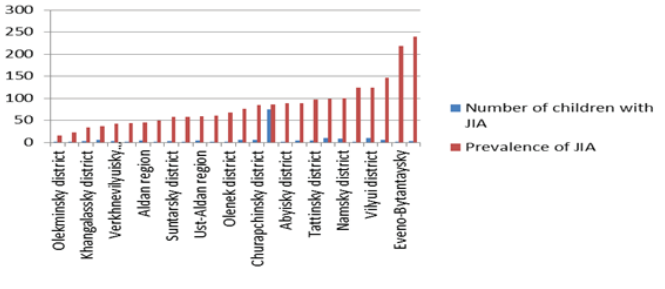
$$\frac{\text{The number of initial visits for diseases, identified in this year and in previous years}}{\text{The average population}} \bullet 100{,}000$$

Ethical examination: this scientific research work has passed the examination on biomedical ethics at the Yakut Science Centre of complex• 100 000. medical problems SB RAMS (extract from the minutes No. 18 of June 16, 2009).

Statistical analysis: The sample size was not pre-calculated. The analysis of the data obtained was carried out using the statistical software packages Statistica v. 10.0 (StatSoft Inc., the USA) and MedCalc (MedCalc Software, Belgium). The description of quantitative indicators is carried out with the indication of the median (25th; 75th percentile). The comparison of quantitative indicators in two independent groups was carried out using the Mann-Whitney test, qualitative indicators - using the Chi-square test ($\chi 2$) or Fisher's exact test if the expected frequency in one of the cells of the table 2 × 2 was <5. Differences or relationships were considered statistically significant at $p < 0.05$.

Results and discussion:

The prevalence of JIA among children under 18 years of age in Yakutia was 64.3 per 100,000 population (0-17 years); among children under 14 the prevalence was 67.2; among adolescents - 47.3 per 100,000 population. Among the JIA cases, the indigenous population accounted for 30.9% of cases, while the Caucasians accounted for 7.4%. The average prevalence of JIA in the Republic of Sakha (Yakutia) is comparable to the all-Russian indicator, but there are significant differences across regions. In 14 districts and the city of Yakutsk, the prevalence of JIA is higher than the nationwide indicator. In 9 regions of Yakutia, no children with JIA were found (figure 1).



Prevalence of JIA in the Republic of Sakha (Yakutia) 100,000 population

Of the features, it should be noted the male predominance in the indigenous population, as well as the later age of arthritis onset. In children of the indigenous people of Yakutia, there was higher prevalence of patients with enthesitis-associated JIA, with a relatively low specific gravity of psoriatic arthritis and rare incidence of systemic arthritis, RF (+) polyarthritis. More than half of the indigenous patients were hereditary tainted by rheumatic diseases, while in Caucasians only a third of patients had a tainted family history. The indigenous children had twice frequent enthesitis compared to Caucasians. When studying the features of articular lesions, it should be noted that children of the indigenous population more often had lesions of the hip and knee joints and sacroiliac joints and relatively less often had the involvement of the small joints of the feet. The detailed description of the patients included in the study is presented in Table 1. Among laboratory tests, children of the indigenous population tended to have a higher degree of laboratory activity, they had higher CRP and platelet counts. There were no significant differences in the frequency of children seropositive for antinuclear and rheumatoid factors.

There was significant difference in the overwhelming number of indigenous children with the HLAB27 antigen. There were no differences in provoking factors between the study groups.

When studying the social status, it was found that the children of the indigenous population more often lived in rural areas and had higher frequency of infection with Mycobacterium tuberculosis.

When studying the features of therapy, it was found that children of the indigenous population more often received sulfasalazine therapy and, less often, methotrexate therapy. The need for GIBD therapy was higher in European children, while more often Caucasian children were 1.5 times more likely to use adalimumab than children of the indigenous population.

Discussion: This study presents data on the prevalence of JIA in the Republic of Sakha (Yakutia). The main differences are associated with higher frequency of the HLAB27 antigen and the associated enthesitis-associated variant of JIA among children of the indigenous population of Yakutia. The influence of HLA on arthritis is associated with such biological intracellular phenomena as endoplasmic reticulum stress (ER) and autophagy. The most important function of the ER is folding of proteins. Disruption of normal folding under the influence of various "triggers" (inflammation, viral and bacterial infections, etc.) and accumulation of altered or incorrectly folded proteins in the EPR lumen with their subsequent aggregation was called “EPR stress”, and the system for controlling the quality of protein folding - UPR (unfolded protein response) [20,13,9]

In arthritis, under the influence of excess IL23 production, the folding of the HLA-B27 heavy chain occurs more slowly than in other HLA alleles, which leads to the formation of misfolding chains [17,13]. During EPR stress, their excessive accumulation occurs, leading to the activation of not only UPR, but also the nuclear factor NF-κB, a key transcriptional regulator of the synthesis of pro-inflammatory cytokines, including IL-17 and TNF-α, which also play an important role in the development of inflammation [18, 19].

According to the results of our studies, it has been shown the prevalence of the HLAB27 antigen in the mid-indigenous population of MS (Y) is 32.9%. The prevalence of the HLA B27 antigen in different populations is different (Table 2).

Enthesitis-associated JIA is the only form associated with male sex. Due to the high rate of enthesitis-associated arthritis among the indigenous population the prevalence of JIA is higher at boys, while there are more girls affected by JIA in most of the known populations. The wide distribution of the HLAB27 antigen is due to the fact that this antigen presents in all JIA subtypes in children of the indigenous people of Yakutia, not revealed in other populations. Thus, the HLAB27 antigen is found in 70% of children with enthesi-

Table1

Demographic characteristics of patients included in the study

Signs	Indigenous. n=144	Caucasians. n=26	p
Gender. male. n (%)	85 (59.0)	11 (42.3)	0.114
Debut age. y.	10.6 (6.0; 13.4)	7.8 (4.6; 11.6)	0.174
JIA subtypes. n (%)			
Oligoarthritis polyarthritis. RF (-) polyarthritis. RF (+) systemic arthritis enthesitis-associated arthritis psoriatic arthritis	36 (25.0) 21 (14.6) 1 (0.7) 4 (2.8) 76 (52.8) 6 (4.2)	5 (19.2) 6 (23.1) 1 (3.9) 2 (7.7) 10 (38.5) 2 (7.7)	0.292
NAJ	4.0 (3.0; 6.0)	3.0 (2.0; 6.0)	0.412
Enthesite. n (%)	36 (25.0)	3/26 (11.5)	0.133
Uveitis. n (%)	16 (11.1)	2/25 (8.0)	0.642
Psoriasis. n (%)	3/143 (2.1)	2/25 (8.0)	0.109
Family anamnesis. n (%)	75/136 (55.2)	8/22 (36.4)	0.102
Laboratory characteristic			
Erythrocyte sedimentation rate. mm / h	26.0 (15.0; 52.0)	23.0 (13.0; 38.0)	0.327
C-reactive protein. mg / l	33.0 (10.0; 58.0)	22.0 (10.0; 26.0)	0.262
Hemoglobin. g / l	116.0 (107.0; 128.0)	119.0 (108.0; 129.0)	0.570
Leukocytes x109 / l	7.7 (5.8; 10.0)	7.2 (6.4; 10.0)	0.787
Platelets x109 / l	339.0 (279.0; 455.0)	310.0 (254.0; 365.0)	0.077
Positivity for HLA B27. n (%)	76/131 (58.0)	8/24 (33.3)	0.026
ANF seropositivity. n (%)	4/46 (8.7)	0/16 (0.0)	0.223
Seropositivity in RF. n (%)	3/141 (2.1)	1/25 (4.0)	0.574
Provoking factor. n (%)			
Not installed Acute intestinal infection Acute respiratory infection Joint injury	36 (25.7) 48 (34.3) 29 (20.7) 17 (19.3)	8 (34.8) 10 (43.5) 2 (8.7) 3 (13.0)	0.393
Social factors. n (%)			
City dwellers	69/142 (48.6)	21/25 (84.0)	0.001
Villager	73/142 (51.4)	4/25 (16.0)	0.001
Infection with mycobacterium tuberculosis	16/141 (11.4)	1/24 (4.2)	0.285
Passive smoking	23/66 (34.9)	7/16 (43.8)	0.507
Therapy. n (%):			
Non-steroidal anti-inflammatory drugs	117/134 (87.3)	21/23 (91.3)	0.588
Sulfasalazine	25 (17.4)	2/25 (8.0)	0.238
Glucocorticosteroids	9/143 (6.3)	1/25 (4.0)	0.655
Methotrexate	97/142 (68.3)	21/24 (87.5)	0.055
Leflunomide	5/143 (3.5)	0/25 (0.0)	0.343
Cyclosporin A	3/144 (2.1)	0/25 (0.0)	0.467
Genetically engineered biological drugs (primary purpose). n (%): Etanercept Adalimumab Tocilizumab Infliximab Golimumab Abatacept	70/144 (48.6) 49 (70.0) 4 (5.7) 9 (12.9) 6 (8.6) 1 (1.4) 1 (1.4)	20/26 (76.9) 14 (70.0) 3 (15.0) 2 (10.0) 1 (5.0) 0 (0.0) 0 (0.0)	0.101
Genetically engineered biological products (second line of therapy). n (%):	8 (5.6)	1 (3.9)	0.720
Adalimumab Golimumab Infliximab Etanercept	4 (50.0) 2 (25.0) 1 (12.5) 1 (12.5)	1 (100.0) 0 (0.0) 0 (0.0) 0 (0.0)	0.936
Time until the first GEBP. y.	0.6 (0.3; 1.4)	1.0 (0.3; 1.9)	0.857

Abbreviations: ANF - antinuclear factor. GEBP - genetically engineered biological preparation. RF - rheumatoid factor.

tis-associated JIA, 44% of children with oligoarthritis, 60% of children with systemic arthritis, 33% of children with psoriatic arthritis, 39% of children with polyarthritis, which makes it impossible to apply the ILAR classification to populations with a high frequency of the HLAB27 antigen, since the HLAB27 antigen is a criterion for excluding several subtypes of JIA, such as systemic arthritis and psoriatic arthritis. The predominance of the HLAB27 antigen among Yakut children with JIA explains the later age of onset, the high incidence of enthesitis, and a family history of arthritis from the HLA B27 group, since this antigen can be transmitted from generation to generation. In the HLAB27 antigen risks of developing ankylosing spondylitis are doubled in a case if there is a relative diagnosed with one of the HLAB27 antigen circle [21]. It is interesting to note that psoriasis and psoriatic arthritis diagnosed as "HLAB27 circle" are very rare in the population of children of the indigenous population of Yakutia, who have high frequency of this antigen. The high prevalence of enthesitis-associated arthritis explains the higher frequency of sulfasalazine use and the lower frequency of methotrexate use in children of the indigenous population of Yakutia, since methotrexate has proven itself better in for the treatment of articular forms of JIA [12]. Among the peculiarities of the use of HIBP, it should be noted that the frequency of adalimumab use in indigenous children is lower, which is associated with a lower frequency of severe uveitis associated with oligoarticular JIA, since uveitis in patients with HLAB27 is more often acute, symptomatic and does not always require aggressive HIBT [17]. The second factor limiting the use of monoclonal antibodies is a higher incidence of infection with Mycobacterium tuberculosis, which increases the risks of reactivation of latent tuberculosis infection into active one under the influence of monoclonal antibodies that bind necrosis factor-a [12,10]. The absence of severe forms of uveitis and the prevalence of infection with Mycobacterium tuberculosis make etanercept the drug of choice in indigenous children with JIA, which is associated with its safe use in children of this group, and its effectiveness has been shown in various forms of JIA [11].

Limitation of the study: the retrospective nature of the study, that caused the insufficiency of information available in the medical records was considered the main drawback of this study. The division of patients according to ethnicity was conditional, especially the group of children of Caucasian origin, who, in fact

Table2

Frequency distribution of HLAB27 in different populations and associated arthritis

Population	HLA B27 frequency (%)	HLA B27 incidence in associated arthritis (%)	link
Koryaks	39.6	38.5	[7]
Eskimos (USA)	39	25	[7]
Russians (Chelyabinsk region)	9.6	22.4	[8]
Bengalis	10.7	49.2	[15]
Chinese	2.4	36.6	[14]

referred to a multinational group. The inability to determine the HLAB27 antigen in all patients led to the fact that this antigen was detected in patients with clinical signs of enthesitis-associated arthritis, which could lead to an artificial increase in the frequency of the HLAB27 antigen among patients with JIA.

Conclusions:

1. The prevalence of JIA in children (0-17 years old) in the Republic of Sakha (Yakutia) is comparable to the all-Russian indicator and amounted to 64.3 per 100,000 population. In 14 districts and the city of Yakutsk, the prevalence of JIA is higher than the nationwide indicator.
2. For the first time in the Republic of Sakha (Yakutia), the structure of juvenile idiopathic arthritis was studied. Enthesitis-associated arthritis is the most common form of juvenile idiopathic arthritis.
3. The HLAB27 antigen associated with juvenile idiopathic arthritis is higher in indigenous children than in Caucasian children.

The work was done within the framework of the research topic of the FGBU "YSC KMP" SB RAMS, "Monitoring the health status of children in the Republic of Sakha (Yakutia)" (state registration number: 0120-128-07-98), the basic part of the state order of the Ministry of Science and Education of the Russian Federation (FSRG-2020-0016) and with the financial support of the RFBR grant (No. 18-05-60035_Arktika).

References

1. Алексеева Е.И. и др. Обзор международных регистров пациентов с системным ювенильным идиопатическим артритом. Вопрос современной педиатрии 2017;15(1):18-23 с. [Alekseeva EL et.al. Review of international registers of patients with systemic juvenile idiopathic arthritis. *Question of modern Pediatrics.* 2017; 15(1): P.18-23.]

2. Баранов А.А. Ювенильный артрит: клинические рекомендации для педиатров. Детская ревматология. Под ред. А.А.Баранова, Е.И.Алексеевой. - М.: ПедитрЪ,2013. 5-18с. [Baranov AA, Alekseeva EI. Juvenile arthritis: clinical recommendations for pediatricians. *Pediatric rheumatology*. Ed. by A.A. Baranov, E.I. Alekseeva. - M.: Peditr, 2013. P.5-18.]

3. Криволапова И.М. Пашнина И.А, Черешнев В.А. Концентрация противовоспалительных цитокинов в супернатантах культур цельной крови у детей с ювенильным идиопатическим артритом. Медицинская иммунология, 2019; 21(4): 725-736 с. doi: 10.15789/1563-0625-2019-4-725-736. [Krivolapova IM, Pashnina IA, Chereshnev VA. Concentration of anti-inflammatory cytokines in supernatants of whole blood cultures in children with juvenile idiopathic arthritis. *Medical immunology*, 2019; 21(4): P.725-736 doi: 10.15789 / 1563-0625-2019-4-725-736]

4. Ломакина О.Л. «Общероссийский регистр пациентов с системным ювенильным идиопатическим артритом» - эффективный инструмент мониторинга заболевания и медицинской помощи // диссертация. М.2016. [Lomakina OL. "All-Russian register of patients with systemic juvenile idiopathic arthritis" - an effective tool for monitoring the disease and medical care / dissertation. M. 2016].

5. Малиевский В.А. Распространённость и структура ювенильных идиопатических артритов среди детей в Республике Башкортостан. Научно-практическая ревматология 2006:56-60 с. [Malievsky VA. Prevalence and structure of juvenile idiopathic arthritis among children in the Republic of Bashkortostan. *Scientific and practical rheumatology.* 2006: 56-60 p.]

6. Севостьянов В.К., Жолобова Е.С., Мелик Гусейнов Д.В. Структура ювенильного идиопатического артрита по данным регистра детей с ревматическими заболеваниями в Москве. РМЖ «Медицинское обозрение». -2017. - №1. -С.6-10. [Sevostyanov VK, Zholobova ES, Melik-Huseynov DV. Structure of juvenile idiopathic arthritis according to the register of children with rheumatic diseases in Moscow. *RMJ "Medical review"*. -2017. - No. 1. – P.6-10.]

7. Фефелова В.В. Антиген HLAB27и спондилоартропатии у арктических монголоидов. Бюллетень СО РАМН. 2010;30(6).2010. [Fefelova VV. HLA Antigen in spondyloarthropathy In Arctic Mongoloids. *Bulletin of the Russian Academy of medical Sciences*. 2010; 30(6).2010.]

8. Шилова Т.В.,Пищальников А.Ю., Волосников Д.Н. Ювенильный идиопатический артрит у детей Челябинской области. Клинико-генетическая характеристика. Трудный пациент. -2018. – Т. 16. – С.58-62. [Shilova TV, Pishchalnikov AY, Volosnikov DN et.al. Juvenile idiopathic arthritis in children of the Chelyabinsk region. Clinical and genetic characteristics. *Difficult patient*. -2018. – Vol. 16. – P. 58-62.]

9. Barrera, MJ, Aguilera, S., Castro, I., González, S., Carvajal, P., Molina, C., Hermoso. Endoplasmic reticulum stress in autoimmune diseases: Can altered protein quality control and/or unfolded protein response contribute to autoimmunity? A critical review on Sjögren's syndrome. *Autoimmunity reviews*, 2018 17(8), 796–808. https://doi.org/10.1016/j.autrev.2018.02.009

10. Carter JD, Hudson AP. Recent advances and future directions in understanding and treating Chlamydia-induced reactive arthritis. *Expert Rev Clin Immunol*. 2017 Mar;13(3):197-206. doi:10.1080/1744666X.2017.1233816. Epub 2016 Sep 20. PMID: 27627462.

11. Duba AS, Mathew SD. The Seronegative Spondyloarthropathies. *Prim Care*. 2018 Jun;45(2):271-287. doi: 10.1016/j.pop.2018.02.005. PMID: 29759124.

12. Giancane, G., Consolaro, et.al. A. Juvenile Idiopathic Arthritis: Diagnosis and Treatment. *Rheumatol Ther*. – 2016. – Vol. 3. – № 2. – P. 187–207.

13. Liu Q, Körner, H, Wu, H., Wei W. Endoplasmic reticulum stress in autoimmune diseases. *Immunobiology*, 2020, 225(2), 151881. https://doi.org/10.1016/j.imbio.2019.11.016

14. Liu X, Li YR, Hu LH, Zhou ZM, Chen FH, Ning Y, Yao QF. High frequencies of HLA-B27 in Chinese patients with suspected of ankylosing spondylitis. *Rheumatol Int*. 2010 Aug;30(10):1305-9. doi: 10.1007/s00296-009-1148-4. Epub 2009 Sep 23. PMID: 19774380.

15. Nessa A, Tabassum S, Sultana S. HLA-B27 antigen frequency among suspected attaining a tertiary level hospital of Bangladesh. *Bangladesh Med Res Counc Bull* 2014; 40(3):102-106. https://doi.org/10.3329/bmrcb.v40i3.25231

16. Petty RE, Southwood TR, Manners P, Baum J, Glass DN, Goldenberg J, et al. International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. *J Rheumatol*. 2004;31(2):390-392.

17. Razumova IY, Godzenko AA, Guseva IA, Vorob'eva OK. Uveitis-associated HLA class 1 histocompatibility antigens. *Vestn Oftalmol*. 2017;133(5):11-15. Russian. doi: 10.17116/oftalma2017133511-15. PMID: 29165407.

18. Rehart S. Interdisziplinäre Rheumatologie [Interdisciplinary rheumatology]. *Orthopade*. 2018 Nov;47(11):889-890. German. doi: 10.1007/s00132-018-3653-1. PMID: 30421002.

19. Schaeverbeke T, Truchetet ME, Richez C. Gut metagenome and spondyloarthritis. *Joint Bone Spine*. 2013 Jul;80(4):349–52.

20. So JS. Roles of Endoplasmic Reticulum Stress in Immune Responses. *Molecules and cells*, 2018, 41(8), 705–716. https://doi.org/10.14348/molcells.2018.0241

21. Weiss PF. Diagnosis and treatment of enthesitis-related arthritis Adolesc. *Health Med. Ther*. — 2012. — Vol. 12, № 3. — P. 67-74.