About authors:

Golubeva Marina Viktorovna, MD, PhD, Professor, Head of the Department of children's infectious diseases;
tel.: (8652)264312; e-mail: mmvg@rambler.ru; <https://orcid.org/0000-0002-0225-3672>

Rakitina Elena Nikolaevna, postgraduate student;
tel.: +79187618224; e-mail: rakitina_1989@bk.ru; <https://orcid.org/0000-0003-0150-2662>

Minaev Sergey Viktorovich, MD, PhD, Professor, Head of the Department of pediatric surgery;
tel.: +79624507653; e-mail: sminaev@yandex.ru; <https://orcid.org/0000-0002-8405-6022>

Kirgizov Igor Vitalevich, MD, PhD, Professor, Professor of the Department of pediatric surgery;
tel.: +79057720953; e-mail: drkirgizov@yandex.ru; <https://orcid.org/0000-0001-5796-5266>

Obedin Alexander Nikolaevich, MD, PhD, Associate Professor, Head of the Department of anesthesiology, reanimatology and emergency medical care; tel.: +79034169771; e-mail: volander@mail.ru; <https://orcid.org/0000-0002-9990-7272>

Axelrov Mikhail Alexandrovich, MD, PhD, Professor, Head of the Department of pediatric surgery;
tel.: +79292694933; e-mail: akselrov@mail.ru; <https://orcid.org/0000-0001-6814-8894>

Barova Natusya Kaplanovna, MD, CMSc, Associate Professor of the Department of pediatric surgery;
tel.: 89882420449; e-mail: nbarova@yandex.ru; <https://orcid.org/0000-0001-5857-2296>

Bochnyuk Elena Aleksandrovna, MD, CMSc, Head of the clinical diagnostic laboratory;
tel.: +79624464533; e-mail: kdplab@mail.ru; <https://orcid.org/0000-0002-6014-0801>

© Group of authors, 2021

UDC 616.61-002.3-053.3/.5

DOI – <https://doi.org/10.14300/mnnc.2021.16033>

ISSN – 2073-8137

IMMUNOGENETIC FEATURES OF DIFFERENT FORMS OF SECONDARY PYELONEPHRITIS IN CHILDREN

Kulygina E. S.¹, Razin M. P.¹, Minaev S. V.², Ignatiev S. V.³,
Akselrov M. A.⁴, Agalakova T. B.⁴

¹ Kirov State Medical University, Russian Federation

² Stavropol State Medical University, Russian Federation

³ Kirov Research Institute of Hematology and Blood Transfusion, Russian Federation

⁴ Tyumen State Medical University, Russian Federation

ИММУНОГЕНЕТИЧЕСКИЕ ОСОБЕННОСТИ РАЗЛИЧНЫХ ФОРМ ВТОРИЧНОГО ПИЕЛОНЕФРИТА У ДЕТЕЙ

Е. С. Кулыгина¹, М. П. Разин¹, С. В. Минаев², С. В. Игнатьев³,
М. А. Аксельров⁴, Т. Б. Агалакова¹

¹ Кировский государственный медицинский университет, Российская Федерация

² Ставропольский государственный медицинский университет,
Российская Федерация

³ Кировский научно-исследовательский институт гематологии и переливания крови
федерального медико-биологического агентства, Российская Федерация

⁴ Тюменский государственный медицинский университет, Российская Федерация

In recent years, many studies have documented an increased incidence of urinary system pathology in children, especially congenital anomalies of the urinary system with secondary pyelonephritis (SP). We carried out immunogenetic typing in 200 children aged 5–15 years with SP (100 children with latent SP and 100 children with recurrent SP). The distribution of human leukocyte antigen (HLA) alleles at the A, B, C, DR, DQ loci, as well as their phenotypic and haplotype combinations, was determined. We found that the latent course of SP in children was associated with interlocus combinations of the class 1 antigens HLA-A2/B17 and HLA-A3/B13. Resistance to latent SP was associated with the alleles HLA-DRB1*07, HLA-DRB1*15 (2), and HLA-DQB1*0302, the phenotypic combinations of antigens HLA-A1/A9 and HLA-A9/A11, and the haplotype combinations HLA-A3/B7, HLA-A11/B35, and HLA-A19/B27. The recurrent course of SP in children was associated with the haplotype combination HLA-A11/B27. Resistance to recurrent SP was associated with the alleles HLA-DRB1*07, HLA-DRB1*09, and HLA-DRB1*15 (2), the intralocus antigenic combination HLA-A9/A11, and the interlocus combinations HLA-A2/B12, HLA-A3/B7, and HLA-A11/B35. In conclusions, HLA typing in children with various forms of SP enables the identification of factors predisposing to the development of this disease. These data may help clinicians understand the prognosis and disease course of various forms of SP.

Keywords: secondary pyelonephritis, immunogenetics, HLA, children

Многими авторами в последние годы отмечается рост встречаемости патологии мочевой системы у детей вообще и врожденных аномалий мочевой системы с вторичным пиелонефритом (ВП) в частности. Проведено иммуногенетическое типирование у 200 детей от 5 до 15 лет с вторичным пиелонефритом (100 – латентная форма и 100 – рецидивирующая). Исследовалось распределение в тканях антигенов HLA локусов A, B, C, DR, DQ, а также их фенотипические и гаплотипические комбинации. Для латентного течения ВП у детей характерно представительство в тканях межлокусных сочетаний антигенов 1-го класса HLA-A2, B17 и A3, B13; в качестве факторов резистентности к развитию этого вида патологии выступает представительство в тканях аллелей HLA-DRB1*07, DRB1*15(2) и DQB1*0302; фенотипических сочетаний антигенов A1, A9, A9, A11 и гаплотипических комбинаций HLA-A3, B7, A11, B35, A19, B27. Для рецидивирующего течения ВП у детей характерно представительство в тканях гаплотипической комбинации антигенов A11, B27; фактором резистентности к развитию этого вида патологии является представительство в тканях антигенов HLA-DRB1*07, DRB1*09, DRB1*15(2), внутрилокусного антигенного сочетания HLA-A9,A11 и межлокусных комбинаций HLA-A2, B12, A3, B7, A11, B35. Таким образом, полученные данные HLA-типирования у больных с различными формами ВП позволяют уточнить факторы, предрасполагающие к развитию заболевания у детей, а также определить прогноз манифестации и течения различных форм ВП.

Ключевые слова: вторичный пиелонефрит, иммуногенетика, HLA-комплекс, дети

For citation: Kulygina E. S., Razin M. P., Minaev S. V., Ignatiev S. V., Akselrov M. A., Agalakova T. B. IMMUNOGENETIC FEATURES OF DIFFERENT FORMS OF SECONDARY PYELONEPHRITIS IN CHILDREN. *Medical News of North Caucasus*. 2021;16(2):148-153. DOI – <https://doi.org/10.14300/mnnc.2021.16033>

Для цитирования: Кулыгина Е. С., Разин М. П., Минаев С. В., Игнатьев С. В., Аксельров М. А., Агалакова Т. Б. ИММУНОГЕНЕТИЧЕСКИЕ ОСОБЕННОСТИ РАЗЛИЧНЫХ ФОРМ ВТОРИЧНОГО ПИЕЛОНЕФРИТА У ДЕТЕЙ. *Медицинский вестник Северного Кавказа*. 2021;16(2):148-153. DOI – <https://doi.org/10.14300/mnnc.2021.16033>

COU – congenital obstructive uropathy
EF – etiological fraction
HLA – human leukocyte antigen
PCR – polymerase chain reaction

PF – preventive fraction
RR – relative risk
SP – secondary pyelonephritis

Comprehensive study of secondary pyelonephritis (SP) is urgently needed because of the increasing incidence of pediatric urinary system pathology in recent years [1–3]. Immediate surgical interventional to address congenital urodynamic disorders such as congenital obstructive uropathy (COU) is key to successful treatment of patients. However, subsequent treatment of SP also presents many difficulties for clinicians [4, 5]. The pathogenetic aspects of SP development and variation in the clinical manifestations of its forms (e.g., latent and recurrent) are only partially understood. Immunogenetic data are of great importance in differential diagnosis of SP and prognosis of the disease. However, the immunogenetic characteristics of SP have received limited attention from researchers [6–8].

The major goal of this study was to understand human leukocyte antigen (HLA) allele distribution as well as phenotypic and haplotype combinations in children with SP. The specific objectives were as follows: (1) to identify predisposing factors for SP development in children; (2) to determine the immunogenetic parameters characteristic of the latent and recurrent forms of SP; and (3) to identify HLA features associated with resistance to the development of SP.

Material and Methods. We studied two groups of Russian children (aged 5–15 years) who had previously been operated on for COU (hydronephrosis, vesicoureteral reflux, or obstructive megaureter). These children received a diagnosis of SP from a pediatric nephrologist. Group 1 included 100 children with latent SP. In these children, no clinical manifestations of the disease were reported for 1–5 years after surgery; inflammation was occasionally detected using either the Nechiporenko test, the Amburzhe test, the Kanatbaeva test, or the Kakovsky-Addis test. Group 2 included 100 children with recurrent SP. We studied HLA complex antigen distribution including HLA phenotype and haplotype combinations in these children.

The study was carried out in the immunohematology laboratory of Kirov Research Institute of Hematology and Blood Transfusion.

HLA-A, HLA-B, and HLA-C loci were typed using the standard two-step microlymphocytotoxicity assay with sera provided by Gisans, St. Petersburg Research Institute of Hematology and Blood Transfusion. HLA-DRB1 and HLA-DQB1 loci were typed using a polymerase chain reaction (PCR) kit (DNA-technology, Moscow, Russia). At the HLA-A locus, 15 alleles were detected; at the HLA-B locus, 28 alleles were detected; at the HLA-C locus, four alleles were detected; at the HLA-DR locus, 14 alleles were detected; and at the HLA-DQ locus, 12 alleles were detected. During the PCR procedure the following antigens in the HLA-DR locus were detected: HLA-DRB1*11 and HLA-DRB1* (serologically DR5); HLA-DRB1*13 and HLA-DRB1*14 (serologically DR6); HLA-DRB1*17 and HLA-DRB1*18 (serologically DR3); and HLA-DRB1*16 and HLA-DRB1*15 (serologically DR2). Furthermore, the HLA-DR1, HLA-DR4, HLA-DR7, HLA-DR8, HLA-DR9, and HLA-DR10 antigens were detected by PCR. The frequency of antigens was calculated as the percentage of individuals positive for the antigen divided by the total number of individuals in the group. The frequency of phenotype combinations was determined for both the HLA-A and HLA-B loci; haplotype frequencies were calculated using the Mattiuz formula. Differences in the distribution of antigens between groups were assessed using Pearson's chi-square test.

To identify associations between different forms of COU (either complicated by chronic obstructive SP with preserved renal function, or not complicated) and immunogenetic parameters (HLA antigens), we used the relative risk (RR) formula proposed by Svejgaard and Ryder [6]:

$$RR = \frac{(a + 0.5) \times (d + 0.5)}{(b + 0.5) \times (c + 0.5)},$$

where a represents the number of patients with the antigen studied, b represents the number of healthy

individuals with the antigen, c represents the number of patients without the antigen, and d represents the number of healthy individuals without the antigen.

The RR measures how often the disease develops in individuals with a specific HLA antigen in comparison with individuals without the antigen. It is generally accepted that a RR of 2.0 or greater indicates a positive association with disease (predisposition to development of the disease), while a RR less than 1.0 indicates resistance to disease. To quantitate the strength of HLA associations, we calculated the etiologic fraction (EF) and preventive fraction (PF).

The EF characterizes the strength of a positive HLA association with the disease ($RR > 2.0$):

$$EF = \frac{RR - 1}{RR} \times F,$$

where F represents the antigen frequency expressed as a decimal.

The PF characterizes the strength of a negative HLA association with the disease ($RR < 1.0$):

$$PF = \frac{(1 - RR) \times F}{RR \times (1 - F) + F},$$

where F is the antigen frequency expressed as a decimal.

The EF is expressed as a decimal quantity and depends on both RR and antigen (or allele) frequency. EF is calculated for $RR > 2.0$ and indicates the proportion of diseased individuals in the total population. Assuming equivalent RR values, the EF will be higher when the disease-associated marker is more prevalent in the population. If $RR < 1.0$, the PF is calculated. The PF indicates the proportional reduction in the number of cases among the population owing to the association of a particular HLA antigen or allele with the disease. The PF also depends on both the RR and the marker's frequency in the population.

The frequency of phenotype and haplotype combinations (intra-locus and inter-locus associations, respectively) was calculated using the formula:

$$H = pa \times pb + \Delta ab,$$

where pa and pb represent the frequencies of the corresponding alleles and Δab represents linkage disequilibrium between the alleles. Δab is calculated using the formula:

$$\Delta = \sqrt{\frac{d}{N}} - \sqrt{\frac{b+d}{N}} \times \sqrt{\frac{c+d}{N}},$$

where a represents the number of individuals with both HLA markers, b represents the number of individuals who have the first marker only, c represents the number of individuals who have the second marker only, d represents the number of individuals who lack both HLA markers, and $N = a + b + c + d$.

Statistical analysis of the results of immunogenotyping was performed using the above formulas in Excel version 10.0 (Microsoft, Seattle, WA, USA). The control group consisted of 153 healthy Russian children living in the city of Kirov and in Kirov Region.

Results and Discussion. The study did not detect any reliable associations between antigens of the HLA-C locus and predisposition or resistance to the development of SP in children. However, associations were observed between frequencies of antigens of the HLA-A, HLA-B, HLA-DRB1, HLA-DQB1 loci, as well as their phenotype and haplotype combinations, and different forms of COU (Table 1).

The latent course of SP was positively associated with the HLA-B8 antigen (19.9 % of patients compared with 10.5 % of controls; $X^2=4.3$; $p<0.05$; $RR=2.1$; $EF=0.14$) and with the inter-locus combinations of HLA class I antigens HLA-A2/B17 (5.15 % of patients compared with 0.2 % of

controls, $RR=8.49$) and HLA-A3/B13 (3.4 % of patients compared with 0.9 % of controls, $RR=3.1$) (Table 2).

Table 1

Distribution of HLA antigens and phenotype combinations in patients with latent SP

HLA antigens	Frequency				X ²	RR	EF	PF
	Controls, n=153		Patients, n=100					
	n	%	n	%				
A-11	6	3.92	11	11.0	1.568	2.08		
B-26	5	3.3	11	11.0	2.344	2.47		
B-8	16	10.46	27	27.0	4.33	2.09	0.14	
B-17	9	5.9	15	15.0	1.875	1.94		
DRB1*01	32	29.9	32	32.0	0.771	0.56		
DRB1*04	21	13.7	22	22.0	0.314	0.64		
DRB1*07	31	20.26	23	23.0	4.231	0.39		0.264
DRB1*08	3	1.9	7	7.0	0.535	1.49		
DRB1*09	2	1.3	1	1.0	1.642	0.41		
DRB1*10	2	1.3	4	4.0	0.060	1.25		
DRB1*11(5)	26	16.99	23	23.0	1.556	0.51		
DRB1*12(5)	5	3.3	7	7.0	0.000	0.91		
DRB1*13(6)	14	9.1	24	24.00	1.185	1.18		
DRB1*14(6)	2	1.9	3	3.0	0.023	0.96		
DRB1*15(2)	38	36.9	30	30.0	4.286	0.38		0.328
DRB1*16(2)	2	1.3	3	3.0	0.023	0.96		
DRB1*17(3)	15	9.8	35	35.0	5.947	1.78		
DRB1*18(3)	0	0	0	0	0.000	0.68		
DQB1*0201	30	20.9	28	28.0	0.400	1.29		
DQB1*0301	32	29.9	19	19.0	1.730	0.69		
DQB1*0302	20	13.1	8	8.0	3.970	0.47		0.08
DQB1*0303	24	15.7	13	13.0	1.969	0.64		
DQB1*0304	0	0	0	0	0.000	1.27		
DQB1*0305	1	0.65	2	2.0	0.038	2.11		
DQB1*0401-2	2	1.3	4	4.0	0.542	2.40		
DQB1*0501	32	29.9	26	26.0	0.000	1.05		
DQB1*0502-4	4	2.61	3	3.0	0.209	0.98		
DQB1*0503	1	0.65	0	0	3.602	0.41		
DQB1*0601	5	3.3	6	6.0	0.159	1.53		
DQB1*0602-8	39	25.5	29	29.0	0.199	0.92		
Phenotypic combinations								
A1, A9	6	3.92	1	1.0	4.588	0.25		
A2, A9	12	7.84	9	9.0	0.394	0.84		
A9, A11	7	4.58	1	1.0	5.500	0.22		
B7, B12	4	2.61	1	1.0	2.805	0.37		
B7, B17	2	1.3	4	4.0	0.313	2.06		
B7, B27	1	0.65	5	5.0	1.920	4.25		
B8, B12	1	0.65	5	5.0	1.920	4.25		
B8, B17	0	0	4	4.0	2.663	10.43		
B8, B27	1	0.65	3	3.0	0.388	2.67		
B8, B35	1	0.65	5	5.0	1.920	4.25		

Abbreviations: SP – secondary pyelonephritis; HLA – human leukocyte antigen; RR – relative risk; EF – etiologic fraction; PF – preventive fraction.

Table 2

Distribution of HLA haplotype combinations in patients with latent SP

Haplotype combinations	Frequency (%)		RR
	Controls, n=153	Patients, n=100	
A1, B12	16.0	2.21	0.14
A1, B27	1.9	3.68	1.77
A2, B8	13.9	11.03	0.78
A2, B17	0.2	5.15	8.49
A3, B7	84.1	8.09	0.02
A3, B13	0.9	3.68	3.07
A9, B27	4.4	3.68	0.85
A11, B12	11.7	1.47	0.14
A11, B35	29.9	2.94	0.08
A19, B12	8.4	2.21	0.29
A19, B27	13.4	1.47	0.12

Abbreviations: HLA – human leukocyte antigen; SP – secondary pyelonephritis; RR – relative risk.

We also found a significant negative association between latent SP and HLA-DRB1*07 (Tables 1 and 2) (19.17 % of patients compared with 30.1 % of controls, $X^2=4.2$; $p<0.05$; $RR=0.39$; $PF=0.26$), DRB1*15 (2) (25.0 % of patients compared with 37.0 % of controls, $X^2=4.3$; $p<0.05$; $RR=0.38$; $PF=0.33$), and DQB1*0302 (9.9 % of patients compared with 19.4 % of controls, $X^2=3.97$; $p<0.05$; $RR=0.47$; $PF=0.08$). Negative associations were also identified with the phenotypic combinations of antigens HLA-A1/A9 (0.7 % of patients compared with 3.9 % of controls, $X^2=4.6$; $p<0.05$; $RR=0.25$), HLA-A9/A11 (0.7 % of patients compared with 4.6 % of controls, $X^2=5.5$; $RR=0.22$) and the haplotype combinations HLA-A3/B7 (8.1 % of patients compared with 84.1 % of controls, $RR=0.02$), HLA-A11/B35 (2.9 % of patients compared with 29.9 % of controls, $RR=0.08$), and HLA-A19/B27 (1.5 % of patients compared with 13.4 % of controls, $RR=0.12$).

Polymorphisms of the most common HLA antigens and haplotypes in patients with the latent course of SP are shown in Figure 1.

Fig. 1. Frequencies of the most common HLA antigens and haplotypes in patients with latent secondary pyelonephritis (SP)

The clinical manifestations of SP and disease severity depend on the form of pyelonephritis. Therefore, identification of immunogenetic markers for the relapsing course of chronic obstructive SP may be useful for predicting the course of the disease. Thus, we conducted HLA typing in a group of children with chronic obstructive SP and preserved renal function. The results (Table 3) showed a significant positive association between relapsing SP and the interlocus combination of HLA-A11/B27 (0.85 % of patients versus 0.01 % of controls, $RR=2.7$).

Table 3

Distribution of HLA antigens and phenotypic combinations in patients with relapsing SP

HLA antigens	Frequency				χ ²	RR	EF	PF
	Controls, n=153		Patients, n=100					
	n	%	n	%				
A8	16	10.46	20	22.0	1.985	1.75		
DRB1*01	32	20.9	31	31.0	0.028	1.00		
DRB1*04	21	13.7	19	19.0	0.182	0.92		
DRB1*07	31	20.3	16	16.0	6.489	0.45		0.163
DRB1*08	3	1.9	6	6.0	0.536	1.98		
DRB1*09	2	1.3	0	0	4.425	0.21		0
DRB1*10	2	1.3	4	4.0	0.221	1.93		
DRB1*11(5)	26	16.99	20	20.0	1.108	0.75		
DRB1*12(5)	5	3.27	5	5.0	0.085	1.02		
DRB1*13(6)	14	9.15	22	22.0	1.912	1.77		
DRB1*14(6)	2	1.9	2	2.0	0.208	1.05		
DRB1*15(2)	38	36.9	22	22.0	6.149	0.49		0.186
DRB1*16(2)	2	1.3	2	2.0	0.208	1.05		
DRB1*17(3)	15	9.8	26	26.0	3.412	2.03		
DRB1*18(3)	0	0	0	0	-	1.03		
DQB1*0201	30	19.6	23	23.0	0.014	1.10		
DQB1*0301	32	20.9	19	19.0	0.910	0.77		
DQB1*0302	20	13.07	10	10.0	1.520	0.66		
DQB1*0303	24	15.69	11	11.0	2.500	0.59		
DQB1*0304	0	0	0	0	-	1.39		
DQB1*0305	1	0.65	1	1.0	0.249	1.37		
DQB1*0401-2	2	1.3	4	4.0	0.728	2.64		
DQB1*0501	32	20.9	27	27.0	0.346	1.27		
DQB1*0502-4	4	2.61	3	3.0	0.115	1.08		
DQB1*0503	1	0.65	0	0	3.476	0.45		
DQB1*0601	5	3.27	4	4.0	0.038	1.13		
DQB1*0602-8	39	25.49	29	29.0	0.000	1.06		
Phenotypic combinations								
A1, A9	6	3.92	1	1.0	3.833	0.29		
A2, A9	18	11.76	8	8.0	2.459	0.57		
A9, A11	7	4.58	1	1.0	4.617	0.25		
B7, B17	2	1.3	4	4.0	0.562	2.40		
B7, B27	1	0.65	4	4.0	1.475	4.03		
B8, B12	1	0.65	3	3.0	0.607	3.11		
B8, B35	1	0.65	4	4.0	1.475	4.03		

Abbreviations: HLA – human leukocyte antigen; SP – spontaneous pyelonephritis; RR – relative risk; EF – etiologic fraction; PF – preventive fraction.

The following HLA alleles associated with resistance to SP were identified (Table 3): HLA-DRB1*07 (16 % of patients versus 30.1 % of controls, $X^2=6.5$; $p<0.05$; $RR=0.45$; $PF=0.16$), DRB1*09 (0 % of patients versus 2 % of controls, $X^2=4.4$; $p<0.05$; $RR=0.21$; $PF=0$), and DRB1*15 (2) (22.0 % of patients versus 36.9 % of controls, $X^2=6.15$; $p<0.05$; $RR=0.49$; $PF=0.19$). Furthermore, the intralocus antigen combination HLA-A9/A11 (0.85 % of patients versus 7 % of controls, $X^2=4.6$; $p<0.05$; $RR=0.25$) and the haplotype combinations HLA-A2/B12 (8.6 % of patients versus 62.1 % of controls, $RR=0.06$), A3/B7 (7.7 % of patients versus 84.1 % of controls, $RR=0.02$), and A11/B35 (2.6 % of patients versus 29.9 % of controls, $RR=0.07$) were associated with resistance to SP (Table 4).

Table 4
Distribution of HLA features in patients
with relapsing SP

Haplotype combinations	Frequency (%)		RR
	Controls, n=153	Patients, n=100	
A1, B7	8.1	8.55	1.06
A1, B12	16.0	3.42	0.21
A2, B12	62.1	8.55	0.06
A3, B7	84.1	7.69	0.02
A9, B8	4.4	4.27	0.97
A9, B27	4.4	4.27	0.97
A11, B12	11.7	1.71	0.16
A11, B27	0.01	0.85	2.68
A11, B35	29.9	2.56	0.07
A19, B12	8.4	1.71	0.23
A19, B27	13.3	1.71	0.14

Abbreviations: HLA – human leukocyte antigen; SP – spontaneous pyelonephritis; RR – relative risk.

Polymorphisms of the most common HLA antigen phenotypic combinations in patients with the relapsing course of SP are shown in Figure 2.

Fig. 2. Frequency of the HLA-A11/B27 haplotype combination in healthy controls and patients with recurrent spontaneous pyelonephritis (SP)

These data provided evidence of a reliable positive association between the interlocus combination of HLA-A11/B17 antigens and recurrent SP. This haplotype combination increases the risk of the disease by 2.7-fold ($RR=2.7$). Individuals with the HLA-DRB1*07, HLA-DRB1*09, and HLA-DRB1*15 (2) alleles, the HLA-A9/A11 phenotype, and the HLA-A2/B12, HLA-A3/B7, and HLA-A11/B35 haplotype combinations showed resistance to disease. There was a positive association between latent SP and the interlocus combinations HLA-A2/B17 and HLA-A3/B13. These haplotypes increased the risk of latent SP by 8.5- and 3.1-fold, respectively ($RR=8.49$ and $RR=3.1$). Individuals with the HLA-DRB1*07, HLA-DRB1*15 (2), and HLA-DQB1*0302 antigens, the phenotypic combinations HLA-A1/A9 and HLA-A9/A11, and the haplotype combinations HLA-A3/B7, HLA-A11/B35, and HLA-A19/B27 showed resistance to disease.

To facilitate the diagnosis of different forms of SP in children, a computer program has been written and registered [9, 10]. Our HLA typing data in patients with different forms of SP can be used to clarify the predisposing factors for SP development in children, as well as for differential diagnosis of other conditions with similar signs and symptoms [11, 12]. This may help to inform prognosis and understand the clinical manifestations and severity of the disease.

Conclusions. Interlocus combinations of the class I antigens HLA-A2/B17 and HLA-A3/B13 were found in the tissues of children with latent SP. The HLA-DRB1*07, HLA-DRB1*15(2) and HLA-DQB1*0302 alleles, the phenotypic combinations A1/A9 and A9/A11, and the haplotype combinations HLA-A3/B7, HLA-A11/B35, HLA-A19/B27 may have a protective role against latent SP. The HLA-A11/B27 haplotype combination was associated with the relapsing course of SP. The HLA-DRB1*07, HLA-DRB1*09, and HLA-DRB1*15(2) antigens, the intralocus antigen combination HLA-A9/A11, and the interlocus combinations HLA-A2/B12, HLA-A3/B7, and HLA-A11/B35 may have a protective role against recurrent SP.

Disclosures: The authors declare no conflict of interest.

Acknowledgements. We thank Edanz (<https://www.edanz.com/ac>) for editing a draft of this manuscript.

References

1. Averyanova N. I., Kolomeets N. Yu., Kozlova V. V., Rudavina T. I. Study on Antimicrobial Effects of Phytotherapy in the Treatment of Children with Pyelonephritis. *Pediatricheskaya farmakologiya. – Pediatric pharmacology*. 2017;14(5):408-410. <https://doi.org/10.15690/pf.v14i5.1791>
2. Eskild-Jensen A., Frokiaer J., Djurhuus J. C., Jorgensen T. M. Reduced number of glomeruli in kidneys with neonatally induced partial ureteropelvic in pigs. *J. Urol*. 2002;167(3):1435-1439.
3. Illek Ya. Yu., Razin M. P., Zajceva G. A., Galanina A. V., Sizova O. G. Chronic pyelonephritis in childhood. Kirov, 2009.
4. Averyanova N. I., Dolotkazina E. V., Shirinkin A. V., Balueva L. G. Analysis of the frequency and nature of congenital renal failure in children according postnatal ultrasound screening. *Modern problems of science and education. – Sovremennye problemy nauki i obrazovaniya*. 2017;6:114. Available at: <http://science-education.ru/ru/article/view?id=27306> (Application: 01.07.2021).
5. Svejgaard A., Ryder L. P. HLA and disease associations: detecting the strongest association. *Tissue Antigens*. 1994;43:18-27. <https://doi.org/10.1111/j.1399-0039.1994.tb02291.x>
6. Faiz S., Zaveri M. P., Perry J. C., Schuetz T. M., Canca-revic I. Role of Antibiotic Prophylaxis in the Management of Antenatal Hydronephrosis, Vesicoureteral Reflux, and Ureterocele in Infants. *Cureus*. 2020 8;12(7):e9064. <https://doi.org/10.7759/cureus.9064>
7. Zareba P., Lorenzo A. J., Braga L. H. Risk factors for febrile urinary tract infection in infants with prenatal hydronephrosis: comprehensive single center analysis. *J. Urol*. 2014;191(5):1614-1618. <https://doi.org/10.1016/j.juro.2013.10.035>
8. Razin M. P., Kulygina E. S., Lukash Yu. V., Smirnov A. V., Mishchenko I. Yu. Evolution of views on mechanisms of development and treatment of secondary pyelonephritis in children (Review). *Vyatskij medicinskij vestnik*. 2017;3(55):78-88.
9. Razin M. P., Zajceva G. A., Illek Ya. Yu. Immunogenetics of congenital obstructive uropathies in children. *Urologiya*. 2007;2:71-76.
10. Kalfa N., Lopez M., Galifer R.-B., Veyrac C., Lopez C. Multicenter assessment of ultrasound of the spermatic cord in children with acute scrotum. *The Journal of Urology*. 2007;1(177):297-301. <https://doi.org/10.1016/j.juro.2006.08.128>
11. Razin M. P., Zaitseva G. A., Sukhikh N. K. The role of hla-polymorphism in resistance to the development of urological pathology in children of Kirov. *Medical News of North Caucasus*. 2015;10(3):228-231. <https://doi.org/10.14300/mnnc.2015.10052>
12. Honderlick P., Callen P., Gravis J., Vignon D. Uncomplicated urinary tract infections, what about fosfomycin and nitrofurantoin in 2006? (In French). *Pathol Biol*. 2006;54(8-9):462-466. <https://doi.org/10.1016/j.patbio.2006.07.016>

About authors:

Kulygina Elena Sergeevna, postgraduate student of the Department of pediatric surgery;
tel.: +79531374666; e-mail: elenakulygina1990@mail.ru; <https://orcid.org/0000-0002-8876-5360>

Razin Maxim Petrovich, MD, PhD, Professor, Head of the Department of pediatric surgery;
tel.: +79128281527; e-mail: mprazin@yandex.ru; <https://orcid.org/0000-0003-3561-3256>

Minaev Sergey Viktorovich, MD, PhD, Professor, Head of the Department of pediatric surgery;
tel.: +79624507653; e-mail: sminaev@yandex.ru; <https://orcid.org/0000-0002-8405-6022>

Ignatiev Sergey Viktorovich, PhD, Senior Researcher, Center for Hemostasis Pathology,
tel.: +79226688920; e-mail: feb74@yandex.ru; <https://orcid.org/0000-0002-8457-2967>

Akselrov Mikhail Aleksandrovich, MD, PhD, Professor, Head of the Department of pediatric surgery;
tel.: +79292694933; e-mail: akselrov@mail.ru; <https://orcid.org/0000-0001-6814-8894>

Agalakova Tatyana Borisovna, PhD, Associate Professor, Head of the Department of foreign languages;
tel.: +79123650696; e-mail: tbalakova@yandex.ru; <https://orcid.org/0000-0002-5452-098X>

© Group of authors, 2021

UDC 612.216-112:615.37(470.063)

DOI – <https://doi.org/10.14300/mnnc.2021.16034>

ISSN – 2073-8137

CONGENITAL DEFECTS IN THE IMMUNE SYSTEM IN THE STAVROPOL REGION

Barycheva L. Yu., Khachirova L. S., Golubeva M. V., Kubanova L. T.

Stavropol State Medical University, Russian Federation

ВРОЖДЕННЫЕ ДЕФЕКТЫ ИММУННОЙ СИСТЕМЫ В СТАВРОПОЛЬСКОМ КРАЕ

Л. Ю. Барычева, Л. С. Хачирова, М. В. Голубева, Л. Т. Кубанова

Ставропольский государственный медицинский университет,
Российская Федерация

The study analyzed 88 patients with congenital immunodeficiencies registered in the Stavropol Region (SR) during a 10-year period (2009–2019). The results established that the prevalence of primary immunodeficiencies (PID) in the SR was 3.1 per 100,000 population. Children affected by PID predominated (74.7 %) in the cohort of living patients. Twenty-seven nosological forms of PID were verified in the SR register. The most common was defective humoral component of the immune system (44.3 %), followed by combined immune disorders with syndromic manifestations (15.9 %) and phagocytosis defects (10.2 %). The molecular genetic diagnosis was confirmed in 38.6 % of patients. Hematopoietic cell transplantation was performed in 11.4 % of patients. Intravenous immunoglobulin medications were administered in 20.2 % of patients. Mortality in the PID cohort within the SR register was 6.9 %.

Keywords: primary immunodeficiencies, register, epidemiological characteristics, therapy

В исследовании осуществлен анализ врожденных дефектов системы иммунитета, выявленных в регионе Ставропольского края (СК) в течение 10 лет (2009–2019). Установлено, что распространенность первичных иммунодефицитов (ПИД) в СК составляет 3,1 на 100 000 населения. В когорте живых пациентов преобладают дети (74,7 %). Наиболее распространенными являются дефекты антителообразования (44,3 %), синдромальные комбинированные иммунодефициты (15,9 %), дефекты фагоцитирующих клеток (10,2 %). В 38,6 % случаев диагноз подтвержден молекулярно-генетическими методами. Иммунореконструкция выполнена у 11,4 % детей. Внутривенные препараты иммуноглобулина вводили 20,2 % пациентов. Смертность ПИД составила 6,9 %.

Ключевые слова: первичные иммунодефициты, регистр, эпидемиологическая характеристика, терапия

For citation: Barycheva L. Yu., Khachirova L. S., Golubeva M. V., Kubanova L. T. CONGENITAL DEFECTS IN THE IMMUNE SYSTEM IN THE STAVROPOL REGION. *Medical News of North Caucasus*. 2021;16(2):153-158.
DOI – <https://doi.org/10.14300/mnnc.2021.16034>

Для цитирования: Барычева Л. Ю., Хачирова Л. С., Голубева М. В., Кубанова Л. Т. ВРОЖДЕННЫЕ ДЕФЕКТЫ ИММУННОЙ СИСТЕМЫ В СТАВРОПОЛЬСКОМ КРАЕ. *Медицинский вестник Северного Кавказа*. 2021;16(2):153-158.
DOI – <https://doi.org/10.14300/mnnc.2021.16034>