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CLINICAL AND EPIDEMIOLOGICAL CHARACTERISTICS OF SYSTEMIC LUPUS ERYTHEMATOSUS IN THE REPUBLIC OF SAKHA (YAKUTIA)

A retrospective epidemiological study based on the data of the republican register of systemic lupus erythematosus of the Department of Cardio-Rheumatology of the Pediatric Center RH No.1 – M.E. Nikolaev National Centre of Medicine is presented in the article. The peculiarities of the clinical course and therapy of the disease were analyzed taking into account the ethnicity of the patients. It was found out that the incidence of SLE **is higher among the residents of the Republic of Sakha (Yakutia) compared to the neighboring regions of the Russian Federation.**

Keywords: systemic lupus erythematosus, children, Sakha, Russian, Yakutia.

Introduction. Juvenile systemic lupus erythematosus is one of the most common systemic connective tissue diseases in children with multisystem involvement, serious prognosis, and unpredicTable course [26,8,3]. The severity of the course of SLE in children and adolescents is due to a higher incidence of kidney, CNS, and blood system damage, as well as more severe damage to these organs and systems [22].

The literature data demonstrate a wide variability in the prevalence of systemic lupus erythematosus in children. The prevalence of SLE in children and adolescents is thought to vary according to ethnicity and age [18]. The true prevalence of this disease can be judged only by the results of epidemiologic studies [1,7,2]. According to foreign contemporary sources, the incidence of JUSLE is 0.3-0.9/100,000 children per year [18,28]. The prevalence of JUSLE in children from 1 to 9 years of age ranges from 1.0-6.2, and in 10-19 years of age - from 4.4 to 31.1 cases per 100,000 children [15,16]. The peak of the disease occurs at the age of 10-13 years [6,18]. At the same time, patients with a very early disease debut (up to 5 years of age) usually have an atypical disease pattern (e.g., absence of autoantibodies), a more severe course, and a poor prognosis [16].

The diagnosis of systemic lupus erythematosus is made on the basis of clinical and laboratory findings. There are several classification criteria: ACR 1977, SLICC 2012, EULAR 2019. According to the Russian clinical guidelines for the management of patients with SLE, the diagnosis can be esTableished using the criteria of ACR 1977, SLICC 2012.

The European Alliance of Associations for Rheumatology 2019 criteria are the most relevant in the world literature, but they are not currently included in clinical guidelines for the management of patients with SLE. Therefore, they can be used as confirmatory criteria, but they cannot be used as the sole criteria for diagnosis. These criteria include an entry criterion - the presence of a positive antinuclear factor (ANF) titer on HER-2 cells greater than 1:80 [8]. EsTableishing the diagnosis of SLE requires the presence of at least one clinical criterion and ≥10 points (if the inclusion criteria are met). The criteria are summarized in Table 1.

The main goals of SLE therapy are to minimize damage to involved organs and systems, prevent exacerbations during remission, and improve patients' health-related quality of life [26,13].

Current standards for the management of SLE include combinations of GCS, disease-modifying antirheumatic cytostatic (DMARD) and antimalarial drugs; however, the place of biological therapy has not yet been defined. According to current recommendations, the starting therapy for SLE includes the use of antimalarials at any disease activity [6,8]. The use of systemic glucocorticosteroids can alleviate the course of the disease; it is recommended as pulse therapy with subsequent transition to oral administration in highly active disease course [8]. Prolonged use of GCS has serious consequences, therefore, minimizing their use is required. However, no uniform regimens and rates of reduction until their withdrawal have been developed so far, with the exception of lupus nephritis [26,24,20].

Among the cytostatic drugs used in the therapy of SLE the following are considered: mycophenolate mofetil/mycophenolic acid, azathiprine, methotrexate, cyclosporine and cyclophosphamide.

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Table 1

EULAR 2019 classification criteria for SLE [8]

Clinical criteria	Points
Constitutional criteria:	
- fever (> 38.3° C)	2
Hematological criteria:	
- leukopenia (< 4000/μl)	3
- thrombocytopenia (< 100,000/μl)	4
- autoimmune hemolysis Evidence of autoimmune hemolysis (presence of reticulocytosis, low haptoglobin, increased indirect bilirubin, increased LDH) and a positive direct Coombs test should be presented	4
Psychoneurological criteria:	
- delirium Characteristic features: 1) change in consciousness or level of excitability with a decrease in the ability to focus, 2) development of symptoms from several hours to 2 days, 3) changes in the severity of symptoms during the day, 4a) acute/subacute change in cognitive functions (for example, memory loss or confusion) or 4b) changes in behavior, mood or affect (eg, anxiety, sleep/wake cycle reversal)	2
- psychosis Characteristic features: 1) illusions and/or hallucinations 2) absence of delirium	3
- convulsions (generalized or partial)	5
Damage to skin and mucous membranes:	
- scarless alopecia	2
- oral ulcers	2
- subacute cutaneous lupus erythematosus (SCLE) or discoid lupus erythematosus (DLE)	4
- acute cutaneous form of SLE	6
Damage to the serous membranes:	
- pleural effusion or pericardial effusion (as determined by radiography, CT or MRI)	5
- acute pericarditis Two or more signs must be presented: 1) pericardial pain in the chest (usually acute, worsening with inspiration, decreasing with bending forward), 2) pericardial friction noise, 3) ECG with new widespread ST elevation or PR depression, 4) new or worsened pericardial effusion according to ultrasound, x-ray, CT, MRI	6
Musculoskeletal manifestations:	
- joint damage: 1 Synovitis involving ≥ 2 joints, characterized by swelling or effusion or 2 Tenderness in two or more joints and at least 30 minutes of morning stiffness	6
Kidney disorders:	
- proteinuria (> 0.5 g/24 hours)	4
- lupus nephritis according to kidney biopsy (class II or V according to ISN/RPS 2003)	8
- lupus nephritis according to kidney biopsy (class III or IV according to ISN/RPS 2003)	10
Immunological criteria	Points
Antiphospholipid antibodies:	
- antibodies to cardiolipin (IgA, IgG or IgM) in medium or high titer - or antibodies to β2-glycoprotein I (IgA, IgG or IgM) - or lupus anticoagulant	2
Complement system proteins:	
- low C3 level or low C4 level	3
- low level of C3 and low level of C4	4
SLE-specific antibodies	
- AT to Sm antigen - AT to dsDNA	6

Initiation of therapy with disease-modifying antirheumatic drugs (DMARDs) is recommended to initiate disease remission and thus shorten the duration of GCS. These drugs are considered as first-line therapy for the treatment of SLE with moderate to active disease [6,8]. In turn, treatment with cytostatic drugs may be accompanied by such adverse events as damage to the blood system, liver and kidneys, as well as an increased risk of infertility and cancer [8,22]. In connection with the above, it is necessary to change the therapy regimen. The use of biologic drugs allows to achieve remission faster and minimize side effects of cytostatic therapy [12]. Several biologic agents have been approved for the treatment of SLE: belimumab, which is approved for use in adults and children; anifrolumab, which is approved in adult practice; and rituximab, which has not yet been officially approved despite its known clinical efficacy [10,17]. Rituximab, a chimeric antibody against CD20; currently has conflicting about its efficacy. On the one hand, in the largest RCTs, the efficacy of rituximab was not different from that of standard therapy [14]. On the other hand, many non-randomized studies, including domestic studies, have shown its efficacy [26,21,9,4,5].

In recent years, the rapid development of rheumatology has made it possible to achieve persistent remission in children with systemic lupus erythematosus using biological therapy [11].

The Republic of Sakha (Yakutia) having a centralized system of rheumatological care for children can be a region for conducting in-depth epidemiological studies based on registers and monitoring of rheumatic diseases. The article presents the data of the regional register of systemic lupus erythematosus in children of the Republic of Sakha (Yakutia) according to the data of the cardio-rheumatology department of the Pediatric Center of the State Budgetary Institution of the Republic of Sakha (Yakutia) "RH № 1-NCoM named after M.E. Nikolaev". The description of clinical and epidemiological characteristics of this disease will allow to improve the routing of these patients and to choose the most effective treatment.

Materials and Methods. In order to describe the clinical and epidemiological characteristics of systemic lupus erythematosus in the Republic of Sakha (Yakutia), we analyzed the data of the regional register according to the data of the Cardio-Rheumatology Department of the Pediatric Center of the State Budgetary Institution of the Republic of Sakha (Yakutia) "RH № 1-NCoM named after M.E. Nikolaev" as the head institution of the diagnostics of the disease. A total of 21 children diagnosed with systemic lupus erythematosus were registered.

Results. By the end of 2023, according to the data of V.M. Argunova, Chief External Rheumatologist of the Far Eastern Federal District, the largest number of children with systemic lupus erythematosus in the regions of the Far Eastern Federal District was registered in the Republic of Sakha (Yakutia) - 21 children, in Primorsky Krai - 4, in the Republic of Buryatia - 3, in Amur Oblast - 1, in Khabarovsk Krai - 1.

The prevalence of systemic lupus erythematosus in the regions of the Far Eastern Federal District is presented in Table 1. As shown in Table 2, the highest prevalence of SLE is registered in the Republic of Sakha (Yakutia) (7.88 cases per 100,000 children), Primorsky Krai (1.23), Republic of Buryatia (1.15), Amur Oblast (0.63), Khabarovsk Krai (0.39).

In the Republic of Sakha (Yakutia) on the basis of the cardio-rheumatology department of the Pediatric Center of the State Autonomous Institution of the Republic of Sakha (Yakutia) " RH № 1-NCM named after M.E. Nikolaev" a register of patients with systemic lupus erythematosus is being formed.

Distribution of children with systemic lupus erythematosus:

Yakutsk - 8 children;

rural area: Ust-Aldan District - 2, Megino-Kangalassky District - 1, Namsky District - 1, Suntarsky District - 1, Nyurbinsky District - 1, Verkhnevilyuysky District - 1;

industrial zone: Mirninsky - 2, Aldansky - 1, Lensky - 1,

mixed zone: Khangalassky - 1;

Arctic zone: Anabarsky - 1.

Most patients live in the central part of the Republic of Sakha (Yakutia), including the city of Yakutsk - 8 (38%), rural zone - 7 (33%), industrial zone - 4 (19%), mixed zone -1 (4.7%), Arctic zone - 1(4.7%).

According to the register - 12 (57.1%) children are Sakha, 9 (42.9%) are Russian.

The most frequent cases are girls - 16 out of 21 children (76.2%), 5 of them are boys (23.8%), which corresponds to the published data [2,7]. At the same time, the number of male patients in the group of Sakha children is higher compared to Russian children and makes up 1/3 of patients.

The most frequent clinical manifestations of the disease in the general group were skin lesions (100%), alopecia (33.3%), mucous membrane lesions (42.8%), joints (76.2%), nervous system (23.8%), hematologic and immunologic disorders (71.4 and 100%, respectively). Lupus nephritis was detected in 4 (19%) patients. Severe serositis was rare - 19%.

Treatment of children with systemic lupus erythematosus was carried out strictly according to clinical recommendations. 90.4% of patients were prescribed glucocorticoids, in 28.5% of patients pulse therapy with methylprednisolone was carried out in the debut. Hydroxychloroquine was given to 95% of children, mycophenolic acid to 52.3%. Genetically Engineered Biological Drugs were administered to eleven patients: nine children received rituximab and two received belimumab.

Rituximab was prescribed in cases of aggressive and highly active course of SLE with kidney, central nervous system or blood system damage in the presence of resistance to standard therapy, as well as in cases of glucocorticosteroid toxic-

Table 2

Prevalence of systemic lupus erythematosus in the FEFD regions

Republic of Sakha (Yakutia)	Absolute number	Child population according to census data, 2020	Prevalence 100,000 child population
Primorsky Region	21	266 293	7.88
Republic of Buryatia	4	323 962	1.23
Amur Province	3	260 067	1.15
Khabarovsk Region	1	157 007	0.63
Хабаровский край	1	250 201	0.39

Table 3

Clinical and epidemiologic characteristics of children with systemic lupus erythematosus in the Republic of Sakha (Yakutia)

	Sakha, n (%)	Russian, n (%)	Total, n (%)
Total	12	9	21
Boys	4 (33)	1 (11)	5 (23)
Girls	8 (66)	8 (88)	16 (76)
City	5 (41)	6 (66)	11 (52)
Rural	7 (58)	3 (33)	10 (47)
Clinical characteristics			
Skin lesions including alopecia	12 (100)	9 (100)	21 (100)
Mucous membrane lesions	3 (25)	6 (66)	11 (52)
Joint lesions	9 (75)	7 (77)	16 (76)
Nervous system lesions	3 (25)	2 (22)	5 (23)
Hematologic disorders	9 (75)	6 (66)	15 (71)
Immunologic disorders	12 (100)	9 (100)	21(100)
Kidney lesions	4 (33)	1 (11)	5 (23)
Pleurisy	2 (16)	2 (22)	4 (19)
Treatment			
Glucocorticosteroids	12 (100)	7 (77)	19 (90)
Pulse therapy with methylprednisolone	3 (25)	3 (33)	6 (28)
Hydroxychloroquine	11 (91)	8 (88)	19 (90)
Mycophenolic acid	8 (66)	3 (33)	11 (52)
Rituximab	7 (58)	2 (22)	9 (42)
Belimumab	0 (0)	2 (22)	2 (9)

ity and inability to withdraw GCS on the background of standard therapy.

Characteristics of children in the general group and subgroups of Russian and Sakha children are presented in Table 3.

Discussion. Systemic lupus erythematosus is one of the most severe diseases and unpredicTable connective tissue diseases in childhood. One of its main features is the possibility of affecting any organs and systems.

In this study, all children had skin lesions, more than ¾ of the observed patients had arthritis manifestations, which coincides with the data of other studies [4,23].

CNS involvement was noted in 23% of patients, which coincides with the data of a foreign study [23]. However, this figure is significantly lower than the data of Russian studies, in which CNS involvement was noted in more than 50% of patients [4,5]. The frequency of lupus nephritis in our group of patients was also 23%, which is significantly lower compared to the frequency of renal damage in SLE in other studies [4,5,21,23,29]. Separately, we would like to note that kidney lesions were more frequent in Saha children, while the frequency of central nervous system lesions was the same in the two groups. Hematologic disorders were slightly more frequent in Sakha children.

Laboratory changes, namely immunologic activity were noted in 100% of cases. The above clinical data have been reported by other authors [11,23].

Regarding epidemiologic data, in our cohort of patients, girls suffer 3 times more often from the disease compared to boys, which correlates with the data of modern studies [25,19]. The prevalence of SCD in the Sakha Republic correlates with the data of world studies [15,16].

Therapy with systemic glucocorticosteroids was received by 90.4% of patients, which corresponds to the tactics of patient management according to the data of modern domestic and foreign clinical recommendations. Pulse therapy with methylprednisolone was received by 28%, which is significantly lower compared to domestic studies [4]. Also, hydroxychloroquine was prescribed as a baseline therapy in our cohort of patients in almost all patients; mycophenolic acid preparations were received by more than 50%. Genetically engineered biologic therapy was received by 11 of 21 patients, among whom 9 were treated with rituximab, which is used only as an off-label agent according to current guidelines [27].

In the Sakha subgroup, all children received hormonal therapy, while only 3/4 of the Russian patients received it. Also in the subgroup of Sakha children, the proportion of children receiving mycophenolic acid and rituximab is higher, which allows us to indirectly judge about a more severe course of the disease in this subgroup.

Conclusion. Systemic lupus erythematosus is one of the most important diseases of childhood. The prevalence of this disease in the pediatric population of the Sakha Republic is higher than in neighboring regions, but correlates with the results of studies in Asian populations. According to the register data, the majority of patients live in the central part of the republic, including Yakutsk, while the smallest number of patients live in Khangalassky (mixed zone) and Anabarsky districts (Arctic zone). The most frequent clinical manifestations are skin, joints and mucous membranes. Affection of vital organs: CNS, kidney llesions are noted in 1/4 of patients. Patients from the Republic of Sakha (Yakutia) received genetically engineered biological therapy more often. Further epidemiologic studies are needed to compare the results of juvenile SLE with epidemiologic data in adult patients of the Republic of Sakha (Yakutia) with systemic lupus erythematosus.

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