Systemic lupus erythematosus in children

Pakhitkanym Kabdukaevna Ishuova[1], Raihan Sadykpekovna Maytbasova[1], Lyudmila Viktorovna Lim[1], Aida Zhaksybaevna Ahenbekova[1], Lidiya Kikbaeyvna Khituova[2], Zhanar Zhenisovna Nurgaliyeva[2]

[1]Scientific Center of Pediatrics and Children's Surgery, Al-Farabi Street, 146, Almaty, 050040, The Republic of Kazakhstan
[2]S.D. Asfendiyarov Kazakh National Medical University, Tole-Bi Street, 88, Almaty, 050000, The Republic of Kazakhstan

Abstract. The study involved an analysis of medical records and the SLE database of an inception cohort of 153 patients with SLE (female to male ratio, 2,3:1). Children of Kazakh nationality 120 (78,4%), Russian - 33(21,6%). The most common clinical manifestations were arthritis (77,4%), malar rash (53%), cardiac (84,3%), nephritis (51%), and cerebrovasculitis (37,3%). In children due to the persistent viral infection comes to pathological changes in the immune system that bring to the manifestation of SLE ($p< 0,001$).
[Ishuova P.K., Maytbasova R.S., Lim L.V., Ahenbekova A.Z., Khituova L.K., Nurgaliyeva Z.Z. **Systemic lupus erythematosus in children.** *Life Sci J* 2014;11(12s):456-460] (ISSN:1097-8135). http://www.lifesciencesite.com. 98

Keywords: Systemic lupus erythematosus, children, clinical features, virus positive SLE

1.Introduction

Systemic lupus erythematosus (SLE) – severe autoimmune pathology with a negative outcome, which is based on systemic inflammation of the connective tissue structure. In children, systemic lupus erythematosus occurs even severe than in adults, and characterized by rapid progress of the pathological process that is likely due to genetic determinism and immature of the immune system [1,2, 3]. In recent years there has been an increased incidence of SLE in childhood, but this diagnosis requires a complex and expensive treatment and rehabilitation [2,3].

The epidemiology of systemic lupus erythematosus is an average of 40-50 (4 to 250) cases per 100,000 population per year [4,5]. Most often manifestation of SLE we could see among girls, young women and representatives of the yellow and the black race. About 20% of patients shows first symptoms at the age of 16 years. According to J.A. Mills (1994), the incidence of SLE in children under 15 years is 1 in 100 000 per year. Ratio of girls to boys among patients is 8:1, 9:1 [5,6,7].

Etiology and pathogenesis of SLE still remains unknown. In recent years persisting virus was determinate as an etiological provocative factor of the disease and there was found some similarities between the immune abnormalities in SLE and AIDS [7,8, 9]. However, it is an accepted fact that the genetic, endocrine, and environmental factors ambient play an important role in pathogenesis of SLE. In this multidirectional immunological disorders and different types of inflammation did not conclusively reveal[10,11].

Research devoted to the study of systemic lupus erythematosus in children are rare; they were conducted primarily in adults. Therefore, in the children's rheumatology still remain undifferentiated features of the initial period of the disease, clinical variants, age and ethnic differences, the course and outcomes[12,13, 14]. The research objective is the study the clinical and laboratory features of systemic lupus erythematosus in pathogenesis of the disease in children.

2. Data and methods of research

The basis of this work amounted to survey results and data archival materials of 153 SLE patients observed in the clinic of the Scientific Center of Pediatrics and Pediatric Surgery of Republic of Kazakhstan since 2007 till 2012 survey of patients conducted from 2005 to 2012. Most of the children surveyed in the dynamics. The observation continued from 2 to 97 months, the multiple of admission to hospital - from 1 to 8 times (usually 2 - 4).All SLE patients corresponded to the diagnostic criteria of the American Rheumatology Association for SLE revision in 1997. For the diagnosis of antiphospholipid syndrome (APS) was used criteria of Nasonova E.L (1999) and Alarcon-Segovia et al. (1992); modification Plette J.C. (1996) [2, 3].

Distribution of patients was according to the classification of V.A.Nasonova (1967), and activity scales SLEDAI–1 (Systemic Lupus Erythematosus Disease Activity Index) and ECLAM (European Consensus Lupus Activity Measurement).

3. Results

Demographic data

We observed 153 patients with SLE in age from 3 to 15 years (mean age 10,8±5,9 years) of age and older, including 120 children Kazakh nationality (78,4%), Russian - 33(21,6%). Of them - 132 girls

(86,3%), including - 103 - Kazakh nationality (85,8%) and 29 - Russian (87,9%); 22 boys (14,3%), including - Kazakhs 17 (14,2%), Russian - 4 (12,1%).Was distributed as follows: 29,4% of children were under the age of 7 years, 36,6% - over 7 years and 52,3% - over 12 years. We examined 107 girls and 46 boys (ratio, 2,3:1) (Table 1).

Table 1. Age and gender characteristics of the observed children with SLE

Number of patients	Sex		Age in years			
	female	male	3 – 7	8 - 11	12 - 15	older 15
Kazakhs:	103	17	9	38	67	6
120–78,4%	85,8%	14,2%	7,5%	31,7%	58,3%	5%
Russian:	29	4	4	10	17	2
33–21,6%	87,9%	12,1%	12,1%	30,3%	51,5%	6,1%
Total:	132	21	13	48	84	8
153–100%	86,3%	13,7%	8,5%	31,4%	54,9%	5,2%

Clinical characteristics

The clinical picture of the disease characterized by variation syndroms. The most common manifestations are presented in table2.

Table 2. Clinical characteristics of patients with systemic lupus erythematosus (*n*=153)

Sign	Graduationfeature	Abs.	%
Skin and mucous syndrome	exudative erythema, including: type "butterfly"	77	50,3
	type "neck"	15	19,5
	rash, including:	128	83,7
	maculopapular	68	44,4
	ulcerativehaemorrhagic	65	42,5
	kapillyarity	82	53,6
	cheilitis	89	58,5
	stomatitis, gingivitis	75	49,1
	stomatitis, gingivitis	48	31,4
	hairloss, alopecia	37	24,2
Articular syndrome	arthralgia	123	80,4
	arthritis, including:	119	77,4
Muscle syndrome		48	31,4
Weight loss of 3.0 kg or more		139	90,8
Fever		135	88,2
Pleural pulmonary syndrome		47	30,7
Cardiac syndrome		129	84,3
Neurotic syndrome		57	37,3
Raynaud's syndrome		6	3,9
Polyserositis		72	47,1
Nephritic syndrome		78	51,0
Hepato-splenic syndrome		69	45,1
Antiphospholipid syndrome		40	26,1
The defeat of the blood system, immune and coagulate data	Anemia (Hb 40 -108 г/л)	133	86,9
	Leukopenia(1,8 – 3,9)	75	49,0
	Leukemoid reaction (neutrophil L-type 25 - 39 x 109 / l)	9	5,9
	Thrombocytopenia	31	20,3
	ANF	92	60,1
	Antibodies to n. DNA	78	51,0
	Antibodies to cardiolipin	21	52,5
	Lupus anticoagulant	17	45,5
	Low C3,C4	75	49,0
	Circulating immune complexes	119	77,4

Among the most typical cutaneous manifestations of erythema were in the form of "butterfly" (50,3%). There was a high frequency thumb capillaritis (53,6%), ulcerative necrotic lesions of the skin and mucous membranes (42,5%).

As already mentioned, a significant portion of patients with the disease had a kidney involvement (51,0%). In 27 children (17,6%) had signs of active lupus nephritis, of whom eight patients had development of nephrotic syndrome. In the remaining patients was detected only in the form of signs of renal proteinuria, microhematuria and other urine lesions.

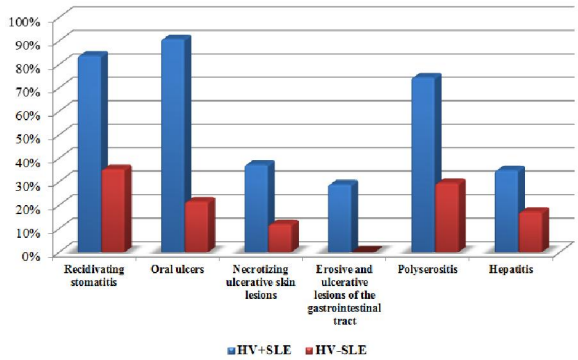
The main manifestations were arthritis syndrome (77,4%) and polyarthralgia (80,4%). Quite often, was the development serositis (47,1%). And, pericardial effusion (62,5%), less often - pleural effusion (31,9%). Adhesive pleuritis and pericarditis were detected in a few cases (5,4%). Frequent manifestation of the children had pneumonitis (30,7%). CNS lesions observed in 31,1% of cases. The most common were psychoorganic syndrome (26,3%) and neurotic disorders (22,8%), which is manifested by increased excitability, irritability, emotional lability, sleep disorders. Rarely recorded migrene - type headache (21,0%), convulsions (17,5%) and depression (12,3%).Based on clinical and laboratory criteria of APS was diagnosed in 26,1% of children with SLE. Clinical manifestations of APS in children have varying degrees of severity venous thrombosis (palmar and plantar erythema, superficial skin necrosis, skin ulcers), and moderate thrombocytopenia.

Among the most frequent hematological disorders was anemia (86,9%), lymphopenia (56,8%), which were detected in patients with leukopenia, and under the normal leukocytes. Rarely detected leukopenia (49,5%) and thrombocytopenia (20,3%) . More than half of the patients had accelerated erythrocyte sedimentation rate of more than 40 mm / hour.The majority of patients (60,8%) were positive for antinuclear factor. In 51% of cases found to have elevated antibody titer to n.DNK (taking into account its increase by 25% or more of the norm). Lupus anticoagulant in 40 children with APS was positive in 45,5% of children, and antibodies to cardiolipin in 52,5% of cases. A significant number of patients showed increased levels of circulating immune complexes (77,4%).

The main provocate factor of disease and infection were hyperinsolation (42,6% and 28,7 %). Our results confirm the high frequency (78%) carriers of herpes virus infection (HSV type I and II, CMV and EBV) in SLE. Among the markers of viral hepatitis were more prevalent anti-HBs antibodies (33,3%).

Clinical manifestations of SLE is almost certain frequently detected in children with infectious form of the disease ($p<0,05 – 0,001$). Thus, almost all children detected erythema type "butterfly » (93,0±2,3%, 82,4±2,4% , respectively , $p> 0,1$). Recurrent stomatitis significantly more registered in HV(+) group as compared with the HV(-) group (83,7±2,0% and 35,3±2,4% , respectively). Manifestations cheilitis and gingivitis were more

common in the first group (95,3±2,4 vs. 90,3±2,4%, p>0,1). Further, by analyzing particular clinical lesions should be noted that the ulcer necrotic skin lesions (37,2±1,5% and 11,8±2,0% respectively) polyserositis (74,4±2,5% and 29,4±3,0%, respectively) , liver (69,8±2,5% and 47,1±1%, respectively) , errosive and ulcerative changes in the gastrointestinal tract (48,8±1,9% and 0±1,0 %, respectively) were significantly more detected in virus positive SLE (p<0,001). Other organ damage (carditis, polyarthritis, cerebrovascular) although with less certainty, but also more frequently observed in the test group (p<0,05) (Picture 1).



Picture1. Some features of organ damage in SLE HV + children

Must be noted that all patients with mixed infection (HSV, CMV, HBV) were characterized by the most pronounced disorders of many organ: recurrent stomatitis, abdominal swelling, ulcer – necrotic lesions of the skin and mucous membranes, ulcerative hemorrhagic shock syndrome, diffuse liver disease, convulsions, kidney disease with proteinuria> 3 g/l, etc.

Study of cellular and humoral immunity, depending on the HV- infection using monoclonal antibodies revealed the following. We examined children with both HV (+), and with HV (-) the genesis of the disease was found to decrease the overall level of performance of T-lymphocytes (CD3 +) and T-helper cells (CD4 +) (15,6±1,46 and 22,4±1,1; 20,7±1,0 and 29,8±1,0 as compared to 35,0±2,4 norm and 47,1±1,7, p<0,001). And virus positive pathology characterized by significantly lower numbers of the above indicators. Well above normal in the two groups identified by the T-suppressor (CD8+) (38,4±1,6 and 30,4±1,4, p> 0,1). Differences were also found with regard to T killer cells (CD16 + 56). Found a decrease in this indicator at virus positive pathology compared with virus negative SLE (5,1±0,9 and 6,8±0,7 against the norm 9,1±1,1, p<0,01 and p> 0,05).

Study of humoral immune system in children with SLE depending on HV- infection revealed the following. There was a significant difference in relation to the B- lymphocytes (SD19+) compared with the control group (p <0,001), while groups with HV (+) and HV- CFC indicators did not differ (or 26,4±1,6 and 25,1±1,2, p>0,1).

However, indicators of functional activity of B-lymphocytes in the two groups differed. Thus, the concentration of serum immunoglobulins was broken in most patients, which was reflected in lower levels of Ig A and increase immunoglobulin G and IgM. These changes were more pronounced in a HV (+) - group and at least HV- CFC (1,6±0,2 and 1,0±0,2, vs. Control 0,8±0,2, p<0,05).

Decrease in the phagocytic activity of neutrophils detected in all the examined children was most pronounced in patients with HV (+) SLE. This figure was three times less than the standard value (respectively 21,1±1,3% and 60±0,31%, p<0,001), and more than twice less than in children with HV (-) (21,1±1,3% and 45,0±2,8%, p<0,001).

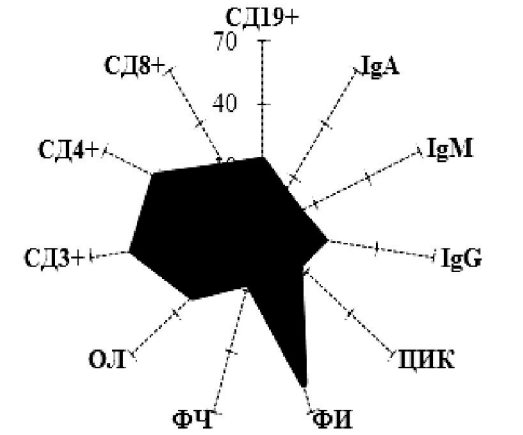
In general it can be noted that in children with SLE had significant (P<0,05 – 0,001) difference in the content of the investigated subpopulations of peripheral blood lymphocytes as compared with the comparison group, the content of subpopulations of CD19 + (B cells), CD8+ (T cytotoxic lymphocytes), CD3+HLA-DR + (activated T-lymphocytes) and CD16+56+(natural killer) cells was higher, and the content of CD3 + (T-lymphocytes) and CD4 + (T-helper) - was lower. Also noted a decrease in the index immunoregulatory study groups.

Reduced and increased rates of T-and B - lymphocytes and phagocytic cells was observed in patients with SLE without the expressed pronounced comorbidities, and the lowest rates were studied in patients with SLE HV + in conjunction with chronic infection and disease (GI and HVG) (Picture 2).

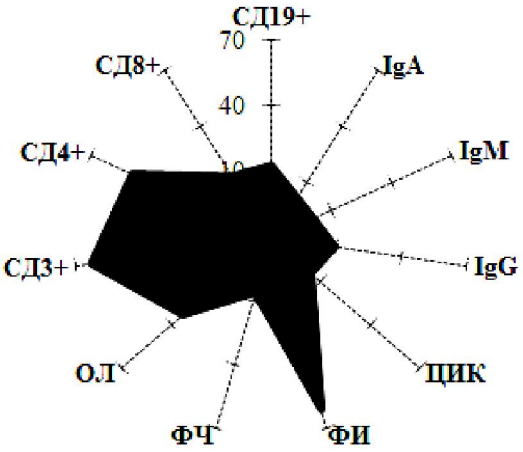
Duration of disease severity determined bacterial sensitiveness, education and the concentration of the CEC, as well as contribute to further deflection of immunological parameters.

4. Discussion

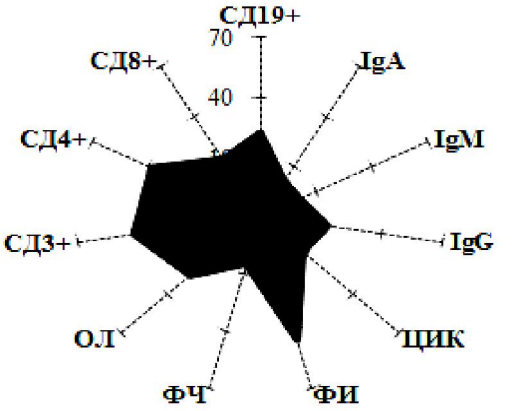
Despite significant advances in diagnosis and therapy for SLE, in many cases, the disease is progressive, often catastrophic, and for poor prognosis [1–5]. According to the concept of viral genetic occurrence of SLE may be associated with chronic viral infection transmitted vertically, and a complex of genetically determined constitutional features that are "implemented" in the disease under the influence of triggering factors [3, 6, 9, 12]. SLE infection rate ranges from 27 to 55% [7,8].



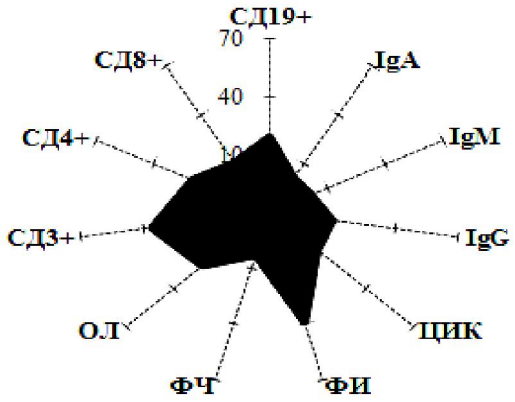
SLE without pronounced comorbidity



Control group



SLE + chronic centers of infection + the gastrointestinal tract



SLE + the chronic viral hepatitis

Picture 2. Immunological images with different comorbidities HV + SLE

In childhood and adolescence (during the first two decades of life), the disease begins in 17–25% of patients [12]. According to different authors in the prepubertal and pubertal periods the ratio of girls to boys is 8:1, 9:1 [2, 5]. Studying variants of the distinctive features and other characteristics of SLE in children in Kazakhstan, we identified 153 children with SLE were: children of Kazakh nationality 120 (78,4%), Russian – 33 (21,6%). Of them – 132 girls (86,3%), including - 103 - Kazakh nationality (85,8%) and 29 – Russian (87,9%); 22 boys (14,3%), including – Kazakhs 17 (14,2%), Russian – 4 (12,1%). It is known that SLE – a disease predominantly of young women and girls. Indeed, in men, especially the elderly is a great rarity of SLE [4, 5].

Relatively larger number of boys, SLE is particularly frequency ratio patients girls and boys in Kazakhstan, based on the fact that all these years, almost all patients of the areas usually passed inspection and treatment in our clinic to confirm the diagnosis and determine the program nearest and further treatment.

The clinical picture of the disease characterized by various syndroms .

Were the most frequent lesions of the skin and mucous membranes (83,7%) and carditis (84,3%). Half of the patients had involvement in the kidney (51%). Articular syndrome (80,4 %) are also often encountered, but unlike other displays, arthralgias and arthritis have been no signs of erosive and patients disappeared completely, without any consequences from 1 month to 1.5.

Among the most typical cutaneous manifestations of erythema were in the form of "butterfly" (50,3%). There was a high frequency of

thumb capillaritis (53,6%) , ulcerative necrotic lesions of the skin and mucous membranes (42,5%)

Quite often, was the development serosity (47,1%). And, more often met pericardial effusion (62,5%), at least - pleuritis (31,9%). Adhesive pleuritis and pericarditis were detected in a few cases (5.4%). Frequent manifestation of the children was pneumonitis (24,1%).

Central nervous system (CNS) was observed in 31,0% of cases. The most common were psycho - organic syndrome (26,3 %) and neurotic disorders (22,8%), which is manifested by increased excitability, irritability, tearfulness, sleep disorders. Rarely recorded migren-type headache (21,0%), convulsions (17,5%) and depression (12,3%) , which did not differ consistently and were fully in the treatment.

SLE infection rate ranges from 27 to 55% [7–9]. It is known that viruses can disturb the properties of immune cells and cell antigens remodeling own tissue, resulting in the formation of cross immune response [7,8]. Our results confirm the high frequency (78%) carriers of herpes virus infection (HSV type I and II, CMV and EBV) in SLE. Among the markers of viral hepatitis were more prevalent anti-HBs antibodies (33,3%).

In children with SLE revealed the features of pathological changes in the immune system associated with persistent viral infection. For the virus associated of SLE was characterized by a more pronounced suppression of the immune system, which is expressed by a decrease in T-cell immunity, the number of T-helper cells, increased numbers of T-suppressor and a significant decrease in the phagocytic activity of neutrophils ($p<0,001$).

5. Conclusions

1. Particularly systemic lupus erythematosus in children in the country is slightly different frequency ratio of patients. In contrast to the literature data (4,0:1) ratio of girls to boys was 2,3:1.

2. Ethnic characteristics of the disease were to a higher frequency of SLE in the Kazakh population (79,8%) was significantly higher (II - III) the extent of its activity (84,1%) than the Russian population (20,2% and 64,5%) respectively. Active SLE Kazakhs, according to the scale SLEDAI-, amounted to 38,9±9,1 vs. 26,1±8,1 points.

3. At 71,8% of SLE patients with a certain constancy revealed increased titers of antibodies to antigens of herpes simplex virus 1 and 2; CMV (62,2 %), Epstein -Barr virus (59,6%), to markers of hepatitis B (33,3%). For these patients was typical progressive course of the disease and reducing its activity in the appointment of courses of therapy by Viferon and Acyclovir.

4. For the virus associated of SLE is characterized by a more pronounced suppression of the immune system, which is defined by a decrease in T- cell immunity , the number of T - helper cells, increased numbers of T- suppressor and a sharp decrease in the phagocytes' activity of neutrophils($p< 0,001$).

Corresponding Author:
Dr.Ishuova Pakhitkanym Kabdukaevna
Scientific Center of Pediatrics and Children's Surgery
Al-Farabi Street, 146 Almaty, 050040, The Republic of Kazakhstan

References

1. Kalyagin A.N., 2006. Classification and diagnostic criteria for rheumatic diseases: handbook for students, interns, medical residents and doctors. – Irkutsk: HPE IGMU Health Institute. –P. 21–26.
2. Nasonov E.L., 2008. Rheumatology: National guidelines– M.: GEOTAR Media. –P. 419–422.
3. Hiraki L.T., Benseler S.M., Tyrrell P.N.,et al., 2008. Clinical and laboratory characteristics and long term outcome of pediatric system lupus erythematosus: a longitudinal study. Journal of Pediatr, 152(4):550–6.
4. Habibi S.,Saleem M.A.,Ramanan A.V., 2011. Juvenile systemic lupus erythematosus: review of clinical features and management.Indian Pediatrics, 48(11):879–87.
5. Houghton K.M., Page J., Cabral D.A., Petty R.E., Tucker L.B. Systemic lupus.
6. Erythematosus in the pediatric North American native population of British Columbia.J Rheumatol 2006;33:161-3.
7. Geppe N.A., Podchernyaeva N.S.,LyskinaG.A., 2011. Guide to Children's Rheumatology. – M.: GEOTAR Media. – P.326–364.
8. Elzhov N.N., 2002.Pathogenetic features of systemic lupus erythematosus associated with markers of hepatitis viruses B and C: dis.cand. sciences.
9. Vilaichone R.K., Mahachai V., Eimong S. et al., 2001. Necrotizing ileitis caused by cytomegalovirus inpatient with systemic lupus erythematosus: casereport. J. Med.Assoc. Thai.–P. 469-473.
10. Iliopoulus A.G., Tsokos G.C., 1996. Immunopathogenesis and spectrum of infections in systemic lupus erythematosus.Sem. Arthr.Rheum. – P. 318-336.
11. Nasonova E.L., 2006. Clinical guidelines: Rheumatology.– M.: GEOTAR Media, –P.141- 158.
12. Nasonov E.L., 2004.Antiphospholipid syndrome. – M.: Litterra. – P. 36–45/
13. Samsygina G.A.,ShcherbakovM., 2004.Cardiology and pediatric rheumatology.A practical guide.– Moscow: Medpraktika–M. – Vol. 3. – P. 672–694.
14. Font J., Cervera R., Espinosa G., Pallares L., Ramos-Casals M., Jimenez S. et al.Systemic lupus erythematosus (SLE) in childhood: analysis of clinical and immunologicalfindings in 34 patients and comparison with SLE characteristics in adults. Ann Rheum Dis 1998;57:456-9.
15. Costenbader K.H., Desai A., Alarcon G.S., et al., 2011. Trends in the incidence, demographics, and outcomes of end-stage renal disease due to lupus nephritis in the U.S. from 1995 to 2006.Arthritis Rheum, 63(6): 1681–8.

7/13/2014