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CLINICAL SIGNIFICANCE OF B-CELL ACTIVATING FACTOR BAFF IN CHILDREN WITH SYSTEMIC LUPUS ERYTHEMATOSUS

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The study involved 17 children with systemic lupus erythematosus receiving treatment at the Educational Therapeutic Clinic of Azerbaijan Medical University. The mean age was 15.7±0.5 years. In all patients amount of B-cell activating factor–BAFF, anti nuclear antibodies, anti-double-stranded deoxyribonucleic acid and single-stranded deoxyribonucleic acid antibodies, IgA, IgM, IgG, IgE, circulating immune complexes in serum were determined. The disease activity level was calculated according to the SLEDAI–2k scale. The amount of BAFF increased in SLE patients, and more so in patients with high activity compared with patients with moderate activity (6.6 ng/ml and 4.3 ng/ml, respectively). There is a positive reliable relationship between BAFF and the circulating immune complexes (ρ=0.829; p=0.021), anti-double-stranded deoxyribonucleic acid antibodies (ρ=0.854; p=0.003) and the SLEDAI–2k index (ρ=0.613; p=0.009). The development and improvement of anti-BAFF therapy in children may be considered more appropriate than the conventional therapy used.

Key words: systemic lupus erythematosus, B-lymphocytes, BAFF, circulating immune complexes, SLEDAI–2k scale.

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КЛІНІЧНЕ ЗНАЧЕННЯ ФАКТОРА АКТИВАЦІЇ В-КЛІТИН BAFF У ДІТЕЙ ІЗ СИСТЕМНИМ ЧЕРВОНИМ ВОВЧАКОМ

У дослідженні взяли участь 17 дітей із системним червоним вовчаком, які проходили лікування в Навчально-терапевтичній клініці Азербайджанського медичного університету. Середній вік становив 15,7±0,5 року. У всіх хворих визначалася кількість В-клітинного активуючого фактора-BAFF, антинуклеарних антитіл, антитіл до дволанцюжкової дезоксирибонуклеїнової кислоти та одноланцюгової дезоксирибонуклеїнової кислоти, IgA, IgM, IgG, IgE, циркулюючих імунних комплексів у сироватці крові. Рівень активності захворювання розраховувався за шкалою SLEDAI-2k. У дітей із системним червоним вовчаком кількість BAFF була підвищена, причому переважно у хворих з високою активністю в порівнянні з хворими з середньою активністю (6,6 нг/мл і 4,3 нг/мл відповідно). Існує позитивний достовірний зв'язок між BAFF та циркулюючими імунними комплексами (ρ=0,829; p=0,021), антитілами до дволанцюжкової дезоксирибонуклеїнової кислоти (ρ=0,854; p=0,003) та індексом SLEDAI–2k (ρ=0,6) Розробка та вдосконалення анти-BAFF терапії у дітей може вважатися більш доцільною, ніж традиційна терапія.

Ключові слова: системний червоний вовчак, В-лімфоцити, BAFF, циркулюючі імунні комплекси, шкала SLEDAI-2k.

Systemic lupus erythematosus (SLE) is an autoimmune pathology characterized by widespread inflammation of the connective tissue and blood vessels. In 10–20 % of cases, it debuts in childhood and is distinguished by a more aggressive onset and more severe course than in adults [3].

The disease is based on chronic autoimmune inflammation, which occurs as a result of a violation of humoral and cellular immunity. Autoimmune inflammation, which develops as a consequence of a multifaceted violation of innate and acquired immunity, is formed due to interaction of genetic and environmental factors. It is these multifaceted violations that provide the heterogeneity of SLE, which leads to the fact that the onset and clinical course of the disease are colored, figuratively speaking, by various clinical signs [2].

It is obvious, that B lymphocytes play a central role in the immune pathogenesis of SLE. Polyclonal activation of B lymphocytes as a result of the loss of negative selection leads to their hyperreactivity, which in turn leads to the synthesis of autoantibodies against the cell nucleus and cytoplasm. In general, hypersynthesis of autoantibodies, pathological changes in the function of B lymphocytes, as well as the presentation of antigens (autoantigens), differentiation and activation of T lymphocytes, and the synthesis of various cytokines are considered to be the main factors in the pathogenesis of systemic diseases [11].

Disruption of B lymphocyte function not only leads to the synthesis of autoantibodies, but also, as antigen-presenting cells, presents antigen epitopes to autoreactive T lymphocytes, T lymphocytes also synthesize various mediators, which leads to the maintenance and further deepening of the inflammatory process. Presentation of antigen triggers the activation mechanism of T lymphocytes, plays a role in the synthesis of cytokines, etc. [7].

Thus, B lymphocytes play a critical role in the development and maintenance of autoimmunity. It has been established that the activation of B lymphocytes is regulated by a specific factor called BAFF. BAFF is a cytokine of 285 amino acids belonging to the TNF family. This factor is also called BlyS (B lymphocyte stimulator), TALL1 (TNF and APOL related leukocyte expressed ligand–1). BAFF has 3

receptors, which belong to the TGF receptor family: B-cell maturation antigen (BCMA, CD269 or TNFRSF17), transmembrane activator and cyclophilin ligand interactor (TACI, CD267 or TNFRSF13b) and BAFF–R, CD268 or TNFRSF13c receptor. These receptors are mainly expressed on B lymphocytes, such as TACI on B lymphocytes, macrophages, BCMA on B lymphocytes and plasma cells, and BAFF–R on B lymphocytes, activated and regulatory T lymphocytes. The association of BAFF with these 3 receptors allows it to play a role in the homeostasis, functional and self-tolerance regulation of B lymphocytes. It is precisely in this system that disorders lead to the loss of immunological self-tolerance and the development of autoimmune diseases [5, 6, 9].

Serologically, SLE is characterized by pathological activation and differentiation of B lymphocytes with high antibody titers.

Experimental studies have shown that transgenic mice with BAFF hyperexpression develop a syndrome similar to systemic lupus erythematosus: high titers of autoantibodies, hypergammaglobulinemia, glomerulonephritis. At the same time, the number of B lymphocytes decreases in mice with BAFF deficiency [7]. In this regard, the study of this factor in patients with systemic lupus erythematosus, especially in children, is of great importance.

The purpose of the study was to evaluate the amount of B–cell activating factor in patients with systemic lupus erythematosus and to clarify the relationship between the clinical and laboratory parameters in this group of patients.

Materials and methods. The study involved 17 children with SLE receiving treatment at the Educational Therapeutic Clinic of Azerbaijan Medical University. The mean age was 15.7±0.5 years.

The diagnosis was confirmed according to the criteria of the American College of Rheumatology (ACR) – 1997 [4].

An extensive anamnesis was collected from all patients using a specially developed questionnaire, the symptoms of SLE were specifically analyzed, and a detailed clinical examination was performed.

Table 1

The changes in immunological parameters in children with moderate and high activities of SLE

		Degree of activity		pF	pU
		Moderate	High		
BAFF, ng/ml	Median	4.3	6.6	0.017	0.027
	Minimum	3.3	5.2		
	Maximum	7.2	7.7		
IgA, g/l	Median	5.1	3.9	0.679	0.548
	Minimum	0.0	3.4		
	Maximum	7.7	4.0		
IgM, g/l	Median	2.9	2.4	0.577	0.714
	Minimum	1.1	0.9		
	Maximum	13.9	4.6		
IgG, g/l	Median	15.1	10.8	0.417	0.381
	Minimum	8.7	7.7		
	Maximum	29.0	19.6		
IgE, IU/ml	Median	50.0	368.9	0.866	0.786
	Minimum	11.4	83.4		
	Maximum	713.8	483.0		
ANA	Median	2.03	4.79	0.038	0.048
	Minimum	0.05	2.86		
	Maximum	3.00	10.7		
CICs, U	Median	78.0	90.0	0.043	0.057
	Minimum	70.0	89.0		
	Maximum	87.0	90.0		
Anti-dsDNA, IU/ml	Median	157.5	323.9	0.034	0.095
	Minimum	26.0	318.0		
	Maximum	328.5	486.9		
Anti-ssDNA, IU/ml	Median	139.4	294.7	0.072	0.167
	Minimum	45.0	218.7		
	Maximum	334.3	523.0		

Note: pU–coefficient of significance (U–Mann-Whitney), pF–coefficient of significance (F–Fisher).

The patients were also subjected to laboratory and instrumental examinations: general blood analysis, biochemical blood analysis, immunological analyses – amount of anti nuclear antibodies (ANA),

anti-double-stranded deoxyribonucleic acid (anti-dsDNA), antibodies against single-stranded deoxyribonucleic acid (anti-ssDNA), IgA, IgM, IgG, IgE, circulating immune complexes (CICs) in the serum.

The amount of BAFF in the serum of all patients was studied using the ELISA method on the automatic biochemical and immunoassay analyzer ChemWell 2910 (Awareness Technology Inc., USA). The disease activity level was calculated according to the SLEDAI–2k (Systemic Lupus Erythematosus Disease Activity Index 2000) scale. According to the scale, 6–10 points were considered "moderate activity", and 11–19 points were considered "high activity" [1].

The numerical indicators obtained in our study were statistically analyzed. The median, maximum and minimum numerical value of the indicators was calculated. Statistical analysis was performed in the SPSS–22 package using dispersion (F–Fisher), variation (U–Mann-Whitney) and correlation (ρ-Spearman) methods.

Results of the study and their discussion. The main clinical signs were skin lesions, hematological disorders, and kidney damage. Antiphospholipid syndrome was not recorded in any patient.

As a result of our study, we found that the amount of BAFF increased in all patients with SLE. It increased more in patients with moderate and high activity (4.3 ng/ml and 6.6 ng/ml, respectively), and the amount increased statistically significantly (p=0.027). At the same time, the amount of CICs and anti-dsDNA and anti-ssDNA also increased, but not statistically significantly (according to pU, p=0.057, p=0.095, p=0.167, respectively). The above changes are reflected in the Table 1.

In patients with high activity (SLEDAI–2k>10) assessed by the SLEDAI–2k index, the amount of BAFF was higher than in patients with moderate activity (SLEDAI–2k<10) (6.6 ng/ml). In addition, there were signigicant differences in levels of ANA, CICs and anti-dsDNA (according to pF) in children with high activities of SLE compared to moderate.

The graphical representation of the difference in BAFF levels between patients with different disease activity is shown in Fig. 1.

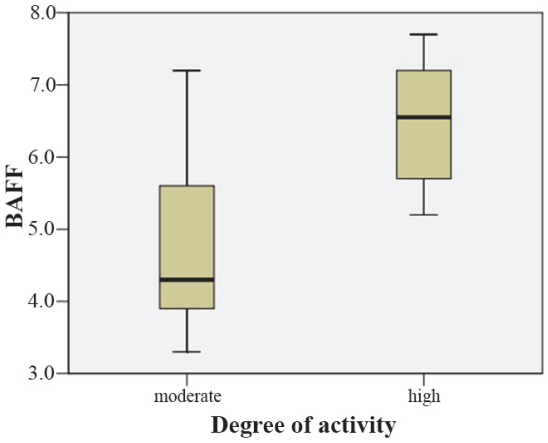

Fig. 1. Serum BAFF levels between patients with different disease activity.

Conducting a correlation analysis between the studied parameters revealed that there is a positive reliable relationship between BAFF and the CICs (ρ=0.829; p=0.021), anti-dsDNA (ρ=0.854; p=0.003) and the SLEDAI–2k index (ρ=0.613; p=0.009). So, as the SLEDAI–2k index increased, an increase in the level of the biomarker was also noted. The same can be noted for the ANA level (ρ=0,894; p=0.001). The increase in BAFF was associated with CICs and anti-dsDNA, which was reflected in correlation.

BAFF demonstrated a negative relationship with a number of immunoglobulins (IgA (ρ=–0.133; p=0.732) and with IgG (ρ=–0.167; p=0.668)), while the correlation with IgM (ρ=0.075; p=0.847) and IgE (ρ=0.333; p=0.420) was negative. However, in all cases the relationship was unreliable. Among other immunological parameters, a reliable positive correlation can be distinguished between CICs and ANA (ρ=0.900; p=0.037) and between CICs and anti-dsDNA (ρ=0.841; p=0.036), as well as between IgE and ANA, IgE and anti-dsDNA (in both cases (ρ=0.900; p=0.037). In addition to BAFF, ANA showed a positive correlation with the SLEDAI–2k index (ρ=0.894; p=0.001), which is logical from the point of view of the pathogenesis of the disease.

Comparing the literature data and our results, it can be noted that they coincide with the results of many studies. In the studies conducted by Vitri, et al in adults, the studies of also concluded with the same results [12]. It is worth noting that these studies were conducted in adults and there is not enough information in the literature about such studies conducted in children. The amount of BAFF (4.3 ng/ml in moderate activity) gives reason to think that BAFF plays a major role in the pathogenesis of the disease. As a result of the influence of this factor, autoreactive clones are excluded from negative selection. This leads to the development of the disease and the determination of the degree of activity depending on the amount of the factor. In particular, the fact that the degree of activity is higher in patients whose level of activity is estimated to be high compared to others gives reason to use this factor in clinical practice as a marker of the degree of activity.

The positive correlation we found between BAFF and anti-dsDNA suggests that BAFF impacts on the number of pathogenic autoreactive clones of B lymphocytes. Examining of the literature data, in can be obvious that some authors have reported an increase of BAFF [10]. If we assume that autoreactive clones do not undergo apoptosis in the degree of disease activity, anti-BAFF therapy may lead to a specific decrease in pathogenic B lymphocytes.

Salazar-Camarena DC, et al (2019) evaluated the expression of the cytokine BAFF and their association with the receptors BAFF–R and TACI on CD3+ T cells in patients with SLE. The authors revealed that BAFF-R expression correlates inversely with disease activity ($r=–0.538$, $p<0.01$), while TACI correlates with disease activity ($r=0.530$, $p<0.05$). To assessment of diseases activity index Mex–SLEDAI was implemented. According to their data, serum BAFF level was high in SLE patients and correlated with the disease activity index Mex–SLEDAI ($r=0.621$, $p<0.01$). Thus, the researchers agreed with the majority of opinions that associations of BAFF with disease activity, suggest that BAFF generated in the autoimmunity context could through still unknown mechanisms, modulate the microenvironment, and perpetuate the inflammatory response, autoantibody production and organ damage observed in SLE patients [9].

The similar results were obtained by Rosales M.M, et al (2019) in their work (BAFF correlated with increasing disease activity ($r=0.320$, $p<0.001$). Typical changes in BAFF levels with increasing disease activity were expected given the pathogenetic mechanisms above mentioned [5].

These results are consistent with other studies from different countries. However, a study by Mercado, et al. in 2016 showed a strong correlation ($r=0.45$) between serum BAFF and disease activity [6]. However, in the study by Vitri et al., a relatively weak correlation ($r=0.327$) was found. This can be attributed to the inclusion of treated patients in the study. In our study, a higher correlation ($\rho=0.613$) was obtained. We included patients who were not involved in treatment and newly involved in treatment. The strong correlation between BAFF and SLEDAI–2k can be attributed to this [12].

This study showed that there is a correlation between BAFF levels and disease activity. This is consistent with many studies that suggest elevated BAFF levels in active SLE. Some studies have indicated that BAFF is a predictor of the degree of SLE activity [5, 6, 8]. However, in our study, we measured BAFF and SLEDAI–2K only at one time point; therefore, this study cannot draw a conclusion about BAFF level as a predictor of SLE flares.

Conclusions

1. The amount of BAFF increased in SLE patients, and more so in patients with high activity compared with patients with moderate activity (6.6 ng/ml and 4.3 ng/ml, respectively).

2.There is a positive reliable relationship between BAFF and the CICs ($\rho=0.829$; $p=0.021$), anti-dsDNA ($\rho=0.854$; $p=0.003$) and the SLEDAI–2k index ($\rho=0.613$; $p=0.009$).

The development and improvement of anti-BAFF therapy in children may be considered more appropriate than the conventional therapy used. It may be considered as a more specific approach, since anti-B lymphocyte therapy can be used to achieve maximum therapeutic effect.

References

1. Ceccarelli F, Perricone C, Massaro L, Cipriano E, Alessandri C, Spinelli FR, et al. Assessment of disease activity in Systemic Lupus Erythematosus: Lights and shadows. Autoimmun Rev. 2015 Jul;14(7):601-8. doi: 10.1016/j.autrev.2015.02.008.

2. Friebus-Kardash J, Trendelenburg M, Eisenberger U, Ribi C, Chizzolini C, Huynh-Do U, et al. Susceptibility of BAFF-var allele carriers to severe SLE with occurrence of lupus nephritis. BMC Nephrol. 2019 Nov 21;20(1):430. doi: 10.1186/s12882-019-1623-4.

3. Harry O, Yasin S, Brunner H. Childhood-Onset Systemic Lupus Erythematosus: A Review and Update. J Pediatr. 2018 May; 196:22-30.e2. doi: 10.1016/j.jpeds.2018.01.045.

4. Lu W, Zhong Y, Weng C, Wang Q, Tang M, Liu Z, et al. Utility of the ACR-1997, SLICC-2012 and EULAR/ACR-2019 classification criteria for systemic lupus erythematosus: a single-centre retrospective study. Lupus Sci Med. 2022 Sep 7;9(1):e000718. doi: 10.1136/lupus-2022-000718.

5. Marín-Rosales M, Cruz A, Salazar-Camarena DC, Santillán-López E, Espinoza-García N, Muñoz-Valle JF, et al. High BAFF expression associated with active disease in systemic lupus erythematosus and relationship with rs9514828C>T polymorphism in TNFSF13B gene. Clin Exp Med. 2019 May;19(2):183-190. doi: 10.1007/s10238-019-00549-8.

6. Mercado U, Díaz-Molina R. Nivel de estimulador de linfocitos B (BLyS/BAFF) en el suero de pacientes con lupus [B lymphocyte stimulator (BLyS/BAFF) level in sera of patients with lupus]. Rev Med Inst Mex Seguro Soc. 2016 May-Jun;54(3):334-7. PMID: 27100979. [In Spanish].

7. Möckel T, Basta F, Weinmann-Menke J, Schdwarting A. B cell activating factor (BAFF): Structure, functions, autoimmunity and clinical implications in Systemic Lupus Erythematosus (SLE). Autoimmun Rev. 2021 Feb;20(2):102736. doi: 10.1016/j.autrev.2020.102736.

8. Rezazadeh M, Jokar MH, Mehrnaz Aghili S, Mirfeizi Z, Mahmoudi M, Morovatdar N, et al. Association between levels of serum and urinary B cell-activating factor and systemic lupus erythematosus disease activity. Arch Rheumatol. 2023 Jun 14;38(3):429-440. doi: 10.46497/ArchRheumatol.2023.9549.

9.Salazar-Camarena DC, Ortíz-Lazareno P, Marín-Rosales M, Cruz A, Muñoz-Valle F, Tapia-Llanos R, et al. BAFF-R and TACI expression on CD3+ T cells: Interplay among BAFF, APRIL and T helper cytokines profile in systemic lupus erythematosus. Cytokine. 2019 Feb;114:115-127. doi: 10.1016/j.cyto.2018.11.008.
10. Sarı S, İnanç M. BLyS (BAFF) and APRIL in the pathogenesis of systemic lupus erythematosus. J Turk Soc Rheumatol. 2019 Dec;11(2):110-116. doi:10.2399/raed.19.43434.
11. Tsokos GC, Lo MS, Costa Reis P, Sullivan KE. New insights into the immunopathogenesis of systemic lupus erythematosus. Nat Rev Rheumatol. 2016 Nov 22;12(12):716-730. doi: 10.1038/nrrheum.2016.186.
12. Vitri RY, Wachjudi RG, Ghassani NG, Hamijoyo L. Correlation of B-Cell-Activating Factor Levels and Diseases Activity in Systemic Lupus Erythematosus Patients. Indian Journal of Rheumatology 16(1):p 13-17, March 2021. doi: 10.4103/injr.injr_122_20.

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IMPLEMENTATION OF REHABILITATION PROGRAM IN PATIENTS UNDERGOING CORONARY ARTERY BYPASS GRAFTING IN THE EARLY POSTOPERATIVE PERIOD

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With the purpose to develop the recovery protocol for the patients undergoing coronary artery bypass grafting 132 patients were observed (30 of them received isolated coronary artery bypass grafting, 30–mitral valve prosthesis, 72–concomitant coronary artery bypass grafting and mitral valve surgery). The rehabilitation program (physical and psychological therapy) was initiated from the first postoperative day (physical therapy within 10–12 days with a further transition to the next stage of rehabilitation during hospital stay). Of the 132 operated patients, only 37 (28 %) had an adequate mental state, 95 (72 %)– significant mental changes: neurosis (20 cases), anxiety-depressive state (49 cases), hypochondria (19 cases), hysteria (7 cases). At the end of the program 121 (91.7 %) patients had an adequate mental state on days 12–14 postoperatively. The mortality was in 8.3 %. The implementation of rehabilitation programs in early period accelerates convalescence period of coronary artery bypass grafting patients.

Key words: ischemic heart disease, coronary artery bypass grafting, rehabilitation, mitral valve prosthesis, mental disorders.

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РЕАЛІЗАЦІЯ ПРОГРАМИ РЕАБІЛІТАЦІЇ У ХВОРИХ, ЩО ПЕРЕНЕСЛИ АОРТОКОРОНАРНЕ ШУНТУВАННЯ, У РАНЬОМУ ПІСЛЯОПЕРАЦІЙНОМУ ПЕРІОДІ

З метою розробки протоколу відновлення пацієнтів, які перенесли аортокоронарне шунтування, спостерігалося 132 пацієнти (з них 30 перенесли ізоловане аортокоронарне шунтування, 30 – протезування мітрального клапана, 72 – поєднане аортокоронарне шунтування та операцію на мітральному клапані). Реабілітаційна програма (фізична та психологічна терапія) починалася з першої післяопераційної доби (фізична терапія протягом 10–12 днів з наступним переходом на наступний етап реабілітації в період перебування у стаціонарі). Зі 132 прооперованих хворих лише у 37 (28 %) спостерігався адекватний психічний стан, у 95 (72 %) – виражені психічні зміни: неврози (20 випадків), тривожно-депресивний стан (49 випадків), іпохондрія (19 випадків), істерія (7 випадків). Після закінчення програми у 121 (91,7 %) пацієнта на 12–14 добу після операції зберігався адекватний психічний стан. Летальність становила 8,3 %. Реалізація реабілітаційних програм у ранні терміни прискорює період реконвалесценції у пацієнтів, які перенесли аортокоронарне шунтування.

Ключові слова: ішемічна хвороба серця, аортокоронарне шунтування, реабілітація, протез мітрального клапана, психічні розлади.

Ischemic heart disease (IHD), or coronary heart disease, is the leading causes of mortality in developed countries. According to the data, it annually claims the lives of more than 2.5 million of population globally, which more than one third of them are people of middle age [13]. In recent years, significant progress has been made in the management of this disease. The landscape has changed considerably since the inception of surgical coronary artery revascularization. An important achievement in the treatment of the ischemic heart disease was the performing of direct surgical myocardial revascularization, which is also referred to as coronary artery revascularization or coronary artery bypass grafting (CABG), which considerably improves the quality and the life expectancy of patients, and reduces the risk of developing of possible complications of the disease [10].

The prognosis of patients who have undergone CABG operation depends on a number of circumstances. The first is the “technical” features of the performed surgical intervention (for example,