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Variants of the influence of endogenous uric acid on the blood level of theophylline-sensitive T-lymphocytes can be predicted without error

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Abstract

Background. During the implementation of the project "Physiological activity of uric acid", our group discovered three variants of relationships between changes in uricemia and blood level of theophylline-sensitive $CD8^+$ T-lymphocytes. The **aim** of this study is to find out the possibility of predicting one or another variants based on the set of initial parameters (predictors) of the patient.

Materials and methods. Under an observations were 34 males (23-70 years) and 10 females (33-76 years) with chronic pyelonephritis in the phase of remission. Testing was performed twice - on admission and after 7-10 days of standard balneotherapy on Truskavets Spa. The main object of the study was serum and urine levels of uric acid. Other metabolic, endocrine and immune parameters were determined in the same blood and urine samples. In addition, EEG and HRV was recorded almost synchronously.

Results. As a result of discriminant analysis, 23 predictors were selected. Among them, 10 reflect the power spectral density of all 4 EEG rhythms, 2 – EEG entropy, autonomous

reactivity, 2 – hormones, 4 – immunity, 2 – metabolism, and another 2 – Popovych's leukocytary indices of Strain and Adaptation. Prediction accuracy is 100%.
Conclusion. The uric acid molecule, as a structural analog of methylxanthines and adenosine, exerts effects on neurons, endocrinocytes, and immunocytes, presumably through their adenosine receptors. The nature of the interaction of uric acid and adenosine receptors of theophylline-sensitive $CD8^+$ T-lymphocytes is determined by a certain biochemical and physiological situation.

Keywords: uric acid, EEG, HRV, adaptation hormones, immunity, electrolytes, urea, creatinine, relationships.

INTRODUCTION

In a seminal landmark study by Limatibul S, Shore A, Dosch HM and Gelfand EW [19], three subpopulations of rosette-forming T-lymphocytes were delineated: theophylline-sensitive T-cells (TS), which lose their ability to form an E-rosette after treatment; theophylline-resistant T-cells (TR), which are not affected by the drug; and theophylline-dependent cells, which acquire the ability to form E-rosettes after incubation with theophylline. It was shown that the effect of theophylline is dose-dependent (in the range 10^{-5}÷10 мМ/л). Concentrations in the range of 1÷5 mM/l are usually used for immunoassays. TR-lymphocytes possess RFcμ receptors, but lack RFcγ receptors and function as inducers of B-lymphocyte differentiation. In contrast, TS-lymphocytes express RFcγ receptors, but are devoid of RFcμ receptors and suppress the differentiation of B-lymphocytes. Birch RE, Rosenthall AK and Polmer SH [2] first showed that treatment with adenosine (0,01 mM/l) resulted in changes in OKT4 and OKT8 reactivity within the TR subgroup. OKT4 expression was reduced from 71,8% to 58,3% after adenosine treatment, while the percentage of OKT8 reactive cells increased from 16,5% to 33,0%. The twofold increase in OKT8 expression is approximately equal in magnitude to the change observed in RFcγ expression under the same conditions. After treatment with adenosine, only a slight change in reactivity to OKT4 was observed in the T_{total} fraction, but a significantly increased percentage of $OKT8^+$ cells was observed. According to the authors, TR cells expressing OKT8 after treatment with adenosine most likely derive, at least in part, from TR cells that were OKT4. This is evidenced by the fact that the sum of $OKT4^+$ and $OKT8^+$ TR cells remains constant before and after adenosine treatment. The authors brilliantly suggested that the expression of Fcγ receptors of T-lymphocytes is regulated by agents acting on adenosine receptors. It became known later that the immunotropic effect of adenosine is realized through its receptors (A_1, A_{2A}, A_{2B}, A_3), which are expressed by almost all populations of immunocytes: T-, NK-, B-lymphocytes, macrophages, neutrophils, dendritic and endothelial cells [1,14,15,31]. Theophylline is a structural homologue of adenosine and at a dose of 30 mg/l (0,2 mM/l) is able to block adenosine receptors A_1 and A_{2A} [26]. Caffeine and other methylxanthines, which are introduced into the human body almost daily with coffee, tea, cocoa, etc, are non-selective antagonists of adenosine receptors, mainly A_{2A} [20,21]. Back in 2004 Ivassivka SV, Popovych IL, Aksentiychuk BI and Flyunt IS [16] suggested that uric acid is an endogenous non-selective antagonist of adenosine receptors. During the realization of the project "Physiological activity of uric acid", our group new data were obtained in favor of this assumption. In particular, the level of uric acid in the serum through the corresponding nuclei of the cortex, amygdala, brainstem and medulla upregulate sympathetic tone and

downregulate vagal tone [3,4,5], that is, it acts similarly to caffeine. However, the fact we obtained about a weak, but still **positive** (r=0,22) relationship between changes in uricemia (the level of which is comparable to the concentrations of adenosine and theophylline in in vitro immune tests) and relative content of $CD8^+$ T cells in the blood, that is, theophylline-sensitive, at first glance, contradicts the classical position.

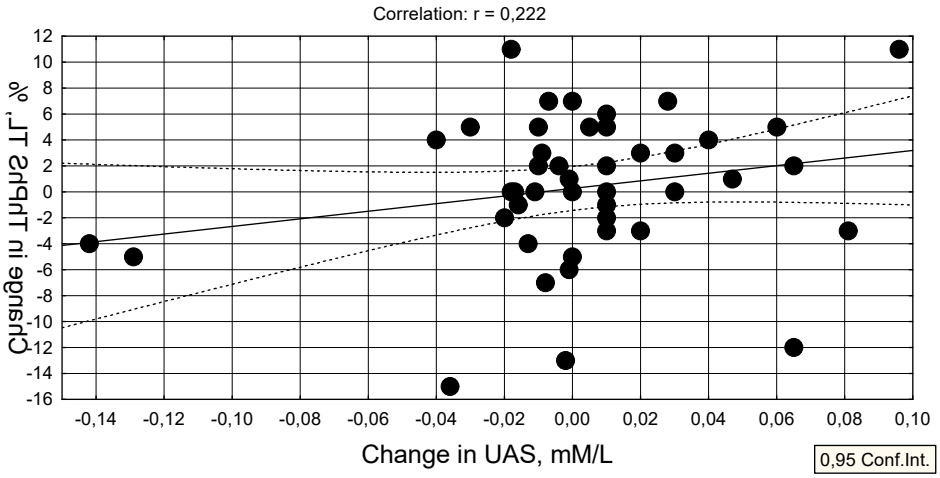
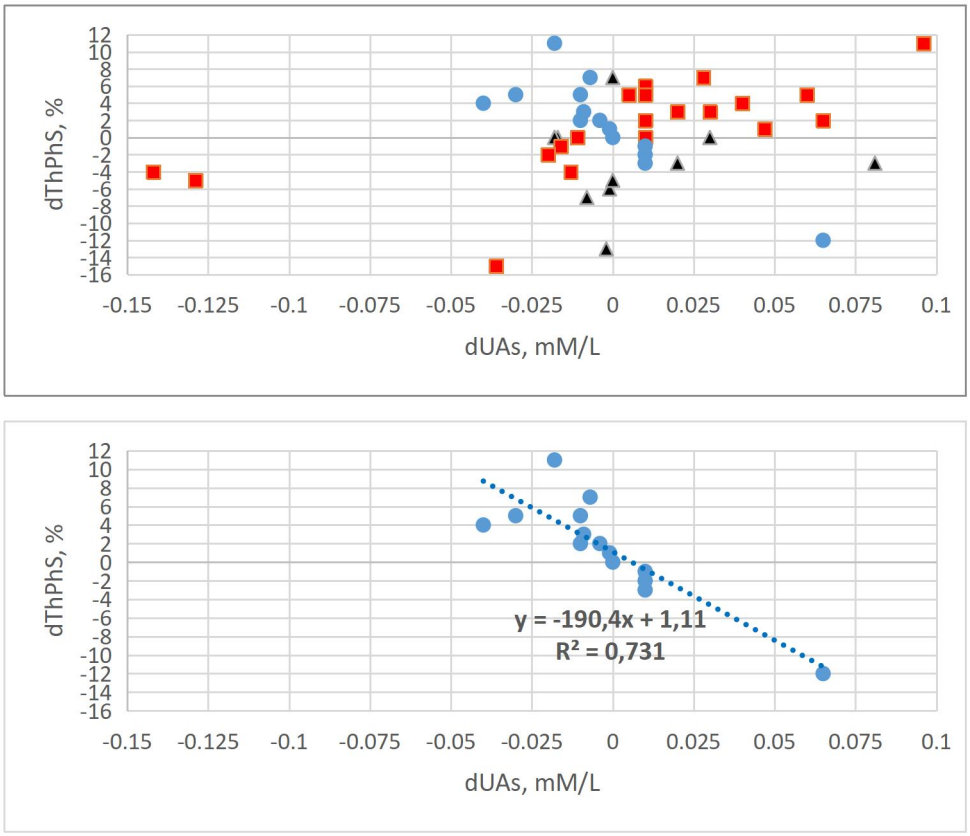


Fig. 1. Relationships between changes in Uricemia (X-line) and theophylline-sensitive $CD8^+$ T-lymphocytes (Y-line) n the sample as a whole

However, other authors found that caffeine increases the death and migration of $CD8^+$ T-lymphocytes (but not $CD4^+$ T-lymphocytes, as well as B-lymphocytes) in caffeine-accustomed, but not naïve, individuals after moderate-intensity exercise [21]. That is, the situation is ambiguous. These data led us to divide the sample into three clusters (Fig. 2).



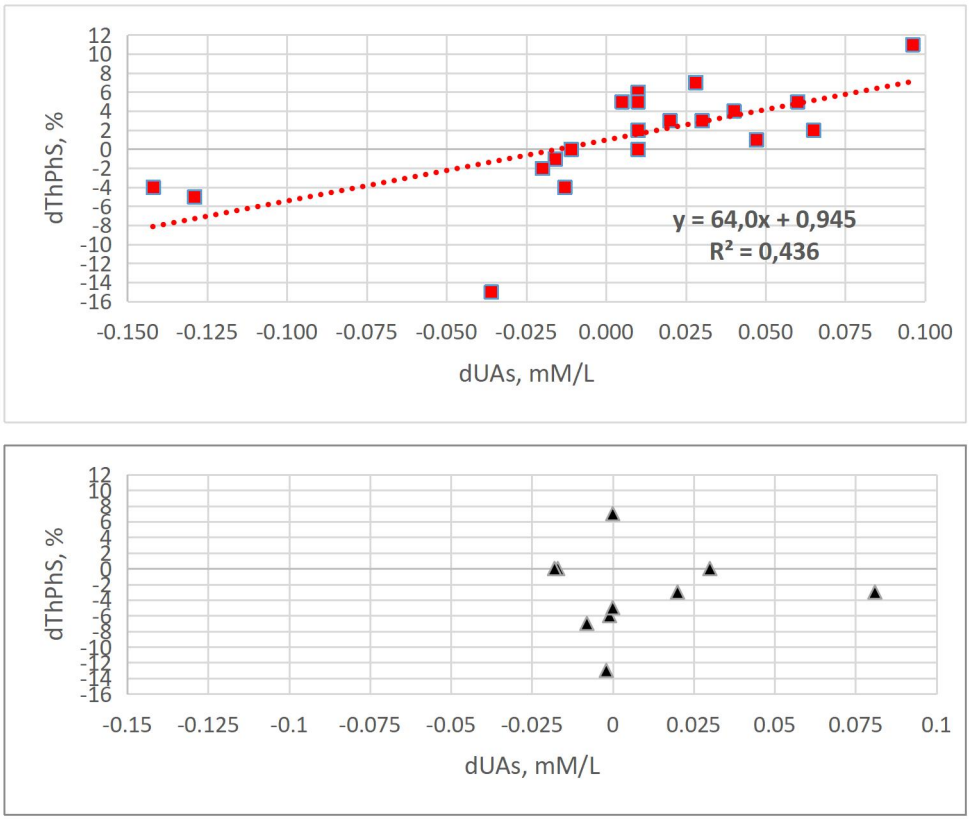


Fig. 2. Variants of relationships between changes in Uricemia (X-line) and $CD8^+$ T-lymphocyte (Y-line)

In 14 patients, a close inverse correlation (r=-0,85) was found between the dynamics of uricemia and the percentage of theophylline-sensitive T-lymphocytes, that is, uric acid acted similarly to caffeine, blocking adenosine receptors, therefore the cluster is designated **AR-**. Instead, in 19 patients of the second cluster, a direct correlation was established (r=0,66), i.e., uric acid acted as an adenosine receptor agonist (**AR+** cluster). In the remaining 11 people, no connection was found between changes in the levels of uricemia and theophylline-sensitive T-lymphocytes (**R0**).

The purpose of this study is to find out the possibility of predicting one or another variants of relationships between changes in uricemia and $CD8^+$ T-lymphocytes based on the set of initial parameters (predictors) of the patient.

MATERIALS AND METHODS

Under an observations were 34 males (23-70 years) and 10 females (33-76 years) with chronic pyelonephritis in the phase of remission. Testing was performed twice - on admission and after 7-10 days of standard balneotherapy on Truskavets Spa (drinking of Naftussya bioactive water, applications of ozokerite, mineral pools). We determined EEG, HRV, immunity parameters, serum levels of adaptation hormones as well as electrolithes and nitrogenous metabolithes in serum and daily urine. Please see details in previous publications [3,4,5,10,11,12,13,23,27].

Normal (reference) values of variables are taken from the instructions and/or database of the Truskavetsian Scientific School of Balneology [11,24].

For statistical analysis used the software package "Statistica 6.4 StatSoft Inc" (Tulsa, OK, USA).

RESULTS

Following the previously accepted algorithm [22,25], the registered baseline parameters of the patients were normalized. A subsequent screening revealed those by which the three clusters differ from each other. Then the 9 patterns were formed (Fig. 3).

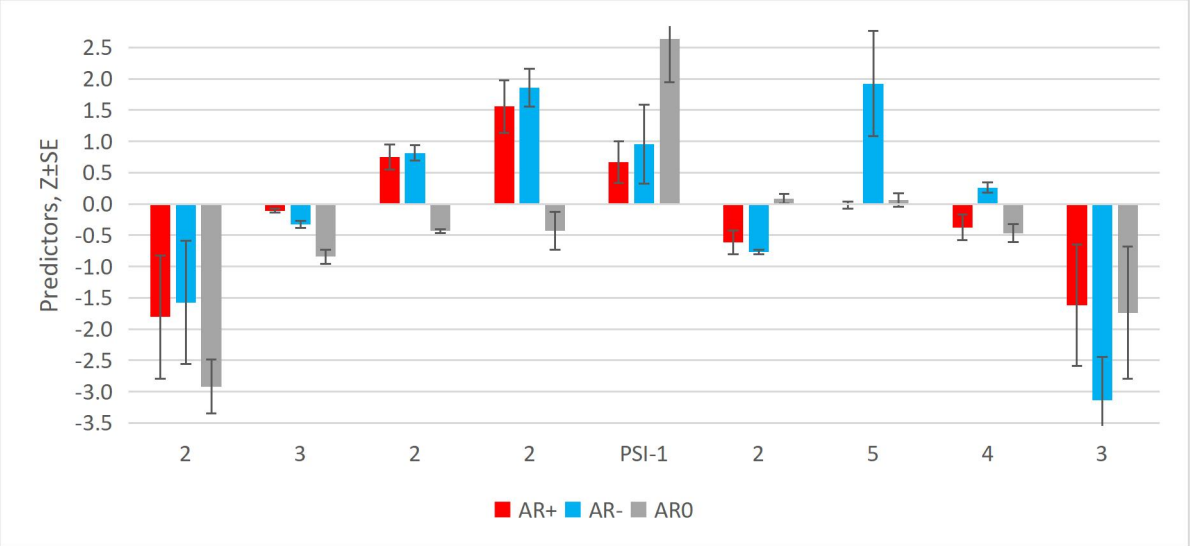


Fig. 3. Patterns of predictors of three variants of relationships between changes in uricemia and blood level of theophylline-sensitive T-lymphocytes. ***The number of parameters in the pattern is indicated; see Table 3 for details***

As a result of discriminant analysis (forward stepwise method) [18], 23 predictors were included in the model, and one was left out of the model due to duplication/excess of discriminating information (Table 1). Among the predictors, 10 reflect the power spectral density (PSD) of all 4 **EEG rhythms**, 2 – **EEG entropy**, **Autonomous reactivity**, 2 – **hormones**, 4 – **immunity**, 2 – **metabolism,** and another 2 – **leukocytary indices** of Strain and Adaptation.

Table 1. Summary of discriminant function analysis for predictors

Step 23, N of vars in model: 23; Grouping: 3 grps; Wilks' Λ: 0,0187; appro. $F_{(46)}$=5,21; $p<10^{-6}$

Variables currently in the model	Clusters of UA/CD8$^+$ relationship (n)			Parameters of Wilks' Statistics					
	AR+ (19)	AR- (14)	AR0 (11)	Wilks Λ	Partial Λ	F-remove (2,19)	p-level	Tolerancy	Reference Cv
Triglycerides, mM/L	1,20 0,13	1,50 0,18	0,81 0,13	0,026	0,709	3,898	0,038	0,384	1,16 0,606
IgG Serum, g/L	15,3 0,7	15,2 1,1	11,7 1,0	0,042	0,447	11,77	10^{-3}	0,193	12,75 0,206
Popovych's Adaptation Index-2, points	0,84 0,09	0,60 0,07	0,76 0,07	0,024	0,776	2,736	0,090	0,377	1,71 0,245
PSD F8-δ, μV^2/Hz	64 20	349 134	139 64	0,025	0,750	3,172	0,065	0,088	92 1,642
PSD F7-0, %	7,2 0,7	11,3 1,6	6,3 1,4	0,067	0,278	24,71	10^{-5}	0,040	10,0 0,458
PSD F7 Entropy	0,77 0,03	0,80 0,07	0,58 0,08	0,053	0,352	17,50	10^{-4}	0,085	0,821 0,187
Popovych's Strain Index-1, points	0,13 0,02	0,15 0,03	0,24 0,04	0,035	0,533	8,337	0,003	0,207	0,10 0,559

PSD T5-θ, $\mu V^2/Hz$	26 6	51 11	32 9	0,026	0,707	3,937	0,037	0,190	29 0,906
Aldosterone, pM/L	231 5	227 6	209 9	0,030	0,627	5,648	0,012	0,217	238 0,187
PSD Fp1-β, $\mu V^2/Hz$	69 12	85 16	50 6	0,026	0,719	3,707	0,044	0,361	63 0,721
PSD T4-θ, %	9,8 1,8	12,7 1,5	8,2 1,3	0,022	0,859	1,558	0,236	0,223	9,7 0,482
PSD F8-α, $\mu V^2/Hz$	31 4	51 9	34 8	0,037	0,505	9,310	0,002	0,226	42 1,202
PSD F7-α, %	27 4	23 4	13 2	0,025	0,746	3,227	0,062	0,119	27,6 0,522
Autonomous reactivity, units	1,98 0,71	2,16 0,63	-1,15 1,36	0,045	0,412	13,57	10^{-3}	0,057	3,10
PSD F3 Entropy	0,77 0,04	0,87 0,03	0,79 0,05	0,035	0,532	8,359	0,002	0,240	0,862 0,130
IgM Serum, g/L	1,46 0,08	1,57 0,06	1,23 0,06	0,023	0,813	2,187	0,140	0,348	1,15 0,239
Potassium Plasma, mM/L	4,17 0,16	4,21 0,15	4,62 0,16	0,024	0,783	2,629	0,098	0,288	4,55 0,104
Bactericidity vs *Staph. aureus*, 10^9 Bacteria/L	96 5	77 4	98 6	0,027	0,705	3,973	0,036	0,284	106 0,100
PSD C3-θ, $\mu V^2/Hz$	47 10	88 19	44 13	0,024	0,782	2,641	0,097	0,145	44 0,851
PSD Fp1-δ, $\mu V^2/Hz$	64 16	398 172	67 20	0,025	0,750	3,166	0,065	0,105	58 1,132
PSD T5-α, %	20 4	33 4	27 5	0,023	0,803	2,326	0,125	0,099	35 0,516
PTH, pM/L	3,39 0,17	3,06 0,18	3,75 0,22	0,023	0,803	2,333	0,124	0,394	3,75 0,130
$CD4^+$ T-helper Lymphocytes, %	30,5 2,1	31,2 1,6	28,6 2,8	0,022	0,857	1,580	0,232	0,300	39,5 0,082
Variable currently not in the model	**AR+ (19)**	**AR- (14)**	**AR0 (11)**	Wilks Λ	Par-tial Λ	F to enter	p-level	Tole-rancy	Refe-rence Cv
Bactericidity vs *Escherichia coli*, 10^9 B/L	95 8	77 5	92 7	0,018	0,950	0,450	0,640	0,250	99 0,100

Next, we transform the 23-dimensional space of discriminant variables into the 2-dimensional space of canonical roots. The canonical correlation coefficient for the first root is 0,960 (Wilks' Λ=0,019; $\chi^2_{(46)}$=119; $p<10^{-6}$), for the second 0,873 (Wilks' Λ=0,238; $\chi^2_{(22)}$=43; p=0,005). The major root contains 78,5% of the discriminant possibilities, the minor – 21,5%.

Table 2 presents the standardized and raw coefficients for the discriminant variables needed to calculate the values of the discriminant roots for each person as the sum of the products of the raw coefficients by the individual values of the discriminant variables together with a constant.

Table 2. Standardized and raw coefficients and constants for predictors

Coefficients	Standardized		Raw	
Variables	Root 1	Root 2	Root 1	Root 2
Triglycerides, mM/L	-0,879	-0,245	-1,996	-0,556
IgG Serum, g/L	-1,759	0,176	-0,503	0,050
Popovych's Adaptation Index-2, pts	0,681	0,467	2,125	1,458
PSD F8-δ, $\mu V^2/Hz$	-1,566	0,868	-0,006	0,003
PSD F7-θ, %	4,262	-1,354	1,014	-0,322
PSD F7 Entropy	-2,874	0,187	-15,01	0,979
Popovych's Strain Index-1, points	1,552	0,229	14,18	2,092
PSD T5-θ, $\mu V^2/Hz$	-1,289	-0,127	-0,043	-0,004
Aldosterone, pM/L	-1,360	0,129	-0,055	0,005
PSD Fp1-β, $\mu V^2/Hz$	-0,782	-0,531	-0,017	-0,011
PSD T4-θ, %	-0,827	-0,010	-0,137	-0,002
PSD F8-α, $\mu V^2/Hz$	1,459	-0,551	0,070	-0,027
PSD F7-α, %	-1,260	0,931	-0,085	0,063
Autonomous reactivity, units	-3,202	1,044	-26,10	8,508
PSD F3 Entropy	1,410	-0,389	10,53	-2,903
IgM Serum, g/L	0,641	-0,456	2,304	-1,640
Potassium Plasma, mM/L	-0,826	0,403	-1,547	0,754
Bactericidity vs *Staph. aur.*, 10^9 B/L	-0,311	1,116	-0,016	0,058
PSD C3-θ, $\mu V^2/Hz$	-0,033	1,403	-0,001	0,028
PSD Fp1-δ, $\mu V^2/Hz$	-1,212	-1,165	-0,004	-0,003
PSD T5-α, %	-1,385	-0,521	-0,083	-0,031
PTH, pM/L	0,713	-0,208	0,975	-0,285
$CD4^+$ T-helper Lymphocytes, %	0,670	-0,283	0,081	-0,034
	Constants		40,72	-9,612
	Eigenvalues		11,70	3,203
Cumulative Proportion			,785	1

At the next stage of the analysis, normalized parameters were grouped into three discriminant roots based on the structural coefficients (Table 3). In addition to discriminant variables, the table also presents variables that are not included in the model, but are still informal carriers of identifying information.

Table 3. Correlations of variables with canonical roots, root mean values and Z-values of predictors

Variables	Correlations Variables-Roots		AR+ (19)	AR- (14)	AR0 (11)
Root 1 (78,5%)	**R 1**	**R 2**	**-3,22**	**0,41**	**5,05**
PSD F7 Entropy	**-0,085**	-0,115	-0,82	-0,59	**-2,49**
CD4⁺ T-helper Lymphocytes	**-0,025**	-0,050	-2,79	-2,56	**-3,35**
Aldosterone	**-0,105**	-0,059	-0,15	-0,25	**-0,65**
PSD T5-α	**-0,074**	0,010	-0,13	-0,43	**-0,83**
PSD F7-α	**-0,092**	-0,027	-0,05	-0,30	**-1,04**
Triglycerides	**-0,109**	-0,236	0,55	0,69	**-0,46**
IgG Serum	**-0,118**	-0,117	0,95	0,94	**-0,40**
Autonomous reactivity	**-0,090**	-0,088	1,98	2,16	**-1,15**
IgM Serum	**-0,092**	-0,206	1,14	1,54	**0,29**
Popovych's Strain Index-1	**0,116**	0,078	0,67	0,96	**2,64**
Potassium	**0,109**	0,138	-0,80	-0,73	**0,16**
PTH	**0,053**	0,178	-0,42	-0,80	**0,01**
Root 2 (21,5%)	**R 1**	**R 2**	1,04	**-2,52**	1,41
PSD Fp1-δ	0,019	**-0,224**	0,10	**5,21**	0,15
PSD F8-δ	0,043	**-0,208**	-0,19	**1,70**	0,31
PSD C3-θ	0,011	**-0,193**	0,09	**1,19**	0,02
PSD T5-θ	0,037	**-0,178**	-0,12	**0,87**	0,15
PSD T4-θ	-0,013	**-0,132**	0,01	**0,64**	-0,31
PSD F7-θ	0,001	**-0,245**	-0,62	**0,29**	-0,80
PSD F8-α	0,030	**-0,215**	-0,21	**0,20**	-0,16
PSD Fp1-β	-0,031	**-0,110**	0,13	**0,47**	-0,29
PSD F3 Entropy	0,027	**-0,154**	-0,79	**0,08**	-0,61
Bactericidity vs *Staph. aureus*	0,003	**0,279**	-0,96	**-2,75**	-0,73
Bactericidity vs E. *coli*	currently not in model		-0,37	**-2,17**	-0,64
Popovych's Adaptation Index-2, points	-0,053	**0,155**	-3,53	**-4,50**	-3,85

The result of the analysis is the visualization of each patient in the information space of discriminant roots (Fig. 1, see also Fig 2.).

The localization of members of the R0 cluster in the extreme right zone of the axis of the first root reflects, first, drastically reduced levels of EEG entropy in the F7 locus, autonomous reactivity, and theophylline-resistant $CD4^+$ T-lymphocytes; secondly, moderately reduced levels of PSD of alpha-rhythm in F7 and T5 loci as well as serum aldosterone, thirdly, normal, but minimal for the sample levels of triglycerides and Igg G&M, which are negatively correlated with the root.

On the other hand, predictors of insensitivity of adenosine receptors of $CD8^+$ T-lymphocytes to uric acid are drastically high Popovych's Strain Index-1, as well as normal, but maximum for the sample, potassium and PTH levels. At the opposite pole of the axis of the first root, there are patients whose levels of the listed parameters differ significantly from those in the previous cluster, but are approximately the same.

Instead, there are significant differences between the parameters, the information about which is condensed in the second root. Patients in whom uric acid exerts a caffeine-like effect on theophylline-sensitive T-lymphocytes, i.e. downregulates adenosine receptors, are characterized by significantly increased levels of PSD of delta-rhythm in Fp1 and F8 loci as well as theta-rhythm in C3, T4 and T5 loci in combination with significantly reduced levels of Popovych's Adaptation Index-2 and Bactericidity of neutrophils against both gram-positive and gram-negative bacteria.

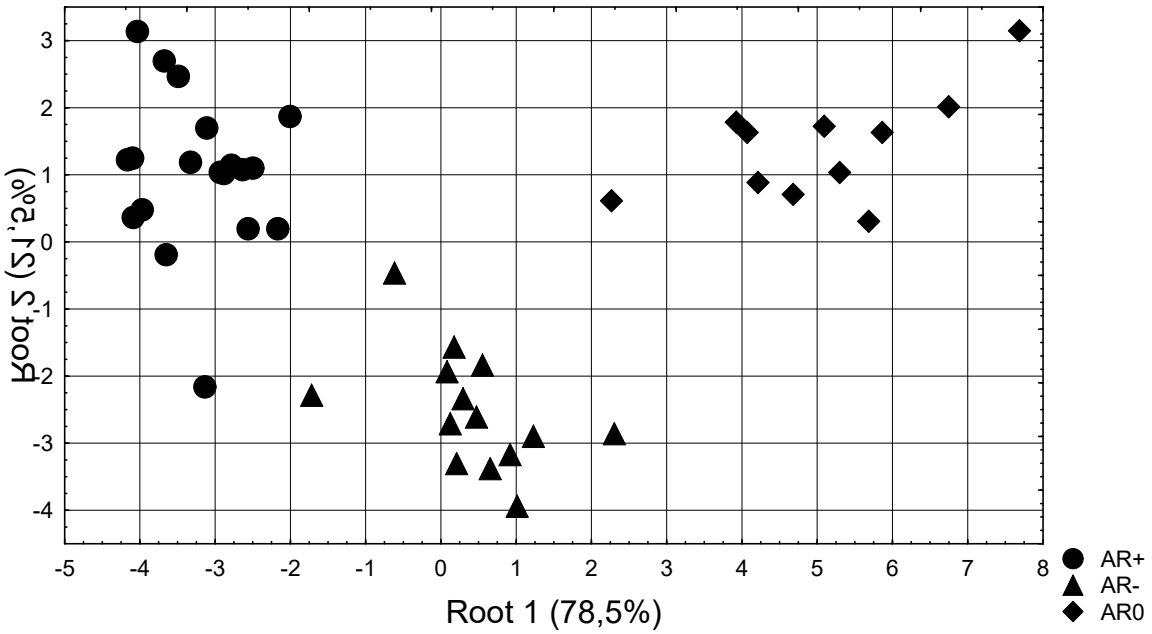


Fig. 3. Scattering of individual values of the discriminant roots of patients with different relationships between changes in Uricemia and blood level of theophylline-sensitive T-lymphocytes

The apparent clear demarcation of all four clusters is documented by the calculation of Mahalanobis distances (Table 4).

Table 4. Squares of Mahalanobis distances between clusters, F-criterions (df=23,2) and p-levels

Clusters	**AR+ (19)**	**AR- (14)**	**AR0 (11)**
AR+ (19)	0	25,9	68,5
AR- (14)	**4,2** 10^{-3}	0	37,0
AR0 (11)	**9,6** 10^{-6}	**4,6** 10^{-3}	0

The main goal of discriminant analysis - predicting each of the three variants of the relationship between changes in uricemia and the blood level of theophylline-sensitive T-lymphocytes - is achieved by calculating individual classification functions by summing the products of predictors by coefficients with the addition of constants (Table. 5). The accuracy of the forecast is 100%.

Table 5. Coefficients and constants for classification functions

Clusters	AR+	AR-	AR0
Variables	p=,43	p=,32	p=,25
Triglycerides, mM/L	137,4	132,1	120,7
IgG Serum, g/L	32,05	30,04	27,90
Popovych's Adaptation Index-2, points	-103,2	-100,6	-85,06
PSD F8-δ, μV^2/Hz	0,486	0,455	0,441
PSD F7-θ, %	-41,98	-37,15	-33,71
PSD F7 Entropy	601,1	543,1	477,3
Popovych's Strain Index-1, points	-354,8	-310,8	-236,8
PSD T5-θ, μV^2/Hz	1,065	0,924	0,707
Aldosterone, pM/L	4,488	4,269	4,034
PSD Fp1-β, μV^2/Hz	0,793	0,772	0,650
PSD T4-θ, %	3,244	2,754	2,112
PSD F8-α, μV^2/Hz	-3,432	-3,082	-2,859
PSD F7-α, %	5,220	4,686	4,537
Autonomous reactivity, units	1547	1422	1334
PSD F3 Entropy	-426,4	-377,9	-340,4
IgM Serum, g/L	-128,0	-113,8	-109,6
Potassium Plasma, mM/L	172,2	163,9	159,7
Bactericidity vs *Staph. aur.*, 10^9 B/L	2,649	2,383	2,537
PSD C3-θ, μV^2/Hz	0,398	0,295	0,403
PSD Fp1-δ, μV^2/Hz	0,094	0,093	0,064
PSD T5-α, %	3,366	3,176	2,668
PTH, pM/L	-0,922	3,629	7,035
$CD4^+$ T-helper Lymphocytes, %	-3,253	-2,835	-2,593
Constants	-1875	-1691	-1550

It seems that the nature of the interaction of uric acid and adenosine receptors expressed by both immunocytes and neurons [6,7,17] is determined by a certain biochemical and physiological situation determined by the interaction of the nervous, endocrine and immune systems within the framework of a triune complex [24,25,29,30,32]. A somewhat similar situation, such as A_{2A} receptor dependent and A_{2A} receptor independent effects of extracellular adenosine, was discovered by Apasov S et al [1].

CONCLUSION

Allow us to conclude the article by expressing the hope that the results we have obtained confirms and develops both old [16,28] and modern [8,9,20,33] hypotheses about the physiological activity of uric acid.

Uric acid is the end product of nucleic acid metabolism. About 500-800 mg is formed per day, and clearance is about 10% of creatinine. Consequently, most of it is retained in the body. This suggests that retention of most of the uric acid is necessary to perform some function. Considering that uric acid is not used in metabolism and its role in the regulation of water exchange is rather not of great importance, it can be assumed that it plays a regulatory role. The antioxidant role has been proven, but our data on the effect of uric acid on the neuro-endocrine-immune complex indicate its direct regulatory role.

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ACCORDANCE TO ETHICS STANDARDS

Tests in patients are conducted in accordance with positions of Helsinki Declaration 1975, revised and complemented in 2002, and directive of National Committee on ethics of scientific researches. During realization of tests from all parent of participants the informed consent is got and used all measures for providing of anonymity of participants.

For all authors any conflict of interests is absent.

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