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PECULIARITIES OF NEURO-ENDOCRINE-IMMUNE ACCOMPANIMENTS OF URATE-LOSING/RETAINING KIDNEYS

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ОСОБЛИВОСТІ НЕЙРО-ЕНДОКРИННО-ІМУННОГО СУПРОВОДУ УРАТОВТРАЧУЮЧИХ/ЗТРИМУЮЧИХ НИРОК

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Summaty/Резюме

Background. On the first stage of project “Neuro-endocrine regulation of the clearance of nitrogenous metabolites” implementation, we found out of peculiarities of metabolic and neuro-endocrine accompaniments of urate-losing and urate-retaining kidneys. In this study, the battery of tests was supplemented with electroencephalography and immune tests performed on the same sample of patients.

Materials and Methods. The object of observations were patients with chronic pyelonephritis in the phase of remission (34 males aged 23-70 years and 10 females aged 33-76 years). Testing was performed twice - on admission and after 7-10 days of standard balneotherapy on Truskavets’ Spa. The battery of tests was created in line with concepts functional-metabolic continuum and neuro-endocrine-immune network. The content of uric acid and creatinine was determined in daily urine and blood serum. In addition, the serum level of the main adaptation hormones and immune parameters was determined. The state of the autonomic and central nervous systems was assessed by the HRV and EEG methods respectively.

Results. In 63.6% of cases, the renal clearance of uric acid was within the classical norm (±2y), in 12.5% it was moderately reduced, but in the remaining cases it was increased, including drastically in 3 cases. The method of discriminant analysis revealed 32 variables (in addition to clearance, fractional excretion, uricosuria and uricemia by definition, 14 EEG, 7 HRV, 4 blood pressure, and 3 endocrine), according to the totality of which all 4 clusters of uric acid clearance clearly differ from each other (classification accuracy 100%). **Conclusion**. Constitutionally distinct types of uric acid metabolism are accompanied by a specific constellation of EEG, HRV, endocrine and immune variables.

Keywords: *uric acid clearance, EEG, HRV, adaptation hormones, immunity, chronic pyelonephritis.*

Актуальність. На першому етапі реалізації проекту «Нейро-ендокринна регуля-

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ція кліренсу азотистих метаболітів» ми з'ясували особливості метаболічного та нейроендокринного супроводу урат-втрачаючих і урат-утримуючих нирок. У цьому дослідженні набір тестів було доповнено електроенцефалографією та імунними тестами, проведеними на тій же вибірці пацієнтів.

Матеріали та методи. Об'єктом спостереження були хворі на хронічний пієлонефрит у фазі ремісії (34 чоловіки віком 23–70 років та 10 жінок віком 33–76 років). Тестування проводили двічі — при надходженні та після 7-10 днів стандартної бальнеотерапії на курорті Трускавець. Батарея тестів була створена відповідно до концепцій функціонально-метаболічного континууму та нейро-ендокринно-імунної мережі. У добовій сечі та сироватці крові визначали вміст сечової кислоти та креатиніну. Крім того, визначали сироватковий рівень основних гормонів адаптації та показники імунітету. Стан вегетативної та центральної нервової системи оцінювали відповідно методом ВСР та ЕЕГ.

Результати. У 63,6% випадків нирковий кліренс сечової кислоти знаходився в межах класичної норми (±2у), у 12,5% був помірно знижений, але в решті випадків був підвищений, у тому числі різко у 3 випадках. Метод дискримінантного аналізу виявив 32 змінні (крім кліренсу, фракційної екскреції, урикозурії та урикемії за визначенням, 14 ЕЕГ, 7 ВСР, 4 артеріального тиску та 3 ендокринних), за сукупністю яких всі 4 кластери кліренсу сечової кислоти чітко відрізняються один від одного (точність класифікації 100%). *Висновок*. Конституційно відмінні типи метаболізму сечової кислоти супроводжуються певною констеляцією ЕЕГ, ВСР, ендокринних та імунних змінних.

Ключові слова: *кліренс сечової кислоти, ЕЕГ, ВСР, гормони адаптації, імунітет, хронічний пієлонефрит.*

Inroduction

On the first stage of project "Neuro-endocrine regulation of the clearance of nitrogenous metabolites" implementation, we found out of peculiarities of metabolic and neuro-endocrine accompaniments of urate-losing and urate-retaining kidneys. Using the method of discriminant analysis, it was found that constitutionally distinct types of uric acid metabolism are characterized, in addition to clearance, uricosuria and uricemia by definition, by specific constellations of 11 metabolic and 7 autonomic variables as well as serum calcitonin and Stange's test [1]. In this study, the battery of tests was supplemented with electroencephalography performed on the same sample of patients.

Materials And Methods

The object of observations were patients with chronic pyelonephritis in the phase of remission (34 males aged 23-70 years and 10 females aged 33-76 years). 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) [2].

Daily urine was collected on the eve, in which was determined the concentration of uric acid (estimated by uricase method) and creatinine (by Jaffe's color reaction by Popper's method) [3]. The same metabolic parameters were determined in serum. In addition, we determined serum levels of main adaptation hormones such as Cortisol, Aldosterone, Testosterone, Triiodothyronine, Calcitonin and PTH as well as the parameters of heart rate variability (HRV) [5] and blood pressure in triple test [4]. The good old Stange's and Genchy's tests were carried out on occasion. Please see the details in the previous article [1].

EEG recorded a hardware-software complex "NeuroCom Standard" (KhAI Medica, Kharkiv, Ukraine) monopolar in 16 loci (Fp1, Fp2, F3, F4, F7, F8, C3, C4, T3, T4, P3, P4, T5, T6, O1, O2) by 10-20

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international system, with the reference electrodes A and Ref on the earlobes. Two minutes after the eyes had been closed, 25 sec of artifact free EEG data were collected by computer. Among the options considered the average EEG amplitude (мV), average frequency (Hz), frequency deviation (Hz), index (%), coefficient of asymmetry (%), absolute ($мV^2$/Hz) and relative (%) PSD of basic rhythms: в (35м13 Hz), б (13-8 Hz), и (8-4 Hz) and д (4-0,5 Hz) in all loci, according to the instructions of the device. In addition, calculated coefficient of Asymmetry (As) and Laterality Index (LI) for PSD each Rhythm using formulas (1):

We calculated for each locus EEG the Entropy (h) of normalized PSD using Popovych's IL formulas [6] based on classic annon's CE [1948] formula (2)

$$As, \% = 100 \bullet (Max - Min)/Min;\ LI, \% = \Sigma[200 \bullet (Right - Left)/(Right + Left)]/8. \quad (1)$$

$$hEEG = -[PSD\alpha \bullet \log_2 PSD\alpha + PSD\beta \bullet \log_2 PSD\beta + PSD\theta \bullet \log_2 PSD\theta + PSD\delta \bullet \log_2 PSD\delta]/\log_2 4. \quad (2)$$

Immune status evaluated as described in the manuals [7]. For phenotyping subpopulations of lymphocytes used the methods of rosette formation with sheep erythrocytes on which adsorbed monoclonal antibodies against receptors CD3, CD4, CD8, CD25, CD22 and CD56 from company "Granum" (Kharkiv) with visualization under light microscope with immersion system. The state of humoral immunity judged by the concentration in serum of Immunoglobulins of classes G, A, M (ELISA, analyser "Immunochem", USA) and circulating0 immune complexes (by polyethylene glycol precipitation method).

Parameters of phagocytic function of neutrophils estimated as described by Kovbasnyuk MM [8]. The objects of phagocytosis served daily cultures of Staphylococcus aureus (ATCC N 25423 F49) as typical specimen for Gram-positive Bacteria and Escherichia coli (O55 K59) as typical representative of Gram-negative Bacteria. Take into account the following parameters of Phagocytosis: activity (percentage of neutrophils, in which found microbes - Hamburger's Phagocytic Index PhI), intensity (number of microbes absorbed one phagocytes - Microbial Count MC or Right's Index) and completeness (percentage of dead microbes - Killing Index KI).

Normal (reference) values of variables are taken from the instructions and/or database of our group [4, 9; 20].

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

Results

We will remind that in 56 cases the values of renal clearance of uric acid were in the classical normal range, in 11 cases reduced clearance, that is, a urate-retaining kidney, was established, instead, in 21 cases were diagnosed a urate-losing kidney, including in three cases drastically expressed, therefore they were allocated to a separate cluster (Fig. 1). It has been found that in patients with normal and reduced clearance Fractional Excretion is moderately increased and normal, that is, the patterns of two key parameters of uric acid metabolism differ both quantitatively and qualitatively. This discrepancy is caused by the rate of glomerular filtration that follows from the equation:

Fractional excretion = 100•Clearance/ Glomerular filtration rate. Correlation between variables is significant but only mediocre strength (r=0.46).

Further, following the Truskavetsian Scientific School algorithm [10, 11], all registered variables were normalized. Screening has found a number of variables that deviated from normal levels, followed by grouping in clusters.

The most similar to the clearance pattern is the pattern of the 5 variables: Total Power of HRV, PSD of LF band HRV, pNN_{50} and Triangular index HRV as well as PTH level (Fig. 2). To the Fractional Excretion pattern is similar the pattern of Uricosuria and relative PSD of LF band HRV. Last pattern differs from the previous ones.

Pattern of Uricemia, by definition, is a

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mirror to such a Clearance (Fig. 3). The most similar to it is the pattern of constellation of 6 variables: index of б-rhythm, PSD of д-rhythm in T6 and O2 loci, relative PSD of VLF band HRV, serum Calcitonin normalized by sex, and Stange's test. The latter correlates with the relative PSD of в-rhythm in Fp1 (r= -0.30) and O1 (r= -0.21) loci, that is, can be considered a neural marker. Other patterns differs from the previous ones.

Discriminant analysis (method forward stepwise) was used to identify the specific accompaniment of uric acid clearance. The discriminant model includes, in addition to clearance, fractional excretion, uricosuria and uricemia by definition, 14 EEG, 7 HRV, 4 blood pressure and 3 endocrine variables.

Instead, some parameters, despite their obvious recognition ability, were outside the discriminant model, apparently due to duplication/redundancy of information.

Calculating the values of the discriminant roots for each person based on raw coefficients and constants allows to visualize each patient in the information space of these roots (Fig. 4).

At the next stage of the analysis, the normalized values of the variables were grouped into three discriminant roots based on the structural coefficients. 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.

Extreme localization along the axis of the first root (Fig. 4, see also Fig. 2) of three patients with drastically increased clearance of uric acid reflects, in addition to hyperuricosuria by definition, their drastically increased PSD of LF band of HRV (reflects barorecertor activity as well as both vagal and sympathetic tone [12]) as well as increased levels of HRV-markers both vagal (total power, pNN_{50}, TNN) and sympathetic (PSD LF relative and LFnu, Baevskiy's ARSI) tone. It is significant that diastolic blood pressure and Pd2/Pd1 Ratio, which are subject to the influence of the autonomic nervous system, were also found in this series of variables [11, 13] as well as PTH (more on it later).

At the opposite pole are localized patients with reduced uric acid clearance, which is accompanied by reduced or minimal for the sample levels of the listed variables. The intermediate position of the members of the other two clusters reflects the intermediate levels of the listed variables, which are negatively correlated with the first root.

On the other hand, the extreme localization of patients with drastically increased uric acid clearance reflects, above all, their hypouricemia by definition, which is accompanied by reduced or minimal for the sample levels of variables that are positively correlated with the first root. These are, firstly, the index of the б-rhythm, the amplitude of the в-rhythm and its PSD in T3 and O1 loci (*left*-sided) and the PSD of the д-rhythm in T6 and O2 loci (*right*-sided); secondly, PSD of ULF and VLF bands of HRV, the physiological interpretation of which remains a subject of debate, but a connection with aldosterone, testosterone, catecholamines, sympathetic and vagal tone, etc. is assumed [12, 20]; thirdly, calcitonin; and, finally, Stange's test, somehow related to в-rhythm generating neurons, apparently inhibiting exhalation.

Hyperuricemia, on the contrary, is accompanied by elevated or maximum for the sample levels of the listed variables, and their intermediate quasi-normal levels occur in members of the other two clusters.

Patients with increased clearance of uric acid are additionally distinguished from others along the axis of the second root. Their top position reflects the minimum for the sample aldosterone and triiodothyronine levels in combination with the maximum for the sample levels of PSD of the в-rhythm in Fp1, T5 and F3 loci (*left*-sided). The lower position is occupied by a cluster of persons with reduced clearance, and the intermediate position is occupied by a cluster of persons with normal clearance.

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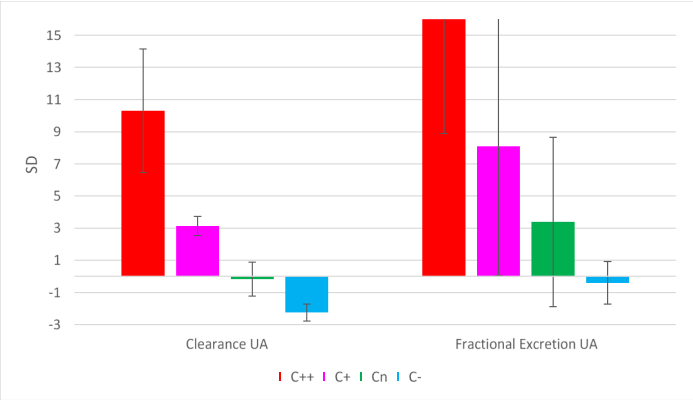

Fig. 1. Clusters of uric acid clearance (C) and their fractional excretion accompaniment

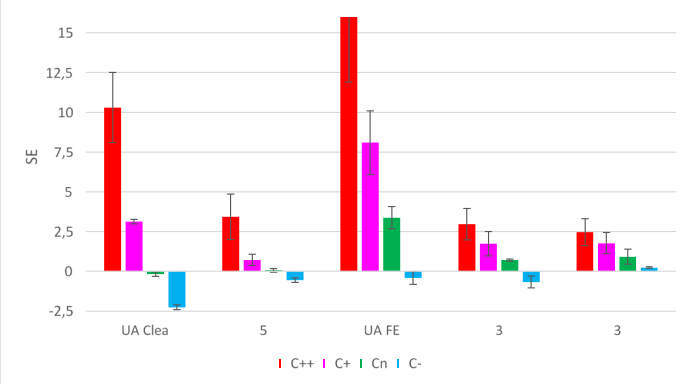

Fig. 2. Patterns of accompanied levels of neuro-endocrine parameters and uric acid fractional excretion at four clusters of uric acid clearance. *Under each pattern the number of variables is indicated*

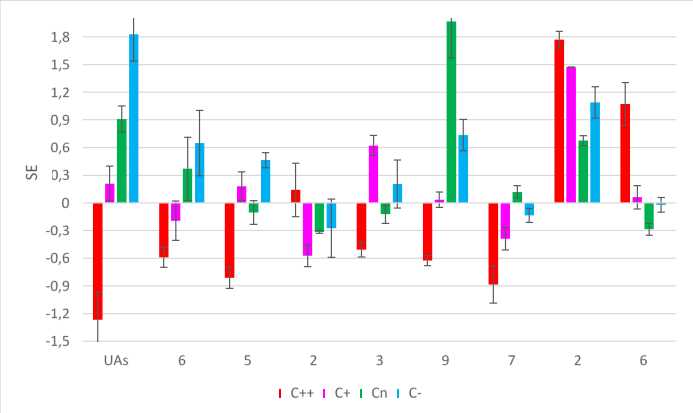

Fig. 3. Patterns of accompanied serum uric acid and neuro-endocrine parameters levels at four clusters of uric acid clearance. *Under each pattern the number of variables is indicated*

Finally, patients with normal uric acid clearance are additionally separated from the two adjacent ones along the axis of the third root. Their top position reflects, firstly, the maximally increased PSD levels of the д-rhythm in seven loci on both sides of the scalp, as well as its amplitude and index; and secondly, the amplitude and PSD of the б-rhythm in both occipital and parietal loci, as well as the intensity of phagocytosis of Staphylococus aureus by neutrophils and Ps2/Ps1 Ratio, are normal, but maximal for the sample.

On the other hand, normal clearance of uric acid is accompanied, firstly, by minimally elevated levels of systolic pressure and Pd3/Pd1 Ratio; and secondly, by normal, but minimal for the sample, levels of HRV-markers of vagal tone, as well as entropy in T3 and P3 loci and PSD of в-rhythm in O1 locus.

In general, in the information field of the three discriminant roots, the demarcation of the four clusters is very clear, which is documented by Mahalanobis distance calculations (Table 1).

With the help of classification functions coefficients and constants (Table 2), we will find out the possibility of identifying the belonging of this or that person to this or that cluster without errors (Table 3).

Discussion

So, in this and the previous [1] articles, we revived the forgotten concept of Karve MD of the urate-conserving and urate-losing kidney and significantly supplemented it with data on the specific metabolic, as well as neural, endocrine and immune accompaniments of uric acid metabolism in line with the concepts of the functional-metabolic continuum [14] and the neuro-endocrine-immune complex [4]. It is significant that the specificity is so pronounced that it allows retrospectively to identify without error even a rare cluster consisting of only three members with a drastically high clearance of urates.

We specified the role of the nervous

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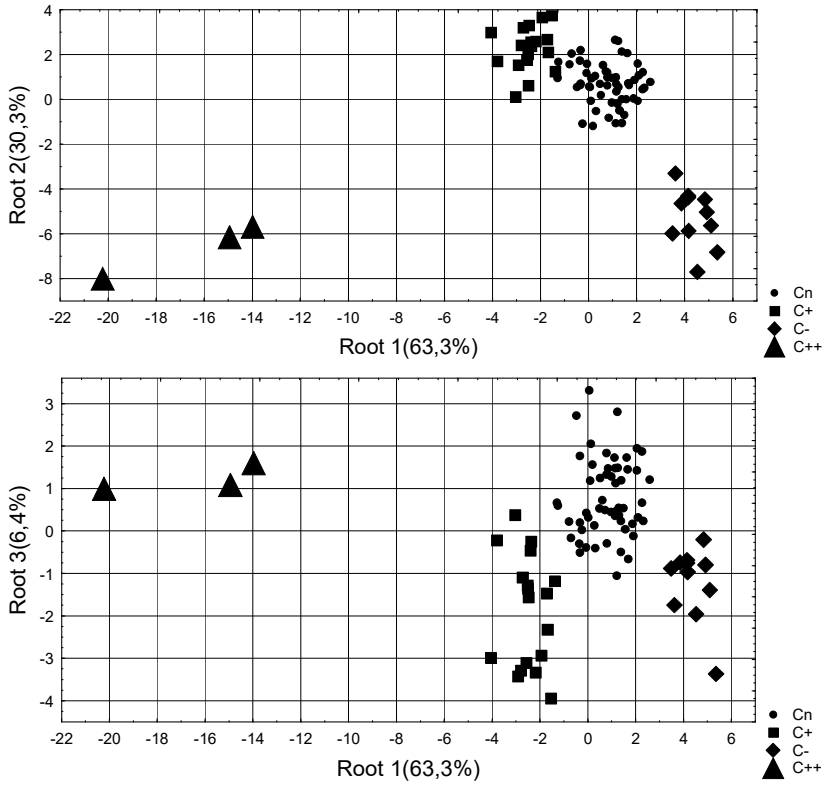

Fig. 4. Scattering of individual values of the discriminant roots of patients from different clusters of uric acid clearance

Table 1

Mahalanobis distances between clusters, F-values (df=32.5) and p-levels

Clusters	Cn	C+	C-	C++
Cn	0	20	52	349
C+	5.5 10^{-6}	0	105	282
C-	9.5 10^{-6}	14.1 10^{-6}	0	439
C++	19.6 10^{-6}	14.3 10^{-6}	20.4 10^{-6}	0

system in the regulation of uric acid clearance.

Authors have also demonstrated that Type II nerves are immuno-reactive for neuropeptide Y while Type I nerves are not. This led them to hypothesis that in the kidney, distinct populations of nerves innervate specific effector tissues and that these nerves may be selectively activated, setting the basis for the differential neural control of glomerular filtration rate. In physiological studies, authors demonstrated that differential changes in glomerular capillary pressure occurred in response to graded reflex activation of the renal nerves, compatible with their hypothesis. Thus, sympathetic outflow may be capable of selectively increasing or decreasing glomerular capillary pressure and hence glomerular filtration rate by differentially activating separate populations of renal nerves. This has important implications for our understanding of the neural control of body fluid balance in health and disease.

We found out that the increased clearance of urates is accompanied by the strengthening, and the reduced clearance - by the weakening of both sympathetic and vagal regulatory influences. Now we found the connection of urate clearance with arterial pressure, especially diastolic.

Patients with different conditions associated with hyperuricemia and hypouricemia were classified into 1 of these 4 categories: (a) increased synthesis of uric acid, manifested by hyperuricemia and increased uric acid excretion (eg, patients with phosphoribosylpyrophosphate synthetase [PRPPs] overactivity [Online Mendelian Inheritance in Man {OMIM}, 300661] and Lesch-Nyhan disease [OMIM, 300322] or its variants [OMIM, 300323] due to complete and partial hypoxanthine phosphoribosyltransferase [HPRT] deficiency, respectively; (b) diminished uric acid synthesis, manifested by hypouricemia and reduced uric acid excretion (eg, patients with hereditary xanthinuria [OMIM, 278300]); (c) increased uric acid excretion, manifested by hypouricemia and enhanced urinary uric acid output (eg, patients with renal hypouricemia or medul-

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lary thyroid carcinoma); or (d) diminished uric acid excretion, manifested by hyperuricemia with decreased uric acid excretion (eg, men and women with primary gout) or uromodulin-associated kidney disease [OMIM, 162000]).

Urate handing in the human body is a complex system including three major processes: production, renal elimination, and intestinal elimination. A change in any one of these can affect both the steady-state serum urate concentration as well as other urate processes. The remarkable complexity underlying urate regulation and its maintenance at high levels in humans suggests that this molecule could potentially play an interesting role other than as a mere waste product to be eliminated as rapidly as pos-

Table 2

Coefficients and constants for cluster classification functions

Clusters	Cn	C+	C-	C++
Variables	p=,636	p=,205	P=,125	p=,034
Uric Acid Clearance, mL/min	21,87	23,05	25,13	47,57
Uricosuria, mM/24 h	-54,72	-51,47	-66,32	-99,13
Uricemia, μM/L	628,7	565,5	825,6	1069
PSD Fp1-β, %	0,976	0,939	0,820	0,775
BP systolic, mmHg	0,292	0,266	0,595	0,875
VLF band HRV, msec^2	-0,009	-0,009	-0,007	-0,017
Calcitonin normalized, Z	-8,240	-9,855	-5,469	-16,30
ULF band HRV, %	2,655	2,626	4,216	4,068
PSD T5-β, μV^2/Hz	-0,272	-0,256	-0,192	-0,402
PSD O1-α, μV^2/Hz	0,031	0,026	0,045	0,016
PSD T5-δ, μV^2/Hz	0,012	0,015	0,003	0,009
BP diastolic, mmHg	1,463	1,509	0,916	1,349
pNN$_{50}$ HRV, %	-4,573	-3,881	-6,005	-4,724
RMSSD HRV, msec	2,049	1,552	3,375	0,701
UA Fractional Excretion, %	46,76	63,42	6,118	126,2
PTH, pM/L	5,952	7,529	2,098	10,23
Total Power HRV, msec^2	0,025	0,024	0,022	0,041
Pd2/Pd1 Ratio	113,0	125,5	22,57	110,9
LFnu HRV, %	-0,280	-0,287	-0,257	-1,020
PSD F3-β, μV^2/Hz	-0,485	-0,459	-0,586	-0,680
Pd3/Pd1 Ratio	370,2	362,5	431,7	350,6
PSD T3 Entropy	34,93	29,96	78,97	21,18
PSD T3-β, μV^2/Hz	0,233	0,227	0,217	0,377
ULF band HRV, msec^2	-0,202	-0,186	-0,217	-0,292
PSD T6-δ, μV^2/Hz	-0,105	-0,106	-0,032	-0,161
Index-α, %	0,691	0,619	1,006	0,671
PSD O1-δ, μV^2/Hz	0,037	0,035	0,020	0,057
PSD F7-δ, μV^2/Hz	0,017	0,016	0,007	0,023
PSD P3 Entropy	193,6	188,7	169,0	264,5
Amplitude-α, μV	0,050	0,113	-1,352	1,215
Amplitude-β, μV	0,085	0,425	1,081	0,185
Aldosterone, pM/L	0,365	0,395	0,276	0,566
Constants	-604,0	-620,3	-648,0	-1074

Table 3

Classification Matrix. Rows: observed, columns: predicted classification

Clusters of Clearance	Percent correct	Cn p=,636	C+ p=,205	C- p=,125	C++ p=,034
Normal	100	56	0	0	0
Increased	100	0	18	0	0
Decreased	100	0	0	11	0
Very increased	100	0	0	0	3
Total	100	56	18	11	3

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sible [15].

Under normal conditions, nearly 300 - 400 mg (17.8 - 20.7 mM) is produced from de novo synthesis and tissue catabolism. Endogenous production of urate derives from the normal cellular metabolism (turnover) of purines such as DNA, RNA, and ATP: purine'!free nucleic acids'!inosinic acid'!hypoxanthine'!xanthine (by xanthine oxidase)'!uric acid. Abnormally high synthesis of uric acid occurs with gout, myeloproliferative disorders, certain congenital metabolic defects and patients receiving chemotherapy due to rapid cell turnover. The other source of substrates for urate production is dietary purines that are metabolized to urate in the intestine [*16*]. Therefore, the amount of purines in diet can affect urate production, though a significant reduction in dietary purines is required to have clinically relevant decreases in serum UA [*17*]. Other factors that appear to impact production are consumption of fructose and beer [*18*]. As a result of environmental and physiological changes, serum UA levels can vary significantly from day to day. Elimination of urate occurs via two routes: renal elimination (1.5–4.5 mM/24h) and extra-renal elimination. Urate elimination is a dynamic process mediated by multiple specific import and export transporters in the renal proximal tubule, salivary glands and the intestinal mucosa [*19*]. The amount of urate excreted via these elimination routes can be quantified as clearance in milliliters per minute of serum (or blood) in the circulation that is cleared. Thus, the total clearance of urate is the sum of the renal clearance and the extra-renal clearance. The total rate of urate removed per minute is the product of the total clearance and the serum UA concentration. So, at steady state, for a given rate of production, serum UA will settle at a point at which total elimination is equal to production. These relationships form the basis for understanding the dynamics of urate concentration in the serum [15].

Our current view is that, after glomerular filtration, 90–97% of urate is reabsorbed in the proximal tubule. Tubular secretion of urate does occur; however, it is not yet clear if the secretion happens concomitantly with reabsorption and/or if there is post-reabsorptive secretion within the tubule. Given the ~180 L of water cycled through the kidney each day together with the rapid cycle of urate filtration, reabsorption and secretion, any given molecule of urate may pass through the kidney multiple times a day before being excreted. This is accomplished via an array of renal transporters driving both reabsorption and secretion of urate. No method is available to measure renal urate reabsorption directly. However, because urine urate excretion is less than 10% of the filtered urate load, there is no question that reabsorption represents a significant component of urate handling by the kidney.

Acknowledgment

We express sincere gratitude to colleagues from sanatorium "Moldova" for help in conducting this investigation.

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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