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Peculiarities of relationships between plasma levels of nitrogenous metabolites and EEG & HRV parameters in patients with postradiation encephalopaty

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Summary
Background. Recently we shown that nitrogenous plasma metabolites (uric acid, bilirubin, urea and creatinine), even in the absence of uremia, are able to influence the state of the anxiety, autonomic and central nervous and endocrine systems, apparently through aryl hydrocarbon and adenosine receptors of neurons and endocrine cells and/or directly. Sexual dimorphism in the neurotropic effects of uric acid in neurologically healthy patients was also revealed. The purpose of this study is to compare nitrogenous-neural relationships in neurologically healthy men and those with post-radiation encephalopathy (PREP). **Materials and Methods**. The object of observation were neurologically healthy 31 men (24÷69 y) and 19 patients (26÷61 y) with PREP. The relationships between plasma levels of nitrogenous metabolites, on the one hand, and EEG and HRV parameters, on the other, were analyzed. **Results**. By constructing regression models with stepwise elimination it was found that the multiple correlation coefficient (R±μ) of creatinine with neural parameters in patients with PREP significantly exceeded that of control patients (0,762±0,069 vs 0,409±0,107; t=2,62; p=0,011). With regard to urea, the differences are insignificant (0,801±0,059 vs 0,694±0,066; t=1,17; p>0,2), and with regard to bilirubin (0,548±0,115 vs 0,402±0,107; t=0,94) and uric acid (0,496±0,124 vs 0,549±0,089; t=0,32), there are practically no differences. **Conclusion.** Post-radiation encephalopathy is accompanied not only by deviations from the norm of a number of EEG and HRV parameters, but also by their increased sensitivity to creatinine and, to a lesser extent, urea, but not to bilirubin and uric acid.
Keywords: plasma bilirubin, uric acid, urea, creatinine, ongoing EEG and HRV, relationships, post-radiation encephalopathy, men.

INTRODUCTION

Recently we shown that nitrogenous plasma metabolites (uric acid, bilirubin, urea and creatinine), even in the absence of uremia, are able to influence the state of the anxiety, autonomic and central nervous and endocrine systems, apparently through aryl hydrocarbon and adenosine receptors of neurons and endocrine cells and/or directly [3-5,15,]. Sexual dimorphism in the neurotropic effects of uric acid in neurologically healthy patients was also revealed [21]. Apparently, the sensitivity of neurons to endogenous nitrogenous metabolites is also affected by neurological diseases. Based on this hypothesis, purpose of this study is to compare nitrogenous-neural connections in neurologically healthy men and those with post-radiation encephalopathy.

MATERIAL AND METHODS

The object of observation was two cohorts of men. The first cohort consisted of neurologically healthy employees (n=31; 24÷69 years) of the clinical sanatorium "Moldova" and PrJSC “Truskavets' Spa”. The second cohort consisted of 19 men (26÷61 years) liquidators of the accident at the Chornobyl NPP in 1986 [2,7], who in 1997 were undergoing rehabilitation treatment of urate urolithiasis and chronic pyelonephritis in the sanatorium of the Ministry of Internal Affairs "Perlyna Prykarpattya" [8,16,22,23]. According to the documents, the total effective radiation dose was 10÷25 cGy, which caused encephalopathy [6,13,17-20,27,29], the manifestations of which was confirmed by us by EEG changes [28].

The survey was conducted twice with an interval of 4-14 days.

We analyzed the plasma levels of the Bilirubin (by diazoreaction using the Jedrashik-Kleghorn-Grof method), Uric acid (by uricase method), Urea (by urease method by reaction with phenol hypochlorite) and Creatinine (by Jaffe's color reaction by Popper's method).

The analyzes were carried out according to the instructions described in the manual [9]. The analyzers “Pointe-180” ("Scientific", USA) and “Reflotron” (Boehringer Mannheim, BRD) were used. The reference values are taken from the manual [14].

To assess the parameters of heart rate variability (HRV) recorded during 7 min electrocardiogram in II lead (software-hardware complex "CardioLab+HRV", KhAI-MEDICA, Kharkiv). For further analysis the following parameters HRV were selected [1,12]. Temporal parameters (Time Domain Methods): the standard deviation of all NN intervals (SDNN), the square root of the mean of the sum of the squares of differences between adjacent NN intervals (RMSSD), the percent of interval differences of successive NN intervals greater than 50 msec (pNN_{50}). Spectral parameters (Frequency Domain Methods): power spectrum density (PSD) bands of HRV: high-frequency (HF, range 0,4÷0,15 Hz), low-frequency (LF, range 0,15÷0,04 Hz), very low-frequency (VLF, range 0,04÷0,015 Hz) and ultralow-frequency (ULF, range 0,015÷0,003 Hz). Derived indices were calculated: Baevskiy's Activity Regulatory Systems (BARSI), Centralization Index=(VLF+LF)/HF; LF/HF, HFnu.

Simultaneosly EEG recorded a hardware-software complex “NeuroCom Standard” (KhAI MEDICA, Kharkiv) monopolar in 16 loci (Fp1, Fp2, F3, F4, F7, F8, C3, C4, T3, T4, P3, P4, T5, T6, O1, O2) by 10-20 international system, with the reference electrodes A and Ref on tassels the ears. The duration of the epoch was 25 sec. Among the options considered the average EEG amplitude (μV), average frequency (Hz), frequency deviation (Hz) as well as absolute ($\mu V^2/Hz$) and relative (%) PSD of basic rhythms: β (35÷13 Hz), α (13÷8 Hz), θ (8÷4 Hz) and δ (4÷0,5 Hz) in all loci, according to the instructions of the device.

We calculated also for HRV and each locus of EEG the Entropy (h) of normalized PSD using Popovych's IL [11,26] formulas based on classic Shannon's CE [30] formulas:

$hEEG = - [PSD\alpha \bullet \log_2 PSD\alpha + PSD\beta \bullet \log_2 PSD\beta + PSD\theta \bullet \log_2 PSD\theta + PSD\delta \bullet \log_2 PSD\delta]/\log_2 4$

$hHRV =-[PSHF \bullet \log_2 PSHF+PSLF \bullet \log_2 PSLF+PSVLF \bullet \log_2 PSVLF+PSULF \bullet \log_2 PSULF]/\log_2 4$

The need for simultaneous registration of HRV and EEG parameters is justified by the presence of regular bilateral relationships between them [24,25,31].

Results processed by using the software package "Statistica 64".

RESULTS AND DISCUSSION

Adhering to the repeatedly tested algorithm of the Truskavetsian Scientific School of Balneology, proposed by IL Popovych, a screening of correlations between parameters of nitrogenous metabolites, on the one hand, and parameters of EEG and HRV, on the other, was first performed. Next, regression models were built with stepwise exclusion of variables until the maximum Adjusted R^2 values were reached.

In patients with PREP uric acid upregulates relative PSD of VLF band HRV (Fig. 1) and theta-rhythm EEG in F3 locus, while downregulates alpha-rhythm EEG in Fp1 locus (Fig. 2). In general, uric acid determines these parameters by 24,6% (Table 1 and Fig. 3).

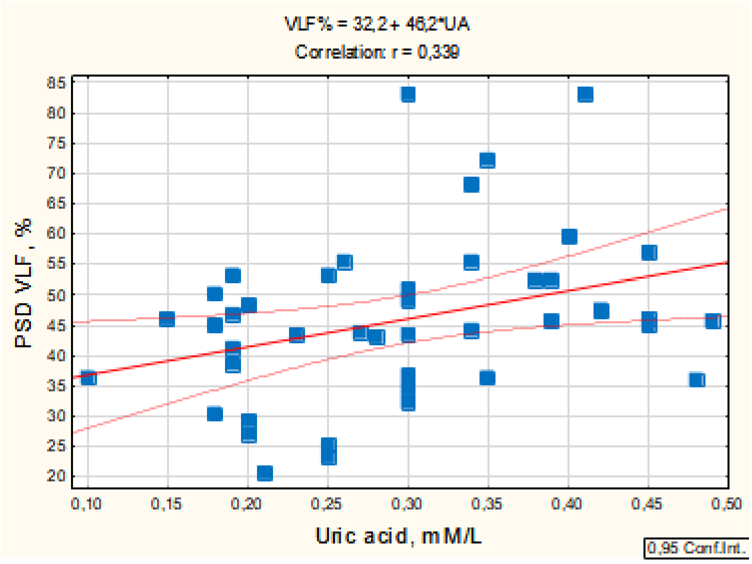


Fig. 1. Scatterplot of correlation between plasma uric acid (X-line) and relative PSD VLF band (Y-line) in patients with PREP

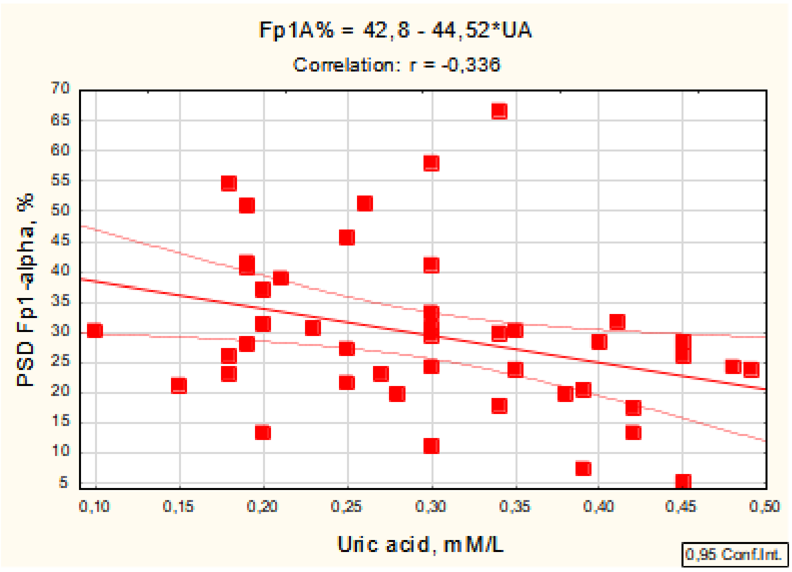
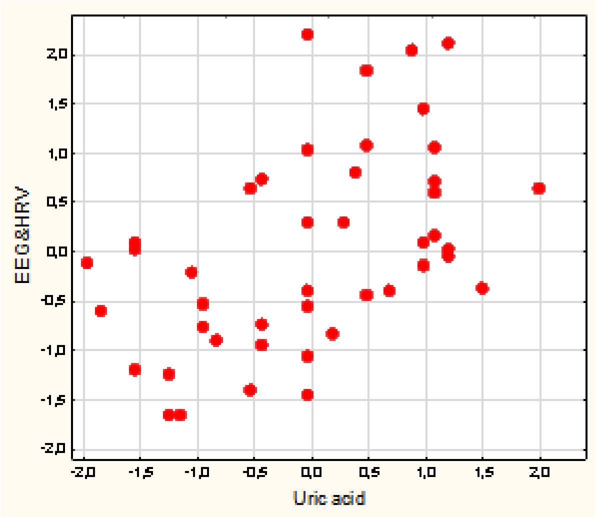


Fig. 2. Scatterplot of correlation between plasma uric acid (X-line) and relative PSD of alpha-rhythm in locus Fp1 (Y-line) in patients with PREP

Table 1. Regression Summary for Uric acid (mM/L) in patients with PREP
R=0,496; R^2=0,246; Adjusted R^2=0,189; $F_{(3,4)}$=4,3; p=0,010

N=38		Beta	St. Err. of Beta	B	St. Err. of B	$t_{(40)}$	p-level
Variables	r		Intercpt	0,216	0,068	3,17	0,003
VLF HRV PSD, %	**0,34**	0,306	0,138	0,0022	0,0010	2,22	0,032
F3-θ PSD, %	**0,28**	0,180	0,143	0,0032	0,0025	1,26	0,213
Fp1-α PSD, %	**-0,34**	-0,273	0,142	-0,0021	0,0011	-1,92	0,062



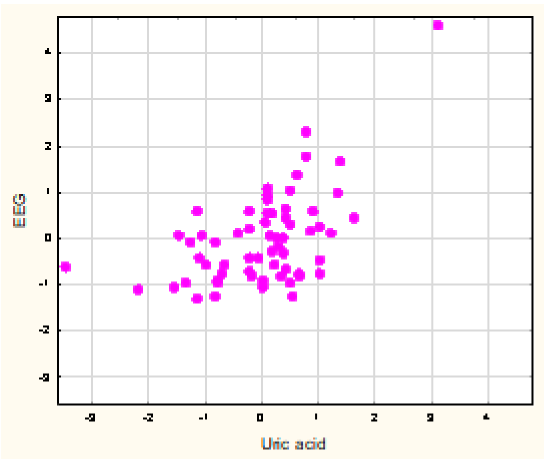
R=0,496; R^2=0,246; $\chi^2_{(3)}$=11; p=0,010; Λ Prime=0,754

Fig. 3. Scatterplot of canonical correlation between plasma uric acid (X-line) and EEG&HRV parameters (Y-line) in patients with PREP

In control patients, the degree of determination of neural parameters by uric acid was approximately similar, but the factor structure was completely different (Table 2 and Fig. 4).

Table 2. Regression Summary for Uric acid (mM/L) in control patients
R=0,549; R^2=0,302; Adjusted R^2=0,266; $F_{(3,6)}$=8,4; p=0,00011

N=62		Beta	St. Err. of Beta	B	St. Err. of B	$t_{(58)}$	p-level
Variables	r		Intercpt	288,5	37,1	7,78	10^{-6}
Entropy PSD O1	**0,30**	0,299	0,115	107,5	41,3	2,60	0,012
P4-β PSD, %	**-0,30**	-0,385	0,112	-2,237	0,651	-3,44	0,001
T6-δ PSD, %	**-0,33**	-0,296	0,113	-0,766	0,293	-2,62	0,011



R=0,549; R^2=0,302; $\chi^2_{(3)}$=21; p=0,00011; Λ Prime=0,698

Fig. 4. Scatterplot of canonical correlation between plasma uric acid (X-line) and EEG parameters (Y-line) in control patients

A similar situation was found in relation to the determination of neural parameters by bilirubin: the same measure of determination with a different factor structure (Figs 5-7 and Tables 3-4).

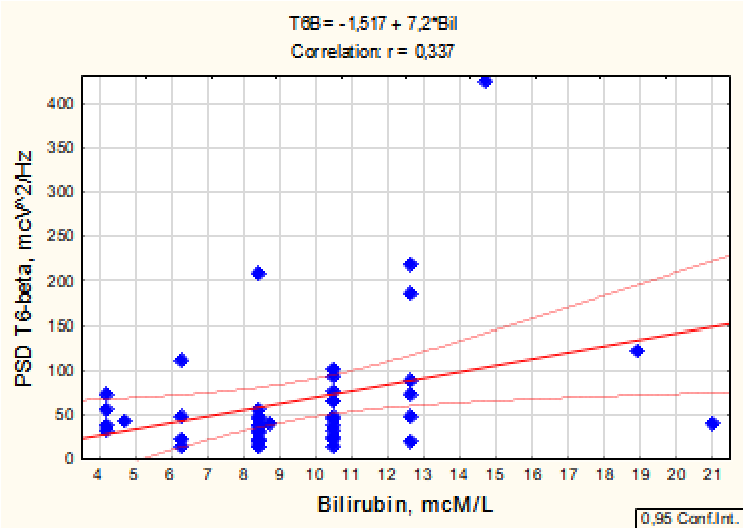
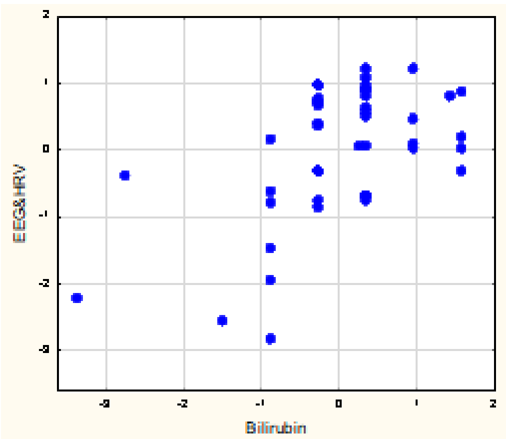


Fig. 5. Scatterplot of correlation between plasma bilirubin (X-line) and PSD of beta-rhythm in locus T6 (Y-line) in patients with PREP

Table 3. Regression Summary for Bilirubin (µM/L) in patients with PREP
$R=0,548$; $R^2=0,300$; Adjusted $R^2=0,247$; $F_{(3)}=5,7$; $p=0,002$

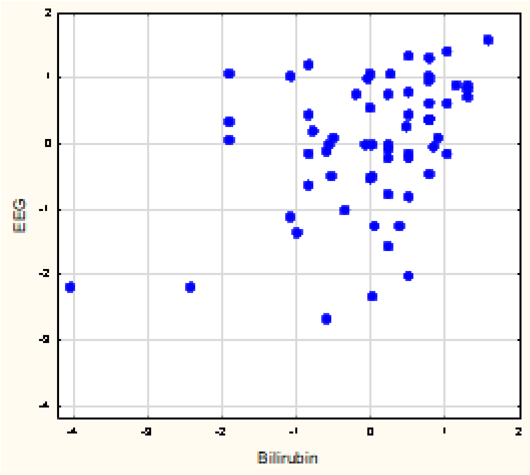
N=38		Beta	St. Err. of Beta	B	St. Err. of B	$t_{(40)}$	p-level
Variables	r		Intercpt	6,547	0,933	7,02	10^{-6}
T6-β PSD, µV²/Hz	**0,36**	0,370	0,133	0,017	0,006	2,78	0,008
Index θ, %	**0,35**	0,321	0,135	0,030	0,013	2,37	0,023
(VLF+LF)/HF ratio	**0,27**	0,232	0,136	0,098	0,058	1,71	0,095



$R=0,548$; $R^2=0,300$; $\chi^2_{(3)}=14$; $p=0,002$; Λ Prime=0,700
Fig. 6. Scatterplot of canonical correlation between plasma bilirubin (X-line) and EEG&HRV parameters (Y-line) in patients with PREP

Table 4. Regression Summary for Bilirubin (µM/L) in control patients
$R=0,402$; $R^2=0,162$; Adjusted $R^2=0,133$; $F_{(2,6)}=5,7$; $p=0,006$

N=62		Beta	St. Err. of Beta	B	St. Err. of B	$t_{(59)}$	p-level
Variables	r		Intercpt	10,40	1,22	8,51	10^{-6}
Deviation β, Hz	**0,35**	0,299	0,122	1,993	0,815	2,44	0,018
Fp2-β PSD, %	**0,28**	0,208	0,122	0,057	0,034	1,70	0,094



R=0,402; R^2=0,162; $\chi^2_{(2)}$=10,4; p=0,006; Λ Prime=0,838

Fig. 7. Scatterplot of canonical correlation between plasma bilirubin (X-line) and EEG&HRV parameters (Y-line) in control patients

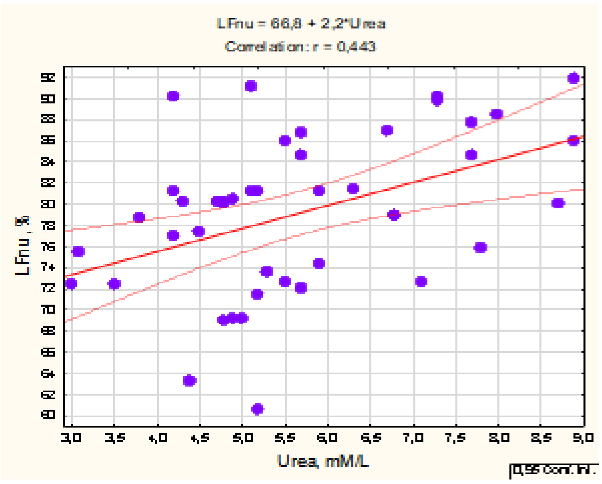


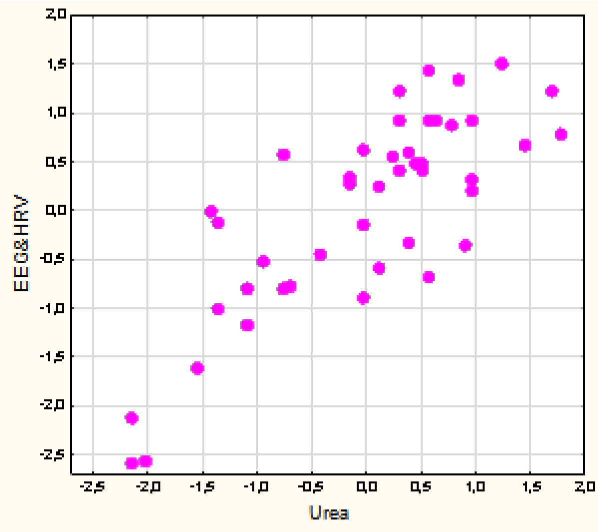
Fig. 8. Scatterplot of correlation between plasma urea (X-line) and LF/(LF+HF) ratio HRV (Y-line) in patients with PREP

The neurotropic activity of urea was significantly more pronounced in patients of both cohorts without statistically significant differences in multiple correlation coefficients R (t=1,17; p>0,2), but again with a different factor structure, except for the level of circulating catecholamines (HRV marker 1/Mo) (Tables 5-6 and Figs. 9-11).

Table 5. Regression Summary for Urea (mM/L) in patients with PREP

R=0,801; R^2=0,642; Adjusted R^2=0,547; $F_{(9)}$=6,8; p<10^{-4}

N=38		Beta	St. Err. of Beta	B	St. Err. of B	$t_{(34)}$	p-level
Variables	r		Intercpt	15,69	5,70	2,75	0,009
Entropy HRV	**-0,42**	-0,436	0,135	-5,727	1,774	-3,23	0,003
O1-δ PSD, %	**-0,33**	-0,498	0,155	-0,0403	0,0126	-3,21	0,003
Frequency α, Hz	**-0,31**	-0,269	0,121	-0,4010	0,1810	-2,22	0,033
Index β, Hz	**-0,31**	-0,253	0,110	-0,0261	0,0114	-2,29	0,028
HF HRV PSD, %	**-0,29**	0,229	0,229	0,0791	0,0791	1,00	0,324
LFnu HRV, %	**0,44**	0,281	0,218	0,0571	0,0443	1,29	0,206
O1-α PSD, %	**0,31**	-0,205	0,142	-0,0146	0,0101	-1,44	0,158
1/Mode HRV PSD, ms^{-}	**0,27**	-0,295	0,152	-0,0039	0,0020	-1,94	0,061
ULF HRV PSD, msec^2	**0,27**	0,223	0,127	0,0009	0,0005	1,76	0,087



R=0,801; R^2=0,642; $\chi^2_{(9)}$=38; $p<10^{-4}$; Λ Prime=0,358

Fig. 9. Scatterplot of canonical correlation between plasma urea (X-line) and EEG&HRV parameters (Y-line) in patients with PREP

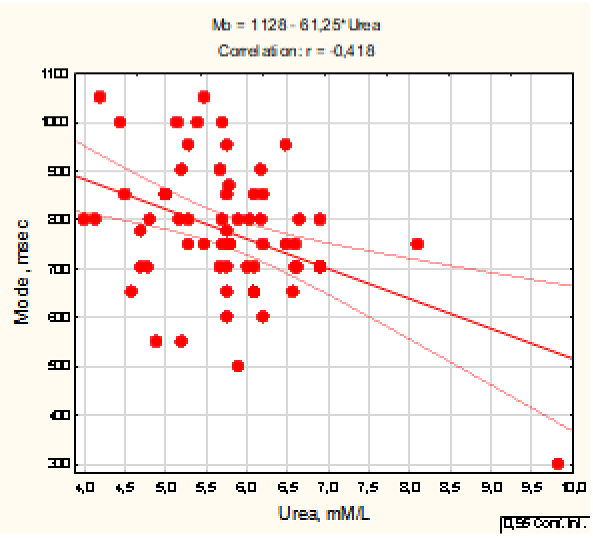
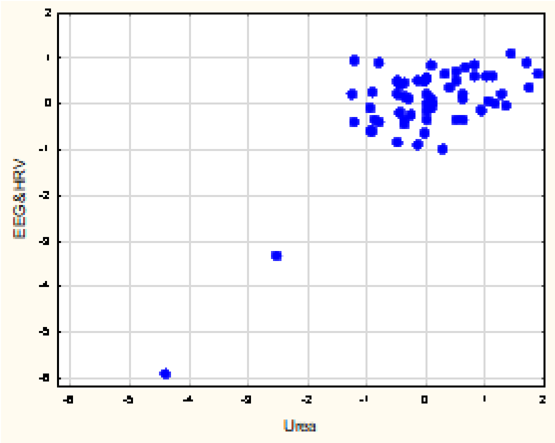


Fig. 10. Scatterplot of correlation between plasma urea (X-line) and the Mode HRV (Y-line) in control patients

Table 6. Regression Summary for Urea {mM/L} in control patients

R=0,694; R^2=0,482; Adjusted R^2=0,445; $F_{(4,6)}$=13,3; $p<10^{-5}$

N=38		Beta	St. Err. of Beta	B	St. Err. of B	$t_{(57)}$	p-level
Variables	r		Intercpt	6,57	0,58	11,34	10^{-6}
VLF HRV PSD, msec²	**0,46**	0,354	0,101	0,00016	0,00005	3,5	0,001
1/Mode HRV PSD, ms⁻	**0,42**	-0,311	0,098	-0,0021	0,0007	-3,18	0,002
C3-β PSD, %	**0,28**	0,262	0,102	0,023	0,009	2,57	0,013
T5-δ PSD, μV²/Hz	**0,28**	0,389	0,099	0,0005	0,0001	3,94	10^{-3}



R=0,694; R^2=0,482; $\chi^2_{(4)}$=38; p<10^{-6}; Λ Prime=0,518

Fig. 11. Scatterplot of canonical correlation between plasma urea (X-line) and EEG&HRV parameters (Y-line) in control patients

Instead, significant differences were found regarding the neurotropic activity of creatinine (Figs. 12-15 and Tables 7-8).

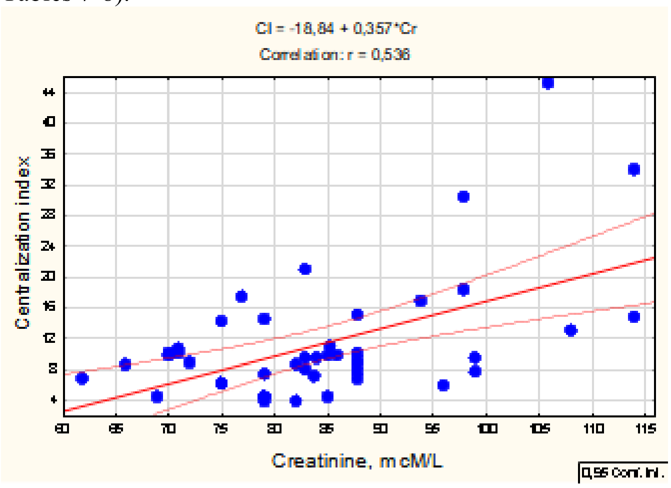


Fig. 12. Scatterplot of correlation between plasma creatinine (X-line) and centralization index HRV (Y-line) in patients with PREP

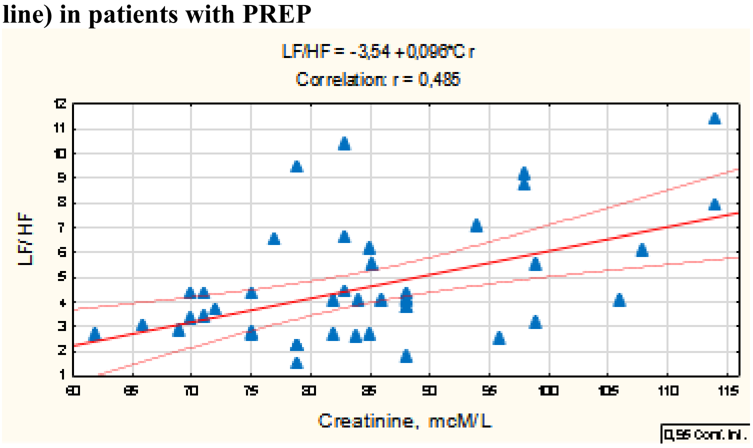
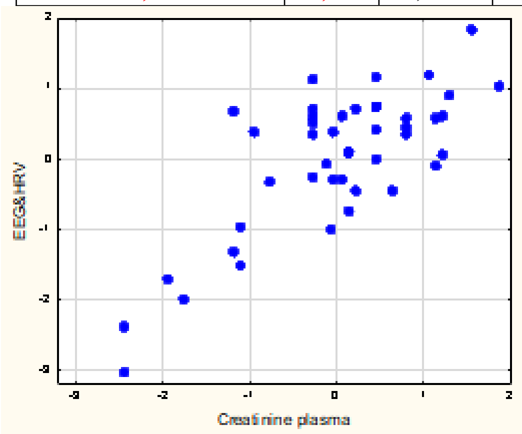


Fig. 13. Scatterplot of correlation between plasma creatinine (X-line) and LF/HF ratio HRV (Y-line) in patients with PREP

Table 7. Regression Summary for Creatinine (µM/L) in patients with PREP

R=0,762; R^2=0,581; Adjusted R^2=0,485; $F_{(8)}$=6,1; p<10^{-4}

N=38		Beta	St. Err. of Beta	B	St. Err. of B	$t_{(35)}$	p-level
Variables	r		Intercpt	155,5	38,1	4,08	10^{-3}
(VLF+LF)/HF ratio	**0,54**	0,410	0,133	0,616	0,200	3,08	0,004
LF/HF ratio	**0,49**	0,360	0,290	1,820	1,466	1,24	0,223
LFnu HRV, %	**0,42**	-0,345	0,292	-0,562	0,475	-1,18	0,245
Index θ, %	**0,35**	0,199	0,136	0,067	0,046	1,47	0,152
1/Mode HRV, msec^{-}	**0,26**	-0,237	0,134	-0,025	0,014	-1,77	0,085
ULF HRV PSD, %	**-0,36**	-0,176	0,122	-0,482	0,334	-1,44	0,158
Index β, Hz	**-0,28**	-0,215	0,120	-0,178	0,099	-1,79	0,083
T5-δ PSD, %	**-0,24**	-0,317	0,127	-0,217	0,087	-2,50	0,017



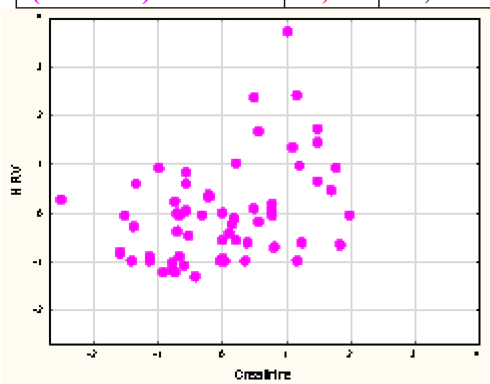
R=0,762; R^2=0,581; $\chi^2_{(8)}$=33; p<10^{-4}; Λ Prime=0,419

Fig. 14. Scatterplot of canonical correlation between plasma creatinine (X-line) and EEG&HRV parameters (Y-line) in patients with PREP

Table 8. Regression Summary for Creatinine (µM/L) in control patients

R=0,409; R^2=0,167; Adjusted R^2=0,124; $F_{(3,6)}$=3,9; p=0,014

N=62		Beta	St. Err. of Beta	B	St. Err. of B	$t_{(58)}$	p-level
Variables	r		Intercpt	61,5	19,8	3,10	0,003
LF HRV PSD, %	**0,30**	0,256	0,121	0,198	0,094	2,11	0,039
VLF HRV PSD, %	**-0,34**	0,159	0,121	0,271	0,206	-1,31	0,194
(VLF+LF)/HF ratio	**-0,26**	-0,222	0,121	-0,196	0,107	-1,84	0,071



R=0,409; R^2=0,167; $\chi^2_{(3)}$=10; p=0,014; Λ Prime=0,847

Fig. 15. Scatterplot of canonical correlation between plasma creatinine (X-line) and EEG&HRV parameters (Y-line) in control patients

The neurotropic activity of creatinine, judging by the coefficient of multiple correlation, in patients with PREP in general significantly exceeds that in control neurologically normal patients (t=2,62; p=0,011) (Fig. 16).

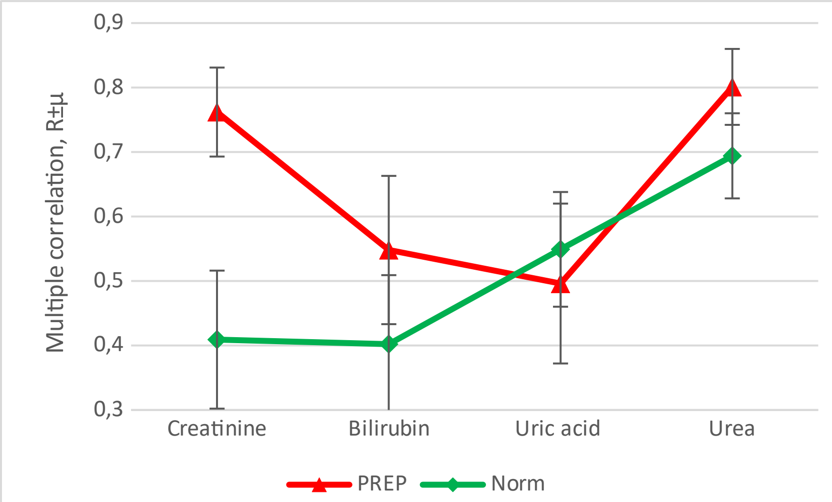


Fig. 16. Multiple correlations between plasma nitrogenous metabolites and EEG&HRV parameters in neurologically normal patients (Norm) and patients with post-radiation encephalopathy (PREP)

Further, following the algorithm, a canonical analysis of the relationships between the constellation of nitrogenous metabolites, on the one hand, and those EEG and HRV parameters that were previously included in their regression models was performed.

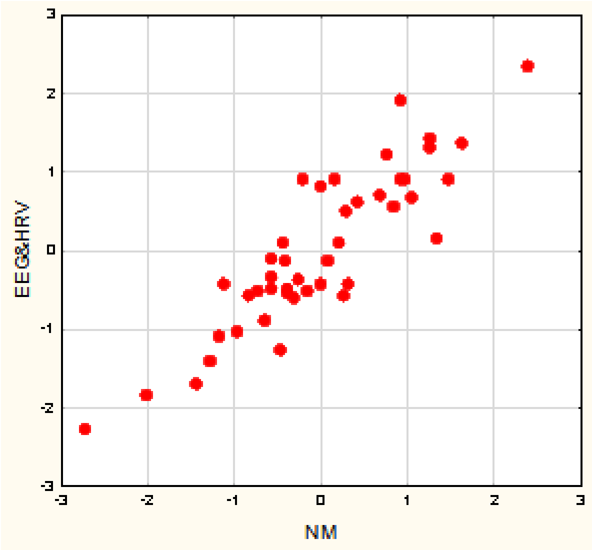
The program found in patients with PREP two pairs of significant canonical roots (Table 9). The factor structure of the nitrogenous root of the first pair is formed, first of all, by bilirubin and uric acid and, to a lesser extent and with the opposite load, urea. At the same time, the factor load on the part of creatinine is negligible.

Most of the factor structure of the neural root is represented by variables that are upregulated by bilirubin and/or uric acid, and other variables are subject to downregulation. The regulatory effect of urea on these parameters is the opposite.

Table 9. Factor structure of first pair of canonical Roots representing the plasma nitrogenous metabolites and EEG&HRV parameters in patients with PREP

Left side	**R1**
Bilirubin	**-0,544**
Uric acid	**-0,470**
Creatinine	**-0,143**
Urea	**0,243**
Right side	**R1**
O1-δ PSD, %	**-0,454**
VLF HRV PSD, %	**-0,326**
Index θ, %	**-0,324**
Index β, %	**-0,287**
T6-δ PSD, %	**-0,284**
Frequency α, Hz	**-0,250**
T6-β PSD, μV^2/Hz	**-0,241**
T5-δ PSD, %	**-0,219**
O1-α PSD, %	**0,583**
Fp1-α PSD, %	**0,477**
LF HRV PSD, %	**0,266**
Entropy HRV	**0,253**

In general, this neural constellation is determined by nitrogenous metabolites by 79,0% (Fig. 17).



R=0,889; R^2=0,790; $\chi^2_{(80)}$=112; p=0,011; Λ Prime=0,025

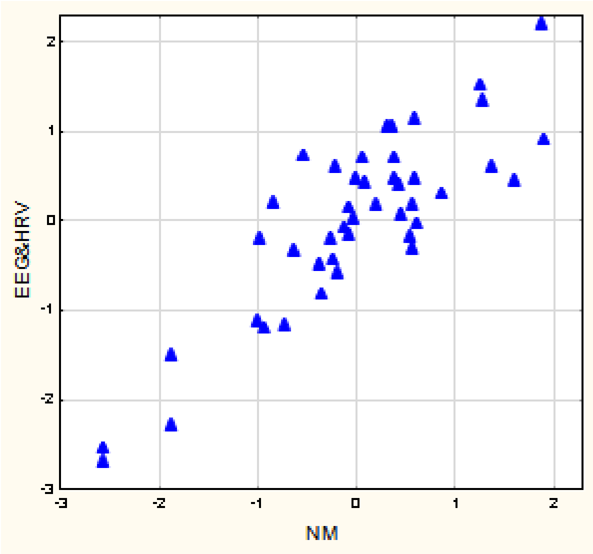
Fig. 17. Scatterplot of canonical correlation between plasma nitrogenous metabolites (X-line) and EEG&HRV parameters (Y-line) in patients with PREP. First pair of Roots

Instead, the nitrogenous root of the second pair receives maximum loads from creatinine and urea with a negligible contribution of uric acid (Table 10).

The factor structure of the neural root of the second pair is half represented by the same variables as the first pair. In general, the measure of their nitrogenous determination is 73,3% (Fig. 18).

Table 10. Factor structure of second pair of canonical Roots representing the plasma nitrogenous metabolites and EEG&HRV parameters in patients with PREP

Left side	**R2**
Creatinine	**-0,933**
Urea	**-0,920**
Bilirubin	**-0,433**
Uric acid	**0,014**
Right side	**R2**
(VLF+LF)/HF ratio	**-0,617**
LF/HF ratio	**-0,605**
LF/(LF+HF)	**-0,547**
Index θ, %	**-0,406**
1/Mode HRV, msec^{-}	**-0,401**
ULF HRV PSD, msec^2	**-0,275**
O1-α PSD, %	**-0,253**
LF HRV PSD, %	**-0,252**
Fp1-α PSD, %	**-0,238**
T6-β PSD, μV^2/Hz	**-0,236**
Entropy HRV	**0,574**
HF HRV PSD, %	**0,395**
ULF HRV PSD, %	**0,392**
Index β, %	**0,345**
T5-δ PSD, %	**0,340**
O1-δ PSD, %	**0,265**
Frequency α, Hz	**0,257**



R=0,856; R^2=0,733; $\chi^2_{(57)}$=64; p=0,236; Λ Prime=0,121

Fig. 18. Scatterplot of canonical correlation between plasma nitrogenous metabolites (X-line) and EEG&HRV parameters (Y-line) in patients with PREP. Second pair of Roots

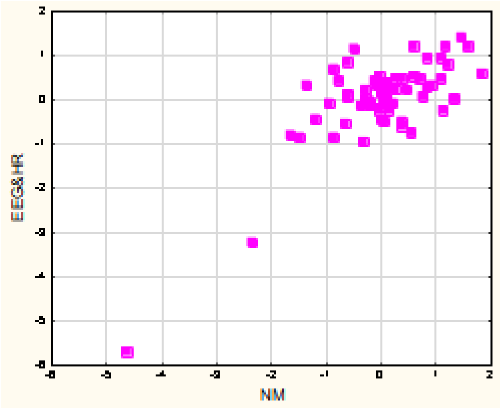
In control patients, the nitrogenous canonical radical of the first pair receives the lion's share of the factor load from urea with negligible contributions from uric acid and creatinine (Table 11).

The neural root is mainly represented by EEG&HRV parameters upregulated by nitrogenous metabolites. In general, the rate of determination is 57,4% (Fig. 19), which is significantly (t=1,99; p=0,05) inferior to nitrogen-neural determination in patients with PREP.

The factor structure of the nitrogenous radical of the second pair is formed mainly by bilirubin and uric acid with scant and opposite contributions of urea and creatinine (Table 12). Among the neural parameters of the second pair, only three in common with the first pair were found. The rate of nitrogen-neural determination (Fig. 20) is also weaker than that in patients with PREP (t=2,42; p<0,02).

Table 11. Factor structure of first pair of canonical Roots representing the plasma nitrogenous metabolites and EEG&HRV parameters in control patients

Left side	**R1**
Urea	**-0,961**
Bilirubin	**-0,298**
Uric acid	**-0,122**
Creatinine	**-0,097**
Right side	**R1**
VLF HRV PSD, msec^2	**-0,632**
1/Mode HRV, msec$^-$	**-0,492**
C3-β PSD, %	**-0,360**
T5-δ PSD, μV^2/Hz	**-0,325**
T6-δ PSD, μV^2/Hz	**-0,305**
Entropy PSD O1	**-0,259**
P4-β PSD, %	**-0,202**
(VLF+LF)/HF ratio	**-0,137**
O1-δ PSD, μV^2/Hz	**0,290**
Entropy HRV	**0,228**
T6-δ PSD, %	**0,205**

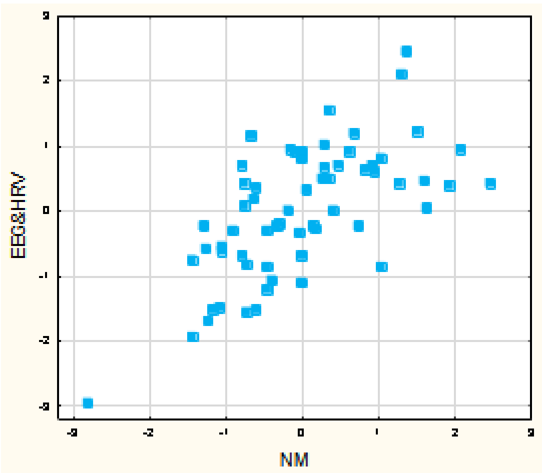


R=0,757; R^2=0,574; $\chi^2_{(64)}$=103; p=0,001; Λ Prime=0,129

Fig. 19. Scatterplot of canonical correlation between plasma nitrogenous metabolites (X-line) and EEG&HRV parameters (Y-line) in control patients. First pair of Roots

Table 12. Factor structure of second pair of canonical Roots representing the plasma nitrogenous metabolites and EEG&HRV parameters in control patients

Left side	**R2**
Bilirubin	**0,773**
Uric acid	**0,715**
Urea	**-0,213**
Creatinine	**-0,097**
Right side	**R2**
Entropy PSD T3	**0,553**
Deviation β, Hz	**0,518**
Entropy PSD O1	**0,462**
Fp2-β PSD, %	**0,461**
VLF HRV PSD, %	**0,258**
T6-δ PSD, %	**-0,503**
O1-δ PSD, μV^2/Hz	**-0,440**
1/Mode HRV, msec^{-}	**-0,427**
P4-β PSD, %	**-0,264**
LF HRV PSD, %	**-0,262**



R=0,651; R^2=0,424; $\chi^2_{(45)}$=60; p=0,062; Λ Prime=0,302

Fig. 20. Scatterplot of canonical correlation between plasma nitrogenous metabolites (X-line) and EEG&HRV parameters (Y-line) in control patients. Second pair of Roots

At the final stage of the comparative analysis, paired profiles of correlation coefficients with neural parameters were created for each individual nitrogenous metabolite, followed by their fragmentation into clusters.

The longest paired profile was found for urea (Fig. 21). Clear differences between its connections with neural parameters become even clearer after their clustering (Fig. 22; see digital data in the appendix).

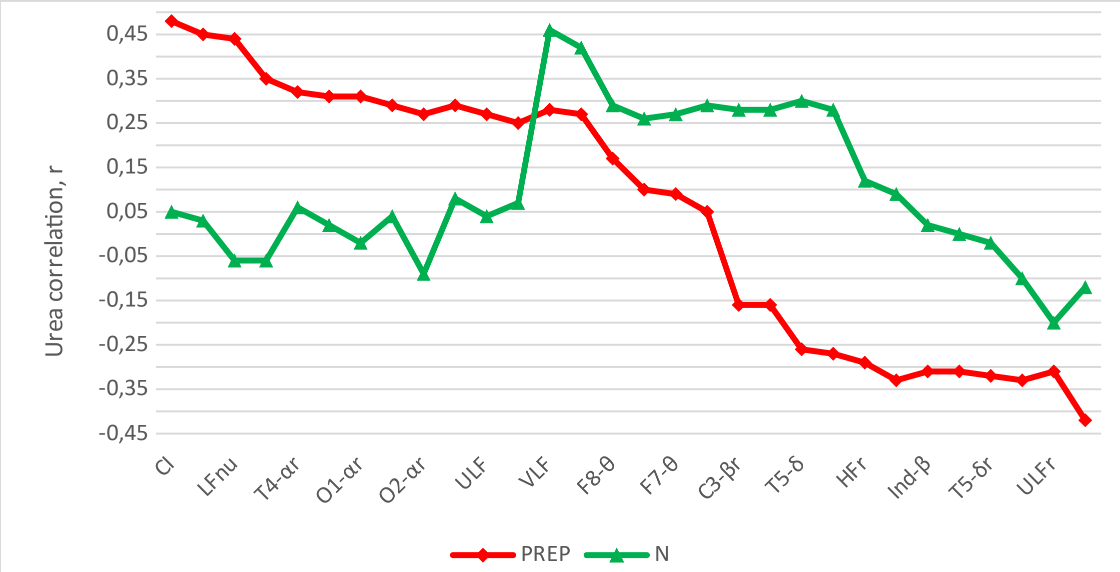


Fig. 21. Profiles of correlation coefficients between urea plasma level and EEG&HRV parameters in patients with post-radiation encephalopathy (PREP) and neurologically healthy (N)

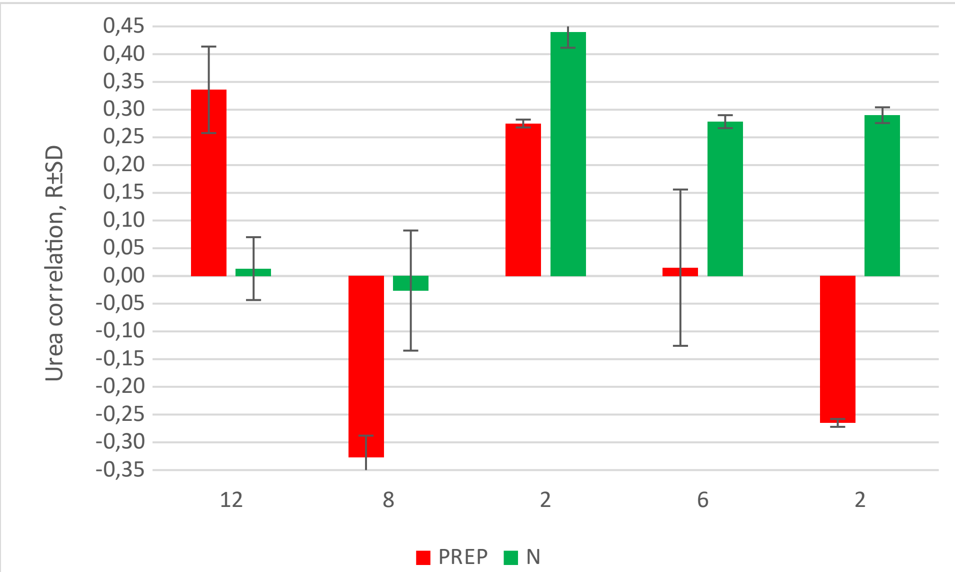


Fig. 22. Clusters of correlation coefficients between urea plasma level and EEG&HRV parameters in patients with post-radiation encephalopathy (PREP) and neurologically healthy (N). The number of pairs of variables is indicated under each cluster

As we can see, encephalopathy causes the appearance of 12 upregulatory and 8 downregulatory neural connections of urea, which are absent in control patients. Two positive connections under the influence of encephalopathy are weakened to the limit of significance, 6 more are nullified, and 2 more are reversed.

With regard to other nitrogenous metabolites, the situation is, in principle, similar in terms of the direction of the effect of encephalopathy, the differences concern only specific variables.

In particular, 4 positive and 5 negative connections are newly formed with creatinine, the opposite connections with LF and VLF bands are leveled off, as well as the negative connection with the centralization index is reversed (Figs. 23-24).

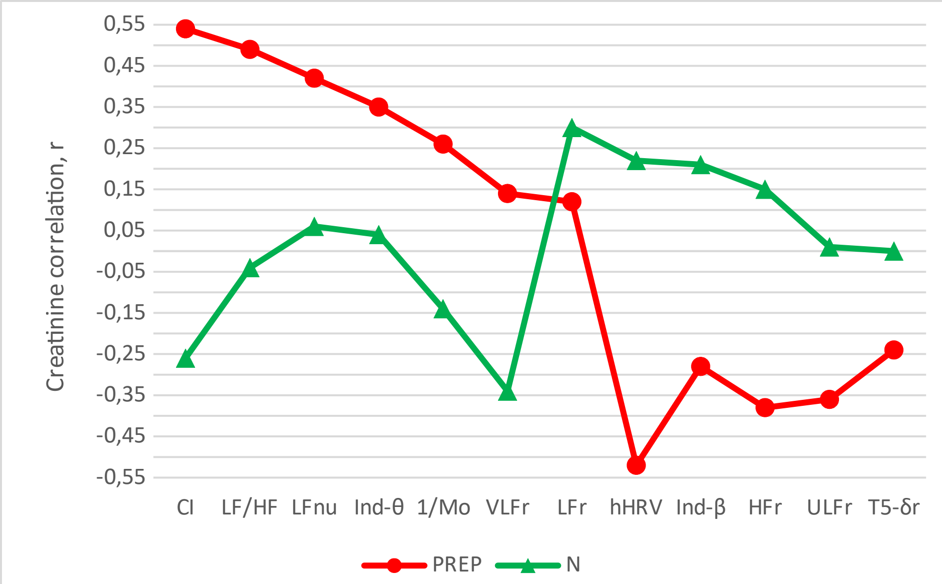


Fig. 23. Profiles of correlation coefficients between creatinine plasma level and EEG&HRV parameters in patients with post-radiation encephalopathy (PREP) and neurologically healthy (N)

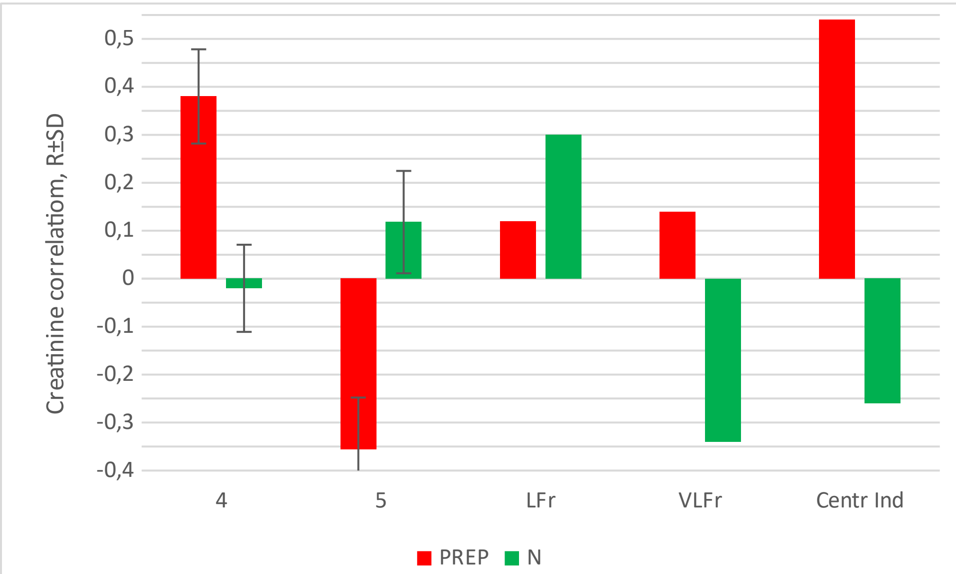


Fig. 24. Clusters of correlation coefficients between creatinine plasma level and EEG&HRV parameters in patients with post-radiation encephalopathy (PREP) and neurologically healthy (N). The number of pairs of variables or single is indicated under each cluster

With regard to bilirubin, encephalopathy causes, on the one hand, the formation of 12 positive and 3 negative connections, and on the other hand, the disappearance of one negative and 4 positive connections (Figs. 25-26).

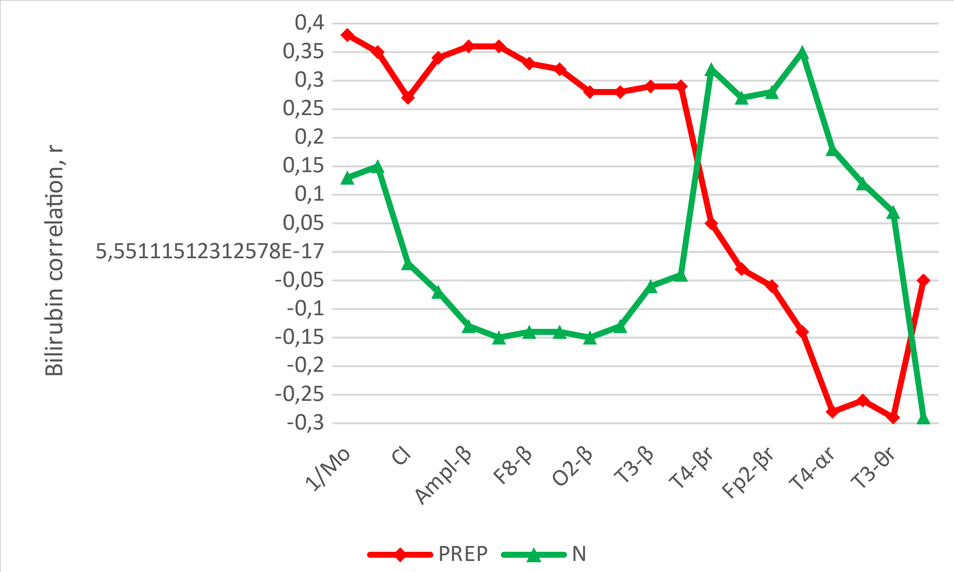


Fig. 25. Profiles of correlation coefficients between bilirubin plasma level and EEG&HRV parameters in patients with post-radiation encephalopathy (PREP) and neurologically healthy (N)

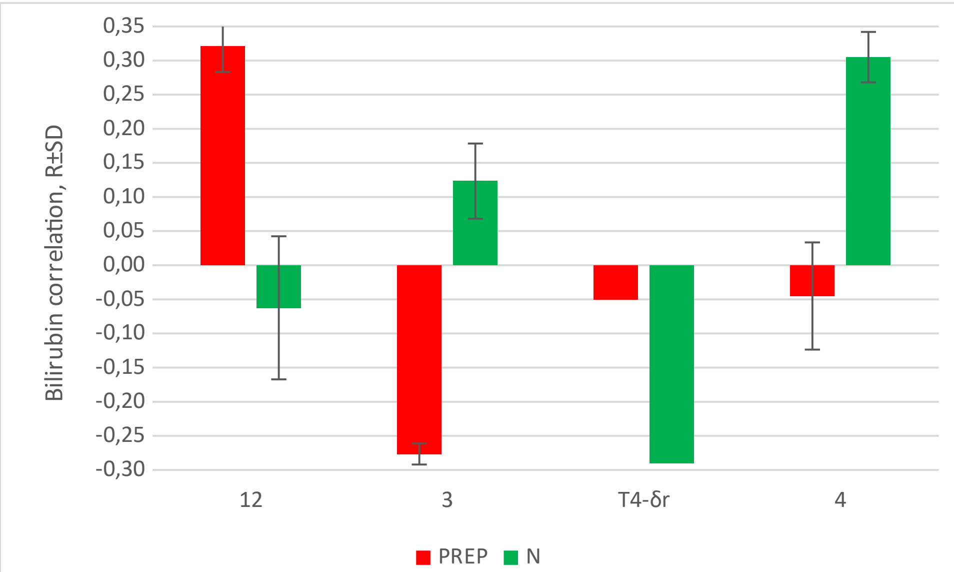


Fig. 26. Clusters of correlation coefficients between creatinine plasma level and EEG&HRV parameters in patients with post-radiation encephalopathy (PREP) and neurologically healthy (N). The number of pairs of variables or single is indicated under each cluster

Finally, with regard to uric acid, encephalopathy causes the formation of 2 positive and 7 negative connections, and the disappearance of 5 negative and 5 positive connections as well as the reversion of 2 connections (Figs. 27-28).

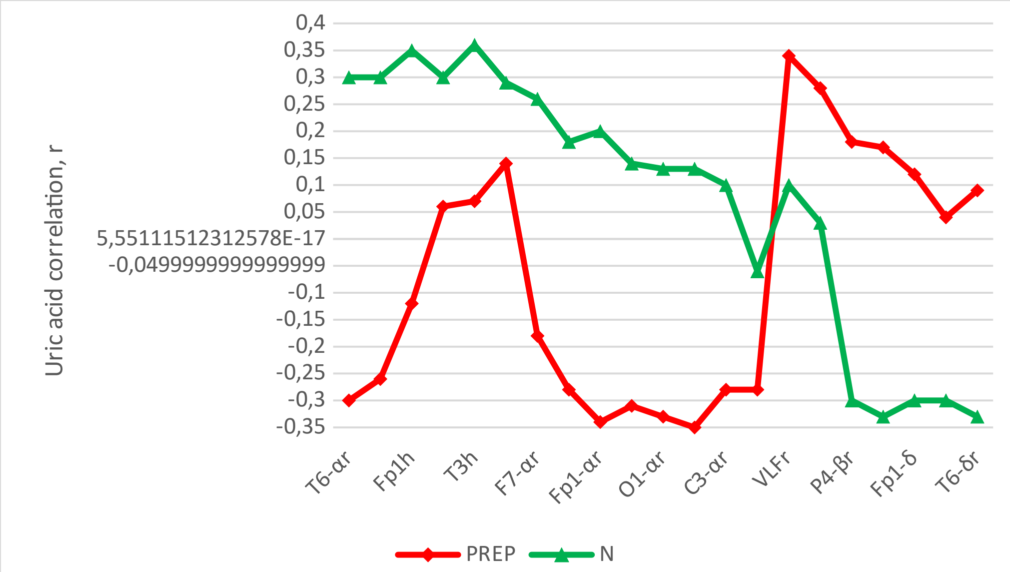


Fig. 27. Profiles of correlation coefficients between uric acid plasma level and EEG&HRV parameters in patients with post-radiation encephalopathy (PREP) and neurologically healthy (N)

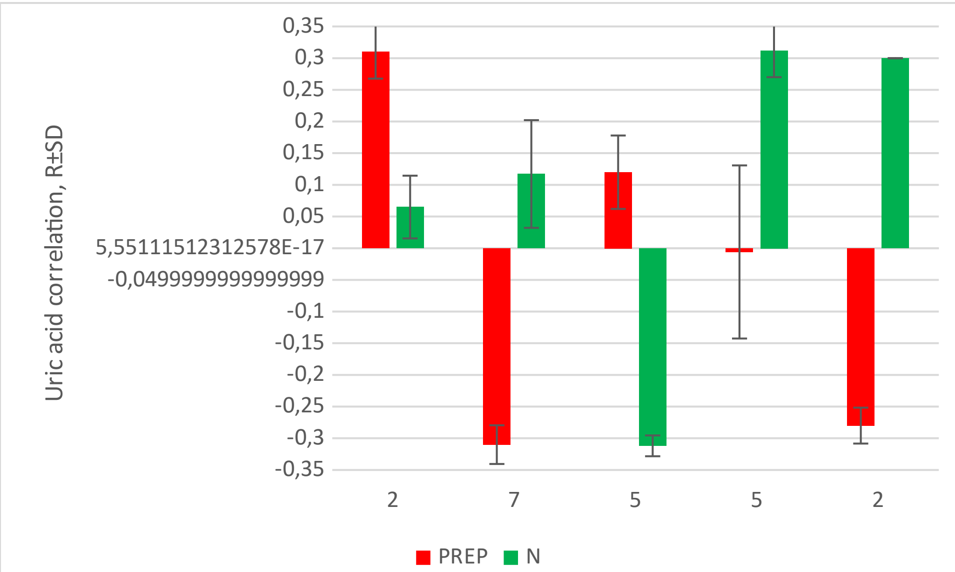


Fig. 28. Clusters of correlation coefficients between uric acid plasma level and EEG&HRV parameters in patients with post-radiation encephalopathy (PREP) and neurologically healthy (N). The number of pairs of variables is indicated under each cluster

It should be noted that the mean levels (M±SD) of nitrogenous metabolites in PREP and control cohorts did not differ both among themselves and from the reference levels: urea - 5,68±1,52; 5,76±0,98 and 5,66±1,00 mM/L; creatinine - 85±12; 91±13 and 92±16 μM/L; bilirubin – 9,6±3,4; 14,2±4,2 and 11,7±4,2 μM/L; uric acid - 289±100; 296±65 and 387±70 μM/L respectively. This can be considered as additional evidence that it is encephalopathy that is the cause of both the formation of new and the destruction of existing nitrogenous-neural connections.

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ACCORDANCE TO ETHICS STANDARDS

Tests in patients are carried out conducted in accordance with positions of Helsinki Declaration 1975. During realization of tests from all participants the informed consent is got and used all measures for providing of anonymity of participants.

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Appendix. Correlation coefficients between nitrogenous metabolites plasma levels and EEG&HRV parameters in patients with post-radiation encephalopathy (PREP) and neurologically healthy (N)

Urea	PREP	N
CI	0,48	0,05
LF/HF	0,45	0,03
LFnu	0,44	-0,06
T5-αr	0,35	-0,06
T4-αr	0,32	0,06
F4-αr	0,31	0,02
O1-αr	0,31	-0,02
F7-αr	0,29	0,04
O2-αr	0,27	-0,09
F8-αr	0,29	0,08
ULF	0,27	0,04
Fp1-αr	0,25	0,07
12	**0,34**	**0,01**
	0,08	**0,06**
	0,02	**0,02**
VLF	0,28	0,46
1/Mo	0,27	0,42
2	**0,28**	**0,44**
	0,01	**0,03**
	0,01	**0,02**
F8-θ	0,17	0,29
Fp1-β	0,10	0,26
F7-θ	0,09	0,27
ARSI	0,05	0,29
C3-βr	-0,16	0,28
T6-δ	-0,16	0,28

6	**0,02**	**0,28**
	0,14	**0,01**
	0,06	**0,00**
T5-δ	-0,26	0,30
F7-δ	-0,27	0,28
2	**-0,27**	**0,29**
	0,01	**0,01**
	0,01	**0,01**
HFr	-0,29	0,12
O2-δr	-0,33	0,09
Ind-β	-0,31	0,02
F-α	-0,31	0,00
T5-δr	-0,32	-0,02
O1-δr	-0,33	-0,10
ULFr	-0,31	-0,20
hHRV	-0,42	-0,12
8	**-0,33**	**-0,03**
	0,04	**0,11**
	0,01	**0,04**
Crea tinine	PREP	N
CI	**0,54**	**-0,26**
LF/HF	0,49	-0,04
LFnu	0,42	0,06
Ind-θ	0,35	0,04
1/Mo	0,26	-0,14
4	**0,38**	**-0,02**
	0,10	**0,09**
	0,05	**0,05**
VLFr	0,14	-0,34
LFr	0,12	0,30
hHRV	-0,52	0,22
Ind-β	-0,28	0,21
HFr	-0,38	0,15
ULFr	-0,36	0,01
T5-δr	-0,24	0
5	**-0,36**	**0,12**
	0,11	**0,11**
	0,05	**0,05**
Bilirubin	PREP	N
1/Mo	0,38	0,13
Ind-θ	0,35	0,15
CI	0,27	-0,02
T6-β	0,34	-0,07
Ampl-β	0,36	-0,13
T5-β	0,36	-0,15
F8-β	0,33	-0,14
O1-β	0,32	-0,14
O2-β	0,28	-0,15
F7-β	0,28	-0,13
T3-β	0,29	-0,06
T4-β	0,29	-0,04
12	**0,32**	**-0,06**
	0,04	**0,10**
	0,01	**0,03**
T4-βr	0,05	0,32

T4h		-0,03	0,27
Fp2-βr		-0,06	0,28
Dev-β		-0,14	0,35
	4	**-0,05**	**0,31**
		0,08	**0,04**
		0,04	**0,02**
T4-αr		-0,28	0,18
hHRV		-0,26	0,12
T3-θr		-0,29	0,07
	3	**-0,28**	**0,12**
		0,02	**0,06**
		0,01	**0,03**
T4-δr		-0,05	-0,29
Uric acid		PREP	N
T6-αr		-0,30	0,30
T6h		-0,26	0,30
	2	**-0,28**	**0,30**
		0,03	**0,00**
		0,02	**0,00**
Fp1h		-0,12	0,35
O1h		0,06	0,3
T3h		0,07	0,36
F7-θr		0,14	0,29
F7-αr		-0,18	0,26
	5	**-0,01**	**0,31**
		0,14	**0,04**
		0,06	**0,02**
T4-αr		-0,28	0,18
Fp1-αr		-0,34	0,2
F4-αr		-0,31	0,14
O1-αr		-0,33	0,13
O2-αr		-0,35	0,13
C3-αr		-0,28	0,1
LFr		-0,28	-0,06
	7	**-0,31**	**0,12**
		0,03	**0,08**
		0,01	**0,03**
VLFr		0,34	0,10
F3-θr		0,28	0,03
	2	**0,31**	**0,07**
		0,04	**0,05**
		0,03	**0,04**
P4-βr		0,18	-0,3
O1-δ		0,17	-0,33
Fp1-δ		0,12	-0,3
F7-δr		0,04	-0,3
T6-δr		0,09	-0,33
	5	**0,12**	**-0,31**
		0,06	**0,02**
		0,03	**0,01**