ОРИГИНАЛЬНЫЕ ИССЛЕДОВАНИЯ

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PROGNOSIS OF SYMPTOMATIC EPILEPSY DEVELOPMENT IN PATIENTS WITH BRAIN TUMORS THROUGH ANALYSIS OF NEUROPHYSIOLOGICAL PARAMETERS AND BINARY LOGISTIC REGRESSION

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Aim: this study was aimed at identifying prognostic potential of electroencephalographic and cardiointervalometric neurophysiological parameters using logistic regression modeling in patients with brain tumors manifesting with symptomatic epilepsy. Methods: the primary group of participants in the study consisted of 88 patients, aged 22 to 83 years admitted at Ryazan State regional hospital neurosurgical department with brain tumor as the admitting diagnosis. The control group consisted of 20 relatively healthy individuals of equal gender distribution. The primary group was further subdivided into groups of patients with brain tumor associated epilepsy and brain tumors with no epileptic seizures. Five minute electrocardiogram as well as electroencephalograms were recorded in 3 functional probes (baseline, hyperventilation and post-hyperventilation) on admission followed by statistical correlational analysis and logistic regression. Results: based on significantly strong correlations the selected electroencephalogram predictor factors included Average power of the delta wave diapazon in F3-A1 and O2-A2 during hyperventilation probe as well as Mode (Mo) and very low frequency component of total power (%VLF) cardiointerval parameters during post-hyperventilation probe. Selected predictors used in the logistic regression model were able to predict possible prognoses in patients with brain tumor induced epilepsy with 73% sensitivity and 96% specificity. Conclusion: logistic regression analysis of pre-defined neurophysiological predictor factors is perspective in neuro-oncological patients including patients with brain tumor induced epilepsy in terms of its clinical prognostic value and structuring of complex and effective treatment schemes.

Keywords: *brain tumors, epileptic syndrome, logistic regression.*

Neurophysiological evaluation of brain functional state is currently undergoing active research and is being considered as one of the main diagnostic schemes in patients with brain tumors (BT). The issue of treatment of patients with BT remains an actual, and urgent problem of modern oncology, due to low survival rate of patients with BT. Despite significant advances of medicine worldwide, BT lead to early disability and unfavourable quality of life [1, 2]. Neurovisualization enables us to only understand tumor morphology. Functional activity of the brain in patients with central nervous system (CNS) tumors is to an extent always disrupted [2]. One of the most significant indicators of regulatory system distress is the variability of cardiac rhythm. These cardiac rhythm peculiarities precede hemodynamic, metabolic and energetic discrepancies, hence being the earliest prognostic signs of a patient's unfavourable prognosis [3, 4]. Extremely low efficiency of existing methods of treating malignant BT fuels the search for new methodological approaches and the development of innovative therapeutic strategies to combat these malignancies [5]. The estimation of functional reserves by the degree of stress on regulatory systems allows us to characterize adaptive changes in the organism [6-8].

Materials and Methods

The study included 88 patients aged 22 to 83 years (mean age 56,4±14,7) who were diagnosed and admitted with BT at the Ryazan Regional Hospital's neurosurgical department. The diagnosis was established in accordance with the histological findings, taking into account the morphological criteria of malignancy. 66 (75%) patients were diagnosed with primary BT. Tumors were localized in the parietal lobes – 27 (30,1%) patients, frontal lobes – 17 (19,3%) patients, temporal lobes – 16 (18,2%) patients, cerebellum – 8 (9%) patients, petroclival region – 6 (6,8%) patients, occipital lobes – 5 (5,7%) patients, parasagittal region – 5 (5,7%) patients, suprasellar region – 2 (2,2%) patients and 2 (2,2%) patients with lesions in multiple localizations. 41 (46,6%) patients were diagnosed with malignant BTs of high degree; glioblastoma multiforme – 24 (27%) patients, anaplastic astrocytoma – 10 (11,4%) patients, ependymoma – 3 (3,4%) patients, oligodendroglioma – 3 (3,4%) patients and lymphoma – (1,1%) patient. 25 (28,4%) patients had lower degree of malignancy; meningioma – 19 (22%) patients and pituitary adenoma – 2 (2,3%) patients. 22 (25%) patients were diagnosed with secondary (metastatic) BT from the following organ systems; lungs (11 patients), colon (4 patients), ovaries (2 patients), skin (2 patients), breast (1 patient), thyroid (1 patient), and urinary bladder (1 patient).

Partial (focal) seizures were observed in 8 (36,4%) patients with BT associated epileptic syndrome; motor – 5 (62,5%) patients, sensory – 1 (12,5%) patient, vegetative – 1 (12,5%) patient and psychoemotional – 1 (12,5%) patient. Partial seizures with secondary generalization were observed in 8 (36,4%) patients. Patients with generalized tonic-clonic seizures accounted for 13,6% of all patients in this group. Epileptogenic properties were dominated by the following histological types of tumors; glioblastoma multiforme – in 8 (36,4%) patients, meningioma – 6 (27%) patients, metastatic BT – 4 (18,2%) patients, anaplastic astrocytoma – 3 (13,6%) patients and craniopharyngioma – 1 (4,5%) patient.

Inclusion criteria for the study; adult patients with BT being treated in the neurosurgical department of the Ryazan Regional Hospital. Exclusion criteria: concomitant inflammatory, demyelinating diseases of the brain and cardiac arrhythmias. The main group was divided into 2 subgroups; 22 patients with BT induced epileptic syndrome (group 1) and 66 patients without epileptic syndrome (group 2). The control group consisted of 20 (average age 45±12,1 years) relatively healthy people.

Cardiac rate variability (VCR) analysis was used as an electrophysiological method in this study. All patients had a five-minute electrocardiogram recording during three functional states (baseline, hyperventilation and post hyperventilation). We used hardware and software complex «Varicard 2.51» and «Iskim 6.0». The state of the autonomic nervous system and its regulatory mechanisms were estimated by statistical, geometric and spectral characteristics. A monopolar 16-channel electroencephalograph (Neuron-Spectrum-3 EEG) and «Neurosoft» software were also used in the study. Recording electrodes were located on the scalp according to the universal «10-20%» scheme. EEG recordings were also carried out during three functional states. Spectral, cross-correlation and coherence analyzes were performed for α (8-13 Hz), β (13-30 Hz), δ (0,5-4 Hz) and θ (4-8 Hz) rhythm ranges. The statistical analysis was carried out nonparametricaly (Mann-Whitney U test) using SPSS (SPSS for Mac Version 23.0: SPSS Inc.). The data obtained in the subgroups was described using the mean values of parameters, median (Me), upper (UQ) and lower quantile (LQ). Significance level of $p<0,05$. Binary logistic regression method was used to predicting the occurrence of epileptic syndrome in newly diagnosed patients with BT. To construct the logistic regression model, a method of stepwise exclusion of prognostic factors was applied with the determination of the minimum set of predictors by estimating the approximation coefficient (Nagelkerke square – R^2).

This study, as part of dissertation data collection was conducted at the department of neurology, neurosurgery and medical genetics – Ryazan State Medical University named after academician I.P. Pavlov from 2015-2016.

Results and discussion

The analyzed variability of cardiac rhythm variability (VCR) parameters depict the most prominent discrepancies in higher neuro-metabolic regulatory mechanisms including humoral as well as autonomic nervous systems which eventually lead to suppression of higher functional reserves of the cardiovascular system. BT have a negative influence on the relationship between central and autonomic regulatory mechanisms. Significant stress on regulatory systems also alters the adaptive potential on the organism. Concomitant epileptic syndrome in patients with BT is an additional burden on adaptive mechanisms, manifested by the predominance of the sympathetic component of the autonomic nervous system and the centralization of control of the heart rhythm (tabl. 1).

Table 1

VCR parameters in patients with BT

	B		HV		PHV	
	Group 1 (n=22)	Group 2 (n=66)	Group 1 (n=22)	Group 2 (n=66)	Group 1 (n=22)	Group 2 (n=66)
SDNN,мс.	178 [101;275]	148 [83;205]	202* [119;267]	134 [68;201]	172 [134;252]	155 [89;206]
Mo, мs.	783* [665;817]	828 [733;962]	753* [632;843]	823 [701;959]	744* [667;829]	826 [738;1000]
SI, I.U.	449* [204;877]	243 [60; 576]	301 [55; 701]	289 [74; 625]	418 [175;717]	259 [58; 621]
CI, I.U.	2,8* [1,3; 4,4]	1,1 [0,5; 2,8]	3,1 [0,7; 4]	2,2 [0,5; 3,3]	2,1* [1,3; 5,1]	1,1 [0,6; 2,7]
LF/HF, I.U.	1,4* [0,9; 2,6]	0,8 [0,4; 1,8]	1,3 [0,5; 2,4]	0,8 [0,4; 1,8]	1,3* [0,8; 2,3]	0,8 [0,4; 1,8]
HF, %	26,4* [19; 43]	48,5 [27; 69]	26,2 [20; 59]	46,4 [23; 65]	32* [17; 43]	47,2 [28; 62]
VLF, %	28* [17; 44]	16 [6,4; 37]	25 [11; 46]	14 [6; 28]	28* [14; 39]	14 [6; 25]

*Note:**- significance p<0,05; B – baseline probe; HV – hyperventilation probe; PHV – post-hyperventilation probe; I.U. – international units; ms- milliseconds; SDNN – square deviation; Mo – mode; SI – stress index; CI – centralization index; LF/HF – coefficient of vagosympathetic balance; HF – High frequency component of total spectrum capacity; VLF – very low frequency component of total spectrum capacity

We propose a regression model for predicting occurrence of epileptic syndrome in newly diagnosed patients with BT (tabl. 2). The following neurophysiological parameters were used in construction of the regression model; δ-μV^2 F3 (during hyperventilation), δ-μV^2 O2 (during hyperventilation), Mo (during post-hyperventilation) and %VLF (during post-hyperventilation). These parameters were statistically significant and highly correlated. Using these parameters as predictors of the clinical course of the disease, a regression model was obtained. For p<0,5, patients belong to the group of patients without epileptic syndrome, and at p>0,5 – to the group of patients with BT associated epileptic syndrome (cut-off is 0,5).

Table 2

Coefficients of logistic regression

Parameters (predictors)	Code	B	SE	Wald's statistic	Significance (p)	OR	95% (CI)	
							OR lower border	OR upper border
δ-μV^2F3 (HV)	B_1	-0,051	0,018	8,465	0,004	0,950	0,918	0,983
δ-μV^2O2 (HV)	B_2	-0,047	0,018	7,082	0,008	0,954	0,922	0,988
Mo (PHV)	B_3	0,006	0,003	4,318	0,038	1,006	1,000	1,011
%VLF (PHV)	B_4	-0,067	0,028	5,737	0,017	0,935	0,886	0,988
Constant	B_0	0,791				2,207		

Note: B – regression coefficient; SE – standard effort; OR – odds ratio; CI – confidence interval; HV – hyperventilation probe; PHV – post-hyperventilation probe; Mo – mode; %VL – very low frequency component of total spectrum capacity; δ-μV^2F3 – Average spectrum capacity of delta (δ) waves along F3 scalp zone on EEG; δ-μV^2O2 – Average spectrum capacity of delta (δ) waves along O2 scalp zone on EEG

When using the above-mentioned neurophysiological parameters chosen as predictors, the following regression model is obtained:

$$y = B_0 + B_1(\delta\text{-}\mu V^2F3) + B_2(\delta\text{-}\mu V^2O2) + B_3(Mo) + B_4(\%VLF)$$

where y – regression function, δ-μV^2F3 (B1 = -0,051), δ-μV^2O2 (B2 = -0,047), Mo (B3 = 0,006), %VLF (B4 = -0,067) and constant (B0 = 0,791).

$$y = 0{,}791 - 0{,}051(\delta\text{-}mV^2F3) - 0{,}047(\delta\text{-}mV^2O2) + 0{,}006(Mo) - 0{,}067(\%VLF)$$

Within the framework of logistic regression analysis, the probability of a favorable course of the disease, expressed through logistic regression, can be represented as the following equation:

$$Logit\ (p) = 1/(1+e^{-y})$$

To test the consistency of the model with the data used, the Hosmer-Lemeshow consent test was used. The following results were obtained during the verification; The Hosmer-Lemeshow test allows one to test the null hypothesis about the coincidence of the distribution of events with a certain predetermined distribution. The value of the p-value test Chi-square can serve as a measure of the accuracy of estimating the probability of default: the closer the p-value to zero, the worse the estimate.

According to the regression analysis data, the evaluation of the efficiency of the equations using the attached formula is 89,8%. Step 0: The total percentage of correct predictions is 75%. Step 4: The total percentage of correct predictions is 89,8%. The approximation coefficient (Nagelkerke square – R^2) = 0,66, which indicates that this equation explains 66% of the initial data. R^2 shows the share of influence of all descriptive variables of the model on the variance of the dependent variable and reflects the degree of improvement of the model when adding predictors to the constant. There is an increase in the percentage of correct predictions (tabl. 3) from 75% (Step 0) to 89,8% (Step 4). The coefficients of the determination (approximation) of the Cox & Snell R Square model (44%) and Nagelkerke R Square (66%) obtained on the basis of the ratio of the likelihood function of models with only a constant and with all coefficients indicate that part of the variance that can be determined using logistic regression.

Table 3

Results of testing the logistic regression function

	Predicted		
	Epileptic syndrome		% of correct predictions
	0	1	
Step 4.Epi. syndrome 0	16	6	72,7
1	3	63	95,5
Total Percentage			89,8

The analysis allows to formulate the clinical course and outcome of the disease of patients with BT associated epileptic syndrome. Regression analysis of neurophysiological (EEG and VCR) indicators established that the unfavorable course of the disease developed more often in patients with BT associated epileptic syndrome. The most significant neurophysiological prognostic factors were; δ-μV^2 F3 during hyperventilation [OR=0,95; 95% CI: 0,918-0,983; p=0,004], δ-μV^2 O2 during hyperventilation [OR=0,954; 95% CI: 0,922-0,988; p=0,008], Moduring post-hyperventilation [OR=1,006; 95% CI: 1-1,011; p=0,038] and %VLF in the post-hyperventilation probe [OR=0,935; 95% CI: 0,886-0,988; p=0,017]. Sensitivity of the obtained prediction model in the training sample was 73%, and specificity was 96%.

Functional activity of the brain in patients with BT has always to some extent altered corresponding to the preservation of compensatory-adaptive reactions of the body. This, together with existing clinical and paraclinical factors, determines the choice of the optimal treatment tactics for this contingent of patients. The clinical semiotics of BT are diverse and regularly include epileptic seizures as a sign of brain irritation, reflecting, on one hand, subcompensation and decompensation of the patients' condition, and on the other hand, the «willingness» of the nervous system to realize paroxysmal reactions, which are of protective-compensatory value. The identified characteristics of VCR in patients with BT – associated epileptic syndrome, indicate excessive stress-realizing mechanisms by activation of the sympathetic component of the autonomic nervous system.

Our proposed logistic regression model with predefined predictor parameters effectively divides patients with BT into groups with or without symptomatic epilepsy. Selected EEG delta wave peculiarities during hyperventilation characterize both regional cortical brain changes in bioelectrogenesis (synchronizing influences) and the modulating effects of brain stem structures. The characteristics of VLF in the proposed model indicate the role of the activity of ergotropic suprasegmental mechanisms of vegetative regulation, whilst Mo takes on the role of the total effect of vegetative regulation of cardiac activity.

Conclusion

1. Determination of clinico-physiological characteristics in patients with brain tumors (with or without associated epileptic syndrome) requires complex physiological approaches using electroencephalogram and cardiac rate variability with dynamic stress tests.

2. The most significant physiological parameters (predictors) in determining the development of epilepsy in patients with brain tumors include; characteristics of ergotropic mechanisms of vegetative regulation, indices of the total effect of autonomic regulation (according to cardiac rate variability data) and parameters of the pathological activity of synchronizing mechanisms (according to electroencephalogram data).

3. Complex physiological studies using electroencephalogram and cardiac rate variability with dynamic hyperventilation stress tests in patients with brain tumors, alongside our proposed logistic regression model can be used to quantitatively predict the possible occurrence of epileptic syndrome in newly diagnosed patients with brain tumors.

Authors declare no conflict of interest.

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