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RECURRENCE OF ISHEMIC STROKE IN PATIENTS WITH CONFIRMED MANIFESTIVE VIRAL INFECTION

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Introduction: The incidence of stroke in the world is increasing not only in the elderly, but also in the so-called young adults (<55 years) [1], in whom stroke has a significant and prolonged impact on the quality of life, given the longer socio-economically demanding stage in life. Of the 795,000 strokes that occur in the United States each year, 691,000 are ischemic strokes and 185,000 (23.2%) are recurrent. According to Allen NB et al. [2], the recurrence of stroke in the United States is observed in 13.2% -12.6 % during the year.

Young patients with stroke have a significant risk of recurrent vascular events during the first years after stroke [3, 4, 5]; 20 years after ischemic stroke in this age group the cumulative risk is 33% [1]. This recurrence rate has not changed significantly over the past 10 years [6]. According to the German Stroke Registry [7], the five-year recurrence rate was 20.1%. According to the Memorial Neurological Center in Manila, out of 1,155 patients with the first ischemic stroke, 12.8% had a recurrent within the next year. [8]. The frequency of recurrence of stroke by subtype of the initial one, according to Jones W.S. et al., 2012 [9]. Regardless of age, sex, and follow-up period, patients with atherothrombotic, cardioembolic, and lacunar strokes have a higher risk of recurrent stroke than other subtypes according to TOAST

criteria [1].Recent studies have shown that the infection is a temporary, independent trigger for ischemic stroke [10].

Aim: to assess the risk of manifest viral infection impact on the three-year recurrence rate and to identify its independent predictors.

Materials and methods. The main group (MG) included 70 patients with ischemic stroke, in whom viruses were detected in the blood within 2 weeks before hospitalization on the background of viral manifestations; to the comparison group (CG) - 220 patients who did not have a viral manifestation two weeks before hospitalization. The diagnosis was confirmed according to the current protocol for the diagnosis of ischemic stroke, using CT (MRI), ultrasound, Echocardiography (if necessary); the severity of neurological deficits was determined by the NIHSS scale [11]. The presence of viral infection (family of herpesviruses and influenza virus) was detected by polymerase chain reaction (PCR): DNA of herpesviruses and influenza virus RNA was isolated from cells using a set of reagents DNA-sorb-BDNAkit ("AmpliSens", Russia) or «innuPREPVirusDNAKit». Statistical processing of the results was performed using the statistical analysis program IBM SPSS Statistics Base v.22. Correlation analysis was performed according to Spearman. The prognostic value of the indicator was assessed using ROC analysis with calculation of sensitivity and specificity. The area under the curve (AUC) was calculated with a 95% confidence limit (CI) for these variables. The null hypothesis (regarding the absence of discrepancies between variables was rejected in the case of $p < 0.05$.

Patients in the study groups did not differ statistically by mean age: 64.2 ± 1.2 years (from 41 years to 81 years) in MG, 63.6 ± 0.6 years (from 40 years to 81 years) in CG, $p = 0.644$. The study groups were also gender representative ($p = 0.440$). At the time of hospitalization, the mean value of the score of neurological deficits according to NIHSS scale was 11.77 ± 0.30 in MG patients, in CG patients - 11.81±0.17 points, $p=0.913$. Hemodynamically significant stenosis (over 50%) among patients with stenosis were identified in 36 (64.3%) patients of MG and 102 (63.4%) patients of CG, $p =0.901$.The study groups did not differ statistically in the average values of the percentage of stenosis: 59.8 ± 2.8% in MG and 56.1 ± 1.7% in

CG, p = 0.271. The thickness of the intima-media complex averaged 1.04 ± 0.03 mm in the MG, 1.09 ± 0.02 mm in the CG, p = 0.181.

In patients from MG, HSV1 DNA was detected in 43 (61.4%) cases, HSV2 - in 30 (42.9%); EBV - in 19 (27.1%); CMV - in 18 (25.7%); HNV6 - in 27 (38.6%); Influenza RNA - in 16 (22.9%). One type of virus, or their association, was identified in this group of patients. One type of virus was present in 21 (30.0%) patients, two types of viruses were identified in 31 (44.3%), three or more types of viruses - in 18 (25.7%).

Results and discussion. During the three years of the study, stroke recurrence occurred in 38 patients: 12 in MG and 26 patients in CG. The three-year cumulative recurrence rate of stroke, based on censored data, was 13.3% overall (recurrence-free survival 86.7 ± 2.1%) and was higher in MG patients: 17.4% (recurrence-free survival 82.6 ± 4.58%). compared to CG patients - 12.1% (recurrence-free survival 87.9±2.2%), but the differences did not reach statistical significance, p = 0.240.

The presence of viruses increased the cumulative risk of stroke recurrence within three years in MG patients compared to CG patients in 1.45 times, but did not reach to be significant: RR (Relative Risk) = 1.45; 95% CI: 0.77-2.72 (p = 0.246). At the same time, in the case of the three-year recurrence frequency comparing in MG patients, who had at least 2 viruses, the discrepancy between the groups became statistically significant. Thus, in MG the stroke recurrence frequency was 22.8% (probability of recurrence-free survival 77.2 ± 6.05%), in CG - 12.1% (probability of recurrence-free survival 87.9 ± 2.2%), p = 0,0470.

The presence of two or more viruses increased the cumulative risk of stroke recurrence within three years in patients with MG relative to CG by 1.89 times: RR=1.89; 95% CI: 1.08-3.57 (p = 0.047). There were differences in the three-year recurrence rate for certain viruses, in particular in other viral associations. Thus, in the presence of HSV1, the risk of stroke recurrence within three years in patients with MG relatively to CG increased in 2.16 times: RR = 2.16; 95% CI: 1.15-4.04 (p=0.0154); HSV2 – 1.69 times: RR = 1.69; 95% CI: 0.76-3.77 (p = 0.1983); HNV6– 2.49 times: RR = 2.49; 95% CI: 1.05-4.56 (p = 0.0356), CMV - 2.82 times: RR=2.82;

95% CI: 1.34-5.95 (p=0.0065); EBV - 2.67 times: RR = 2.67; 95% CI: 1.26-5.68 (p=0.0106); influenza virus - 2.64 times: RR = 2.64; 95% CI: 1.17-5.95 (p = 0.0188). In patients, quite often (44.3%) two types of viruses in the association were identified, as well as three or more types of viruses - 25.7%. In the presence of certain combinations of viruses, including in the composition of various viral associations, the relative risk of three-year recurrence increased.

We created a mathematical model using step-by-step multivariate binary logistic regression to determine the independent prognostic factors of stroke recurrence. The analysis included such variables as: age of patients; sex; BMI; pathogenetic subtype of stroke; vascular territory of lesions; the severity of the primary stroke according to the NIHSS scale; the presence of ICA stenosis; degree of ICA stenosis; the thickness of IM; virus type (HSV1,CMV, Influenza), combination of viruses (at least 2).

After correlation analysis, 9 variables were included in the multivariate step-by-step logistic regression analysis (all types of viruses that were identified, IMT, the presence of the viral association "2 or more types of viruses", NIHSS score at hospitalization. According to the analysis, independent prognostic markers of three-year stroke recurrence were the following: IMT (B coefficient = 8,522) and the presence of viruses association (B coefficient = - 20,537), the value of the constant=-10,917. Therefore, the probability of stroke recurrence for each MG patient within three years can be calculated by the formula

$$p = \frac{1}{1+e^{-z}}$$

where Z = -10,917 + 8,522 * IMT - 20,537 * the presence of association of viruses. According to this model, independent prognostic factors for three-year stroke recurrence in patients with viral manifestations were the following: HSV1 (B coefficient = 4.52), CMV (B coefficient = 3.63), influenza virus (B coefficient=4.11), and IMT (B coefficient = 10.77), constant -20.57. Therefore, the probability of

recurrence within three years for each patient with MG can be calculated by the above formula, where

Z = -20,562 +4,523 * HSV1 + 3,628 * CMV + 4,110 * Influenza + 10,773 * IMT

The prognostic value of the model was high with the area of the figure under the curve ROC = 0.971, 95% CI: 0.900-0.966, with the sensitivity of the model 100.0%, 95% CI: 71.5-100.0% and specificity 83.1% (95 % CI: 71.0-91.6%). It is noteworthy that in case of one-factor regression analysis, the probability of three-year recurrence of more than 50% is predicted in the case of IMT values above 1.3 mm. Thus, a performed study of the recurrent stroke risk within 3 years in patients with the initial ischemic stroke on the background of confirmed manifest viral infection (by PCR), determined that the recurrence rate in this group of patients is generally - 17.4%, which exceeds the same indicator in CG - 12.1%. However, the differences between the groups reached the significant level only in the case of at least 2 types of viruses presence in the blood, with the recurrence rate increased to 22.8%. For certain viral combinations, in particular HSV1 + EBV; HSV1 + CMV - up to 45.5%; 60%, respectively, exceeding the recurrence rate in CG by 3.5-5 times. Our data on the increased risk of stroke event in case of reactivation of EBV and CMV infection are consistent with the data of other authors [10, 12]. Evidence of the latter is the increased risk of stroke in immunocompromised individuals with acute CMV infection or its reactivation [10].

Conclusions

The cumulative three-year incidence of stroke recurrence in patients with viral manifestations and the presence of herpesviruses and influenza virus is: 17.4%; the risk of stroke recurrence is significantly increased in the case of presence of two or more types of viruses by 1.89 times. Independent prognostic factors for three-year recurrence of stroke in patients with viral manifestations according to the developed mathematical model using step-by-step multivariate binary logistic regression is the presence of HSV1 DNA, CMV, Influenza RNA, and IMT. The prognostic value of the model is high with the area of the figure under the curve ROC = 0.971, 95% CI: 0.900-0.966. Sensitivity of the model 100.0%, specificity 83.1%. In patients with

PCR-confirmed viral manifested infection, a IMT more than 1.3 mm is associated with a high (over 50%) probability of a three-year recurrence of stroke.

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