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RECURRENCE OF STROKE IN PATIENTS WITH CONFIRMED VIRAL INFECTION

Turchina N. S.,
MD, associate professor neurological department
Zavodnova Z. I.,
c.med.n.,
Heletuk Y. L.
c.med.n.neurological department
O.O. Bogomolets National Medical University Kyiv Ukraine

Stroke remains a key public health issue in the world due to the number of patients suffering from ischemic stroke. 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.

Stroke prognosis studies focus on functional dependence, death, and risk of recurrence. 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. [3], the recurrence of stroke in the United States is observed in 13.2% -12.6 % during the year.

The frequency of recurrent stroke differs significantly depending on the geographical location and economic development of the country, age group, racial differences, etc. It has been shown that young patients with stroke have a significant risk of recurrent vascular events during the first years after stroke [4, 5, 6]; 20 years after ischemic stroke in this age group the cumulative risk is 33% [1].

Among the 600 stroke patients in the Nordic region who have been observing for 2 years, 55 (9.2%) had a recurrent stroke, 15 (2.5%) suffered from a TIA, 4 (0.7%) developed a coronary event, and 24 (4.0%) died [7].

According to the South London Stroke Registry in early 2000, among 1,626 stroke patients, 47% had a second stroke. During the first, second, third, fourth and

fifth years, 8% (6.5% –9.8%), 3.3% (2.2% –4.9%), 3.5% (2.1% –5.8%), 1.2% (0.4% –3.7%) had a second stroke and 1.8% (0.4% –7.4%), respectively. The cumulative risk of recurrence of the first stroke (95% CI) for 1 year was 8.0% (6.5% -9.8%), for 3 years - 14.1% (11.8% -16.7%) and 16.6% (13.5% –20.4%) for 5 years [8]. This recurrence rate has not changed significantly over the past 10 years [9]. After the initial stroke in life, 17% of patients developed a recurrent stroke within 5 years and its frequency did not differ depending on the pathogenetic subtype.

According to the German Stroke Registry [10], the five-year recurrence rate was 20.1%. The highest risk of recurrence was observed in the case of unknown cause of stroke (22.3% for women, 21.4% for men). 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. The probability of recurrence event was higher during the first year with a decrease in the annual level to 6.3% (95% CI: 5.0-7.9) during the second year and to 5.1% (95% CI: 4.0-6), 5) during the 3rd year. None of the traditional risk factors included in the multivariate regression analysis showed an association with recurrent stroke [11].

The frequency of recurrence of stroke by subtype of the initial one, according to Jones W.S. et al., 2012 [12], is 7.9% for atherothrombotic, 6.5% for cardioembolic and 6.5% for lacunar events. With the exception of lacunar, more than half of strokes have a different pathogenetic subtype than the initial, and this, according to researchers, suggests a multifactorial nature of the recurrent stroke [8].

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].

In the case of recurrent stroke according to Lee B.I. et al [13] more often atherosclerotic lesions of the greater artery is determined to compare with the first. According to Scandinavian researchers, recurrent stroke occurs in 19.2% of patients with the first atherothrombotic stroke, 8.2% - with cardiac embolic cause, 5.6% - with cryptogenic cause, 4.9% - with small vascular disease and in 12.8% - with another and uncertain cause together [7].

From the first method of ABCD for easy risk assessment of stroke recurrence proposed by Rothwell PM and Giles MF [14] and the introduction of an improved ABCD2 index, which had a certain prognostic value for recurrence [15], other prognostic models for assessing the risk of recurrent stroke have been developed over the past 15 years [16, 17].

Most stroke recurrences remain unclear in terms of traditional risk factors. According to a number of studies, recurrent stroke is not associated with dyslipidemia, smoking and diabetes [8, 18], its recurrence is associated with more number of risk factors than primary [13, 19]. Recent studies have shown that the infection is a temporary, independent trigger for ischemic stroke [20].

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

Materials and methods of research. 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 - 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 [21].

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 (atherotrombotic (AT), cardioembolic (CE), lacunar (LAC)); vascular territory of lesions (left MCA (LMCA), right (RMCA), vertebra-basilar system (VBS)); 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, HSV2, HHV6, EBV, CMV, Influenza), combination of viruses (at least 2). These variables are included in the correlation analysis.

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.

The prognostic value of the model for three-year stroke recurrence prediction in the presence of viral manifestations was high, with the area of the figure under the curve ROC = 0.919, 95% CI: 0.829-0.971. The sensitivity of this mathematical model was 81.82%, specificity - 88.14%.

This model indicates that any association of two or more viruses is more important in predicting of recurrent cerebrovascular event than a single type. Instead, it is important to know whether certain types of persistent viral infection differ in their impact on the risk of stroke recurrence. Therefore, in the next mathematical model, we decided not to take into account this predictor. 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 [20, 22].

The increasing of stroke recurrence risk in case of viral load increasing in the presence of several types of herpesviruses at the same time and clinical manifestations, may be due to the accelerated atherosclerotic process and its complications due to, on the one hand, greater imbalance of proinflammatory and anti-inflammatory mediators. Evidence of the latter is the increased risk of stroke in immunocompromised individuals with acute CMV infection or its reactivation [20, 23].

Indirect evidence of viral effects on the decompensation of cerebral atherosclerosis is the fact that the presence of viruses significantly increases the risk of three-year recurrence with greater IMT - (over 1.3 mm). The obtained facts, including the prognostic role of influenza virus, pay attention to the need for

differentiated secondary prevention measures in patients with recurrent viral infection, as well as to an active use of influenza vaccination in at-risk groups.

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.

REFERENCES

1. Черенько Т.М. Фартушна О.Є., Віничук С.М. Прогноз виникнення інсульту у хворих після транзиторної ішемічної атаки: підтипоспецифічна шкала ABN (s) // Укр. неврол. журнал. – 2011. – № 3. – С. 21–27. Cherenko T.M. Fartushna O.Ie., Vinychuk S.M. [Prohnoz vynyknennia insultu u khvorykh pislia tranzytornoi ishemichnoi ataky: pidtypospetsyfichna shkala ABN (s)] (in Ukrainian).// Ukr. nevrol. zhurnal. – 2011. – N 3. – S. 21–27.

2. Allen N.B., Holford T.R., Bracken M.B., et al. Trends in one-year recurrent ischemic stroke among the elderly in the USA: 1994-2002 // Cerebrovasc. Dis. – 2010. – Vol. 30. – P. 525–532. doi: 10.1159/000319028.

3. Buenaflor F.G., Navarro J.C,, Lara K.J.A, Venketasubramanian N. Recurrence rate of ischemic stroke: A single center experience austin // J. Cerebrovasc. Dis. & Stroke. – 2017. – Vol. 4, N 2. – P. 1057.

4. Camerlingo M, Casto L, Censori B, et al. Recurrence after first cerebral infarction in young adults // Acta Neurol. Scand. – 2000. – Vol. 102, N 2. – P. 87–93. doi: 10.1034/j.1600-0404.2000.102002087.x.

5. Clery A., Bhalla A., Bisquera A., et al. Long-term trends in stroke survivors discharged to care homes: The South London Stroke Register // Stroke. – 2020. – Vol. 51, N 1. – P. 179–185. doi: 10.1161/STROKEAHA.119.026618.

6. Feng W., Hendry R.M., Adams R.J. Risk of recurrent stroke, myocardial infarction, or death in hospitalized stroke patients. // Neurology. – 2010. – Vol. 74. – P. 588–593. doi: 10.1212/WNL.0b013e3181cff776.

7. Flach C., Muruet W., Wolfe C.D.A, et al. Risk and secondary prevention of stroke recurrence: A population-base cohort study // Stroke. – 2020. – Vol. 51, N 8. – P. 2435–2444. doi: 10.1161/STROKEAHA.120.028992.

8. Forbes I.D., Harriet J., Williamson E., at al. Association of herpesviruses and stroke: Systematic review and meta-analysis // PLoS One. – 2018. – Vol. 13, N 11. –e0206163. doi: 10.1371/journal.pone.0206163.

9. Hillen T., Coshall C., Tilling K., et al. Cause of stroke recurrence is multifactorial: patterns, risk factors, and outcomes of stroke recurrence in the South London Stroke Register // Stroke. – 2003. – Vol. 34, N 6. – P. 1457–1463. doi: 10.1161/01.STR.0000072985.24967.7F.

10. Johnston S.C., Rothwell P.M., Nguyen-Huynh M.N., et al. Validation and refinement of scores to predict very early stroke risk after transient ischaemic attack // Lancet. – 2007. – Vol. 369, N 9558. – P. 283–292. doi: 10.1016/S0140-6736(07)60150-0.

11. Jones W.S., Patel M.R., Dai D., Vemulapalli S., et al. High mortality risks after major lower extremity amputation in Medicare patients with peripheral artery disease. // Am. Heart. J. – 2013. – Vol. 165. – P. 809–815. doi: 10.1016/j.ahj.2012.12.00.

12. Lee B.I., Nam H.S., Heo J.H., Kim D.I. Yonsei stroke registry. Analysis of 1,000 patients with acute cerebral infarctions // Cerebrovasc. Dis. – 2001. – Vol. 12, N 3. – P. 145–151. doi: 10.1159/000047697.

13. Li X.M., Wang X.Y., Feng X.W., et al. Serum interleukin-33 as a novel marker for long-term prognosis and recurrence in acute ischemic stroke patients // Brain Behav. 2019. – Vol. 9, N 9. – P. e01369. doi: 10.1002/brb3.1369.

14. Mozaffarian D., Benjamin E.J., Go A.S., et al. Heart disease and stroke statistics-2016 update a report from the American Heart Association // Circulation. – 2016. – Vol. 133, N 4. – P. e38–e48.

15. Nedeltchev K., Der Maur T.A., Georgiadis D., et al. Ischaemic stroke in young adults: predictors of outcome and recurrence // J. Neurol. Neurosurg. Psychiatry. – 2005. – Vol. 76, N 2. – P. 191–195. doi: 10.1136/jnnp.2004.040543.

16. Odderson I.R. The National Institutes of Health Stroke Scale and its importance in acute stroke management // Phys. Med. Rehabil. Clin. N. Am. – 1999. – Vol. 10, N 4. – P. 787–800.

17. Putaala J., Haapaniemi E., Metso A.J., et al. Recurrent ischemic events in young adults after first-ever ischemic stroke // Ann. Neurol. – 2010. – Vol. 68, N 5. – P. 661–671. doi: 10.1002/ana.22091. PMID: 21031581.

18. Redfors P., Jood K., Holmegaard L., et al. Stroke subtype predicts outcome in young and middle-aged stroke sufferers // Acta Neurol. Scand. – 2012. – Vol. 126. – P. 329–335. doi: 10.1111/j.1600-0404.2012.01653.

19. Rothwell P.M., Giles M.F., Flossmann E., et al. A simple score (ABCD) to identify individuals at high early risk of stroke after transient ischaemic attack // Lancet. – 2005. – Vol. 66, N 9479. – P. 29–36. doi: 10.1016/S0140-6736(05)66702-5.

20. Rutten-Jacobs L.C., Maaijwee N.A., Arntz R.M., et al. Long-term risk of recurrent vascular events after young stroke: the FUTURE study // Ann. Neurol. – 2013. – Vol. 74. – P. 592–601. doi: 10.1002/ana.23953.

21. Wang H., Peng G., Bai J., et al. Cytomegalovirus Infection and relative risk of cardiovascular disease (ischemic heart disease, stroke, and cardiovascular death): A meta-analysis of prospective studies up to 2016 // J. Am. Heart Assoc. – 2017. – Vol. 6, N 7. – e005025. doi:10.1161/JAHA.116.005025.

22. Wu Y.P., Sun D.D., Wang Y., et al. Herpes Simplex Virus Type 1 and Type 2 infection increases atherosclerosis risk: Evidence based on a meta-analysis // Biomed. Res. Int. – 2016. – Vol. 2016. – P. 2630865. doi:10.1155/2016/2630865.

23. Zhuo Y., Wu J., Qu Y., et al. Clinical risk factors associated with recurrence of ischemic stroke within two years: A cohort study // Medicine (Baltimore). – 2020. – Vol. 99, N 26. – P. e20830. doi: 10.1097/MD.0000000000020830.