

## Vascular Endothelial Growth Factor-1 Level and Functional Neurologic Recovery after Ischemic Hemispheric Stroke

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### Abstract

**Background:** Vascular endothelial growth factor-1 (VEGF-1) acts as endogeneous angiopoetic and neuroprotective factor. The aim of the study to investigate an interrelationship between VEGF-1 elevation and neurologic recovery in short-term period among patients with ischemic hemispheric stroke.

**Methods:** Seventy eight patients with ischemic hemispheric stroke were included in the study. Neurological impairment at presentation was assessed according National Institute of Health Stroke Scale. The Barthel Index and the modified Rankin Scale (mRS) were used to assess functional disability. Concentrations of VEGF-1 were measured at baseline using ELISA laboratory kit.

**Results:** The total prevalence of hypertension was 100% (78 patients). 79.5% patients had dyslipidemia, 18% were diabetic, 15.4% of the total population was smokers. Among study patient population a total of 19.2% subjects had a past history of ischemic heart diseases in their families and 11.5% had experienced a previous ischemic heart episode. Within 6 month after baseline the favorable neurologic recovery defined as mRS  $\leq 2$  was found in 64 patients (82.1%). We calculated Modified Rankin Score  $\geq 3$  in 14 patients (17.9%). Depending on Modified Rankin Score at 6 month ( $\leq 2$  and  $\geq 3$ ) we have divided all patients into two sub-groups respectively. We found a higher prevalence of subjects with dyslipidemia ( $P=0.044$ ), diabetes mellitus ( $P=0.024$ ), smokers ( $P=0.025$ ) and as well as those with ischemic heart disease in their family histories ( $P=0.026$ ) and previous ischemic heart episode ( $P=0.032$ ) in subgroup with mRS  $\geq 3$ . At baseline VEGF-1 concentration in entire patient cohort was 348.55 pg/mL (IQR=241.70-493.80 pg/mL). We found higher VEGF-1 level in mRS  $\geq 3$  vs mRS  $\leq 2$  population sub-groups ( $P<0.05$ ). Using multivariate Cox regression analysis we reported that VEGF-1 (increased per 125 pg / mL) and type two diabetes mellitus (present versus absent) were found as independent predictors for favorable neurologic recovery.

**Conclusion:** In Conclusion, We found that VEGF-1 (increased per 125 pg / mL) measured at baseline positively predicts improved neurologic recovery at six month among subjects with acute ischemic stroke who were not enrolled for invasive or thrombolytic strategy. Type two diabetes mellitus (present versus absent) were found as independent predictor for favorable neurologic recovery in follow up period.

**Keywords:** Acute ischemic stroke; Vascular endothelial growth factor-1; Neurologic recovery

**Abbreviations:** BMI: Body Mass Index; LDL: Low Density Lipoproteins; HDL: High Density Lipoproteins; LAAS: Large Artery Atherosclerosis; LAC: Lacunar Infarct; UDE: Stroke of Undetermined Etiology

### Introduction

Stroke remains a major public health problem worldwide, although stroke mortality has been declining since the early 20th century [1]. These significant improvements in stroke outcomes are concurrent with cardiovascular (CV) risk factor control interventions, more widely use of revascularization procedure technologies, post-stroke rehabilitation, etc. [2,3]. Because of the heterogeneity of stroke, it is uncertain whether other stroke subtypes should be considered to be at the same high levels of risk [3]. Probably, biomarker-guided therapy of stroke might be useful instrument to optimize CV risk factor and stroke treatment scheme and post-stroke rehabilitation. However, there are uncertainties surrounding the optimal management of patients with ischemic stroke under biomarker control to improve neurological recovery [4,5]. Therefore, the impact of biomarker in risk prediction of CV outcome cluster and post-stroke rehabilitation is under investigations [6]. Vascular endothelial growth factor-1 (VEGF-1) as a ligand for  $\alpha$ -5 /  $\beta$ -1 integrin is a key factor in angiogenesis that may not only stimulate vasculogenesis via mobilizing of endothelial progenitor cells, but it is

able to regulate production of several endogeneous pro-angiogenic factors, i.e., insulin-like growth factor-1, platelet-derived growth factor [7-9]. Most biological effects of VEGF are mediated via two receptor tyrosine kinases, i.e., VEGFR1 and VEGFR2. They contribute transcriptional and post-translational signaling pathways respectively [10]. There is evidence that VEGF-1 stimulates phosphoinositide 3' kinase/AKT/endothelial nitric oxide synthase pathway and suppresses reactive oxygen species overproduction, accumulation of advanced glycation end products [11]. Therefore, VEGF-1 has neurotrophic effect on neuronal and glial cells in culture and *in vivo*, and may stimulate the proliferation and survival of neural stem cells [10]. Overall, VEGF-1 acts as trophic factor with angiopoetic and neuroprotective properties

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[10,12]. Elevated level of VEGF-1 was recently found in patients after acute stroke and they were demonstrated predictive value for recurrent CV events in long-term follow up [13,14]. Although a neurologic deficit of sudden onset conforming to a vascular territory is a clear clinical indication in acute ischemic stroke, the predictive role of VEGF-1 for neurologic recovery in short-term period is still not clear. The aim of the study: to investigate an interrelationship between VEGF-1 elevation and neurologic recovery in short-term period among patients with ischemic hemispheric stroke.

## Methods

### Study population

This prospective, observational and population study took place over a six month period. A sample size was estimated considering an alpha error of 5%, a statistical power of 95% and an estimated loss ratio of 5%. A total of 78 patients, who had previously defined ischemic hemispheric stroke and who were not enrolled for further intravenous thrombolysis due to technical reasons, were included in the study. Ischemic hemispheric stroke was defined according criteria of Stroke Council of the American Heart Association/American Stroke Association [4]. All the patients have given their voluntary informed written consent for participation in the study. The study was approved by the local ethics committee of State Medical University, Zaporozhye, Ukraine. The study was performed in conformity with the Declaration of Helsinki.

### Clinical and demographic data

The clinical and demographic data was collected in regard to their case history: age, weight, height, family history, personal information, prior atherosclerotic vascular disease (defined as prior coronary heart disease, cerebral vascular disease), hypertension (defined as blood pressure >140 / 90 mm Hg), diabetes mellitus (DM), dyslipidemia, and having a smoking habit. Current smoking was defined as consumption of one cigarette daily for three months. Anthropometric measurements were made using standard procedures.

### Neurological status

Neurological impairment at presentation was assessed by National Institute of Health Stroke Scale (NIHSS) (National Institute of Health Stroke Scale) [4]. The Barthel Index [15] and the modified Rankin Scale [16] were used to assess functional disability.

### Contrast-enhanced computer spiral tomography

To define brain infarct and exclude intracranial hemorrhage among all patients suspected ischemic stroke at baseline contrast-enhanced computer spiral tomography (CT) was performed on a "Somatom Spirit" scanner (Siemens, Germany). Nonionic contrast "Omnipak" (Amersham Health, Ireland) was used. The acute ischemic stroke type was classified according to the TOAST classification: 1) large artery atherosclerosis (LAAS); 2) cardioembolic infarct (CEI); 3) lacunar infarct (LAC); 4) stroke of other determined etiology (ODE); 5) stroke of undetermined etiology (UDE) [17].

### Calculation of glomerular filtration rate

Glomerular filtration rate (GFR) was calculated with CKD-EPI formula [18].

### Measurement of circulating biomarkers

To determine circulating biomarkers, blood samples were collected

at baseline in the morning (at 7-8 AM) into cooled silicone test tubes wherein 2 mL of 5% Trilon B solution were added. Then they were centrifuged upon permanent cooling at 6,000 rpm for 3 minutes. Plasma was collected and refrigerated immediately to be stored at a temperature -70°C. Concentrations of VEGF-1 were measured by ELISA at baseline using laboratory kits produced by Bioscience (USA). All determinations were done by duplicate. Concentrations of total cholesterol (TC), cholesterol of high-density lipoproteins (LDL-C), and cholesterol of high-density lipoproteins (HDL-C) at baseline were measured by enzymatic colorimetric method according standardized methodology on Beckman Synchron LX20 chemistry analyzer.

### Statistical analysis

The statistical calculations were made with the IBM statistical package Statistical Package for Social Sciences (SPSS), version 20. The normal distribution test was carried out with the Shapiro-Wilk test. The continuous variables followed a normal and abnormal distribution were expressed as mean (M) and average standard deviation (SD) and median (Me) and interquartile range (IQR). Categorical variables were expressed with frequencies in percentages. To compare the qualitative variables the Chi<sup>2</sup> test and the Fisher exact test were applied. The analysis of the two independent samples was made with the Student's t-test (normal distribution) or the Mann-Whitney U test. Age- and sex adjusted univariate and multivariate regression analysis for neurologic recovery defined as Modified Rankin Score ≤ 2 at 6 month. In the Cox regression model the significance of Odds Ratios (OR) was tested on the basis of Wald statistics. A two-tailed probability value of <0.05 was considered as significant.

## Results

The general characteristics of the clinical population are set forth in Table 1. The total prevalence of hypertension was 100% (78 patients). 79.5% were dyslipidemic, 18% were diabetic, 15.4% of the total population were smokers. A total of 19.2% had a past history of ischemic heart diseases in their families and 11.5% had experienced a previous ischemic heart episode. According TOAST criteria LAAS was defined in 47.4% patients, LAC was found in 41.0%, and UDE was detected in 11.6% subjects. Median of brain infarct volume at baseline defined using contrast-enhanced spiral CT was 3.52 cm<sup>3</sup> (1.47-8.51 cm<sup>3</sup>). Right side and left side localization of infarct was detected in 37.2% and 62.8% respectively. At baseline median of NIHSS score and Modified Rankin Score were 5.00 and 3.00 respectively. All patients were treated with optionally strategy (ACE inhibitors or angiotensin-II receptor antagonists, antiplatelets, statins) within 6 month. In 6 month after baseline the favorable neurologic recovery defined as Modified Rankin Score ≤ 2 was found in 64 patients (82.1%). In contrast, Modified Rankin Score ≥ 3 was calculated in 14 patients (17.9%). Depending on Modified Rankin Score at 6 month (≤ 2 and ≥ 3) we divided all patients into two groups respectively. Both groups were matched age, male sex, CV risk factors, BMI, brain infarct volume, types of ischemic stroke, systolic and diastolic blood pressure, biochemistry data, and treatment strategy.

In our analysis of Modified Rankin Score ≥ 3 vs Modified Rankin Score ≤ 2 population sub-groups, we observed a higher prevalence of dyslipidemic subjects (P=0.044), diabetics (P=0.024), smokers (P=0.025) and as well as those with ischemic heart disease in their family histories (P=0.026) and previous ischemic heart episode (P=0.032) At baseline VEGF-1 concentration in entire patient cohort was 348.55 pg/mL (IQR=241.70-493.80 pg/mL). There was significant difference between VEGF-1 in both population sub-groups at baseline

|   | Entire patient cohort at baseline (n=78) | Both patient subgroups at 6 month |                                  | P value |
|---|--|-----------------------------------|----------------------------------|---------|
|   |  | Modified Rankin Score ≤ 2 (n=64)  | Modified Rankin Score ≥ 3 (n=14) |         |
| Age, years                              | 58.5 ± 0.9                               | 57.6 ± 0.6                        | 59.3 ± 0.5                       | 0.99    |
| Male, n (%)                             | 58 (74.3%)                               | 47 (73.4%)                        | 11 (78.5%)                       | 0.86    |
| Hypertension, n (%)                     | 78 (100%)                                | 64 (100%)                         | 14 (100%)                        | 1.0     |
| Dyslipemia, n (%)                       | 62 (79.5%)                               | 50 (78.1%)                        | 12 (85.7%)                       | 0.044   |
| Type two diabetes mellitus, n (%)       | 14 (18%)                                 | 8 (12.5%)                         | 6 (42.9%)                        | 0.024   |
| Current smoking status, n (%)           | 12 (15.4%)                               | 7 (11.0%)                         | 5 (35.7%)                        | 0.025   |
| Past history of ischemic heart diseases | 15 (19.2%)                               | 9 (14.0%)                         | 6 (42.9%)                        | 0.026   |
| Previous ischemic heart episode         | 9 (11.5%)                                | 5 (7.8%)                          | 4 (28.6%)                        | 0.032   |
| LAAS, n (%)                             | 37 (47.4 %)                              | 30 (46.9%)                        | 7 (50.0 □)                       | 0.34    |
| LAC, n (%)                              | 32 (41.0%)                               | 26 (40.6%)                        | 6 (42.8%)                        | 0.72    |
| UDE, n (%)                              | 9 (11.6%)                                | 8 (12.5%)                         | 1 (7.1%)                         | 0.24    |
| Brain infarct volume, cm <sup>3</sup>   | 3.52 (1.47-8.51)                         | 3.40 (1.14-6.59)                  | 4.82 (3.25-14.33)                | 0.18    |
| Left-side localization, n (%)           | 49 (62.8%)                               | 40 (63.0%)                        | 9 (64.2%)                        | 0.98    |
| Right-side localization, n (%)          | 29 (37.2%),                              | 24 (37.0%)                        | 5 (35.8%)                        | 0.92    |
| NIHSS score at baseline                 | 5.00 (3.25-7.75)                         | 4.00 (3.00-7.00)                  | 9.00 (7.00-9.75)                 | 0.12    |
| Modified Rankin Score at baseline       | 3.00 (2.00-3.00)                         | 3.00 (2.00-3.00)                  | 4.00 (3.25-4.00)                 | 0.68    |
| BMI, kg/m <sup>2</sup>                  | 26.95 (24.49-30.47)                      | 27.05 (24.62-30.47)               | 26.09 (23.75-29.23)              | 0.72    |
| Systolic BP, mm Hg                      | 135 (125-150)                            | 130 (120-150)                     | 140 (130-140)                    | 0.88    |
| Diastolic BP, mm Hg                     | 82 (71-89)                               | 83 (70-87)                        | 80 (80-95)                       | 0.86    |
| Glucose, mmol/L                         | 4.70 (4.31-5.45)                         | 4.65 (4.30-5.45)                  | 5.00 (4.51-6.15)                 | 0.68    |
| Creatinine, mmol/L                      | 0.10 (0.09-0.11)                         | 0.10 (0.09-0.11)                  | 0.10 (0.09-0.11)                 | 1.00    |
| GFR, mL/min × 1.78m <sup>2</sup>        | 81.00 (72.25-95.75)                      | 82.50 (73.75-97.25)               | 74.00 (68.25-82.50)              | 0.78    |
| Total cholesterol, mmol/L               | 6.52 (6.00-7.00)                         | 5.66 (4.54-6.55)                  | 4.25 (3.67-6.26)                 | 0.46    |
| LDL cholesterol, mmol/L                 | 4.44 (3.90-4.80)                         | 6.,45 (6.08-6.93)                 | 7.60 (5.75-8.30)                 | 0.48    |
| HDL cholesterol, mmol/L                 | 1.15 (1.08-1.30)                         | 4.34 (3.95-4.65)                  | 5.40 (3.85-6.30)                 | 0.72    |
| Triglycerides, mmol/L                   | 1.81 (1.40-2.36)                         | 1.18 (1.04-1.35)                  | 1.10 (1.10-1.20)                 | 0.77    |

**Table 1:** General characteristic of the patients enrolled in the study.

(Figure 1). Higher VEGF-1 level was found in Modified Rankin Score ≥ 3 vs Modified Rankin Score ≤ 2 population sub-groups ( $P < 0.05$ ). Age- and sex adjusted univariate regression analysis has shown that VEGF-1 were determined as predictors for neurologic recovery defined as Modified Rankin Score ≤ 2 at 6 month (Table 2). However, after including in multivariate regression model all variables with  $p$  value  $< 0.2$ , we found that VEGF-1, dyslipidemia, and type two diabetes mellitus has remained independent predictors for favorable neurologic recovery. Table 3 shows the results of the Multivariate Cox regression analysis for favorable neurologic recovery (Modified Rankin Score ≥ 3 vs Modified Rankin Score ≤ 2). As one can see, VEGF-1 (increased per 125 pg / mL) and type two diabetes mellitus (present vs absent) were found as independent predictors for favorable neurologic recovery.

## Discussion

Atherosclerosis is the main pathophysiological mechanism in patients with non-cardioembolic stroke, including large- and small-vessel disease. While an induction of VEGF-1 on endogenous neurogenesis and angiogenesis is known, the innate mechanisms of a thrombotic-related evolution of injury and activated endogenous repair mechanisms are not fully understood. In the study we reported that increased baseline concentration of VEGF-1 may predict favorable neurologic recovery at 6 month defined as Modified Rankin Score ≤ 2 in patients with acute ischemic stroke. There are large bodies of evidences regarding sex, age, stroke etiology, behavioral, genetic, neurological deficiency, and CV predictors of faster recovery of function following a stroke [19-21]. On the one hand, for most acute ischemic stroke patients the recovery of function during the first six months after stroke is 70% of the maximum possible [5]. On the other hand, the recovery after stroke is limited extremely deep and severe paresis, which is independent predictor of movement recovery in patients after stroke

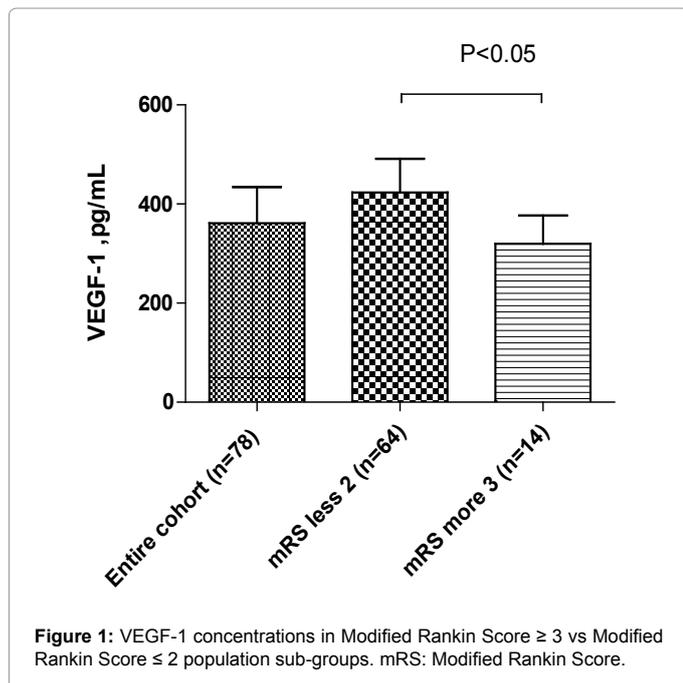
[22,23]. Nevertheless, the reliable predictors of this response are not fully determined. Our findings indicate that increased circulating level of peak VEGF-1 in acute stroke patients without severe disability might be discussed a marker for faster recovery of function within 6 month. This biomarker associated with low grade Modified Rankin Score at 6 month, while type two diabetes mellitus required to be taken into consideration as the second independent predictor. In is noted that the results were receive using age- and sex adjusted multivariable analysis that explain lack of serious impact of these important variables on risk of faster recovery. We did not find similar data in recently published reports. However, we believe that more investigations need to explain these findings and clear the role and underlying molecular effect of exaggerated level of VEGF-1 in ischemic stroke subjects. Because of a significant recovery in impaired functional domains can be expected during neuropsychological rehabilitation, treatment strategy based on measurements of circulating VEGF-1 could be appeared attractive. Whether measurement of circulating VEGF-1 may help to predict cognition impairment is not fully understood and it is required more scrutinizes.

## Conclusion

For subjects with acute ischemic stroke who were not enrolled for invasive or thrombolytic strategy, VEGF-1 (increased per 125 pg/mL) measured at baseline positively predicts improved neurologic recovery at six month. In contrast, type two diabetes mellitus (present vs absent) were found as independent predictor for favorable neurologic recovery in follow up.

## Limitations of the Study

This study has some limitations. We relied on clinical data to rule



| Variable                                | Univariable analysis |         | Multivariable analysis |         |
|---|----------------------|---------|------------------------|---------|
|   | B coefficient        | P value | B coefficient          | P value |
| BMI                                     | 0.22                 | 0.034   | 0.11                   | 0.12    |
| VEGF-1                                  | 0.48                 | 0.001   | 0.41                   | 0.001   |
| Dyslipemia                              | 0.54                 | 0.001   | 0.40                   | 0.042   |
| Type two diabetes mellitus              | 0.24                 | 0.002   | 0.12                   | 0.048   |
| Current smoking status                  | 0.28                 | 0.001   | 0.15                   | 0.23    |
| Past history of ischemic heart diseases | 0.12                 | 0.026   | 0.06                   | 0.12    |
| Previous ischemic heart episode         | 0.18                 | 0.001   | 0.04                   | 0.14    |

**Table 2:** Age- and sex adjusted univariate and multivariate regression analysis for neurologic recovery defined as Modified Rankin Score  $\leq 2$  at 6 month. Note: The multivariate regression model included all variables with p value  $< 0.2$ .

| Variables                                      | OR   | 95% CI      | Wald coefficients | P value |
|--|------|-------------|-------------------|---------|
| Dyslipidemia (present vs absent)               | 1.02 | 1.00 - 1.05 | 6.37              | 0.28    |
| VEGF-1 per 125 pg / mL                         | 0.92 | 0.88 - 0.98 | 7.5               | 0.001   |
| Type two diabetes mellitus (present vs absent) | 1.05 | 1.01 - 1.08 | 15.4              | 0.001   |

**Table 3:** Multivariate Cox regression analysis for favorable neurologic recovery. Modified Rankin Score  $\geq 3$  versus Modified Rankin Score  $\leq 2$ .

out infection and other inflammatory diseases before sampling, but we cannot exclude that some patients had unrecognized conditions responsible for the elevated VEGF-1 levels observed. However, additional verification of atherosclerosis as well as intracranial artery occlusive disease can be required. We supposed that these limitations might not have a significant influence to study data interpretation.

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