



CORRELATION ANALYSIS BETWEEN DEPRESSIVE MANIFESTATIONS AND MORPHOLOGICAL LESION CHARACTERISTICS IN PATIENTS WITH STROKE

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Abstract: **Introduction:** Knowledge of etiopathogenesis of post-stroke depressive phenomena contributes to early diagnostics which shortens recovery to a great extent and suits the social and professional rehabilitation of patients, if followed by proper psycho/pharmacotherapy. The aim of this work is to research dependence of depressive manifestations considering the size and anatomical localization of lesion. **Subjects and Methods:** The research included 118 patients with stroke. Lesion localization was defined on computerized axial tomography records, whereas the area and perimeter of lesion were measured by AutoCAD 2004 software. Examinations by means of Hamilton Rating Scale for Depression were carried out by the method of random selection 11–40 days after stroke. Correlation analysis was made by simple linear/non-linear regression and Cox's hazard regression model. **Results:** Negative correlation was observed between the intensity of depressive manifestations and the size of cerebrovascular lesion (Spearman's $r = -0.263$, $P = 0.004$). By means of Cox's regression model we determined 4.389 times higher risk for depression occurrence in female patients ($P < 0.001$), as well as higher risk due to lobus limbicus structure damages (hazard ratio e^b (HR) = 2.661, $P = 0.019$). **Conclusion:** Lower intensity of depressive manifestations with larger cerebrovascular lesions, we have explained by activation of reparation mechanisms with energy savings and decrease (due to neurological deficits) of afferent peripheral sensations which antecedent the occurrence of emotions (James-Lange peripheral theory of emotions).

Key words: stroke; lesion; depression; correlation; analysis.

INTRODUCTION

Disorders in the form of depression and anxiety represent the most often clinical psychiatric entities

that occur in persons suffering from cerebrovascular stroke. It has been confirmed that anxiety and depression significantly inhibit physical and cognitive recovery and the quality of life of these patients. It is similar with other disorders of psychic functions too (1, 2). Knowledge of etiopathogenesis of post-stroke depressive phenomena contributes to early diagnostics which shortens recovery to a great extent and suits the social and professional rehabilitation of patients, if followed by proper psycho/pharmacotherapy. The aim of this work is to examine dependence of depressive manifestations on organic brain damages, since they are explained by disorders of dynamic mechanisms; also, to estimate the influence of gender and dominancy of hemisphere in the pathoplasticity of depressive disorders. Work hypothesis: H1a. There is statistically significant correlation between the size of cerebrovascular lesion and intensity of depressive manifestations; H1b. Lesion localization depending on affected morpho-anatomical structures (damages of lobus frontalis, corpus striatum, lobus limbicus and diencephalon) shall condition specific psycho-pathological picture.

SUBJECTS AND METHODS

Participants

The research included the total of 118 persons suffering from cerebrovascular stroke (of ischemic and hemorrhagic origin) who had no previously diagnosed psychiatric disorders: 59 male persons and 59 female persons at the age span 44–87 years. The patients were inquired at Neurological Department of the Institute for Physical Medicine, Rehabilitation and Orthopaedic Surgery "Dr. Miroslav Zotovic" Banja Luka. The study had two phases. In the first phase we have assessed inclusion criteria, in the second phase we carried out psy-

chological testing. The study included patients with first stroke and macroscopic lesions of prosencephalon on computerized axial tomography (CAT) records. CAT records were done in the period of 72 hours after stroke. Because we were interested in emotional changes of patients in subacute phase of stroke we have decided to perform psychometric examination in the period 11–40 days after stroke. Patients were assessed once, and the exact day of psychometric testing for each patient was defined by means of the method of random selection. Study has been approved by the Faculty of Medicine Ethic Committee and participants gave informed consent prior to their inclusion in the study. Details that disclose the identity of the participants were omitted.

Criteria of including patients into second phase of study

Due to significant mixture of influences, patients in heavier, comorbid states (heart decompensation, unstable angina, infarctus myocardii in the previous year and the year of examination, infective diseases, malign and chronic immunological diseases) were excluded. Also, the study included only patients with baseline NIHSS (National Institute of Health Stroke Scale) score at the moment of psychological testing $2 \leq X \leq 10$. Total score on NIHSS scale ranges between 0–42, where higher values reflect greater weight of cerebral infarction. According to Brott et al. NIHSS score of less than 10 includes patients with mild and adequately severe neurological deficit (3). Among patients with mild neurological deficit, those were included with whom “drift test” was positive on both same sided extremities (NIHSS = 1 + 1) or NIHSS score had the value of minimum 2 on one of the extremities. Exclusion criteria were also moderate and severe sensory and motor dysphasia in the first phase of study since they complicate to a great extent the carrying out of neuro-psychological testing, since we have used verbal neuropsychological tests.

Research instruments — CAT brain records

Morphometric research comprised superacute (up to 24h) and acute ischemic/hemorrhagic lesions (24h up to 3 days). Sensitivity of CAT scanner in detection of early ischemic lesions is limited, and only one half of all strokes are visualised within 48h after the stroke (4, 5). Acute phase of stroke (the first week after the stroke) is characterised by intensified hypodensity of affected brain tissue (gray and white matter). Brain oedema and the mass effect reach their maximum values usually 3 to 5 days after the stroke (4). Given that in

this case pathological process spreads more and more into the healthy tissue, in our study morphological research was limited to lesions that appeared up to 72h after the stroke. The surface of hemorrhagic lesions being defined (in 13 patients) included the zone of cytotoxic oedema too.

AutoCAD digital planimetry of cerebrovascular lesions

Localization of lesions with clearly stated affected morpho-anatomic structures (cortex, basal ganglia, structures of diencephalon, white matter) (6, 7) was defined on non-contrast CAT records (5 mm layer thickness) on the surface of the biggest lesion cross section. Cerebral lesions were classified into the following categories: 1. frontal lobe/other forebrain segments damages, 2. striate body damages (yes/no), 3. limbic lobe i.e. limbic cortex, adjacent white matter, limbic nuclei damages (yes/no), and 4. interbrain damages (thalamus and/or hypothalamus) (yes/no). The aforementioned lobe categories have included both cortical and subcortical lesions. To define deep (subcortical) frontal lesions, the border of the frontal lobe at the level of insular cortex and para-insular structure sections was the orthogonal line drawn through the front end of sulcus circularis insulae on the axis of neuraxis (mediosagittal plane), thus comprising precaudate structures. However, the most of frontal lobe lesions were mixed and they caught adjacent lobes (25 of 35 lesions).

Area and perimeter of lesions were measured by AutoCAD digital planimetry (Figure 1) with previous transformation of CAT records into the digital format by means of digital camera with resolution 8 Mpx. AutoCAD version 2004 for PC Windows (developed

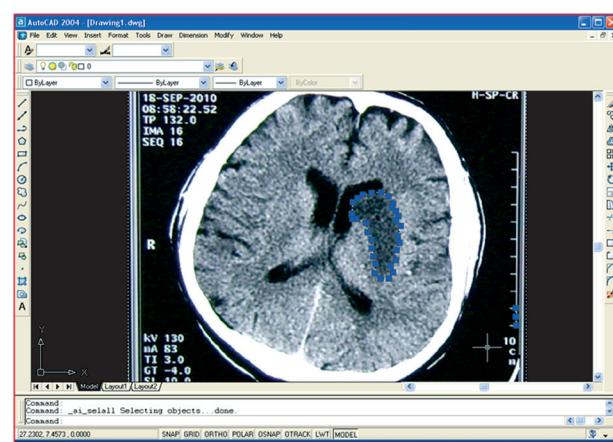


Figure 1. AutoCAD digital planimetry

*Morphometry of cerebrovascular lesion affecting the anterior limb of capsula interna and the left corpus striatum (caput nc. caudati, putamen and the lateral segment of globus pallidus). Area = 766.13 mm², perimeter = 14.044 cm

by Autodesk, Inc. San Rafael, California, USA; see <http://usa.autodesk.com/autocad/>) belongs to programme package groups meant for drawing, projecting and other forms of computer application in engineering practice. This programme package can be used for measuring of surfaces having irregular geometric forms, such as structures of central nervous system (8).

Psychometric tests

The following psychometric tests were used to test disorders in psychic functions:

1. Hamilton Rating Scale for Depression (HRSD); 21 items, application time 15–20 min (9). Although the Hamilton scale consists of twenty one items, only the first seventeen are being scored. Values 8–13 indicate mild depression, 14–18 moderate depression, 19–22 severe depression, whereas values ≥ 23 indicate very severe depression.

2. Questionnaire for qualitative evaluation of object relations in etiopathogenesis of post-stroke behavioural and emotional disturbances (10). For the purpose of an orientation insight into quality of object relations in patients affected by cerebrovascular stroke (in childhood- up to age 18), the following parameters were tested: The patient's primary family profile compared to its integrity: presence of divorce, or death of a parent; Continuous separation of the patient from his/her mother: death of mother during childbirth, custody of a child given to father after divorce, the adopted child, woman immature for the role of a mother gives her child to someone else; Discontinuous separation of mother from the patient: prolonged hospitalisation of mother due to mental illness, prolonged hospitalisation of mother due to somatic illness, parental substitutes — “weekend” mother, which was justified with housing and economic reasons. Patients who presented one or more positive answers were classified into category: detachment from parents = yes, which was used for further statistical analysis. 3. To evaluate dominance of brain hemisphere in sensory-motor functions, Handedness Questionnaire was used (11, 12).

Statistic data processing

The size of focal lesion was brought in connection with the intensity of depressive manifestations by applying Pearson's coefficient of linear correlation. Basic assumptions of the linear model (normality, homoscedasticity) were tested (13). In order to make a difference between whether depressive symptomatology is a reaction on the very disease or to a specific morpho-anatomic lesion localization, the significance of difference in dependence of affected structure of the central

nervous system was examined (the significant differences would indicate specific locus deficiencies of psychic functions). The significance of difference was examined by means of non-parametric Fisher's exact test. The dependence of depressive reactions on the surface of lesion was also examined via simple non-linear regression as well as Spearman's rank correlation. To estimate the risk of psycho-pathological manifestations, besides classical parameters such odds ratio (OR) and relative risk (RR), Kaplan-Meier's and Cox's hazard model were used. Analyses were performed using SPSS version 16.0 for Windows. Statistic conclusions were derived on the basis of 2-tailed P values and the level of significance $P < 0.05$.

RESULTS

The frequency of cerebrovascular lesion localization in dependence of affected brain structures is presented in Table 1.

Table 1. Distribution of cerebrovascular lesions in dependence of forebrain's affected structures

| Affected structure | n^a | % |
|---|-------|------|
| Frontal lobe | 35 | 29.7 |
| Striate body | 33 | 28.0 |
| Limbic lobe | 19 | 16.1 |
| Interbrain (thalamus and/or hypothalamus) | 15 | 12.7 |

^aNote: The total number of lesions in Table 1 is not 118, because for instance frontal lobe lesions overlap with limbic lobe lesions (e.g. limbic structures such as anterior segment of gyrus cinguli are positioned on frontal lobe). Also, mixed lesions have influenced the result.

Depression (HRSD positive) on the examined sample ($n = 118$) was found in 28.8% of the patients. Descriptive values of HRSD score of the examined group of patients are presented in Table 2.

Table 2. Hamilton Rating Scale for Depression (HRSD) score values of patients with stroke

| HRSD score | |
|--------------------|-------|
| n | 118 |
| Mean | 5.45 |
| Median | 5 |
| Mode | 4 |
| Standard deviation | 3.327 |
| Minimum | 1 |
| Maximum | 15 |

Table 3. Determination coefficient (r^2) of the largest cross-section area of cerebrovascular lesions and the level intensity of depressive manifestations (HRSD score values)

| Model summary and parameter estimates | | | | | | | |
|---|-------|-------|-------|-------|-------|---------------------|---------------------------|
| Dependent variable: Hamilton Rating Scale for Depression (HRSD) score | | | | | | | |
| Model summary | | | | | | Parameter estimates | |
| Equation | r^2 | F | d.f.1 | d.f.2 | P | Regression constant | Regression coefficient b1 |
| Linear | 0.056 | 6.896 | 1 | 116 | 0.010 | 6.384 | -0.002 |
| Logarithmic | 0.046 | 5.591 | 1 | 116 | 0.020 | 11.312 | -0.966 |
| Power | 0.063 | 7.830 | 1 | 116 | 0.006 | 18.734 | -0.239 |
| Exponential | 0.069 | 8.560 | 1 | 116 | 0.004 | 5.473 | -0.0004 |
| The independent variable: lesion area (mm^2) | | | | | | | |
| Linear $-0.002 \cdot x + 6.384$ | | | | | | | |
| Exponential $5.473 \cdot e^{(-0.0004 \cdot x)}$ | | | | | | | |
| Euler's constant e ≈ 2.718 | | | | | | | |

Table 4. Spearman rank correlation between the largest cross-section area of cerebrovascular lesions and the level intensity of depressive manifestations (HRSD score values)

| | | Value | Asymptotic s.e. ^a | Approximate t ^b | Approximate P |
|----------------------|----------------------|--------|------------------------------|----------------------------|--------------------|
| Interval by interval | Pearson's r | -0.237 | 0.073 | -2.626 | 0.010 ^c |
| Ordinal by ordinal | Spearman correlation | -0.263 | 0.088 | -2.930 | 0.004 ^c |
| Total Sample n | | 118 | | | |

^a Not assuming the null hypothesis.

^b Using the asymptotic standard error assuming the null hypothesis.

^c Based on normal approximation.

HRSD, Hamilton Rating Scale for Depression.

Table 5. Odds ratio and a relative risk of depression occurrence in patients with stroke

| Variable | Odds ratio (OR) | Relative risk (RR) | Fisher's exact test (2-sided) P |
|--|-----------------|--------------------|---------------------------------|
| Gender (female/male) | 2.788 | 2.091 | 0.025 |
| Detachment from parents (e.g. death of parent or divorce before age 18) (yes/no) | 3.472 | 2.171 | 0.024 |
| Hand-dominant hemisphere (yes/no) | 1.125 | 1.087 | 0.839 |
| Frontal lobe/other forebrain segments | 1.745 | 1.468 | 0.266 |
| Striate body (yes/no) | 0.900 | 0.927 | 0.999 |
| Limbic lobe (limbic cortex, adjacent white matter, limbic nuclei) (yes/no) | 2.664 | 1.876 | 0.094 |
| Interbrain (yes/no) | 1.276 | 1.184 | 0.762 |
| Hemorrhagic lesion (yes/no) | 1.111 | 1.077 | 0.999 |

Table 6a. Cox regression analysis of depression occurrence in patients with stroke — affected limbic lobe

| Categorical variable codings | | | | |
|------------------------------|---------------|----|---|--|
| | Frequency (1) | | | |
| Gender | Female | 59 | 1 | |
| | Male | 59 | 0 | |
| Hand-dominant hemisphere | Yes | 67 | 1 | |
| | No | 51 | 0 | |
| Limbic lobe | Yes | 19 | 1 | |
| | No | 99 | 0 | |
| Detachment from parents | Yes | 19 | 1 | |
| | No | 99 | 0 | |

Table 6b. Variables in the equation

| | Regression coefficient b | s.e. | d.f. | P | Hazard ratio e ^b (HR) | 95.0% CI for HR | |
|--------------------------------|--------------------------|---------|------|---------|----------------------------------|-----------------|-------|
| | | | | | | Lower | Upper |
| Gender | 1.479 | 0.414 | 1 | < 0.001 | 4.389 | 1.951 | 9.876 |
| Detachment from parents | 0.518 | 0.384 | 1 | 0.178 | 1.678 | 0.790 | 3.564 |
| Lesion area (mm ²) | -0.0002 | 0.00047 | 1 | 0.742 | 0.9998 | 0.9989 | 1.001 |
| Hand-dominant hemisphere | -0.092 | 0.353 | 1 | 0.795 | 0.912 | 0.457 | 1.822 |
| Limbic lobe | 0.979 | 0.419 | 1 | 0.019 | 2.661 | 1.171 | 6.046 |

By means of regressive analysis of the coefficient of determination (r^2), a statistically significant linear dependence of the surface of the highest cross section of cerebrovascular lesion and the intensity of depressive manifestations (HRSD values) was determined ($P = 0.010$) (Figure 2, Table 3).

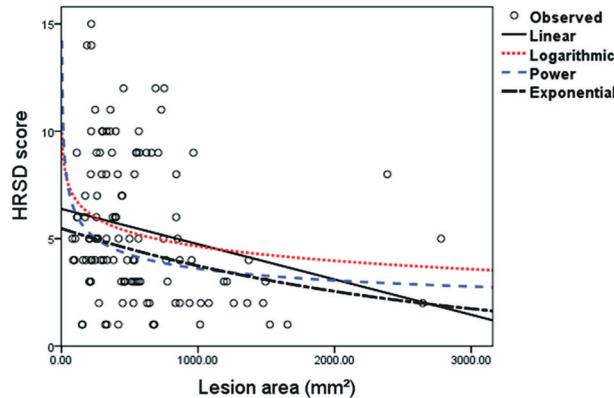
Due to distortion of the basic assumptions of linear regression model (normality and homoscedasticity), to estimate the intensity and direction of correlation Spearman's rank correlation was used (Table 4).

Negative correlation of the values of HRSD score and the surface of the biggest cross section of cerebrovascular lesion with a high level of significance was found ($P < 0.01$) (Table 4).

Excluding the high leverage values and values with large Cook's distance from regression model (lesion area: 2386.58 mm², 2645.20 mm², and 2780.08 mm²) changed Pearson's (linear) correlation coefficient from $r = -0.237$ ($P = 0.010$) to $r = -0.303$ ($P = 0.001$), and Spearman's from $r = -0.263$ ($P = 0.004$) to $r = -0.274$ ($P = 0.003$). Spearman's r, as expected, showed greater stability.

In Table 5 we presented the analysis of occurrence of depression (according to HRSD criteria) in dependence on the affected brain regions of interest.

Kaplan-Meier's analysis (Figure 3) confirmed a greater hazard of the occurrence of depression in female persons (Log Rank, $P < 0.001$).

**Figure 2.** Regression analysis between the largest cross-section area of cerebrovascular lesions and the level intensity of depressive manifestations in patients with stroke

*X-axis shows values of the area of cerebrovascular lesions (in mm²) measured through the largest cross-section, while Y-axis shows observed Hamilton Rating Scale for Depression (HRSD) score values of patients included in the study. Using the method of least squares line and curves (logarithmic, power, and exponential) which best fit the observed data are plotted.

Hazard ratio e^b (HR) represents a numerical expression of Cox hazard. The value > 1 indicates higher, and the values < 1 lower risk of explanatory variable (e.g. gender) on the occurrence of depression. In the Table 6b, the risk of that modality of used explanatory

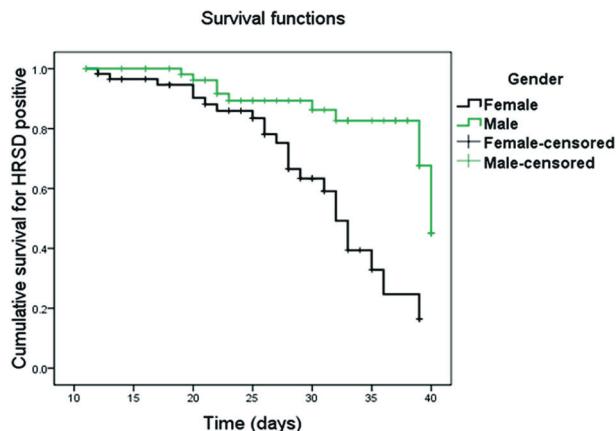


Figure 3. Kaplan-Meier hazard analysis of depression in patients with stroke depending on the patients' gender

*Survival functions is the common name for presented functions, since the initial tests were used to assess the risk of death from the diseases. The lower the curve of an event (in our example the occurrence of depression) for the modality of tested characteristics (gender of respondents), the higher is the risk. HRSD, Hamilton Rating Scale for Depression.

variable which is coded in the Table 6a with the value 1 (e.g. female gender) is presented. Via Cox's analysis, the dependence of the occurrence of depression on the person's gender was determined. Higher risk of women ($HR = 4.389, P < 0.001$) was found. Also, higher risk of the occurrence of depression due to the affected lobus limbicus structures ($HR = 2.661, P = 0.019$) is seen. The risk of occurrence of depression in the case of 200 mm² bigger surface is 3.92% lower ($P = 0.742$), which was calculated via the formula $100\% \times (1 - (0.9998)^{200})$. By including only two explanatory variables (gender and lobus limbicus affectedness) in the model the results did not change statistical significance (female: $HR = 4.256, P < 0.001$; lobus limbicus: $HR = 2.704, P = 0.015$). After adjustment to fit, for the same explanatory variables as in Table 6b, the risk of occurrence of depression due to the damages of other regions of interest did not show statistically significant differences (lobus frontalis: $HR = 1.284, P = 0.535$; corpus striatum: $HR = 0.853, P = 0.695$).

DISCUSSION

Incidence of depressive manifestations in patients with stroke

The frequency of depression in patients with stroke depends to a great extent on the time of psycho-metric examinations after stroke as well as on psycho-metric test used thereby. This complicates the comparison of results between studies, although the subject of research is the same. Starkstein et al. discover apathy in the

first ten days after stroke in 22.5% of cases, and depression in 33.8% (14). Brodaty et al. describe apathy as an analogue to depression three to six months after stroke in 26.7% of patients (15). Some authors (16) point to a higher frequency of apathy (50%) as well as to dependence of this emotional disorder on lower blood flow in the right dorsolateral parts of frontal lobe and left fronttemporal regions. Aström et al. find major depression in 25% of patients in the first month after stroke, in 31% three months after stroke, in 16% twelve months after, in 19% two years after and in 29% three years after (17). The study Starkstein et al. determines major depression in acute phase of stroke in 18.3% of patients, and minor depression in 11.8% of cases (18). It is interesting to mention the study Schwartz et al. which finds depression in men in the period of acute post-stroke rehabilitation in 40% of patients (19). One year (fifteen months) after stroke Brodaty et al. determine depression in 20.7% of patients (20). Three to five years after stroke the frequency of depression is 18.3%, and seven years after stroke 20% (21, 22). Some studies point to the significance of passivity and indifference of patients with acute stroke. Aybek et al. notice passivity in acute stroke in 49% of cases, and emotional indifference in 53% (23). The frequency of depressive manifestation in patients suffering from cerebrovascular stroke amounted in our research to 28.8%. This frequency approximates to the frequency of study Starkstein et al. who determines depression in acute phase of stroke (first month) in 30.1% of patients ($n = 93$) (18).

Correlation between depression intensity and the size of a cerebrovascular lesion

By applying a regression analysis of dependence between the highest cross-section of the lesion area and the level of the depression intensity we found linear determination coefficient $r^2 = 0.056 (P = 0.010)$. The violation of normality and homoscedasticity parameters of the linear model was observed. The observed HRSD values significantly deviate from normal distribution (Shapiro-Wilk, $P < 0.000$). The heteroscedasticity i.e. dispersion of the standardized residuals of the HRSD score to the right side — “fan out” is present. Due to violation of the model's hypotheses and low values of Pearson (linear) correlation coefficient ($r = -0.237, P = 0.010$), which indicates a weak correlation between the examined phenomena, and to avoid false positive results, the Spearman rank correlation was applied. The Spearman correlation coefficient proved a monotonously decreasing relationship ($r = -0.263, P = 0.004$).

The positive correlation between depression and the size of the right hemisphere lesion and the intensity

of the neurological deficit was confirmed by various studies (19, 24, 25). The studies (21, 26, 27) also confirmed the existence of the correlation between the lesion extent, neurological deficit and intensity of depression, while the studies (20, 28) deny it. In contrast with the mentioned studies, the negative correlation has been confirmed within our study. We explain our finding by differences in period of assessment of depressive phenomena. In our study we have examined these phenomena in earlier- subacute phase (11–40 days) after stroke, where heavier general medical condition plausibly altered the finding. From the point of evolutionary psychology and work of some behaviourists, e.g. Engel, the role of depression withdrawal is the preservation of bodily energy (29). In accordance with that, large brain lesions may as well activate defence mechanisms resulting in depression inactivation and energy savings. Lower intensity of depressive manifestations with larger cerebrovascular lesions, is explained by the fact that afferent sensations, which precede emotions, are diminished due to a neurological deficit (based on the James-Lange peripheral theory of emotions). Although this concept was abandoned after McLean-Papez central theory of emotions, Damasio (2000) used similar peripheral mechanisms to explain the origin of the consciousness (30). According to the ICD-10 classification, depression disorders refer to hyperthymia, which support the aforementioned statement. Inactivation of depressive manifestations spectrum and indifference are defence mechanisms. Therefore, it is not surprising that Aybek et al. find that 53% of people suffering from cerebrovascular stroke are indifferent (23). Statistically insignificant difference of correlation between lesion size and depression by Cox model (Table 6b) compared to Spearman model is the result of comparison between lesion area and positive cases of depression, rather than the range of HRSD scores. It is observed that the risk of depression is lower by 3.92% if a lesion is by 200 mm² larger ($P > 0.05$).

Significance of stroke lesion localization for the consequent depression

Beblo et al. (28) came with the conclusion that post-stroke depression is in relation with the basal ganglia lesions; for Finset et al. (31) it is related to deep retrorolandic lesions, while Starkstein et al. (18) connect post-stroke depression with the parietal cortex lesions. Zhang et al. (32) associate depression with lesions at posterior limb and genu of internal capsule and cortical-subcortical area of the temporal lobe, while Tham et al. (33) have highlighted pathology of white matter in prefrontal brain region. In our study, the correlation between lesions of the limbic system (lobus limbicus)

and depressive manifestations is observed by applying Cox's regression model ($HR = 2.661, P = 0.019$). The lobus limbicus category has included lesions of both medial and basolateral limbic cortical regions, as well as lesions of subcortical limbic nuclei (e.g. corpus amygdaloideum). Similar results have been obtained by Terroni et al. (34) who indicate that depression due to stroke is etiologically related to the disruption of the limbic-cortical-striatal-pallidal-thalamic circuit, and Farinelli et al. (35) who emphasize the damage of the anterior subcortical-cortical midline system (as core of the limbic system) and its relationships to depression. The risk of depression in our study is by 1.284 times higher when frontal lobe is affected, compared to other regions of prosencephalon and by 14.7% lower if corpus striatum is affected, but these are without statistical significances ($P > 0.05$).

Gender and hemisphere dominance as variables in pathoplasticity of depressive phenomena

Considering the gender as a risk factor, Pohjasvaa et al. did not find statistically significant differences in depressive disorders frequency (27). Kishi et al. identified the differences and described more frequent depressive disorders with women (36). In our study, the female gender was accompanied by a higher risk of depression ($OR = 2.788, P = 0.025$), and also the dependence is established on the object's relations structure distortion, that is, detachment from parents — death or divorce of the patient's parents before the age of eighteen ($OR = 3.472, P = 0.024$). Kaplan-Meier's analysis confirmed a higher hazard with women (Log Rank, $P = 0.000$). The same hazard is confirmed by Cox's regression model. In case of *risk classification lobus limbicus/other regions of prosencephalon*, the risk of the development of depression with women is by 4.389 times higher than with men (Table 6b). Statistical significance of the correlation between occurrence of depression and gender in the Kaplan-Meier and Cox model is explained by an earlier period of emotional reactions of women to stress since for the calculation of risk these models take into account the time of the observed event occurrence. If we take into account the specific characteristics of the emotions: time accumulation of affects/abreactions, we can conclude that men are more tolerant to stress than women and have a higher threshold of emotional reaction than women. By changing the threshold of emotional reaction, lesions of anatomic structures (lobus frontalis, corpus striatum and lobus limbicus) could also influence the occurrence and frequency of depressive disorders in patients with stroke.

One of the risk factors in the etiopathogenesis of post-stroke depressive disorders is frontal left hemisphere lesions (17, 37–41). Terroni et al. (34) also point to left side of lesions. Kishi et al. suggest that left-sided lesions are more frequent with patients with self-acknowledged depression than in case of patients whose depression is observed by others (36). Vataja et al. do not correlate depression-dysexecutive syndrome (DES) with hemisphere side, but stress the importance of frontal-subcortical ischemic lesions (42). Brodaty et al. (20) also deny correlation between depression and the side of hemisphere, while Sharpe et al., Aben et al. and House et al. exclude the possibility of correlation of post-stroke depression with frontal left lesions (21, 26, 43). In order to assess the pathoplasticity of psychological functions and due to higher functional deficit, we have analysed the correlation between depression and motor-dominant hemisphere damage. By application of the Cox's model, higher risk of motor-dominant vs. non-dominant hemisphere damage for depression occurrence isn't confirmed in our study.

Reactivity vs. organic changes

It is interesting to note that patients in psychometric tests didn't express feelings of guilt, which is, according to psychoanalytic teachings, the basis of dynamic mechanisms. This supports the reactivity of the depression in patients with stroke, which largely increases the importance of implementing measures of mental hygiene, not only by psychiatrists but also other services and health workers.

Strength and limitations

The strength of this study in comparison to the aforementioned researches is reflected in a more precise definition of anatomic localization of lesion. Specific design of study enabled application of Cox multiple regression model which attenuates confounding effects. A relatively small number of positive cases of depression as well as positive frequencies of some explanatory variables on the examined sample of patients can be considered as a limitation. However, it should be noted that achieving the statistical significance on a smaller sample requires greater numerical differences, which may indicate a more powerful influence of explanatory variable on the observed disorder. We emp-

hasize that our study is applicable only to the population of patients with subacute stroke (11–40 days after stroke), because associated heavier somatic condition of patients had significant influence on the results. Also, for assessment of correlation between lesion size and depression we used all values of HRSD score, and hence indicated to symptoms rather than depression itself. Results considering the risk for depression occurrence on frontal lobe damages must be taken with precaution because high frequency of mixed lesions disabled adequate distinction between frontal lobe lesions and lesions of other forebrain segments.

CONCLUSION

Our conclusions, as well as the overall results, have confirmed the working hypothesis H1a. The H1b hypothesis has been confirmed in case of depression caused by lesions of limbic lobe structures. The identified risk factors of depressive phenomena development in patients with stroke (female gender, size and localization of cerebrovascular lesion) obliges us to timely identify vulnerable groups of patients and implement an early treatment of mental disorders, bearing always in mind that the word is cure as well.

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Conflict of interest

None to declare.

Abbreviations

CAT — computerized axial tomography

HR — hazard ratio

HRSD — Hamilton Rating Scale for Depression

NIHSS — National Institute of Health Stroke Scale

OR — odds ratio

RR — relative risk

Sažetak

KORELACIONA ANALIZA DEPRESIVNIH ISPOLJAVANJA I MORFOLOŠKIH KARAKTERISTIKA MOŽDANIH LEZIJA KOD BOLESNIKA SA INZULTOM

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Uvod: Poznavanje etiopatogeneze postinzultnih depresivnih fenomena doprinosi ranoj dijagnostici koja ukoliko je praćena adekvatnom psiho/farmakoterapijom u velikoj meri skraćuje oporavak, i pogoduje socijalnoj i profesionalnoj rehabilitaciji pacijenata. Cilj ovog rada je da se istraži zavisnost pojave depresivnih ispoljavanja od veličine i anatomske lokalizacije lezije. **Ispitanici i metode:** Istraživanje je obuhvatilo 118 osoba oboljelih od cerebrovaskularnog inzulta. Lokalizacija lezije određivana je na aksijalnim nekontrasnim CT snimcima, a površina i obim lezije primenom AutoCAD digitalne planimetrije. Psihometrijsko ispitivanje pomoću Hamiltonove skale za depresiju izvođeno je metodom slučajnog odabira 11–40 dana nakon inzulta. Korelaciona analiza vršena je prostom linearном/nelinearnom regresijom, i Coxo-

vim hazardnim regresionim modelom. **Rezultati:** Uočena je negativna korelacija između intenziteta depresivnog ispoljavanja i veličine cerebrovaskularne lezije (Spearman $r = -0.263; P = 0.004$). Coxovim regresionim modelom utvrdili smo 4.389 puta veći rizik za pojavu depresije kod osoba ženskog pola, kao i veći rizik usled oštećenja struktura lobus limbicusa (hazard ratio e^b (HR) = 2.661, $P = 0.019$). **Zaključak:** Manji intenzitet depresivnog ispoljavanja kod većih cerebrovaskularnih lezija objasnili smo aktivacijom reparacionih mehanizama sa uštedom energije i smanjenjem (usled neuroloških ispada) aferentnih perifernih senzacija koje prethode pojavi emocija (James-Langeova periferna teorija emocija).

Ključne reči: inzult, lezija, depresija, korelacija, analiza.

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