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MORPHOLOGICAL ASSOCIATIONS BETWEEN WHITE MATTER DISEASE AND INDEX STROKE LESION

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Annotation. *The aim of the research is to investigate the associations between white matter disease (WMD) parameters and index stroke lesion characteristics in patients with acute stroke. There are a number of studies that have examined the effect of WMD on the consequences of cerebral stroke, but few of them have addressed the issues of its effect on stroke focus parameters. The aim of the study is to establish relationships between WMD parameters and stroke focus characteristics in patients with acute cerebral stroke. 294 consecutive patients with acute stroke were enrolled. All participants underwent magnetic resonance imaging (MRI) and computed tomography (CT). Assessment for WMD markers and index stroke lesion parameters as well as clinical-neurological testing were performed. Statistical analysis was performed using the jamovi project (2022). Jamovi (Version 2.2.5) [Computer Software]. Sydney, Australia. In the multivariable analysis, WMD grade 3 significantly associated with stroke volume (b = 30.0; 95% CI 3.6 - 56.5, p = 0.026), more severe brain edema (OR = 2.4; 95% CI 1.0 - 5.8, p = 0.047). Irregular shape of WMD associated with brain edema (b = 0.4; 95% CI 0.1 - 0.7, p = 0.019) and ischemic penumbra growth (b = -0.7; 95% CI 1.2 - -0.1, p = 0.014). Patients with severe WMD had significantly higher prevalence of hemorrhagic transformation: 2 (3%) vs 29 (13%), p < 0.05 and more often had neuroimaging evidence of previous stroke lesions: 3 (5%) vs 34 (32%), p <0.001. Thus, WMD characteristics are independent predictors of larger index stroke volume, brain edema growth, early ischemic changes preceding thrombolytic therapy and hemorrhagic transformation of ischemic stroke lesion, which is important for better prognosis and preventive strategies.*

Keywords: *white matter disease, stroke, ischemic penumbra, CT.*

Introduction

White matter disease (WMD) is a common neuroimaging finding, seen in the deep and periventricular brain areas and is a marker of cerebral small vessel disease. It mainly observed in elderly people and appears as hyperintense regions on fluid-attenuated inversion recovery (FLAIR) of magnetic resonance images (MRI) or hypodense areas on computed tomography (CT). The other terms for WMD are white mater hyperintensity or leukoaraiosis. At about 90% of European people between 60 and 90 years have neuroimaging evidence of WMD. In many studies, WMD was linked to an increased risk of stroke, dementia, and death [16].

The risk factors of WMD include age and hypertension along with genetic predisposition (such as the apolipoprotein Ee4 allele). The pathogenesis of leukoaraiosis is complex and multifactorial. Vascular stenosis, arteriosclerosis, venous collagenosis and endothelial dysfunction lead to diffuse loss of dynamic cerebral autoregulation. As a result hypoperfusion, white matter ischemia and damage to the blood-brain barrier, resulting in the plasma or cerebrospinal fluid components extravasation into the brain parenchyma. All of that lead to inflammation, demyelination, axonal injury, apoptosis and gliosis, which eventually seen as white matter changes [9].

Stroke is a leading cause of long-term disability and the second most common cause of death on the globe. About 130000 strokes occur in Ukraine annually. 30-40% of people with stroke die within 30 days. About 70% of stroke survivors have permanent neurological deficits. A third of patients with a stroke in Ukraine are people of working age. In Ukraine, twice as many people die from stroke compared to the countries of Western Europe [18].

There are studies which explored WMD burden and stroke outcome [4, 7], but few have studied its impact on acute stroke lesion features. Therefore, understanding the relationship between WMD parameters and acute stroke lesion characteristics is important for the prognosis and preventive measures. We tested the hypothesis that patients with more severe white matter disease burden are presented with worsen neuroimaging parameters of index stroke lesion.

The aim of the research is to investigate the associations between WMD parameters and index stroke lesion characteristics in patients with acute stroke.

Materials and methods

Written informed consent was obtained from all subjects participating in the research. The inclusion criteria consist of patients above 18 years of age with a clinical diagnosis of stroke based on the World Health Organization criteria and presence of a brain MRI or CT study of good quality. We excluded patients with prior history of non-stroke brain pathology, with abnormal brain MRI or CT findings, related to non-vascular pathology and patients with suboptimal quality of brain images.

It was a single-center prospective cohort study based at specialized stroke department (Stroke Unit) № 22 of the Vinnytsia Regional Clinical Psychoneurological Hospital named after acad. O.I. Yushchenko VRC. Between 2016 and 2019, a total of 294 consecutive patients with acute

stroke were recruited.

In the total population, 174 patients underwent computed tomography, 120 magnetic resonance imaging. Some of the subjects were imaged with either MRI or CT, some of them - with MRI and CT both. MRI was performed on a Philips Achieva with a magnetic field strength of 1.5 T. The standard brain scanning protocol included the following whole brain scans: T1-weighted, T2-weighted, fluid-attenuated inversion recovery (FRAIR) and DWI sequences, slice thickness was 3.5-5 mm. CT was performed on a General Electric CT/e (Italy) with a tomographic slices of 3-7 mm.

Stroke was defined according to World Health Organization criteria as a syndrome of rapidly developing clinical signs of focal or global disturbance of cerebral function lasting $\geq$ 24 hours or leading to death with no apparent cause other than of vascular origin [3]. Stroke diagnoses were verified by an experienced vascular neurologist and classified as ischemic or hemorrhagic based on neuroimaging reports (CT and/or MRI) of experienced radiologists.

The severity of WMD was assessed using the Fazekas scale. The scale grades the severity from 0 to 3. Periventricular: Fazekas = 0: absent; Fazekas = 1: cap or pencil-like thin layer; Fazekas = 2: smooth halo; Fazekas = 3: extension into deep white matter. Deep white matter: Fazekas = 0: absent; Fazekas = 1: punctate lesions; Fazekas = 2: lesions beginning to confluence; Fazekas = 3: lesions confluent and united in sheets [14]. The type of WMD was also evaluated: periventricular without deep (if its length from the ventricles was up to 10 mm), confluent (if its length was more than 10 mm), deep (not adjacent to the ventricles, but subcortical), periventricular with deep, confluent with deep. The shape of leukoaraiosis was also visually assessed (smooth or irregular), based on the templates as well as the form of deep WMD (punctiform or ellipsoid) [5]. For groups comparison we divided patients to WMD grade 0-1 versus WMD 3.

We assessed volume of the stroke lesion according to the (ABC/2) formula [15], the severity of brain edema [17], vascular and anatomical localization of the stroke. We also recorded neuroimaging evidence of previous stroke lesions.

The Alberta Stroke Program Early CT score scale (ASPECTS) was used to quantify early ischemic changes on baseline CT in the anterior circulation before thrombolytic therapy [13]. A similar scale was used for the posterior circulation Pc-SPECTS [11].

We assessed hemorrhagic transformation of ischemic lesion and categorized it as asymptomatic or symptomatic.

We measured density of cortical brain tissue on the CT scans.

We used univariable and multivariable regression analysis to establish the associations between WMD parameters and stroke lesion characteristics. Logistic regression was used in case of binomial dependent variable. Linear regression was used in case of linear dependent variable. The results are shown as odds ratio (OR) and 95% confidence intervals (CI) or as a b-coefficient in case of linear regression. A p value < 0.05 was considered statistically significant. Continuous variables were presented as mean±standard deviations (SD) or median and interquartile range (ICR). Two groups comparison were performed by Students t-test in normal distribution or Mann-Whitney U test if the variables were not normally distributed. Categorical variables were presented as percentages and were compared with Pearsons chi square test or Fishers exact test (if the number of observations were <5). Statistical analyses were performed by the jamovi project (2022). Jamovi (Version 2.2.5) [Computer Software]. Sydney, Australia.

Committee on Bioethics of National Pirogov Memorial Medical University, Vinnytsya (Protocol № 9 from 14.11.2016) found that the study does not contradict the basic bioethical standards of the Declaration of Helsinki, the Council of Europe Convention on Human Rights and Biomedicine (1977), the relevant WHO regulations and laws of Ukraine.

The study was conducted as a fragment of a research work of the neurology department of Vinnytsia National Pirogov Memorial Medical University: “Diagnosis and predictive value of cerebral small vessel disease in the acute phase of cerebral stroke” (state registration number 0196U004916).

Results

The patients demographic and clinical characteristics depending on the WMD severity (grade 0-1 in comparison to WMD grade 3) are summarized in Table 1.

In the total population (mean age 61.9±10.1, 115 (39%) females), white matter disease had 97% participants, among them 106 (36%) had severe WMD (Fazekas score 3), 122 (42%) moderate WMD (Fazekas score 2), 56 (19%) mild WMD (Fazekas score 1). Irregular shape of WMD was noted in 76 (27%), smooth in 207 (73%) participants. 155 (55%) subjects had only periventricular leukoaraiosis, 61 (21%) periventricular and deep, 35 (12%) confluent, 28 (10%) deep and confluent, 3 (1%) only deep. In 58 (54%) subjects deep leukoaraiosis was punctiform, in 50 (46%) ellipsoidal.

Patients with leukoaraiosis were advanced age, had significantly longer hospitalization period and more often had history of hypertension and previous stroke, as well as higher Charlson comorbidity index, and more severe index stroke based on NIHSS scale (table 1). WMD grade 3 patients had complications during hospitalization: 41 (39%) versus 8 (12%) WMD grade 0-1 ($p<0.001$).

Differences in index stroke lesion between WMD grade 0-1 vs WMD grade 2 are shown in Table 2.

Patients with severe WMD had greater stroke volume and brain edema, more severe early ischemic changes preceding thrombolytic therapy, had significantly higher prevalence of hemorrhagic transformation and more often had neuroimaging evidence of previous stroke lesions (Fig. 1).

In the linear regression model, adjusted for age and sex, WMD grade 3 significantly associated with stroke

Table 1. Clinical and demographic data based on WMD severity.

Variable	WMD grade 0-1, 66	WMD grade 3, 106
Age, years	53.5±10.8	66.6±7.6***
Sex male female	 41 (62%) 25 (38%)	 66 (62%) 66 (62%)
Period of hospitalization, days	8.3±3.4	9.9±4.6*
Stroke classification, n (%) large artery atherosclerosis cardioembolism small vessel occlusion other determined stroke undetermined stroke	 31 (48%) 12 (19%) 6 (9%) 1 (2%) 14 (22%)	 52 (53%) 24 (24%) 18 (18%), p = 0.178 0 (0%) 5 (5%)**
Smoking	18 (31%)	26 (31%)
Alcohol overuse	3 (5%)	10 (12%), p = 0.238
History of previous stroke	9 (14%)	39 (37%)***
Hypertension	49 (77%)	106 (100%)***
Ischemic heart disease	6 (10%)	15 (14%)
Atrial fibrillation	13 (20%)	36 (34%)*
Diabetes Mellitus	9 (14%)	20 (19%)
Peripheral arterial disease	1 (2%)	1 (2%)
Charlson comorbidity index	Median 1 (IQR 1 - 2)	2 (1 - 3)***
BMI, kg/m^2	30.0±6.2	29.6±4.5
Hyperlipidemia	34 (58%)	63 (62%)
NIHSS upon admission	10 (7 - 14)	13 (9 - 17.75)**
mRS upon admission	4 (4 - 4)	4 (4 - 5)

Note: *p value < 0.05, **p value < 0.01, ***p value < 0.001. WMD: white matter disease, BMI: body mass index, IQR: interquartile range, NIHSS: National Institutes of Health Stroke Scale, mRS: modified Rankin scale.

Table 2. Morphological stroke parameters based on WMD severity.

Variable	WMD grade 0-1, 66	WMD grade 3, 106
Stroke size, ml	25.3±42.9	47.8±81.7, p=0.087
ASPECTS	9.3±1.0	8.5±1.7*
Pc-ASPECTS	9.0±1.4	8.7±0.9
Right hemisphere cortex density	33.8±1.8	33.4±1.8, p=0.137
Left hemisphere cortex density	33.5±1.7	33.2±1.9, p=0.378
Previous stroke lesion	3 (5%)	34 (32%)***
Vascular localization Anterior circulation Posterior circulation Brainstem	 54 (83%) 11 (17%) 3 (5%)	 83 (79%) 23 (21%) 12 (11%), p=0.263
Anatomical localization Subcortical Cortical-subcortical Brainstem Cerebellum	 12 (25%) 27 (56%) 3 (6%) 6 (13%)	 26 (29%) 53 (58%) 11 (12%) 1 (1%)**
Brain edema median (IQR) mean±SD	 0.5 (0 - 1) 0.5 (0 - 1)	 1 (0 - 2), p=0.057 1.3±1.4, p=0.057
Brain edema Grade 0-1 Grade 2-5	 51 (77%) 15 (23%)	 63 (61%)* 41 (39%)*
Any hemorrhagic transformation	2 (3%)	2 (3%)
Symptomatic hemorrhagic transformation	0 (0%)	5 (5%), p = 0.091

Note: *p value < 0.05, **p value < 0.01, ***p value < 0.001. WMD: white matter disease, ASPECTS: Alberta stroke programme early CT score, Pc: posterior circulation, IQR: interquartile range, SD: standard deviation.

volume (b = 30.0; 95% CI 3.6 - 56.5, p = 0.026).

In the binomial regression analysis, adjusted for age and sex, WMD grade 3 significantly associated with more severe brain edema (grade 2-5 vs grade 0-1): (OR = 2.4; 95% CI 1.0 - 5.8, p = 0.047) (Fig. 2).

In the multivariable linear regression model, adjusted for age, sex and NIHSS score on admission, irregular shape of WMD associated with ischemic penumbra growth, measured by ASPECTS (b = -0.7; 95% CI 1.2 - -0.1, p = 0.014).

In the same model, irregular shape of WMD was associated with brain edema (b = 0.4; 95% CI 0.1 - 0.7, p = 0.019).

Discussion

In this study we found significant associations between white matter disease and stroke volume as well as brain edema, which is in line with some other research [1, 6]. The explanation may be that WMD is associated with

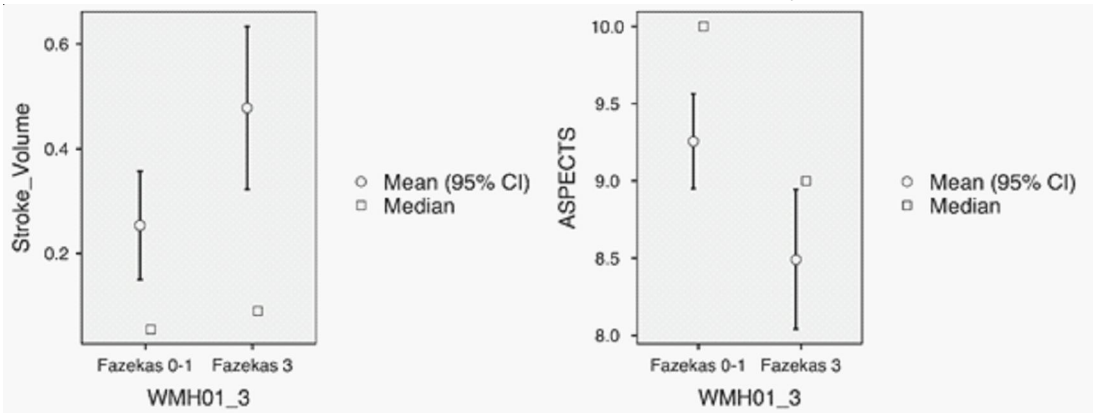

Fig. 1. Comparisons of stroke volume (25.3±42.9 vs 47.8±81.7 ml., p = 0.087) and severity of early ischemic changes preceding thrombolysis, measured by ASPECTS (Alberta Stroke Program Early CT score scale), (9.3±1.0 vs 8.5±1.7 scores, p = 0.016) in patients with WMH (white matter

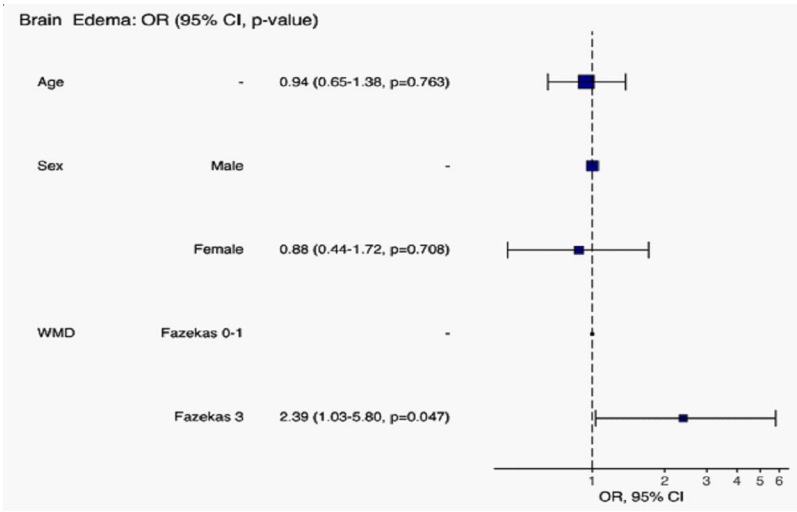

Fig. 2. Effect of white matter disease (WMD) on stroke lesion edema, along with sex and age (per 10 years).

structural and functional vascular changes and factors like vessels lumen narrowing, impaired autoregulation and reduced cerebral blood flow, vessel tortuosity, increased platelet activation and hypercoagulability that may compromise tissue perfusion at the microvascular level as well as tissue capacity for handling of ischemia [1].

Greater brain edema growth can be explained, in addition to aforementioned factors, by small venules collagenosis and as a consequence deterioration of edema resolution.

According to our data, patients with severe WMD had greater ischemic penumbra growth in the hyperacute phase of stroke. A possible explanation may be that in WMD rarefaction tissue cannot properly handle ischemia. Furthermore, changed small arteries in WMD are unable to dilate in response to reduced blood flow. In general, WMD leads to impaired collateral blood flow channels and deteriorates brain ability to cope with ischemic injury. Also, endothelial disfunctions along with blood-brain barrier abnormalities can contribute to worsened tissue outcome [1]. Moreover, WMD decreased vascular density in the area of leukoaraiosis and outside those regions to approximately four fifths that of a normal tissue [10].

A more irregular shape of WMD was also associated with brain edema and ischemic penumbra growth, measured by ASPECTS scale. The explanation for it may be that more irregular shape of WMD represents more severe cerebral small vessel disease subtype [12].

Patients with severe WMD exhibit a significantly higher prevalence of all-types of hemorrhagic transformations (including petechial, small parenchymatous and large parenchymatous) of ischemic stroke lesion. The amount of symptomatic hemorrhagic transformation also tends to be higher in severe WMD subjects. The cause of that can be excessive fragility of blood vessels, associated with WMD.

Demographics and vascular risk factor profiles also were compared across WMD severity groups. Severe WMD patients were advanced age, had higher comorbidity index and had longer hospitalization period. Overall, history of previous stroke, hypertension and atrial fibrillation emerged higher in severe WMD burden. It may reflect potentially competing underlying stroke etiologies and the impact of these risk factors on the progression of WMD.

These findings possibly hint a vicious circle in which existing WMD increases the risk for further cerebral tissue injury and vice versa.

Some studies suggest that WMD has the potential to regress over time [2, 8], so it is necessarily to precisely diagnose, monitor and conquer related risk factors of WMD progression.

There are some limitations of our research. We did not use automated image processing techniques for WMD assessment. We used 1.5T MRI instead of 3.0T MRI, which is likely more sensitive in detecting small WMD lesions. Neuroimaging sequences were used with relatively large slice thickness, which is less sensitive to detect some WMD features, like its shape.

Conclusions and prospects for further development

1. WMD burden and shape are independent predictors of index stroke volume, brain edema growth, early ischemic changes preceding thrombolytic therapy and hemorrhagic transformation of ischemic stroke lesion.

It is necessarily to thoroughly assess neuroimaging white matter disease markers as well as vascular risk factors for better prognosis and preventive strategies.

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МОРФОЛОГІЧНІ ВЗАЄМОЗВЯЗКИ МІЖ ПАТОЛОГІЄЮ БІЛОЇ РЕЧОВИНИ ГОЛОВНОГО МОЗКУ ТА ПАРАМЕТРАМИ ГОСТРОГО ІНСУЛЬТНОГО ВОГНИЩА

Бартюк Р. С., Московко С. П., Смолко Д. Г., Смотрицька Т. В., Желіба Л. М., Марункевич Я. Ю.

Анотація. *Патологія білої речовини головного мозку (ПБР) часта нейровізуалізаційна ознака, що асоціюється із підвищеним ризиком інсульту, деменції та смерті. Існують ряд досліджень, що вивчали вплив ПБР на наслідки мозкового інсульту, проте незначна їх кількість торкалась питань її впливу на параметри інсультного вогнища. Мета дослідження встановити взаємозвязки між параметрами ПБР та характеристиками інсультного вогнища у хворих з гострим мозковим інсультом. 294 хворих з гострим мозковим інсультом прийняли участь у дослідженні. Усім хворим було виконано магнітно-резонансну томографію та/або компютерну томографію. Був проведений нейровізуалізаційний аналіз маркерів ПБП та гострого інсультного вогнища, а також клініко-неврологічне тестування хворих. Статистичний аналіз виконували у програмі the jamovi project (2022). Jamovi (Version 2.2.5) [Computer Software] Sydney, Australia. У багатофакторному аналізі, ПБР 3 ступеню тяжкості достовірно асоціювалась із обємом інсультного вогнища (b = 30,0; 95% CI 3,6 56,5, p = 0,026) та набряком мозку (ВШ = 2,4; 95% CI 1,0 5,8, p = 0,047). Неправильна форма ПБР була повязана з тяжкістю набряку мозку (b = 0,4; 95% CI 0,1 0,7, p = 0,019), швидкістю ішемізації мозкової тканини за шкалою ASPECTS (b = -0.7; 95% CI 1.2 - -0.1, p = 0.014). Пацієнти з тяжким ступенем ПБР мали достовірно більшу частоту випадків геморагічної трансформації: 2 (3%) проти 29 (13%), p<0,05 та частіше мали нейровізуалізаційні ознаки перенесених інсультів: 3 (5%) проти 34 (32%), p<0,001. Отже нейровізуалізаційні характеристики ПБР є незалежними предикторами більшого обєму інсультного вогнища, набряку мозку, ранніх ішемічних змін перед тромболітичною терапією та геморагічної трансфомації гострого інсультного вогнища, що є ключовим для кращого прогнозування та імплементації превентивних стратегій.*

Ключові слова: *патологія білої речовини, інсульт, ішемічна пенумбра, КТ.*