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STRUCTURAL ANALYSIS OF THE DIFFUSION VIOLATIONS IN THE ISCHEMIC FOCUS OF THE PATIENTS WITH IMPAIRED CARBOHYDRATE METABOLISM

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ABSTRACT

The method for structure learning of DWI-images, based on the analysis of the few fractal dimensions of the set of image pixels was developed. It is shown that the study about the structure of DWI-images using few fractal dimensions can be used to describe the ischemic focus and to identify areas of irreversible changes in the brain. The statistically significant differences and correlations between fractal dimensions of healthy tissue and ischemic focus were detected. It confirms the sensitivity of the method and demonstrates the dependence of the infarction area structure from the original morphology state of the brain tissue, that is determined not only the features of the formation of the ischemic focus, but the clinical severity of stroke. It was found that the structural change of the ischemic focus deceased patients significantly different from that of the surviving patients, which may be due to more accurate identification of areas of irreversible changes in comparison with the calculation of the diffusion coefficient. This increases the opportunity of usage of this method as a predictor of stroke outcome.

INTRODUCTION

The basis for therapeutic intervention in acute stroke is the assertion that ischemic focus is heterogeneous in the tissue damage degree. Currently, the various methods of neuroimaging are used to identify the areas of irreversible and potentially reversible changes in tissue. Magnetic resonance tomography (MRT) in DWI regime is the most informative; it shall be deemed that discovered hyperintense centres are corresponded to the zone of irreversible changes. The use of echo-planar sequence pulses for the construction of diffusion-weighted tomograms is the most promising. Quantification estimation of diffusion properties of water in the tissue may be made using map of parametric diffusion on which color of each tomogram pixel corresponds to the measured diffusion coefficient (DC). However, when calculating the average DC for the selected volume all of its peak values which are calculated for each pixel of the image are lost, and, thus, we can get the same DC values with a different distribution of minima and maxima of these values. It is important to develop and apply the structural methods of DWI-images handling to solve this problem.

The purpose of this study is to develop the structural method of DWI-images handling, based on the variety of image pixel fractal dimensions analysis, connected with some properties of the elements of the variety. The limits where the structure of MRT-image shows fractal properties are studied, and also characteristics of the studied processes which are led to the formation of fractal structure of the patients with ischemic stroke (IS) with varying degrees of carbohydrate metabolism violation are found out.

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MATERIALS AND METHODS

The study involved 42 patients with atherothrombotic or with cardioembolic ischemic stroke in the region of the middle cerebral artery, admitted to the hospital in the first 6 hours of onset of the disease. Hyperglycemia (GG) was observed among 35 (83.3%) patients, 15 patients of whom (35.7%) were diagnosed with type 2 diabetes mellitus (DM). The 7 patients (16.7%) had euglycemia during the observation period. Depending on the status of carbohydrate metabolism all patients were divided into groups. The first group consisted of 20 patients with ischemic stroke (IS) and accompanied by stressed GG. The second group included 15 patients with type 2 diabetes, 6 patients of which were diagnosed with diabetes for the first time. The comparison group consisted of 7 patients without disorders of carbohydrate metabolism. Assessment of the patients' state was carried out using clinical scales in the dynamics of acute period of ischemic stroke every day during the first five days, as well as 7 and 14 days of onset of the disease. Neurological status was assessed using the stroke scale of the National Institute of Health (NIHSS). Disease outcome was assessed by the modified Rankin scale. The glycaemia level was determined in the morning on an empty stomach for 1-5, 7 and 14 days of the disease. Upon admission the patient in the hospital and in the future, if necessary diagnosed diabetes, the level of glucose in the venous blood was determined. Also it was investigated the level of glycated hemoglobin A1c in the venous blood upon the admission of the patient in the hospital. The criterion of stress hyperglycemia was considered as blood glucose levels rise above 6.1 mmol/liter at normal glycated hemoglobin [1].

The diagnosis of type 2 diabetes was established by endocrinologist on basis of medical history, physical examination, glucose dynamics data in fasting blood, postprandial blood glucose levels (measured 2 hours after a meal) and glycated hemoglobin according to WHO criteria [2]. Diagnose of IS was confirmed, and the volume of ischemic focus was assessed with the MRT in the spin-echo (SE), in the inversion recovery (FLAIR), in the diffusion (DWI) and in the angio (3D TOF) modes on the 1 tesla tomograph. Area of ischemic focus on DWI was measured using manual delineation of the affected area at each obtained sections with a further automatic calculation. Infarct volume was calculated as the sum of the areas of all received zones on each slice multiplied by the slice thickness and by the distance between it. If the patient has identified two or more of acute ischemic focus, volume of lesions of the brain was calculated as the sum of the volumes of acute ischemic focus. In the same volumes DC was calculated. DWI-image of the brain is characterized by a high rate of self-similarity, what allows us to study the structure of the distribution of the DC using the fractal methods (fractal dimensions) [3].

To solve this problem the following algorithm was developed: it was considered partially ordered finite set (image pixels with color corresponding to the DC in the image area) $A(N^2)$, where N^2 - the number of elements $a_{i,j}$ in the set of $a_{i,j} \in A(N^2)$, where $i, j = 1\ldots N$. Elements of the set have some properties $H_\xi(a)$, unique to the elements of the set $\forall a_{i,j}\left(a_{i,j} \in \left\{a \middle| H_\xi(a)\right\}\right)$. Since there are a few common properties ($\xi > 1$), the description of the set must be done with the help of several fractal dimensions.

We represent the set $A(N^2)$ in the form $A(N^2) = Q^{(1)}(n^2) \cup Q^{(2)}(n^2) \cup \ldots \cup Q^{(\alpha^2)}(n^2)$, where $Q^{(1)}(n^2)$ - disjoint subsets of the set $A(N^2)$: $Q^{(k)}(n^2) \cap Q^{(k')}(n^2) = \varnothing$, $\alpha = \dfrac{N}{n}$, $\sim$ and n – integer. Then $\sim$ and n represent a set $\forall\alpha \in \{\alpha_\gamma\}$ and $\forall\alpha \in \{n_\gamma\}$. Besides

$$n_{\max} = \sup\{n_\gamma\} \in \{n_\gamma\} = N, \quad n_{\min} = \inf\{n_\gamma\} \in \{n_\gamma\} = 1$$

$$\alpha_{\max} = \sup\{\alpha_\gamma\} \in \{\alpha_\gamma\} = N, \quad \alpha_{\min} = \inf\{\alpha_\gamma\} \in \{\alpha_\gamma\} = 1$$

If there are upper and lower bounds of the set $A(N^2)$ for all properties $H_\xi(a)$:

$G_\xi = \sup A(N^2)$ and $g_\xi = \inf A(N^2)$,

so as $G_\xi \in A(N^2)$ and $g_\xi \in A(N^2)$ then in this case the set $A(N^2)$ may be scaled over all properties. For this purpose for upper $G_\P$ and for lower g_ξ bounds of the set $A(N^2)$ some numbers R_ξ and r_ξ may be respectively comparable. Then in the space of each property the set $A(N^2)$ may be covered by a cube of volume $V_\P = (R_\P - r_\P)^2$. In this case on each element of a set $A(N^2)$ a domain in the space of properties will account for the area $s_\P = \dfrac{(R_\P - r_\P)^2}{N^2}$.

Accordingly, each subset $Q^{(k)}(n^2)$ can be covered by cubes with volumes $\nu_\xi = \dfrac{V_\xi}{\alpha^3}$, and their number is determined by the value of $\sup Q^{(k)}(n^2) \in Q^{(k)}(n^2)$ in the properties scale. Then the area occupied by elements of the subset will be $S_\xi(n^2) = s_\xi n^2$. The fractal dimension $D_\P$ for a set $A(N^2)$ by property $H_\P(a)$ may be defined as:

$$D_\P = \sum_{\yen} \frac{\log\Gamma_\P(n^2_{\yen+1}) - \log\Gamma_\P(n^2_{\yen})}{abs(\log S_\P(n^2_{\yen+1})) - abs(\log(\log S_\P(n^2_{\yen})}\left(\frac{\sim_{\yen+1} - \sim_{\yen}}{N-1}\right),$$

where $\Gamma_\xi(n^2)$ is a number of noncontiguous surfaces cubes covering a subset of $Q^{(k)}(n^2)$. In the study of fractal properties of DWI-image as $H_\P(a)$ properties three key defining palette of pixel colors were selected: red $(H_1 = R)$ green $(H_2 = G)$ and blue $(H_3 = B)$. Thus, the description of the structure of the image in this case was realized by three fractal dimensions: D_R, D_G and D_B, which were used to calculate the area of a triangle in the coordinate system properties (SRGB) in the area of 96x96 pixels for hearth ischemia and normal tissue for one slice with the largest area of infarction of each patient, which has a high sensitivity to changes in the structure of the color image. Analysis of the fractal structure of DWI-image was done in PicColorFrac program. At the same time a statistical analysis of the results was conducted. The data in this study are presented as M±SD (M – mean, SD – standard deviation). The comparison of group was carried out using the Mann-Whitney criterion, median (Me), 1 and 3 percentiles were calculated in case of absence of normal distribution. The critical significance level of p=0.05 was assumed. To investigate the relationship between the values of the studied features it was used Spearman's rank correlation coefficient. For the features which are difficult to describe with the quantitative characteristics, we developed a special scale (Table 1).

The results of the study

The infarct volume in the first day of IS of the patients with stress GG was 966.9 (620.6, 3535.9) mm³, patients with diabetes – 1429.8 (279, 4083) mm³, the comparison group – 2348 (1627.2, 3966.1) mm³ (p>0.05).

Table 1. The mark scale of parameters, which are used in the work

Parameters	Marks		
	0	1	2
	The absence of carbohydrate metabolism disorders	The stress hyperglycemia	The diabetes mellitus

Table 2. Dynamics of acute ischemic stroke, depending on the state of carbohydrate metabolism according to the scale NIHSS (in points)

Days of IS	M±SD		
	Group 1 (n=20)	Group 2 (n=15)	Group 3 (n=7)
1	11,9±6,0	12,7±8,6	9,7±5,5
2	10,1±6,5	15,3±8,1*	7,7±5,9
3	10,1±7,3	14,6±8,2**	6,9±5,7
4	9,7±7,0	14,3±8,8**	5,7±5,0
5	9,6±7,5	14,1±8,7***	5,3±5,0
7	9,2±8,0	12,7±8,8*	5,3±4,9
14	9,4±9,1	11,4±9,0*	4,4±4,8

* - p <0.05 between groups 2 and 3 ** - p<0.02 between groups 2 and 3;
*** - p<0.01 between groups 2 and 3

Table 3. Outcomes of ischemic stroke in patients with impaired carbohydrate metabolism

Outcomes of ischemic stroke on Rankin scale (points)	M±SD		
	Group 1 (n= 20)	Group 2 (n= 15)	Group 3 (n= 7)
	1,9±1,7	3,0±1,6*	1,4±1,1

*p<0,05 between groups 2 and 3

Table 4. Fractal properties of DWI-images of the brain and diffusion coefficients of the patients with ischemic stroke

Ischemic focus	SRGB (Me (1 and 3 percentiles))	CD (M±SD)
	12,3 (-3,9; 25,1)*	0,00055±0,000085#
Healthy tissue	27,3 (12,2; 37,9)*	0,00091±0,000075#

*p<0,001; # p<0,001

Table 5. Fractal properties of DWI-image of brain and diffusion coefficients in patients with different outcomes of ischemic stroke

	The outcome on the Rankin scale = 6 (death) (n= 7)		The outcome on the Rankin scale < 6 (n= 35)	
	SRGB Me (1 and 3 percentiles)	DC M±SD	SRGB Me (1 and 3 percentiles)	DC M±SD
Ischemic focus	-11,1 (-15,5; 7) *	0,00063± 0,00009	14,4 (0,6; 26,4) *	0,00054± 0,00008
Healthy tissue	26,9 (11,6; 49,3)	0,00095± 0,000032	27,7 (12,2; 36,8)	0,00091± 0,000072

*p<0,001 (of Mann-Whitney criterion)

Table 6. Fractal properties of DWI-image of brain and diffusion coefficients among patients with ischemic stroke with a different state of carbohydrate metabolism

	Group 1 (n= 20)		Group 2 (n= 15)		Group 3 (n= 7)	
	SRGB Me (1 and 3 percentiles)	DC M±SD	SRGB Me (1 and 3 percentiles)	DC M±SD	SRGB Me (1 and 3 percentiles)	DC M±SD
Ischemic focus	8,2 (-14,9;25,4)	0,00058± 0,00009	14,4 (5,4; 24,1)	0,00054± 0,00009	13 (1,7; 20,9)	0,00052± 0,00006
Healthy tissue	34,5 (21,4; 45,0) *	0,0009± 0,00007	12,9 (9,7; 26,9)*	0,00095± 0,00004	34,7 (15;38,2)*	0,00086± 0,00008

*p < 0,05 between groups 1 and 2, 2 and 3

Assessment of patients by scale NIHSS at their admission to the hospital revealed no statistically significant differences between groups (p> 0.05). Dynamics of neurological status of the patients with ischemic stroke characterized by growing of the neurological deficits of the patients with diabetes from the second day of the disease (p> 0.05). In the group of patients with stress GG, as well as in the comparison group, with the first day of the beginning of IS regression of neurological deficit was marked (p <0.05). The condition of patients stabilized in all groups of patients by 14 day (Table 2). Thus, groups of patients with IS with varying degrees of violation of carbohydrate metabolism were comparable in terms of volume of ischemic focus, depth of defeat tissue of the brain (data DC) and the severity of neurological symptoms upon admission to the hospital. At the same time it was revealed a more severe course and outcome of IS of the patients with diabetes with the increase of neurological disorders and profound disability compared to patients without disorders of carbohydrate metabolism (p <0.05) (Table 3).

The fractal analysis of color images of tissue structure of the brain of all patients with IS revealed the statistically significant differences between SRGB of healthy tissue and SRGB of ischemic focus (Fig. 1, Table 4). In this case a statistically significant correlation between SRGB of the ischemic focus and SRGB of the healthy tissue (correlation coefficient r = -0,3, p<0.05) was found among the patients with IS and different states of carbohydrate metabolism, i.e. the structure of ischemic focus is directly depend on the initial state of the brain tissue. It is interesting that data SRGB ischemic focus among the deceased patients with IS differed from the same data for the survivors in the absence of significant differences in DC (Table 5). The general structure of SRGB distribution depending on the outcome of stroke according to the Rankin scale revealed the highest SRGB values for a group of patients with a favorable outcome.

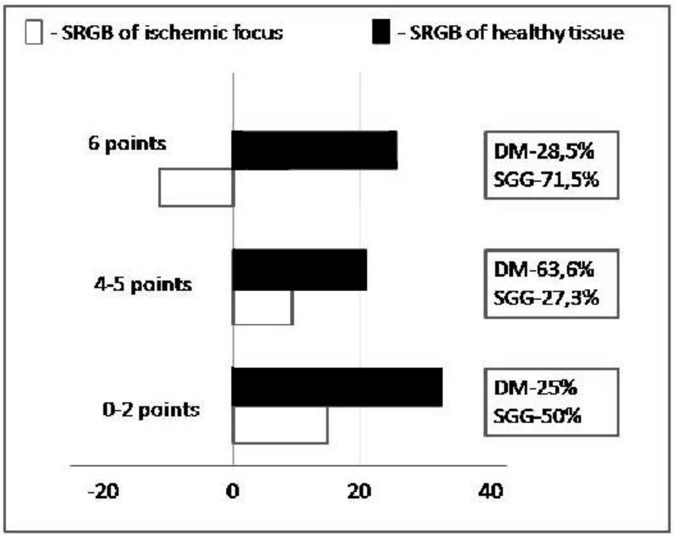

Fig. 1. Fractal properties of DWI-images of brain among patients with different outcomes of ischemic stroke according to Rankin Scale

A group of patients with outcomes at 3 points on the Rankin scale was represented with one patient and therefore wasn't included in the analysis. Among patients with profound disability (Rankin scale score 4-5) for brain tissue in intact hemisphere the values of SRGB were lower, while this group was represented mainly by the patients with diabetes (63.6%) (Fig. 1). In addition it was showed that there is correlation of SRGB for healthy tissue from deceased patients with data of NIHSS for the entire period of observation (r = -0,7 (- 0,9); p <0.05), i.e. when the value of SRGB for brain tissue in intact hemisphere is high, the neurological deficit is less pronounced during the acute period of IS.

Analysis of SRGB for healthy tissue and SRGB for ischemic focus among patients of the different groups revealed statistically significant differences (Table 6). As we can see from Table 4, SRGB for brain tissue in intact hemisphere is significantly different among patients with DM, stress GG and patients without disorders of carbohydrate metabolism (p<0.05), what is confirmed by the correlation coefficient between SRGB for brain tissue in intact hemisphere and to the fact of the diabetes existence (r = - 0.4, p <0.05). At the same time, the analysis of the complete data matrix showed statistically significant relationship SRGB for brain tissue in intact hemisphere with the level of glycaemia at 2-7 day of IS (r = - 0,3 (- 0,4); p<0.05), i.e. SRGB values decrease with increasing of the blood glucose concentration.

RESULTS AND DISCUSSION

Zone of irreversible changes formation during IS is a complex process associated with necrotic or apoptotic death of brain cells. The central section of necrosis is surrounded by ischemic, but living tissue (penumbra area) for hours. The degree of recovery of these cells during normalization of blood flow is remained unknown. It can be determined by the duration of hypoxia, environmental conditions, individual's sensitivity to oxygen deficiency, features of the metabolic processes, level of trophic assurance before a stroke, and other factors. Due to the penumbra zone there is a gradual increase of the infarct size [4, 10]. One of the methods to assess the state of cell membranes in the ischemic focus is to calculate the DC, which is not considered as an accurate criterion of irreversible changes. Tissue with a slight reduction of DC can be irreversibly damaged and, on the contrary, even a serious decline of DC can be fully normalized by the end of the acute period of IS [4]. At the same time, this criterion is objective because it evaluates water diffusion, which stops with destruction of the cell membrane, i.e. with necrosis. Therefore, structural analysis method was applied to estimate the diffusion violations, similar to the calculation of DC, but with all the peaks in its distribution in the ischemic area. In medical researches this method has not previously been used.

Thus, statistically significant revealed differences and correlations between SRGB for healthy tissue and SRGB for ischemic focus confirm the sensitivity of the method and demonstrate the dependence of the structure of infarct zone from the initial morphology and function of the brain tissue, which determines not only the peculiarities of the ischemic focus, but the clinical severity of stroke. It was found that the change in the structure of the ischemic focus of deceased patients was significantly different from that among the surviving patients (p<0.001), which may be due to better identification of the areas of irreversible changes than during the calculation of DC. This increases the probability of using SRGB as a prognostic criterion of stroke outcomes. A full range of metabolic disorders, structural and functional changes that are specific for this nosology is involved in the formation of the myocardium among the patients with diabetes. Most of the works of the contemporary authors indicate the more severe course and worse outcome of stroke in patients with diabetes, what was confirmed in this study [5]. The reasons leading to complication of the vascular process of these patients are varied and primarily associated with impaired microcirculation and blood rheology, the negative impact of GG on the formation of ischemic focus [6, 7]. However, the direct relationship between the volume of the ischemic focus, DC, outcomes of IS and data of glycemia in diabetic patients wasn't found, what corresponds to the known literature [8]. At the same time it was found that the patients with diabetes have the changed structure of the brain tissue of the healthy hemisphere due to the direct effect of GG and probably the presence before the onset of diabetic microangiopathy stroke, which determines the features of the formation zone of ischemia and outcome of stroke.

Conclusions

Therefore the study of the structure of DWI-image using multiple fractal dimensions can be used to describe and identify the ischemia zone and irreversible changes. At the same time, the significant scatter of SRGB values demonstrates the need for further research with a larger number of patients with specific criteria of standardization of this technique to make it more informative.

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