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ABSTRACT

of the dissertation for the degree of Doctor of Philosophy

THE FREQUENCY OF T2 HYPERİNTENSE FOCİES İN THE WHİTE MATTER OF THE BRAİN IN A VARİOUS POPULATİON

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GENERAL CHARACTERISTICS OF THE RESEARCH

The relevance of the subject.

One of the reasons why T2 hyperintense foci, which in our opinion are still mostly referred non-specific in the brain these days, are more visible on Magnit resonance imaging (MRI) scans is also examinations with a higher quality and this factor makes it more relevant to identify their specificity.

Conducted tomographic and physical examinations propose solid clinical evidence that white matter hyperintensities are associated with the increased risk of stroke, intellectual disability, death, depression, and gait and movement disorders.[1] The abovementioned medical conditions are closely related to cerebral atrophy and other complications of small vessel disease (SVD), focal progressive visible brain damage, and subtle invisible brain damage, leading to infarct expansion and deterioration of large arterial stroke area. They are neuroradiological indicators of brain weakness.[2]

Confluent foci indicative of periventricular involvement are observed on MRI scans due to age-related expanded dilated perivascular spaces, high interstitial fluid concentration, increased brain-blood barrier permeability, and plasma pooling. Histopathological comparison of these areas exhibits mild demyelination.[3] Nevertheless, as autopsy is not available for living patients, it is important to distinguish these foci using a diagnostic MRI scan. In the literature, T2 hyperintense foci are more common in elderly patients, but not all patients have histopathological demyelination.[3] However, today it is still not possible to distinguish which parts of foci in elderly pa-

[1] Altermatt, A. Clinical associations of T2-weighted lesion load and lesion location in small vessel disease: Insights from a large prospective cohort study / Gaetano, L., Magon, S., Bauer, L. [et al.] // NeuroImage, – 2019, V.189, - p. 727–733.

[2] Wardlaw, J.M., White matter hyperintensity reduction and outcomes after minor stroke / Chappell, F.M., Valdés Hernández, M.D.C., Makin, S.D.J. [et al.] // Neurology, - 2017, V.89(10), - p. 1003–1010.

[3] Haller, S., Do brain T2/FLAIR white matter hyperintensities correspond to myelin loss in normal aging? A radiologic-neuropathologic correlation study / Kövari, E., Herrmann, F.R., Cuvinciuc, V. [et al.] // Acta Neuropathologica Communications, - 2013, V.1(1), 14, - p. 1-7.

tients are age-related and which parts are disease-related. With functional MRI scans, modern literature studied the location of such T2 hyperintense foci in healthy adults causing specific cognitive impairment.[4]

Researchers have highlighted that aura and headache severity amplify T2 hyperintense foci in migraine patients.[5] However, the parts of the brain where additional foci are formed are still being studied. Moreover, the link between T2 hyperintense foci and genders was also studied in the literature and the findings proved that it was relatively more common in women. However, over 80% of the difference in causes remains unknown. The objective of the research on T2 hyperintense foci in the white matter should be conducted in a higher stage than cerebrovascular diseases.[6]

Diabetes mellitus (DM) is a major risk factor for the formation of T2 hyperintense foci in the white matter of the brain in young people without arterial hypertension (AH). Increased insulin resistance and/or decreased insulin secretion cause type 2 diabetes mellitus from pancreatic beta cells. The disease reduces the patients` quality of life and increases the costs of managing their medical and social welfare.[7]

Various features of foci on MRI scans (number, size, location, presence of oedema, response to contrast agent, and changes over time) are the main distinguishing elements.[8]

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[4] Lampe L. Lesion location matters: The relationships between white matter hyperintensities on cognition in the healthy elderly / Kharabian-Masouleh S, Kynast J, Arelin K. [et al.] // J Cereb Blood Flow Metab, - 2019, V.39(1), -p. 36–43.

[5] Negm M. Relation between migraine pattern and white matter hyperintensities in brain magnetic resonance imaging / Housseini A.M., Abdelfatah M., Asran A. // Neurol Psychiatr Neurosurg, - 2018, V.54(1):24, -p. 1-8

[6] Sachdev P. Sex differences in the causes and consequences of white matter hyperintensities / Parslow R., Wen W., Anstey K.J. [et al.] // Neurobiol Aging, - 2009, V.30(6), -p. 946–956.

[7] Tamura, Y., Araki, A2004: DM and white matter hyperintensity // Geriatrics & Gerontology International, - 2015, 15 Suppl 1, - p. 34–42.

[8] Amier, R.P., Hypertensive exposure markers by MRI in relation to cerebral small vessel disease and cognitive impairment / Marcks, N., Hooghiemstra, A.M., Nijveldt, R. [et al.] // JACC. Cardiovascular Imaging, - 2021, V.14(1), - p. 176–185.

Given the above-mentioned points regarding studying this issue, it is considered relevant to do research on the problems that will be clinically beneficial in the diagnosis of T2 hyperintense foci.

Object and subject of the research

To achieve the goals and objectives set in the research work, patients with type 2 DM, arterial hypertension, as well as patients with a smoking history who approached Zafaran Hospital for a brain MRI scan were examined (between 35-70 years old, 355 person). Patients with brain tumours, radiation and chemotherapy treatment, demyelinating diseases, brain surgery, trauma anamnesis, and migraine diagnosis were not involved in the examination.

Purpose of the research: The purpose of the research study is to identify T2 hyperintense foci detected during an MRI of the brain in patients with various complaints, assess their frequency in different groups and pinpoint whether they are associated with the complaints we are looking into.

Objectives of research

1. To study diagnostic aspects of T2 hyperintense foci detected during an MRI examination in healthy controls.

2. To assess radiological characteristics of T2 hyperintense foci in patients with an anamnesis of arterial hypertension, type 2 diabetes mellitus separately and together, and smoking history.

3. To research the existing correlation between the number, location and size of T2 hyperintense foci and arterial hypertension, type 2 diabetes and smoking.

4. To systematize the results based on the cut-off point values for the groups we are researching.

Research methods: In the study, the anamnestic data of patients who applied for brain MRI examination to Zafaran hospital in 2020-2023 were analyzed. Based on this, foci were counted and measured in the TIRM mode obtained during MRI in patients with arterial hypertension, type 2 diabetes mellitus separately and together, smoking, as well as practically healthy ones. A computer database of the collected materials was created, and the obtained data were processed using statistical methods.

Main provisions of the defended dissertation:

1. Arterial hypertension, type 2 diabetes (DM), arterial hypertension + type 2 diabetes, smoking are criteria significantly affecting the increase in the number and size (except for smokers) of T2 hyperintense foci detected during an MRI scan of the brain.

2. The cut-off point values of the number and the average size of T2 hyperintense foci observed during the MRI scan of the brain can be regarded predictors of these medical conditions in patients with no history of arterial hypertension or type 2 diabetes.

3. The number and average size of T2 hyperintense foci in patients with arterial hypertension, type 2 diabetes, arterial hypertension + type 2 diabetes have a statistically reliable positive correlation. As the number of detected foci increases, so does their size, and the brain parenchyma becomes progressively damaged.

Scientific novelty of research work. Until recently, there are studies in foreign literature sources on how to solve the problem in this manner. However, this research study differs from the previous ones in that it examines and compares multiple groups simultaneously, as well as studies the link of specific parameters (arterial hypertension (AH), type 2 diabetes mellitus (DM), and smoking) with the frequency and size of foci. In the research study, the results obtained based on the cut-off values were systematized according to the studied groups. Thin FLAIR scans were used to differentiate between T2 hyperintense foci and tiny vessels.

Practical significance of the research study. The findings of the research study, which detected the diagnostic features of T2 hyperintense foci observed during MRI scans of the brain in different groups (arterial hypertension, type 2 diabetes, smoking), allow for the selection of a path in the evaluation of these problems in patients with no history of type 2 DM or AH.

Approbation of dissertation. The results of the dissertation work were reported and discussed at the inter-departmental meeting at AMU on December 5, 2023 protocol, and at the Scientific seminar of the FD 1.02 Dissertation Council operating under NCO of the Ministry of health of the Republic of Azerbaijan on May 14,

2024(Protocol №2).

Application of the results to practice. The conclusions of the dissertation are used in the teaching process at the Department of Radiology and Radiotherapy of the Azerbaijan Medical University and the clinical application at Zafaran Hospital.

The organisation in which the dissertation was performed. The dissertation work was performed in Zafaran hospital.

The volume and and structure of the dissertation.

The dissertation includes an introduction, literature review, material and methods, 2 chapter-interpretation of the findings of personal research, conclusion, practical recommendation and list of literary sources and it consists of 186 pages (238800 characters). Introduction 8439 characters, literature review 52059 characters, materials and methods 18339 characters, two chapters of personal research 121154 characters, total 32291 characters, conclusions and practical recommendations consists of the 3159 characters. Dissertation work is organized from 39 tables, 37 pictures and graphs. The literary list includes 102 sources of works by Azerbaijani and foreign scientists.

MATERIALS AND METHODS OF RESEARCH

General characteristics of the studied patients

The research included results from 355 patients who underwent brain MRI. The results of 86 healthy controls were used as a control group and the results of all groups were compared. 210 patients were men (59.2%), 145 were women (40.8%). The patients were between 35 to 75 years of age. Patients over 70 years of age were not included in the research due to the presence of the age-related T2 hyperintense foci in the brain with increasing age. Patients with history of oncological diseases, trauma, brain surgery anamnesis, demyelinating, granulomatous diseases, alcoholism and migraine were not included in the research. Due to the fact that the white matter hyperintensities formed to this end can lead to erroneous results in the research.

Patients were divided into four groups: Group 1 - patients with arterial hypertension (AH): 77 (21.7%) patients; Group 2 – patients

with type 2 DM: 51 (14.4%) patients; Group 3 - patients with both AH and type 2 DM: 61 (17.2%) patients; Group 4 – patients with smoking history: 80 (22.5%) patients; In addition, 86 (24.2%) healthy controls were included in the research as a control group.

Group 4 includes only male (100%) patients. Female patients in this group were not included in the research due to the very low smoking prevalence among women in Azerbaijan. From this perspective, a subgroup of only male healthy controls was created and compared with the smoking group, and 47 (13.2%) male patients were compared with the smoking group. Of the healthy controls, 47 (54.7%) are men and 39 (45.3%) are women.

Disease duration in AH patients in the first group was between 10-15 years. In the second group of patients with type 2 DM, the disease duration was between 5-10 years. Patients diagnosed with type 2 DM with blood glucose levels above 7 mmol/l were included in the research. The smoking duration of patients with smoking history in the fourth group was at least 15 years and at most 50 years (on average 23.1 ± 1.0 years). 34 of them (42.5%) have been smoking for less than 20 years, 21 (26.3%) for 20-29 years, and 25 (31.3%) for more than 30 years. In the course of our research, we found links among systolic blood pressure, type 2 DM, both together and with cigarette use, as well as the duration of smoking and the number, size, location (topography) of the foci.

The subjects of this research were selected from patients who applied for brain MRI scan at our hospital with various complaints (headache, dizziness, feeling of pressure in the head, nausea, hemiparesis-hemiplegia, gait and movement disorders, facial nerve paralysis, facial swelling, etc.). The 1.5 Tesla Siemens Magnetom Aera MRI scanner was used in the research with images obtained in the thin T2 turbo inversion recovery magnitude (TIRM) mode. In the T2 TIRM mode, both the cerebrospinal fluid signal is reset and the cortical hyperintensity is relatively reduced, thus making T2 hyperintense foci more visible and distinguishable. Terms such as bright-hyperintense foci, WMH, white matter lesions, white matter diseases, and leukoaraiosis are used interchangeably

in the literature.[9,10]

To this end, T2 hyperintense foci and WMH were used synonymously throughout our dissertation. For the brain MRI scan, in the T2 turbo inversion recovery magnitude (TIRM) mode, each patient`s white matter hyperintensities were first counted and their maximal length was measured. We then determined which lobes (frontal, parietal, temporal, occipital), periventricular or deep white matter had WMH and recorded the data. We divided the patients into age groups and compared the results between these groups. At the same time, the results obtained were compared by sex.

Mathematical statistical examination methods

Research study is classified as following: according to the design – analytical; according to the method - clinical; according to the volume - selection; according to the type – scientific; according to the material - prospective; according to the location - clinical.

Quantitative and qualitative indicators identified in the research were performed in MS EXCEL-2019 and IBM Statistics SPSS-26 programs using variational analysis, discriminant analysis, correlation analysis, dispersion analysis, ROC analysis, and best scientifically proven practices in medicine.

When analysing quantitative indicators, variation orders are displayed in the tables with mean (M, ±m) and median (Me, Q1, Q3, min, max) indicators. The t-Stüdent-Bonferroni, U-Mann-Whitney and H-Kruskal-Wallis tests were used to compare rows.

ROC-analysis binary classification model determined the integral value (ROC-curve) of the sensitivity and specificity indicators over the entire variation range of the studied parameters. At this point, we calculated the area of the ROC-curve and assessed

[9] Wang, D.-Q., Relationship between type 2 diabetes and white matter hyperintensity: A systematic review / Wang, L., Wei, M.-M., Xia, X.-S. [et al.] // Frontiers in Endocrinology, - 2020, V.11, - p. 1-12.

[10] Sun, J. The mechanisms of type 2 diabetes-related white matter intensities: A review / Xu, B., Zhang, X., He, Z. // Frontiers in Public Health, - 2020, 8, 498056. - p. 1-5.

the results statistically. The identification of the cut off point, which is the farthest point of the ROC-curve from the reference line, allowed this test to be used as selection criteria in subsequent studies.[11]

RESEARCH CONCLUSIONS AND THEIR DISCUSSION

Characteristics of T2 hyperintense foci in the control group according to age groups

Patients in the control group were divided into 3 age groups and studied as follows: 35-50, 51-60, 61-70 years old. The control group consisted of 23 patients aged between 35-50 years. Of these, 4 (17.4%) are women, 19 (82.6%) are men. T2 hyperintense foci were detected in 11 (47.8%) patients in this age group. In the control group, patients aged 35-50 years had a minimum number of foci of 1 and a maximum of 20 (6.8 ± 1.7). In the control group of patients aged 35-50 years, the average size of the maximum foci length was 2.11 ± 0.15 mm (1.5-3 mm). There are 30 patients of 51-60 years in the control group. Of these, 13 (43.3%) of them are women, 17 (56.7%) are men. T2 hyperintense focus was observed in 19 (63.3%) patients in this age group. The number of foci in patients in the control group is minimum 1, maximum 10 (5.5 ± 0.8). In the control group of patients of 51-60 years, the average size of the maximum foci length was 1.77 ± 0.14 mm (1-3.25 mm). There are 33 patients of 61-70 years in the control group. 22 (66.7%) of them are women, 11 (33.3%) are men. T2 hyperintense focus was noted in 21 (63.6%) patients in this age group. The minimum number of foci noted in patients in the control group is 1, and the maximum is 40 (6.3 ± 1.8). In the control group of patients aged 61-70 years, the average size of the maximum length of foci was 1.92 ± 0.17 mm (1-4 mm).

The cut off point for foci number in the control group is 12. That is, the number of foci less than 12 is an informative value for identifying healthy controls. Thus, the total diagnostic value of the test (the ratio of patients with true positive results and true

[11] Qafarov İ.A. Biostatistika. Bakı, 2021, 238 s.

negative results (207) to the total number of patients (273)) is 75.8%±2.6%.

The positive predictive value (pPV) of having the number of foci less than 12 was 98.1±1.1%. The negative predictive value (nPV) of having the number of foci being less than 12 was 43.2±4.7%, the practical value of this finding was concluded to be satisfactory.

The cut off point for the average size foci in healthy controls was 2.9 mm. The sensitivity for this cut off point is 47.3%±3.4%. In 47 out of 51 healthy controls, the average size was less than 2.9 mm, the specificity is 92.2±3.8%. Thus, the total diagnostic value of the test (the ratio of patients with true positive results and true negative results (152) to the total number of patients (273)) is 55.7±3.0%.

Comparative assessment of T2 hyperintense foci in all patient groups

Patients included in the research were divided into several groups, the number, size, and location of T2 hyperintense foci in the brain, their differences in men and women, and the results of their differences in different age groups were recorded collectively and separately for each group, compared with the control group and with each other, and the statistical validity of the obtained results was checked. First, the results of the main group, AH (arterial hypertension), DM (type 2 diabetes mellitus), AH+ type 2 DM patients and the control group were compared in general. In addition, the results of patients with smoking history were also studied in a similar manner.

There are no statistically valid differences by age and sex among patients participated in the research (by sex $p_{\chi 2}=0.390$, $p_H=0.392$, by age $p_H=0.358$ $p_F=0.471$).

T2 hyperintense foci were identified in 273 (76.9%) of 355 patients involved in the research. No T2 hyperintense foci were noted in the remaining 82 (23.1%) patients. When comparing the indicators

of four groups (control group, AH, type 2 DM, AH+ type 2 DM) simultaneously, the focus detection is stronger in the main groups than in the control group ($p_{\chi 2}$<0.001, p_H <0.001). As can be seen from the table, the number of patients with detected foci in the main groups and the number of patients in the foci number groups are different with statistically validity from the control group ($p_{\chi 2}$<0.001, p_H<0.001). In male healthy controls (55.3%) foci detection is lower than in women (64.1%).

Table

Detection of T2 hyperintense foci and grouping for the number

Patients		Groups				$p_{\chi 2}$	p_H
		Control	AH	Type 2 DM	AH + type 2 DM		
foci	yes	59,3%	88,3%	90,2%	91,8%	<0,001	<0,001
	no	40,7%	11,7%	9,8%	8,2%		
foci number group	< 10	76,5%	13,2%	15,2%	0,0%	<0,001	<0,001
	10-49	23,5%	45,6%	54,3%	19,6%		
	50-99	0,0%	29,4%	26,1%	48,2%		
	≥ 100	0,0%	11,8%	4,3%	32,1%		

Note: Statistical evaluation of the difference between the indicators of the 4 groups was evaluated: $p_{\chi 2}$ – by the Pearson test, p_H – by the Kruskal-Wallis test.

Characteristics of T2 hyperintense foci in patients with arterial hypertension

There are 33 male and 44 female patients in the AH group. In this group, 68 (88.3%) patients, and in 51 (59.3%) patients in the control group, T2 hyperintense foci were noted. MRI scan detected more foci in the patients` brain with AH compared to control groups ($p_{\chi 2}$<0.001, p_u<0.001).

Brain foci are more common in male patients with AH than in female patients. This difference is statistically valid (p_u=0.042). In women with AH, 83.4% of patients have foci number between 10-49 and 50-99, whereas the patients with this number of foci in the control group is 32%. In the control group, 68% of patients had less than 10

foci. The difference between indicators is statistically valid ($p_{\chi 2}$<0.001, p_u <0.001).

T2 hyperintense focus was noted in the frontal lobe in the group with AH, 67 (98.5%) of the patients, and in 50 (98.0%) of the patients in the control group according to the location of foci in the frontal lobe ($p_{\chi 2}$=0.613, p_u=0.838). T2 hyperintense focus was detected in the parietal lobe in the group with AH, 54 (79.4%) of the patients, and in 14 (27.5%) of the patients in the control group ($p_{\chi 2}$<0.001, p_u<0.001). In the group with AH, 7 (10.3%) patients have a T2 hyperintense focus in the temporal lobe. No T2 hyperintense foci were detected in the temporal lobe in patients in the control group (p_u=0.019). When comparing the AH group with the control group, this difference between the number of patients with T2 hyperintense focus with deep white matter was statistically valid ($p_{\chi 2}$<0.001, p_u <0.001). T2 hyperintense foci were periventricular in the group with AH, 67.6% of patients, and in 13.7% of patients in the control group ($p_{\chi 2}$<0.001, p_u <0.001).

In 68 (88.3%) patients with AH, T2 hyperintense foci were identified, the minimum number of foci was 1 and the maximum was 150 (45.1 ± 4.6) on MRI scan. The number of foci in patients in the control group is minimum 1, maximum 40 (6.1 ± 0.9) (p_t<0.001, p_u<0.001).

Nonetheless, the average size of the maximum length of foci in the AH group was between 2.97 ± 0.16 mm (1.5-5.5 mm). The minimum size of the maximum length of foci identified in the AH group was between 1.21 ± 0.08 mm (1.0-4.0 mm). The maximum size of the maximum length of noted foci was between 4.74 ± 0.30 mm (2-10 mm).

In the control group, the average size of the maximum length of foci was 1.90 ± 0.09 mm (1-4 mm), minimum size was 1.16 ± 0.06 mm (1-2.5 mm), maximum size was 2.65 ± 0.16 mm (1-6 mm) (p_t <0,001, p_u<0,001).

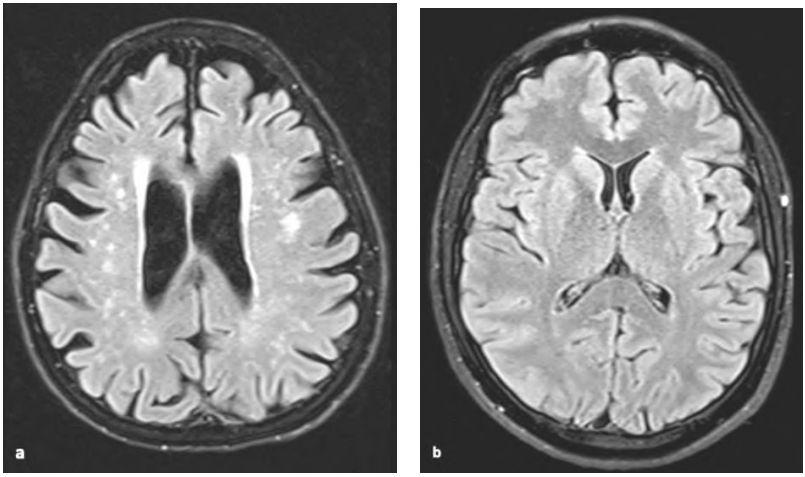


Image. Brain MRI axial T2 TIRM image. a. In a patient with AH, multiple T2 hyperintense foci are noted in both frontal lobe and parietal lobe. b. A T2 hyperintense focus is not noted in a healthy control.

The cut off point for the number of foci in patients with AH is 14. The sensitivity for this cut off point is 77.9±5.0%. 48 out of 51 healthy controls had less than 14 foci, while specificity being 94.1±3.3%. Consequently, the total diagnostic value of the test (the ratio of patients with true positive results and true negative results (101) to the total number of patients (119)) is 84.9%±3.3%.

The positive predictive value (pPV) of having the number of foci exceeding 14 is 94.6±3.0%. To determine the clinical application (value) of this, the accuracy ratio of the positive results was calculated, as a result, the clinical application of this value with the help of a special scale was assessed as excellent. The negative predictive value (nPV) of having the number of foci exceeding 14 was 76.2±5.4%, and the practical value of this finding was considered satisfactory.

The cut off point for the average size of foci in patients with AH is 1.9 mm. The sensitivity for this cut off point is 83.8%±4.5%. In 27 out of 51 healthy controls, the average size was less than 1.9 mm, whereas the specificity is 52.9±7.0%. Consequently, the total diagnostic value of the test (the ratio of patients with true positive

results and true negative results (84) to the total number of patients (119)) is 70.6±4.2%.

The positive predictive value (pPV) of having the average size of foci exceeding 1.9 mm is 70.4±5.1%. The negative predictive value (nPV) of having the average size of foci more than 1.9 mm was 71.1±7.4%, and the clinical value of this finding was considered to be satisfactory.

In our research, we detected a statistically valid negative correlation between the location of foci in the frontal lobe and temporal lobe (ρ= -0.361) in patients with AH ($p<0.05$).

Characteristics of T2 hyperintense foci in patients with type 2 diabetes mellitus

There are 24 male and 27 female patients in the group with type 2 DM. In this group, 46 (90.2%) and 51 (59.3%) patients in the general control group had a T2 hyperintense focus ($p_{\chi 2}<0,001$, $p_u<0,001$). This is the evidence of the increased detection of T2 hyperintense foci in the brain when the patient only suffers from type 2 DM without comorbidity.

In the type 2 DM group, 46 (100.0%) of the patients, and in 50 (98.0%) of the patients in the control group, a T2 hyperintense focus was noted in the frontal lobe ($p_{\chi 2}=0,613$, $p_u=0,342$). In the group with type 2 DM, 38 (82.6%) of the patients, and in 14 (27.5%) of the patients in the control group, a T2 hyperintense focus was noted in the parietal lobe. Between these two groups, the number of patients with a T2 hyperintense focus in the parietal lobe is statistically different ($p_{\chi 2}<0.001$, $p_u<0.001$). In the group with type 2 DM, 3 (6.5%) patients have a T2 hyperintense focus in the temporal lobe ($p_u=0.065$). In the group with type 2 DM, 93.5% of patients and 74.5% of patients in the control group had T2 hyperintense foci with deep white matter ($p_{\chi 2}<0.001$, $p_u=0.012$). In the group with type 2 DM, 71.7% of patients and in 13.7% of patients in the control group, T2 hyperintense foci are periventricular ($p_{\chi 2}<0.001$, $p_u<0.001$).

In 46 (90.2%) type 2 DM patients with T2 hyperintense foci, the minimum number of foci was 2 and the maximum was 150

(35.6±4.4) on MRI scan. The number of foci in patients in the control group is minimum 1, maximum 40 (6.1 ± 0.9) (p_t <0,001, p_u<0,001).

The number of foci in female patients with type 2 DM is 37.2±7.1 (5-150), while in men it is 33.9 ± 5.0 (2-80). Both sexes with type 2 DM had more foci compared to the control group (females 6.5± 0.9(1-20), males 5.7±1.5(1-40)) (p_u<0,001, in women p_t=0,003, in men p_t =0,015).

Moreover, the average size of the maximum length of the foci was 2.83 ± 0.16 mm (1.5-5.5 mm). The minimum size of the maximum length of foci detected in the Type 2 DM group was 1.09±0.04 mm (1-2 mm). The maximum size of the maximum length of observed foci was 4.57±0.31 mm (2-10 mm). In addition, the average size of the maximum length of the foci was 2.83±0.16 mm (1.5-5.5 mm), minimum size was 1.09±0.04 mm (1-2 mm), maximum size was 4.57±0.31 mm (2-10 mm).

The cut off point for foci number in type 2 DM patients is 14. The sensitivity for this cut off point is 71.7±6.6%. Out of 51 healthy controls, the number of foci was less than 14 in 48, whereas the specificity is 94.1±3.3. Consequently, the total diagnostic value of the test (the ratio of patients with true positive results and true negative results (81) to the total number of patients (97)) is 83.5%±3.8%.

The positive predictive value (pPV) of having the number of foci exceeding 14 is 91.7±4.6%. With the purpose of identifying clinical importance (value) of this, the accuracy ratio of the positive results was calculated. As a result, the clinical application of this value with the help of a special scale was considered excellent. The negative predictive value (nPV) of having the number of foci greater than 14 was 78.7±5.2, and the practical value of this finding was considered satisfactory.

The cut off point for the average size of foci in type 2 DM patients is 2.9 mm. The sensitivity for this cut off point is 45.7%±7.3%. In 47 out of 51 healthy controls, the average size was less than 2.9 mm, the specificity is 92.2±3.8%. Consequently, the total diagnostic value of the test (the ratio of patients with true positive results and

true negative results (68) to the total number of patients (97) is 70.1±4.6%. The positive predictive value (pPV) for the average size of foci exceeding 2.9 mm is 84.0±7.3. The negative predictive value (nPV) for the average size of foci exceeding 2.9 mm was 65.3±5.6, and this finding was considered to have no practical value. In type 2 DM patients, patients were divided into 3 age groups to be studied: 35-50 years, 51-60 years, 61-70 years.

Characteristics of T2 hyperintense foci in patients with both arterial hypertension and type 2 diabetes mellitus

This group with both AH and type 2 DM included 26 male and 35 female patients. In this group, 56 (91.8%) patients and 51 (59.3%) patients in the control group had a T2 hyperintense focus ($p_{\chi 2}$<0.001, p_u <0.001).

In the group with both AH and type 2 DM, 56 (100.0%) of the patients and 50 (98.0%) of the patients in the control group have a T2 hyperintense focus in the frontal lobe ($p_{\chi 2}$=0,613, p_u=0,295). T2 hyperintense focus was observed in the parietal lobe in 55 (98.2%) patients in this group, and in 14 (27.5%) patients in the control group ($p_{\chi 2}$<0,001, p_u<0,001). In the group with both AH and type 2 DM, 14 (25.0%) patients had a T2 hyperintense focus in the temporal lobe. No T2 hyperintense foci were identified in the temporal lobe in patients in the control group (p_u<0.001). T2 hyperintense foci are involved in deep white matter in 98.2% of patients in the group with both AH and type 2 DM, and in 74.5% of patients in the control group ($p_{\chi 2}$<0.001, p_u<0.001). Periventricular T2 hyperintense foci were noted in 91.1% of patients in the group with both AH and type 2 DM, and in 13.7% of patients in the control group ($p_{\chi 2}$<0.001, pu<0.001). In the AH+ type 2 DM group, the location of foci in women and men exhibits little difference, and this difference is not considered statistically valid between the sexes (p_u >0.05).

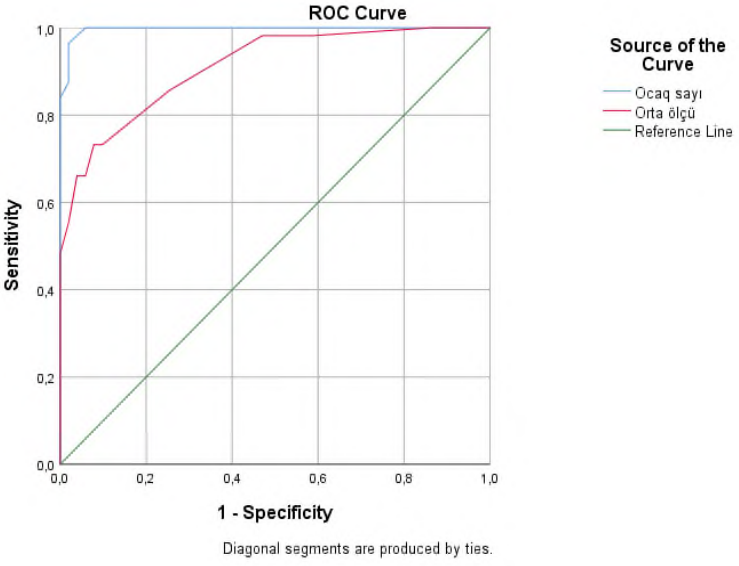
In 56 (91.8%) patients suffering from both AH and type 2 DM, the number of T2 hyperintense foci in the brain was minimum 15 and maximum 150 (80±5.2) on MRI scan. The number of foci in patients in the control group is minimum 1, maximum 40 (6.1±0.9)

(p_t <0,001, p_u<0,001). The number of foci in female patients with AH+ type 2 DM is 64.6 ± 5.7 (15-150), whereas in male patients it is 99.0 ± 7.7 (30-150). The number of foci is substantially higher in both sexes with AH + type 2 DM compared to the control group (6.5±0.9 (1-20) in women, 5.7±1.5 (1-40) in men) (p_t <0,001, p_u<0,001).

In the group with patient suffering from both AH and type 2 DM, the average size of the maximum length of foci was 4.01±0.19 mm (1.5-7.5 mm), minimum size was 1.14 ± 0.05 mm (1-2 mm), maximum size was 6.88 ± 0.37 mm (2-14 mm) (p_t<0,001, p_u<0,001). The area of the ROC curve, which is an integral indicator of sensitivity and specificity in diagnosis of AH + type 2 DM for the foci number is 0,996±0,003. This indicator is 0,911 ± 0,026 on average size for the foci.

The cut off point for foci number in patients with both AH and type 2 DM is 23. The sensitivity for this cut off point is 96.4±2.5%. 47 out of 51 healthy controls had less than 23 foci, specificity is 98.0±1.9%. Consequently, the total diagnostic value of the test (the ratio of patients with true positive results and true negative results (104) to the total number of patients (107)) is 97.2%±1.6%.

The positive predictive value (pPV) of having the number of foci exceeding 23 is 98.2±1.8%. The negative predictive value (nPV) of having the number of foci exceeding 23 was 96.2±2.7, and the clinical application of this finding was also assessed as excellent.



Test Result Variable(s)	Area	Std. Error [a]	Asymptotic Sig.[b]	95% Confidence Interval	
				Lower Bound	Upper Bound
Foci number	0,996	0,003	0,000	0,990	1,000
Average size	0,911	0,026	0,000	0,859	0,963

Chart. The area of the ROC curve for the AH + type 2 DM group in terms of foci number and average size.

The cut off point for average foci size in patients suffering from both AH and type 2 DM is 2.9 mm. The sensitivity for this cut-off value is 73.2%±5.9%. In 47 out of 51 healthy controls, the average size was less than 2.9 mm while the specificity being 92.2±3.8%. As a result, the total diagnostic value of the test (the ratio of patients with true positive results and true negative results (88) to the total number of patients (107)) is 82.2±3.7%.

The positive predictive value (pPV) for the average size of foci exceeding 2.9 mm is 91.1±4.2. The negative predictive value (nPV) of the average size of foci greater than 2.9 mm was 75.8±5.4, and the practical value of this finding was considered satisfactory.

When the patient has both diseases simultaneously, the maximum and average dimensions of the maximum length of foci identified in patients are greater (p_u<0.001). This indicates that the size of the foci formed in the brain is greater in those with both AH and type 2 DM.

We compared the results (number, size, and location of T2 hyperintense foci in the brain) of the group with both AH and type 2 DM patients with the group with only type 2 DM patients and these differences were confirmed to be statistically valid. A statistically valid difference manifests itself in the classification of the detected foci into numerical groups (p_u <0.001).

Characteristics of T2 hyperintense foci in patients with smoking history

The results of the number, size, and location of T2 hyperintense foci in the patients with smoking history included in the research were recorded in comparison with the control group of only men, and it was examined to be statistical valid. The average age of patients with smoking history was 50.7±1.0 years, and in the control group it was 52.7±1.4 years (p_F=0,257, p_u=0,221).

T2 hyperintense foci were observed in 52 (65%) patients in the group of smoker patients and 26 (55.3%) patients in the sub-control group consisting of only men ($p_{\chi 2}$=0,279, p_u=0,281). 51 (98.1%) of the group of patients with smoking history and 26 (100.0%) of the patients in the corresponding sub-control group have a T2 hyperintense focus in the frontal lobe ($p_{\chi 2}$=0.477, p_u =0.480).

23 (44.2%) patients in the smokers group and 7 (26.9%) patients in the control group had a T2 hyperintense focus in the parietal lobe. Patients with smoking history are not easy to be distinguished from those in the control group due to the location of the damage foci in the parietal lobe. Although the number of patients with a T2 hyperintense focus in the parietal lobe was detected in patients with smoking history compared to their subgroup of control, it does not exhibit a statistically valid difference ($p_{\chi 2}$=0.139, p_u=0.141). In the group of patients with smoking history, 2 patients (3.8%) had a T2

hyperintense focus in the temporal lobe. In the control group, no T2 hyperintense foci were detected in the temporal lobe. T2 hyperintense foci in the deep white matter were detected in 51 (98.1%) of patients in the group of smokers and 13 (50.0%) of patients in the control group. The number of patients with T2 hyperintense foci with deep white matter in patients with smoking history exhibits a statistically valid difference ($p_{\chi 2}<0.001$, $p_u<0.001$) according to their control subgroup. T2 hyperintense foci were periventricular in 7 (13.5%) patients in the group of smokers and 2 (7.7%) patients in the control group ($p_{\chi 2}=0.452$, $p_u=0.455$).

In 52 (65%) patients with smoking history with T2 hyperintense foci, the minimum number of foci is 1, while the maximum number is 70 (13.5±2.1) ($p_t=0.013$, $p_u=0.012$). The average size of the maximum length of foci in patients with smoking history was 2.25±0.13 mm (1-6 mm).

The cut off point for the number of foci in the patients with smoking history is 5. The sensitivity for this cut off point is 63.5±6.7%. Out of 26 healthy controls, the number of foci was less than 5 in 20, whereas the specificity is 76.9±8.3%. Accordingly, the total diagnostic value of the test (the ratio of patients with true positive results and true negative results (53) to the total number of patients (78)) is 67.9%±5.3%.

The cut off point for the average size of foci in patients with smoking history is 1.3 mm. The sensitivity for this cut off point is 98.1%±1.9%. In 7 out of 26 healthy controls, the average size was less than 1.3 mm, while the specificity is 26.9±8.7%. As a result, the total diagnostic value of the test (the ratio of patients with true positive results and true negative results (58) to the total number of patients (78)) is 74.4±4.9%.

Patients with smoking history were divided into 3 groups according to the duration of smoking: less than 20 years, 20-29 years, more than 30 years. No statistically significant difference was found in the detection of foci and the number of groups according to the duration of smoking ($p>0.05$). Patients with smoking history were divided into 3 age groups and the indicators were studied: 35-50

years, 51-60 years, 61-70 years. No statistically significant difference was identified between the number and size of foci detected in all three age groups (maximum size increases relatively with age, average size remains unchanging) in all three age groups ($p>0.05$).

Studies strongly support the existence of a linear relationship between increased arterial pressure and increased the volume of T2 hyperintense foci. The latter multivariate regression analysis shows that the T2 hyperintense focal volume is closely related to hypertension, diabetes, smoking and education level.[12] In our research, the detection, number and size of T2 hyperintense foci were significantly higher in the AH group than in the control group ($p<0.001$).

A strong evidence suggests that hypertension is an independent (in the absence of comorbidity) risk factor for the development and progression of T2 hyperintense foci. During hypertension, microstructural white matter damage are formed and do not persist to cease despite proper treatment.[13] It has been proven that AH-induced changes further exists even during controlled hypertension, and it is known that the prevention of the disease is more important than its treatment.[14]

In our research, we detected a statistically valid negative correlation between the location of foci in the frontal lobe and temporal lobe ($\rho= -0.361$) in patients with AH ($p<0.05$). In other words, as T2 hyperintense foci increase in the frontal lobe, it decreases in the temporal lobe. In demyelinating diseases (multiple sclerosis) temporal

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lobe involvement is a typical sign.[15] The above-mentioned sign detected in our research is another confirmation hereof. AH is caused by SVD and foci are more common in the frontal and parietal lobe with minimal engagement of the temporal lobe.

The number of patients with type 2 DM further grows, and this is a global health problem of concern. T2 hyperintense focus is a silent brain lesion in the periventricular and deep white matter. Although hypertension is a risk factor for T2 hyperintense foci, studies show that diabetes produces more and larger T2 hyperintense foci.[10] In our research, the cut off point for foci size in Azerbaijani patients with AH is 1.9 mm, whereas in patients with type 2 DM, it is 2.9 mm (sensitivity 45.7%±7.3%, specificity 92.2±3.8%).

In middle-aged patients, structural changes in the brain begin in the prediabetes stage.[9] In our research, when dividing the patients into age groups, more number (57.7±5.9) and larger average-sized (3.73±0.30 mm) foci were detected in type 2 DM patients between 35-50 years of age compared to other age groups (51-60, 61-70) and this is an evidence that type 2 DM causes more severe changes in the brain at an early age ($p<0.001$). In the research conducted by Jongen and his co-authors, no significant interaction between age and type 2 diabetes was noted.[16] In our research, also there is a statistically significant difference between the number and size(average, maximum) of T2 hyperintense foci, as well as in the parietal lobe, temporal lobe and periventricular location in AH patients ($p<0.05$).

More numerous and larger foci are detected on brain MRI scan in patients with type 2 DM, as well as with AH. At this point, intensive treatment of both medical conditions slows down the structural changes in the brain and reduces the risk of future dementia.

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There is no need for a program (software) performing volumetric calculations to use our obtained results. All radiologists can easily apply these cut off points to their practice.

CONCLUSION

1. T2 hyperintense foci are not detected in temporal lobe of healthy controls. In healthy male patients (55.3%) in the control group, T2 hyperintense foci detection was less common than in female patients (64.1%) (p_u=0.412). In healthy controls of the control group, the number and size of foci are significantly less than the other pathologies we are doing research on(p_u<0,001) [8].
2. Compared to the control group, the number of patients with T2 hyperintense foci (accordingly 88.3%, 90.2%, 91.8%), the number of foci (45.1±4, 6 , 35.6±4.4 , 80±5.2) and the average size (2.97±0.16 mm, 2.83±0.16 mm, 4.01±0.19 mm) is high in the AH, type 2 DM, AH + type 2 DM groups(p_u<0,001) [6].
   Male patients with AH (97%) were detected more T2 hyperintense foci in the brain than female patients (81.8%) (p_u=0.042). Foci detected in male patients with AH + type 2 DM are more numerous than in females (p_u=0.008). The number of T2 hyperintense foci detected in patients with a smoking history (13.5±2.1) compared to the control group (5.7±1.5) is higher (p_u =0.012).
3. In the AH group, a negative statistically reliable correlation was observed between the location of the foci on the frontal lobe and temporal lobe (ρ=-0.361) (p<0.05). The foci detected in patients with type 2 DM are noted to be more numerous and larger at earlier ages (p<0.05). According to the smoking duration of a patient (less than 20 years, 20-29 years, more than 30 years) there is no statistically significant difference in the detection, number and size of foci (p>0.05) [8].
4. Cut off values in the groups we researched:
   The cut-off value was 12 for foci number (Sn 71.6±3.0%, Sp 94.1±3.3%, GDV 75.8±2.6%) and 2.9 mm for average size in healthy controls (Sn 47.3±3.4%, Sp 92.2±3.8%, GDV 55.7±3.0%).
   The cut-off value was 14 for foci number (Sn 77.9±5.0%, Sp

94.1±3.3%, GDV 84.9±3.3%) and 1.9 mm for average size in AH patients (Sn 83.8±4.5%, Sp 52.9±7.0%, GDV 70.6±4.2%)[11].

The cut-off value for type 2 DM patients was 14 for the number of foci (Sn 71.7±6.6%, Sp 94.1±3.3%, GDV 83.5±3.8%) and 2.9 mm for the average size (Sn 45.7±7.3%, Sp 92.2±3.8%, GDV 70.1±4.6%).

The cut-off value for the number of foci in AH + type 2 DM patients was 23 (Sn 96.4±2.5%, Sp 98.0±1.9%, GDV 97.2±1.6%), with an average size of 2.9 mm (Sn 73.2±5.9%, Sp 92.2±3.8%, GDV 82.2±3.7%) [9].

In patients with a smoking history, the cut-off value was 5 for foci number (Sn 63.5±6.7%, Sp 76.9±8.3%, GDV 76,9± 8,3%), while it is 1.3 mm for average size (Sn 98.1±1.9%, Sp 26.9±8.7%, GDV 74.4±4.9%).

PRACTICAL RECOMMENDATIONS

1. The cut-off value for the number of foci detected in healthy controls was 12, and 2.9 mm for the average size. Given these indicators (with appropriate percentages of specificity and sensitivity), we regard a group of patients with T2 hyperintense foci to be practically healthy and disregard pathology.
2. Approximately half (46%) of patients with AH are unaware of their condition. Radiologists can guide treating physicians in these individuals, as well as those with undiagnosed type 2 DM, by establishing cut-off values for the number and size of T2 hyperintense foci discovered during MRI scans of the brain taken for headache or other causes.
3. If patients with type 2 DM also have AH, more numerous and larger foci are observed during an MRI of the brain. At this point, both disorders should be treated intensively on an individual basis. This will reduce the chance of dementia in the future by slowing the structural changes in the brain.
4. Utilization of the obtained results do not require any software that perform complex calculations. These cut-off values are simple to implement in the practice of all radiologists.

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LIST OF ABBREVIATIONS

AH- Arterial hypertension

WMH - white matter hyperintensity

SVD- Small vessel disease

MRI- Magnit resonance imaging

DM- Diabetus Mellitus

TIRM- Turbo inversion recovery magnitude

OR - Odds ratio

CI- Confidence interval

Sn- Sensitivity

Sp- Specificity

GDV-General diaqnostic value

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