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ABSTRACT
of the dissertation for the degree of Doctor of Philosophy

DIAGNOSTIC AND PROQNOSTIC CRITERIA OF MAGNETIC-RESONANCE TOMOGRAPHIC MORPHOMETRY OF THE BRAIN INMULTIPLE SCLEROSIS

Speciality:3225.01 – Radiation diagnostics and therapy

Branch of science:Medicine

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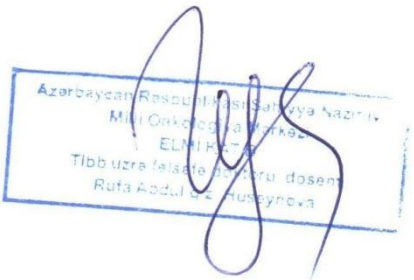

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INTRODUCTION

Relevance of the theme: Multiple sclerosis (MS) is one of the most important medical and social problems of modern neurology. MS is a relatively common disease that causes degenerative changes in the central nervous system, most commonly occurring at a young age, with multiple demyelinating foci in the brain, with persistently progressive diffuse neurological symptoms, and resulting in rapid disability.[1,2]

Although some progress has been made in studying the pathogenesis and clinical course of MS, the mechanisms of development of its symptoms are still unclear. The involvement of many components in the pathogenesis of the disease, such as immunological, biochemical, degenerative processes, leads to the formation of numerous foci of demyelination and diffuse atrophic changes in the central nervous system[3].

MS is one of the most severe organic pathologies of the central nervous system and one of the most common causes of severe disability at a young age. The incidence of MS is increasing worldwide; This is due not only to the prolongation of patients' lives and the improvement of the quality of diagnostics, but also to an increase in the number of patients.[4].

The medical and social significance of MS is mainly due to the fact that the disease makes people disabled in middle age, and in connection with this, medical and social costs are growing rapidly.Therefore, scientific - research works on the etiology,

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[1]Şirəliyeva, R.K. Dağınıq sklerozun klinikası və diaqnostikası. Dərs vəsaiti. / R.K. Şirəliyeva, A.K. Məmmədbəyli, R.R. Əliyev - Bakı, - 2014. – 363 s.

[2]Brownlee, W. J., Hardy, T. A., Fazekas, F. Diagnosis of multiple sclerosis: progress and challenges // The Lancet, - 2017. 389(10076), - p. 1336-1346.

[3]De Stefano, N. Establishing pathological cut-offs of brain atrophy rates in multiple sclerosis / N.De Stefano, M.L.Stromillo, A.Giorgio [et al.] // Journal of Neurology, Neurosurgery & Psychiatry, - 2016. 87(1), - p. 93-99.

[4]Галда, Л. Посиндромная диагностика рассеянного склероза // - Пушкино: Центральный научный вестник, - 2016, Т.1, №13, - с.18

immune-genetic aspects and treatment of the MS are continued in recent years[5,6].

The literature suggests that the clinical features of MS, including impaired higher mental function, have not been adequately studied to date. However, in practice, the management of a patient with MS remains a serious clinical issue.Thus, the diagnosis of MS is usually made on the basis of the patient's medical history and clinical neurological signs. However, there is always a need to use additional laboratory, instrumental and radiological examination methods. In this case, MRI examination is more informative in the topical diagnosis of the disease and its activity[7].

A number of progressive protocols are used to determine the activity of the pathological process in the central nervous system during MS by MRI. In this regard, the informativeness of MRI examinations conducted with contrast drugs of better quality has recently increased. It is important to determine the adequate diagnostic and treatment algorithm for patients with MS using such examinations.[8].

A number of researchers have noted that MRI contrast is more sensitive in the remitting form of MS.Other clinicians suggest that new enhanced foci detected on MRI by contrast may prevent clinical signs, which may be important in monitoring disease activity[9].

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[5]Dobson, R., Giovannoni, G. Multiple sclerosis–a review // European journal of neurology, - 2019. 26(1), - p. 27-40.

[6]Inglese, M.,Petracca, M. MRI in multiple sclerosis: clinical and research update. // Current Opinion in Neurology, 2018. 31(3), - p. 249-255.

[7]Брюхов, В. Современный взгляд на МРТ-диагностику рассеянного склероза: обновленные МРТ-критерии 2016 г. / В.Брюхов, И.А. Кротенкова, С.Н. Морозова, М.В.Кротенкова //- Москва: Журнал неврологии и психиатрии им. СС Корсакова. (Спецвыпуски)- 2017. Т.117, №2, - с. 66-73

[8]Chu, R., Kim, G., Tauhid, S., Khalid, F., et al (2018). Whole brain and deep gray matter atrophy detection over 5 years with 3T MRI in multiple sclerosis using a variety of automated segmentation pipelines // PLoS One, 13(11), - e0206939.

[9]Chung, K. K., Altmann, D., Barkhof, F. A 30-Year Clinical and Magnetic Resonance Imaging Observational Study of Multiple Sclerosis and Clinically Isolated Syndromes // Annals of neurology,2020. 87(1), - p. 63-74

Recent studies have shown that high-dose contrast MRI can increase diagnostic accuracy compared to standard doses. Some clinicians note that the level of contrast and the number of contrast foci detected also depend on the injection of the contrast agent and the duration of the examination.[10,11].

In recent years, degenerative processes of the CNS are assessed by a special method - morphometry. Both global (brain as a whole) and regional atrophies are identified using various MRI measurement methods to assess degenerative changes in the brain – atrophy[12]. Voxel MRI-morphometry is performed by computerized statistical analysis of structural MRI images. During morphometry, emphasis is placed on the selection of specific features for the personal computer, which allows a statistical parametric view (SPM-statistical parametric mapping) to accurately assess the structure of the brain. Detection of demyelinated foci in the central nervous system is assessed as the most accurate diagnostic sign of MS[13].

The clinical course of the disease and its features manifest themselves in each patient individually. Therefore, determining the relationship between the variability of the clinical picture and the polymorphism of damage to the central nervous system is one of the most pressing issues in clinical neurology and radiology.

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[10]Goischke, H.K. Comorbidities in multiple sclerosis—a plea for interdisciplinary collaboration to improve the quality of life of MS patients. // Degenerative Neurological and Neuromuscular Disease, - 2019. 9, - p. 39.

[11]Haacke, E. M. Characterizing iron deposition in multiple sclerosis lesions using susceptibility weighted imaging / E.M.Haacke, M. Makki, Y.Ge, [et al.] // Journal of Magnetic Resonance Imaging: An Official Journal of the International Society for Magnetic Resonance in Medicine, - 2009. 29(3), - p. 537-544.

[12]Кротенкова, И., Атрофия центральной нервной системы при рассеянном склерозе: данные МРТ-морфометрии / И. Кротенкова, В.В. Брюхов, А.В. Переседова [и др.] // - Москва: Журнал неврологии и психиатрии им. СС Корсакова.(Спецвыпуск)-2014. Т.114, №10, - с. 50-56

[13]Lansley, J. Localized grey matter atrophy in multiple sclerosis: a meta-analysis of voxel-based morphometry studies and associations with functional disability / J.Lansley, D. Mataix-Cols, M.Grau [et al.]// Neuroscience & Biobehavioral Reviews, - 2013. 37(5), - p. 819-830.

Object of study. In the study, patients who were in inpatient treatment with the diagnosis of multiple sclerosis in 2011-2020 were selected as the object of observation, and MRT - morphometric diagnosis of various spectrum lesions of the central nervous system in these patients was selected as the subject of the study.

Aim of the study. To determine the pathogenetic, early diagnostic and prognostic significance of degenerative changes in the brain by co-evaluating MRI findings with clinical signs found in multiple sclerosis.

Objectives of the study:

1. To evaluate the degree of manifestation of neurological symptomatology in patients with multiple sclerosis on the Kurtske extended scale of functional systems.
2. To determine the sequence of development of degenerative processes in the individual structures of the brain during relapse-remitic multiple sclerosis.
3. To determine the volume and characteristics of active and inactive foci of demyelination, depending on the duration, activity and clinical course of multiple sclerosis in different parts of the brain (right and left hemispheres, brainstem and cerebellum) on MRI examination.
4. To evaluate the diffuse-atrophic and focal lesions of the brain detected on MRI in comparison with the frequency of development of neurological dysfunction and disability; to determine the dependence of the correlation between radiological and clinical signs on the duration of the disease, the age of the patient, the indicators on the EDSS scale.
5. To develop a prognostic algorithm for the course of multiple sclerosis with a comparative assessment of neurological and MRI-morphometric indicators.

Research methods.

- Clinical neurological examinations
- MRI-morphometric examination of the brain
- I.F. Kurtzke scale for the assessment of multiple sclerosis
- Extensive Scale of Life Disorders (EDSS)

– Evaluation scale of functional systems for disability in multiple sclerosis
– Instrumental examination methods
– Statisticalmethods

Key theses to be defended:

1. The development of neurodegenerative processes in the brain during recurrent remittance and secondary progressive multiple sclerosis is characterized by MRI patterns.
2. The sequence of involvement of individual structures of the brain in the degenerative process in multiple sclerosis: in the early stages of the disease is determined atrophic degenerative process of subcortical gray matter, then cortex, and then white matter.
3. The degree of disability and progression of neurological symptoms in patients with multiple sclerosis is primarily associated with degenerative processes occurring in individual structures in the brain.

Scientific novelty of the study:

For the first time, a complex clinical-MRI-morphometric comparison of degenerative changes in the gray and white matter of the brain during recurrent-remitic and secondary progressive multiple sclerosis was performed.

For the first time, the sequence of development of the neurode-generative process in relapsing-remittant multiple sclerosis was determined.

For the first time in the case of multiple sclerosis, the relationship between the cerebral cortex and subcortical MRI-morphometric parameters and clinical indicators was determined.

Practical significance of the work.

Voxel MRI-morphometry in multiple sclerosis allows to assess the degree and topical features of degenerative changes in different structures of the brain.

The link between degenerative changes in the cortical and subcortical structures of the brain and the degree of disability

requires that treatment be directed at preventing the neurodegenerative process.

The combined use of MRI-morphometric markers with clinical indicators allows to predict the course of multiple sclerosis.

Approbation of dissertation. The initial discussion of the dissertation was held at the interdepartmental meeting at the Azerbaijan State Advanced Training Institute for Doctors named after A.Aliyev. Scientific seminar protocol №7 was held on20 october2022 under FD 1.02 Dissertation Council.

Published research articles. The dissertation have been published in the journals on the relevant list of the Supreme Attestation Commission for the last 5 years. 7 journal articles and 4 theses on the topic of the dissertation were published, two of which were published in foreign journals.

Application of the study. The morphometric indicators mentioned in the early diagnosis of multiple sclerosis are applied at the Azerbaijan State Advanced Training Institute for Doctors named after A.Aliyev, Diagnosis Medical Center. Relevant acts on the effectiveness of the application of research results were obtained.

Place of research: Azerbaijan State Advanced Training Institute for Doctors named after A.Aliyev of the Ministry of Health of the Republic of Azerbaijan.

Volume and structure of the dissertation. The dissertation is presented on 171 printed pages, consist of introduction-9982characters, I chapter (literature review) - 104225 characters, II chapter (materials research and methods) - 28055 characters, III chapters – 18297characters, IV chapters – 9285characters, V chapters – 13635 characters, summary - 21807 characters, results - 1484, practical recommendations - 561 characters and bibliography. In the list of literature - 4 sources of literature in Azerbaijani, 42 in Russian and 255 in English were used.

The total volume of the dissertation by signs (excluding tables, graphs and bibliography) - consists of 207331characters, 11 tables and 24 graphs.

MATERIALS AND METHODS OF RESEARCH

General characteristics of the clinical part

The research was carried out in the neurological departments and Diagnosis Medical Center, which are the bases of the Azerbaijan State Advanced Training Institute for Doctors named after A.Aliyev.The study involved 88 patients with multiple sclerosis (MS) and 20 healthy volunteers. Recurrent-remittant MS (RRMS) was diagnosed in 56 patients and secondary progressive MS (SPMS) was diagnosed in 32 patients.Of all those examined, 58 were women and 30 were men, ranging in age from 18 to 60 (median 34 [27; 49] age-here and then: median [Q1; Q3]). Healthy volunteers (15 women, 5 men) were also compared by age (35 [30.2; 48.4] years).

34 patients with RRMS (28 of them - women) were examined at the age of 20-48 years (32 [28; 40] years old) in dynamics: during the attack, examined 3 months after remission and 1 year after the first examination. 10 patients from this group were also re-examined 3 years after the first examination.

In addition to the above, 22 patients with RRMS (12 women) were 26-28 years old (36 [28; 52.5] years old) and 32 patients with SPMS (18 women) were 21-60 years old (38 [30.8; 54,6] years old) were examined once during the attack.

The time of the initial examination in all patients was up to 28 days from the onset of the attack. All patients were examined before corticosteroid therapy was started and until the subjective reduction of symptoms observed during the current attack was observed.

Research methods

Clinical examination-neurological examination:

1. The proposed EDSS (Expanded Disability Status Scale) was used to objectively assess the extent of neurological deficits and disability in all patients with MS. This scale reflects disorders in all functional systems: FS-1, symptoms of pyramidal pathways damage, FS-2, coordination disorders, FS-3, sensory disorders, FS-4, column disorders,F-5, optic nerve damage, FS-6, pelvic organ function disorders.

2. Functional MSFC (Multiple Sclerosis Functional Composite) and PASAT (Paced Auditory Serial Addition Test) were used to assess cognitive impairment in all patients examined once with recurrent-remitic and secondary progressive course.

Instrumental examination methods:

All subjects underwent MRI examination of the brain, cervical spine and spinal cord:

- magnetic resonance imaging 1.5 Tesla magnetic induction measurement was used in patients with recurrent-remittance DS examined in dynamics;
- Magnetic resonance imaging with 3.0 Tesla magnetic induction measurements were used in 1-time study of patients with recurrent remission and secondary progressive MS, as well as in the control group.

The results of 1.5 and 3.0 Tesla magnetic induction measurements on MRI were compared, and the scan parameters were consistent in all modes.The following were the exception criteria for MRI:

- somatic and hereditary pathologies;
- co-morbidities in the brain (derivatives, arteriovenous malformations);
- autoimmune diseases;
- corticosteroid therapy less than 3 months after the current attack

Modes used during MRI examination:

Standard T2 dark-fluid (FLAIR) and T2-weighted images (T2-W1) were used during MRI of the brain to assess focal lesions in the brain substance and to rule out other pathologies.In addition, 3D-T1 mode was used to reconstruct and detailed anatomical parameters in any projection of the following images, as well as to conduct voxel MRI-morphometry.

Voxel morphometry was performed in 4 stages:

1-anatomical scan with correction of head movement (T1MPR);

2-segmented images of the brain: gray matter (A), white matter (B) and cerebrospinal fluid (C);

3-normalized images of white and gray matter;

4- smoothed images of white and gray matter.

Thus, in our study, 30 different structures were identified, including the total volume of gray matter (GM) in the brain, individual gyrumes, frontal, parietal, occipital, and temporal lobe, as well as subcortical gray matter.In addition, the total volume of white matter in the brain, the WM of the cerebral hemisphere and corpus callosum separately, as well as the volume of the cerebrospinal fluid - lateral, third and fourth cerebral ventricles and subarachnoid area were studied.

Statistical processing of the material.

In addition to the statistical analysis of MRI indicators based on the MATLAB database, Microsoft Excell program was used in the biometric processing of the obtained results, as well as the application computer package program SPSS 20.Subsequent biometric analysis used non-parametric methods: comparison of quantitative indicators of two independent groups (Mann-WhiCNey U-test); Comparison of indicators of 2 groups that depend on each other on quantitative indicators (Wilcoxon matched paris test-Wilcoxon criterion).The analysis of the correlation between the two traits was also calculated using the formula proposed by Spearman.The results are given in median form: Me [Q1; Q3] and were considered statistically significant when $p < 0.05$.

A.Waldin's systematic biometric method was used to predict the course of degenerative lesions of the CNS in the examined patients and the effectiveness of the treatment.

RESULTS OF THE RESEARCH

In the present study, 88 patients with MS were examined. RRMS was diagnosed in 56 patients and SPMS in 32; 34 patients were examined in dynamics.

It was determined that the degree of disability on the EDSS scale was 3.5 [2.5; 4] points in patients with RRMS, 5 [2.5; 6] points

in patients with SPMS and differed significantly (p <0.01). In the assessment of the cognitive PASAT test, the percentage of correct answers was 71.5 [56; 80] during RRMS and 52.4 [31; 54] during SPMS.The median for FS-coordination disorders was 3 points in patients with SPMS and significantly different from patients with RRMS (p <0.05). The median for symptoms of FS-pyramidal tract injury was 3 [2; 4] in patients with RRMS and 4 [2,5; 5] in patients with SPMS (p = 0,02).

In addition, the duration of the disease for years was twice as long in patients with SPMS as in patients with RRMS. The latter has manifested itself in most cases with the transition from RRMS to SPMS and more with disability.

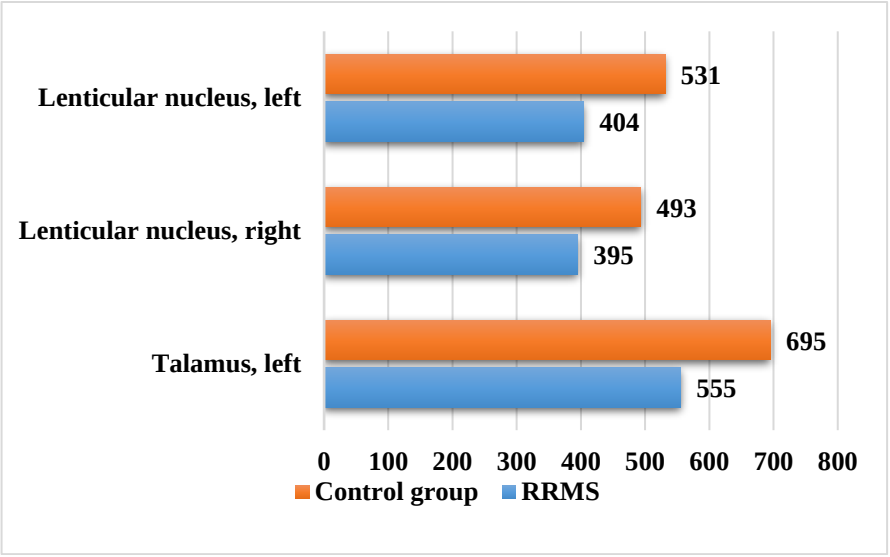

Figure 1. Atrophy of the lenticular nucleus and thalamus during RRMS (P <0.001).

Statistically significant (p <0.01) atrophy was observed in the left thalamus, right and left lenticular nucleus, body and head of the

caudate nucleus compared to the control group during RRMS (Figure 1.2).

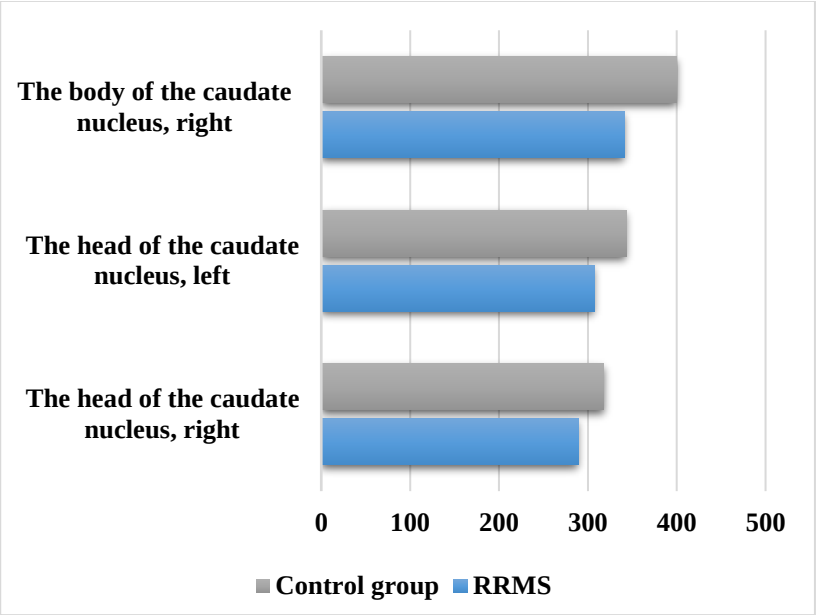

Figure 2. Atrophy of the body and head of the caudate nucleus during RRMS (P = 0.001).

As the duration of the disease increases during RRDS, the number of areas of the brain where atrophy is detected increases; In 2 structures (TL, LN) during RRMS for less than 5 years, and 6 times more in 12 districts during RRMS for more than 10 years (TL, LN, CN, WMW, CS, PCS, UFL, MFL, PL, WMW, WMCH, CC) atrophy has been identified.

Table 1 shows the brain sections in which RRMS was found to have greater atrophy compared to SPMS during 5-10 years of illness.

The results of the study show that atrophic changes occur in most parts of the brain during MS, with significant changes in the thalamus, lenticular nucleus, and caudal nucleus compared to the

control group during both RRMS and SPMS.

Table 1.Brain sections with severe atrophy during 5-10 years of RRMS (compared to SPMS)

Branches of the brain, side	Volume (voxels)		P
	RRMS	SPMS	
Lenticular nucleus, left	441	312	0,028
Lenticular nucleus, right	389	303	0,042
White matter (whole)	152508	130250	0,021
White matter of large hemispheres	100647	30001	0,042
The third ventricle	111	133	0,015

Note:*P -Significance compared to control group.*

The lenticular nucleus and the caudate nucleus together are called striped bodies or striatum.Among them there are not only WM, but also GM bridges - small and large multipolar neurons.The striped body is located deep in the cerebral hemispheres and "circles" the lateral ventricles and the third ventricle. The feedback between the subcortical structures of the brain, the thalamus and the volume of the ventricles - the increase in the volume of the lateral ventricle and 3rd ventricle against the background of atrophy attracts attention.

In our study, in patients with SPMS, in addition to changes in the subcortical structures, atrophy is observed in different areas of the cerebral cortex –precentralgyrum, frontal and parietal lobe of cortex, middle frontal, cortex of frontal area of cerebellum.The processes that cause atrophy of the cerebral cortex during MS can be directly attributed to the presence of foci of demyelination and degenerative changes in axons.

In our study, atrophy of the frontal lobe of the brain was found in patients with SPMS. It is known that the cerebellum provides important mechanisms in the body, consisting of numerous connections between the motor and somatosensory cortex and the spinal cord; acts as a coordination center; It also provides body

balance, muscle tone, smooth and precise movements.However, in recent years the role of the cerebellum in cognitive functions has been identified. The mechanism of atrophy of the GM in the cerebellum is primarily due to the detection of numerous foci of demyelination in the cortex and their detrimental effect.In addition, the retrograde effect of demyelinating changes in inflammation on WM, axon damage and death play an important role in this mechanism. Finally, the detection of T2-hypointensive zones in the gear nucleus of the brain, which reflects the pathological accumulation of iron and can lead to the process of atrophy.

The study identified the involvement of WM along with GM in the degenerative process. Previously, it was thought that only AM was damaged during MS, so atrophy develops in WM and plays an important role in the formation of neurological symptoms.However, modern research shows that the process of atrophy in WM does not play a major role, it starts late and is slower than GM. Other researchers have shown that WM atrophy is masked by a more pronounced inflammatory process compared to GM atrophy and is less noticeable.

WM atrophy in patients with MS covers certain areas of the brain — both hemispheres, the spinal cord, and the cerebellum. In our study, in addition to those noted during SPMS, atrophy of the corpus callosum was identified.The corpus callosum connects the homotopic regions of the frontal, parietal, occipital, and temporal lobes in the brain.No decrease in volume of white matter in the cerebral hemispheres during SPMS was detected in the control group, which may be due to pseudo-enlargement of the active demyelination sites with edema.

WM atrophy during MS is associated with several mechanisms; damage and complete destruction of axons, first in demyelination centers, and then shielding and descending degeneration associated with lesions.

The grouping of patients with RRMS according to the duration of the pathological process allowed to reveal the patterns of development of atrophy in different departments of the brain. Thus,

in the early stages of the disease, atrophy of the subcortical structures, mainly damage of the thalamus, in the later stage, the involvement of the brain cortex and then only WM, and a decrease in volume is observed when the disease lasts more than 10 years.

It has been found that there is a clear correlation between neurological symptoms and many morphometric parameters in patients with RRMS.Thus, between the degree of disability and the left lenticular nucleus and the corpus callosumwas found negative correlation ($r = -0.52$; -0.51; $p<0.01$, respectively), andwith the volume of the subarachnoid area – positive correlation ($r = 0.42$; $p<0,05$), between the left thalamus and the corpus callosumwith the duration of the disease was noted negative correlation ($r = -0.48$; $p<0.05$; $r = -0.59$; $p<0.01$; respectively), the left lower parietal lobe with cognitive impairment was noted a positive correlation ($r = 0.48$; $p<0.05$).

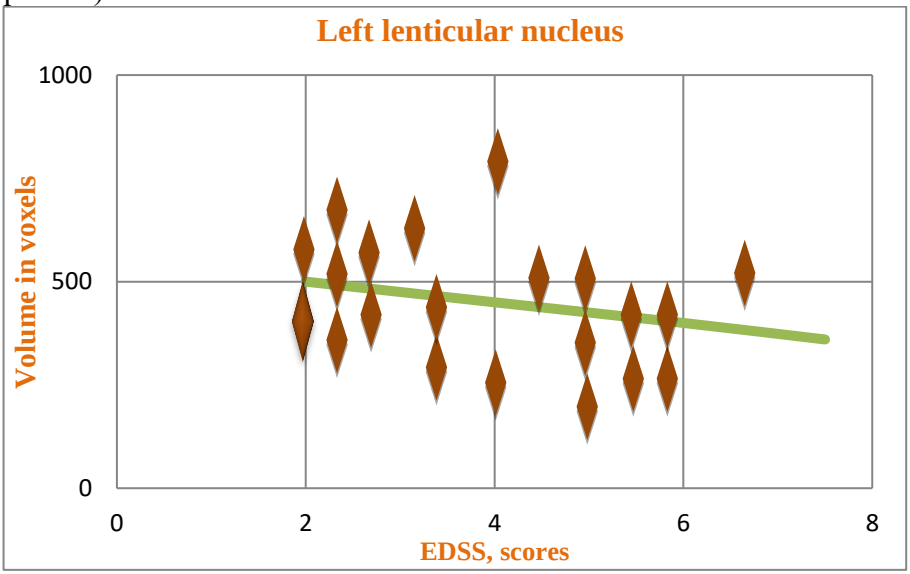

Figure 3. Negative (inverse) correlation between the volume of the left lenticular nucleus and the degree of disability in a patient with RMS

There is also a positive correlation between the volume of the 3rd ventricle and FS-1, FS-2, FS-3, FS-4 and FS-6 (r = 0.64; 0.65; 0.59; 0.56 and 0,54; p<0.01 respectively).Similar correlation relations between functional systems (FS-1; FS-2; FS-3; FS-4; FS-6) and the volume of the lateral ventricle (r = 0.60; 0.68; 0.62; 0.58 and 0.69; p<0.01) was determined.However, during RRMS, a correct correlation (r = 0.48; p<0.05) was found between cognitive impairment and left lower parietal lobe (Figure 3,4,5,6).

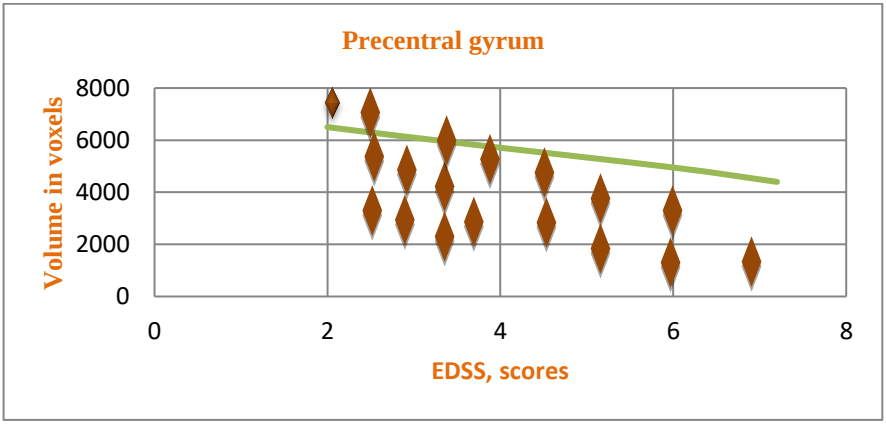

Figure 4.Negative (inverse) correlation between the volume ofcentral gyrum and the degree of disability in a patient with RRMS.

In patients with SPMS, a negative correlation (r = -0.52; -0.51; -0.55; p<0.01, respectively) between the degree of disability and the volume of the left and right lenticular nuclei and the corpus callosum, positive correlation (r = 0.44; p<0.05) was found between the duration of the diseaseand the volume of subarachnoidal area, and a negative correlation(r = -0.65; p<0.01) - with the corpus callosum.

When comparing functional systems, more correlations were determined between symptoms of cerebellum damage (FS-2) and morphometric parameters: left central gyrum (r = -0.58; p<0.01), left

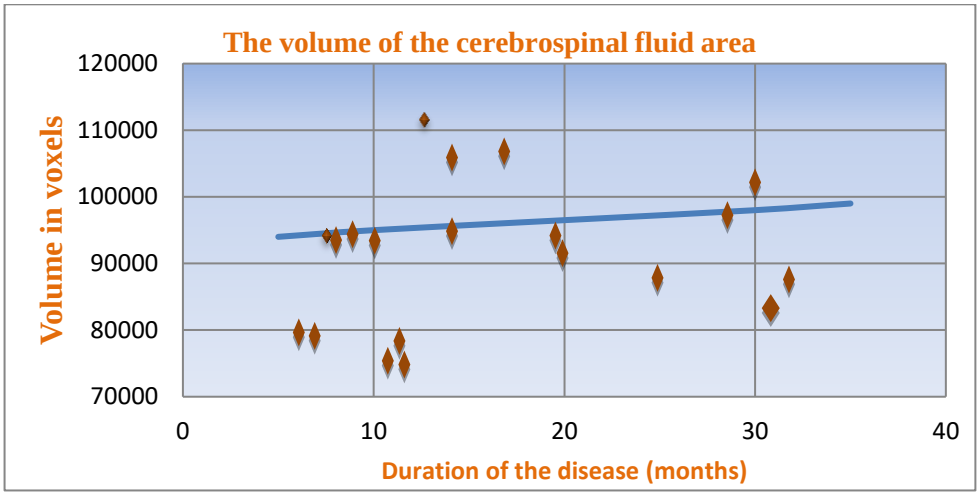

Figure 5.Positive (direct) correlation between cerebro-spinal fluid volume and disease duration in patients with SPMS

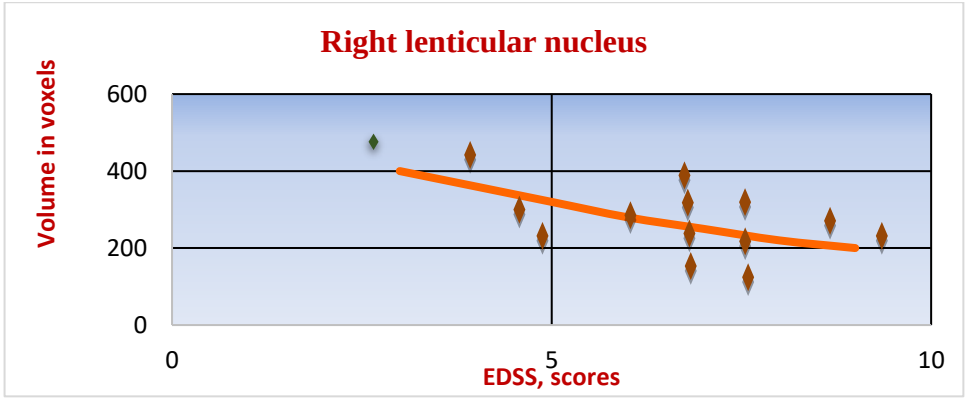

Figure 6. Negative (inverse) correlation between the volume of the right lenticular nucleus and the degree of disability in patients with SPMS.

upper parietal area (r = -0.55; p<0.01), left middle occipitalgyrum (r = -0.54; p<0.01), right middle occipitalgyrum (r = -0.59; p<0.01),

corpus callosum (r = -0.67; p<0.01), volume of the 3rd ventricle and the lateral ventricle (r = 0.61; 0.64; p<0.01, respectively).Also, the correct correlation was between the symptoms of pyramidal pathway damage (r = -0.50; p<0.01) andcorpus callosum (r = -0.67; p<0.01), andthe volume of the 3rd and the lateral ventricles (r = 0.68; 0.62; p<0,01 respectively).At the same time, between the sensory disturbances and the corpus callosum is negative (r = -0.60; p<0.01), between the volume of the 3rd ventricle and the lateral ventricle is positive (r = 0.62; 0.59; p<0,01 respectively) correlation was determined.The same correlation relationships were noted between column disturbances (FS-4) and morphometric indicators- corpus callosum (r=-0,69; p<0,01), 3rd ventricular volume (r=0,60;p<0,01), lateral ventricular volume (r=0,63; p<0,01); correct (positive) correlation between pelvic function disorders (FS-6) and 3rd ventricular and lateral ventricular volume (r=0,59; 0,68; p<0,01).

When analyzing the relationships between cognitive impairment and brain volume,a positive correlation (r=0,69; p<0,01) between the left lower parietal lobe and the PASAT test was noted.

In our study, in patients with RRMS, between the volume of the left thalamus and the duration of the disease (r = -0.48; p<0.01), between the volume of the left lenticular nucleus and the degree of disability (r =-0.52; p<0.01) positiverelationship has been established.A negative (reverse) relationship between the volume of the left ventricular nucleus and the degree of disability (r = -0.49; p<0.01) was also found in patients with SPMS.The mechanism of the correlation between neurological symptoms and the structures of the left hemisphere of the brain in both groups of patients is not fully understood; this may be due to the fact that atrophy is more pronounced in the left hemisphere than in the right hemisphere.The lack of an positive relationship between atrophy of GM and neurological symptoms, most likely, is associated with the uniformity of the selected group, with the manifestation of both mild neurological symptoms and severe neurological symptoms with disability in the examined patients.

A positive correlation ($r = 0.44$; $p<0.01$) was found between the duration of the disease and the extent of focal lesions in the brain during RRMS; It was noted that the size of the foci increases as the duration of the disease increases. A similar relationship was found in patients with SPMS.

There is a positive correlation between the size of the subarachnoid space and the degree of disability in patients with RRMS.

No correlation was found between the extent of focal brain damage during RRMS and SPMS, including active foci absorbed by the contrast agent with the degree of disability. However, a negative correlation ($r = -0.69$; $p<0.01$) was found between the extent of focal lesions and cognitive function (PASAT) in patients with RRMS.

During SPMS,between FS-cerebellum symptoms (coordination disorders) and volume of left central gyrum ($r = -0.58$; $p<0.01$), left upper parietal area ($r = -0.55$; $p<0.01$), between the right middle occipital gyrum ($r = -0.59$; $p<0.01$), as well as the volume of the corpus callosum ($r = -0.65$; $p<0.01$) was a negative correlation No correlation was found between other FS indicators and brain volume.

Thus, MRI examination of patients with RRMS and SPMS can reveal different patterns of the disease.

Determining the dynamics of the localization of lesions with the help of MRI over time while the patient is alive is important for the differential diagnosis of MS and, above all, to determine the pseudotumor course of the disease.In our study, MRI-morphometric parameters of patients with MS were compared with the leading clinical syndromes, depending on the form, course and duration of the disease, and the relationship between them was clarified.

It has been established that 28(50%) patients with RRMS have one pathological symptom (75% of them have ventricular enlargement, 25% have subarachnoidal area enlargement), and 12(21.4%) have two combinations of MRT-morphometric signs.

Thus, the predominance of 2 main types of pathological changes during MRI-morphometric examination of patients with MS

was established.

1. Enlargement of the ventricle and subarachnoid space with atrophy.

2. Isolated atrophic changes.

MRT-morphometric examination of joint atrophy areas is of particular importance, which corresponds to the process of demyelination of white matter in the brain.

It is noteworthy that during the MRI examination, 13 patients were not initially diagnosed during the clinical examination, were examined as suspicious and the diagnosis was confirmed.

When studying the dependence of the nature and number of MRI-morphometric indicators on the stage and duration of the disease, it was found that the areas of atrophy depend on the severity of the disease.Analysis of the results shows that in the acute phase of the disease, the neurological symptoms corresponded to the topical and anatomical localization of foci and increased in number. In this case, as a rule, one or two foci were found, which were localized in the white matter.However, this situation does not fully reflect the activity of demyelination processes, the deterioration of the patient's condition is accompanied by decompensation, the detection of new foci on the tomogram.However, it is in this category of patients that the determination of the phase of the disease is of primary importance, which is important for the initiation of adequate treatment. First of all, it should be clarified whether new demyelination centers or old ones have become decompensated.

As shown in previous chapters, contrast enhancement of demyelinating foci indicates impaired hematoncephalic barrier permeability. It is believed that this phenomenon characterizes the acute phase of the pathological process; but this view is not accepted by all authors. Therefore, in our research, we focused on the voxel morphometric method.

In patients with MS, MRI examination in the remission phase of the disease reveals a single hypodensive focus in contrast acceleration.It is found that an increase in the volume of the subarachnoid space and an increase in the size of the ventricle are

more common during the course of the disease for more than 5 years. At the same time, the vizualization of low-density foci depended on the duration of the disease.

Thus, during MRT-morphometric examination in patients with MS, the following positive(correct) and negative (reverse) correlation relationships were identified:

- dependence between the frequency of detection of low-density foci and the aggravation of the pathological process;
- dependence on detection frequency of expansion of ventricles and subarachnoidal area and duration of disease;
- detection of dependence between frequency of expansion in ventricular and subarachnoidal area and stage of disease in MRI;
- the dependence of the frequency of detection of low-density foci on the duration of the disease.

Summing up the results of MRI-morphometric examination during MS, it should be noted that this method is important not only for the diagnosis of demyelinating damage to the brain, but also to assess its degree of activity. The latter has a clear correlation with the clinical signs of disease exacerbation. This study also shows that the function of the hematoencephalic barrier is impaired during the exacerbation of MS.

A prognostic algorithm consisting of14 clinical-morphometric indicators was developed based on a detailed analysis of the existing correlations between clinical and morphometric indicators (Table 2).

The algorithm included mentally disturbed manifestations of the first clinical signs(PC=+3,5; İC=0,52), polysymptomatic onset (PC=+4,2;İC=0,66), multiple foci during the first application (PC=+4,2;İC=0,51), more than 80% correct answer on the PASAT scale, pronounced neurological disorders during the first 2 years of the disease (PC=+3,0;İC=0,46),and an EDSS scale of more than 6 points is considered (PC=+3,4; İC=0,44).

MRI-morphometric indicators show atrophy of the corpus callosumless than - ME<3251 voxel (PC=+5,8;İC=0,78), dilatation of the lateral ventricle – ME ≥4397 voxel (PC=+4,6;İC=0,60), volume

Table 2.Prognostic algorithm of MS

Clinical-morphometric indicators	PC 2	İC 3
Clinical signs:		
Age at which the first clinical symptom was observed:		
<30 years old	+2,0	0,34
31-40 years old	+2,4	0,36
>41 years old	+2,8	0,38
Manifestation of the first clinical sign:		
- damage to the optic nerve;	+2,0	0,32
- column disorders;	+2,4	0,38
- movement disorders;	+2,6	0,38
- mental disorders;	+3,5	0,52
- functional disorders of the pelvic organs;	+2,0	0,32
- polysymptomatic onset.	+4,2	0,66
Duration of the 1st remission:		
- long-lasting (more than 1 year);	+2,1	0,36
- short-term (less than 1 year).	+2,6	0,38
After the first attack:		
- complete remission;	+2,0	0,35
- incomplete recovery.	+3,0	0,36
During the first 2 years of the disease:		
- presence of 1 attack;	+2,2	0,30
- 2 or more attacks;	+3,2	0,38
- mild neurological deficit;	+2,0	0,32
- bulge of neurological disorders.	+3,0	0,42
Numerous hotspots during the 1st application:		
- present;	+4,2	0,51
- absent.	-2,0	0,38

Table 2. (conti.)

EDSS rating:		
- <3 points	+2,0	0,35
- 3.5-5.5 points	+2,4	0,38
- 6 points	+3,4	0,42
PASAT (correct answer %)		
- <56,0	-2,0	0,30
- 71,5	+2,0	0,42
- >80,0	+2,4	0,48
MRI morphometric indicators:Thalamus, left. Me:		
- ≥549	+2,0	0,38
- 548-536	+2,4	0,44
- ≤535	+3,2	0,56
Lenticular nucleus, left.Me:		
- ≥398	+2,5	0,42
- 397-326	+3,6	0,48
- ≤325	+4,8	0,66
Caudate nucleus, left.Me:		
- ≥336	+2,1	0,34
- 335-290	+2,5	0,38
- ≤289	+3,2	0,52
Corpus callosum: Me:		
- ≥3350	+3,2	0,48
- 3349-3252	+3,6	0,56
- ≤3251	+5,8	0,78
3rd ventricle: Me		
- ≤118	+3,0	0,46
- 119-124	+3,8	0,52
- ≥125	+4,2	0,60
Lateral ventricles; Me		
- ≤4205	+3,2	0,48
- 4204-4396	+4,0	0,56
- ≥4397	+4,6	0,69

of the third ventricle greater than 125 voxel (PC=+4,2;İC=0,60), volume of the left ventricular nucleus less than 325 voxel (PC=+4,8;İC=0,66), volume of the left thalamus less than 535 voxel (PC=+3,2;İC=0,56), volume of the caudate nucleus is less than 289 voxels was highly informative.

Comparative analysis of clinical and MRI-morphometric indicators revealed that the indicators of the subcortical structures of the brain are more informative.Thus, the prognostic and informativeness coefficient (PE=+5.8;OE=0.78) of atrophy of corpus callosum (ME<3251 voxel) was significantly higher than the polysimptome onset with the highest prognostic coefficient (PC=+4.2) in clinical indicators.In addition, the simultaneous detection of 3 morphometric indicators in patients with MS - atrophy of the lenticular nucleus and corpus callosum (PC = + 4.8; +5.8 respectively) and dilatation of the lateral ventricle(PC=+4,6) - provides a basis for predicting the unsatisfactory course of the disease based on the sum of their prognostic factors (PC=4,8+5,8+4,6=+15,6).

The degree of atrophy during the dynamic examination of patients with RRMS did not depend on the rate of progression of the disability, which may be due to several factors. First, the inflammatory process, edema, and neuroaxonal degeneration together can significantly affect the manifestation of neurological symptoms.Second, in patients with RRMS, clinical symptoms in the early stages of the disease are mainly associated with incomplete restoration of new demyelinating foci after exacerbation, which is often localized in the brain.

Thus, in conclusion, it should be noted that neurodegenerative changes in the brain - atrophy of the cortex and subcortical structures affect the development and progression of neurological disability in multiple sclerosis, including the degree of atrophy of gray matter and white matter affects the rate of disability, which provides a basis for the development and use of individual treatment tactics.

CONCLUSIONS

1. The degenerative process found in different structures of the brain in relapsing remission multiple sclerosis follows a certain developmental sequence: atrophy of the subcortical gray matter (thalamus, lenticular nucleus) in the early stages of the disease, followed by damage to the central cortex, and then the brain. atrophy of the white matter develops (2).

2. In relapsing-remitting multiple sclerosis, the number of areas of the brain where atrophy is detected increases as the disease progresses; In less than 5 years in 2 structures (TL, LN), in 5-10 years in 4 structures (TL, LN, CN, GM) and in more than 10 years in 12 districts (TL, LN, CN, GM, preSC, postSC, UFG, MFS, PL, CBA, WMCH, CC), atrophy is determined (3).

3. In secondary progressive multiple sclerosis, statistically significant atrophy ($p < 0.001$) compared with the control group is detected in the thalamus (left and right), caudal nucleus (left and right), left middle foreheadgyrum; these changes are observed with a pronounced enlargement of the third ventricle (9).

4. There is a direct correlation between the degree of disability and cognitive impairment ($r > 0.56$; $p < 0.01$) with morphometric indicators of atrophy of gray and white matter in the brain in relapsing-remittant and secondaryprogressivemultiple sclerosis (6).

5. There is a negative correlation between the volume of the left central gyrum($r = -0.58$; $p < 0.01$), the left upper parietal area ($r = -0.55$; $p < 0.01$), the right middle occipitalgyrum ($r = -0.59$; $p < 0.01$), as well as the volume of corpus callosum($r = -0.65$; $p < 0.01$)with symptoms of FS-cerebellum in secondaryprogressive multiple sclerosis (5).

6. In patients with multiple sclerosis, the simultaneous detection of 3 morphometric indicators - atrophy of the lenticular nucleus and corpus callosum (PE = + 4.8; +5.8, respectively) and

dilatation of the lateral ventricle (PE = + 4.6)allows to predict unsatisfactory course of the pathological process.

PRACTICAL RECOMMENDATIONS

1. It is recommended to use MRI-morphometric criteria for early detection and dynamic assessment of degenerative changes in the cortical and subcortical structures of the brain in multiple sclerosis.

2. It is recommended to use the morphometric indicator of atrophy of gray and white matter in the brain to assess the degree of disability in multiple sclerosis of different course.

3. It is recommended to use a clinical MRI-morphometric algorithm to predict its course, depending on the duration and clinical forms of the pathological process in patients with multiple sclerosis.

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LIST OF ABBREVIATIONS

CC - corpus callosum
CN – caudate nucleus
GM - gray matter
GMW – gray matter as a whole
LN - lenticular nucleus
MFG - medium forehead gyrum
MFL medium frontal lobe
MS - multiple sclerosis
PL – parietal lobe
postCG -postcentral gyrum
preCG - central gyrum
RRMS - relapse- remitik MS
SPMS - secondary progressive MS
TL – thalamus
UFG – upper frontal gyrum
UFL – upper frontal lobe
WM - white matter
WMCH - white matter of the cerebral hemispheres
WMW -white matter as a whole

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