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Modern possibilities of MRI-based diagnosis of multiple sclerosis. Literature review

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ABSTRACT

Multiple sclerosis remains the most common demyelinating disease of the central nervous system and ranks first among neurological diseases that lead to disability in young people. The most important diagnostic and prognostic marker, especially at an early stage of the disease, is magnetic resonance imaging (MRI), which currently remains the only method that allows to explore the entire central nervous system *in vivo*.

The review presents literature data on modern achievements in MRI-based diagnosis of multiple sclerosis. Key attention is paid to such promising methods as assessment of brain and spinal cord atrophy, brain perfusion MRI, and diffusion tensor imaging. Implementation of these approaches in MRI can help solve the problem of early diagnosis of multiple sclerosis and determine more reliable markers of a response to ongoing therapy.

Keywords: magnetic resonance imaging, multiple sclerosis, DWI, MR perfusion

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Современные возможности магнитно-резонансной диагностики рассеянного склероза. Обзор литературы

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РЕЗЮМЕ

Рассеянный склероз остается наиболее часто встречаемым демиелинизирующим заболеванием центральной нервной системы и занимает первое место среди неврологических заболеваний, приводящих к инвалидизации лиц молодого возраста. Наиболее важной лучевой модальностью с диагностической и прогностической точек зрения, особенно на ранней стадии заболевания, является магнитно-резонансная томография (МРТ), которая в настоящее время остается единственным методом, позволяющим исследовать центральную нервную систему на всем протяжении *in vivo*.

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В настоящем обзоре приведены литературные данные о современных достижениях магнитно-резонансной диагностики рассеянного склероза. Ключевое внимание уделяется таким ее перспективным аспектам, как оценка атрофии головного и спинного мозга, оценка перфузии головного мозга и диффузионно-тензорная МРТ. Внедрение данных подходов в МРТ помогает приблизить решение проблемы ранней диагностики рассеянного склероза и повысить информативность оценки клинического ответа на проводимую терапию.

Ключевые слова: магнитно-резонансная томография, рассеянный склероз, DWI, МР-перфузия

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INTRODUCTION

Multiple sclerosis (MS) is the most common autoimmune demyelinating disease of the central nervous system (CNS), characterized by the formation of multiple foci of demyelination and a variety of neurological symptoms. MS ranks first among neurological diseases leading to disability in young people. The disease is characterized by fully or partially reversible episodes of neurological disability that usually last from several days to several weeks [1].

More than 2.8 million people worldwide are diagnosed with MS [2]. MS is now more common in women, but this has not always been the case. Since the early 1900s, the sex ratio has been nearly equal, but since then it has steadily increased toward predominance of women, currently approaching 3:1 [3]. Although the first manifestation of the disease can occur at any age, in most patients with MS it occurs at the age of 20–40 years. The disease has a huge negative impact on their functional activity, financial security, and quality of life. The costs of medical care for MS are extremely high and increase as disability progresses [4].

PATHOGENESIS

To date, the pathogenesis of MS remains not fully understood, mainly due to limited understanding of the ethology of this disease. Various risk factors for the development of MS have been identified so far, such as serum vitamin D levels, genetic predisposition, and certain viral infections [5]. However, none of these factors has been recognized as etiological. This suggests that the etiopathogenesis of the disease is multifactorial [6].

Although the triggering mechanisms of MS remain unknown, the dominant scientific view on the pathogenesis of this disease is that the activation of autoaggression against myelin proteins, which form a multilayered sheath around the axons and cell bodies of neurons, plays a major role in its occurrence [7]. Thus, disruptions in immune mechanisms have been proposed as the main factors in the pathogenesis of MS. This is due to the fact that T and B lymphocytes are selectively sensitized by specific target antigens (probably autoantigens), which are expressed only in the central nervous system. This is indirectly confirmed by the discovery of a correlation between a decrease in the number and activity of circulating regulatory T cells in the peripheral blood with exacerbation of disease symptoms [8].

Currently, numerous forms of MS (cerebrospinal, spinal, cerebellar, optic, brainstem and others) are not separately identified and are not indicated in the diagnosis. To standardize terminology and increase the homogeneity of clinical studies, an internationally recognized and unified classification of MS was introduced, which distinguishes four variants of its clinical course (phenotype):

1. Relapsing remitting MS (RRMS) is characterized by the presence of periodic exacerbations with almost complete recovery or the presence of minimal residual neurological deficit and the absence of progression of symptoms in the period between relapses.

2. Primary progressive MS (PPMS) is characterized by the presence of steady progression

of neurological deficits from the onset of the disease in the absence of obvious exacerbations.

3. Secondary progressive MS (SPMS) is characterized by steady progression of the disease after a certain period of the relapsing remitting course.

4. Progressive MS with exacerbations is characterized by the presence of exacerbations of the disease with a steady aggravation of neurological symptoms.

Establishing the type of MS course in a particular patient is a key aspect in the diagnosis of this disease. An accurate description of the clinical course (phenotype) of the disease is important for predicting, planning, and clarifying the scope of necessary clinical trials, as well as for choosing the optimal treatment strategy [9].

This classification was partially revised in 2013 [10]. It now takes into account additional criteria for MS, such as its activity and progression (based on clinical presentation and MRI), thereby stratifying patient characteristics along two axes that can be assessed separately [11]. Thus, MS can be active or inactive, progressive or non-progressive. Distinguishing disease activity from disease progression has proven to be clinically meaningful, as MS treatment methods may be effective in actively progressive forms, but not in inactive progressive forms. The addition of MS classification to MRI data also reflects the understanding that, along with clinical observation, other parameters can be used to establish the characteristics of the course of this disease [11].

There is also clinically isolated syndrome (CIS), which is an early manifestation of MS. CIS involves an acute clinical attack affecting one or more areas of the central nervous system, which can lead to the onset of relapsing remitting MS. According to studies, CIS converts to RRMS after 20 years only in 21% of patients with a normal MRI image of the brain during CIS and in 82% of patients if MRI had one or more clinically asymptomatic lesions of the white matter of the brain [12].

At early stages of MS, clinical data alone are not enough to diagnose it accurately. On the other hand, instrumental and laboratory studies cannot always provide the necessary accuracy in diagnosing MS. It should also be noted that a large number of publications about numerous methods proposed for the diagnosis of MS do not reflect their real significance, since most of them do not analyze the assessment of their diagnostic effectiveness (primarily sensitivity and specificity). Unfortunately, the generally accepted magnetic resonance criteria for MS are used only as basic ones, making it impossible to conduct a reliable assessment of the risk of disease progression.

Another problem remains establishing the exact type of course of MS, as well as predictors of the transition of RRMS to SPMS, which must be taken into account for timely and effective correction of appropriate therapy. The development of various methods, including both imaging and laboratory diagnosis, to solve these problems is an extremely relevant area in the development of MS diagnosis.

CRITERIA FOR MAGNETIC RESONANCE MANIFESTATIONS OF LESIONS IN MULTIPLE SCLEROSIS

It is well known that the features of pathological processes in MS, including inflammation, demyelination, axonal loss, and gliosis, can be studied *in vivo* using both traditional and advanced medical imaging methods [13]. MRI is the most important radiation modality for MS from the point of view of its diagnosis and prognosis, especially at the early stage of the disease, which currently remains the only method that allows to study the entire central nervous system *in vivo.* Traditional MRI pulse sequences in the diagnosis of MS can determine the number, location, and activity of demyelinating lesions, although the sensitivity of these sequences is thought to be highly variable.

On the other hand, routine MRI has low sensitivity in detecting the heterogeneity of focal lesions and pathological changes observed in the tissue of the central nervous system outside the foci of demyelination. In addition, MRI is unable to separately quantify the level of damage to various CNS tissue components, such as myelin, axons, and glia [14].

It is preferable to visualize demyelinating processes on high-field MRI scanners (with a magnetic induction value equal to or greater than 1.0 T). T2-WI sequences with long TE (time echo) and TR (time repetition) are the most sensitive to damage to the brain matter in MS. This is due to the fact that demyelinating lesions in MS have a

longer T2 relaxation time compared to apparently unchanged white matter.

Numerous comparisons of neuroimaging data and histologic studies made it possible to identify a pathological substrate corresponding to changes in signal characteristics in various MRI modes. Thus, as a result of disruption of the protein – lipid bilayer, a decrease in the amount of lipids and an increase in water content, foci of demyelination in MS are visualized as areas of a magnetic resonance signal of increased intensity on T2-WI and decreased intensity on T1-WI. The MR signal from recently formed lesions is determined mainly by edema and from long-existing ones – by gliosis. Thus, MRI is capable of reflecting the polymorphism of pathological changes observed in the central nervous system in MS [15].

The currently accepted MRI criteria for MS are the McDonald criteria, first published in 2001 and then revised and updated in 2005 and 2010. The last revision was carried out in 2017. As with previous revisions of these criteria, the diagnosis of MS requires a combination of clinical and radiological signs. MS can be diagnosed if any of the following five groups of criteria are met, depending on the number of clinical attacks, the presence of dissemination in space and dissemination in time [16, 17].

Foci of demyelization in MS usually have a round or oval shape, and their diameter varies from a few millimeters to a centimeter or more [18]. To a certain degree, differences in the shape of the lesions is due to the passage of the tomographic slice at an angle to the cerebral venule, which often represents the center of the demyelination focus in MS. At the initial stage of the disease, the lesions appear elongated in the form of so-called Dawson's fingers, which is probably associated with inflammatory edema of the brain matter along the medullary venules [19].

It should be noted that the typical localization of lesions in MS is the periventricular white matter, including the corpus callosum, subcortical white matter, and infratentorial region. Isolated hyperintense lesions on T2- WI adjacent to the body or temporal horn of the lateral ventricle are very characteristic of MS and are rarely found in other pathologies [20].

The diagnostic potential of MRI is enhanced by the use of contrast enhancement, which involves intravenous administration of a contrast agent (CA). Firstly, contrast-enhanced MRI can determine the degree of disease activity, which has important prognostic value and great clinical value in choosing the most effective therapeutic strategy. Secondly, this method allows to obtain additional evidence of the dissemination of demyelination foci over time by simultaneous visualization of both active foci that accumulate CA and inactive ones that do not accumulate it. Thirdly, CA injection can help identify atypical lesions and detect latent structural lesions that are not visible on non-contrast images [21].

Contrast agents based on trivalent gadolinium, which belongs to the group of positive paramagnetic agents, do not normally penetrate the blood – brain barrier (BBB). It is believed that in MS it passes through the capillary walls and lingers for some time in the extracellular space [22].

Neuroimaging and pathomorphological comparisons confirm that the accumulation of CA occurs exclusively in active demyelination foci with pronounced inflammatory changes in the form of edema and cellular infiltration. At the same time, contrast-enhanced MRI may be more sensitive in detecting subclinical activity of RRMS than assessing the clinical status. With the accumulation of CA, pathological areas can change the shape and size. Usually, at first these are foci that evenly accumulate CAs, which subsequently, as the disease progresses, transform into foci that accumulate CAs in the "ring" or "semi-ring" type, after which the degree of CA capture by such foci decreases, since they become "chronic".

At the same time, there are known difficulties in the differential diagnosis of both typical and atypical forms of MS with tumor lesions of the central nervous system. Thus, lesions in MS in certain cases can be mistaken for hematogenous metastases accumulating CA, as well as primary brain tumors (in the so-called pseudotumor form of MS). At the same time, the "ring-shaped" type of their contrast is considered more characteristic of tumor lesions, while "ring-shaped-rupture" type is more typical of demyelination foci in MS [23].

MODERN POSSIBILITIES OF MRI-BASED DIAGNOSIS OF MULTIPLE SCLEROSIS

Effective treatment methods have made early diagnosis of MS highly desirable, and MRI criteria for MS have been revised to exclude conditions

that mimic the disease more accurately. However, identifying changes detected on MRI as clinically significant in MS still presents known difficulties due to the fact that traditional MRI data (total number and volume of lesions) poorly correlate with the degree of neurological deficit. This phenomenon called the clinico-radiological paradox led to the need to study pathological processes developing in the central nervous system along with demyelination and to develop new methods for assessing ultrastructural, biochemical, and functional changes in the central nervous system [24].

To date, there is no consensus on how to assess and monitor response to MS treatment. Currently, the concepts of "response" and "non-response", as well as the time frame for this criterion, are widely discussed in the scientific literature. Typically, failure to respond to treatment is determined based on three factors or a combination of factors, including increasing severity of neurological deficit, relapse rate, and the presence of active T2 lesions (defined as new lesions that increase the total number of lesions) or contrast-enhancing lesions on MRI. On the other hand, the clinical significance of detecting minimal MS activity using MRI data is controversial, which raises the issue of further development of guidelines regarding the determination and monitoring of the response to treatment [25].

It is now generally accepted that focal lesions detected by routine MRI represent only one aspect of the disease [26]. At the same time, advanced MRI technologies that have emerged over the past few decades have made it possible to detect microstructural changes in the brain in patients with MS, even in apparently normal white matter [27]. In addition, cortical lesions and atrophy of the gray matter of the brain may be important additional features of this disease [28].

It has been established that atrophy of the brain and spinal cord is becoming one of the main manifestations of MS and represents a very relevant finding [29]. In addition to tissue loss caused by locally destructive white matter lesions and secondary tissue loss due to tract-specific loss of axons and neurons, there are many other potential mechanisms for this process, including iron accumulation, mitochondrial damage, microglial activation, and oxidative stress [30]. Thus, brain atrophy begins at the early stages of MS and progresses annually in untreated patients at a rate of 0.5–1.0% per year, regardless of the clinical subtype of the disease [31]. It is worth noting that global brain atrophy can be observed not only during the onset of the first symptoms of MS, but even at its preclinical stages [32–34]. Atrophy has a stronger association with neurological deficits and cognitive impairment compared to traditional MRI criteria for nerve tissue damage in MS [35].

Brain atrophy can be easily measured using a wide range of MRI techniques. Qualitatively, atrophy can be established based on an increase in the cerebrospinal fluid spaces in combination with a decrease in the volume of brain tissue, as well as by measuring the width of the ventricles of the brain or the cross-sectional area of the corpus callosum. For more efficient and reproducible measurements in research and clinical trials, fully automated computer methods for segmenting diagnostic images based on high-resolution T1-WI are usually used, which allows for separate assessment of the white and gray matter of the brain and, by determining their ratio, identifying regional atrophy. However, the results of such studies should be interpreted carefully, as CNS volume is also influenced by non-MS factors, such as medications taken, daily fluctuations and hydration status, as well as MS-related edema, inflammation, and gliosis [36, 37].

Unfortunately, atrophy scoring criteria are not yet used in daily clinical practice due to many technical problems and a lack of consensus on the choice of a standardized method for their determination [38]. In this regard, the development of portable, fully automated methods for measuring atrophic changes in the brain, which are promising for widespread use in the future, continues [39].

In addition to the above data on morphological changes in the brain in MS, there are reports in the literature about changes in perfusion both in lesions and in tissues with a normal image of the brain [40]. Common MRI techniques for assessing cerebral perfusion include dynamic susceptibility contrast (DSC) magnetic resonance, dynamic contrast-enhanced (DCE) MRI, and arterial spin labeling (ASL) MRI. All of these methods can quantify cerebral blood flow velocity (CBF), cerebral blood volume (CBV), and mean cerebral transit time (MTT) of CA. The DSC and DCE methods involve visualization of the dynamic passage of a gadolinium-containing contrast agent bolus. The first one is

based on T2* weighted sequences, and the second one is based on T1-weighted sequences. Unlike DSC and DCE, the ASL method is based on the use of contrast properties of endogenous water molecules, which, being part of the blood, are marked using radiofrequency inversion pulses before they reach the brain [41].

It is still unclear whether changes in perfusion in MS are a primary process or simply an epiphenomenon caused by Wallerian degeneration or atrophy [38, 39]. However, accumulating evidence suggests that changes in cerebral perfusion in MS are an important part of this disease. Thus, there is evidence that a decrease in perfusion in the medulla can occur even in its apparently intact areas [42]. It has also been shown that hypoperfusion is not necessarily associated with demyelination areas. Moreover, it is assumed that changes in perfusion precede atrophy and lesion formation [43]. Additionally, a relationship between cerebral perfusion and the distribution of white matter lesions has been observed in a broad cohort of MS patients. In particular, white matter lesions in patients with secondary progressive MS were found in regions characterized by lower perfusion than in contralateral healthy regions. In contrast, in patients with RRMS, brain lesions were more common in areas with increased perfusion. This fact indicates that remyelination processes, which are more effective at the early stage of the disease, may be associated with changes in local perfusion [44].

Another study found a statistically significant decrease in CBF in the frontal cortex, thalamus, and caudate nucleus in patients with MS, without evidence of loss of gray matter volume and decrease in cortical thickness, and such abnormalities were more common in SPMS compared to RRMS [45]. The reasons for these changes in cerebral perfusion in MS are not fully understood, and today there are several hypotheses trying to explain them. Firstly, hypoperfusion may be associated with neuroaxonal loss. However, most studies did not find a relationship between perfusion and brain atrophy, while others reported only a partial relationship between changes in perfusion and the degree of brain damage detected on T2-weighted images.

In addition, decreased perfusion was also not associated with parameters of brain atrophy, supporting the idea that it may be driven by other mechanisms. Other possible explanations for the origin of cerebral atrophy include a decrease in energy requirements or a slowdown in tissue metabolism, primary ischemia, impaired cerebrovascular reactivity, mitochondrial dysfunction, and even a latent process of neurodegeneration before its manifestation at the macromorphological level. In this case, knowledge of the extent of atrophic changes in the brain may provide more therapeutic options than detection of a pronounced and widespread demyelination process.

The relationship between brain perfusion and contrast enhancement of lesions in MS is of considerable scientific interest. The literature provides data according to which in patients with RRMS, there is an increase in CBF and CBV by 20% compared to the baseline values 3 weeks before the accumulation of CA in lesions, a CBF and CBV increase by 25% during the period of CA accumulation, and a slow decrease in CA accumulation in the lesions in MS compared to baseline values within 20 weeks after initial gadolinium enhancement [46].

Patients need to undergo MRI repeatedly and frequently to monitor rapidly occurring changes in the central nervous system during periods of manifestation of MS and its increased activity. MR perfusion study is the mainstay for objectifying hemodynamic disorders in MS. However, this study is associated with an increased risk of dose-dependent deposition of gadolinium in brain tissue due to frequent repeated administration of CA.

Thus, impaired cerebral perfusion in MS is most likely one of the links in a complex cascade of pathophysiological processes occurring in this disease. However, it is yet to be determined whether the phenomena described above are closely related phenomena of the same order (possibly secondary to known immunological abnormalities in MS) or simply represent disparate aspects of MS. The identified correlations of changes in cerebral perfusion with various types of MS course raise the question of the advisability of using MRI perfusion parameters as markers for the early diagnosis of MS and the characteristics of its course.

Another promising advanced neuroimaging technique is diffusion tensor MRI (DTI), which allows for the assessment of the integrity of neural pathways. DTI can analyze and evaluate elements of the microstructural architecture of the brain that are not visualized using traditional pulse sequences.

Thus, DTI provides important additional information about the spatial organization of nerve fibers, directional coherence of axons, and the degree of integrity of a particular neural tract [47]. DTI has provided valuable insight into the pathogenesis of MS both within lesions and in the white matter of the brain, which appears intact according to routine MRI.

Animal models have shown that DTI can differentiate axonal damage caused by demyelination, suggesting that DTI can be used to evaluate neuroprotective treatments. Thus, DTI has a high diagnostic potential, making it possible to detect changes in MS lesions at the earliest stages of the disease, including in the white matter of the brain whose macromorphological characteristics are unchanged. DTI can also be used to describe the microstructures of biological tissues by quantifying water diffusion processes in affected brain regions in MS. Moreover, DTI makes it possible to determine the extent of white matter lesions more accurately than using T2-weighted images [48]. DTI parameters, including fractional anisotropy (FA), radial diffusivity (RD), and mean diffusivity (MD), can accurately characterize the state of neuronal structures and their disorders in patients suffering from MS [49].

This method is based on a non-invasive assessment of the molecular (Brownian) motion of water, which in biological tissues is limited by various cellular structures. In the white matter tracts of the brain, water mainly diffuses parallel to the direction of the axons (axial diffusivity), and visualization of this physical process allows for detailed mapping of the structural integrity of the white matter at the micro level. Using directional magnetic gradients in three planes within DTI, it is possible to evaluate water diffusion processes in directions perpendicular to the neural tracts (radial diffusivity). In this regard, axial diffusivity is thought to reflect the integrity of axons, and radial diffusivity reflects the degree of their myelination, while FA is an integral parameter characterizing the degree of the diffusion direction in a specific volume of the medulla. In this case, a low FA coefficient corresponds to a low degree of vectoriality of water diffusion, while a high FA coefficient is a consequence of highly directional movement of water along axons.

It has been established that lesions of the medulla in MS are associated with reduced values of the FA coefficient, which indicates that structural disorders of the nerve conduction tracts occur as part of this disease. It has been suggested that a decrease in the FA coefficient may act as a marker of acute brain lesions and, therefore, be one of the criteria for disease activity. RD represents the rate of water diffusion perpendicular to axons, which is largely related to the processes of demyelination and remyelination [50]. It was found that increased RD values are potentially associated with lesions detected on T2-weighted images, as well as with myelin damage. It was also shown that an increase in this coefficient can also be determined in the white matter of the brain, in which, according to traditional MRI, structural changes are completely absent. A relative increase in RD values was also observed in affected nerve fibers, which is consistent with Wallerian degeneration [51].

Unfortunately, obtaining high-quality diffusion tensor images is associated with technical difficulties, which limits the clinical use of DTI. However, recent advances in image post-processing technology have improved the reliability of DTI in assessing nerve fiber integrity, resulting in increased sensitivity for detecting changes in MS compared to standard MRI [52].

CONCLUSION

Thus, today there is no generally accepted and reliable neuroimaging technique for assessing the course of MS, and the diagnostic criteria used for this are based mainly on clinical relapses and the presence of brain changes detected on MRI. Although traditionally used MRI sequences provide high sensitivity for diagnosing MS, they do not reliably identify predictors of deterioration in the clinical course of MS, and the results of such studies poorly correlate with the clinical status of the patient.

The introduction of new technologies implemented within the framework of MR imaging can contribute to solving the problem of early diagnosis of MS and determining more reliable criteria for response to therapy. A better understanding of the relationship between perfusion changes, MS, and clinical outcomes may be important to obtain new potential markers to assess the effects of pharmacological and rehabilitation interventions.

In addition, the use of DTI for these purposes seems very promising. But the current body of research using DTI is relatively limited, indicating

that these studies are at an early stage. However, these data already indicate that the quantitative parameter of FA measured by DTI successfully correlates with impairments in MS. Low level of evidence suggests that FA indicates tissue damage in a range of disorders, but the evidence is insufficient to support its use as a diagnostic test or as a predictor of clinical outcomes.

Thus, data collection methods, data processing, and data interpretation require further improvement, followed by standardization and validation, before new technologies are ready for widespread clinical use.

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