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Current Highlights in the Use of Magnetic Resonance Spectroscopy in Multiple Sclerosis

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ABSTRACT

Magnetic resonance spectroscopy is a non-invasive method used to measure concentrations of selected metabolites in brain such as: N-acetylaspartate, creatine, choline, glutamic acid, myo-inositol, lactic acid or γ -aminobutyric acid. The MRS allows the researcher to obtain information about biochemical composition in selected localizations of the examined CNS and is based on the interpretation of spectra of specific chemical compounds. The aim of this study is a literature review of papers from last 5 years involving the use of MRS in multiple sclerosis. Magnetic resonance spectroscopy is a modern, promising metabolomic imaging method enabling the assessment of brain metabolite concentrations and the dynamism of their changes in healthy people and patients suffering from multiple sclerosis at every stage of the disease. MRS is helpful not only in correlating changes in metabolite concentrations at various central nervous system locations with clinical manifestations, but is also an increasingly improving tool for predicting disease progression. Magnetic resonance spectroscopy may also be useful in more specific clinical situations such as differential diagnosis between multiple sclerosis and Devic's syndrome or between tumefactive demyelinating lesions and gliomas. Especially in the latter case, the development of this technology may in the future result in the

possibility of avoiding invasive biopsy in patients during the diagnosis of focal changes in the CNS. One should also not forget about the role that MRS may play in the future in monitoring the course of treatment with modern MS drugs, not only in everyday clinical practice but also at the stage of clinical trials. The development of fast MRS techniques, significantly shortening the acquisition time and 7 T magnetic resonance spectroscopy, precise and repeatable method of quantitative analysis of brain metabolites may be particularly helpful in achieving these goals.

Keywords: Multiple sclerosis, magnetic resonance spectroscopy, magnetic resonance imaging, demyelination, brain metabolites, N-acetylaspartate

1. INTRODUCTION

The aim of the study is to provide a literature review of works published in last 5 years concerning the use of Magnetic Resonance Spectroscopy in diagnosis, differentiation, outcome prognosis and monitoring of treatment of Multiple Sclerosis.

1. 1. Multiple sclerosis – background knowledge

Multiple sclerosis (MS) is a heterogenous demyelinating disease with a wide spectrum of clinical and imaging changes ranging from clinically silent focal MRI abnormalities to fully blown clinical syndrome with severe neurological deficits. Therefore it is essential to properly recognize its progression from the earliest stages of the disease process in order to plan the optimal management of patients and this is in line with newly proposed criteria. Early diagnosis of multiple sclerosis is becoming the burning clinical problem as the currently available treatment might delay the progressive phase of the MS only when used before the focal damage occurs. [1] The disease has a chronic progressive course and affects the central nervous system. It is characterized by occurrence of multifocal and multiperiodic lesions (called *plaques*) in the brain and the spinal cord. Until recently it was stated, that the disease affects only white matter, however many authors of the scientific reports from the last few years proved, that pathological changes develop also in the gray matter. According to the reports, it is uncertain, where is the primary molecular location of the initiation of the inflammatory process leading to demyelination and if there are white matter lesions, that can be detected before the development of this process. Nonetheless, the pathogenesis of lesions in white and gray matter stays different. The main reason for white matter lesions development is T lymphocyte migration. In turn, the etiology of cortical lesions is still poorly understood. Moreover, a progressive, generalized cerebral atrophy affecting both white and gray matter, develops constantly and can appear even at the earliest stages of the disease. Multiple sclerosis is the disease that occurs mainly in the group of young people, often leading to their disability. Their life plans are ruined because of illness, therefore it is a significant problem for the entire society.

1. 2. Magnetic resonance spectroscopy as a promising tool of metabolomic imaging

Magnetic resonance spectroscopy (MRS) is a non-invasive method used to measure concentrations of selected metabolites in brain such as: N-acetyl aspartate (NAA), creatine (Cr), choline (Cho), glutamic acid (Glx), myo-inositol (mI), lactic acid (Lac) or γ -aminobutyric acid (GABA).

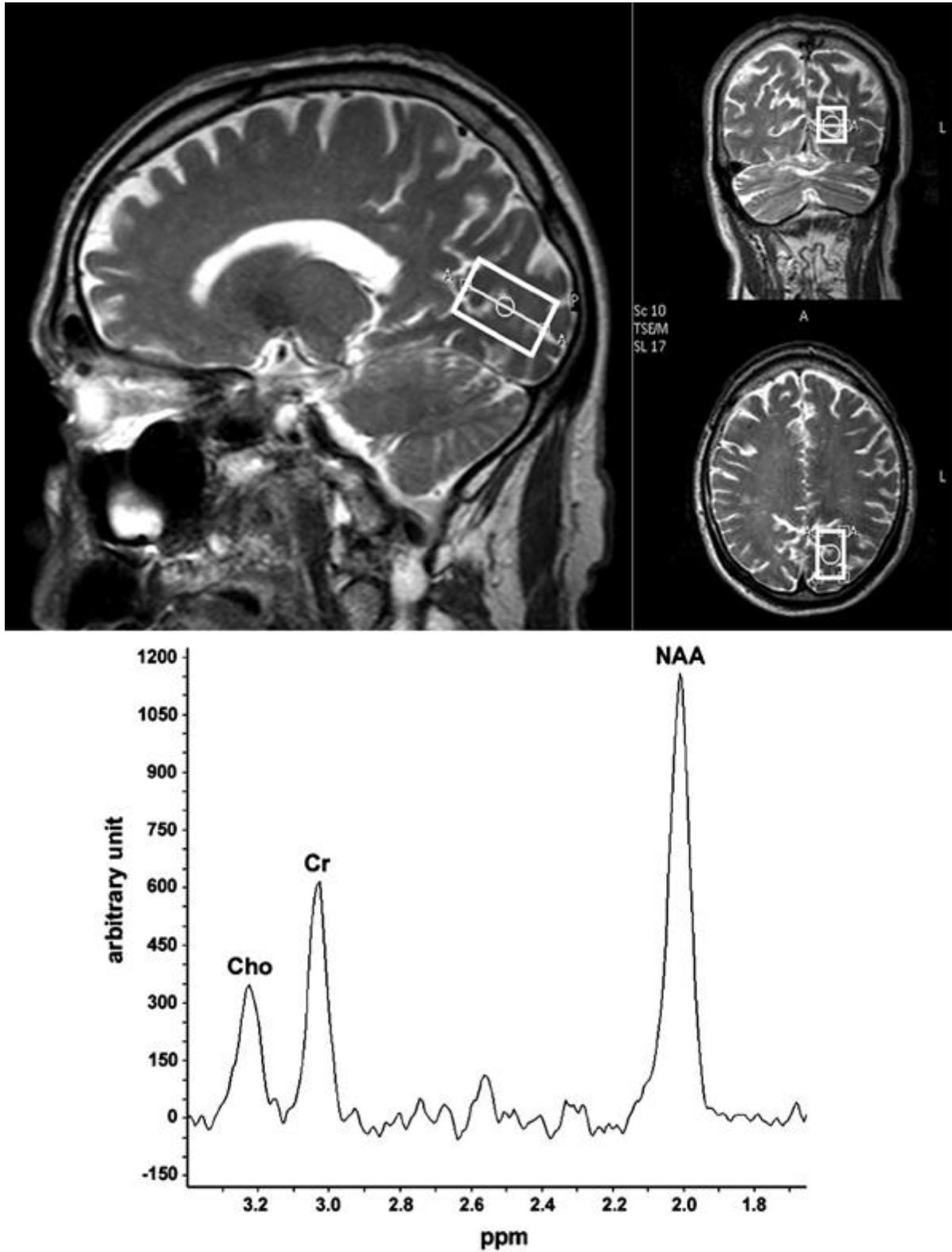


Figure 1. Representative spectrum from occipital visual field from vortex marked above.

The MRS allows the researcher to obtain information about biochemical composition in selected localizations of the examined CNS and is based on the interpretation of spectra of specific chemical compounds.

One of the most promising metabolites to analyze is N-acetyl aspartate, which appears in neurons and is a potential marker of the axonal loss. In the course of demyelinating process NAA concentration decreases. Last few years findings focus on concentrations ratio of myo-inositol, astrocyte marker and NAA in MS. Bearing in mind this ratio it seems to be possible to determine the stage of cerebral atrophy and disability progression.

Examples of the MRS spectra and representative MRI images are depicted in Figures 1, 2 and 3.

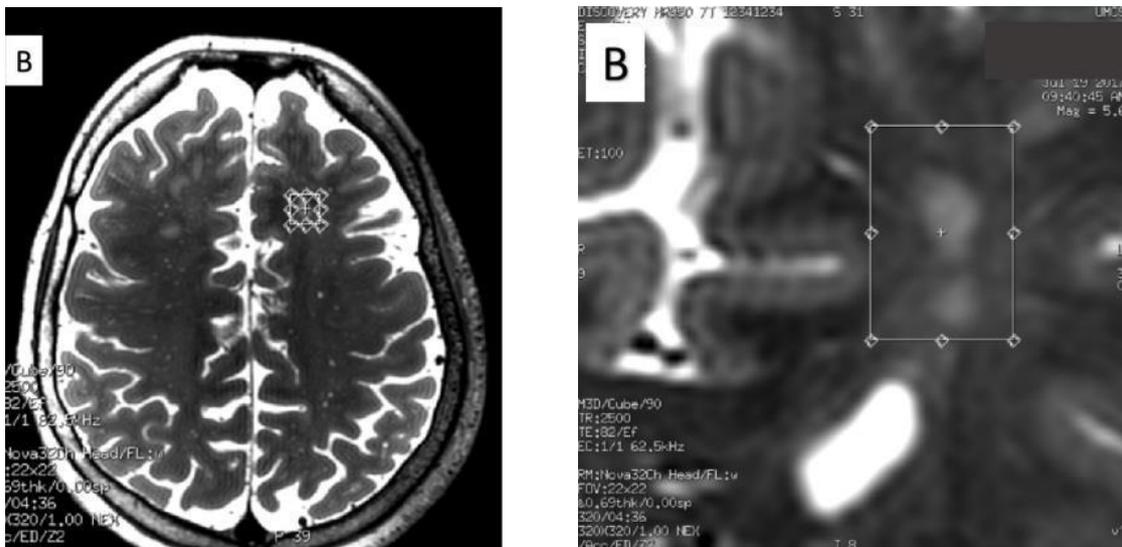


Figure 2. and 3. Representative T2-weighted images with a voxel including the demyelinating plaque.

The material from Figure 1 comes from: Von Boucard CC, Hoogduin JM, van der Grond J, Cornelissen FW - Boucard CC, Hoogduin JM, van der Grond J, Cornelissen FW: Occipital proton magnetic resonance spectroscopy (1H-MRS) reveals normal metabolite concentrations in retinal visual field defects. In: PLoS ONE 2007 Feb 21;2(2):e222. PMID 17311099, CC BY 2.5, <https://commons.wikimedia.org/w/index.php?curid=6273938> - and was modified due to present MR imaging and the corresponding spectrum vertically.

The material from Figures 2 and 3 come from own research in the Department of Radiography of the Medical University of Lublin.

2. MATERIALS AND METHODS

The literature review of papers from NCBI/NLM PubMed database published from last 5 years was performed. The following combinations of search terms were used: ("Multiple Sclerosis"[Mesh]) AND "Magnetic Resonance Spectroscopy"[Mesh].

3. RESULTS

The results of the literature review on possible use of magnetic resonance spectroscopy in multiple sclerosis were grouped as below.

3. 1. Metabolites concentrations in healthy and in lesional tissue

Most of the papers published during last five years focus on basic findings about different metabolites concentrations within the central nervous system, both in healthy white matter, as well as chronic and acute lesions.

A French follow-up study of acute lesions in early relapsing-remitting MS (RRMS) showed increased choline (Cho) to creatine (Cr) ratio during the entire two-month follow-up. The patients were also observed to have increased myo-inositol (mI) to creatine ratio. Although the meaning of this finding is not fully clear yet, it is believed that MRS, together with DTI (diffusion tensor imaging, used for tractography) may play a role in identifying the correlation between blood-brain barrier disruption and demyelination. Moreover, especially myo-inositol profiles may lead to better understanding of phenomena such as remyelination, that occur after the pathologic lesion formation. [2]

In terms of comparison of metabolites concentrations in MS patients and healthy controls, numerous publications confirm the significant increase of mI and Cho, as well as decrease in NAA concentrations in patients with MS. Moreover, the NAA/Cr and NAA/Cho ratios are also significantly lower in MS patients than in healthy controls, and the Cho/NAA ratio is increased. These metabolic changes appear even in NAWM (normal appearing white matter) of MS individuals, and not exclusively in pathologic lesions. Besides, the EDSS (expanded disability status scale) results in MS patients seem to be correlated with NAA/Cr and Cho/Cr ratios. The decrease of this ratio is even more higher in the parietal NAWM than in frontal or parietal-occipital NAWM. [3-6]

Chronic lesions are less in the field of interest of researchers in last few years. A German work on the comparison of metabolic patterns in chronic MS lesions and NAWM, published in 2016, showed no significant differences between metabolic changes in chronic lesions and NAWM, what supports the statement that such lesions may be not as relevant in stratification of the risk of progression of the disease and further outcomes. [7]

3. 2. Role of specific metabolites in multiple sclerosis

The role of specific metabolites in multiple sclerosis is not fully clear. However, the biggest concerns are connected with the concentrations of NAA in brain tissue of MS patients. It is believed, that N-acetyl aspartate reflects axonal health, as it is proved that the further decrease in NAA concentrations is observed in patients, who are experiencing clinical or radiological evidence of inflammatory activity.

There are also attempts being made to find a correlation between NAA/Cr ratio in pons and fatigue in MS patients, but the results remain unclear. However, the most important connection is found between NAA/Cr concentration ratio which is robustly associated with disability level regardless different statistical approaches, along with lesion volume in T1-weighted images. Lower total NAA is associated with higher disability, measured and assessed by both EDSS and MAS (Modified Ashworth Scale), as well as vibration perception thresholds and postural sway. [8-11]

For motor functions, the clearest correlations were found between lower GABA levels and worse performance on motor functions tests. Compared with healthy controls, MS patients present significantly lower GABA levels in the hippocampus and sensorimotor cortex. A British research from 2015 involving thirty patients with SPMS (secondary progressive multiple sclerosis) suggests, that the abovementioned GABA concentration decrease may be a consequence of GABA neurotransmission disruptions, changes in the density of inhibitory neurons and are connected with axonal degeneration as well. Moreover, according to the latest reports, lower gamma-aminobutyric acid concentrations correlate with worse cognitive performance in MS patients and disruptions in GABAergic neurotransmission may play a role in developing cognitive impairment in patients with multiple sclerosis. [12-14]

Other promising metabolites include myo-inositol, which concentration appears as a good marker of inflammatory processes, which are involved in the pathogenesis of multiple sclerosis and β -ATP, which, in correlation with EDSS, may be a novel candidate for assessment of multiple sclerosis severity. [15-16]

3. 3. Prediction of the progression of the disease

Lesions of demyelination show higher Cho, Cr and mI, what reflects a probable higher myelin turnover, faster metabolism and elevated glial activity than normal appearing white matter. It is investigated, if these changes may be helpful in determining the dynamism of the progression of the disease. Reports show, that even a pre-lesional tissue, in comparison with normal appearing white matter, presents higher Cr and Cho concentrations, although still higher NAA than acute lesions, whereas chronic lesions showed an increased myo-inositol, with the lesion volume as promising prognostic tool for disease progression. Both reduced NAA and elevated mI are sensitive indices for differentiation between MS patients and healthy controls. Even the decreased NAA in NAWM enables to evaluate MS progression, especially if the parietal NAWM is taken into account. In early RRMS (relapsing-remitting multiple sclerosis), the cortical NAA/Cr concentrations ratio is proven to be a valuable predictor of long-term disease outcome, especially when correlated with optical coherence tomography changes (retinal nerve fibre layer thickness). [4-5, 17-20]

The biggest hope is raised by possible use of glutamate in MS progression risk stratification. Some of the latest results show, that higher Glu concentrations increase the rate of NAA decline, and, simultaneously, higher Glu/NAA concentrations ratio also increases the rate of decline of brain volume. A Slovak research conducted in 2017 also suggests, that an increase of Glu in MS patients' hypothalamus is linked to higher severity of the disease, as well as it is connected with extended fatigue and depressive mood. This shows that Glu may be even more sensitive factor for MS outcome prognosis than other abovementioned metabolites. [21-23]

3. 4. Differentiation between gliomas and tumefactive demyelinating lesions

Tumefactive demyelinating lesions (TDLs) are areas of demyelination that are usually greater than 2 cm in diameter and often mimic neoplasm in head CT or even brain MRI. Basing only on radiological evaluation, it is very difficult to distinguish these two findings, therefore an invasive brain biopsy is required. However, MRS use seems to be beneficial in some patients and prevent them from invasive diagnostics. It is proven, that Cho/NAA concentrations ratio is significantly higher in gliomas (especially high-grade gliomas) than in TDLs. The effective

differentiation of these two conditions by the use of MRS may likely enhance patients outcomes in the future, as a part of them will no longer be exposed to invasive biopsy. [24-25]

3. 5. Differentiation between multiple sclerosis and neuromyelitis optica

Neuromyelitis optica (NMO, Devic's syndrome) is a demyelinating disease that previously was considered to be a variant of multiple sclerosis. However, a present-day approach characterizes NMO as a separate entity. Differentiation between these two conditions sometimes is still problematic for clinicians, though. The use of MRS may be helpful in distinguishing the diseases. As compared to healthy individuals, in NMO a mild increase of Cho is observed, without evident changes in NAA concentrations, whereas in MS the reduction of NAA is apparent, what suggests that in NMO the neuronal damage is absent in normal appearing white matter. [6]

The alternative approach is MRS examination of cerebrospinal fluid. Most of the metabolites levels behave similarly both in NMO and MS, including acetone, formate, pyroglutamate and 2-hydroxybutyrate. However, citrate was showed to be specifically lower in multiple sclerosis patients samples, while lactate was increased in neuromyelitis optica exclusively. [26]

3. 6. Monitoring of multiple sclerosis treatment

There are only few works from the last five years concerning the treatment monitoring when MRS is in use. The drugs that were evaluated this way were beta interferon, natalizumab, erhuangfang and laquinimod. In these research approaches, beta interferon was showed to have a stabilizing effect on brain metabolite ratios, which possibly reflects its positive effect on the course of multiple sclerosis. In turn, more modern drug, natalizumab, a monoclonal antibody against cell adhesion molecule $\alpha 4$ -integrin, was proven to even increase NAA, Cr and phosphocreatine in lesional white matter, what probably is a consequence of an enhancement of the axonal metabolism under the influence of the therapy. Laquinimod, an immunomodulator, was also found to increase NAA/Cr concentrations ratio, therefore probably it also reduces pathological processes in relapsing-remitting MS. In turn, erhuangfang use did not effect in any significant difference in NAA/Cr ratio before and after treatment, suggesting lack of effectiveness of this medication. [27-30]

Progressive multifocal encephalopathy (PML), which is caused by JC virus and is a rare side effect of mainly natalizumab treatment, can be also monitored by MR spectroscopy. Taking into account together with JCV status, the promising markers to monitor the disease activity are Cho/Cr and NAA/Cho ratios. [31]

3. 7. Possible future approaches in MRS use in multiple sclerosis

Magnetic resonance spectroscopy is still a method requiring further research and analysis both including the methodology of examination itself, as well as the meaning of gained results.

Development of the fast MRS method may lead in the future to reduce scanning time which now requires very long acquisition in order to collect adequate spectra. Improvement of different fast MRS sequences including spiral, echo-planar, parallel and turbo imaging will lead to a broader use of MRS in clinical practice, not only in MS but also epilepsy, strokes and neurooncology. [32-33] The other promising approach is 7 Tesla MRS. This methodology is

preliminary showed to have high accuracy and reproducibility in determining biomarkers associated with MS including GABA and glutamate. [34]

4. CONCLUSIONS

Magnetic resonance spectroscopy is a modern, promising metabolomic imaging method enabling the assessment of brain metabolite concentrations and the dynamism of their changes in healthy people and patients suffering from multiple sclerosis at every stage of the disease. MRS is helpful not only in correlating changes in metabolite concentrations at various central nervous system locations with clinical manifestations, but is also an increasingly improving tool for predicting disease progression.

Magnetic resonance spectroscopy may also be useful in more specific clinical situations such as differential diagnosis between multiple sclerosis and Devic's syndrome or between tumefactive demyelinating lesions and gliomas. Especially in the latter case, the development of this technology may in the future result in the possibility of avoiding invasive biopsy in patients during the diagnosis of focal changes in the CNS.

One should also not forget about the role that MRS may play in the future in monitoring the course of treatment with modern MS drugs, not only in everyday clinical practice but also at the stage of clinical trials. The development of fast MRS techniques, significantly shortening the acquisition time and 7 T magnetic resonance spectroscopy, precise and repeatable method of quantitative analysis of brain metabolites may be particularly helpful in achieving these goals.

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