folia medica

Folia Medica 64(5):746-753
DOI: 10.3897/folmed.64.e66002

Original Article

Normal Appearing White Matter Metabolite Pattern and Sex Differences in Multiple Sclerosis Patients Compared to Healthy Controls

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Received: 16 Mar 2021 ♦ **Accepted:** 13 May 2021 ♦ **Published:** 31 Oct 2022

Citation: Petrova V, Genov K. Normal appearing white matter metabolite pattern and sex differences in multiple sclerosis patients compared to healthy controls. Folia Med (Plovdiv) 2022;64(5):746-753. doi: 10.3897/folmed.64.e66002.

Abstract

Introduction: Proton magnetic resonance spectroscopy (PrMRS) detects changes in brain metabolite levels in vivo.

Aim: The aim of the present study was to evaluate the brain metabolites choline (Cho), creatine (Cr), and N-acetyl aspartate (NAA) in lesion free normal appearing white matter (NAWM) in patients with relapsing-remitting multiple sclerosis (RRMS) versus healthy controls. The second aim was to explore the impact of sex on brain metabolite changes.

Materials and methods: Fifty RRMS patients received PrMRS evaluation of their brain NAWM regions. The results were compared with the findings in 28 healthy demographically matched controls.

Results: We found elevated levels of Cho, Cr, and NAA in NAWM of MS patients in comparison with healthy controls. The NAA/Cr and Cr/NAA ratios were collated. A statistically significant difference between both groups was found only for NAA/Cr and Cr/NAA ratios. It is due to metabolite changes in the female MS patients.

Conclusions: The results of the present study using PrMRS proved metabolic changes in NAWM. Accompanying pathological process should be assumed, preceding plaques of demyelination. The gender impact needs further investigation.

Keywords

disconnection, gender, magnetic resonance spectroscopy

INTRODUCTION

Over the last 25-30 years, magnetic resonance imaging has been accepted as an important and essential method for specifying the multiple sclerosis (MS) diagnosis as well as for monitoring the disease in vivo. Proton magnetic resonance spectroscopy (PrMRS) is a method of investigating brain metabolites and the changes in their concentrations. The PrMRS is the only method specific for injuries of definite cell types.[1] In MS patients, three types of metabolite patterns have been found: of acute and chronic plaques of demyelination, and of normal brain parenchyma (white brain matter outside the zones of demyelination). Studies over the last years have focused on the changes occurring in the brain parenchyma in MS outside the plaques of demyelination. In normal appearing white matter (NAWM) axon damage, without demyelination markers, microglia and astrocyte activation, and inflammation abnormalities

of low intensity are found. MS is an autoimmune disease of genetic predisposition which in combination with factors from the environment, activates a cascade of immune responses and damages the blood-brain barrier. Inflammatory demyelination of the white brain matter of the central nervous system (CNS) occurs with the participation of T and B lymphocytes and macrophages.[2] Conduction of nerve impulses to the CNS is damaged which is clinically manifested as neurologic deficit.[3] The disease affects predominantly young people aged between 30-34 years. Twice as many females are disease-prone compared to males.[3]

AIM

The objective of the study was to measure the metabolite markers choline (Cho), creatine (Cr), and N-acetyl aspartate (NAA) in zones of NAWM (brain regions in the white matter without demyelination lesions) using PrMRS. The second goal of the study was to search for sex-determined differences in the parameters studied.

MATERIALS AND METHODS

Proton magnetic resonance spectroscopy

MRT was performed on MT Signa 1.5T HDxt. The protocol for PrMRS we applied is used at the Department of Diagnostic Imaging of St Ivan Rilski University Multiprofile Hospital for Active Treatment, Sofia. PrMRS is a method in which signals are recorded reflected by the protons of organic molecules – metabolites in CNS. Their concentrations are 1000 times lower than those of water in tissues. The normal brain spectrum is presented by three resonance peaks of the metabolites. The first peak is formed by tetramethyl amines (Cho), which are mainly choline phospholipids. They participate in the synthesis and decomposition of cellular membranes. A second peak is formed by the content of Cr and phosphocreatine. They participate in the energy metabolism. The third peak is of the NAA groups which comprise the NAA localized within the neurons. A fourth peak may be formed, especially in pathologic processes, by lactates and lipids.[1]

For the objective of our study, PrMRS was performed measuring Cho, Cr, and NAA in the zones of subcortical white brain matter free of demyelination lesions. Regions of normal T2 image in the conventional MRI were selected, i.e. zones of NAWM. In the group of healthy controls corresponding zones of testing were selected. The data from the spectroscope measurement were compared. The frequencies of the metabolites tested were measured in units called parts per million (ppm) and they were graphically presented by peaks of different magnitude for the different metabolites **(Fig. 1)**.

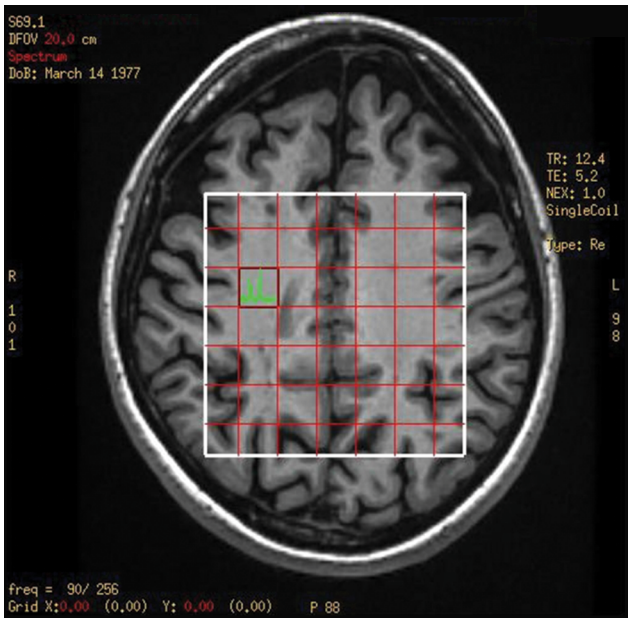

Figure 1. PrMRS in an MS patient. T2 image. The NAWM zone of interest is marked, which is free of demyelination lesions, in the right brain hemisphere parietally.

Patients

The study included 50 patients with specified MS diagnosis, according to the revised criteria of McDonald.[1,3] Patients with a history of the disease shorter than 10 years were selected, because of the fact that in 70% of the patients with RRMS the disease progresses to secondary progressive MS within 6-10 years after the onset.[1] The group of the patients studied was compared to a group of 28 healthy individuals, selected according to the corresponding demographic criteria.

Demographic data

Inclusion criteria:

- patients with clinically proven MS
- age between 20-40 years
- relapsing-remitting type of the disease
- time elapsed since specifying the diagnose up to 10 years
- currently receiving disease-modifying therapy interferon beta-1a[1,4,5]
- Expanded Disability Status Scale (EDSS) up to 3.5
- with no evidence of relapse of the disease over the last 2 to 6 months[6]
- with no administration of corticosteroid at least 2 months prior the study[6]

Exclusion criteria:

- relapse of the disease over the last 6 months prior to the study[6]
- administration of corticosteroid over the last 2 months prior to the study[6]

- other autoimmune disease
- history of specified diagnosis of depression, severe depressive episodes and/or treatment with antidepressants for symptoms of depression found
- active inflammatory process
- treatment with other type of disease-modifying therapy
- motor deficit, visual or auditory disorders
- alcohol or other psychotropic medications and substances abuse.

Control group:

Inclusion criteria:

- age between 20-40 years
- clinically healthy individuals

Exclusion criteria:

- history of other neurologic disease in the past – epilepsy, insult, encephalitis, meningitis, disorders of the CNS development
- other autoimmune disease
- history of specified diagnosis of depression, severe depressive episodes and/or treatment with antidepressants for symptoms of depression
- active inflammatory process
- alcohol and other psychotropic medications and substances abuse.

All participants signed an informed consent. Demographic data were collected. Neurological examination was performed. PrMRS was performed for both groups. Cho, Cr, and NAA levels were measured in ppm in fronto-parietal NAWM. Corresponding zones of interest were selected in healthy controls. The data obtained were compared.

Statistical analysis

The data obtained with PrMRS were analyzed using the independent samples t-test and the Mann-Whitney test. IBM SPSS statistics v. 23 was used for data processing.[7-12]

RESULTS

We studied 50 patients with clinically definitive RRMS. The distribution by sex was 29 (58%) female and 21 male (42%) MS patients. The individuals tested were 21-40 years old, with a mean age of 33±7 years, and duration of the disease of 4.85±2.68 years. The disease duration from the moment of diagnosis ranged between 5 months and 10 years. The control group counted 28 healthy controls. There were 14 female and 14 male subjects (50% : 50%), aged 27-40 years. The mean age was 33±5 years. All MS patients were employed on a full-time working day. There were 80% full-time employed healthy controls, 6% students and 6% unemployed individuals in the control group. The MS patients were on disease-modifying treatment (mean duration of the treatment of 2.40±2.21 years). They were in a stable condition – remission at least 2 months prior to the tests, (minimal period of since on disease-modifying treatment 3 months, maximum period 8 years and 8 months). EDSS score ranged from 1.0 to 3.5. The distribution by EDSS score was as follows: 1.0 – 16 patients (pts); 1.5 – 10 pts, 2.0 – 11 pts; 2.5 – 11 pts; 3.0 – 0 pts, and 3.5 – 2 pts. Pyramidal functions deterioration was found in 18.5% of the MS patients. Cerebellar system symptoms were found in 8% and sensory symptoms in 7.5% of the patients. There were no abnormal signs with disability for upper limbs. Only 5% had brainstem symptoms and 4.2% had bowel-bladder dysfunction. There were no patients with visual or cerebral function disability included.

All patients and healthy controls underwent conventional MRI and PrMRS. Concentrations of brain metabolites in zones free of demyelination plaques (NAWM) were measured, respectively Cho, Cr, and NAA. Metabolic ratios NAA/Cr, NAA/Cho, Cho/NAA, Cr/NAA, Cho/Cr were registered, respectively. The data of the MRI were analyzed and compared to the data of the control group of healthy individuals in the respective age group **(Fig. 2)**.

The data obtained were indicative of distinct changes in the metabolite concentrations with higher peaks registered in the MS patients.

Higher levels of Cho, Cr, and NAA were found in the MS patients. Statistically significant difference was found only when comparing the mean levels of Cr in healthy (controls) (x=61057±14334.29) and in patients (x=70228±17326.47) with a 5% risk of error. Kolmogorov-Smirnov test was ap-

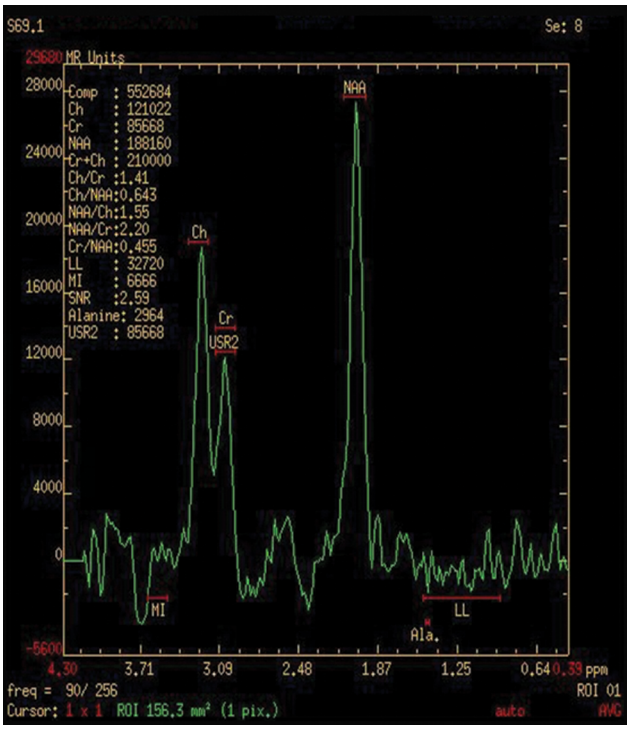

Figure 2. PrMRS – spectrogram of an MS patient. Graphical representation of the particular metabolites tested with marking the respective peak corresponding to the metabolite concentration measured (ppm).

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plied to check the normality of data distribution. The metabolites studied were not normally distributed. We applied the non-parametric Man-Whitney test for comparision **(Table 1)**.

Only the result of the comparison of the mean values of Cr had a *p*-value (p=0.025) lower than the risk of error (α=0.05). Therefore, it could be said with 95% probability of certainty that there was a statistically significant difference between the healthy controls and the MS patients regarding the mean levels of this metabolite.

To read the clinical significance of the changes of the brain metabolites found comparative analysis of the changes in the ratios between the metabolites measured was performed, as follows: Cho/Cr, Cho/NAA, Cr/NAA, NAA/Cho, and NAA/Cr. The comparision of the mean values of the NAA/Cr ratio in healthy controls and in MS patients found statistically significant difference respectively in healthy controls (x=2.59±0.46) and MS patients (x=2.36 ±0.45) with a 5% risk of error. In healthy controls, higher levels of the ratio were found.

The comparison of the mean values of the Cr/NAA ratio in healthy controls and MS patients found a difference in the mean values in healthy individuals (x=0.40±0.08) and MS patients (x=0.44±0.08), which was statistically significant with a 5% risk of error. Higher levels of the ratio were found in the MS patients.

When testing the ratios for normal distribution (Kolmogorov-Smirnov test) it turned out that only one ratio was normally distributed (NAA/Cr) and a parametric method of verifying the hypothesis about the difference between the mean values in MS patients and healthy controls was applied (T-test) for it. In all the rest non-parametric test (Mann-Whitney test) was applied to verify the differences **(Table 2)**.

The results of comparison of the NAA/Cr ratio between healthy controls and MS patients had a *p*-value (p=0.035) – smaller than the risk of error (α=0.05). Therefore, it could be claimed with a 95% probability of certainty that there was statistically significant difference between healthy controls and MS patients regarding the mean ratio of NAA/Cr metabolites.

The comparison of the Cr/NAA ratio between healthy controls and MS patients had a *p*-value (p=0.041) – smaller than the risk of error (α=0.05). Therefore, it could be claimed with a 95% probability of certainty that there was statistically significant difference between healthy controls and MS patients regarding the mean ratio of Cr/NAA metabolites.

Table 1. Comparative analysis between healthy controls and MS patients for Cho, Cr, and NAA mean values with non-parametric Man-Whitney test

Metabolite	Group	N	Mean	SD	*p*
Cho	Group*	28	78196.43	15798.724	0.122
	Group**	50	85682.92	20018.070	
Cr	Group*	28	61056.96	14334.289	0.025
	Group**	50	70227.98	17326.469	
NAA	Group*	28	153609.43	23048.165	0.151
	Group**	50	160673.88	28647.211	

Cho: choline; Cr: creatine; NAA: N-acetyl aspartate; *: healthy controls; **: MS patients

Table 2. Comparative analysis between healthy controls and MS patients for Cho, Cr, and NAA mean values with non-parametric Man-Whitney test

Ratio	Group	N	Mean	SD	*p*
NAA/Cr	Group*	28	2.592	0.458	0.035
	Group**	50	2.362	0.454	
Cho/Cr	Group*	28	1.332	0.384	0.567
	Group**	50	1.280	0.417	
Cho/NAA	Group*	28	0.512	0.098	0.525
	Group**	50	0.545	0.156	
NAA/Cho	Group*	28	2.025	0.392	0.525
	Group**	50	1.980	0.612	
Cr/NAA	Group*	28	0.398	0.076	0.041
	Group**	50	0.439	0.083	

*: healthy controls; **: MS patients

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There was a change in all the ratios studied in the group of MS patients.

Statistically significant difference was confirmed only for the NAA/Cr and Cr/NAA ratios.

Twice as many females are disease-prone than males.[3] A possible impact of sex on the changes of brain metabolites was studied. The statistical difference assumed between the ratios of the metabolites Cho/Cr, Cho/NAA, Cr/NAA, NAA/Cho, and NAA/Cr studied was analyzed according to sex.

Males

The Kolmogorov-Smirnov test for normality of data distribution revealed that only the Cho/Cr ratio was not normally distributed and non-parametric method of testing the hypothesis about the difference between the mean values in MS patients and healthy controls was applied (Mann-Whitney test). In all the rest, parametric test (T-test) was applied to verify the differences **(Table 3)**.

No statistically significant difference was found when comparing the two groups of individuals studied.

Females

The difference between the mean values in female healthy controls (x=2.74±0.39) and female MS patients (x=2.38±0.45) was statistically significant with a 5% risk of error. In female healthy controls, increased levels of the ratio were found.

The difference between the mean values in female healthy controls (x=0.44±0.08) and female MS patients (x=0.37±0.06) was statistically significant with 5% risk of error. In female MS patients, increased levels of the ratio were found.

When testing the ratios of normal distribution (Kolmogorov-Smirnov test), it turned out that NAA/Cr and Cho/Cr were normally distributed. A parametric method of testing the hypothesis about the difference between the mean values in female MS patients and female healthy controls (T-test) was applied for them. In all the rest, non-parametric test (Mann-Whitney test) was applied to verify the differences **(Table 4)**.

The result of the comparison of the NAA/Cr ratio between female healthy controls and female MS pa-

Table 3. Comparative analysis between male healthy controls and male MS patients for differences in metabolite ratios (Cho/Cr ratio analyzed with Mann-Whitney test, Cho/NAA, NAA/Cho, NAA/Cr, and Cr/NAA with independent samples t-test)

Ratio	Group	N	Mean	SD	*p*
Cho/Cr	Group*	14	1.264	0.432	0.567
	Group**	21	1.291	0.404	
Cho/NAA	Group*	14	0.515	0.115	0.436
	Group**	21	0.551	0.146	
NAA/Cho	Group*	14	2.031	0.438	0.453
	Group**	21	1.917	0.437	
NAA/Cr	Group*	14	2.447	0.490	0.530
	Group**	21	2.343	0.467	
Cr/NAA	Group*	14	0.423	0.083	0.505
	Group**	21	0.443	0.086	

*: male healthy controls; **: male MS patients

Table 4. Comparative analysis between female healthy controls and female MS patients for differences in metabolite ratios (NAA/Cr and Cho/Cr ratios with independent samples t-test, Cho/NAA, NAA/Cho and Cr/NAA with Mann-Whitney test)

Ratio	Group	N	Mean	SD	*p*
NAA/Cr	Group*	14	2.738	0.387	0.014
	Group**	29	2.376	0.451	
Cho/Cr	Group*	14	1.400	0.330	0.337
	Group**	29	1.272	0.433	
Cho/NAA	Group*	14	0.509	0.082	0.917
	Group**	29	0.541	0.165	
NAA/Cho	Group*	14	2.018	0.357	0.917
	Group**	29	2.026	0.717	
Cr/NAA	Group*	14	0.378	0.062	0.005
	Group**	29	0.436	0.082	

*: female healthy controls;**: female MS patients

tients had a p=0.014 p-value, smaller than the risk of error (α=0.05). Therefore, with a 95% probability of certainty, it could be claimed that there was a statistically significant difference between healthy controls and MS patients regarding the mean ratio of the NAA/Cr metabolites.

The result of the comparison of the Cr/NAA ratio between female healthy controls and female MS patients had a p=0.005 p-value, smaller than the risk of error (α=0.05). Therefore, with a 95% probability of certainty it could be said that there was a statistically significant difference between healthy controls and MS patients regarding the mean ratio of the Cr/NAA metabolites.

The results of the comparison between female healthy controls and female MS patients regarding the rest of the metabolites Cho/Cr, Cho/NAA, and NAA/Cho had a p-value greater than the risk of error (α=0.05). Therefore, with a 95% probability of certainty, it could be said that there was no statistically significant difference between healthy controls and MS patients regarding their mean ratios.

After verifying the difference between the changes found in the ratios between the brain metabolites and the sex of the individuals, it was found that only in females there was a statistically significant difference in the ratios studied.

Therefore, the female sex factor exerted considerable influence on the changes observed. The role of estrogen in the biosynthetic processes was to be considered.

DISCUSSION

Cho is a marker of cellular and membrane turnover. Therefore, an increased level of choline phospholipids is found. The reference about the stages preceding the appearance of a new plaque of demyelination in NAWM reports the increase of the levels of Cho metabolites. The data correspond to the changes found in NAWM in MS patients with PrMRS presented in studies of other research groups.[13] The increased levels of Cho reflect increased activity of Cho metabolism. Cho provides structural integrity and signal function of the cellular membranes. As a phospholipid component (phosphatidylcholine and sphingomyelin), it builds up the cellular membrane. It participates in the formation of the myelin sheath of the nerve fibers.[14,15] The changes found are in the zones free of demyelination. Regarding the levels of Cr, a difference is found between the two groups again with higher levels of the metabolite tested in the group of the MS patients. Cr is a marker of the energy homeostasis. The data obtained show increased energy exchange, i.e. intensity of the biochemical processes in NAWM in the MS patients tested. Statistically significant differences have been read only for Cr and that for the MS patients.[13] This fact can be interpreted as an increase of the energy utilization in NAWM. The increased energy resources and activity are probably related to a necessity of conducting an electrical signal under the conditions of changed ion homeostasis[16] – role of the virtual hypoxia[17,18] in the demyelinated axons, and they are also a testimony of active metabolite biosynthetic processes. Cr is a marker of energy reserve, and NAA – of neuronal integrity. The data obtained show statistically significant changes in the energy homeostasis and neuronal and glial integrity. From the analysis of the changes, it could be assumed that there is an increased energy exchange in the NAWM zones of interest, considering the maintenance of neuronal integrity. Previous studies showed decreased NAA/Cr ratio within the plaques of demyelination in MS patients. Decreased NAA/Cr and elevated Cho/NAA ratios in NAWM in MS patients when compared to healthy controls were also reported.[13,19,20] The findings were registered at an early stage of the disease development.[21] Decrease in NAA/Cr ratio is found also in normal appearing gray matter regions without inflammatory infiltration.[19] Comparative data analysis in our study revealed decrease in NAA/Cr ratio in RRMS patients which corresponds to data from published studies on metabolite changes in MS patients.[13,20,21] Statistically significant difference between both groups was found. The changes found in the brain metabolites and their ratios in NAWM show the presence of morphological changes in the white brain matter. These changes are an early indicator of breaking out of energy and structural disorders which, in turn, provoke disorders of the neuron-neuron communication and a potential of disconnection occurring.[22] An original study of brain tissue abnormalities in NAWM in MS patients treated with disease-modifying therapy and with no evidence of clinical activity of the disease is presented. An original comparative study of the metabolite pattern of NAWM in MS patients and healthy controls is presented. Sex-determined differences in the metabolite pattern of NAWM in patients with RRMS are found.

CONCLUSIONS

The use of PrMRS in our study proved metabolic changes in the regions free of demyelination (NAWM), which suggested the presence of parallel pathologic process prior to the appearance of demyelination plaque. Increased levels of Cho, Cr, and NAA in NAWM in patients with MS were measured. Statistically significant difference when comparing the NAA/Cr and Cr/NAA ratios in female MS patients was found.

Funding

The authors have no funding to report.

Disclosure statement

The authors declare no actual or potential conflicts of interest.

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Нормальный вид метаболитов белого вещества и половые различия у пациентов с рассеянным склерозом по сравнению со здоровыми пациентами контрольной группы

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Дата получения: 16 марта 2021 ♦ **Дата приемки:** 13 мая 2021 ♦ **Дата публикации:** 31 октября 2022

Образец цитирования: Petrova V, Genov K. Normal appearing white matter metabolite pattern and sex differences in multiple sclerosis patients compared to healthy controls. Folia Med (Plovdiv) 2022;64(5):746-753. doi: 10.3897/folmed.64.e66002.

Резюме

Введение: Протонная магнитно-резонансная спектроскопия (PrMRS) выявляет изменения уровня метаболитов в головном мозге *in vivo*.

Цель: Целью настоящего исследования было оценить метаболиты головного мозга холина (Cho), креатина (Cr) и N-ацетиласпартата (NAA) в нормально выглядящем белом веществе без поражений (NAWM) у пациентов с рецидивирующе-ремиттирующим рассеянным склерозом (RRMS) по сравнению со здоровыми пациентами контрольной группы. Вторая цель заключалась в изучении влияния пола на изменения метаболитов в головном мозге.

Материалы и методы: Пятьдесят пациентов с RRMS получили оценку PrMRS областей NAWM головного мозга. Результаты сравнивали с результатами 28 здоровых демографически сопоставимых пациентов контрольных групп.

Результаты: Мы обнаружили повышенные уровни Cho, Cr и NAA в NAWM у пациентов с рассеянным склерозом по сравнению со здоровыми пациентами контрольной группы. Соотношения NAA/Cr и Cr/NAA сопоставляли. Статистически значимая разница между обеими группами была обнаружена только для соотношений NAA/Cr и Cr/NAA. Это связано с изменениями метаболитов у больных женского пола с рассеянным склерозом.

Заключение: Результаты настоящего исследования с использованием PrMRS подтвердили метаболические изменения при NAWM. Следует предполагать сопутствующий патологический процесс, предшествующий развитию бляшек демиелинизации. Гендерное воздействие требует дальнейшего изучения.

Ключевые слова

разъединение, пол, магнитно-резонансная спектроскопия