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Apparent diffusion coefficient measurements in normal appearing white matter may support the differential diagnosis between multiple sclerosis lesions and other white matter hyperintensities

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ABSTRACT

Aims: The objectives of the study were to assess the usefulness of measurements of apparent diffusion coefficient (ADC) in normal appearing white and grey matter (NAWM, NAGM) in differential diagnosis between patients with hyperintense demyelinating plaques in the course of multiple sclerosis (MS) and other conditions presenting white matter hyperintensities (WMHs), as well as to evaluate the relationship between clinical data and ADC values in MS patients.

Material and methods: The study comprised 66 patients with MS before treatment, 66 patients with WMHs and 64 control subjects (control group, CG), who underwent MRI (magnetic resonance imaging) examination including diffusion weighted imaging (DWI) with a 1.5 T MR unit. ADC measurements were obtained from NAWM of the cerebellum, pons as well as frontal, fronto-parietal and temporal regions bilaterally, and from NAGM of thalami and heads of caudate nuclei, using round region of interest (ROI) sized 200mm^2.

Results: The mean ADC values in frontal, fronto-parietal and temporal NAWM were significantly higher in the MS group than in subjects with WMHs and CG ($p < .001$), whereas the mean ADC value in pons was higher in MS than in CG ($p < .05$). In the MS group we observed a positive correlation between the Expanded Disability Status Scale (EDSS) and lesion load, between duration of the disease and mean ADC values and between lesion load and mean ADC values.

Conclusion: Our results suggest that ADC measurements may support the differential diagnosis between MS and other conditions associated with white matter hyperintensities. The most significant changes were observed in temporal white matter regions.

1. Introduction and aims

Multiple sclerosis (MS) is a chronic, inflammatory disease that causes demyelination, inflammation, gliosis and neuronal loss in the central nervous system (CNS), affecting most frequently young people, with a predominance in women. It is an important social problem as it leads to significant disability [1,2]. The diagnosis of MS is made on the basis of clinical manifestations and results of imaging and laboratory findings. Magnetic resonance imaging (MRI) is one of the paraclinical tools included in the current McDonald diagnostic criteria, which supports confirmation of the diagnosis of MS and allows the follow-up of the course of the disease. The other important role of MR is to provide radiological features which may rule out MS [2,3].

Hyperintense lesions in white matter on T2-weighted and FLAIR images, although typical for MS, are not disease-specific. Demyelinating plaques require differentiation mainly with very common white matter

Abbreviations: MS, multiple sclerosis; WMHs, white matter hyperintensities; CG, control group; CSVD, cerebral small vessel disease; MRI, magnetic resonance imaging; ROI, region of interest; NAWM, normal appearing white matter; NAGM, normal appearing grey matter; NABT, normal appearing brain tissue; DWI, diffusion-weighted imaging; ADC, apparent diffusion coefficient; DTI, diffusion tensor imaging; MD, mean diffusivity; FA, fractional anisotropy; MRS, magnetic resonance spectroscopy; PWI, perfusion-weighted imaging; EDSS, Expanded Disability Status Scale; ROC, receiver-operating characteristic; RIS, radiologically isolated syndrome

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hyperintensities (WMHs) caused by cerebral small vessel disease (CSVD) [4,5], with WMHs concomitant with migraine [6,7] or even incidentally seen WMHs in healthy individuals [8], which could mimic MS-lesions [3]. The differential diagnosis is particularly important in patients with an atypical clinical manifestation of MS, late onset of MS or coexisting risk factors for cerebrovascular disease [3,9], as well as in cases of suspected cerebral vasculitis in the course of connective tissue diseases, which can mimc MS both clinically and radiologically [10].

Plain MRI findings of CSVD include the presence of WMHs and/or recent small subcortical infarcts and/or lacunes and/or prominent perivascular spaces and/or cerebral microbleeds and/or atrophy, which may have been symptomatic or asymptomatic. CSVD more often pertains to older people [4], whereas younger age is more suggestive of MS [9]. However, it should be stressed that even young people, especially affected by migraines or tension headaches, may exhibit multiple WMHs [7], which make a correct diagnosis even more difficult [3].

MRI differentiation between the MS plaques and WMHs in CSVD is usually possible on the basis of different lesion distribution patterns: in the case of MS juxtacortical (abutting the cortex), cortical, periventricular (abutting lateral ventricles), pericallosal, callosal, infratentorial and spinal cord locations are predominant [2], while in the case of CSVD a subcortical and brainstem distribution is the most frequent [4]. Unfortunately, the distribution pattern may not suffice in equivocal cases [2,10]. Migraine- and headache-associated WMHs typically resemble those in CSVD - small, round lesions sparing the juxtacortical region. However, it was reported that they may fulfil the radiological criteria of MS even in 34,5% of cases [6].

It seems reasonable to find additional diagnostic tools to support the distinction of MS and other WMHs, which would be useful in everyday radiological practice.

Recently, with the development of advanced MRI techniques such as MRS (magnetic resonance spectroscopy), DWI (diffusion-weighted imaging), DTI (diffusion-tensor imaging) and PWI (perfusion-weighted imaging) it has been evidenced that the pathological process in multiple sclerosis is not confined selectively to demyelinating plaques, but is diffuse and also affects the so-called normal-appearing white and grey matter (NAWM, NAGM) [11–13]. These techniques are presumed to be a very useful tool in understanding the pathological processes occurring in plaques and in normal appearing brain tissue (NABT) in patients with MS [14], as well as in prognosing and monitoring effectiveness of immunomodulatory treatment [15,16].

DWI is a technique based on the random movements of the water molecules in extracellular space which provides an assessment of tissue integrity. Measurements of a mathematically calculated diffusion coefficient (apparent diffusion coefficient, ADC) allow detection of changes in the overall diffusion of water molecules irrespective of the direction of motion. Even subtle pathological impairment which disturbs the tissue architecture may result in a facilitated mobility of water molecules and consequently in increased values of ADC [14]. On the contrary, decline of extracellular space leads to the restriction of diffusion and decreased values of ADC [17].

In the literature there is a scarcity of data comparing ADC values of NAWM and NAGM between patients with MS and other WMHs. The aim of our study was to assess the usefulness of ADC measurements within NAWM and deep NAGM in the differential diagnosis between patients with white matter hyperintensities in the course of MS and other entities, as well as to explore the potential correlations between the radiological (lesion load, mean ADC values in NAWM and NAGM) and clinical (Expanded Disability Status Scale - EDSS, duration of the disease) features.

2. Material and methods

2.1. Group characteristics

The study comprised 196 patients divided into three groups:

Table 1
Clinical and demographic data in investigated groups: MS – patients with multiple sclerosis, WMHs – patients with white matter hyperintensities, CG – control group.

	MS	WMHs	CG
Mean age (years, range)	37.5 (19–61)	35.2 (21–59)	35.9 (20–61)
Gender			
Male	18	19	18
Female	48	47	46
Duration of MS (years, range)	2.2 (0.08–17.5)	N/A	N/A
Baseline EDSS (mean, range)	2.2 (1–7)	N/A	N/A
Number of hyperintense white matter lesions (mean, range)	18.4 (1–45)	9.1 (2–44)	0

EDSS – expanded disability status scale, N/A – not applicable.

- MS: treatment-naïve patients with clinically defined MS (n = 66, 48 women, 18 men; average age: 37.5; age ranged from 19 to 61), according to current McDonald's criteria;
- WMHs: patients with white matter lesions distributed typically for CSVD (n = 66, 47 women, 19 men; average age: 35.2 years, age ranged from 21 to 59),
- CG: control group of patients with no intracranial pathology (n = 64, 46 women, 18 men; average age: 35.9 years, age ranged from 20 to 61).

The clinical and demographic characteristics of the studied groups are shown in Table 1.

The inclusion criteria for patients with MS were as follows:

1. Clinically defined relapsing-remitting course of MS;
2. No treatment with any immunomodulatory therapy before MR examination;
3. Up to 50 cerebral hyperintense lesions visible on conventional MRI;
4. No visible changes on conventional MRI sequences within the white and grey matter within regions of interest.

All MS patients who did not fulfil the criteria mentioned above were excluded.

In each MS patient the duration and type of the disease were determined on the basis of medical records. Disability was evaluated using EDSS, by an experienced neurologist. A lesion load was evaluated as a total number of plaques visible on T2-weighted and FLAIR images, counted by an experienced radiologist.

The group of patients with WMHs consisted mainly of patients diagnosed for other reasons (including headache, vertigo, or tinnitus). Patients with a diagnosed brain tumour, inflammatory process, epilepsy or after any intracranial surgical procedure were excluded.

The control group consisted of sex- and age-matched persons diagnosed due to headache, vertigo or tinnitus without any WMHs or another visible intracranial pathology on MRI, who were considered as healthy subjects.

This retrospective case-control study followed ethical rules and was approved by the local Ethics Committee. Each patient signed an informed consent before participation in the MR examination.

2.2. Image aquisition

MR examinations were performed with a 1.5 T Signa Hdx (GE Healthcare) MR scanner using a 16-channel HNS coil. The conventional MR imaging protocol for MS patients included sagittal and coronal T2-weighted FRFSE, axial T1-weighted SE, T2-weighted FSE and FLAIR sequences, axial DWI SE/EPI sequence and gadolinium-enhanced T1-weighted 3D-FSPGR images. Patients with WMHs and healthy subjects were examined with the same protocol except for contrast administration.

DWI was performed in all patients using an axial single shot, spin-

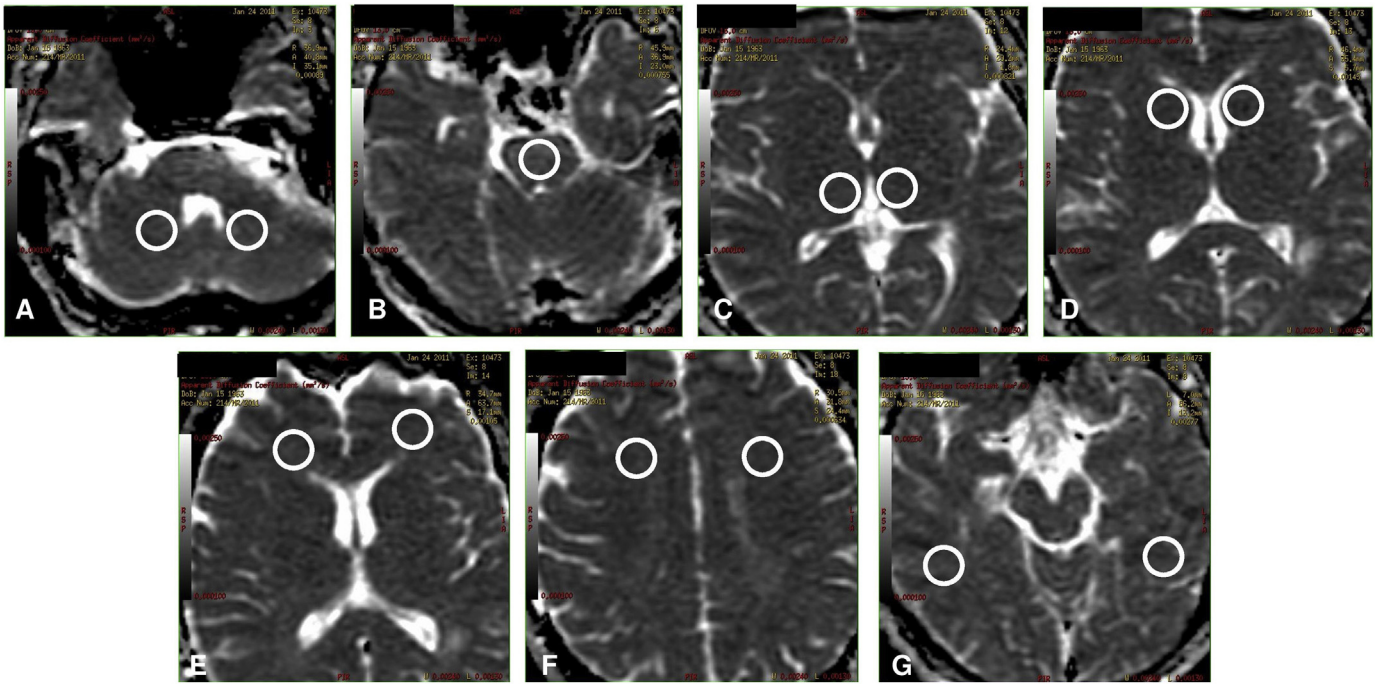

Fig. 1. Representative ADC maps (transverse cross-section) indicating regions of interest (ROIs) placement. Measurements of ADC were obtained from regions of NAGM and NAWM, as follows:
- 1, 2 – cerebellar white matter right and left, respectively (a).
- 3 – pons (b).
- 4, 5 – thalamus right and left, respectively (c).
- 6, 7 – caudate nuclei right and left, respectively (d).
- 8, 9 – frontal white matter regions right and left, respectively (e).
- 10, 11 – fronto-parietal white matter at the convexity right and left, respectively (f).
- 12, 13 – temporal white matter of inferior temporal gyri right and left, respectively (g).

echo type echo-planar images b = 0 and b = 1000 mm^2/s (TR 8000 ms, TE 89.9 ms, FOV 26 cm, matrix 128 × 128), thickness: 5 mm, spacing: 0, time of acqusition: 40 s.

2.3. Image analysis and statistics

DWI data were transferred to a GE Advantage Workstation 4.6 and post-processed using Functool software, provided by the manufacturer. ADC values were obtained by placing a regions of interest (ROI), sized approx. 200mm^2 with DFOV = 13.0 cm on ADC maps in the following selected NAWM and NAGM regions:

- 1, 2 – cerebellar white matter, right and left, respectively (Fig. 1a).
- 3 – pons (Fig. 1b).
- 4, 5 – thalamus, right and left, respectively (Fig. 1c).
- 6, 7 – caudate nuclei, right and left, respectively (Fig. 1d).
- 8, 9 – frontal white matter regions, right and left, respectively (Fig. 1e).
- 10, 11 – fronto-parietal white matter at the convexity, right and left, respectively (Fig. 1f).
- 12, 13 – temporal white matter of inferior temporal gyri, right and left, respectively (Fig. 1g).

ROIs were put in particular location under visual control using T2-weighted images or FLAIR images in order to avoid measurements from demyelinating plaques or other white matter hyperintensities. Fig. 2 depicts analogous slices of the same patients from Fig. 1 on T2-weighted imaging with visible demyalinating plaques and areas, where ROIs were placed on ADC map in normal appearing white and grey matter.

We decided to choose many regions of interest in order to get a more comprehensive insight in a potentially diffused pathology involving NAWM and NAGM.

2.4. Statistical methods

The difference in gender between groups was assessed using the Chi-square test. Statistical analysis was performed using the ANOVA post hoc Scheffé test to evaluate differences in age and mean ADC value of each ROI among the groups. In MS group correlations between EDSS, duration of the disease, lesion burden and mean value of ADC in any of the 13 ROIs were calculated using Spearman correlation coefficient.

Additionally, in order to assess sensitivity, specificity and accuracy of ADC measurements in NAWM and NAGM distinguishing MS patients and subjects with other WMHs, receiver-operating characteristic (ROC) analysis was performed for ADC values showing the most significant differences between the groups. The rate of accuracy was based on the area under the ROC curve.

The level of significance was set at $p < .05$.

3. Results

There were no significant differences in age (analysis of variance; $p = .92$) and sex distribution ($p = .98$) among the evaluated groups of subjects.

3.1. Comparison of ADC values among the MS group, WMHs group and CG

In the examined regions of the brain, the mean ADC values were statistically significantly higher in the MS group in comparison to WMHs and CG in ROIs: 8, 9, 10, 11, 12 and 13 (in frontal, fronto-parietal and temporal WM, bilaterally) ($p < .001$).

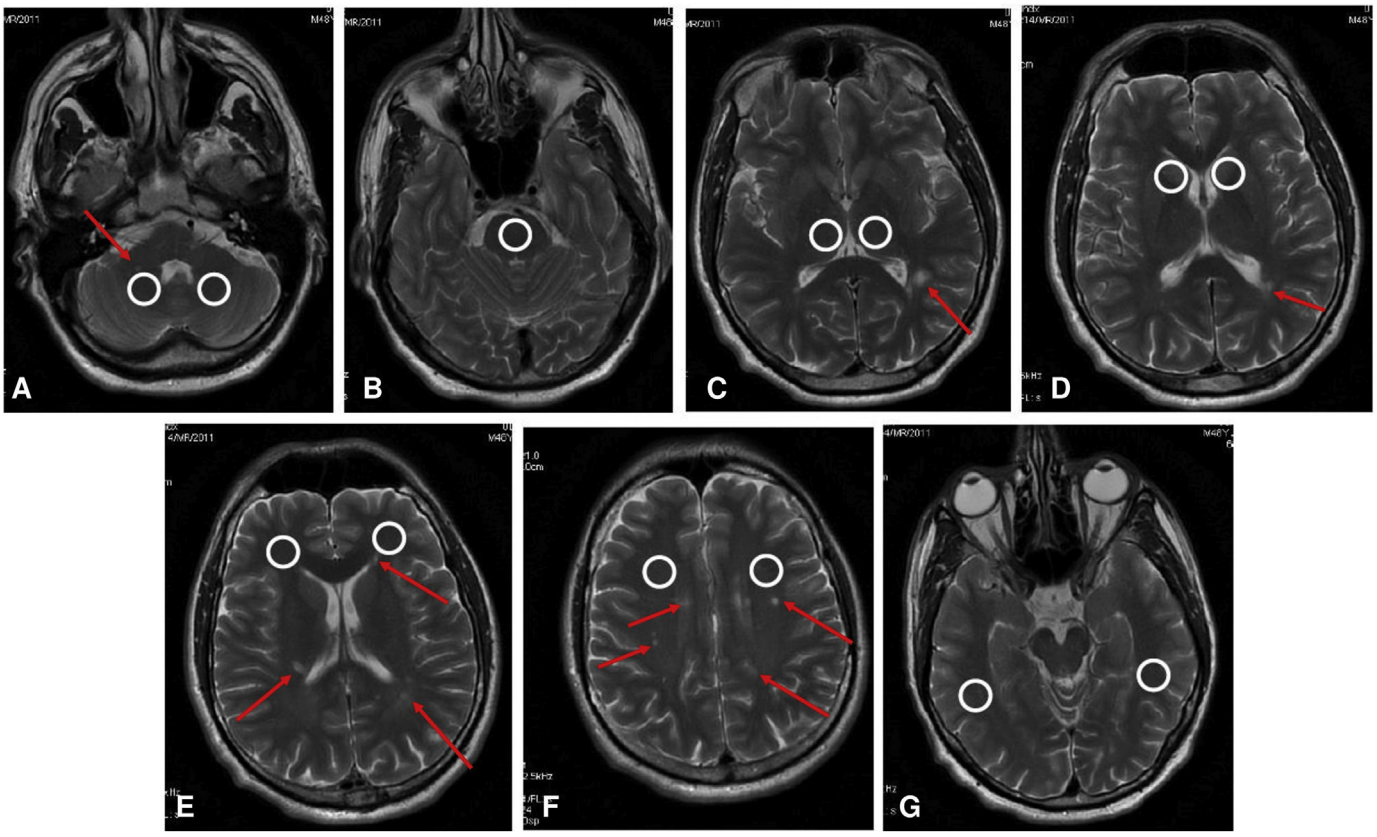

Fig. 2. T2-weighted images at the same levels of the patients shown in Fig. 1. – ROIs (round) are placed in normal appearing white and grey matter, which do not encompass demyelinating hyperintense plaques (arrows).

In ROI 3 (pons) the ADC value was significantly higher in patients with MS than in CG ($p < .05$), but no difference was found in this location in comparison to WMHs.

No other statistically significant differences in ADC values between groups were found (Table 2).

The mean ADC value obtained from ROIs: 8, 9, 10, 11, 12 and 13 ROC curves and cut-off values with accuracy were designed (Table 3). All ROC curves demonstrated good diagnostic accuracy with the area under the curve from 0.70 to 0.77. When a cut-off value for NAWM in the right temporal lobe (ROI 12) was set at $0.800 \times 10^{-3}\,mm^2/s$, the sensitivity and specificity of ADC value in distinguishing patients with MS from other WMHs was 51% and 93% respectively with an accuracy of 77%. When a cut-off ADC value for NAWM in the left temporal lobe (ROI 13) was fixed at $0{,}790 \times 10^{-3}\,mm^2/s$ the sensitivity and specificity reached 59% and 84% respectively, with 76% accuracy (Fig. 3), (Table 3).

3.2. Correlations among mean ADC value of NAWM, lesions load, EDSS value and duration of the disease

In the MS group there was a positive correlation between EDSS and lesion load ($r = 0.32$, $p < .01$).

We also found a positive correlation between duration of the disease and mean ADC values in ROIs: 8, 9, 11, 12, 13 (in right and left frontal,

Table 2
Mean ADC values in patients with MS, WMHs and CG for each ROI with ANOVA post hoc Scheffe test results. Statistically significant differences between groups are marked in bold.

	Mean ADC value ($x10^{-3}\,mm^2/s$)			ANOVA post hoc Scheffe test $p < .05$		
	MS	WMHs	CG	MS vs CG	MS vs WMHs	WMHs vs CG
ROI 1 – right cerebellar white matter	0.734	0.728	0.735	0.57	0.06	0.43
ROI 2 – left cerebellar white matter	0.735	0.731	0.736	0.52	0.10	0.62
ROI 3 – white matter of pons	**0.750**	0.736	**0.733**	**0.02**	0.09	0.84
ROI 4 – right thalamus	0.754	0.746	0.747	0.68	0.50	0.96
ROI 5 – left thalamus	0.752	0.745	0.745	0.98	0.99	0.99
ROI 6 – right caudate nucleus	0.747	0.739	0.737	0.49	0.69	0.94
ROI 7 – left caudate nucleus	0.745	0.735	0.735	0.65	0.69	0.99
ROI 8 – right frontal white matter	**0.810**	0.768	0.764	**< 0.001**	**< 0.001**	0.88
ROI 9 – left frontal white matter	**0.822**	0.777	0.770	**< 0.001**	**< 0.001**	0.50
ROI 10 – right fronto-parietal white matter	**0.767**	0.720	0.714	**< 0.001**	**< 0.001**	0.66
ROI 11 – left fronto-parietal white matter	**0.760**	0.716	0.713	**< 0.001**	**< 0.001**	0.85
ROI 12 – right temporal white matter	**0.798**	0.766	0.771	**< 0.001**	**< 0.001**	0.61
ROI 13 – left temporal white matter	**0.795**	0.770	0.773	**< 0.001**	**< 0.001**	0.79

MS – patients with multiple sclerosis, WMHs – patients with other white matter hyperintensities, CG – control group, ADC – apparent diffusion coefficient.

Table 3
Results of ROC analyses for ADC values in ROIs: 8–13 with the most significant results marked in bold.

	MS vs CG				MS vs WMHs			
	Cutoff ADC value ($x10^{-3}$ mm^2/s)	Sensitivity	Specificity	Accuracy	Cutoff ADC value ($x10^{-3}$ mm^2/s)	Sensitivity	Specificity	Accuracy
ROI 8 – right frontal white matter	0.810	0.40	0.95	0.74	0.770	0.77	0.60	0.73
ROI 9 – left frontal white matter	0.790	0.69	0.75	0.77	0.780	0.80	0.57	0.71
ROI 10 – right fronto-parietal white matter	0.750	0.60	0.82	0.75	0.750	0.60	0.74	0.70
ROI 11 – left fronto-parietal white matter	0.740	0.59	0.81	0.74	0.730	0.69	0.62	0.70
ROI 12 – right temporal white matter	0.790	0.56	0.84	0.74	0.800	**0.51**	**0.93**	**0.77**
ROI 13 – left temporal white matter	0.790	0.59	0.81	0.74	0.790	**0.59**	**0.84**	**0.76**

MS – patients with multiple sclerosis, WMHs – patients with other white matter hyperintensities, CG – control group, ADC – apparent diffusion coefficient.

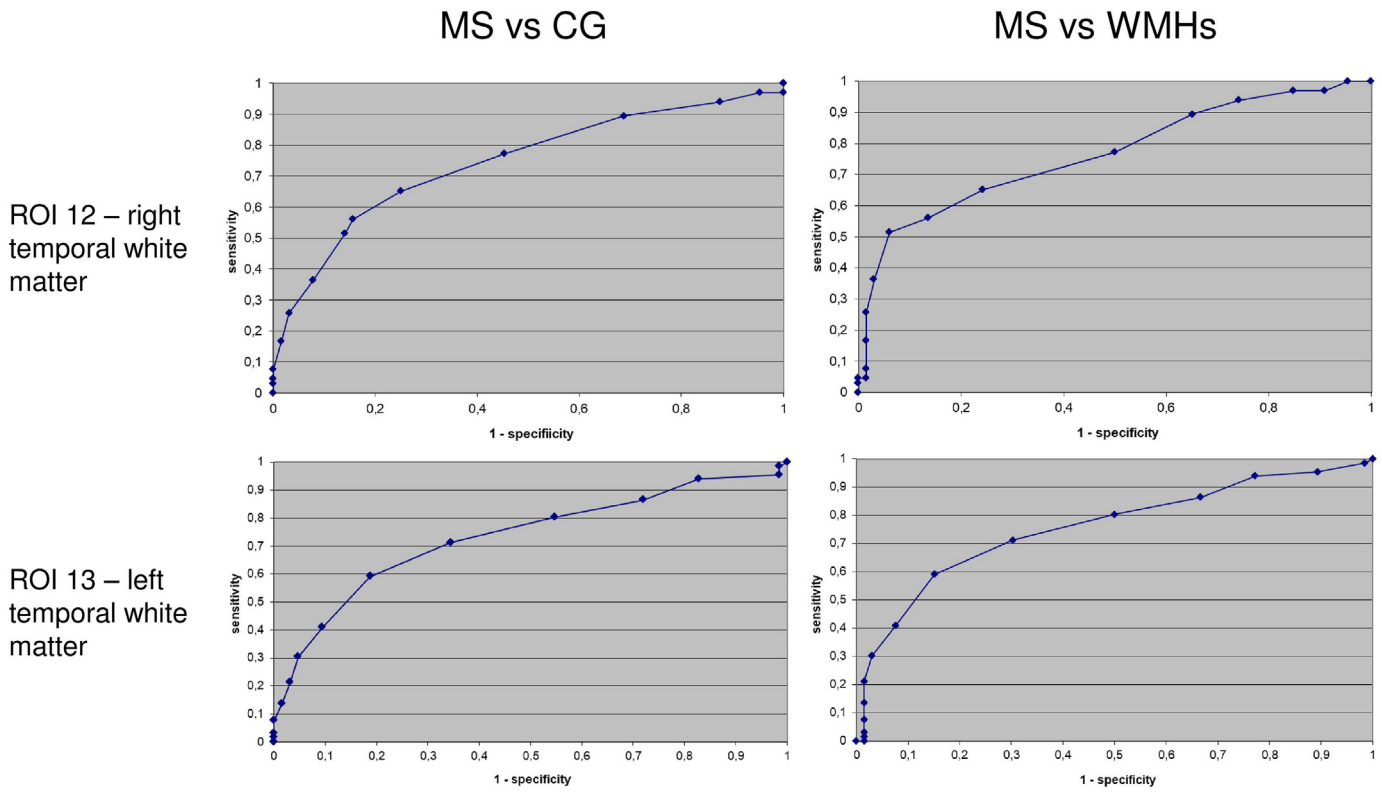

Fig. 3. The receiver-operating characteristic (ROC) curves for mean ADC value from the NAWM in the right temporal white matter(ROI 12) and the left temporal white matter (ROI 13), − ROC curves for comparison between MS patients and control group (left part of the figure), − ROC curves for comparison between MS patients and WMHs group (right part of the figure).

left fronto-parietal, right and left temporal WM) (r = 0.25–0.38 $p < .05$) as well as a positive correlation in ROI 10 (right fronto-parietal) (r = 0.42, $p < .001$).

There was also a positive correlation between lesion load and mean ADC value in ROIs: 4, 5, 8, 9, 10, 11 and 13 (both thalami, frontal and fronto-parietal ROI's as well as left temporal WM) (r = 0.27–0.34, $p < .05$).

There were no other significant correlations between EDSS value, duration of the disease, lesion burden and mean ADC value.

4. Discussion

Numerous MRI studies have recognised the alterations of diffusion in acute and chronic demyalinating plaques [13,14] and in periplaque white matter [15,18,19]. Recently, studies concerning normal appearing white and grey matter in MS have drawn more attention [5,12,20,21]. It is believed that white and grey matters which appear normal on conventional MRI are also involved by pathological process in the course of MS [18,20,22]. There are a few explanations of this phenomenon in the literature. First of all, the conventional MRI 1.5 T or 3 T may be not sufficient in depicting all demyelinating lesions either in white or grey matter – the use of more specific protocols on 3 T or 7 T devices enables the detection of more lesions in areas presumed to be NAWM or NAGM on conventional MRI [23]. Second, diffusion abnormalities can precede the formation of new demyelinating plaques [14]. Thirdly, although MS is thought to be a primarily demyelinating disease, the pathological process leading to axonopathy occurs parallel beyond the plaques even during the early stage of the disease [24,25]. Histopathologic studies supported this approach and revealed that damage of white matter could result from axonal destruction, which may be due to Wallerian degeneration [26] or due to lack of trophic support from oligodendroglia and on-going active demyelination [22]. Moreover, it has been reported that NAWM in MS contains activated microglia even when axonal pathology or myelin loss is absent [27].

Importantly, data obtained from post-mortem histopathologic and radiologic studies are in favour of the association between axonopathy and alterations of DWI measurements [28]. Additionally, it is postulated that the microstructural changes of NAWM and NAGM described above could be involved in the complex process responsible for the development of the disability in MS [24,26].

Most MRI studies have depicted increased ADC or MD (mean diffusivity) values and decreased FA (fractional anisotrophy) values in NAWM and NAGM in MS patients [12,18,25]. According to these studies a facilitated diffusion in NAWM may reflect either demyelination or axonal loss, which both trigger reduction of restricting structural barriers [17,18,25]. There have also been reported conflicting data showing no significant differences in diffusion parameters between MS patients and healthy controls [5,29] or features of decreased diffusion in DWI and DTI, which are hypothesised to be related to cell swelling in the course of acute demyelination [20,30]. Large individual variety of MS clinical and radiological presentation should be also considered, while interpreting these data.

Our study, in line with most of the previous reports [12,18,19,25], showed that NAWM is affected especially in pons and in both frontal, fronto-parietal and temporal regions in MS patients, even in patients at the early stage of the disease and with predominantly mild disability (mean EDSS 2.2), which may hypothetically be attributed to early axonopathy [22,26,28].

CSVD is seen usually in older individuals, but it could be encountered in a younger cohort as well. CSVD is characterised by the presence of focal lesions, which are commonly hyperintense on T2WI and FLAIR. However, nowadays it is postulated to perceive CSVD as a whole-brain disease [4]. Some DWI and DTI studies support this attitude. Alterations of FA and mean diffusivity were described in white matter hyperintensities and in NAWM of older patients with CSVD, which indicate that white matter integrity in WMHs as well as in NAWM is impaired [31,32]. Diffusion abnormalities in CSVD are explained by diffuse involvement of small arteries resulting in hypoperfusion, gliosis and enlargement of the extracellular space [5,31].

Data concerning alterations of diffusion in NAWM in patients with migraine and/or tension headache are limited [7,33]. Beckman et al. have found only a slight increase of the mean ADC value in NAWM of occipital lobes in a heterogenous group of patients with headache or migraine compared to healthy controls and no differences in mean ADC value measured in pons, thalami, and centrum semiovale between examined groups. Increase of ADC in occipital WM is speculated to be associated with microstructural vascular changes related to headache [7]. Orsi et al. in a small ($n = 15$) sample of patients with a migraine did not find any difference in ADC value in NAWM compared with healthy subjects [33].

Contrary to most of the above-mentioned studies [7,31,32], but in keeping with the results of Orsi et al. [33], in the present study we did not find any diffusion alterations in ADC measurements in NAWM and NAGM in the group of other WMHs compared to CG. Our results could be associated with the younger age of our cohort, which was age-matched to MS patients.

There is a scarcity of data regarding comparison between ADC measurements in NAWM and NAGM in differential diagnosis of patients with MS lesions and other WMHs. Zivadinov et al. examined values of PWI and DWI in differential diagnosis between acute vs chronic and ischaemic vs demyelinating lesions and perilesional white matter. They found that patients with ischaemic lesions have prolongated mean transient time and higher ADC values in lesions and in perilesional WM compared to MS [13]. Oztoprak et al. examined ADC of NAGM of both thalami in MS, CSVD and CG and they reported increased ADC values of both thalami in the course of CSVD and normal ADC values in MS compared to CG [5]. Both mentioned studies were conducted irrespective to the subtype of MS and no data about immunomodulatory treatment was provided in those reports. In addition, in these studies older patients with CSVD were compared with the younger cohort of MS patients, which could have biased the results. In one study comparing ADC in NAWM between patients with relapsing-remitting MS and migraine and CG, there were found no statistically significant differences but MS patients were chronically treated with immunomodulatory agents, which could have influenced the results [33].

The advantage of our study was the inclusion of the homogenous group of MS patients with regard to subtype (only relapsing-remitting) and immunomodulatory treatment (only treatment-naïve patients) as well as a selection of age-matched patients with other WMHs. This selection is justified by pursuit to set up common situations from everyday clinical practice, when there is a need to classify WMHs as demyelinating or other lesions particularly in young patients suspected with MS.

In opposite to Oztoprak research [5], in our study the mean ADC values in both thalami of patients with MS, WMHs and control group were comparable. Moreover, ADC values of patients with other WMHs in all ROIs of NAWM and NAGM did not differ significantly from those obtained in the CG. On the other hand ADC values in NAWM in frontal, fronto-parietal and temporal regions bilaterally (ROIs 8–13) were significantly higher in MS patients than in WMHs subjects and CG group ($p < .001$). According to our results the measurement of ADC in these locations (ROIs 8–13), particularly in NAWM of temporal lobes, could help in differential diagnosis of MS and other conditions associated with WMHs in the radiologically equivocal cases, with accuracy ranging from 70% to 77% (Table.3).

Regarding the associations between diffusion parameters and lesion load, clinical disability and duration of the disease, controversial results have been reported. Moderate to strong correlation between EDSS and lesion load and FA value of NAGM [20], low positive correlation between EDSS and increased MD [25] or increased ADC in NAWM [18,29], have been shown, whereas Temel et al. found no correlation of these metrics [19]. The results of our study also demonstrated a lack of correlation between elevated ADC values in NAWM and EDSS, which may be associated with the predominantly mild degree of clinical disability in our patients. On the other hand, we found that increased ADC values of NAWM in frontal, fronto-parietal and temporal white matter regions were significantly correlated with duration of the disease and lesion load ($p < .05$), which suggests that demyelinating white matter lesions could weaken axonal integrity and lead to subsequent Wallerian degeneration and neuronal impairment in distant white matter.

We did not find a strong correlation between EDSS and lesion load ($r = 0.32, p < .01$), what is in accordance with the well-known clinico-radiological paradox, explained by the failure of conventional MRI to detect all subtle microstructural changes of the so-called normal appearing brain tissue, which may have an influence on development and degree of disability [24,34].

There are some limitations of our study. Patients with WMHs were chosen from young (mean age 35.2 years) patients suffering from headache, vertigo, or tinnitus, whose WMHs were diagnosed by chance, and the number of WMHs were usually less pronounced than the lesion load in patients with MS. However, we assumed that it is more important to match patients of both groups with respect to age than of lesion burden, due to the purpose of our study.

The control group consisted of patients diagnosed with vertigo, tinnitus, or headache but without any intracranial pathology instead of healthy volunteers, which might affect the results, too. On the other hand, the most important aim of our study was to assess the usefulness of ADC measurement in differential diagnosis between MS lesions and other WMHs found in examined patients as a simple and easy tool which could be incorporated into everyday clinical practice.

5. Conclusions

To conclude, ADC measurement is a noninvasive and simple technique, which may allow for a better insight into the pathology of NAWM during the course of MS by providing data about

microstructural changes which are not visible on conventional MR.

With increasing availability of MRI, numerous cases of WMHs are being found in persons without clinical symptoms suggestive for MS and need to be differentiated between RIS (radiologically isolated syndrome) and other conditions (with inflammatory, vascular or metabolic background) causing multiple cerebral lesions or clinically insignificant findings. In our opinion measurements of ADC values in routinely performed DWI in NAWM of the frontal, fronto-parietal and particularly temporal white matter regions, seems to be a useful method in differentiation between inconclusive MS cases and patients presenting other WMHs, which could be a real diagnostic problem in everyday clinical practice, especially in young patients.

Conflict of interest

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

The authors declare that they have no conflict of interest.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent was obtained from all individual participants included in the study.

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