Age-related changes of white matter structures in multiple sclerosis patients measured by diffusion MR imaging

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Purpose

Normal brain development is a complex and dynamic process exhibiting a high degree of variability across the lifespan. Existing age-related magnetic resonance imaging (MRI) volumetric studies have revealed an increase in sulcal volume and an enlargement of the lateral ventricles, accompanied by a shrinkage in brain tissue volume [1,2] occurring predominantly in the prefrontal and parietal lobes [3]. However, these studies have focused mainly on macrostructural changes and, consequently, they are limited in resolution. In contrast, neuropathological studies have reported age-related deterioration in the microstructure of white matter, including demyelinisation or axonal loss in the cerebral cortex and subcortical white matter [4,5].

In multiple sclerosis the progressive tissue loss is also well described, along with the underlying molecular changes of brain tissue. In MS, brain atrophy occurs almost 10 times faster than in healthy subjects [6-9] and it is viewed as the result of extensive demyelinisation and axonal loss in both WM and GM [10].

At the microscopic level, brain parenchymal structures have distinct boundaries, including axon membranes and myelin sheaths, which constrain the diffusional propagation of water molecules and force the latter in certain preferential directions. Thus, the water diffusion averaged over the individual voxels, as expressed by the apparent diffusion coefficient (ADC), is reduced in accordance with the local occurrence of these membranes [11]. The microscopic processes of both aging and MS include axon loss, decreased myelinisation and demyelinisation. Since the restriction of water diffusion is most probably caused by myelin structures, increased ADC values in aging brain and in MS can be explained with decreased and disintegrated myelin structures [12]. Based on the findings described above aging and MS disease might cause additive ADC change in brain of MS patients.

The age-dependence of tissue water ADC in MS patients was examined to reveal the possible additive effects of aging and disease-generated microstructural changes in relapsing-remitting type MS patients. In addition to NAWM areas, subcortical gray matter and brain stem structures were also examined. Lesion number and EDSS were also correlated with diffusion data.
Methods and Materials

Subjects

Thirteen patients with multiple sclerosis participating in this study were chosen according to the 2005 modified McDonald criteria. All of the participants (4 males, 9 females, range: 22-50 years, mean age±SD 35.9 ±9.1 years) had relapsing-remitting type of the disease without any restrictions on duration. All of the measurements had taken place in the remission phase of the disease, and the patients were on chronic immunomodulatory therapy at the time of the MRI study.

Ten age-matched healthy volunteers as a control group (3 males, 7 females, range: 19-51 years, mean age±SD: 36.3± 11.0 years) were also measured. All of the individuals with a history of substance abuse (including alcohol), migraine headaches, major psychiatric illness, neurological disease, stroke or transient ischemic attack, are excluded from participation in the study.

Present report was carried out with the support of the ethical committee of the University of Pécs, and every participant signed an informed consent.

Magnetic Resonance Imaging

All of the measurements were carried out using a 3.0T Siemens TIM Trio (Erlangen, Germany) equipped with a 12 channel head coil. Beyond the routine T1 and T2 measurements and diffusion analysis, 3D FLAIR studies were also performed. 3D FLAIR images were acquired with turbo spin echo sequence: TR/TI/TE: 15710/2750.8/105 ms, slice thickness: 1.5 mm, distance factor 0% (e.g. no gap), interleaved slice readout with 2 concatenation, FOV: 220x220 mm2, 192x192 pixel matrix, bandwidth: 400 Hz/pixel, number of echo trains: 14. White matter hyperintensity (WMH) was considered if visible as being hyperintense on T2-weighted and FLAIR images, without hypointensity on T1-weighted scans, and were larger than 3 mm (12). A trace diffusion weighted 2D echo planar imaging sequence was performed with the following parameters: TR/TE = 4000/126ms, slice thickness= 3.5 mm, interslice gap= 1.05 mm, FOV= 188x250mm2, matrix size= 144x192 pixel, voxel size= 1.3x1.3x3.5mm³, bandwidth= 1300Hz/pixel, number of averages=5, number of slices=20, b-value: 0, 500, 1000, s/mm².

Data processing

WMHs were counted, their volumes were measured (ml/patient) and the average volume of the individual hyperintensities (ml/hyperintensity) was calculated for each patient. The results were categorized as the total of all lesions, and the sum of each pair of lobes (frontal, parietal, temporal and occipital).
Data analysis was carried out using Matlab® software curve fitting toolbox in a self written program code. Free-hand region of interests (ROI) were drawn on b0 images in the pre-defined normal appearing areas of the brain (Figure 1). ADC was calculated within each ROI by calculating and mono-exponentially fitting the mean intensity for the b0, b500 and b1000 images using the following equation[Eq.1]:

\[ I = I_0 \times \exp(-b \times D) \]  

where \( I \) is the measured signal intensity in the presence of diffusion sensitization, \( I_0 \) is the signal intensity in the absence of diffusion sensitization, \( b \) the b-value, and \( D \) is the ADC value.

**Statistical analysis**

Data processing was performed using PRISM® version 5 statistical software. After proof of normality for all data sets and subsets using D'Agostino-Pearson and Kolmogorov-Smirnov statistics, we assessed the differences between MS and control groups analysed by t-tests for Gaussian values (below 5% level of significance) with Welch's correction for unequal variances and Mann-Whitney tests for non-Gaussian distributions. Correlation between age and ADC was analyzed with a linear regression model. Statistical significance was considered at \( P \leq 0.05 \).
**Fig. 0:** ROI localisations of ADC measurements: 2 frontal white matter 3 corpus callosum, genu 4 basal ganglia 5 internal capsule 6 occipital white matter 7 putamen 8 thalamus 9 centrum semiovale

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Results

Figures 2. and 3. shows the ADC values in the frontal and occipital white matter respectively, as a function of age in MS patients and in the control group. In that later group relatively lower values were measured that increased gradually with age; this increase was more pronounced in the occipital localization. In young MS patients the frontal and occipital ADC values of NAWM were significantly ((p<0.005, p<0.01)) higher compared to age-matched controls (Table 1./Figure 8.). As a function of patient age these ADC values decreased to about the same level as of control group. Similar ADC values and trend can be seen in the supraventricular white matter (Figure 4.), nevertheless age-dependent decrease of ADC was found in the corpus callosum genu of control group (Figure 5.). In all NAWM localization described above ADC values are generally higher in the MS patients, yet statistically is lnot significant in the elderly group compared to the young (Table 1./Figure 8.).

Tissue water ADC changes are not characteristic as a function of age in the thalamus both in the control group and in MS patients. No differences due to age or MS were found either in the putamen measurements of ADC.

Bilateral average ADC values were collected in Table 1. (Figure 8.) in the two age groups, as 20-30 and 45-55 years). If data of white and gray matter localization were cumulated respectively, there is a high degree of significance between control and MS groups in young and older age. Lesion number of the brains studied in MS patients was investigated and age was correlated with cumulative ADC values of white matter measurements. Figure 6 shows that although no significant relationship exist between age and lesion number in the MS patient in our study, it seems that in young patients there were more lesions. The relationship between cumulative white matter ADC values and lesion number however proved significant and ADC depends linearly on lesion number in MS patients (Figure 7).
Fig. 0: ROI localisations of ADC measurements: 2 frontal white matter 3 corpus callosum, genu 4 basal ganglia 5 internal capsule 6 occipital white matter 7 putamen 8 thalamus 9 centrum semiovale

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Fig. 0: Relationship of age and ADC in the frontal white matter in control (#) and MS (#) groups MS # p = 0.0488 Control # p = 0.3697
Fig. 0: Relationship of age and ADC in the occipital white matter in control (#) and MS (#) groups MS # p = 0.3399 Control # p = 0.0258

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Fig. 0: Relationship of age and ADC in the centrum semiovale in control (#) and MS (#) groups MS # p = 0.0059 Control # p = 0.2618

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**Fig. 0:** Relationship of age and ADC in the corpus callosum, genu in control (#) and MS (#) groups MS # p=0.4775 Control # p=0.1293

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**Fig. 0:** Relationship of age and lesion number p = 0.2773

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Fig. 0: Relationship of number of lesions and cumulative white matter ADC values $p=0.0241$

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### Table 0

<table>
<thead>
<tr>
<th>ROI</th>
<th>ADC±SD</th>
<th>p value</th>
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<tr>
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<td>kontroll</td>
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<tr>
<td>Frontal WM</td>
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<td>15-35 years</td>
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<td>Splenium corporis calloso</td>
<td>7.13±0.26</td>
<td>6.22±0.46</td>
</tr>
</tbody>
</table>

Fig. 0: Comparison of diffusion measurements of normal appearing white matter between young and old multiple sclerosis (MS) patients and controls. Note Monoeexponencial mean ADC (10-4 mm2/s) values ± SD were analyzed using unpaired two-tailed t test from region
of interest (ROI) drawn frontal, occipital white matter (WM), centrum semiovale (CSO), genu and splenium of corporis callosi. * Mann Whitney test ** Welch correction

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Conclusion

Diffusion imaging has become a basic tool for monitoring ultrastructural changes in the human brain. It proved to be quite sensitive in this respect, nevertheless several ultrastructural, cellular and molecular events might contribute to the alteration of mean diffusion constant. Even more minute changes can be detected by diffusion tensor imaging (DTI) measurements of fractional anisotropy. Water diffusion is hindered by several cellular and extracellular structures; however myelin sheaths seem to be of primary importance in shaping ADC and FA values in the subcortical white matter. It has been also described that ADC and FA changes during the life of normal individuals and more rapidly in some pathological states, such that affect cell density or intra-extracellular ratio and myelin sheaths.

The increase of white matter ADC related to aging in normal individuals was described by several research groups [13-15]. These authors suggested that increased ADC was due to the loss of cellular elements, like neurons, pericytes, axons and consequently the enlargement of extracellular space occurs. These changes were present in mostly all white matter areas measured; nevertheless the magnitude of ADC changes was somewhat different. An age-related reduction in isolatable myelin was reported by some investigators, who also found an increase in unsaturated acyl chains in myelin lipids [16]. These findings were considered suggestive of decreased stability of the myelin lamellae [17] that might therefore also facilitate water diffusibility. However, an increase in the "free" intracellular water fraction may also play a role which might relate to factors such as changes in myelin-associated bound water, demyelination, and possible wallerian degeneration related to cell loss, and increasing Virchow-Robin spaces with increasing age [19,20].

Regional ADC differences originate from the specific structural characteristics of white matter areas, but partial volume effect of CSF could also play a role [21]. The gender dependence of white matter ADC was also investigated in normal individuals under 60 years, but no significant difference was found [22]. Also the asymmetry of water diffusion in the right and left hemisphere was described but data are still a matter of controversy [23].

Control measurements in our study showed that the ADC of white matter structures, including frontal, occipital and supraventricular areas increases with age. However, no such trend was found in the corpus callosum, thalamus and putamen, yet averaging all measured white matter structures showed increasing ADC values depending on age (not shown).
Besides MS [24-26], ADC changes in NAWM were described in different pathological states, as neurofibromatosis [17], HIV patients [27], hepatic encephalopathy [28] and Alzheimer disease [21]. ADC changes are similar in conditions mentioned above although the underlying molecular and cellular changes might be different. In multiple sclerosis brain specimens decreased phospholipid levels in myelin structures were demonstrated in NAWM and significant axonal loss was also proved histologically [29], in addition choline and sphingomyelin metabolism is also disturbed [30,31]. These biochemical changes could surely influence water permeability of the membranes and the degradation of cellular components cause the widening of extracellular space which changes conclude in the elevation of water diffusion compared to healthy controls.

The temporal evolution of tissue water diffusivity was investigated by Garaci et al. in relapsing-remitting type MS patients during 3-6 months interval and found higher ADC values in the relapsing compared to the remitting phases [24]. They also demonstrated a correlation between the EDSS scores and ADC values measured in NAWM areas. Similarly, a relationship was described between clinical symptoms and water diffusivity in NAWM in primary progressive MS patients, and ADC values again were higher than in the control group [32]. In a longitudinal study Caramia et al found that ADC increases significantly in NAWM as clinically isolated syndrome (CIS) converts into clinically defined MS after 12 months. [25]. At this stage, lesion volume detected on T2W images showed significant correlation with ADC values measured in NAWM.

In the MS patients of our study significantly higher ADC was found characteristically in the frontal, occipital and supraventricular white matter of younger individuals compared to their age matched controls. This difference is reduced in the 40-55 years group, and no significant difference was found in these localizations between control and MS patients (Table 1). Opposed to that, water diffusivity in the corpus callosum does not show such changes with age, yet ADC values are significantly higher in the older MS group. Linear regression analysis gave good correlation between ADC values and lesion number detected on the FLAIR images (Figure 6.), which might support findings described above: the clinical status of the disease (EDSS score), the number of high signal intensity lesions and ADC in NAWM change together. No significant correlation between lesion number and EDSS was found in the current study (not shown).

In conclusion, these results confirm that quantitative diffusion MR imaging can detect subtle changes in NAWM, beyond the resolution of conventional MR techniques. In the given group of MS patient of our study an inverse relationship of ADC in NAWM and patient age appeared, however in agreement with previous studies [25, 27] a significant correlation between lesion number/volume and ADC in NAWM was also revealed. Based on the latter correlation it seems more sound that the primary reason for ADC increase in NAWM in clinically definitive MS patients is the activity of the disease that manifesting in the elevation of hyperintense lesions on T2W contrast images [33].
References


Personal Information

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