Assessment of degradation of the selected projectile, commissural and association brain fibers in patients with Alzheimer’s disease on diffusion tensor MR imaging

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Summary

Background: Pathological examinations and the increasingly popular diffusion tensor imaging (DTI) show that in Alzheimer’s disease (AD), the pathology involves not only the cortical and hippocampal structures, but also the white matter of the brain. DTI is a well recognized technique for evaluation of the integrity of white matter fibers. The aim of this study was to assess with the use of DTI some selected brain tracts in patients with AD, as well as to analyze the severity and distribution of the identified changes.

Material/Methods: Thirty-five patients with AD (mean age of 71.6 years, MMSE 17.6), and a control group of 15 healthy volunteers (mean age of 69.1 years, MMSE 29.8) were enrolled in the study. All patients were subjected to a thorough psychiatric examination and psychological tests. DTI examinations (TE 8500, TR 100) were performed using a 1.5T MR scanner. Fractional anisotropy (FA) measurements in the selected areas of interest (ROI) of the white matter fibers were performed under the control of color FA maps. The following fibers were evaluated – the middle cerebellar peduncles (MCP), the inferior longitudinal fasciculi (ILF), inferior frontooccipital fasciculi (IFO), genu (GCC) and splenium of the corpus callosum (SCC), posterior limbs of internal capsules (PLIC), superior longitudinal fasciculi (SLF) and posterior cingula (CG).

Results: There was a statistically significant decrease in FA in patients with AD, comparing to the control group. It was particularly strongly expressed in both CG (P<0.0001), followed by both IFO, left IFO, and left SLF. Less pronounced changes were found in GCC, SCC, and left IFO. In both PLICs and MCPs and in the right SLF, there was no significant change of FA.

Conclusions: In Alzheimer’s disease, there is a significant decrease in FA, which suggests degradation of the majority of the assessed white matter tracts. Distribution of these changes is not uniform. They involve the selected association fibers mainly and, to a lesser extent, the commissural fibers, while they are not found in the pyramidal tracts or medial cerebellar peduncles. Definitely, the most pronounced changes were found in the posterior cingula, the assessment of which (in the process of AD diagnostics) seems to be particularly promising.

Key words: Alzheimer’s disease • white matter • diffusion tensor imaging • fractional anisotropy
Background

Alzheimer’s disease (AD) is the most common cause of dementia and represents more than 50% of all cases of late-onset dementia. In the developed countries, AD affects about 8% of the population aged over 65 years and about 30% of the population aged over 85 years. It is estimated that more than 30 million patients suffer from AD worldwide, and about 200 thousand in Poland [1]; these figures are probably underestimated. Histopathologically, AD is characterized by the presence of senile plaques of amyloid and intracellular neurofibrillary tangles, as well as neuronal loss and dysfunction, and atrophy of the cerebral cortex [2]. Generally, it is considered that the changes in AD affect the gray matter mainly and consist in a destruction of large pyramidal neurons (layers III and V), particularly in association areas of the cortex. Distribution of changes is not uniform; as the volumetric studies have shown, the process begins and reaches its highest intensity in the medial temporal lobes, entorhinal cortex and hippocampus, and then spreads along the limbic cortex, leading to memory and cognitive impairment. At the early stages of the disease and with its moderate severity, changes do not involve the visual, sensory and motor cortex [3,4]. Apart from the cortical and gray matter damage, histopathological examinations demonstrate also the presence of white matter changes – rarefaction, axonal loss and degeneration, demyelination, loss of oligodendrocytes and reactive astrogliosis [4,5]. Consistent with histopathological findings is the diffusion tensor imaging (DTI), which is also able to show the damage of the white matter in AD patients. Such lesions would never be detected with a standard MRI examination [6–9].

DTI is a unique, noninvasive magnetic resonance imaging technique that allows for a quantitative assessment of intensity and directionality of free diffusion of water molecules in the living tissue. Due to the presence of cell membranes and axonal myelin sheaths that constitute a diffusion barrier, the movement of water molecules is restricted and anisotropic within the white matter, contrary to the cerebrospinal fluid in the ventricular system. The restriction of diffusion is aligned perpendicular to the white matter fibers and the relative preference of diffusion is parallel to the their course. This is called anisotropy. The degree of diffusion anisotropy in the examined tissue is quantified by fractional anisotropy parameter (FA), derived from diffusion tensor eigenvalues. FA parameter is defined as a marker of white matter integrity. The decrease in FA values indicates the degradation and damage of the examined white matter tracts [10,11].

So far, the vast majority of DTI examinations carried out in patients with AD, demonstrated the presence of microstructural changes in white matter, manifested by the decrease in FA value, with inhomogeneous damage of the white matter and of the cerebral cortex. Most changes were found in the selected association tracts [9,12–16]. Some authors revealed changes in the commissural tracts as well [2,5,6,8,9,15]. On the other hand, the results of FA value measurements, evaluated generally for the white matter of temporal, frontal and parietal lobes, varied and were not consistent [2,5,9]. A large number of studies showed no significant changes in FA in the examined projection fibers (pyramidal and visual tracts) [2,9,13]. However, there were differences and discrepancies between researchers, regarding the distribution and severity of lesions.

The aim of this study was to determine whether DTI examination confirms the presence of white matter lesions in patients with moderate AD [1], as well as to assess the distribution and intensity of these changes by selective measurement of FA values in chosen association, commissural and projection fiber tracts of the cerebral white matter.

Materials and Methods

Patients and control group

The study group included 35 patients diagnosed with probable AD of a moderate stage (22 females and 13 males, mean age of 71.6±11.7), recruited from the patient list of Outpatient Mental Health Clinic of Psychiatry Department at Wroclaw Medical University. The diagnosis of a probable AD was made basing on the current criteria of the National Institute of Neurological and Communicative Disorders and Stroke – Alzheimer’s Disease and Related Disorders Association (NINCDS-ADRDA) [1]. In addition, the study included an age- and sex-matched control group of 15 healthy volunteers (9 females and 6 males, mean age of 69.1±8), excluding subjects with memory and cognitive impairment. The group was recruited from relatives and acquaintances of the employees of Wroclaw Medical University and University Hospital. All patients were subjected to a detailed psychiatric examination and neuropsychological tests, including the Mini-Mental State Examination (MMSE) and the Clinical Dementia Rating (CDR).

The mean score of the Mini-Mental State Examination (MMSE), adjusted for age and education, was 17.6±6.5 for patients with probable AD, and 29.8±0.4 in the control group, while the mean CDR score for the AD patients was 1.7±0.7 and 0±0 in the control group. Demographic data and neuropsychological test results for the studied groups were summarized in Table 1.

Chest X-ray, ECG, full blood count test, ESR, blood level of electrolytes, glucose, urea and creatinine, liver enzymes (AST and ALT), cholesterol and TSH were performed in all

Table 1. Demographic data and neuropsychological test results of the study groups. Mean values, standard deviation in parentheses.

|                         | AD          | CN          |
|-------------------------|-------------|-------------|
| Number of patients      | 35          | 15          |
| Age (years)             | 71.6 (11.7) | 69.1 (8.0)  |
| Sex F/M                 | 22/13       | 9/6         |
| MMSE                    | 17.6 (6.5)  | 29.8 (0.4)  |
| CDR                     | 1.7 (0.7)   | 0 (0)       |

AD – Alzheimer’s disease; CN – control group, MMSE – Mini-Mental State Examination; CDR – Clinical Dementia Rating.
patients before MRI examination of the brain. The patients were qualified into two groups after the exclusion of systemic diseases, psychiatric and neurological disorders, hypertension, diabetes, alcoholism, autoimmune diseases, renal and liver failures. Patients with focal brain lesions such as tumors, post-traumatic and post-inflammatory lesions, as well as major vascular lesions were also excluded from the study, whereas small focal hyperintensities found in T2-weighted images of the white matter were not an exclusion criterion. The study was approved by Ethics Committee of Wrocław Medical University and a written consent was obtained from all patients or their legal guardians.

MRI, DTI, postprocessing

All MR examinations were performed with a Signa hdx MRI scanner for clinical use (General Electric Medical System Milwaukee, USA) with a 1.5 T superconducting magnet. A high density 16-channel HNS (head-neck-spine) array coil was used in the study. MRI of the brain was performed in all patients, prior to DTI examination. The MRI protocol included: 3D localizer, FLAIR Propeller sequence images (TR 8000, TE 120ms) in transverse planes, parallel to the intercommisural line, T2-weighted FRFSE sequence images (TR 4840, TE 93ms) in coronal planes, T2-weighted FRFSE sequence images in sagittal planes (TR 4060, TE 85ms). The slices were 5 mm thick, with a gap of 1 mm and field of view of 24×24.

DTI was performed in single-shot spin-echo sequence of echo-planar type with 25 diffusion-encoding directions (TE 8500, TR 100, matrix 128×128, FOV 24×24cm, with a total number of two excitations and two b-values (b=0 and b=1000 s/mm$^2$), time of data acquisition 7min 29 s). Slices of 4 mm in thickness, with no gaps, were oriented parallel to the intercommisural line connecting anterior and posterior commissure and covered the whole brain, from the foramen magnum to the cerebral convexity.

After transferring all images, DTI data were processed on a workstation (Advantage Workstation 4.4, Functool, General Electric Medical Systems, Buc, France), where after an initial correction of geometric distortions, the following parametric maps were generated: color-coded FA maps according to diffusion directions, FA maps and ADC (Apparent Diffusion Coefficient) maps.

Guided by color-coded FA maps of diffusion orientation, FA maps and T2-weighted images (b=0 s/mm$^2$), elliptical ROIs (area of 30–40 mm$^2$) were positioned, in order to measure the FA parameter in the selected white matter tracts. The long axis of ROI in every case was parallel to the course of the examined fiber tract to allow a selective assessment, and the whole ROI, positioned on color-coded FA map, had to be within a selected fiber tract to avoid the partial volume effect with adjacent structures. To eliminate bias, a special attention was paid to avoid the partial volume effect with cerebrospinal fluid or to cover the gray matter.

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Figure 1. Location of the regions of interest in the right (ROI 1) and left (ROI 2) middle cerebellar peduncle (MCP) on the color-coded FA map (A). Reading the FA values obtained for both MCPs from the FA map (B). Fiber tractography of the MCPs (C).
The presence of focal hyperintensities in T2-weighted images within the ROI was also excluded.

The following fiber tracts were assessed by positioning of properly numbered ROI:
- Right and left middle cerebellar peduncle (MCP) – ROI 1 and ROI 2 positioned entirely in the center of the middle cerebellar peduncles (green on the color-coded FA map).
- Right and left inferior longitudinal fascicle (ILF) – ROI 3 and ROI 4 positioned within ILF on the slice passing through the midbrain and lamina tecti.
- Right and left inferior fronto-occipital fascicle (IFO) – ROI 5 and ROI 6 positioned within IFO, on the slice covering the lower part of the thalamus, directly laterally to the ventricular triangles and the occipital horns of the lateral ventricles.
- Genu of the corpus callosum (GCC) – ROI 7, and splenium of the corpus callosum (SCC) – ROI 8 on the slice passing through basal ganglia and internal capsules, with the long axis running transversely, in accordance to splenium and genu of the corpus callosum (red on the color-coded FA map).
- Posterior limbs of the right (ROI 9) and left (ROI 10) internal capsule (PLIC), blue on the color-coded FA map.
- Right (ROI 11) and left (ROI 12) superior longitudinal fascicle (SLF) assessed on the slice passing through the upper part of the lateral ventricles, clearly visualizing SLF (green on the color-coded FA map).
- The rear part of the right (ROI 13) and left (ROI 14) cingulum (CG) on the supraventricular slice with clearly visualized cinguli (green).

Each fibre tract was identified basing on available atlases and studies [17,18]. The examined tracts, their location, orientation and size of the ROI were presented in Figures 1–4.

The database of the results was created in Excel. The statistical analysis was carried out using STATISTICA. Mean FA

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**Figure 2.** Location of the regions of interest in the course of the right (ROI 3) and the left (ROI 4) inferior longitudinal fascicles (ILF) on the color-coded FA map (A). Fiber tractography of both ILFs (B). Location of the region of interest in the course of the right (ROI 5) and the left (ROI 6) inferior fronto-occipital fascicle (IFO) on the color-coded FA map (C). Fiber tractography of the right IFO (D).
values and standard deviation for each ROI in AD patients group and each ROI in the control group were calculated. The average results obtained in AD group for each ROI separately were compared to those in the control group using Student's t-test for independent samples. The statistically significant difference was established at p<0.05 level.

Results

No statistically significant differences in age were found between the analyzed groups (p=0.14). There were also no statistically significant differences between two sexes in AD group concerning CDR (p=0.9) and MMSE (p=0.24) scores, as well as FA values of the analyzed ROIs. Similarly, there was no statistically significant difference between two sexes in the control group for CDR and MMSE (p=0.8) scores, as well as for FA values of analyzed ROIs, except for ROI 8 (SCC), where the mean FA value for women was slightly higher demonstrating slight, statistically significant difference (p<0.05).

However, statistically significant differences between the study group of patients with AD and the controls were found within CDR (P<0.0001) and MMSE (p<0.0001) scores.

As compared to the control group, patients with AD demonstrated a statistically significant decrease in FA values in the following fiber tracts: most strongly expressed in both CGs, however to a much greater extent on the left side (p<0.0001), followed by the right ILF and the left SLF (p<0.001), as well as the left ILF, right IFO, SCC and left IFO (p<0.01). Less expressed, but statistically significant decrease in the FA value, was also found in GCC (p<0.05), whereas, in both PLICs, both MCPs and right SLF the FA values did not show statistically significant differences.

The obtained mean FA values with standard deviation in the control group and AD group for each analyzed ROI were presented in Table 2.

Discussion

In the classical meaning, AD is considered a cortical dementia, with strongly marked pathological lesions in the gray matter of the medial temporal lobes, including hippocampal structures, entorhinal cortex and limbic cortex; in moderate and advanced stages, the pathological changes can also be found in association areas of the cerebral cortex [19]. However, histopathological examinations indicate that in AD, lesions are formed in the white matter as well [20,21]. They are manifested by degradation of the myelin sheath, demyelination and axonal loss, as well as astrocyte proliferation. It is suggested that such white matter lesions may be associated with Wallerian-type degeneration of axons, secondary to neurodegenerative processes in the cortex. The dominance of microstructural changes in association tracts of white matter connecting association...
areas of cortex affected with AD seem to be an evidence of that [21].

In our study, by comparing patients with moderate AD to the control group of healthy volunteers, we proved a considerable, statistically significant decrease in FA values for majority of selected white matter tracts, suggesting the presence of microstructural changes and degradation of these tracts. Distribution of changes was not uniform, their severity varied within each tract. Moreover, not all tracts were found to be damaged. This is consistent with the previous study reports [8,9,13–15].

The most pronounced changes were found in both cinguli (CG), especially on the left side. It is in accordance to the previous studies, in which cinguli degradation features were observed on DTI as well [8,9,14–16]. This is not surprising, considering the fact that cinguli constitute a part of the limbic system, linking hippocampus and the cingulated gyriuses, which become damaged in the early stages of AD.

Damage and degradation features, expressed by a decrease in FA values, were also found in the vast majority of other association tracts. Microstructural changes were demonstrated in both ILFs that connect association areas of the cortex in the parietal and temporal lobe, in both IFOs that connect frontal and occipital lobes cortex, as well as in the left SLF, linking the parietal and the occipital lobe to the frontal lobe. This also confirms the results of some previously conducted studies [8,9,13,15]. Right SLF happened to be the only association fiber tract among the studied tracts that showed no damage nor degradation features. The asymmetrical changes in both SLFs are worth attention, especially considering the degradation features strongly expressed in the left SLF.

Moreover, the statistically significant, quite strongly marked decrease of the FA values was shown, indicating

Figure 4. Location of the regions of interest in the right (ROI 11) and the left (ROI 12) superior longitudinal fascicle (SLF) on the color-coded FA map (A). Fiber tractography of both SLFs (B). Location of the regions of interest in the posterior right (ROI 13) and left (ROI 14) cingulum (CG) on the color-coded FA map (C). Fiber tractography of both cingula (D).
Table 2. Summary of mean values for FA parameter of the white matter tracts in patients with Alzheimer’s disease (AD) and in control group (CN), and statistical significance of differences between groups. Mean values, standard deviation in parentheses.

| ROI No. | Examined tract | AD        | CN        | p-value* |
|---------|----------------|-----------|-----------|----------|
| ROI 1   | MCP R          | 0.738 (0.042) | 0.737 (0.036) | 0.97     |
| ROI 2   | MCP L          | 0.739 (0.047) | 0.743 (0.038) | 0.78     |
| ROI 3   | ILF R          | 0.552 (0.050) | 0.616 (0.050) | <0.001   |
| ROI 4   | ILF L          | 0.567 (0.049) | 0.613 (0.038) | <0.01    |
| ROI 5   | IFO R          | 0.549 (0.052) | 0.602 (0.049) | <0.01    |
| ROI 6   | IFO L          | 0.547 (0.048) | 0.588 (0.046) | <0.01    |
| ROI 7   | GCC            | 0.737 (0.068) | 0.784 (0.046) | <0.05    |
| ROI 8   | SCC            | 0.797 (0.058) | 0.849 (0.054) | <0.01    |
| ROI 9   | PLIC R         | 0.718 (0.044) | 0.704 (0.034) | 0.28     |
| ROI 10  | PLIC L         | 0.711 (0.052) | 0.718 (0.036) | 0.63     |
| ROI 11  | SLF R          | 0.597 (0.044) | 0.620 (0.048) | 0.1      |
| ROI 12  | SLF L          | 0.579 (0.052) | 0.629 (0.039) | <0.001   |
| ROI 13  | CG R           | 0.552 (0.059) | 0.660 (0.051) | <0.0001  |
| ROI 14  | CG L           | 0.568 (0.051) | 0.687 (0.042) | <0.0001  |

* Student’s t-test for independent samples, AD vs CN; statistical significances are bold typed. MCP – middle cerebellar peduncle; ILF – inferior longitudinal fasciculus; IFO – inferior frontooccipital fasciculus; GCC – genu of the corpus callosum; SCC – splenium of the corpus callosum; PLIC – posterior limb of internal capsule; SLF – superior longitudinal fasciculus; CG – cingulum.

the presence of microstructural changes within the splenium of corpus callosum. This is consistent with previous studies [2,5,6,9,14,15]. It is not surprising either, given that the fibers linking association areas of parietal lobes run through the corpus callosum. Statistically significant, although definitely lesser decrease in the FA values was also found in the genu of the corpus callosum. Similar changes were observed previously [14].

However, our study showed no damage or degradation features in the examined projection tracts. No statistically significant changes in FA values were found for the pyramidal tracts (PLIC) or the middle cerebellar peduncles (MCP), which is also consistent with the majority of the previously performed studies [2,4,5,9] as well as with the fact, that in patients with AD, motor functions remain preserved and the areas of sensory and motor cortex remain intact until the advanced stages of disease.

Our study showed that microstructural changes and degradation of white matter tracts occurring in patients with moderate AD are not uniform with respect to severity and distribution. Predilection of changes for the association tracts and preservation of pyramidal tracts and medial cerebellar peduncles, as determined in our study, corresponds to the distribution of cerebral gray matter damage. It possibly proves that the white matter tract damage and Wallerian-type degeneration of axons are secondary to neuronal damage in association areas of the cerebral cortex and the limbic system.

The study group was a relatively small sample – 35 patients with AD and 15 controls, but the vast majority of DTI studies in AD was also carried out within similar or smaller groups of patients [2,5,6,7,9,12–14]. In this study we excluded patients with mild cognitive impairment, which is considered to be a prodromal and preclinical stage of AD. This is expected to be the scope of our future studies.

In our study, the FA parameter measurements were performed using the ROI method, which is the golden standard [9], but has a number of limitations as well. First of all, it is laborious, relatively time-consuming and requires involvement of a radiologist with extensive experience in neuroradiology and an excellent neuroanatomical knowledge. It also carries the risk of FA measurement bias, resulting from inclusion of the cerebrospinal fluid, gray matter structures or other white matter tracts into one of the ROIs [9].

We tried to minimize these ‘inconveniences’ by applying a precise positioning of ROI, guided by FA color maps, strictly within the selected tract. Particular attention was paid to avoid inclusion of cerebrospinal fluid in the area of ROI and extension of the ROI beyond the analyzed tract.

Many of the authors using the ROI method measured FA values only within a limited number of white matter tracts [14–16]; this paper studied a larger number of white matter tracts, in order to obtain a better insight into the distribution and evolution of changes within the white matter tracts.

Conclusions

Our research study confirmed the presence of microstructural changes and degradation of some white matter tracts in patients with moderate AD. Distribution of these...
changes is not uniform and shows a strong predilection for association fiber tracts, and, to a lesser degree, for commissural tracts. Definitely, the most intense changes were found in the CG, particularly on the left side. No changes were observed within the pyramidal tracts (motor tract) and middle cerebellar peduncles. Distribution of changes within the white matter tracts in AD correlated with lesions observed in the cortex and may suggest that the degradation of white matter tracts is secondary to the damage and loss of neurons. Our study proved that DTI may be a useful method in AD diagnostics. The FA measurements within the CG seem to be particularly promising.

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