Analysis of genu and splenium of the corpus callosum: comparison between healthy subjects with and without Leukoaraiosis

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Abstract. The purpose of this study to investigate whether there are any differences in Diffusion Tensor Imaging (DTI) values in subjects that have leukoaraiosis (LA) in the frontal white matter (fWM) and occipital white matter (oWM) compared to subjects that have no LA in those areas in the brain. DTI indices namely axial diffusivity (AD), radial diffusivity (RD), mean diffusivity (MD), fractional anisotropy (FA) were measured via retrospective study. Finding from this study shows that there is no significant difference in AD, RD, MD, and FA values between both groups. It is concluded that there are no significant differences in DTI values of genu and splenium of the corpus callosum between subjects with and without LA. This study shows that subjects with LA does not having degeneration on fiber bundles of the genu and splenium, in which the genu and splenium function in connecting right and left of hemisphere. Also, it might does not affect or not yet affect the genu and splenium fiber bundles. This finding the differences is important to determine whether any changes in AD and RD values.

Keywords- diffusion tensor imaging; white matter; magnetic resonance imaging; leukoaraiosis; fractional anisotropy

1. Introduction
Leukoaraiosis (LA) is defined as diffuse, confluent white matter abnormality which appears low density on computed tomography (CT) scan, and hyperintensity on T2-weighted or FLAIR MRI. LA also have
irregular shape and size. The term was derived from the Greek stem “leuko-” which means white and referring to the white matter, while the adjective “arraios” means rarefied [1]. LA is very common in elderly and as a risk factor for developing dementia, mobility problems and strokes. It is usually accompanied by the change in corpus callosum morphology [2].

Corpus callosum (CC) consists of over 190 million axons, so it is the largest white matter tract. The CC connects the cerebral hemispheres and provides for interhemispheric integration and transfer of information [3]. It plays an important role in brain development, which involves in transferring sensory, motor and cognitive information between hemispheres [4].

Diffusion tensor imaging (DTI) is an imaging technique in MRI that measures three-dimensional (3D) diffusion of water molecules within tissue by applying diffusion gradient in various directions [5]. In this technique, anisotropic diffusion is used to estimate the organization of the axon in the brain. DTI provides quantitative analysis of magnitude and directionality of water molecules. The parameters derived from DTI data includes axial diffusivity (AD), radial diffusivity (RD), mean diffusivity (MD) and fractional anisotropy (FA). Axial is defined as the longest eigen vector, \( \lambda_1 \) which describes the mean diffusion coefficient of water molecules diffusing parallel to the tract within the voxel of interest. While, radial diffusivity is defined as the average of the two shorter eigen that are \( (\lambda_2 + \lambda_3)/2 \). It shows the magnitude of water diffusion perpendicular to the tract [6]. Recently, AD and RD have been used to obtain further information on the integrity of white matter (WM). Mean diffusivity describes the average extent of water diffusion, that are \( (\lambda_1 + \lambda_2 + \lambda_3)/3 \). It is also as a marker of WM integrity. Meanwhile, fractional anisotropy describes the directionality the diffusion tensor [7].

This study is conducted to further analyze the condition of the CC of subjects with and without LA in the frontal white matter (fWM) and occipital white matter (oWM) areas. Analysis was performed specifically to investigate the differences in DTI values between the two groups of subjects.

![Figure 1. Illustrating Axial Diffusion, Radial Diffusion and Fractional Diffusion][8]

2. Materials and methods

2.1. Data acquisition

This is a retrospective study in which all DTI images were retrieved through USM picture archiving and communication system (PACS) available at Advanced Medical and Dental Institute (AMDI), USM. The data were acquired using 1.5 Tesla MRI System (Signa HDxt, GE Healthcare) available at AMDI. The optimal imaging parameters used were as described elsewhere [9,10]. This study was approved by Human Research Ethics Committee USM (USM/JEPeM/17050265).
2.2. Subjects
Subjects were divided into two groups. The first group consist of those with LA in the fWM and/or oWM areas. This group was labelled as “With LA”, whereas the second group consist of those without LA in those areas, but they do have LA in other areas in their brain. This second group was labelled as “Without LA”. All subjects did not present neurological and/or cardiovascular illnesses when the MRI scanning was performed.

2.3. Post-processing
Analysis was carried out using Osirix software version 4.1.2. Diffusion tensor elements and anisotropy at each voxel were computed. MD, FA, and color-coded FA maps were reconstructed.

2.4. Region of interest and quantitative measurements
Region of interest (ROI)s were located on the center, axial slice at the horizontal level of the striatum containing the genu and splenium of the corpus callosum. Single circular ROI with area of 0.30 ± 0.02 cm² was drawn manually on the genu and splenium area on the MD maps. All ROIs drawn on the MD maps were copied to the FA maps and pasted on the AD, RD, and FA maps to ensure an accurate and standardized placement of the ROIs on all parametric map. Then, the values displayed on each map were recorded.

2.5. Statistical Analysis
Statistical analysis was performed using Microsoft Excel (version 16.0.11425.20202, Microsoft Corporation). F-Test was performed to compare variances between the two groups. Then, t-test was performed to compare the differences between groups. For all comparisons, p < 0.05 was considered statistically significant.

3. Results
3.1 Axial diffusivity
Based on Figure 2, the average AD values recorded for subjects with LA in genu is 1830.95 x 10⁻⁶ mm²/s and 1853.35 mm²/s for those without LA. Whereas the average AD values recorded in splenium for subjects with LA and without LA are 1769.33 x 10⁻⁶ mm²/s and 1825.17 x 10⁻⁶ mm²/s respectively. The result shows that the AD values in genu for subjects with LA are slightly lower than the subjects without LA. Meanwhile, in splenium, the AD values for subjects with LA is also slightly lower than that of the subjects without LA. Statistical analysis, t-test shows that there is no significant difference in AD for both genu (p = 0.70) and splenium (p = 0.46) between the groups as descripted in Figure 1.

3.2 Radial diffusivity
The average RD values recorded for subjects with LA in genu are 324.66 x 10⁻⁶ mm²/s and 315.39 x 10⁻⁶ mm²/s for those without LA. Meanwhile, the RD values for those with LA and without LA in splenium are 272.72 x 10⁻⁶ mm²/s and 261.62 x 10⁻⁶ mm²/s respectively. As displayed in Figure 3, the graph shows the RD values for those with LA in genu is higher than those who do not have LA in fWM an oWM. Whereas, in splenium, the observed RD values of subjects with LA was found slightly higher than the subjects without LA. Statistical analysis, t-test shows that there is no significant difference in RD for both genu (p = 0.67) and splenium (p = 0.59) between the groups.

3.3 Mean diffusivity
Average MD values recorded for subjects with LA in genu is $832.89 \times 10^{-6} \text{ mm}^2/\text{s}$ and the subjects without LA is $827.26 \times 10^{-6} \text{ mm}^2/\text{s}$. Meanwhile, in splenium, the average of MD values for subjects with LA and without LA are $798.08 \times 10^{-6} \text{ mm}^2/\text{s}$ and $779.04 \times 10^{-6} \text{ mm}^2/\text{s}$ respectively. Based on Figure 4, the graph shows the MD values for subjects with LA in genu is slightly higher than subjects without LA. Whereas, in splenium, it shows the MD values for subjects with LA is also higher than subjects without LA. Statistical analysis, t-test shows that there is no significant difference in MD for both genu ($p = 0.71$) and splenium ($p = 0.33$) between the groups.

3.4 Fractional anisotropy

The average FA recorded for subjects with LA and without LA in genu are $7984.83 \times 10^{-4}$ and $8057.27 \times 10^{-4}$ respectively. Whereas in splenium, the subjects with LA are $8160.29 \times 10^{-4}$ and $8403.23 \times 10^{-4}$ for those subjects without LA. The graph in Figure 5 shows that the FA values for subjects with LA in genu is a little bit higher than those subjects without LA. In splenium, we observed that the FA values for subjects with LA is lower than those subjects without LA. Statistical analysis, t-test shows that there is no significant difference in MD for both genu ($p = 0.67$) and splenium ($p = 0.34$) between the groups.

4. Discussion
Based on Figure 2 to Figure 5, the greatest difference between subjects with LA and without LA in genu and splenium was seen in fractional anisotropy values, followed by axial diffusivity, mean diffusivity and radial diffusivity value. The major findings in this study is that there are no significant differences in DTI values between those with LA and without LA for both genu and splenium in which these results are not as expected. From this investigation, we expected this study can confirm that eigenvalues of DTI parameters do not indicate the same microstructural characteristics in both groups since the orientation of eigen vector is different. However, this study results opposed our expectation.

4.1 Axial Diffusivity (AD)
AD measures the diffusion of water parallel to axons. In this study, we found decreases AD in both ROIs of the corpus callosum for the group of subjects that are with LA. However, the difference was not significant. The previous study performed by Takahashi et al. showed that AD increases when the later stages of white matter development of rats, the axonal orientation becomes less asymmetry [11]. This means the AD also portrays the axonal degradation. Therefore, axonal orientation is possible decreases since the axons degraded.

4.2 Radial Diffusivity (RD)
Radial diffusivity appears to be closely with myelination. In normal aging, the axons degenerated causes some myelin sheaths breakdown [12]. This would reflect the myelin degeneration is correlated with increased RD. In our analysis, increased RD were observed in group of subjects with LA for genu and splenium, though it is not significant.

4.3 Mean Diffusivity (MD)
We also found an insignificant difference in MD values between both groups although the values of subjects with LA is higher than those without LA. Based on Liu et. al. (2016), the higher MD values reflect the white matter integrity impairment [13].

4.4 Fractional Anisotropy (FA)
This study shows that decreased FA for subjects with LA in both genu and splenium caused by myelin changes. Due to myelin changes which is myelin degradation, the white matter hyperintensities increases. In previous studies, the lower FA because of myelin degradation or axonal degradation [14]. Based on the previous findings also showed decreases FA due to microstructural changes such as myelination loss, microtubules loss and the deep white matter hyperintensities (WMH) seen on T2-weighted images [15]. These microstructural changes are also known as neurodegenerative process. However, we were suggesting that there may be no apparent changes in the microstructural of subjects with LA and without LA in genu. The causes of this difference in FA for those with LA and without LA is not entirely clear. But the possible causes may be the microstructural phenomenon is same as FA also measures intravoxel coherence as stated by Pfefferbaum.

5. Conclusion
In the current study, it was found that there are no significant differences in all DTI values between subjects with LA and those without LA in both genu and splenium. The value of AD and RD indicate the changes in structure of the axons and myelin sheath respectively. In this case, changes in AD value shows that axonal dyemelination, whereas RD shows that myelin sheath degeneration. This study is important to examine whether any changes in AD and RD values.
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