Altered myelination and axonal integrity in Primary Restless Legs Syndrome Patients: Diffusion Tensor Imaging Study

Jong-su Baeck[1], Jeehye Seo[1], Seong-Uk Jin[1], jang Woo Park[1], Moon Han[1], Yongmin Chang[2,3], and Yong Won Cho[4]

[1]Department Medical & Biological Engineering, kyungpook national University, Daegu, Korea, [2]Department of Radiology, kyungpook national University, Daegu, Korea, [3]Department of Molecular Medicine, kyungpook national University, Daegu, Korea, [4]Department of Neurology, Kemyung University School of Medicine, Daegu, Korea

Background

Alteration in brain white matter was suggested in restless legs syndrome (RLS) from DTI studies [1]. However, the brain areas involved were inconsistent across studies and the underlying pathophysiology of white matter alteration is poorly understood. Therefore, using voxel-based DTI, we aimed to explore the possible mechanism of altered integrity of brain white matter in RLS patients.

Methods

DTI measurement was performed by using a 3.0-T MR imager in 23 patients with RLS and 23 healthy control subjects matched for age and sex. All participants gave their written informed consent. The diagnosis of RLS was made utilizing the validated Korean-language version of the John Hopkins Telephone diagnostic questionnaire. The DTI was performed by using a single-shot echo-planar imaging sequence in 50 axial planes with 15 noncollinear diffusion sensitization gradients (b = 1000 sec/mm ^{2}), as well as a reference image with no diffusion weighting (b_0 image), after using array spatial sensitivity encoding technique to reduce susceptibility and eddy-current artifacts. Imaging parameters were as follows: repetition time msec/echo time msec, 1200/70.8; number of signals acquired, two; field of view, 240 x 240 mm; acquisition matrix, 128 x 128; and 3-mm section thickness without intersection gaps. Fractional anisotropy (FA) and axial and radial diffusivities (AD and RD) were calculated from the eigenvalues of the diffusion tensor, on a voxel-by-voxel basis using 15 diffusion-weighted images from each subject. By using voxel-based analysis, FA, AD and RD were compared between patients and control subjects with a two-sample$t$-test using SPM8. The Pearson correlations were used to evaluate possible correlation between DTI metrics (FA, AD and RD) and disease symptoms (RLS severity scores measured with K-IRLS scores and RLS duration).

Results

RLS patients demonstrated decreased FA in the genu ofcorpus callosum and frontal white matter adjacent to inferior frontal gyrus (Brodmann 10) compared with healthycontrol subjects (P<0.001). For areas of decreased FA, both AD and RD were higher than that in control subjects.Correlation analysis between DTI parameters and clinical measures in RLS patients revealed a negative correlation between FA in the frontal white matter adjacent to inferior frontal gyrus and disease severity measured with K-IRLS score (r = 0.440, P <0.01). At the same frontal white matter region, AD and RD showed positive correlation with K-IRLS score (r = 0.304, P <001 for AD and r = 0, P <0.04 for RD).We did not find any other correlations between DTI parameters and disease duration.

Discussion

Though the pathomechanisms underlying the decreased FA in RLS patients are still unclear, it has been suggested that FA is known to be influenced by neuronal remodeling including both the degree of myelination and axonal packing density [2]. From this point of view, decrease in FA might be a pathologic process caused by neuronal changes in RLS. The decrease in FA in the genu of corpus callosum accompanied with increase in RD, suggesting demyelination of this highly organized inter-hemispheric white matter commissural fibers in RLS. Diffusion change in AD is equally important as change in RD because analysis of the diffusion changes with respect to AD and RD provides insight into the underlying mechanism of the changes in FA. In general, the FA increases when AD increases and/or RD decreases and vice versa. In the present study, both AD and RD were increased in RLS patients.To our knowledge, these findings of abnormal AD and RD in RLS patients have not previously been reported. Although the cellular mechanisms underlying the increased AD in RLS patients are still unclear, it was hypothesized that increased AD might result from reduced axonal density or caliber, increasing the extra-axonal space [3]. Therefore, it is tempting to speculate that the white matter damages in RLS brain may involve both the loss of axonal density and the loss of myelin.

Conclusion

Decreased FA in RLS patients revealed the microstructural abnormalities in the genu of corpus callosum and the frontal white matter. Among these areas, increased RD in the frontal white matter suggested the demyelination of white matter consistent with findings from previous postmortem study. Increased AD seems to be associated with reduced axonal density. Taken together, our findings maysuggest that both loss of axonal density and loss of myelin were responsible for the white matter abnormalitiesin RLS patients.

1. Rizzo G, Manners D, Vetrugno R, Tonon C, Malucelli E, Plazzi G, et al., Eur J Neurol 2011;19:1045-9.
2. Mori S, Zhang J., Neuron 2006;51:527–39.
3. Kumar R , Macey PM , Woo MA , Alger JR , Harper RM., Pediatr Res 2008;64(3): 275–80.

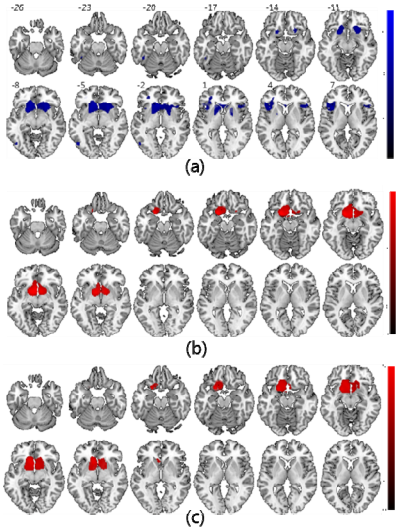

Figure 1.Regions of significantly reduced (a) FA-map in RLS patients with compared to healthy control subject. But Regions of significantly increased (b) AD-map nad (c) RD-map in RLS patients with compared to healthy control subject

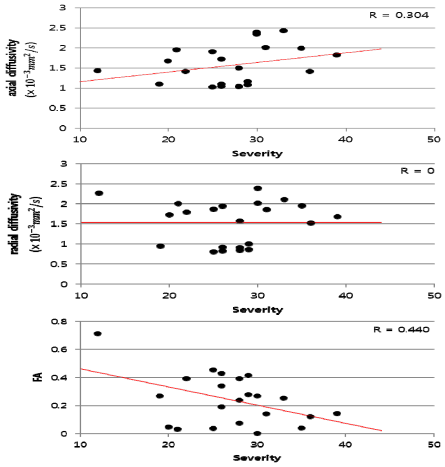

Figure 2. Correlation analysis between DTI metrics and clinical measures in RLS patients revealed a negative correlation between FA in the frontal white matter and disease severity measured with K-IRLS score (r = 0.440, P <0.01). At the same frontal white matter region, AD and RD showed positive correlation with K-IRLS score (r = 0.304, P <001 for AD and r = 0, P <0.04 for RD).