Quantitative MRI Studies for Restless Legs Syndrome: Cerebral Iron, Mophology and DTI

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INTRODUCTION

Restless legs syndrome (RLS) is a sensorimotor disorder that has 5-10% prevalence in Western countries [1]. Its clinical symptoms are characterized by uncontrollable urges to move the legs with uncomfortable sensations, causing severe sleep disturbances. Although a number of studies have suggested that brain iron deficiency is strongly coupled with RLS pathology [2-3], the exact mechanism of how iron deficiency affects brain function or morphology in RLS remains unclear due in part to the lack of integrated multimodal imaging findings. Because of the high demand for iron in the myelination in oligodendrocytes [4], we have hypothesized that cerebral insufficient iron level in RLS may cause myelin deficit, resulting in alterations in integrity of white matter structures. To test our hypothesis, our study design included a voxel-based relaxometry (VBR), voxel-based morphometry (VBM) and DTI for the study of cerebral iron, volumetric measurement, and water diffusivities, respectively.

METHODS

All MRI data were acquired on 3.0 T (Philips) with 8-channel head coil. Twenty-four RLS patients (52.4±14.3 yrs) and 24 age-matched controls (52.9±15 yrs) were studied for the brain iron and volume study. Six RLS patients (54.1±19.3 yrs) and 6 age-matched control subjects (54.4±14.5 yrs) were used for DTI study. ANCOVA was used for the statistical group comparison.

For the water diffusivity study, the DTI images were acquired with single-shot spin-echo EPI, SENSE factor 2.5 and 32 diffusion gradient directions with b value=1000s/mm^2. Radical diffusivity (RA) maps, fractional anisotropy (FA) maps were calculated from DTI data set after eddy current correction using DTI studio.

For the VBR analysis, a series of T_2-weighted images were obtained employing 14 equidistant echoes of 8ms (TR = 3792ms, acquisition matrix = 256×256, slice thickness = 4mm). After generation of the R_2 (1/T2) maps, the R_2 maps were spatially normalized via registration of each R_2 map into the Montreal Neurological Institute (MNI) space using the customized R_2 template. Subsequently, registered images were resampled and smoothed.

For the VBM analysis, high resolution T_1-weighted images (MPRAGE, TR/TE/TI=9.9/4.6/600ms, isotropic 1mm slice thickness) were acquired. All T_1 images were segmented into GM, WM, and CSF with the customized tissue probability maps using VBM5 toolbox [5]. After segmentation, the final tissue maps of GM, WM and CSF were normalized and modulated with the Jacobian determinants deformation parameters in order to analyze volume differences. Finally, the modulated tissue maps were smoothed with 8 mm FWHM.

RESULTS & DISCUSSION

Voxel-based DTI analysis shows a decrease in FA values and an increase in FA values in the sensory-motor pathway in RLS patients compared to normal controls (Fig. 1), which are consistent with previous DTI finding[6]. Radial diffusivity is known to be a sensitive index to the detection of change in the myelin integrity[7]. Importantly, our previous autopsy study revealed a decrease in concentrations of myelin-specific proteins such as myelin basic protein, a key structural protein in myelin, in RLS brains[8], suggesting the altered myelin compaction. In this context, the elevation of RA values reflects that the water diffusion perpendicular to the axons was maximized in RLS due to the increased freedom of cross-fiber. On the other hand, water diffusivity parallel to the axonal fibers is the lower FA values reflect the decreased axial diffusivity parallel to the myelin sheath in RLS. VBR analysis demonstrates lower R2 values in the SM pathway in RLS patients including primary motor and somatosensory cortex regions compared to controls (Fig. 2). R_2 (1/T_2), has been involved in the in vivo MR assessment of brain iron levels due to local magnetic field inhomogeneities caused by the presence of an iron storage protein of ferritin in the tissue[7]. Thus, decrease in R2 values (increased T2) may indicate the lower levels of ferritin due to iron deficiency in RLS compared to normal controls. VBM results also found the same decreased volumes in these regions in the RLS group, probably resulting from the reduced myelin contents in the white matter (Fig. 3).

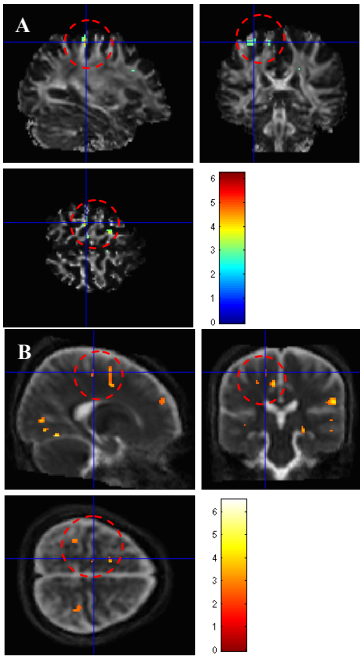

Fig.1 DTI analysis shows A) a decrease in FA values and B) an increase in RA values in sensorimotor circuit (red circle) in RLS compared to controls (P <0.01). Results are displayed on the average of FA maps and RA maps respectively. A color bar is a statistical T-score.

Therefore, taken together, impaired iron availability for myelin production in the brain may cause the alterations in the integrity of myelin sheath. Although we investigated the small sample size, increased radical diffusivity and decreased FA values in the sensorimotor areas may still support the hypothesis of pathology of hypomyelination due to iron deficiency. Therefore, the fusion of multi-modal imaging data provides a realistic approach to understanding the mechanism underlying RLS, and is clinically useful for its early diagnosis and interpretation of the pathological basis of RLS.

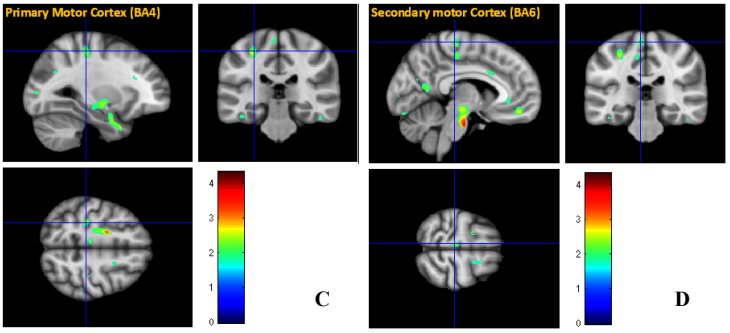

Fig. 2 VBR analysis shows a decrease in R2 values in the sensorimotor pathway involving primary cortex (C) and somatosensory cortex (D) in RLS patients compared to the age-matched controls. ANCOVA at uncorrected P < 0.01 with an age covariate

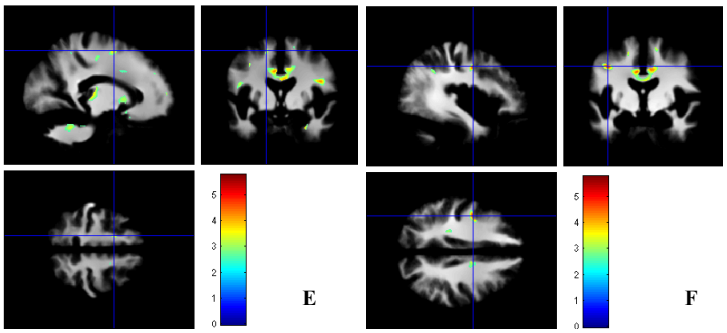

Fig. 3 VBM analysis shows a decrease in WM volume in the regions adjacent to sensorimotor areas in RLS patients compared to the controls. ANCOVA test at P < 0.005 uncorrected with an age covariate.

REFERENCES: [1]Walter et al., Sleep Med. 2004; [2]Ekbom, Neurology 1960; [3]Allen et al., Neurology 2001; [4]Larkin, New York: Springer 1990; [5]VBM5, http://dbm.neuro.uni-jena.de/vbm;[6]Unrath et al., Mov Disord 2007; [7]Song et al., NeuroImage 2002; [8]Lee et al., ISMRM 2009; [9]Bartzokis et al., MRM 1993

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