Global and Regional Mean Diffusivity Changes in Patients with Obstructive Sleep Apnea

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Introduction:

Obstructive sleep apnea (OSA) patients show brain tissue injury, expressed as regional gray matter volume loss (1), increased free water within tissue, as well as axonal deficits (2). The affected tissue is principally localized in autonomic control, limbic regions and interconnecting fibers, likely contributes to the exaggerated sympathetic tone, hypertension and cardiac arrhythmia, as well as cognitive and mood deficits in the condition. Although tissue injury appears in multiple brain structures and fiber bundles, it is unclear whether the predominant pathology is acute or chronic in newly-diagnosed, treatment-naïve OSA subjects. Determining the pathological nature in newly-diagnosed OSA subjects will assist interpretation of the processes contributing to the tissue injury. Diffusion tensor imaging (DTI)-based mean diffusivity (MD), which measures average diffusion of water within tissue, and can differentiate acute from chronic ischemic lesions, may be useful to examine the pathological nature of tissue injury in OSA subjects. Our aim was to assess global and regional MD values in newly-diagnosed, treatment-naïve OSA in comparison to age- and gender-matched control subjects. We hypothesized that global mean MD values will be reduced in OSA compared to control subjects, and localized declines will appear in multiple brain areas.

Materials and methods:

We studied 23 OSA (age, 44.4±9.3 years; body mass index, 30.1±5.4 kg/m^2; 20 male; apnea-hypopnea-index, 34.9±24.1 events/hour) and 23 age- and gender-matched control (age, 45.3±11.0 years; body mass index, 26.2±3.7 kg/m^2; 20 male) subjects. All OSA subjects were newly-diagnosed via overnight polysomnography with at least moderate severity (apnea-hypopnea-index ≥ 15), treatment-naïve, and recruited from the sleep disorders laboratory at the UCLA Medical Center. Control subjects were healthy, without any brain condition that might alter brain tissue, without evidence of sleep disorders (normal score on the Epworth Sleepiness Scale), and were recruited through the Southern California region. The study protocol was approved by the IRB at UCLA, and all subjects provided written informed consent prior to the study. Brain imaging studies were performed using a 3.0-Tesla MRI scanner (Magnetom Tim-Trio; Siemens, Erlangen, Germany). High-resolution T1-weighted images were acquired using a MPRAGE pulse sequence (TR = 2200 ms; TE = 2.2 ms; inversion-time = 900 ms; flip-angle = 9°; matrix-size = 256×256; FOV = 230×230 mm; slice-thickness = 1.0 mm). DTI data were acquired using a single-shot EPI with twice-refocused spin-echo pulse sequence (TR = 10,000 ms; TE = 87 ms; flip-angle = 90°; band-width = 1346 Hz/pixel; matrix-size = 128×128; FOV = 230×230 mm; slice-thickness = 2.0 mm, b = 0 and 700 s/mm^2, diffusion directions = 12, separate series = 4). We used diffusion-weighted images, and non-diffusion images to compute diffusion tensor matrices using DTI-Studio software. The diffusion tensor matrices were diagonalized, principal eigenvalues (λ1, λ2, and λ3) were determined, and MD values [(λ1+λ2+λ3)/3] were calculated using these eigenvalues. We realigned MD maps, computed from each DTI series, normalized to Montreal Neurological Institute (MNI) space, using unified segmentation approach (3), and smoothed with a Gaussian filter (10 mm). High-resolution T1-weighted images of OSA and control subjects were also normalized to MNI space, and normalized images were averaged to create background images for structural identification. Using global brain masks and normalized MD maps, global brain MD values from individual OSA and control subjects were calculated, and compared between groups for significant differences (ANCOVA; covariate, age; SPSS v18.0 software). The normalized and smoothed MD maps were compared voxel-by-voxel between the groups using ANCOVA (covariate, age; SPM8, uncorrected threshold, $p < 0.005$). The brain clusters with significant differences between OSA and control groups were overlaid onto background images for structural identification.

Results:

No significant differences in age ($p = 0.8$) or gender were present between groups. However, body-mass-indices were significantly higher in OSA ($p = 0.007$). The mean global brain MD was significantly reduced in OSA over control subjects (OSA vs controls; $1.003\pm0.062 \times 10^{-3}$ vs $1.045\pm0.072 \times 10^{-3}$ mm^2/s; $p = 0.012$). Multiple brain areas in OSA subjects showed reduced MD values, compared to control subjects (Fig. 1; gray regions). No brain sites showed increased MD values in OSA over control subjects. Brain sites in OSA that showed reduced MD values included the dorsal, ventral, and ventrolateral medulla, left cerebellar uvula, bilateral cerebellar crus I, right cerebellar crus II and middle cerebellar peduncle, right inferior cerebellar peduncle, left ventral temporal lobe, bilateral dorsal temporal white matter extending to occipital cortex, left ventral and right mid hippocampus, bilateral putamen, right insular cortex, bilateral posterior thalamus, left anterior thalamus, left external capsule, anterior corpus callosum, bilateral frontal and occipital white matter, left medial prefrontal cortex, right mid and posterior cingulate and cingulum bundle, and bilateral anterior, mid, and posterior corona radiata.

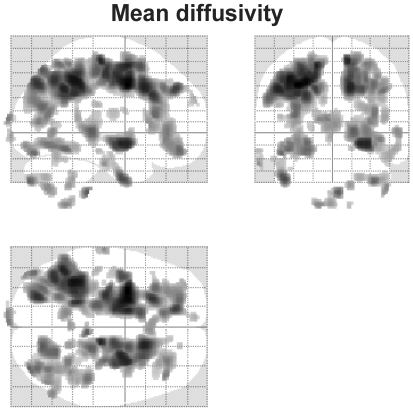

Fig. 1: Brain sites showing decreased MD values in OSA over control subjects.

Discussion:

Global brain mean MD values were significantly reduced in newly-diagnosed, treatment-naïve OSA over control subjects, suggesting that the tissue changes were in acute stages. These brain changes in OSA subjects were principally localized in critical cardiovascular and respiratory areas of the medulla, as well as the cerebellum, basal-ganglia, limbic regions, corpus callosum, and multiple regions in the corona radiata. The pathological mechanisms of tissue injury likely included hypoxemia-induced processes, leading to acute tissue changes in the condition.

References:

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