

## Cerebral Metabolism in Obstructive Sleep Apnea: An In-Vivo Proton MRS Study

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### Introduction:

Obstructive sleep apnea (OSA) is caused by obstruction of the airway characterized by repetitive pauses in breathing during sleep, each last long enough that one or more breaths are missed. In significant cases of OSA, sleep interruption can interfere with normal growth patterns, healing, and immune response, especially in children and young adults. MR spectroscopy (MRS) of brain documented changes in various metabolite ratios caused by hypoxia associated with apnea (1,2). Zimmerman and Aloia recently reviewed the neuro-imaging fMRI and MRS studies in OSA patients. Support for structural abnormalities was mixed, but converging evidence suggests the hippocampus may be atrophic in patients with OSA (3). Neurochemical evidence is supportive of white-matter impairment in OSA, particularly in frontal lobe. Here we report the determination of absolute concentration of cerebral metabolites in OSA patients using proton MRS from various regions of the brain to monitor the regional variation of cerebral metabolites in these patients.

### Patients and Methods:

75 consecutive patients with OSA who fulfilled the following inclusion criteria were enrolled in this study: Apnoea/hypopnoea index (AHI) >5, age <65 yrs, no history of stroke, and absence of neurological disease or history of head injury. Patients with claustrophobia or metallic implants were excluded. All patients were diagnosed in the sleep laboratory of the Department of Medicine. The non-apneic were subjects who had AHI < 5 on polysomnography with similar inclusion criteria as patients and these OSA negative patients served as controls (n=25). All subjects suspected to have OSA underwent polysomnography (PSG) and subsequently underwent proton MRS of brain, the following morning. Anthropometric profiles like body weight, body mass index, waist-to-hip ratio, skin fold thickness, etc were measured. Proton single-voxel MRS was carried at 1.5 T (MAGNETOM Avanto, Siemens Healthcare Sector, Germany). Prior to performing MRS, multi-slice T1-weighted images in three orthogonal planes of the whole brain were acquired. Using these images, the region of interest for MRS was selected that includes areas like frontal, temporal and occipital regions of the brain. Magnetic field shimming both globally and over the voxel was carried. Spectra were obtained at an echo time (TE) of 30 ms using PRESS pulse sequence with a repetition time of 2 sec. MR specialists were blinded for the clinical and PSG data, analyzed the MRS data. Absolute concentration of brain metabolites was estimated using LC Model which allows deconvolution of spectra by using a basis set of reference spectra as well as using the Cramer-Rao lower bounds. Concentration of metabolites was expressed as mmol/L. Institute Ethics Committee approved the study, and written informed consent was obtained.

### Results:

The OSA positive subjects had a mean BMI of  $30.5 \pm 6.3$  kg/m<sup>2</sup> while the control subjects had a mean BMI of  $27.8 \pm 5.8$  kg/m<sup>2</sup> ( $p > 0.05$ ). The waist-hip ratio was significantly high ( $p = 0.05$ ) in OSA positive subjects as compared to control subjects. The apnea/hypopnea index (AHI) were significantly high ( $p = 0.001$ ) in OSA positive subjects ( $38.8 \pm 29.1$  events/hour) compared to control subjects ( $1.0 \pm 1.0$  events/hour). Proton MR spectrum from the frontal white matter is shown in the top panel of the Figure shown. The concentration of tNAA [(N-acetylaspartate (NAA)+NAA glutamate (NAAG)] was statistically significantly lower ( $p < 0.05$ ) in OSA positive patients in the left temporal ( $8.5 \pm 0.8$  versus  $7.3 \pm 1.1$  mmol/L – middle panel of Figure) compared to OSA negative patients (controls). The concentration of mI was higher in the occipital grey matter in OSA positive patients compared controls. The Glx resonance showed higher concentration (but statistically not significant) in the left temporal ( $8.0 \pm 1.2$  vs  $6.9 \pm 1.1$  mmol/L – see middle panel of Figure) and the occipital region ( $10.3 \pm 0.9$  vs.  $9.4 \pm 1.6$  mmol/L) of the brain of OSA positive patients compared to controls while it is reduced in the frontal grey area (see right panel of the Figure shown below). Other metabolites like Cho and Cr did not show any difference between patients and controls in various regions of the brain studied. All the brain metabolites were also similar in the left hippocampal region between OSA positive and control subjects.

### Discussion:

The absolute concentration of metabolites like tNAA, Cr/PCr, mI, Cho and Glx were determined in five regions of the brain, namely left hippocampus, temporal, frontal white and grey matter and occipital grey matter in OSA positive patients and controls. Generally, the concentration of most metabolites were similar in all the five regions studied between controls and OSA positive patients except for lower tNAA in left temporal and lower mI in occipital grey matter compared to controls. Further, our results showed that OSA positive patients had higher concentration of Glx in the left temporal and occipital regions although not statistically significant compared to controls. Reduction in the concentration of tNAA suggests neuronal damage, probably caused by repeated apneic episodes and higher Glx concentration may be indicative of the hypoxic condition that these patients experience. However, the concentration of other brain metabolites in other regions studied was similar between OSA positive patients and controls. This may probably be due to adaptive mechanism of brain which may diminish the detrimental effects of recurrent nocturnal hypoxia in OSA patients [4]. It has been reported that elevated CO<sub>2</sub> increases the oxygen uptake by its influence on the regulation of alveolar ventilation and ventilation-perfusion matching and facilitates oxygen delivery to the tissues and increases cerebral blood flow. These biological effects of hypercapnia may be especially important in patients with severe OSA [4]. However, studies reported in literature documented alterations in the NAA and Cho concentration primarily in the frontal lobe white matter [1,2]. In our study OSA positive patients showed lower tNAA in left temporal and lower mI in the occipital grey matter compared to controls. These observations warrant further systematic study on large cohort of patients from various brain regions in OSA patients with varying grade (severe to mild) to understand the metabolic abnormalities and adaptive mechanisms associated with obstructive sleep apnea.

**References:** (1) Zimmerman ME, Aloia MS. *J Clin Sleep Med.* 2006; 15: 461-71; (2) Kamba M, et al., *Am J Respir Crit Care Med.* 1997; 156 :296-8; (3) Alchantis M et al. *Eur Respir J.* 2004; 24: 980-6. (4) Brzecka A. *Acta Neurobiol Exp (Wars)* 2007; 67: 197-206.

