European Review for Medical and Pharmacological Sciences 2013; 17: 1198-1204

Correlation between hippocampal volume and excessive daytime sleepiness in obstructive sleep apnea syndrome

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Abstract. – BACKGROUND/AIM: The limbic system, specifically the hippocampus, plays a key role in controlling the sleep-wake cycle. Changes in these particular structures of the central nervous system have been suggested to be related to obstructive sleep apnea syndrome (OSAS). We hypothesized that reduced hippocampal volume is a risk factor for excessive daytime sleepiness (EDS) in OSAS.

PATIENTS AND METHODS: Twenty-two patients with newly diagnosed OSAS and 20 healthy controls were included in the present study. Polysomnography was performed for each participant to determine the presence of OSAS. EDS was defined based on the Epworth sleepiness scale (ESS) score, and patients were grouped as sleepy or non-sleepy according to this score. The hippocampal volume was calculated by MR volumetry using a manual tracing technique.

RESULTS: There was no significant difference between groups in demographic variables. The hippocampus was markedly smaller in the OSAS groups than in controls ($p < 0.001$ Hippocampal volume was negatively correlated with the ESS score ($r = -0.631$, $p = 0.002$).

CONCLUSIONS: Our findings suggest that EDS is associated with reduced hippocampal volume in OSAS.

Key Words:

Obstructive sleep apnea syndrome, Excessive daytime sleepiness, Epworth sleepiness scale, Hippocampus, MR volumetry.

Introduction

Obstructive sleep apnea syndrome (OSAS) is a multifactorial disorder characterized by repeated episodes of apnea/hypopnea and arousal, leading to hypoxia[1]. OSAS has a prevalence of 3-7% and male predominance, and it has shown increasing incidence in recent years[2]. OSAS causes serious morbidity and mortality, including increased cardiovascular risk, heart failure, arrhythmia, and systemic or pulmonary hypertension[3].

The limbic system and hippocampus are primary regions of the central nervous system (CNS) that control sleep-wake patterns, light-dark-cycle adaptation, mood regulation, and neuronal excitation[4,5]. The hippocampus is a complex structure that originates from the dorsomedial telencephalon, and its integration with the neocortex exhibits a peculiar developmental pattern during embryogenesis and continuing into adulthood[6]. The hippocampus demonstrates age-related atrophy, and it may be affected by neurotoxic drug abuse, hypoxic injury, diabetes mellitus, hypertension, obesity, sleep disorders, and trauma[7,8]. Repeated episodes of apnea/hypopnea in OSAS have been demonstrated to lead to hypoxia and to result in neurostructural changes[9]. Cellular damage to the hippocampus contributes to neuropsychological impairment, including insomnia and cognitive dysfunction[10,11]. Excessive daytime sleepiness (EDS) is a common symptom in OSAS and is associated with accidents and reduced productivity[12,13]. Sleep fragmentation produces decrements in cortical functioning, leading to EDS, and is correlated with the severity of OSAS and assessed by increased Epworth sleepiness scale (ESS) scores[14,15]. ESS is commonly used to assess the subjective degree of EDS[16].

Magnetic resonance (MR) imaging modalities have been widely used to evaluate neurological and neuropsychiatric disorders[17,18]. MR volumetric studies have used highly efficient and reliable techniques to evaluate neurostructural changes[19,20]. To our knowledge no study has examined the relationship between the hippocampus and severity of OSAS using the manual tracing technique in MR volumetry. We hypothesized that repeated episodes of apnea/hy-

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popnea might cause neurostructural changes in the hippocampus and also contribute to EDS in OSAS. Based on this hypothesis, this study aimed to evaluate the relationship between EDS and the hippocampal volume in a cohort of subjects with OSAS and controls.

Patients and Methods

Patients referred to the Sleep Unit of the Pulmonary Medicine Department between January 2009 and December 2010 with newly diagnosed moderate to severe OSAS to further evaluate disease participated in the present study. Patients with neuropsychiatric diseases, or a history of drug abuse and those who were pregnant or lactating or who were under 18 or over 60 years of age were excluded. The control group consisted of normal subjects who were recruited by a local advertisement. The study was planned according to the Helsinki Declaration and was approved by the Research Ethics Board of our institution. Informed consent was obtained from all participants.

Sleep Study

All individuals underwent polysomnography (P-series; Compumedics Sleep, Melbourne, Australia) that included an electroencephalogram, electrooculogram, electromyogram, and electrocardiogram. Ventilatory monitoring included an oronasal thermistor, finger pulse oximeter, respiratory inductive plethysmograph, and sleep position. Sleep staging score used guidelines as described by Johns[16]. Apnea was defined as airflow interruption equal to or longer than 10 seconds. Hypopnea was defined as airflow amplitude reduction ≥50%, oxygen saturation reduction ≥3%, or reduction associated with arousals. The apnea/hypopnea index (AHI) was defined as the number of occurrences of apnea/hypopneas per hour (/h) during sleep[21]. Individuals with an AHI ≥ 5 were considered to have OSAS, which was further classified as mild (AHI ≥ 5 < 15), moderate (AHI ≥ 15 < 30), or severe (AHI ≥ 30).

ESS is widely used to evaluate EDS and comprises eight items (sitting and reading; watching television; sitting inactively in a public place; sitting as a passenger in a car for an hour; lying down in the afternoon; sitting and talking to someone; sitting quietly after lunch; and sitting in a car while stopped for a few minutes in traffic) that are rated from 0 (no chance of dozing) to 3 (high chance of dozing); thus, possible scores range from 0 (least sleepy) to 24 (most sleepy). EDS was defined as an ESS score higher than 11. Those with OSAS were categorized as sleepy or non-sleepy according to the ESS score[14,16].

Technique

We collected volumetric MR images using a 1.5-Tesla magnet (Magnetom-Vision-Plus; Siemens-Medical-Solutions, Erlangen, Germany) equipped with a standard head coil and using three-dimensional magnetization-prepared rapid-gradient echo sequences [repetition time/echo time/time to inversion (TR/TE/TI) = 10/4/300, flip angle = 10°, field of view (FOV) = 250, slice thickness = 1.25 mm, matrix = 192 × 256, number of excitations (NEX) = 1) with good gray/white matter contrast. Fluid attenuated inversion recovery (FLAIR) sequences (TR/TE = 6000/80, FOV = 250, slice = 5 mm, matrix = 192 × 256, NEX=1) was obtained to exclude CNS pathologies.

A previously described[19,20], manual mouse-driving technique was used for both the right and left hippocampus to outline the hippocampus in the workstation (Leonardo; Siemens-Medical Solutions). Volumetric MR images were re-oriented in the coronal plane using the inter-commissural line. The hippocampal volume was measured from the most anterior slice where the head of the hippocampus was clearly visible to the most posterior slice where the tail of hippocampus was not clearly visible. The dentate gyrus, subiculum, alveus, cornu ammonis, and fimbria were included. The choroid plexus and cerebrospinal fluid spaces around the hippocampus and fornix were excluded. The boundaries of the hippocampus were traced as follows: alveus and uncal recess posteriorly, crus fornicis and plexus choroideus superiorly, subiculum and parahippocampal gyrus inferiorly, temporal horn laterally, and peri-mesencephalic cistern medially. Hippocampal volumes were obtained from coronal slices and were multiplied by the slice thickness. To exclude CNS size variability, a normalization equation was used, multiplying the hippocampal volume by the proportion of the midsagittal area of the CNS:

$$HCV_n = (MSA_m \div MSA_o) \times HCV_o,$$

where HCV_n is the normalized hippocampal volume, MSA_m is the mean value of the midsagittal area, and MSA_o and HCV_o are the measured

original midsagittal area and original hippocampal volume, respectively, as described previously (Figure 1)[17,22].

Manual tracing of the hippocampal border and calculation of the hippocampal volume were performed by one expert (B.H.) trained in MR volumetry and blinded to the diagnosis. On control MR images, to evaluate interobserver reliability, the hippocampal volume was calculated by a second expert (A.D.), and the intraclass correlation coefficient (ICC = 0.85) was good.

Statistical Analysis

Statistical analysis was performed using SPSS software (version 18.0; SPSS, Inc., Chicago, IL, USA). Normally distributed variables were tested using the Shapiro-Wilk test. Nonparametric tests were used in the case of variables that were not normally distributed. Analysis of categorical variables was performed using chi-squared test. Comparisons of groups were performed using the Kruskal-Wallis test and Mann-Whitney *U*-test with Bonferroni's correction for the multiple groups. Logarithmic transformation of AHI and the oxygen desaturation index (ODI) were used to achieve a normal distribution of residuals. We performed a bivariate correlation analysis to evaluate significant relationships between sleep data and the normalized hippocampal volume. Results are expressed as the median (min-max). A *p*-value less than 0.05 was deemed statistically significant.

Results

Twenty-two consecutive adult OSAS patients were divided into two groups: the non-sleepy OSAS [n = 10; 7/3 male/female; median age: 45.5 years (range: 32-53 years)] and the sleepy OSAS [n = 12; 10/2 male/female; median age: 47.3 years (range: 28-60 years)] groups. The control group consisted of healthy people [n = 20; 14/6 male/female; median age: 42.0 years (range: 29-58 years)]. The groups showed no difference in demographic variables (Table I).

The oxygen saturation (SpO_2) was higher and the arousal index, ODI, and oxygen desaturation (SpO_2 < 90%) were lower in control subjects than in sleepy and non-sleepy OSAS subjects. Right ($p < 0.001$) and left ($p < 0.001$) normalized hippocampal volumes of sleepy OSAS patients were significantly lower than those of non-sleepy OSAS and control subjects (Table II).

Right and left normalized hippocampal volumes were negatively correlated with ESS scores ($r = –0.641$, $p = 0.001$; $r = –0.631$, $p = 0.002$), respectively; Figure 2).

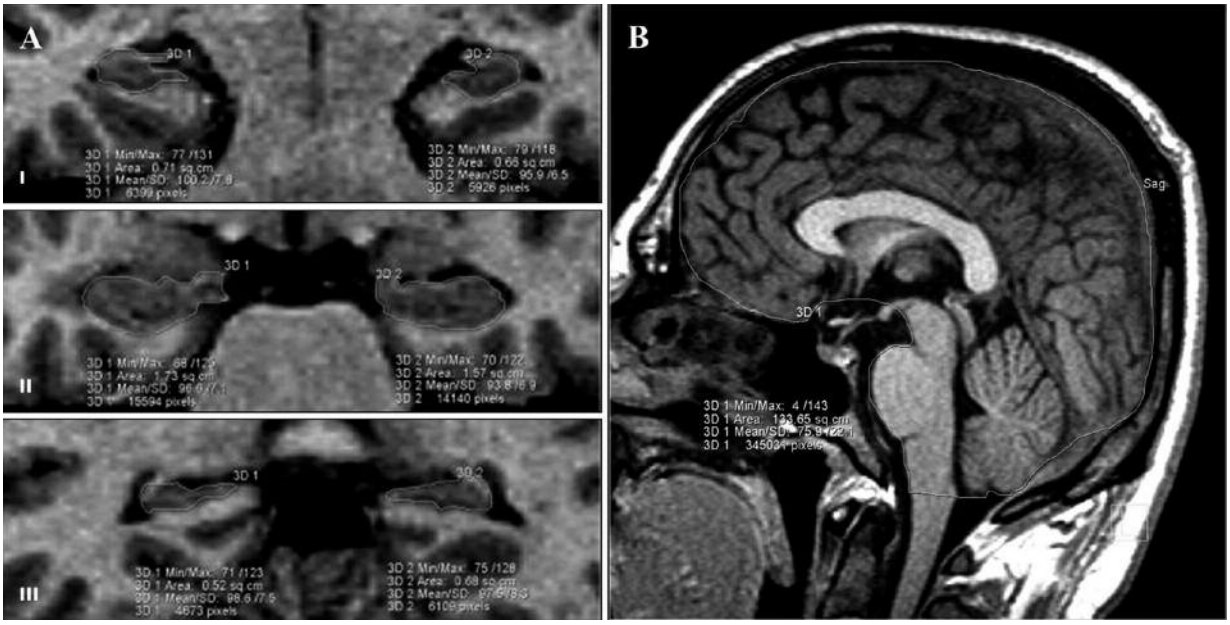

Figure 1. ***A,*** Consecutive coronal volumetric magnetic resonance (MR) images of the hippocampus of an OSAS patient. Delineation of the head (A$_I$), body (A$_{II}$), and tail (A$_{III}$) of the hippocampus. ***B,*** Sagittal T1-weighted MR image from the midsagittal area of the central nervous system was measured with manual tracing.

Table I. Demographic data of groups.

Variables	Median (min-max)			*p*-value
	Control (n = 20)	Non-sleepy OSAS (n = 10)	Sleepy OSAS (n = 12)	
Gender (M/F)	14/6	7/3	10/2	.624
Age (years)	42.0 (29-58)	45.5 (32-53)	49.5 (28-60)	.286
TST (h)	384.3 (303-445)	381.0 (301-451)	378.0 (262-444)	.908

OSAS: obstructive sleep apnea syndrome; M: male; F: female; TST: total sleep time.

Discussion

In the present study, we found significantly reduced hippocampal volume in the OSAS groups compared with the control group, a finding that is consistent with the literature[13-15]. We also found a decrease in the hippocampal volume and a negative correlation with the ESS score in both the sleepy and non-sleepy OSAS groups.

OSAS is characterized by repeated episodes of apnea/hypopnea and arousal[21]. OSAS reduces the oxygen content of breathed air, thereby reducing CNS oxygenation during sleep[23]. CNS structures show different vulnerability patterns to and consequences of hypoxia and reduced perfusion resulting from repeated episodes of apnea/hypopnea[15,24]. In a rodent model, intermittent hypoxia caused apoptosis, neurodegeneration, and neuronal damage, altered dendritic arborization, and reduced neurotransmission in the hippocampus[25]. A study conducted in rats found marked apoptosis in the hippocampus in conjunction with chronic episodes of hypoxia[26]. The hippocampus has been shown to be highly vulnerable to hypoxic damage in humans and animals[27].

Emotional regulation, cognition, and autonomic and somatic functions, including sleep-wake states and breath control, are integrated by a set of limbic system structures that includes the anterior thalamus, hypothalamus, hippocampus, fornix, and mammillary bodies[18,29]. Hippocampal volume varies according to an individual's profession. For example, navigation-related professions are associated with larger hippocampal volume[8]. The hippocampus is characterized by age-related atrophy in individuals > 60 years of age[7]. Neurotoxic and hypoxic injury, diabetes mellitus, hypertension, obesity, sleep disorders, trauma, and aging are associated with reduced hippocampal volume[29].

OSAS develops before clinical findings become severe and apparent, with notable neurobehavioral manifestations[30]. Several studies have demonstrated that neurochemical and morphological alterations might underlie sleep-wake disturbances in sleep disorders[31,32]. Damage to gray matter can

Table II. Polysomnography data and hippocampal volume of groups.

Variables	Median (min-max)			*p*-value			
	Control (n = 20)	Non-sleepy OSAS (n = 10)	Sleepy OSAS (n = 12)	All groups	C&N groups	C&S groups	N&S groups
SpO_2 (%)	95.0 (91-98)	92.0 (84-95)	86.0 (78-92)	< .001	< .001	< .001	= .003
SpO_2 < 90%	0.0 (0-4)	8.0 (1-33)	87.0 (11-194)	< .001	< .001	< .001	= .002
ODI (/h)	4.0 (0-5)	8.0 (5-13)	10.0 (3-18)	< .001	< .001	< .001	= .808
Arousals (/h)	10.5 (2.2-13.6)	27.4 (6.0-51.0)	41.4 (30.7-95.0)	< .001	= .004	< .001	= .007
AHI (/h)	0.9 (0.0-3.0)	26.9 (18.2-50.5)	57.6 (34.4-93.1)	< .001	< .001	< .001	< .001
ESS score	2.0 (1-7)	8.0 (6-10)	17.5 (13-21)	< .001	< .001	< .001	< .001
R HCVn (cm^3)	32.7 (28.4-37.3)	31.8 (29.9-34.7)	27.4 (24.2-30.2)	< .001	= .328	< .001	< .001
L HCVn (cm^3)	32.1 (25.9-37.9)	30.2 (29.3-32.9)	27.2 (24.5-30.9)	< .001	= .183	< .001	< .001

OSAS: Obstructive sleep apnea syndrome; SpO_2: oxygen saturation; SpO_2 < 90%: oxygen desaturation; ODI: oxygen desaturation index; AHI: apnea hypopnea index; ESS: Epworth sleepiness scale; R/L HCVn: right/left normalized hippocampal volume; C&N: control and non-sleepy OSAS; C&S: control and sleepy OSAS; N&S: non-sleepy and sleepy OSAS groups.

contribute to respiratory regulation disturbances, EDS, cognitive impairment, and difficulties with memory due to decreased attention[13,33]. White matter, including axonal linking of the limbic system, is also affected in OSAS with neuropsychological symptoms[4,34]. Mammillary body and fornix degeneration are associated with EDS[35,36]. A high prevalence of EDS with CNS structural changes is found in encephalitis, traumatic CNS injury, temporal lobe epilepsy, carbon monoxide poisoning, Parkinson's disease, Huntington's disease, central hypoventilation syndrome, narcolepsy, hemispheric stroke, heart failure, atherosclerosis, hypertension, and diabetes mellitus[29,37-41]. Areas of gray matter loss cause overlapping symptoms, similar to those with sleep disorders[42,43].

MR imaging modalities, including MR spectroscopy, T2 relaxometry, and diffusion-weighted imaging, have been used to evaluate neurochemical properties of the CNS and hippocampus in OSAS[31,32]. In addition to these modalities, voxel-based morphometry (VBM) has been used to investigate neurostructural changes in sleep disorders. VBM has shown various degree of change in cortical and deep grey matter concentration in OSAS[33,39,44-47]. In two studies performed by Morrell using VBM, different hippocampal effects were reported[48,49]. Controversial results have also been reported in studies by Mackey that used both VBM and fractioned anisotropic mapping techniques and showed varying hippocampal effects in OSAS groups[34,50]. In a single study using the manual tracing MR volumetry technique, Kumar reported diminished mammillary body volume in OSAS groups[36]. However, manual tracing MR volumetry, a highly sensitive technique that is the gold standard, was not used to evaluate the hippocampal volume in OSAS. In the present study, we used manual tracing to assess MR volumetry because of the higher sensitivity and reproducibility of a particular algorithm to evaluate volumetric changes.

Conclusions

Our results showed a correlation between reduced hippocampal volume and the severity of OSAS, a finding that is consistent with the literature[30-32]. We also found a significant relationship between reduced hippocampal volume and EDS in OSAS. Further studies are needed to clarify the complex relationship between hippocampal volume and EDS in OSAS.

Acknowledgements

We thank F. Obuz, MD, Medical Record Committee, G. Ozkaya, PhD, Statistics Department, B. Ozturk, MD, C. Erdogan, MD, and E. Tuncel, MD, Radiology Department, Uludag University.

Conflict of Interest

None declared.

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