The Egyptian Society of Chest Diseases and Tuberculosis

Egyptian Journal of Chest Diseases and Tuberculosis

www.elsevier.com/locate/ejcdt
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ORIGINAL ARTICLE

Proton magnetic resonance spectroscopy of brain in obstructive sleep apnea in Egyptian subjects

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Abstract *Objective:* The overall objective of this work is to study the cerebral metabolic changes in patients with OSA and to determine the usefulness of MRS as an objective method for evaluation of CNS impairment in these patients.

Materials and methods: This study included two groups; group1 fifteen (15) patients diagnosed with obstructive sleep apnea hypopnea syndrome, and group 2 ten (10) healthy volunteers of comparable age.

Magnetic resonance spectra were obtained from frontal periventricular white matter.

For all subjects, height, body weight, and BMI were assessed. Waist and hip circumference were measured and waist/hip ratio (W/H ratio) was calculated.

Overnight polysomnography (PSG) to identify sleep apnea was done. Daytime sleepiness was evaluated by the Epworth Sleepiness Scale. Symptoms of anxiety and depression were measured with the Hospital Anxiety and Depression Scale (HADS).

Results: N-acetylaspartate-to-creatine (NAA/Cr) and choline-to-creatine (Cho/Cr) ratios were significantly lower in the frontal white matter of obstructive sleep apnea patients when compared to controls. Absolute concentrations of N-acetylaspartate (NAA) and choline (Cho) were also significantly reduced in the frontal white matter of patients with sleep apnea. Statistically significant negative correlations existed between AHI and metabolites concentrations and ratios in patients with OSAHS. Significant positive correlations existed in patients with OSAHS between Hospital and depression scale for depression (HAD-D) and AHI ($r = 0.764$, $p = 0.001$), ODI ($r = 0.571$,

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$p = 0.026$), and ESS ($r = 0.644$, $p = 0.010$), respectively. Significant positive correlations existed in patients with OSAHS between Hospital and depression scale for anxiety (HAD-A) and AHI ($r = 0.753$, $p = 0.001$), and ESS ($r = 0.537$, $p = 0.039$), respectively. *Multivariate Linear* regression model of factors predictive showed AHI as the main predictor factor for choline to creatine ratio in patients with OSAHS with $t = 5.180$, at $p < 0.001$.

Conclusion: OSA patients show abnormal brain metabolites related to neuronal damage due to intermittent chronic hypoxemia. Anxious and depressive symptoms are highly prevalent in patients with severe untreated OSAS. The severity of depressive and anxious symptoms may be related to excessive daytime sleepiness and to nocturnal hypoxemia both of which are strongly correlated to brain metabolites. AHI seems to be the main predictor factor for choline to creatine ratio in patients with OSAHS.

Introduction

Obstructive sleep apnea is a major public health problem worldwide [1–3]. It is estimated to affect up to 4% of the general adult population [4]. It is associated with several consequences including neurocognitive impairment [5]. To date, the pathophysiology of the cognitive deficits reported in OSA patients has not been determined.

Repeated sleep apneic episodes may lead to CNS impairment in patients with obstructive sleep apnea (OSA). Excessive daytime sleepiness and cognitive and emotional deficits are common daytime symptoms of OSA. Hypoxic brain damage and fragmentation of sleep are generally thought to be causes of these deficits [6].

Some researchers argue that excessive daytime somnolence is the leading cause of the cognitive deficits, while others propose that nocturnal hypoxemia is the main contributing factor [4,7].

Magnetic resonance spectroscopy (MRS) is a non-invasive method, useful for evaluating local metabolic changes in various conditions affecting the central nervous system as in patients with OSAHS [8].

Several studies have shown that executive dysfunction in OSA patients may persist even after nasal continuous positive airway pressure (nCPAP) treatment. Cognitive executive functions are associated with specific prefrontal-subcortical brain circuits, thus it has been proposed that OSAS may promote irreversible anoxic brain damage affecting the prefrontal cortex [8].

Subjects and methods

This study included two groups:

Group 1: fifteen (15) patients newly diagnosed with severe obstructive sleep apnea hypopnea syndrome, and

Group 2: ten (10) healthy volunteers of comparable age.

Fifteen (15) consecutive patients newly diagnosed with severe obstructive sleep apnea hypopnea syndrome who fulfilled the following inclusion criteria were enrolled in this study: apnea/hypopnea index (AHI) >30, age <65 years, Patients' exclusion criteria were: concomitant metabolic disease (DM, hypertension), history of stroke, presence of cardiac disease, neurological disease or history of head injury or CPAP/BiPAP therapy, presence of other sleep disorders, and presence of obstructive lung disease. Patients with claustrophobia or metallic implants were also excluded.

Anthropometric profile

Body weight was recorded in all patients, in erect position without shoes and wearing only light indoor clothes, height was measured and body mass index (BMI) was calculated as body weight/height^2 (kg/m^2) [9,10].

Waist circumference was measured midway between the lower rib cage margin and the anterior superior iliac spine. Hip circumference was measured at the maximum circumference of the buttocks, the subject standing with feet placed together and waist–hip ratio (W–HR) was calculated [11].

Nocturnal sleep studies

All patients underwent overnight polysomnography using Respironics Alice 5 system (RESPIRONICS, Germany Inc.). It is a level I device that records parameters such as body position, effort (thorax and abdomen), nasal flow (canula and/or thermistor), snoring (canula and/or microphone), SpO$_2$, plethysmogram, pulse rate, ECG, CPAP/BiPAP, and PLM overnight in the hospital. Recordings of at least 5 h were required to validate the sleep study. The analysis was carried out automatically and manually. Respiratory events were scored using standard criteria [12,13].

The apnea hypopnea index (AHI) was defined as the total number of apneas and hypopneas per hour of sleep. As indices of nocturnal hypoxemia we considered the oxygen desaturation index (this is the number of times that the oxygen saturation falls by more than 3 or 4 percent per hour of sleep), T90 (the fraction of sleep time spent below an oxygen saturation of 90 percent) and the minimal value recorded during sleep (minimal SaO$_2$).

Assessment of daytime sleepiness

The Epworth Sleepiness Scale (ESS) [14,15] was used for assessing daytime sleepiness. This is a commonly used self-administered scale with eight items of about how easily the respondent would fall asleep in different situations. The items are scored on a 0–3 scale, which are added to give an overall score of 0–24. Higher scores indicate more sleepiness. ESS

score 2–10 is considered 'normal' and >10 indicative of pathological sleepiness.

Assessment of anxiety and depression

Symptoms of anxiety and depression were measured with the Hospital Anxiety and Depression Scale (HADS) [16]. The HADS is a validated and reliable psychological measure widely used in both hospitalized and primary care patients with chronic diseases. The HADS is divided into an anxiety subscale (HADS-A) and a depression subscale (HADS-D) both containing seven items, rated 0–3, giving a possible maximum score for anxiety and depression of 21. The scores range from 0 to 21 for each subscale, with a score of 0–7 denoting a non case, 8–10 a possible case, and 11 or higher a probable case.

Neuroimaging

^{1}H MR spectroscopy was carried at 1.5 Tesla (AVANTO, Siemens, Germany) using a phased array head coil. Prior to performing ^{1}H MR spectroscopy, multislice T1-weighted images in the axial, coronal and sagittal planes of the whole brain were acquired using a standard spin-echo pulse sequence. These images were then used to select the region of interest for performing the MR spectroscopy.

Multi-voxel proton MR spectra were recorded using the PRESS pulse sequence (Fig. 10). Absolute concentration of metabolites (NAA, Cho and Cr) and ratios (NAA/Cr and Cho/Cr) at prefrontal cortex and frontal periventricular white matter were recorded. The concentration of metabolites was expressed as milli moles per liter (mmol/l).

Statistical analysis

Data were fed to the computer using IBM SPSS software package version 20.0.

Qualitative data were described using number and percent. Comparison between different groups regarding categorical variables was tested using the Chi-square test. When more than 20% of the cells have expected count less than 5, correction for chi-square was conducted using the Fisher's Exact test or Monte Carlo correction.

The distributions of quantitative variables were tested for normality using the Shapiro–Wilk test and D'Agstino test, also the Histogram and QQ plot were used for vision test. If it reveals normal data distribution, parametric tests were applied.

If the data were abnormally distributed, non-parametric tests were used.

Quantitative data were described using mean and standard deviation for normally distributed data while abnormally distributed data were expressed using median, minimum and maximum.

For normally distributed data, comparison between two independent population were done using the independent *t*-test.

For abnormally distributed data, Mann–Whitney Test (for data distribution that was significantly deviated from normal) was used to analyze two independent population.

Significance test results are quoted as two-tailed probabilities. Significance of the obtained results was judged at the 5% level.

Results

A total of 25 subjects underwent overnight polysomnography and had early morning ^{1}H MRS of the brain. Of these, the apneic group consisted of 15 patients who had AHI >30/h (female 4, male 11) while the remaining 10 were non-apneic with AHI <5/h (female 3, male 7). The mean age of apneic and non-apneic was 48.07 ± 6.92 and 49.10 ± 7.64 year, respectively. The apneic patients had a statistically significantly higher mean BMI compared to non-apneic subjects (47.31 ± 13.53 and 26.20 ± 2.12 kg/m^2, respectively, $p < 0.001$. The waist–hip ratio was significantly higher ($P < 0.05$) in apneic patients as compared to non apneic (Table 1).

Seven patients with OSAHS (46.7%) had an anxiety score ⩾11 (probable anxiety), and 15 patients with OSAHS that is to say all of the studied patients (100%) had a depression score ⩾11 (probable depression). Whereas patients without OSAHS did not show evidence of anxiety or depression (Table 2) (Fig. 1).

The mean Epworth Sleepiness Scale (ESS) value in patients with OSAHS (17.73 ± 2.46) was statistically significantly higher ($P < 0.001$) as compared to patients without OSAHS (3.40 ± 1.17). The AHI was statistically significantly higher ($P < 0.001$) in patients with OSAHS (65.47 ± 20.34 events/h) as compared to patients without OSAHS (2.70 ± 1.16 events/h). The average SaO$_2$ *and* minimum SaO2 were statistically significantly lower in patients with OSAHS compared to patients without OSAHS (86.40 ± 6.20, 94.0 ± 2.67%, respectively, $p = 0.001$ *and* 64.27 ± 10.10, 89.90 ± 2.77%, respectively, $p < 0.001$). t90 was statistically significantly

Table 1 Baseline characteristics of the study groups.

	Patients with OSAHS ($n = 15$)	Patients without OSAHS ($n = 10$)	p
Age (years)	48.07 ± 6.92	49.10 ± 7.64	0.729
Gender, *n* (%)			
Male	11 (73.3)	7 (70.0)	1.000
Female	4 (26.7)	3 (30.0)	
BMI (kg/m^2)	47.31 ± 13.53	26.20 ± 2.12	<0.001[*]
Waist–hip ratio	1.03 ± 0.06	0.98 ± 0.02	0.010[*]
ESS	17.73 ± 2.46	3.40 ± 1.17	<0.001[*]

Results are expressed as mean ± standard deviation unless otherwise specified. Definition of abbreviations: *n*, number of patients; BMI, body mass index; ESS, Epworth Sleepiness Scale.
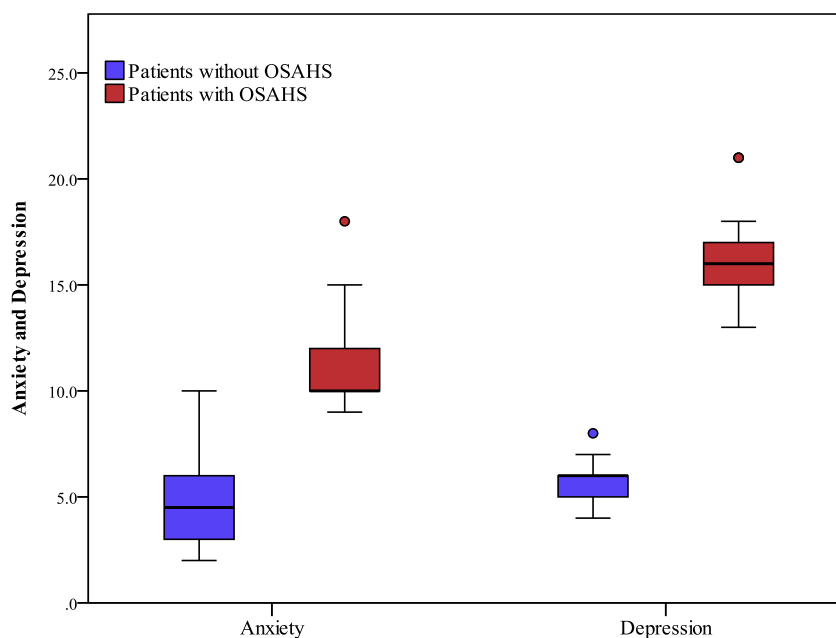[*] Statistically significant at $p \leqslant 0.0$

Table 2 Comparison of the HAD anxiety and depression scales in the patients and control group.

	Patients with OSAHS ($n = 15$)	Patients without OSAHS ($n = 10$)	p
Anxiety	11.33 ± 2.55	4.70 ± 2.36	<0.001[*]
Normal (0–7)	0 (0.0)	9 (90.0)	
Borderline (8–10)	8 (53.3)	1 (10.0)	<0.001[*]
Abnormal (11–21)	7 (46.7)	0 (0.0)	
Depression	16.27 ± 2.34	5.80 ± 1.14	<0.001[*]
Normal (0–7)	0 (0.0)	9 (90.0)	
Borderline (8–10)	0 (0.0)	1 (10.0)	<0.001[*]
Abnormal (11–21)	15 (100.0)	0 (0.0)	

HADS-A: Hospital anxiety and depression subscale for anxiety.
HADS-D: Hospital anxiety and depression subscale for depression.
[*] Statistically significant at $p \leqslant 0.05$. p: p value for Student t-test.

Figure 1 Comparison of the HAD anxiety and depression scales in the patients and control groups.

Table 3 Comparison of polysomnography parameters between the study groups.

	Patients with OSAHS ($n = 15$)	Patients without OSAHS ($n = 10$)	Test of sig.
Average SaO$_2$, (%)	86.40 ± 6.20	94.0 ± 2.67	0.001[*]
Minimum SaO$_2$, (%)	64.27 ± 10.10	89.90 ± 2.77	<0.001[*]
t90 min	0.55 ± 0.28	0.02 ± 0.03	<0.001[*]
AHI events/h-	65.47 ± 20.34	2.70 ± 1.16	<0.001[*]
ODI/h	50.80 ± 19.55	0.70 ± 0.67	<0.001[*]
ESS score	17.73 ± 2.46	3.40 ± 1.17	<0.001[*]

Results are expressed as mean ± standard deviation unless otherwise specified. Definition of abbreviations: ESS: Epworth Sleepiness Scale, AHI: apnea hypopnea index, ODI: oxygen desaturation index, t90: fraction of sleep time spent below an oxygen saturation of 90 percent, SaO$_2$: arterial oxygen saturation.
[*] Statistically significant at $p \leqslant 0.05$. p: p value for Student t-test.

higher in patients with OSAHS (0.55 ± 0.28) compared to patients without OSAHS (0.02 ± 0.03) with $p < 0.001$. The mean value of ODI in patients with OSAHS (50.80 ± 19.55) was statistically significantly higher ($p < 0.001$) as compared to patients without OSAHS (0.70 ± 0.67) (Table 3).

Patients with OSA had significantly decreased NAA and Cho absolute concentrations (Fig. 2) in frontal white matter compared to controls (37.0 ± 4.19 versus 47.0 ± 1.70, $p < 0.001$ and 23.40 ± 0.63 versus 27.50 ± 1.51, $p < 0.001$, respectively). In comparison to the control group, patients
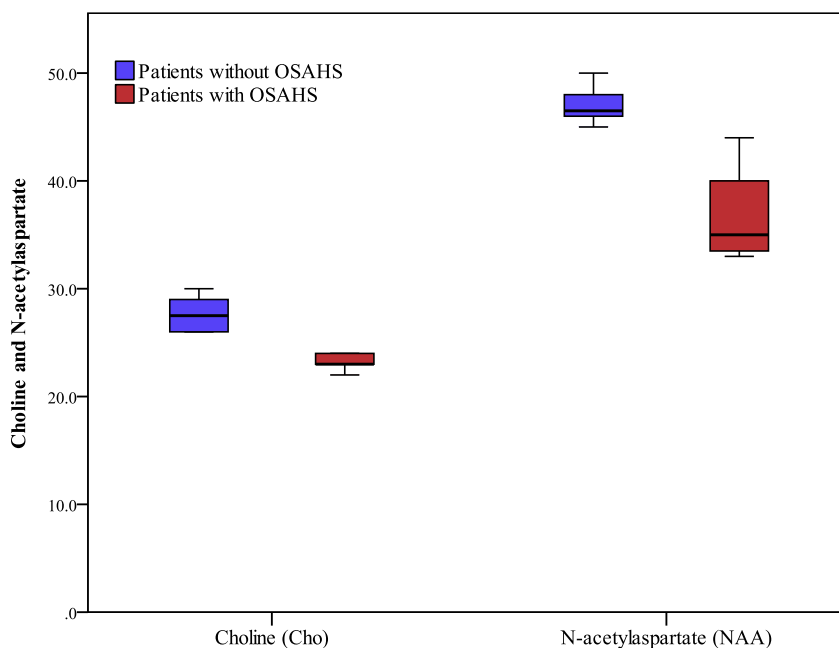
Figure 2 Comparison of absolute metabolite concentrations between patients with obstructive sleep apnea (OSA) and controls.
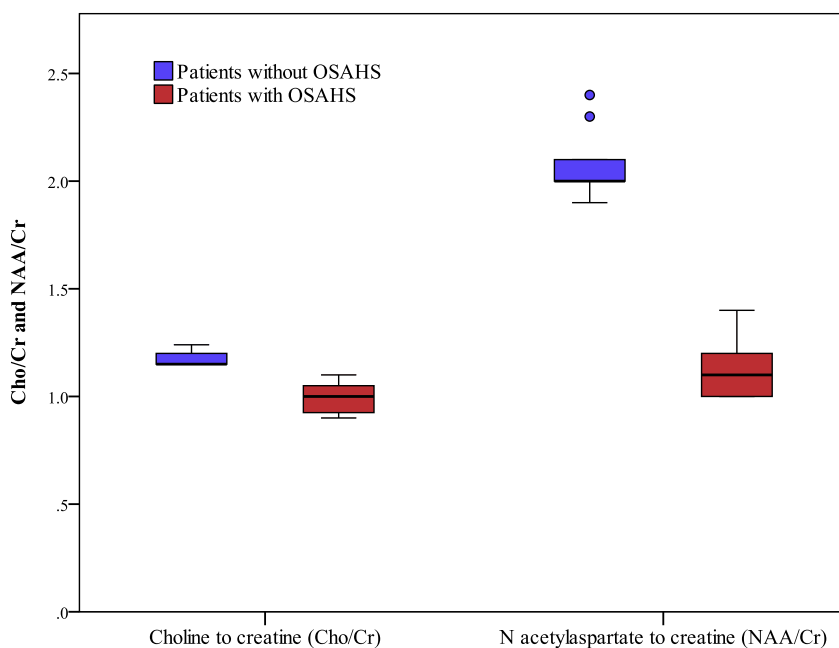

Figure 3 Comparison of metabolite ratios between patients with obstructive sleep apnea (OSA) and controls.

Table 4 Comparison of absolute metabolite concentrations and metabolite ratios between patients with obstructive sleep apnea (OSA) and controls.

	Patients with OSAHS ($n = 15$)	Patients without OSAHS ($n = 10$)	Test of sig.
Choline (Cho)	23.40 ± 0.63	27.50 ± 1.51	$<0.001^*$
N-acetylaspartate (NAA)	37.0 ± 4.19	47.0 ± 1.70	$<0.001^*$
Choline to creatine (Cho/Cr)	0.99 ± 0.08	1.17 ± 0.03	$<0.001^*$
N-acetylaspartate to creatine (NAA/Cr)	1.13 ± 0.13	2.08 ± 0.15	$<0.001^*$

* Statistically significant at $p \leqslant 0.05$.

with OSAHS showed a significant reduction in the Cho/Cr (1.17 ± 0.03 versus 0.99 ± 0.08 respectively) and NAA/Cr ratios (2.08 ± 0.15 versus 1.13 ± 0.13 respectively) in frontal white matter (Fig. 3) (Table 4).

Correlations (Figs. 4–9)

Statistically significant negative correlations existed between AHI and metabolite concentrations and ratios in patients with OSAHS as follows.

- There was a negative correlation between apnea hypopnea index (AHI) and choline in frontal white matter of patients with OSAHS ($r = -0.799$, $p < 0.001$).
- There was a negative correlation between apnea hypopnea index (AHI) and N-acetylaspartate in frontal white matter of patients with OSAHS ($r = -0.693^*$, $p = 0.004$).
- AHI in patients with OSAHS significantly inversely correlated with choline to creatine ratio ($r = -0.878$, $p < 0.001$), and also inversely with N-acetylaspartate to creatine ratio ($r = -0.782$, $p = 0.001$).

ODI in patients with OSAHS significantly inversely correlated with choline to creatine ratio ($r = -0.590$, $p = 0.020$).

Hospital and depression scale for depression (HAD-D) significantly inversely correlated with choline ($r = -0.655$, $p = 0.008$), choline to creatine ratio ($r = -0.618$, $p = 0.014$), and N-acetylaspartate to creatine ratio ($r = -0.596$, $p = 0.019$) in patients with OSAHS.

Hospital and depression scale for anxiety (HAD-A) significantly inversely correlated with choline ($r = -0.752$, $p = 0.001$), and also inversely with N-acetylaspartate ($r = -0.547$, $p = 0.035$) in patients with OSAHS.

Significant positive correlations existed in patients with OSAHS between Hospital and depression scale for depression (HAD-D) and AHI ($r = 0.764$, $p = 0.001$), ODI ($r = 0.571$, $p = 0.026$), and ESS ($r = 0.644$, $p = 0.010$), respectively.

Significant positive correlations existed in patients with OSAHS between Hospital and depression scale for anxiety (HAD-A) and AHI ($r = 0.753$, $p = 0.001$), and ESS ($r = 0.537$, $p = 0.039$), respectively.
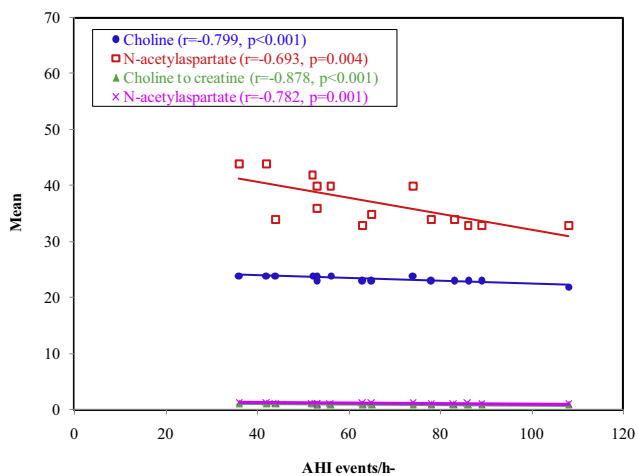

Figure 4 Correlation between AHI events/h- with different metabolites in patients with OSAHS.
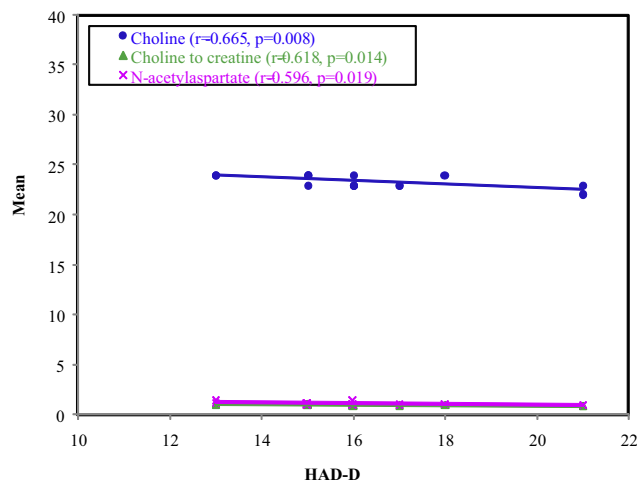

Figure 5 Correlation between HAD-D with different metabolites in patients with OSAHS.

Multivariate Linear regression model of factors predictive showed AHI as the main predictor factor for choline to creatine ratio in patients with OSAHS with $t = 5.180$, at $p < 0.001$.

Discussion

Frontal lobe white matter lesions are known to be associated with cognitive executive dysfunction. This may offer an explanation for the sometimes irreversible cognitive deficits associated with sleep apnea [9].

Decreased NAA in the frontal white matter of OSA patients indicates axonal loss and/or dysfunction. The deep white matter, where metabolic impairment seems to be selectively affected in patients with OSAS [9].

An explanation is that the arterial supply of the deep white matter is not sufficient to compensate for the decreased and fluctuating cerebral perfusion and the impaired cerebral vascular autoregulation reported in OSA patients [5].

M. Alchanatis et al., stated that the results of their study demonstrate that severe obstructive sleep apnea syndrome can promote axonal loss or dysfunction, as well as myelin metabolism impairment in the frontal periventricular white matter. These lesions are in the territory of crucial frontal-subcortical circuits and they could be associated with the, sometimes irreversible, cognitive executive deficits reported in obstructive sleep apnea patients [9].

Kamba, Inoue, Higami, et al., concluded that their MRS findings indicate that a significant relation exists between AHI and the degree of metabolic impairment in cerebral white matter. Magnetic resonance spectroscopy may be useful for evaluation of CNS impairment in patients with OSA [5].

NAA was found to be negatively correlated with AHI in the left frontal region, indicating that higher the AHI, lower is the concentration of NAA, indicating possible neuronal damage of the brain. Similar negative correlation was reported by Sarchielli et al. [10] between AHI and NAA/Cr ratio in the frontal regions of the brain of OSA patients [6].

Patients with OSA frequently have a combination of vascular risk factors, including hypertension, diabetes mellitus,

hyperlipidemia and central obesity. All these factors are associated with an increased risk of stroke and could possibly promote brain metabolic impairment. Nevertheless, in our study, the group of patients with OSA studied was selected without a medical history of cardiac disease or cardiovascular risk factors in order to abolish the effects of confounding factors on brain metabolites [9].

We found that in comparison to the control group, patients with OSAHS showed a significant reduction in the Cho/Cr (1.17 ± 0.03 versus 0.99 ± 0.08, respectively) and NAA/Cr ratios (2.08 ± 0.15 versus 1.13 ± 0.13, respectively) in frontal white matter. Patients with OSA had significantly decreased NAA and Cho absolute concentrations in frontal white matter compared to controls (37.0 ± 4.19 versus 47.0 ± 1.70, $p < 0.001$ and 23.40 ± 0.63 versus 27.50 ± 1.51, $p < 0.001$, respectively [9]).

The results demonstrated a significant decrease in NAA/Cr and Cho/Cr ratios, as well as a reduction in absolute concentrations of NAA and Cho, in the frontal white matter of patients with OSA when compared to controls. This finding suggests that OSAS may promote brain metabolic impairment even in the absence of cardiovascular co-morbidities.

When compared to our study, previous studies applying MRS with chemical shift imaging have demonstrated a decrease in the NAA/Cho ratio in the posterior periventricular white matter [5] and lactate production in the Centrum semiovale of patients with OSA during sleep, indicating that hypoxia is causing anaerobic glycolysis [12]. Absolute concentrations were not calculated in these studies, so it is not clear if the decreased ratio was due to a decrease in NAA and/or an elevation in Cho [9].

In our study, statistically significant negative correlations existed between AHI and metabolite concentrations as well as ratios in patients with OSAHS.

In agreement to our findings, a recent study, using computed tomography, demonstrated that white matter disease severity in patients with acute stroke and OSAS correlated independently with AHI [13]. One possible explanation is that the arterial supply of the deep white matter is not sufficient to compensate for the decreased and fluctuating cerebral perfusion and the impaired cerebral vascular autoregulation that have been reported in OSA patients [14,15]. In fact, the arterial
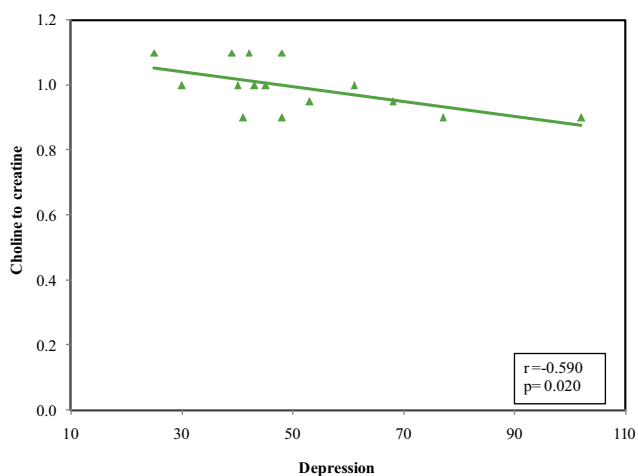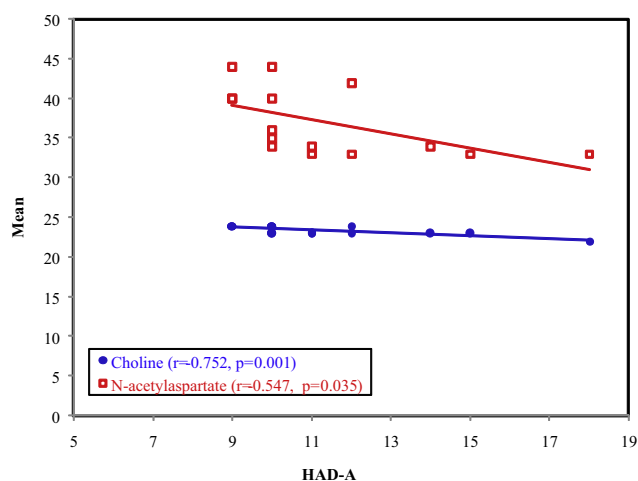

Figure 7 Correlation between HAD-A with choline and N-acetylaspartate concentrations in patients with OSAHS.

networks of the deep white matter, so-called internal border zone, are terminals without collaterals or anastomoses [9]. This perspective was supported in our study by the Multivariate Linear regression model of factors predictive that showed AHI as the main predictor factor for choline to creatine ratio in patients with OSAHS with $t = 5.180$, at $p < 0.001$.

Another study done by Alchanatis, Deligiorgis, Zias demonstrated the decrement of Cho in the frontal white matter of patients with OSA. It has been suggested that decreased in vivo Cho levels indicate loss of myelin lipids or phospholipid metabolism dysfunction [17].

These results are in agreement with the report of Shim et al. [16]. These investigators found a reduction in NAA, Cr and Cho concentrations in the parietal white matter of COPD patients with resting normoxemia and nocturnal desaturation, a respiratory profile similar to OSAS.

A previous study has demonstrated a decrease in Cho metabolites as a consequence of brief ischemic episodes in an experimental animal model [17].

Nevertheless, if chronic hemodynamic impairment was the sole pathogenic factor related to OSA, one would expect an elevation of Cho due to gliosis and myelin breakdown [17].
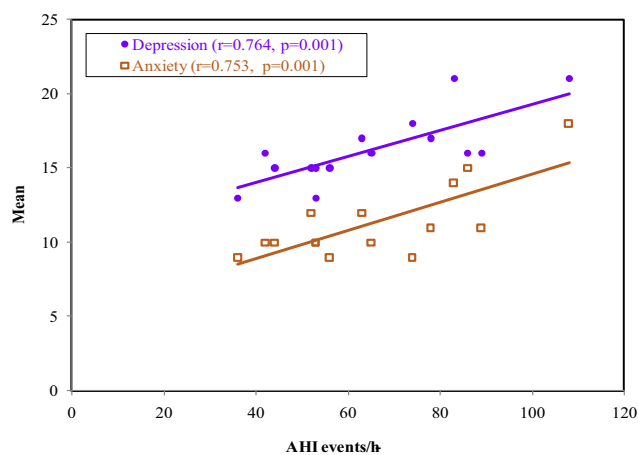

Figure 6 Correlation between HAD-D and choline to creatine ratio in patients with OSAHS.

Figure 8 Correlation between AHI events/h- and depression anxiety scales in patients with OSAHS.
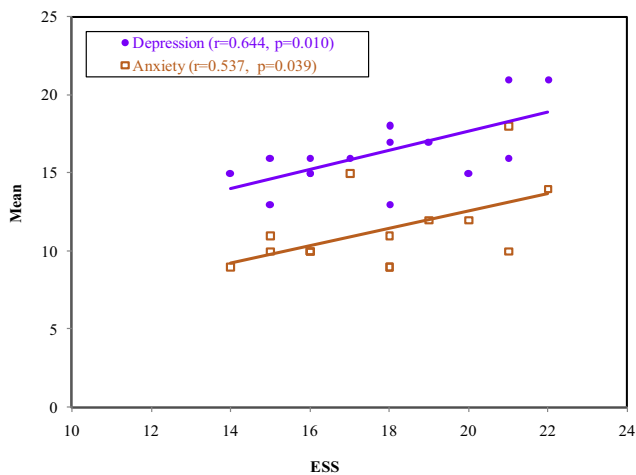
Figure 9 Correlation between ESS and depression anxiety scales in patients with OSAHS.

It was suggested that a possible interpretation for the Cho decrement is that OSA does not promote gliosis but induces brain metabolic impairment through a unique combination of fluctuating hemodynamic impairment, sleep fragmentation and intermittent hypoxia [17].

Dorsey et al. [18] found an increase in glycerophosphocholine concentration in healthy volunteers after the recovery night, following a night of sleep deprivation [18]. In a study done by Alchanatis, Deligiorgis, Zias et al., although the patients did not have severe sleepiness, ESS score is correlated with NAA/Cho ratio, but only in the posterior white matter. However, in our study, no correlation was illustrated between ESS and metabolite concentrations in the brain of patients with OSA.

Frontal white matter lesions could be associated with the neuropsychological deficits that complicate OSAS. Patients with OSAS frequently have mild impairment in attention/concentration, memory and, in particular, executive functions, such as problem solving, planning of goal-oriented behavior and mental flexibility, which are sometimes irreversible, even after nCPAP treatment [8].

In the study done by Alchanatis, Deligiorgis, Zias et al. and also in our study, no metabolic impairment was studied in the examined prefrontal cortex, but it was demonstrated that patients with severe OSAS have metabolic impairment in the frontal white matter. It is, therefore, suggested that these findings may offer an explanation for the specific pattern of cognitive deficits frequently reported in OSA patients, as it is well known that anterior white matter lesions can induce executive dysfunction by interrupting prefrontal-subcortical circuits.

An important limitation to our study is the lack of neuropsychological measures in the examined patients, although it is well documented that frontal lobe-mediated executive functions are usually impaired in patients with severe OSAS [8].

A second limitation is that, because only patients with severe OSA were included, there were not enough variances in the respiratory parameters that could predict the metabolic changes.

An important consideration is about the effect of aging on brain metabolism. MRS studies on the effect of aging on brain metabolites are often discrepant. Results of quantitative MRS studies vary from increased Cr and Cho levels to unchanged or decreased NAA levels and lack of any significant change [19]. In our study, both patient and control groups were selected to be age matched to avoid the confounding effect of age on brain metabolites between both groups that is why detailed assessment of aging on brain metabolism was not done.

In our study, seven patients with OSAHS (46.7%) had an anxiety score $\geqslant 11$ (probable anxiety), and 15 patients with OSAHS that is to say all of the studied patients (100%) had a depression score $\geqslant 11$ (probable depression). Significant positive correlations also existed in patients with OSAHS
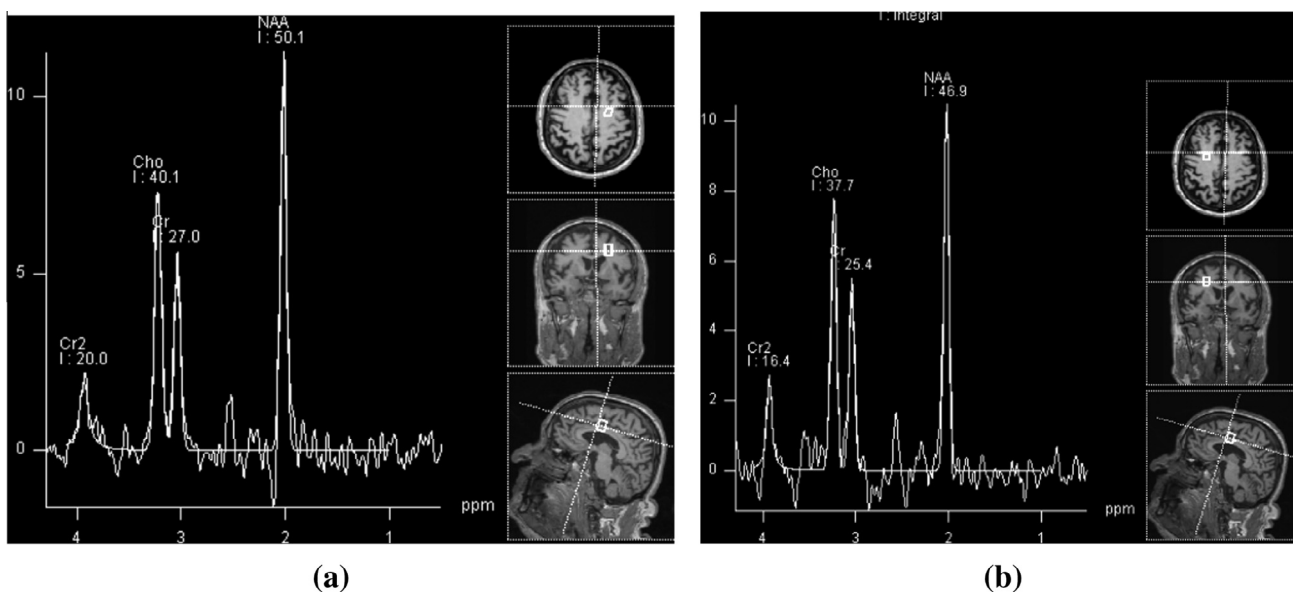

Figure 10 (a–b) Proton MR spectrum from the frontal white matter of an apneic patient. The insert shows the voxel position in the (right and left, respectively). The abbreviations shown in figure correspond to: NAA (N-acetylaspartate); Cr (Creatine); Cho (Choline). They show low levels of choline and NAA.

between the Hospital and depression subscale for depression (HAD-D) and AHI($r = 0.764$, $p = 0.001$), ODI($r = 0.571$, $p = 0.026$), and ESS($r = 0.644$, $p = 0.010$), respectively.

We found that the Hospital and depression subscale for depression (HAD-D) significantly inversely correlated with choline ($r = -0.655$, $p = 0.008$), choline to creatine ratio ($r = -0.618$, $p = 0.014$), N-Acetylaspartate to choline ratio ($r = -0.596$, $p = 0.019$) in patients with OSAHS. We also found that the Hospital and depression subscale for anxiety (HAD-A) significantly inversely correlated with choline ($r = -0.752$, $p = 0.001$), and also inversely with N-acetylaspartate ($r = -0.547$, $p = 0.035$) in patients with OSAHS.

This study has its own limitations; first, the unequal number of males and females, as the gender of subjects may have a significant impact on mood; since women are more vulnerable to mood alterations. Also, it is important to take note of the limitations of mood scales, which are not proper diagnostic tools for the detection of depression or anxiety; they only represent depressive and anxious symptoms, however diagnosis of the clinical entity requires a psychiatric consultation.

In a study done by Daabis and Gharraf [20] anxious and depressive symptoms were highly prevalent in patients with moderate to severe untreated obstructive sleep apnea. The severity of depressive symptoms might have been more related to excessive daytime sleepiness than to nocturnal hypoxemia. This last perspective gained support from their finding that EDS as measured by the Epworth Sleepiness Scale (ESS) was the main predictor for the HAD depression score in the linear regression analysis ($p = 0.001$).

Therefore, in clinical practice we think it is feasible to be alert to psychiatric symptoms in patients with OSAS and routine screening with instruments like the HAD scale should be encouraged, to improve QOL and optimize diagnosis and therapy in these patients. Future research is needed to investigate the causal relationship between psychiatric symptoms and OSAS, as well as the appropriate treatment for these comorbidities.

In conclusion, the results of this study demonstrate that severe obstructive sleep apnea syndrome can promote axonal loss or dysfunction, as well as myelin metabolism impairment in the frontal periventricular white matter. These lesions are in the territory of crucial frontal-sub cortical circuits and they could be associated with the, sometimes irreversible, cognitive executive deficits reported in obstructive sleep apnea patients. Further studies are needed to confirm whether there is a direct correlation between frontal metabolic dysfunction and cognitive impairment in obstructive sleep apnea patients, and to examine the reversibility of the spectroscopic abnormalities after nasal continuous positive airway pressure treatment.

Conflict of interest

None declared.

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