ASSOCIATION BETWEEN SLEEP-DISORDERED BREATHING AND HEARING DISORDERS: CLINICAL OBSERVATION IN SICILIAN PATIENTS

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ABSTRACT

Introduction: To examine the putative association between Sleep-Disordered breathing and hearing disorders

Material and methods: 120 Sicilian subjects ranging from 14 to 85 years of age who were divided in 46 cases suffering from tinnitus (G1 group) and 74 controls (G2 group) were evaluated through STOP BANG screening questionnaire and Four-Variable Screening Tool; after Data collecting each subject underwent Audiological assessment by multi-frequency audiometry (PTA) and Transient-evoked otoacoustic emissions (TEOAE-diagnostic) for each ear.

Results: Cases showed: PTA significantly severe than the control group (58.70% vs. 16.89% hearing loss; P<0.001), such as a lower signal-to-noise ratio (SNRs) (P<0.05). Moreover Tinnitus subjects had a higher risk to develop Sleep-Disordered breathing respect to controls (P<0.001). OSA risk population - subjects positive to both screening questionnaires - had tinnitus, wore hearing threshold mean values and, lower SNRs values than total cohort (P<0.01). The relative risk of Sleep-Disordered breathing and tinnitus was 4.83 (P<0.0001).

Conclusions: Our results stress a probable association between tinnitus, hearing loss and Sleep-Disordered breathing even if further studies will be needed to confirm our findings.

Key words: Sleep-disordered, Tinnitus; Hearing loss, multifrequency audiometry, TEOAE, OSA.

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Introduction

Sleep-Disordered breathing (SDB), including obstructive sleep apnea (OSA) is a condition, affecting 24% of men and 9% of women in their middle age, associated to high values either of Body Mass Index (BMI) and neck circumference, where intermittent obstruction of the airway during sleep causes sleep fragmentation and repeated desaturations. This disorder carries potentially serious consequences: excessive daytime sleepiness, neurocognitive deterioration, endocrine and metabolic derangements, and is universally recognized as independent risk factor for cardiovascular disease and its related mortality(13).

Nazzaro et al. assert that OSA is associated with reduced basal and functional capillarity rarefaction with an additional risk of impaired peripheral perfusion46. The mechanisms involved in this relation are most likely induced by the periodic hypoxia/reoxygenation that typically occurs in OSA, which results in oxidative stress, endothelial dysfunction, and activation of the inflammatory cascade48. These noxious stimuli can, in turn, acti-
vate the sympathetic nervous system, depress parasympathetic activity, provoke oxidative stress and systemic inflammation, activate platelets, and impair vascular endothelial function.

Basing on these clinical evidences some authors studied the association between OSA and a dysfunction of auditory pathway showing an improved risk of sudden sensorineural hearing loss (SNHL), a lower transient-evoked otoacoustic emissions (TEOAE) reproducibility and an impairment of auditory brainstem responses in OSA population(6,7,8). Other authors evidenced a relationship between anthropometric parameters (age, sex, BMI, neck circumference) blood pressure, laboratory findings that are predictive for OSA and SNHL & tinnitus(9,10,11). It is in fact known that the transduction mechanism of the inner ear and the transmission of nerve impulses along the auditory pathway are highly dependent on the oxygen supply; indeed, the cochlea is especially sensitive to circulatory alterations because of its single terminal artery supply and lacks adequate collateral circulation(12,13). Therefore OSA may lead to cerebral vascular insufficiency resulting in hypoxia, acute hemodynamic change, decreased cerebral blood flow during episodes of apnea and ischemic injury to the cochlea(14-18).

Hwang et al. evidenced how through oxidative injury due to a hypoxic stress induced apoptosis in spiral ligament and in the cochlear basal turn of the Organ of Corti of obese CD/1 mice, causes a high frequencies sensorineural hearing loss(19).

Since it is universally accepted that high frequencies SNHL is commonly associated to tinnitus, it could be reasonable to suppose that OSA could cause and/or exacerbate tinnitus disorder(20-22).

The aim of this study was to determine the clinical and audimetric characteristics of patients, who were referred to the Audiology Section of Palermo University, suffering from SDB and analyzing a possible correlation between tinnitus, hearing disorders and OSAS risk population.

Materials and methods

The study was designed as a matched case-control study on 132 consecutive subjects, 86 males and 46 females, ranging from 14 to 85 years of age, who had been evaluated at the Audiology Section of the Department of Bio-technology of Palermo University. The study protocol was completely explained to patients and written informed consent was obtained from each subject. The study design was approved by the Palermo University Human Research Ethics Committee.

The subjects suffering from tinnitus were classified as cases and included in the group 1 (G1) while the subjects without tinnitus were included in the control group (G2). After collecting personal data, patients general medical history was accurately taken to identify audiological pathologies and other diseases. The subjects with cranio-facial abnormalities (CFA), syndromes associated to hearing loss, history of ototoxic drugs administration, otosclerosis, acoustic neuroma, chronic otitis, previous myringotomy, ventilation tube insertion, tympanoplasty, and coexisting psychiatric disorders were excluded from this study. At last ENT history was collected and it was performed an otological examination.

Audiological assessment was performed by multi-frequency audiometry (considering the frequencies 0.25-0.5-1-2-3-4-6-8-9-10-11.2-12.5-14-16 KHz), tympanometry with stapedius reflex and TEOAE diagnostic for each ear.

Audiometric threshold was considered as the pure tone average for the frequencies 0.5-1-2-4 KHz (PTA0.5-4kHz) and divided in: normal hearing (<20 dB); light hearing loss (21-40 dB); moderate hearing loss (41-70 dB); severe hearing loss (71-90 dB); profound hearing loss (>90 dB).

TEOAE measurements were evaluated in reproducibility (expressed as the correlation between two waveforms, namely for responses stored in buffers A and B, acquired alternately) and were done by using defined criteria as response detection in 4/5 different frequency bands (1, 1.5, 2, 3, and 4 KHz); moreover for each frequency band it was chosen minimum SNRs of 6 dB. The tool used was the ‘SENTIERO by Path Medical GmbH’, that is based on the nonlinear cross-correlation method (ILO88) of TEOAE recording. The TEOAE diagnostic was conducted by placing a small probe tip from the ‘Path Medical’ (3.9 mm diameter x 11.7 mm) inside the patient’s ear canal; when powered on, the instrument initiated a routine self-calibration before recordings were made. The click rate was approximately 97 per second and each stimulus (at the probe loud-speaker output) consisted of a single 80µs square pulse. To eliminate passive mechanical artifacts from the recorded waveform, stimuli were presented in blocks of four stimuli: 3 small positive polarity stimuli followed by one big negative polarity stimulus three times as large. Click peak stimulus level was 80 dB SPL. Emissions elicited from the
outer hair cells in response to the clicks were picked up by the internal microphone of the equipment and were windowed and filtered to remove unwanted signals; all response data outside a window from 5mS to 13mS, after the stimulus, were removed to eliminate the stimulus signal.

To value the perceived severity of tinnitus and its impact on life all the cases (G1) completed the Tinnitus Handicap Inventory (THI) that grades five categories of tinnitus severity: 1, slight; 2, mild; 3, moderate; 4, severe; 5, catastrophic.

OSA risk was evaluated through two accurate screening questionnaires (STOP BANG; Four-Variable Screening Tool) for sleep disorders breathing that have been completed by total cohort.

The STOP-BANG questionnaire, previously validated for screening of preoperative surgical patient, is universally recognized as the screening test with highest sensitivity for OSA. It consists of 8-point questionnaire easily remembered by the letters of the name; each letter reminds a parameter to evaluate: S= snoring; T= tiredness during the day; O= observation stop breathing during the sleep; P= blood pressure treated with therapy; B= BMI (> 35 kg/m2); A= age (over 50 years old); N= neck circumference (> 40 cm), and Gender (male). One point was assigned for each affirmative answer, 0 for no answer, therefore high risk of SDB was defined as a score ≥ 5 while low risk of SDB was defined as a score < 5 on the STOP BANG (23-25).

The Four-Variable Screening Tool proposed by Takegami et al. with a specificity >90% utilizes gender, blood pressure (BP), body mass index (BMI), and snoring to determine SDB severity. Specifically in this questionnaire, as far as sex it was assigned a value of 1 for males and 0 for females; BMI kg/m2 categories (< 21.0, 21.0-22.9, 23.0-24.9, 25.0-26.9, 27.0-29.9, ≥ 30) were assigned a value between 1 and 6; BP mm Hg (systolic BP [SBP] < 140 or diastolic BP [DBP] < 90, SBP 140-159 or DBP 90–99, SBP 160-179 or DBP 100–109, SBP ≥ 180 or DBP ≥ 110) was assigned a value between 1 and 4; and snoring was assigned a value of 1 for a response of snoring almost every day or often, and 0 for snoring sometimes, almost never, or unknown. The overall risks for participants were calculated by assigning their screening values for BMI and BP to the associated equation variables. Sex and snoring were factored by values of 4. The following equation was used: SDB = (sex^4)+(BMI category value)+(BP category value)+(snoring^4); the cutoff score of >14 was indicative of a severe SDB.

Statistical analysis was performed using the Matlab® computer software (Copyright 2011 The MathWorks, Inc. published with Matlab® 7.13). To examine the association between OSA risk and occurrence of tinnitus we applied a logistic regression analysis between binary data, calculating chi square (χ^2), relative risk (RR), and comparing mean values (t test).

Results

The total number of subjects examined was 132 but 12 patients were excluded from the study because of CFA (1 case), history of ototoxic drugs administration (5 cases), otosclerosis (2 cases), chronic otitis (3 cases) and previous timpanoplasty (1 case). A total of 120 subjects were analyzed.

The age of cohort ranged from 14 to 85, with a mean age of 57.6 years ± 13.15; 77 (64.16%) were males and 43 were females with a male/female ratio of 1.79.

At the time of the first examination, based on presence/absence of tinnitus, the patients were classified in 2 groups: G1 (tinnitus patients - cases) including 46 subjects (38.33%), and G2 (controls) including 74 subjects (61.67%) without tinnitus. The distribution between the groups among the sex was not significant, in fact males resulted the 67.39% of cases (31 subjects; male/female ratio: 2.06) and the 62.16% of controls (46 subjects; male/female ratio: 1.64) with P=0.5 (table 1).

The 64.16% (77/120) of subjects, 65.21% for G1 and 63.51% for G2, were smokers without statistical difference among the groups (χ^2 = 0.04; P=0.85).

Audiological assessment performed for each ear, evidenced a normal hearing in the 41.30% of cases and in 83.11% of controls while a slight SNHL in 50% and 16.89% respectively of cases and in 83.11% of controls (for each ear) respectively of 6.16 + 5.93 and 9.38 + 3.12 for the frequency 1 KHz, 10.39 + 7.20 and 13.85 + 4.41 for 1.5 KHz, 7.34 + 8.13 and 11.71 + 4.22 for 2 KHz, 2.85 + 3.55 and 4.78 + 5mS to 13mS, after the stimulus, were removed to eliminate the stimulus signal.
4.08 for 3 KHz, and finally 2.07 + 2.72 and 2.95 + 3.33 for 4 KHz with a significant difference at T test among the groups for all the frequencies (P<0.05)(figure 2).

As far as tinnitus annoyance and its impact on quality of life on G1 population, the THI identified five categories of tinnitus severity: slight grade was found in 15.2% (17 cases); mild grade in 32.6% (15 cases); moderate grade in 21.7% (10 cases); severe grade in 26% (12 cases) and catastrophic grade in 4.3% (2 cases).

All the subjects completed either the STOP BANG questionnaire and the Four-Variable Screening Tool (table 1); those positive to both the questionnaires were considered at risk for OSA. The questionnaires evidenced significant differences between cases and controls (P<0.0001)(figure 3). Specifically the 71.73% of G1, corresponding to 33 subjects, with a score > 5 at STOP BANG resulted at risk for OSA respect to the 9.45% (7 participants) of G2. Also the 4-Variable Screening Tool evidenced a risk for OSA in the 41.30% of G1 corresponding to 19 cases respect to the 12.16% corresponding to 9 subjects of G2. Therefore statistical analysis evidenced how tinnitus patients had a relative risk to suffer from SDB of 7.58 (95% C.I.: 3.66-15.70) relative to STOP BANG and of 3.40 (95% C.I.: 1.68-6.86) relative to four-Variable Screening Tool respect to control group (figure 3a).

24 subjects among the total cohort (20%) resulted at risk for OSA by compiling both the questionnaires; of them 75% suffered from tinnitus with

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### Table 1: Analysis of STOP BANG and 4 VARIABLE SCREENING TOOL questionnaire about Tinnitus population and Controls: chi square ($\chi^2$), P-value.

<table>
<thead>
<tr>
<th>STOP BANG questionnaire</th>
<th>TOTAL COHORT</th>
<th>4 VARIABLE SCREENING TOOL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tinnitus patients (G1)</td>
<td>Controls (G2)</td>
<td>Statistical analysis G1 Vs G2</td>
</tr>
<tr>
<td>N (%)</td>
<td>N (%)</td>
<td>$\chi^2$ (P)</td>
</tr>
<tr>
<td>S: Do you snore loudly?</td>
<td>42 (91.3)</td>
<td>57 (77.02)</td>
</tr>
<tr>
<td>T: Do you often feel tired, fatigued, or sleepy during day time?</td>
<td>31 (67.3)</td>
<td>16 (21.62)</td>
</tr>
<tr>
<td>O: Has anyone observed you stop breathing during your sleep?</td>
<td>29 (63)</td>
<td>9 (12.16)</td>
</tr>
<tr>
<td>P: Do you have hight blood pressure?</td>
<td>29 (63)</td>
<td>14 (18.91)</td>
</tr>
<tr>
<td>B: BMI &gt; 35?</td>
<td>20 (43.4)</td>
<td>7 (9.45)</td>
</tr>
<tr>
<td>A: Age &gt;50?</td>
<td>39 (84.7)</td>
<td>54 (72.97)</td>
</tr>
<tr>
<td>N: Neck circumference &gt;40 cm?</td>
<td>20 (43.4)</td>
<td>11 (14.88)</td>
</tr>
<tr>
<td>G: Gender male?</td>
<td>31 (67.3)</td>
<td>46 (62.16)</td>
</tr>
</tbody>
</table>

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regard to 29.07% of the population without risk for OSA (96/120 subjects) ($\chi^2 = 17.06$; $P<0.0001$) with a relative risk to suffered from tinnitus of 4.83 (95% IC: 2.07 - 11.26) (figure 3b).

Smoke exposition was evidenced only in the 36.84% of the cohort with a significant difference respect to the total cohort ($P<0.01$).

The higher hearing threshold mean values at multi-frequency audiometry were evidenced for OSA risk population respect to total cohort with a significant difference for the frequencies 8, 12.5, 14, 16 KHz ($P<0.05$).

Moreover OSA risk population presented at TEOAEs recording a SNRs values lower respect to total cohort for each frequency with a significant difference for the frequencies 1, 2, 3 KHz ($P<0.05$).

Finally the study of regression analysis of the questionnaires completed by total cohort evidenced an high concordance correlation coefficient ($k$ value: 0.83) between the STOP BANG and the 4-Variable Screening Tool.

**Discussion**

Many authors investigated the epidemiologic association between OSA and either sudden SNHL and dysfunction of auditory pathway; particularly Sheu et al. evidenced how in a case-control study performed on 19152 patients, OSA is present on 1.7% of SSNHL population respect to the 1.2% of the controls with a significant difference between the groups ($P<0.04$)\(^6\). Recently Casale et al. studied 30 patients divided in two groups, cases (18 subjects) with severe OSA and controls (21 subjects) with snoring without OSA and evidenced higher mean values at pure tone audiogram and lower TEOAE signal to noise ratio in severe OSA group with significant differences among cases and controls ($P<0.01$)\(^7\). The authors suggested as possible explanation for the association between OSA and SSNHL that OSA indirectly contributes to the development of SSNHL via the effects of cardio-
vascular disease and cardiovascular risk factors and that is associated with reduced basal and functional capillarity rarefaction with an additional risk of impaired peripheral perfusion and therefore dysfunction of cochlear hair cells\(^6,7\).

To our knowledge, this is the first study to investigate if tinnitus subjects with or without SNHL are at risk for OSA.

It is universally accepted that tinnitus - “perception of a sound which results exclusively from activity within the nervous system without any corresponding mechanical, vibratory activity within the cochlea” - can be lead to inner ear dysfunctions, such as those associated with sudden hearing loss, high frequencies SNHL or acoustic trauma, or part of otological and neurological diseases such as Ménière’s disease or severe head injury\(^{27,28}\). Because of these medical disorders usually are associated to cerebral circulatory alterations resulting in hypoxia, acute hemodynamic change, and decreased cerebral blood flow, and because of OSA is characterized by periodic hypo/a/reoxygenation of different anatomical structure as inner ear, is reasonable to assume that OSA could cause and/or exacerbate tinnitus disorder with or without hearing loss.

To study the possible association between tinnitus and OSA we considered a population of 120 subjects aged between 14 and 85 years old who were divided in relation to presence/absence of tinnitus in 46 cases and 74 controls. The cohort resulted the more homogenous possible; in fact with age mean values of 57.6±13.15, 58.10±13.28 and 57.3±13.16 and a male percentage rate of 64.16%, 67.39% and 62.16% respectively for total cohort, cases and controls, there were no statistical differences in the distribution of age (P=0.7) and sex (P=0.5) among the groups.

The gold standard for diagnosis of OSA remains the in-laboratory, monitored polysomnography (PSG), yet this is a cumbersome and expensive test\(^{29}\). In the last five years to contain health costs were introduced and tested many screen tests with the intent to identify the patients at risk for OSA\(^{25,30}\). In a meta-analysis, Ramachandran and Josephs identified in the STOP-Bang questionnaire and in the Four-Variable Screening Tool two excellent methods for predicting severe SDB due to their simplicity and relatively ease of use\(^{31}\). According to literature knowledge OSA risk was investigated through two questionnaire filled by the cohort: the STOP-BANG questionnaire (test with the highest sensitivity for OSA), and the Four-Variable Screening Tool proposed by Takegami et al. with a specificity $\geq90%$\(^{30}\). The results evidenced how the 71.73% and the 41.30% of tinnitus patients resulted positive to OSA risk respectively for STOP BANG and 4-Variable Screening Tool respect to the 9.45% and 12.16% of control group (P<0.001). Because of STOP BANG test (highest sensitivity) and Four-Variable Screening Tool (highest specificity) have an high concordance correlation coefficient (k value: 0.83), it was decided to label as OSA risk population all the patients who resulted positive to both questionnaires. The results showed that among the 24 OSA risk subjects, 18 belong to the tinnitus group, accounting to 75%, while only 6 subjects were controls. Therefore with a $\chi^2 =17.06$; P<0.0001 OSA risk population have a relative risk (RR) of 4.83 to suffer from tinnitus (figure 3).

As for as the audiological assessment the subjects underwent to: 1) multi-frequency audiometry that reflects, especially in presence of an HL limited to high frequencies, an hypothetic hypoxia of auditory pathway and of cochlear basal turn; 2) TEOAE-diagnostic that are the direct reflection of
the cochlear active mechanism, attributed to the active process of outer hair cells that are the more vulnerable to oxygen blood level reduction with consequent lower values of SNRs.

According to literature review our results evidenced that tinnitus in 58.7% is accompanied by SNHL while the auditory dysfunction was present only in the 16.89% of control group. Specifically the 76.39% of the normal hearing resulted of control group while the 53.52% and the 100% respectively of the slight and moderate SNHL belong to tinnitus population (χ² =48.7; P<0.0001). T test relative to hearing threshold mean values showed higher HL for cases (P<0.001)(figure 1); it confirmed that tinnitus patients suffered from a worse cochlear dysfunction than control group and therefore their cochlea could have been damaged by vasospasm, thrombosis, embolism, hypercoagulation caused by the effects of a long period of SDB, as demonstrated in a recent study Chung S. et al.7,32.

The otoacoustic emission (TEOAE-diagnostic) that studied the integrity of outer and inner hair cells relative to the frequencies 1, 1.5, 2, 3, 4 KHz evidenced lower mean values of SNRs for cases respect to controls (P=0.0001 for 1, 1.5, 2, 3 KHz; P=0.03 for 4 KHz)(figure 2). In line with Casale et al., who showed significant differences of otoacoustic emission among OSA group and control group (P<0.01), our TEOAE-diagnostic recording showed lower values of SNRs for OSA risk population respect to no OSA risk subjects (P<0.05).

In conclusion, our study evidencing a higher percentage of: tinnitus, hearing threshold mean values at multi-frequency audiometry and, lower percentage of: tinnitus, hearing threshold mean values showed higher HL for cases (P<0.001)(figure 1); it confirmed that tinnitus patients suffered from a worse cochlear dysfunction than control group and therefore their cochlea could have been damaged by vasospasm, thrombosis, embolism, hypercoagulation caused by the effects of a long period of SDB, as demonstrated in a recent study Chung S. et al.7,32.

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In conclusion, our study evidencing a higher percentage of: tinnitus, hearing threshold mean values at multi-frequency audiometry and, lower values of TEOAE-diagnostic in OSA risk population, supports an association between tinnitus and OSA. The mechanism underlying the association is not clear but may include oxidative stress, vascular insufficiency, and the contribution of cardiovascular risk factors. OSA can contribute to the development of the decline of the neuronal and vascular function of the cochlea resulting in tinnitus and/or high frequencies SNHL. For these reasons in presence of tinnitus is reasonable to assume a risk for OSA but further studies describing OSA severity will need to confirm our results.

References


