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Sleep apnea plays a more important role on sleep N3 stage than chronic tinnitus in adults

Hsin-Hao Tseng, MD[a], Sheng-Wei Hwang[b], Shang-Rung Hwang[c], Juen-Haur Hwang, MD, PhD[a,d,e,*]

Abstract

Sleep apnea is negatively associated with N3 sleep in children. However, the association between tinnitus and sleep N3 stage was still inconclusive. We aimed to clarify the relationship between sleep apnea, chronic tinnitus, and sleep N3 stage in adults. Clinical and overnight polysomnography data of 2847 adults were collected retrospectively. Univariate and multivariate linear regression was used to test the impacts of sleep apnea indices and chronic tinnitus on the percentage of sleep N3 stage in all adults. Univariate linear regression analysis showed that sleep apnea indices, chronic tinnitus, age, sex, hypertension, diabetes mellitus, dyslipidemia, subjective insomnia, sleep efficiency, and rapid eye movement sleep were significantly associated with sleep N3 stage. However, multivariate linear regression showed that apnea–hyponea index, but not chronic tinnitus, has a significant negative association with the percentage of sleep N3 stage. Sleep apnea plays a more important role on sleep N3 stage than chronic tinnitus in adults.

Abbreviations: AHI = apnea–hyponea index, PSG = polysomnography, REM = rapid eye movement, THI = tinnitus handicap inventory.

Keywords: chronic tinnitus, polysomnography, sleep apnea, sleep N3 stage

1. Introduction

Poor sleep is a common and serious problem in the world. Although the precise function of sleep is unknown, slow-wave sleep or sleep N3 stage was known to be involved in central nervous system energy recuperation and cognitive function, and rapid eye movement (REM) sleep was involved in memory, dementia, mood regulation, and possible emotional adaptation.[1,2] Also, sleep problems are related to many human diseases. For example, anxiety, depression, sleep apnea, chronic tinnitus, Parkinson disease, and Alzheimer disease were commonly presented with sleep disorders.[3–8]

The pattern of sleep stages and/or sleep architecture are influenced by biological, behavioral, and clinical variables.[9] Delayed sleep, morning or mid-sleep awakenings, and fewer sleep hours were reported in tinnitus subjects.[6–8] A mild positive correlation was found between the increase of light sleep and the tinnitus handicap inventory (THI) score in tinnitus subjects.[10] However, the sleep problems of tinnitus subjects were almost reported basing on limited case numbers, imperfect matching, and/or imperfect statistical strategy and/or adjustment.[6–8]

Till now, only few studies had reported the sleep characteristics of tinnitus subjects using polysomnography (PSG). Attanasio et al[10] and Teixeira et al[11] found that tinnitus subjects had roughly higher percentages of sleep N1 and N2 stages, but lower percentage of sleep N3 stage and REM stage than nontinnitus subjects had. However, only the percentage of sleep REM stage was significantly different between tinnitus and nontinnitus subjects after adjusting for some variables.[11] Compared to matched controls, tinnitus subjects had lower subjective sleep quality, but no significant difference in objective sleep parameters on PSG.[12] Even so, the negative results about the relationship between tinnitus and sleep N3 stage were still not convincing due to small case numbers, imperfect matching, low statistical power, and/or imperfect statistical strategy.

Besides, the relationship between chronic tinnitus and sleep N3 stage might be confounded by sleep apnea, hypertension, Alzheimer disease, Parkinson diseases, etc.[1,3–5,13] If they were not considered, the results about chronic tinnitus and sleep N3 stage would be not convincing at all. The statistical strategy of previous studies had often regarded chronic tinnitus, but not the sleep N3 stage, as the dependent variable. In such cases, the logic for the relationship between chronic tinnitus and sleep N3 stage would be misleading. Therefore, we aimed to study the actual relationship between sleep apnea, chronic tinnitus, and sleep N3 stage in adults using a larger case number and proper statistical strategy.

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

The study was conducted in accordance with the Declaration of Helsinki and was approved by The Research Ethics Committee of Dalin Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation (no. B10604018).

[a] Department of Otolaryngology-Head and Neck Surgery, Dalin Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, Chiayi, Taiwan, [b] Taichung First Senior High School, Taichung, Taiwan, [c] Taichung Girl's Senior High School, Taichung, Taiwan, [d] School of Medicine, Tzu Chi University, Hualien, Taiwan, [e] Department of Medical Research, China Medical University Hospital, China Medical University, Taichung, Taiwan.

**Correspondence: Juen-Haur Hwang, Department of Otolaryngology-Head and Neck Surgery, Dalin Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, No. 2, Minsheng Road, Dalin, Chiayi 62247, Taiwan (e-mail: g120796@tzuchi.com.tw).*

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2. Methods

From November 2011 to June 2017, clinical data of 2847 adult patients who had received overnight PSG at the Dalin Tzu Chi Hospital were retrospectively collected. The study was conducted in accordance with the Declaration of Helsinki and was approved by the Research Ethics Committee of Dalin Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation (No. B10604018). Informed written consent was waived by the Research Ethics Committee of Dalin Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, because the study was a retrospective de-identified data analysis.

Clinical data including age, sex, several common diseases, subjective insomnia, and various sleep parameters and apnea indices from PSG were recorded. Among those data, several common diseases were graded as "no" and "yes." Chronic tinnitus, which was defined as having persistent tinnitus at least for 3 months before enrollment in this study, was graded as "no" and "yes." Subjective insomnia was graded into 5 grades as "no," "rare," "sometimes,","often," and "usually." Age, sleep onset, sleep efficiency, apnea–hyponea index (AHI), oxygen desaturation index (ODI), mean O_2%, minimal O_2%, percentages of sleep N3 and REM stages, and percentages of oxygen saturation <90% and <85% were continuous data.

2.1. Statistical analysis

Percentage of sleep N3 stage was regarded as a dependent variable in this study. Univariate and multivariate linear regression was used to test the effects of sleep apnea indices and chronic tinnitus on the percentage of sleep N3 stage with adjustment of other variables in all adults. All analyses were performed using STATA 10.0 software (Stata Corp, College Station, TX). A *P* value of <.05 was considered to be significant.

3. Results

Table 1 shows the basic characteristics of all adults. The mean percentage of sleep N3 stage was 1.7% (standard deviation [SD] = 4.0). The ratio of patients with tinnitus was 33.8% (962/2847). The mean AHI was 28.0/hr (SD = 23.9), the mean ODI was 20.2/hr (SD = 23.7), the mean O_2% was 94.8% (SD = 2.8), the minimal O_2% was 82.9% (SD = 9.3), O_2% <90 was 6.0% (SD = 13.8), and O_2% <85 was 2.6% (SD = 9.1).

Table 2 shows the results of each variable on the percentage for sleep N3 stage by univariate linear regression analysis. Tinnitus, AHI, ODI, mean O_2%, minimal O_2%, O_2% <90, O_2% <85, age, sex, hypertension, diabetes mellitus, dyslipidemia, subjective insomnia, sleep efficiency, and REM sleep were significantly associated with sleep N3 stage for all adults.

Table 3 shows the results of sleep apnea indices, chronic tinnitus, and other variables on the percentage for sleep N3 stage by multivariate linear regression analysis. AHI, age, sex, subjective insomnia, and sleep efficiency, but not chronic tinnitus, have a significant negative association with the percentage of sleep N3 stage in all adults. Furthermore, subgroup analysis by chronic tinnitus showed that AHI, age, sex, and subjective insomnia have a significant negative association with the percentage of sleep N3 stage in adults without tinnitus, whereas AHI, O_2% <90, age, and sex have a significant negative association with the percentage of sleep N3 stage in adults without tinnitus.

4. Discussion

This large-scale clinical study has revised our knowledge about the relationship between sleep apnea, chronic tinnitus, and sleep N3 stage in adults. In previous studies,[6–10] no significant association between tinnitus and sleep N3 stage was claimed under imperfect study design, without adjustment of other sleep indices, small case number, and statistical power. Instead, we found that AHI, but not chronic tinnitus, was significantly associated with the percentage of sleep N3 stage under proper statistical logic and well adjustment of other variables in this study.

Diverse relationship between sleep quality and chronic tinnitus existed mainly due to different study methodology. In the studies without PSG, most results were concluded based on various sleep questionnaires. The relationship between chronic tinnitus and sleep N3 stage could not be analyzed objectively. As for studies with PSG, Hebert et al[12] reported that, compared to matched controls, tinnitus subjects had lower subjective sleep quality but no significant difference in objective sleep

Table 1

Basic characteristics for 2847 adults.

	All adults (18–91 years old)
Mean age, yr (SD)	50.6 (13.3)
Females/males	989/1858
HTN	913
DM	310
Dyslipidemia	454
CKD	87
Parkinson disease	25
Dementia	8
Chronic tinnitus	962
Subjective insomnia	614
Sleep onset, min (SD)	24.1 (31.8)
Sleep efficiency, % (SD)	75.6 (15.9)
REM, % (SD)	20.1 (7.7)
Sleep N3 stage, % (SD)	1.7 (4.0)
AHI, /hr (SD)	28.0 (23.9)
ODI, /hr (SD)	20.2 (23.7)
Mean O_2, % (SD)	94.8 (2.8)
Minimal O_2, % (SD)	82.9 (9.3)
O_2% <90, % (SD)	6.0 (13.8)
O_2% <85, % (SD)	2.6 (9.1)

AHI = apnea–hyponea index, CKD = chronic kidney disease, DM = diabetes mellitus, HTN = hypertension, ODI = oxygen desaturation index, REM= rapid eye movement, SD = standard deviation.

Table 2

Results of each variables on the percentage for sleep N3 stage by univariate linear regression analysis.

Variables	Coefficient ± standard error (*P* value)
Age	−0.079 ± 0.005 (<.001)
Sex	−1.028 ± 0.158 (<.001)
HTN	−1.062 ± 0.161 (<.001)
DM	−0.690 ± 0.243 (.005)
Dyslipidemia	−0.610 ± 0.207 (.003)
CKD	−0.834 ± 0.436 (.056)
Parkinson disease	−0.995 ± 0.812 (.220)
Dementia	−1.698 ± 1.432 (.236)
Chronic tinnitus	−0.503 ± 0.160 (.002)
Subjective insomnia	−0.275 ± 0.059 (<.001)
Sleep onset	0.003 ± 0.002 (.202)
Sleep efficiency	0.011 ± 0.005 (.021)
REM	0.033 ± 0.010 (.001)
AHI	−0.029 ± 0.003 (<.001)
ODI	−0.025 ± 0.003 (<.001)
Mean O_2%	0.207 ± 0.027 (<.001)
Minimal O_2%	0.052 ± 0.008 (<.001)
O_2% <90	−0.028 ± 0.005 (<.001)
O_2% <85	−0.033 ± 0.008 (<.001)

AHI = apnea–hyponea index, CKD = chronic kidney disease, DM = diabetes mellitus, HTN = hypertension, ODI = oxygen desaturation index, REM= rapid eye movement.

Table 3

Results of sleep indices, chronic tinnitus, and other variables on the percentage for sleep N3 stage by multivariate linear regression analysis.

Variables	All	Without tinnitus	With tinnitus
AHI	–0.040 ± 0.009 (<.001)	–0.045 ± 0.012 (<.001)	–0.034 ± 0.015 (.020)
ODI	0.017 ± 0.011 (.124)	0.021 ± 0.014 (.134)	0.013 ± 0.017 (.467)
Mean O_2%	0.028 ± 0.062 (.647)	–0.034 ± 0.079 (.661)	0.148 ± 0.099 (.134)
Minimal O_2%	–0.009 ± 0.014 (.527)	–0.012 ± 0.017 (.493)	–0.007 ± 0.023 (.762)
O_2% <90	0.013 ± 0.016 (.410)	–0.013 ± 0.021 (.546)	0.056 ± 0.024 (.019)
O_2% <85	–0.027 ± 0.020 (.181)	–0.013 ± 0.026 (.624)	–0.044 ± 0.033 (.178)
Chronic tinnitus	–0.143 ± 0.163 (.381)		
Age	–0.079 ± 0.007 (<.001)	–0.083 ± 0.008 (<.001)	–0.074 ± 0.011 (<.001)
Sex	–1.047 ± 0.167 (<.001)	–1.237 ± 0.218 (<.001)	–0.743 ± 0.254 (.004)
HTN	–0.086 ± 0.179 (.633)	–0.088 ± 0.233 (.707)	0.004 ± 0.271 (.987)
DM	0.006 ± 0.252 (.981)	0.135 ± 0.328 (.682)	–0.298 ± 0.382 (.436)
Dyslipidemia	–0.044 ± 0.213 (.837)	–0.025 ± 0.283 (.931)	–0.066 ± 0.310 (.832)
CKD	0.035 ± 0.437 (.936)	0.006 ± 0.643 (.993)	–0.025 ± 0.559 (.965)
Parkinson disease	0.484 ± 0.818 (.555)	0.880 ± 1.036 (.396)	–0.592 ± 1.333 (.657)
Dementia	–0.356 ± 1.404 (.800)	–0.849 ± 1.838 (.644)	0.552 ± 2.151 (.797)
Subjective insomnia	–0.324 ± 0.062 (<.001)	–0.414 ± 0.080 (<.001)	–0.156 ± 0.094 (.098)
Sleep onset	0.001 ± 0.003 (.632)	0.004 ± 0.004 (.260)	–0.004 ± 0.005 (.373)
Sleep efficiency	–0.015 ± 0.006 (.016)	–0.015 ± 0.008 (.061)	–0.016 ± 0.010 (.128)
REM	0.015 ± 0.010 (.143)	0.008 ± 0.013 (.563)	0.029 ± 0.016 (.066)

The data in all cells were shown as coefficient ± standard error (*P* value).

AHI = apnea–hyponea index, CKD = chronic kidney disease, DM = diabetes mellitus, HTN = hypertension, ODI = oxygen desaturation index, REM= rapid eye movement.

parameters on PSG. Teixeira et al[10] also claimed that only the percentage of REM sleep, but not sleep N3 stage, could show a significantly negative association with tinnitus. However, these negative results about chronic tinnitus and sleep N3 stage were not convincing enough due to the imperfect matching process of limited items, small case numbers, and lower statistical power.

Most importantly, most studies had set tinnitus as the dependent variable during analysis. By doing so, we could only see roughly which items in the sleep questionnaires or PSG were different in the tinnitus and nontinnitus groups. Those conclusions were directed to say that some kinds of sleep disturbances might contribute to tinnitus roughly. However, the logic might be questionable during statistical analysis because our aim was not to see whether age, sex, common diseases, or any sleep characteristics had any association with tinnitus. On the contrary, due to sleep characteristics being affected by many clinical variables and sleep indexes,[1,3–6,9,14–16] we should treat sleep N3 stage as the dependent variable to test whether tinnitus had any significant association with sleep N3 stage under well adjustment for age, sex, sleep indexes, and other important confounding variables. By doing so, we found that sleep apnea, but not chronic tinnitus, had a specific association with sleep N3 stage.

One study reported that a longer sleep latency and lower percentage of stage N3 sleep were found in children with OSA compared with healthy controls.[3] But, no significant differences in total sleep time, sleep efficiency, percentage of REM stage and N2 stage were found between OSA and healthy control.[3] Now, we found that AHI, but not other sleep apnea indexes, was associated with sleep N3 stage in adults. However, Wächter et al[17] reported that the effects of OSA severity and potential confounders on sleep architecture are small, but sleep-stage transitions are influenced by OSA severity, age, and gender.[17] Higher frequencies of alternating (symmetric) patterns (e.g., N2 → N1 → N2, N2 → wake → N2) in sleepy patients.[17]

In this study, we found that the N3 sleep was most affected by sex and subjective insomnia in order in the view of categorical variables, and by age, AHI, and sleep efficiency in order in the view of continuous variables. As for tinnitus, a higher prevalence (33.8%) of chronic tinnitus was presented in this study due to the higher mean age (50.6 years old). The effect size was estimated initially at 1% of sleep N3 stage between tinnitus and nontinnitus group. By doing 2 group Student *t* test, we found that only 0.5% was found with significance (*P* = .0017) between 2 groups finally. However, tinnitus lost its significance on N3 sleep during multivariate linear regression analysis, in which many more important variables were considered simultaneously.

The strength of this study was that our conclusions were based on a larger case number, PSG data, and a proper statistical strategy with well adjustment of many confounding factors. Even so, our study had some limitations. First, only adult patients who had sleep problems and received overnight PSG were collected. Second, multicollinearity was present more or less in the multivariate analysis, such as between AHI and common diseases, oxygen saturation indexes, sleep efficiency, or chronic tinnitus. It will certainly make the issue of interpreting p values unstable.

5. Conclusion

As we know, N3 sleep stage is an important indicator of sleep quality. This large-scale PSG study renewed our knowledge about the relationship between sleep apnea, chronic tinnitus, and sleep N3. We found that AHI, but not chronic tinnitus, was related to the percentage of sleep N3 stage in adults.

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Author contributions

H.-H.T.: wrote the initial manuscript; S-.W.H., S.-R.H.: data acquisition; J.-H.H.: conception and design, analysis and interpretation of data, final approval of the version to be published.

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