A Pilot Study on the Efficacy of Continuous Positive Airway Pressure on the Manifestations of Ménière's Disease in Patients with Concomitant Obstructive Sleep Apnea Syndrome

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Objective: To evaluate the effect of continuous positive airway pressure (CPAP) therapy on Ménière's disease patients with concomitant obstructive sleep apnea syndrome (OSAS), since recent reports suggest OSAS may cause dysfunction of the vestibular system.

Study Design: Prospective study using CPAP administered to patients diagnosed with "Definite Ménière's disease" according to the guidelines of the American Academy of Otolaryngology—Head and Neck Surgery and combined with OSAS.

Setting: University hospital.

Methods: Twenty consecutive patients, 14 male and 6 female with active, unilateral, cochleovestibular Ménière's disease refractory to medical management who also had concurrent OSAS as defined by International Classification of Sleep Disorders, Second Edition were selected to undergo solitary CPAP therapy. Audiometric testing, caloric testing, and DHI survey were conducted before and after CPAP therapy and compared to assess effectiveness of CPAP therapy as utilized for treatment of Ménière's disease.

Results: Although caloric testing did not show significant difference, audiometric testing and results of dizziness handicap inventory were significantly improved (p < 0.05) after CPAP therapy only, without standard treatment for Ménière's disease.

Conclusions: Recent reports have suggested that OSAS may cause dysfunction of the vestibular system. We investigated whether standard therapy for OSAS would be of benefit in the management of vertigo and hearing loss in Ménière's disease patients. Our study cohort demonstrated significant improvement in both DHI and audiometric testing following solitary CPAP therapy for OSAS. Solitary CPAP therapy may become a new effective treatment strategy for Ménière's disease patients with OSAS, not just only for control of dizziness and vertigo but also for potential benefit of hearing.

Keywords: Ménière's disease, sleep, OSAS, CPAP, audiogram, caloric test, DHI.

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Ménière's disease is characterized by fluctuating and progressive hearing loss, aural fullness, tinnitus, and intermittent attacks of vertigo, an illusory sensation of movement resulting from dysfunction of the labyrinth and cochlea.[1,2] Pathologically, Ménière's disease is associated with hydropic distension of the endolymphatic system, but the etiology of such hydrops remains unknown. Episodes of vertigo, which are often accompanied by nausea and vomiting, are the most prominent and disabling features of the disease. The presentation of Ménière's disease is highly variable, and its clinical course is characterized by acute exacerbation and spontaneous remission.[2–4]

It is well known that insomnia is associated with increased psychological symptomatology and perceived stress, higher predisposition to arousal, and greater impairments to quality of health.[5–7] The relationship between Ménière's disease and stress is well documented, but that between Ménière's disease and insomnia is unclear. In our previous report,[8] we first found

BRIEF SUMMARY

Current Knowledge/Study Rationale: Recent reports indicate that OSAS may cause vestibular dysfunction. The current study was designed to determine whether treatment of patients with Ménière's disease and concomitant OSAS using CPAP ameliorate the manifestations of Ménière's disease.

Study Impact: Ménière's disease encompasses several contributing etiologies. Investigating whether Ménière's patients also have concomitant OSAS may lead to an effective new strategy for the management of this disease in this subset of patients.

that sleep quality of Ménière's disease patients was impaired. Ménière's patients had longer total sleeping time, lack of deep sleep stages, increased arousal, and occasionally also had obstructive sleep apnea syndrome (OSAS) and/or periodic limb movement disorder (PLMD). Poor quality of sleep may cause additional stress and lead Ménière's disease patients to a negative spiral of symptoms. Furthermore, poor sleep quality may

result in Ménière's disease patients being refractory to medical management. Therefore, treatment focusing on the sleep disorders of Ménière's disease patients may become an additional new strategy for terminating the negative spiral of symptoms and reducing exacerbations. Because OSAS is academically well documented and defined, and continuous positive airway pressure (CPAP) is an effective therapy used universally for OSAS, we prospectively investigated the effect of CPAP therapy on the hearing and vestibular function of Ménière's disease patients with concomitant OSAS through our first pilot study.[9]

METHODS

Ménière's Disease Patients with OSAS

Patients diagnosed with "Definite Ménière's disease" according to the guidelines for Ménière's disease by the American Academy of Otolaryngology-Head and Neck Surgery[1] were recruited from the Department of Otolaryngology in Nagoya City University, Nagoya, Japan, from April 2011 to March 2014. The patients' chief complaints were vertigo attacks, dizziness, tinnitus, ear fullness, and/or hearing loss. No patient reported "sleep disturbance" as a chief complaint, and "sleep disturbance" was not brought up by any patients until we asked about that complaint specifically. The patients were instructed to discontinue all medications that could influence sleep, such as benzodiazepines for 2 weeks before polysomnography. Patients enrolled in this study had failed all medical management including diuretic therapy, low salt diet, and oral steroids. Consequently, prior to continuing in the study, patients were taken off all therapies which had failed in order to avoid unnecessary potential side effects. Twenty patients, 14 male and 6 female, were diagnosed as mild-to-severe OSAS (AHI ≥ 20) according to the International Classification of Sleep Disorders, Second Edition[10] and were enrolled in this study. The age of the patients ranged from 33 to 82 (average 60) years, with BMI 20.7 to 28.5 (average 23.5). All patients were designated to receive CPAP therapy only, without reinstitution of previous medical management that they were prescribed for Ménière's disease. Manual titration of CPAP was performed according to standard published criteria to eliminate respiratory events.[11] Patients treated with CPAP are seen in followup monthly in order to monitor for correct application of the CPAP. They undergo a manual CPAP titration at 4 and 8 weeks to guide in the appropriate utilization and to bring the AHI under 5. CPAP titration began at a pressure of 4 cm H_2O, and every few minutes the pressure was increased to eliminate obstructive apneas, hypopneas, and eventually snoring. Standard audiometry, caloric testing, and the Japanese Dizziness Handicap Inventory (J-DHI) scale[12] were performed immediately before and 6 months after CPAP titration to evaluate the effects of this solitary therapy. The present study was approved by the Ethics Review Committee of Nagoya City University (Permit Number: 798, 2013), and informed consent was obtained from each individual prior to the study.

Polysomnography

All study participants underwent full-night polysomnography, and a sleep medicine physician interpreted the results. A 12-channel montage was utilized recording EEG, EOG, EKG, chin and lower extremity EMG, naso-oral airflow, thoracic and abdominal effort, and oxygen saturation by pulse oximeter. All subjects were evaluated in an accredited sleep laboratory in sound attenuated rooms, monitored by an infrared camera. The records were scored by the method of Rechtschaffen and Kales.[13] Electroencephalogram recordings were divided into NREM and REM states for analysis. NREM is conventionally subdivided into 4 stages, stage 1 to 4. Sleep stages 3 and 4 were scored together as delta sleep, and movement time was scored as an arousal (2–15 sec) or awakening (> 15 sec). The various indices of sleep architecture analyzed were total sleep time (TST), sleep efficiency (TST divided by time in bed), percentage of sleep stages, apnea index (AI), hypopnea index (HI), and apnea-hypopnea index (AHI). Arousal index (ArI) was scored as described by the American Sleep Disorders Association.[14] Periodic limb movement index (PLMI) was scored according to standard criteria.[15] Digital videotaping with sound recording was performed throughout the night.

Hearing and Vestibular Evaluation

Hearing function was measured by a pure tone audiometer and was evaluated based on calculating the pre- and post-CPAP 3-tone pure tone average (PTA) formulated by (a + 2b + c)/4 (where a, b, and c are hearing levels at 0.5 kHz, 1 kHz, and 2 kHz, respectively), according to the modified 1995 AAO-HNS criteria for pure tone averaging, as well as explicit comparison of the pre- and post-CPAP threshold at 0.5 kHz, preferentially chosen to represent low frequency responses to treatment. The audiograms of each subject within 6 months prior to CPAP therapy were compared to their respective audiograms within 6 months following institution of CPAP therapy.

Vestibular function was measured by electronystagmography (ENG) recordings during hot and cold water caloric testing. Cold and warm caloric vestibular stimulation was achieved using cold water at 30°C and warm water at 44°C. The rates of reduced vestibular response on caloric testing were compared pre- and post-CPAP therapy. The reduced vestibular response or unilateral weakness (UW) was calculated utilizing the standard Jongkees formulae, calculating the difference of the total cool and warm caloric responses of each ear divided by the addition of total caloric responses of both ears:

[(Unaffected ear cool + warm caloric response) −
(Affected ear cool + warm caloric response)] /
[(Unaffected ear cool + warm caloric response) +
(Affected ear cool + warm caloric response)]

The Japanese version of the Dizziness handicap Inventory (J-DHI) test[12] translated from the original DHI, which has been developed by Jacobson and Newman[16] was used to assess the impact of dizziness on patient's daily life before and after CPAP therapy. The J-DHI has been validated to confer similar clinical results from the original English version DHI previously.[12,16] The J-DHI evaluates the dizziness associated with incapacities and handicap in 3 areas of a patient's life: physical, functional and emotional. In this study, subjects were asked to complete the J-DHI consisting of 25 questions, and a total score (0–100 points) was obtained by summing ordinal scale responses, with

Figure 1—Hearing average.
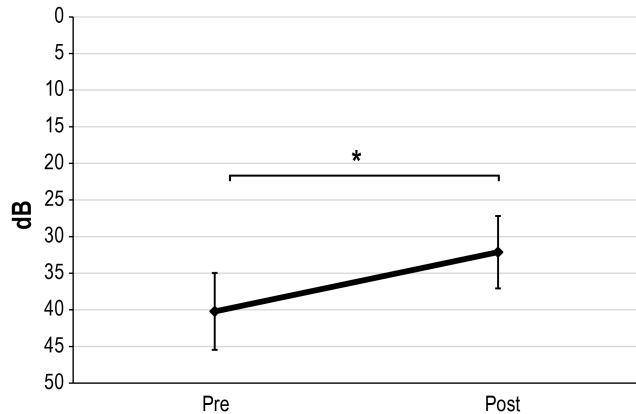
The mean PTA hearing levels for the cohort following institution of CPAP therapy was statistically significantly improved (*p < 0.05). Diamond is mean and whiskers represent standard error.

Figure 2—250 Hz hearing average.

Comparison of hearing level explicitly at 0.5 Hz in post-CPAP testing for the cohort, demonstrating a statistically significant improvement in hearing preferential to the low frequencies (*p < 0.05). Diamond is mean and whiskers represent standard error.

Figure 3—Canal paresis %.

No statistically significant improvement was identified for caloric testing as a result of CPAP therapy (p = 0.19). Diamond is mean and whiskers represent standard error.

higher scores indicating more severe handicap. Then 25 items were grouped into 3 categories—physical, functional, and emotional aspects of dizziness and unsteadiness. Total score for each category—physical, functional, and emotional—were analyzed. Subjects completed the pre-CPAP J-DHI with 6 months of institution of CPAP therapy, and they completed the post-CPAP J-DHI at 6 months after institution of therapy.

Statistics

All statistical analyses were performed using JMP version 9 (SAS Institute Inc., Cary, NC, USA). Differences of 2 groups (before and after CPAP) were analyzed using ANOVA followed by a post hoc test (Steel-Dwass test). A value of $p < 0.05$ was considered statistically significant.
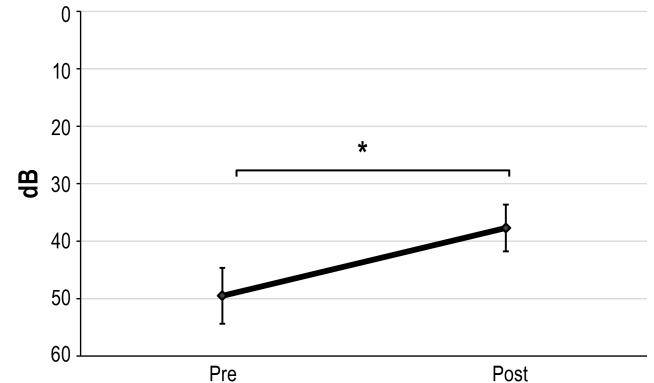
RESULTS

CPAP Adherence

Good adherence to CPAP was evaluated with a mean use ≥ 4 h per night and a mean use ≥ 70% days per month. All cases in this study showed good adherence to CPAP without failure.
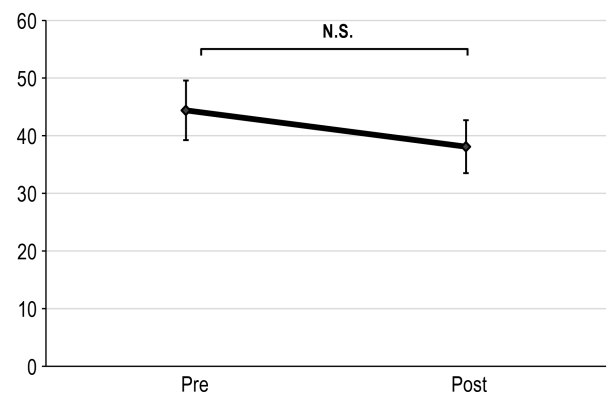
Audiometric Testing

Hearing level of the 3-tone PTA averaged 40.2 dB HL (range from 8–87 dB HL) for the cohort in pre-CPAP testing and averaged 32.1 dB HL (range 6–87 dB HL) for the cohort in post-CPAP testing. This improvement in mean PTA hearing levels for the cohort following institution of CPAP therapy was statistically significant (p < 0.05) (**Figure 1**). Comparison of hearing level explicitly at 0.5 kHz averaged 49.5 dB HL (range 10–90 dB HL) in pre-CPAP testing, and averaged 37.7 dB HL (range 15–90 dB HL) in post-CPAP testing for the cohort. These results demonstrated a statistically significant improvement in hearing at 0.5 kHz following CPAP therapy (p < 0.05; **Figure 2**).

Caloric Testing

No statistically significant improvement was identified for caloric testing as a result of CPAP therapy, with UW averaging

44.4% (range 12% to 92%) in pre-CPAP testing, and averaging 38.1% (range 20% to 92%) in post-CPAP testing (p = 0.19; **Figure 3**).

J-DHI Testing

The total score of J-DHI for the cohort averaged 42.3 (range 12–88) in pre-CPAP testing and averaged 19 (range 6–60) in post-CPAP testing. This reduction in J-DHI total score was statistically significant as a result of CPAP therapy (p < 0.001) (**Figure 4A**). Total score of all dimensions of the J-DHI each demonstrated significant improvement following CPAP therapy. The functional dimension score of J-DHI averaged 15.9 (range 4–36) in pre-CPAP testing and improved to 6.3 (range 2–20) in post-CPAP testing (p < 0.001; **Figure 4B**). The emotional dimension score of J-DHI averaged 15.3 (range 4–30) in pre-CPAP testing and improved to 7.5 (range 2–20) in post-CPAP testing (p < 0.001; **Figure 4C**). The physical dimension score of J-DHI averaged 11.4 (range 4–24) in pre-CPAP testing and improved to 5.7 (range 2–24) in post-CPAP testing (p < 0.01; **Figure 4D**).

Figure 4—DHI average.
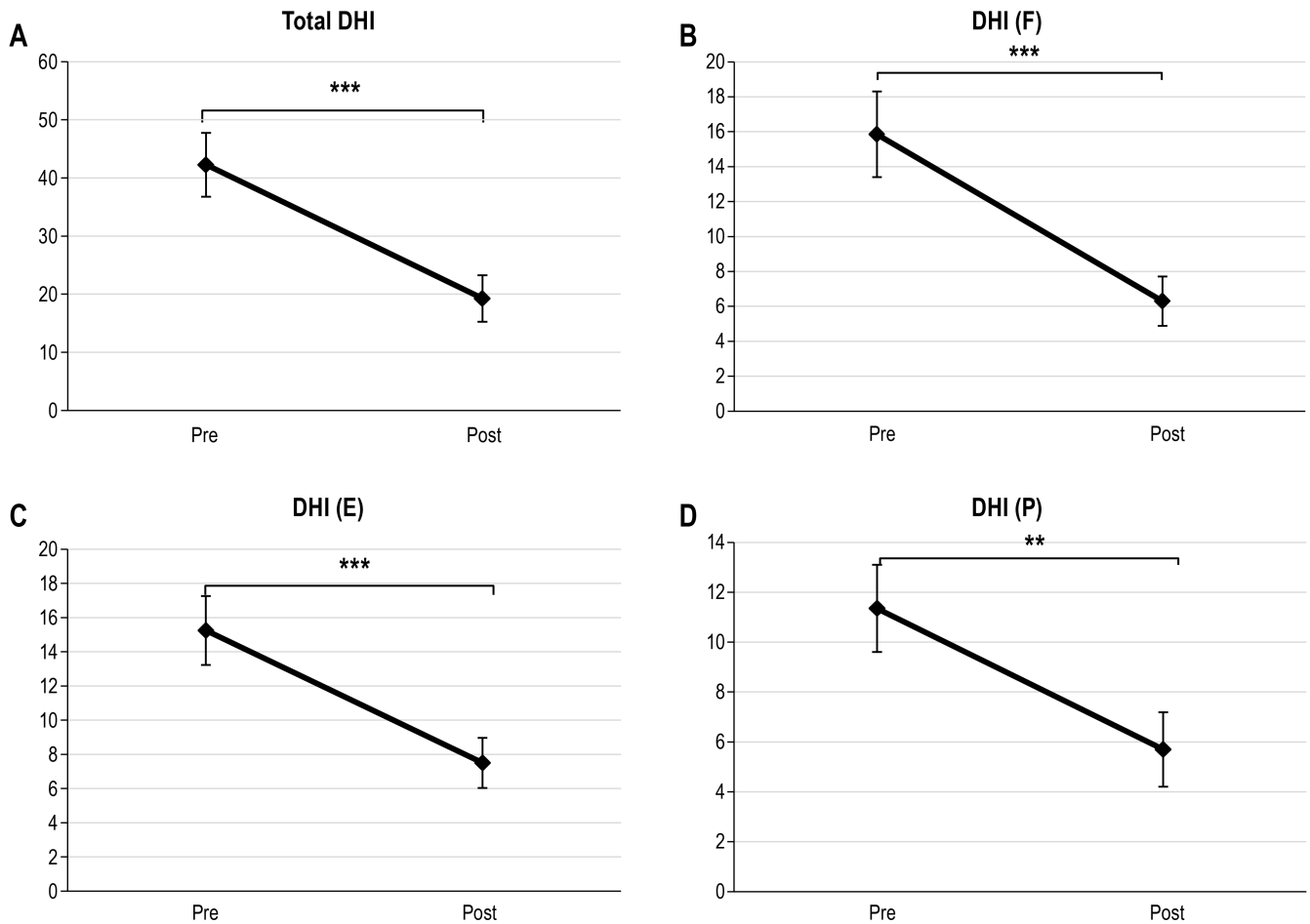
(A) The reduction in total score of J-DHI was statistically significant as a result of CPAP therapy (***p < 0.001). (B) Similar improvement of the functional dimension score of J-DHI was statistically significant (***p < 0.001). (C) Similar improvement of the emotional dimension score of J-DHI was statistically significant (***p < 0.001). (D) Improvement of the physical dimension score of J-DHI was statistically significant (**p < 0.01). Diamond is mean and whiskers represent standard error.

DISCUSSION

The underlying etiology for Ménière's disease is not fully established, but in all likelihood the disease is the result of multiple underlying pathologies and is exacerbated by a host of comorbidities. The variability in response to the various treatments offered to patients with Ménière's disease may be due to these differences in underlying pathogenesis. The premise of this study is that there is a subset of patients with Ménière's disease whose symptoms are exacerbated by the comorbidity of OSAS. The hypothesis tested was whether CPAP can reduce the manifestations of Ménière's disease in the subset of patients with the comorbidity of OSAS. We found that a substantial number of patients with Ménière's disease had unrecognized concomitant OSAS, and that treatment of these patients with CPAP significantly reduced the impact of the vertigo and low-frequency hearing loss associated with the Meniere's disease. The underlying vestibular weakness as measured by ENG did not change significantly between the pre- and post-CPAP treatments.

Treatment of Ménière's disease is generally not individualized to different underlying etiologies or underlying comorbidities other than to identify patients with immunologically mediated disease who respond to steroids. The aim of treatment of Ménière's disease is to reduce the number and severity of acute attacks of vertigo and prevent progression of hearing loss. Besides pharmacotherapy, interventional procedures such as intratympanic injections of gentamicin are frequently performed. Initially, the strategy was to give multiple intratympanic injections of gentamicin until patients develop vestibular hypofunction, resulting in reduced frequency of vertigo attacks, but at a high rate of sensorineural hearing loss (up to 50%).[17–19] Other surgical treatments such as endolymphatic sac decompression, are reported to diminish vertigo attacks in 60% to 70% of patients but have minimal effect on reducing long-term progression of hearing loss.[20–22]

We report on a unique subset of Ménière's patients who also suffer from OSAS. The findings of this study are surprising and encouraging in demonstrating that solitary CPAP therapy may play a role in not just improvement of vertigo attacks, dizziness, and activities of daily living, but also improvement in

Figure 5—Audiogram of a case study before and after CPAP.
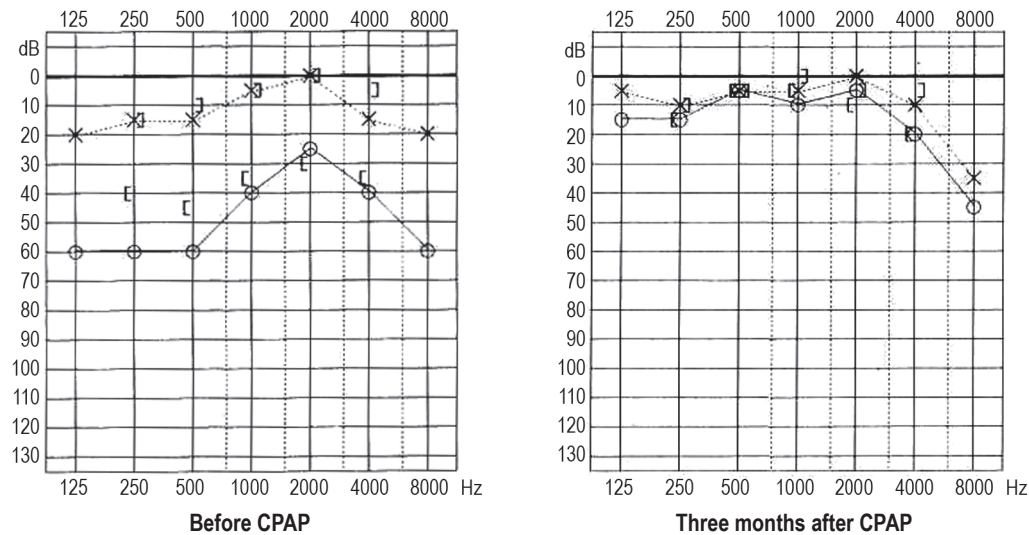
All symptoms associated with a 46-year-old male Ménière's disease patient—including vertigo attacks, aural fullness, and hearing loss—were improved, and audiogram showed normal hearing soon after CPAP therapy.

hearing function in this subset of patients. The effects of CPAP therapy on Ménière's disease patients with OSAS were evaluated six months after initiation of CPAP in this study, and we are in the process of further follow-up to continue to investigate the long-term effectiveness of this treatment strategy. In patients who do not tolerate CPAP, surgical interventions can be considered such as uvulopalatopharyngoplasty, base of tongue resection, hyoid suspension, or bimaxillary advancement, depending on the underlying pathology of the OSAS. Fortunately, all cases in this study maintained good adherence to CPAP over the 6-month protocol.

OSAS is the most common organic disorder of excessive daytime somnolence. Prevalence is highest among men age 40 to 65 years. The highest figures for this age group indicate that the prevalence of clinically significant OSAS in the general adult population may be 8.5% or higher.[23,24] Investigation on the relation between Ménière's disease and OSAS was planned because of the similarly high prevalence of OSAS in Ménière's disease patients, with approximately 10% of OSAS patients found in our previous Ménière's disease study.[8] Ménière's patients frequently receive benzodiazepines or other drugs that have hypnotic, muscle relaxing, anti-anxiety, and anticonvulsant properties.[25,26] These properties may have the effect of aggravating OSAS symptoms. Ménière's disease patients who are refractory to medication may find themselves in a vicious cycle combining disease, quality of sleep, and stress.[5–7] When prescribing sedating drugs to Ménière's disease patients, the possibility should be kept in mind that such drugs could have unintended consequences, in that such medications may have suppressant properties but also increase the severity of preexisting sleep disturbances, thereby counteracting one set of benefits with another set of drawbacks. Although it may be only 10% of Ménière's disease patients who have concomitant OSAS, such patients may be refractory to pharmacotherapy for Ménière's disease and only respond positively to therapies that benefit OSAS.

The potential pathogenic mechanisms by which OSAS affects Ménière's disease remain unestablished. The cardiovascular problems and neurological disturbances due to hypoxia in patients with OSAS are well known.[27,28] But the neurotologic consequences of such physiological derangements are not so clearly identified and are subject to debate. In 2010, Sowerby and colleagues demonstrated a previously undescribed link between idiopathic dizziness, daytime somnolence, and sleep apnea might exist by utilizing the combination of Epworth Sleepiness Scale, the Berlin Questionnaire, and the Multivariable Apnea Risk Index questionnaires.[29] In the same period, Gallina and colleagues evaluated vestibular function in OSAS patients and demonstrated the effects of OSAS and its associated hypoxia on the peripheral and central vestibular systems.[30] Although our study did not show that vestibular function, as measured by caloric testing, improved with CPAP therapy, subjects' symptoms of vertigo attacks or dizziness were remarkably improved as based on their total and dimensional J-DHI scores. Measurements of unilateral weakness are highly dependent on the current activity—or quiescence—of the disease state at the time the ENG is actually performed; hence, demonstration of canal paresis is notoriously variable in Ménière's disease patients, whose disease activity is punctuated and episodic. In addition, Gallina and colleagues suggested the possibility that the peripheral vestibular system may become asymmetric or hyporeflexic due to hypoxic damage while the central vestibular system corrects this disequilibrium.[30] CPAP therapy may not only influence inner ear function but also improve the central vestibular system response.

Pathologically, Ménière's disease is associated with hydropic distension of the endolymphatic system. Normal blood supply to the cochlea is critically important for establishing the endocochlear potential and sustaining production of endolymph. Abnormal cochlear microcirculation has long been considered an etiologic factor in noise-induced hearing loss,

age-related hearing loss, sudden sensorineural hearing loss or vestibular function, and Ménière's disease.[31–35] Thus there likely exists a subset of Ménière's disease patients whose endolymphatic hydrops is caused by a derangement in cochlear microcirculation. As such, there exists the possibility that CPAP therapy, through correction of hypoxia and improvement in cerebral blood flow and central oxygenation, directly improve cochlear microcirculation, and indirectly improves hydropic distension of the endolymphatic system. For the subset of Ménière's disease patients who are diagnosed with OSAS early in the course of their hydropic disease, CPAP therapy—directed towards correction of cochlear microcirculation as posited in this study—affords the possibility for hearing or vestibular improvement before hair cell degeneration and permanent injury to the inner ear can ensue.

The prevalence of Ménière's disease has been reported by numerous investigators to be between 12 and 46 per 100,000 individuals, depending on the geographical localization of study; approximately 15 per 100,000 in the United States,[36] 35 per 100.000 in Japan,[37] and 46 per 100,000 in Sweden.[38] The population of Nagoya city where this study was performed is approximately 2 million people; therefore, there are approximately 700–1,000 Ménière's disease patients here, including suburbs. With four medical universities in this metropolitan region, our institution receives and treats approximately 150–200 such referred patients annually. Thus our institution was able to receive and consent approximately 20 cases annually of Ménière's disease patients concurrent with OSAS.

This study is limited by the absence of a control group to compare with the CPAP study group. The difficulty in including a control group is one of an ethical concern. The ideal control design would be to randomly assign Ménière's patients with concomitant OSAS into either treatment vs sham treatment groups. However, once a patient is identified to have OSAS, it would be inappropriate to withhold CPAP or other appropriate treatment. At best, the experimental group with poorly controlled Ménière's disease and OSAS could be compared with a control group without OSAS and poorly controlled Ménière's receiving no additional treatment but the control group is not truly representative of the same subpopulation of Ménière's patients.

Given the very significant morbidity of OSAS as a disease in and of itself, from a medical and ethical standpoint we felt obligated to provide OSAS treatment to all such Ménière's disease patients whom we found also suffered from OSAS.

The current study supports the hypothesis that the comorbidity of OSAS in patients with Ménière's disease exacerbates the underlying condition and that treatment of OSAS can reduce the morbidity of Ménière's disease and improve the quality of life in these patients.

ABBREVIATIONS

AHI, apnea-hypopnea index
ArL, arousal index
BMI, body mass index
CPAP, continuous positive airway pressure
DHI, Dizziness Handicap Inventory
EEG, electroencephalographm

EKG, electrocardiogram
EMG, electromyogram
EOG, electro-oculogram
HI, hypopnea index
HL, hearing level
J-DHI, Japanese Dizziness Handicap Inventory
NREM, non-rapid eye movement sleep
OSAS, obstructive sleep apnea syndrome
PLMD, periodic limb movement disorder
PTA, pure tone audiogram
REM, rapid eye movement sleep
TST, total sleep time
UW, unilateral weakness

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DISCLOSURE STATEMENT