Prevalence of Obstructive Sleep Apnea (OSA) in Spontaneous Cerebrospinal Fluid (CSF) Leaks: A Prospective Cohort Study

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ABSTRACT

Objective: To determine the prevalence of obstructive sleep apnea (OSA) in a prospective cohort of patients with spontaneous CSF (sCSF) leaks of the temporal bone.

Study Design: Prospective cohort study

Setting: Tertiary referral center.

Patients: Consecutive sCSF leak patients (21) over a 3-year period. Four patients presented with a history of OSA and 17 patients were prospectively offered PSG testing during the initial clinic encounter.

Intervention: Level I polysomnogram (PSG)

Main Outcome Measures: Patient characteristics (age, sex, BMI), apnea hypopnea index (AHI), presence of snoring, and presence of hypoxia (oxygen saturation less than 88% for > 5 minutes). OSA was defined as mild (AHI ≥5 and <15/hr), moderate (AHI ≥15 and <30/hr), and severe (AHI ≥30/hr).

Results: The prevalence of OSA in sCSF leak patients is 83.3%. PSG studies were performed on 18 of the 21 patients. There were 15 females and 6 males with an average age (SD) of 56.3 (11.2) years and an average BMI of 35.3 (7.7) kg/m^2. Objectively, the AHI ranged from mild to severe (range = 5.7 – 92, median = 19.8). Snoring was present in 61% of patients and hypoxia was present in 39% of patients. sCSF leak patients with OSA were significantly older than sCSF leak patients without OSA (56.7 (8.3) vs. 42.7 (14.5) years, p = 0.03).

Conclusions: OSA is highly prevalent among patients with sCSF leaks. All patients with sCSF leaks should undergo formal polysomnogram testing. Future studies are needed to determine the role of OSA in the development of sCSF leaks.

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Key Words: Obstructive Sleep Apnea; Spontaneous; Temporal Bone; Cerebrospinal Fluid Leak; CSF; OSA; Snoring; Prospective; Prevalence; lateral skull base

Level of Evidence: 3

Introduction:

Spontaneous cerebrospinal fluid (sCSF) leaks of the temporal bone result from defects of the bony skull base and meninges in the absence of an inciting cause such as trauma or surgery (1). Communication with the intracranial CSF space increases the risk of meningitis in these patients, and surgical repair is the only definitive treatment (2-4). Multiple studies have described the association of sCSF leaks with obesity, middle age, and female gender (5-8). In addition to skull base bony defects, patients with sCSF leaks have thinning of the calvarium that is not seen in extracranial bones (9). This suggests there is an obesity-associated intracranial process that leads to skull base and calvarial thinning and ultimately to the development of sCSF leaks. While chronically elevated intracranial pressure (ICP) could potentially lead to calvarium thinning and sCSF leaks, it is estimated that only 36% of sCSF leak patients have chronically elevated ICP on lumbar puncture (10).

While most sCSF leak patients do not demonstrate chronically elevated ICP, these patients may have transiently elevated ICP, and obstructive sleep apnea has been associated with transient spikes in ICP (11,12). The prevalence of OSA in the general population is on the rise, attributed in part to the national obesity epidemic (13-16). Similarly, surgical repair of sCSF leaks has nearly doubled in the past decade(5). Thus far, the data regarding the relationship between OSA and spontaneous CSF leaks is limited; the prevalence of OSA in sCSF leak patients has been cited anywhere from 10 to 40% with data primarily based on diagnosis codes in retrospective studies (8,17,18). To date, there has not been a prospective evaluation of the prevalence of OSA in sCSF leak patients. We aim to determine the true prevalence of OSA in sCSF leak patients by prospectively obtaining a formal level 1 diagnostic polysomnogram (PSG) in all patients presenting with sCSF leaks.

Materials and Methods:

Study Approval:

Institutional Review Board approval was obtained from Indiana University (IRB #1704084098).

Patient Selection:

This prospective cohort study included all consecutive patients diagnosed with lateral skull base temporal bone spontaneous CSF leaks over a 3-year period (July 2014 to May 2017). If the patient presented with the diagnosis of OSA or was using CPAP, the records of the PSG were obtained. Patients who had not had formal OSA testing were offered a level 1 diagnostic PSG. A level 1 PSG requires an overnight stay in a sleep laboratory with a technician in attendance. Patients were excluded from the study if they were unwilling or unable to obtain a PSG. Eligible patients were separated into two groups for analysis: a retrospective cohort (N=4) who presented with a history of OSA confirmed by PSG, and a prospective cohort (N = 17) who were offered a PSG after presenting to our clinic. The historic association between OSA and spontaneous CSF leaks was cited in the clinic notes, and this allowed the clinically-indicated sleep studies to be covered by insurance.

Data reviewed from the PSG records included apnea hypopnea index (AHI), lowest O2 saturation, duration of time spent below an O2 saturation of 88%, and snoring. The AHI was defined as events per hour according to the Centers for Medicare & Medicaid Services (CMS) guidelines (hypopnea defined as ≥4% desaturation). OSA was defined as negative (AHI <5/hr), mild (AHI ≥5 and <15/hr), moderate (AHI ≥15 and <30/hr), and severe (AHI ≥30/hr). The rapid eye movement (REM) AHI, supine AHI and the American Association of Sleep Medicine (AASM; hypopnea defined as ≥3% desaturation) AHI were also recorded when noted in the report. The date of initial consultation and PSG were recorded. Patients' ages, gender, and body mass index (BMI) were obtained from medical records.

Hypoxemia was defined as an oxygen saturation less than 88% for > 5 minutes as this is the current threshold used by CMS for supplemental oxygen treatment.

Statistical Analysis

Statistical analysis was carried out between OSA and non-OSA patients using two-sample t-test with respect to age and BMI, while the Fisher exact test was used with respect to gender. *P* values <0.05 were determined a priori to be statistically significant.

Results:

Twenty-one consecutive lateral skull base sCSF leak patients were seen in consultation over the 3-year period. There were 15 females and 6 males with average age (SD) of 56.3 (11.2) years and an average BMI of 35.3 (7.7) kg/m^2 (**Table 1**).

Four patients presented with the diagnosis of OSA and CPAP treatment had been recommended; the polysomnogram tests from these patients were obtained and reviewed. The remaining 17 patients were offered PSG testing and 14 underwent prospective PSG testing. Of the three patients who did not undergo PSG testing, 1 was lost to follow up and 2 refused to have testing. Thus, a total of 18 sCSF leak patients underwent level I PSG testing (**Table 1**). Of those prospectively tested for OSA (N = 14), PSG testing was performed within an average of 5 months of diagnosis of sCSF leak (Range = 1 – 20 months, median = 3.5 months; **Table 1**).

The overall prevalence of OSA in the prospective cohort was 83.3% (15 of 18; **Table 1**). Objectively, the AHI ranged from mild to severe (range = 5.7 – 92, median = 19.8). OSA was mild in 33.3% (5 of 15), moderate in 40% (6 of 15), and severe in 26.7% (4 of 15) of patients (**Table 1**). Next, we evaluated if specific positions or sleep stages were associated with higher AHI levels. As expected, the REM or supine AHI was consistently higher than the average CMS AHI, as 9 of the 15 patients (60%) had REM or supine AHI in the severe range (AHI ≥30; **Table 1**). Of all 18 patients tested, snoring was present in 11 of 18 (61%) patients (**Table 1**). Hypoxemia was present in 7 out of 18 (39%) patients (**Table 1**).

Next we performed a comparison of patients with sCSF leaks with and without OSA with respect to age, BMI and gender (**Table 2**). sCSF leak patients with OSA were significantly older than those without OSA [56.7 (8.3) vs. 42.7 (14.5), P = 0.03] (**Table 2**). BMI and gender were not different between those with and without OSA (**Table 2**).

Discussion:

Obesity, OSA, and increased intracranial pressure have been highlighted in association with sCSF leaks (5,6,8,17,18). Patients with spontaneous CSF leaks have been found to have an increased incidence of elevated ICP in objective measurements (10,19). In addition, these patients often complain of clinical symptoms associated with elevated intracranial pressure, such as vertigo, tinnitus, visual problems, and headaches (20). This increased ICP has been linked to obesity, as sCSF leaks occur most commonly in obese female patients, supporting the notion that elevated BMI is central to this pathology (1). Large-scale studies have demonstrated a positive linear relationship between CSF pressure and BMI (21).

It has been proposed that increased ICP may lead to decreased calvarial and skull base thickness ultimately causing CSF leaks (9,17). The temporal calvarium thickness in patients presenting with sCSF leaks was examined in one study, revealing a 23% thinner skull in sCSF patients when compared with similar controls (9). This bone thinning was not seen in the extracranial zygoma, suggesting that the effect is isolated to an intracranial process. Interestingly, this relationship was demonstrated independent of obesity, as obese and non-obese control groups were found to have similar skull thickness (9). This supports the theory that ‘obesity-related’ factors, rather than obesity alone, may play a role in the pathology of this disease (9).

According to previous studies, 10-36% of spontaneous CSF patients have elevated ICP on lumbar puncture when presenting for surgical repair of their CSF leaks (10,22). This raises the possibility that some of these patients may not have chronically elevated ICP, but instead may have transient spikes in ICP that would not be detected on routine lumbar puncture but can contribute to CSF fistulae. Obstructive sleep apnea (OSA) is at the forefront of this discussion as it is strongly associated with obesity (15,16) and has been shown to cause transient

elevations in ICP during apneic episodes (11,12). This is theorized to occur from apneic events leading to elevated intracranial venous pressures and impaired drainage of CSF, which would then cause transient ICP elevations (17).

In addition to being associated with sCSF leaks, OSA is also associated with multiple co-morbid conditions (23) including cardiovascular disease (24), pulmonary disease (24), chronic fatigue (25), stroke (26), and increased all-cause mortality (27,28). These health concerns highlight the importance of diagnosing and treating OSA, as failing to do so can lead to a significant detrimental effect on patient well-being. Furthermore, sleep-disordered breathing has been associated with carotid intimal thickening and pseudotumor cerebri in previous studies (29-31). Looking specifically at snoring, one study investigated the effects of tissue vibration, a proxy for snoring, on carotid artery endothelial dysfunction in a rabbit model (31); the study found that tissue vibration leads to decreased cGMP levels and endothelial dysfunction, suggesting a possible link between snoring and carotid atherosclerosis (31). A study by Deeb et al further supported this by showing that primary snoring is associated with a greater intima-media thickness (IMT) of the bilateral carotid arteries, a marker used to monitor progression of atherosclerotic disease (29). Another study looked at the relationship between sleep disorders and idiopathic intracranial hypertension (IIH) and found that 13 of 14 IIH patients had a history of sleep-related breathing problems (30). We have a high level of snoring in our patient population (61%), and the association between snoring and carotid intimal thickening and IIH requires further investigation. At this point, we do not know if or how carotid intima thickness may be mechanistically related to the development of sCSF leaks, but this will be the subject of future studies.

To our knowledge, this is the first prospective cohort study examining the prevalence of OSA in sCSF leak patients. Among the patients included in this study we have found a remarkable

association between OSA and sCSF leaks. Although a causal relationship cannot be directly identified, this study does contribute to the theorized role of OSA in the pathophysiology of skull base thinning and sCSF leaks. Further studies examining the impact of OSA on calvarium and skull base thinning would be valuable moving forward.

Notably, we pursued full in-lab PSG studies for all patients, and we believe this improved the accuracy and consistency of the study. Previous authors have highlighted the difficulty of comparing in-lab and home sleep studies, noting that in-lab studies are likely more accurate, and data loss in home sleep studies approaches 30% (32). We know that home sleep apnea testing sensitivity and specificity have a range of 0.55-0.96 and 0.65-0.83 respectively, and these values vary depending on the type of device used (33). Meanwhile, Level 1 PSG testing is known to have sensitivity and specificity close to 100% (33). In addition, home sleep studies are not recommended for patients with various co-morbidities, and guidelines suggest that portable sleep studies should be reserved for those who cannot tolerate in-lab PSG testing due to safety concerns or illness (34). For these reasons, we chose to pursue level 1 PSG testing for all patients, and we feel that this helped consistently and accurately delineate the true OSA status of patients. Notably, one of our patients (#16) obtained a home sleep study showing an AHI of <5, while a repeat in-lab study showed that his AHI was 16 with a supine/REM AHI of >60. We understand that home sleep studies have been used to diagnose sleep apnea in recent years, and providers may wish to pursue a home sleep study as an initial step, but if this is negative, an in-laboratory study should be pursued given the data we have presented in this paper.

We found that OSA patients were older than non-OSA patients, and this highlights a unique subgroup of young patients with no history of OSA who develop sCSF leaks. The development of sCSF leaks is likely multi-factorial. In the younger non-OSA subgroup of patients, factors other than OSA likely lead to the development of sCSF leaks. This subgroup may correlate with

the historical cohort of sCSF leak patients from 20-30 years ago, but older literature on these patients is limited. Ultimately, only three non-OSA patients were available for analysis, so the difference in age between OSA patients and non-OSA patients lacks the power needed to draw definitive conclusions.

The scope of this paper did not allow us to address some potential future areas of investigation. First, we did not evaluate whether hearing improved in our patients following surgical correction of their sCSF leaks. On presentation, all patients had some degree of conductive hearing loss due to fluid in the middle ear space and/or an encephalocele contacting the ossicular chain. Future studies are needed to evaluate the hearing loss of this group of patients, but it does not change the conclusions of our paper. Second, we did not investigate whether OSA severity improved following surgical correction of spontaneous CSF leaks, and we are unaware of any published evidence to support that surgical repair of CSF leaks would lead to improvement in AHI or OSA. This may be the subject of future studies.

The limitations of this study include a relatively low sample size. Despite the low sample size, the percentage of patient with objectively determined OSA is very high. Second, we had 3 patients who refused PSG testing. Despite this, the percentage of sCSF leak patients with OSA would still be very high if all three of those patients tested negative for OSA. Also, it is possible these results are not generalizable to other sCSF leak patients. However, our patient population fits the gender, BMI and age profile of nearly all previously published reports (35). In addition, our associational study cannot draw a definitive causal link between OSA and sCSF leaks. sCSF leaks occur without inciting events (trauma or surgery) and the true etiology of sCSF leaks is still unknown. Postulated mechanisms have included elevated intracranial pressure (ICP), elevated ICP from OSA, and arachnoid granulations (5,35,36). Other still undiscovered causes are also possible. In addition, some sCSF leak patients can have none of these issues

and some patients have a combination of these conditions. Since the true etiology of sCSF leaks is still unknown, we cannot correlate the etiology with levels of AHI. In addition, not all patient elected to have lumbar puncture to measure ICP and thus, we cannot correlate ICP with AHI. Our paper aimed to identify the prevalence of OSA among this group of patients to add evidence to the growing literature investigating specific causes of sCSF leaks. Overall, a prevalence of ~80% of sCSF leak patients having OSA is extremely high and suggests a very strong correlation between sCSF leaks and OSA.

Conclusion:

We found an overall OSA prevalence of 83.3% among lateral skull base sCSF leak patients. Based on these findings, we recommend all patients who present with a sCSF leak undergo formal diagnostic PSG to screen for OSA. Future studies are needed to determine the impact of OSA on the development of sCSF leaks.

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