

Original Investigation

Association Between Obstructive Sleep Apnea and Spontaneous Cerebrospinal Fluid Leaks

A Systematic Review and Meta-analysis

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IMPORTANCE Spontaneous cerebrospinal fluid (CSF) leaks are a morbid condition associated with operative intervention for treatment. Understanding associations are key to diagnosis, treatment, and possible early detection.

OBJECTIVE To determine the clinical association and odds of having obstructive sleep apnea (OSA) and spontaneous CSF leaks.

DATA SOURCES A comprehensive search of the literature was conducted using PubMed (MEDLINE), Cochrane Library, and relevant article bibliographies.

STUDY SELECTION Systematic review and meta-analysis of studies from 2005 to 2015 investigating spontaneous CSF leaks in patients with OSA. The CSF leaks were considered spontaneous when they occurred in the absence of trauma, surgery, infection, and neoplasm. Included studies provided the number of patients diagnosed as having OSA and spontaneous CSF leaks.

DATA EXTRACTION AND SYNTHESIS Two independent investigators reviewed all studies for inclusion. The numbers of patients with OSA were systematically extracted from each study. Studies that compared the prevalence of OSA with spontaneous CSF leaks against their control cohort were pooled in the meta-analysis using a random-effects model.

MAIN OUTCOME AND MEASURE To determine whether there was increased incidence of OSA in patients with spontaneous CSF leaks. This hypothesis was formulated prior to data collection.

RESULTS The search criteria yielded 384 abstracts, and 6 clinical studies involving OSA and CSF leaks met the inclusion and exclusion criteria. They were all retrospective in nature and included 3 comparative (case-control) studies, 2 case series, and 1 case report. The cumulative reported prevalence of having OSA and spontaneous CSF leaks is 16.9% (232 of 1376 patients). Three of the studies were eligible for the meta-analysis. The odds of having OSA with a spontaneous CSF leak were 4.73 times more likely than in control cohorts (95% CI, 1.56-14.31; $P = .006$; $I^2 = 35\%$). In a subgroup analysis of studies including nonspontaneous CSF leaks as their control cohort, the odds of having OSA with a spontaneous CSF leak were 2.85 times more likely than OSA with a nonspontaneous CSF leak (95% CI, 1.22-6.63; $P = .02$; $I^2 = 0\%$). There was a notable difference in the age, BMI, or patients with hypertension in the comparative studies.

CONCLUSIONS AND RELEVANCE The association between OSA and spontaneous CSF leaks as demonstrated by retrospective studies is confounded by heterogeneous patient characteristics. Large prospective controlled studies using polysomnography and elevated intracranial pressure measurements are required to further evaluate the relationship between OSA and spontaneous CSF leaks.

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Spontaneous cerebrospinal fluid (CSF) leaks are characterized by abnormal CSF drainage without preceding surgery, trauma, or inciting cause. Patients with spontaneous CSF leaks have also been shown to have idiopathic intracranial hypertension.¹ Therefore, most patients with CSF leaks demonstrate clinical symptoms and radiographic signs of elevated intracranial pressure (ICP).² While there are a number of theories that describe the pathophysiologic mechanism of idiopathic intracranial hypertension leading to spontaneous CSF leaks, it is not completely understood.

Patients with spontaneous CSF leaks have also been shown to have respiratory physiologic abnormalities during sleep. Ideally, a polysomnogram is used to diagnose obstructive sleep apnea (OSA) and to measure the apnea/hypopnea index. Obstructive sleep apnea can cause cerebral vasodilation due to periods of hypercapnia, which results in increased ICP.^{3,4} Elevated ICP measurements in patients with OSA can also be found while awake. Elevated levels of ICP over time may eventually lead to spontaneous CSF leaks.

Spontaneous CSF leaks have been shown to have a recurrence rate of 46%.⁵ Recent literature⁶⁻⁸ has suggested an association between OSA and spontaneous CSF leaks. The prevalence of OSA was 9% for women and 24% for men,⁹ and the prevalence of OSA in patients with spontaneous CSF leaks ranged from 14.8% to 46.2%.⁶⁻⁸ To our knowledge, there is no review on the clinical association between OSA and spontaneous CSF leaks. Therefore, our goal was to systematically summarize the current literature on the clinical association between OSA and spontaneous CSF leaks. In addition, a meta-analysis was conducted to highlight the odds of having OSA with a spontaneous CSF leak.

Methods

An extensive search of the electronic PubMed database (MEDLINE) and Cochrane Library was conducted until February 1, 2015, to identify studies with the following search terms: spontaneous CSF leak or CSF leak AND sleep apnea or CSF leak AND apnea or CSF otorrhea AND apnea or CSF rhinorrhea AND apnea. Clinical studies from 2005 to 2015 investigating sleep apnea in patients with spontaneous CSF leaks were included. Cerebrospinal fluid leaks were considered spontaneous when they occurred in the absence of trauma, surgery, infection, and neoplasm. We excluded studies that did not investigate patients with OSA or spontaneous CSF leaks. When inclusion or exclusion was unclear based on title and abstract, full-text articles were retrieved. References of included articles were also searched for relevant studies. Additional data extracted from each article included the following: publication year, study type, number of patients, study population and etiologies, assessment or outcome measures, and study conclusions. This study was exempt from institutional review board approval because it was a systematic review and meta-analysis.

Only comparative (case-control) studies with similar control groups were included in the meta-analysis. The meta-analysis was conducted with studies that compared the percentage of patients with OSA and spontaneous CSF leaks

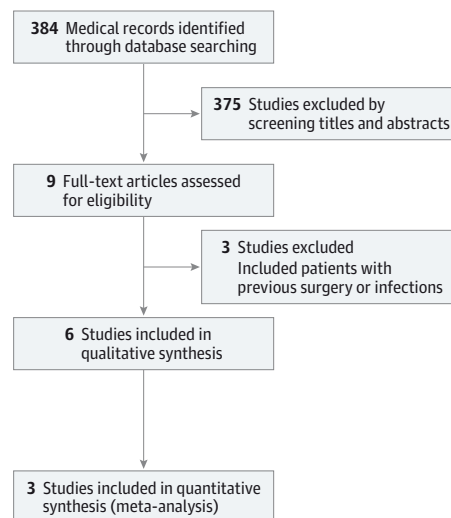
against the percentage of patients with OSA and nonspontaneous CSF leaks. Odds ratios (ORs) were computed from the OSA rate data for each study, weighted by sample size, pooled using the Mantel-Haenszel method and a random effects model, and displayed with forest plots (RevMan; version 5.3, Nordic Cochrane Centre, The Cochrane Collaboration). Analysis of publication bias was performed using funnel plot techniques in the Egger weighted-linear regression method (Comprehensive Meta-Analysis, version 2; Biostat). $P < .05$ was considered statistically significant. Ambiguity or any disagreements between reviewers were resolved through discussion and the addition of a third reviewer as needed.

Results

Summary of Literature Search and Meta-analysis

The search criteria yielded 384 abstracts, and 6 clinical studies involving OSA and CSF leaks met the inclusion and exclusion criteria (Figure 1).^{3,6-8,10,11} These included 3 comparative (case-control) studies,^{6,8,11} 2 case series,^{3,7} and 1 case report¹⁰ (Table). All of the studies were retrospective and are summarized herein. The cumulative reported incidence of having OSA and spontaneous CSF leaks is 16.9% (232 of 1376 patients). Three of the studies were eligible for the meta-analysis. The odds of having OSA with a spontaneous CSF leak was 4.73 times more likely than in control cohorts (95% CI, 1.56-14.31; $P = .006$, $I^2 = 35\%$) (Figure 2A). In a subgroup analysis of studies including nonspontaneous CSF leaks as their control cohort, the odds of having OSA with a spontaneous CSF leak was 2.85 times more likely than OSA with a nonspontaneous CSF leak (95% CI, 1.22-6.63; $P = .02$; $I^2 = 0\%$) (Figure 2B). Patient characteristic heterogeneity is summarized in the Table. Publication bias was assessed using Egger regression intercept (2-tailed $P = .42$) and graphically with a standard error funnel plot (Figure 3).

Figure 1. Flowchart of Literature Review



Inclusion and exclusion criteria were used to arrive at studies to be included for statistical analysis.

Table. Summary of Included Studies

Source	Study Type	Method	Group	Patient Characteristics				
				Age, Mean, y	BMI	OSA	Sex	Empty Sella
Fleischman et al ¹¹	Retrospective comparative	126 Patients with surgical repair of encephalocele or CSF rhinorrhea	Spontaneous leak (n = 70)	51.7	35.64 (n = 40)	21 of 70	11, Male; 59, female	31 of 56
			Nonspontaneous leak (n = 56)	42 ^a	29.99 ^a (n = 42)	8 of 56 ^a	33, Male; 23, female ^a	9 of 37 ^a
LeVay and Kveton ⁶	Retrospective comparative	29 Patients with CSF otorrhea	Spontaneous leak (n = 14)	57	35.2	4 of 14	11, Male; 3, female	NA
			Nonspontaneous leak (n = 15)	47	28.5 ^a	1 of 15 ^a	NA	3 of 15
Nelson et al ⁸	Retrospective comparative	50 Patients with spontaneous CSF leaks, or preop temporal bone CT scans for planned cochlear implants ^b	Spontaneous leak (n = 13)	56.0	43.73	6 of 13	4, Male; 9, female	NA
			Obese control (n = 17)	59.9	37.34	1 of 17 ^a	8, Male; 9, female	NA
			Nonobese control (n = 20)	60.4	24.60 ^a	1 of 20 ^a	8, Male; 12, female	NA
Nelson et al ⁷	Retrospective case series	Patients undergoing spontaneous CSF repair from a national and single institution database	National database, spontaneous leak (n = 1218)	NA	NA	179 of 1218	NA	NA
			Single institution, spontaneous leak (n = 61)	57.03	37.8	22 of 61	17, Male; 44, female	52 of 61
Xie et al ³	Retrospective case series	25 Patients undergoing endoscopic endonasal repair of spontaneous CSF rhinorrhea	Spontaneous leak (n = 25)	49.2	38.5	8 of 25	1, Male; 24, female	NA
Bernstein et al ¹⁰	Case report	1 Patient with spontaneous CSF leak after CPAP treatment modification	Spontaneous leak (n = 1)	NA	NA	NA	1, Female	NA

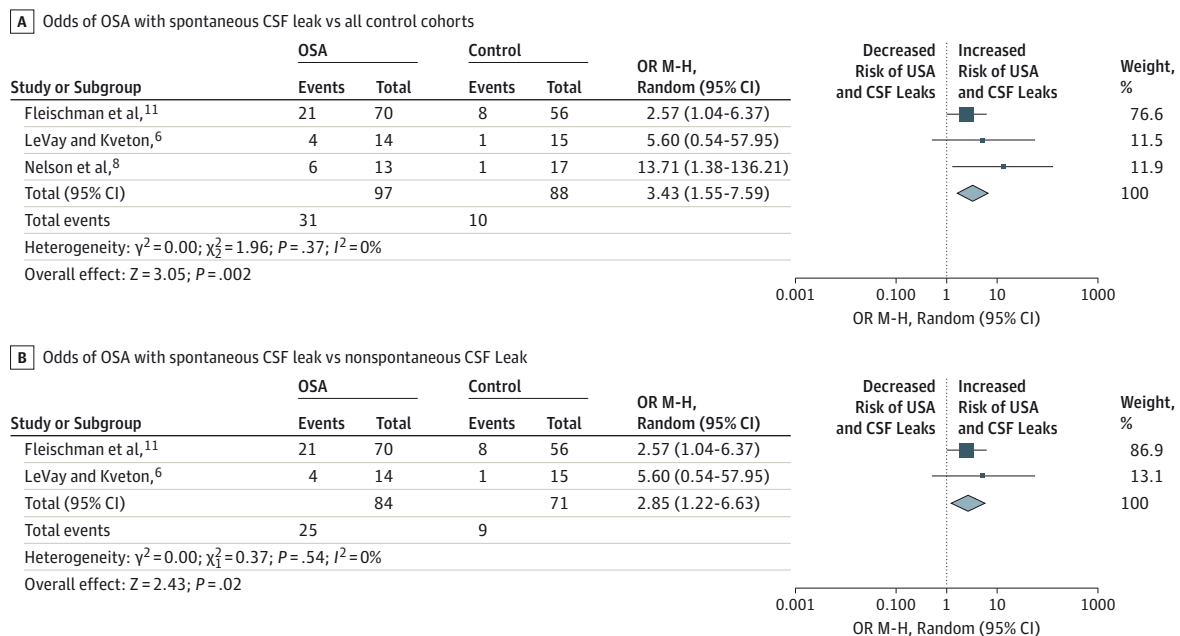
Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared);

^a Statistical difference ($P < .05$).

CPAP, continuous positive airway pressure; CSF, cerebrospinal fluid; HTN, hypertension; NA, not applicable; OSA, obstructive sleep apnea; preop, preoperative.

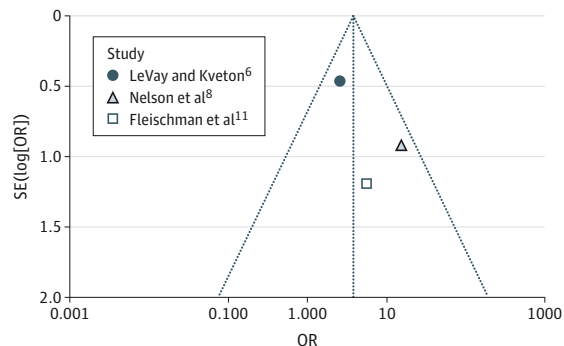
^b Obese and nonobese control groups.

Figure 2. Forest Plot of Odds Ratios (ORs) of Having Obstructive Sleep Apnea (OSA) and Spontaneous Cerebrospinal Fluid (CSF) Leaks



Analysis of the ORs using the random-effects model. The size of the data markers corresponds to the relative weight assigned in pooled analysis. M-H indicates Mantel-Haenszel.

Figure 3. Precision Funnel Plot to Assess Publication Bias



Three published studies were included in the analysis: LeVay and Kveton,⁶ Nelson et al,⁸ and Fleischman et al.¹¹ OR indicates odds ratio of bias; SE, standard error.

Summary of Clinical Studies Investigating OSA and Spontaneous CSF Leaks

Two studies^{6,11} compared the percentage of patients diagnosed as having OSA in spontaneous and nonspontaneous CSF leaks. In 2014, Fleischman et al¹¹ retrospectively compared the demographics of patients who underwent endoscopic surgical repair of CSF leaks. The authors¹¹ included 126 consecutive patients with surgically confirmed anterior skull base dehiscence encephaloceles or CSF leaks. Surgical candidates included patients with CSF leaks that did not resolve with conservative treatment, lumbar drain, or acetazolamide therapy. Of these patients, 70 were found to have spontaneous CSF leaks, and 56 were found to have nonspontaneous CSF leaks.

Only patients with a documented diagnosis of OSA, either diagnosed at an outside institution or with a sleep study, were classified as having OSA. The spontaneous CSF rhinorrhea group had a significantly higher diagnosis rate of OSA (30.0% vs 14.3%), greater body mass index (BMI, calculated as weight in kilograms divided by height in meters squared) (35.6 vs 30.0), greater radiographic evidence of an empty sella (55.4% vs 24.3%), older age (51.7 vs 42.0 years), and were more likely to be female (84.3% vs 41.1%). The authors¹¹ did not report recurrence rates.

LeVay and Kveton⁶ published the second retrospective comparative study in 2008. They compared patient demographics in spontaneous and nonspontaneous CSF otorrhea during a 15-year period. Patients with spontaneous CSF had a significantly higher BMI (35.2 vs 28.5) and higher diagnosis rate of OSA (29% vs 7%), and hypertension was more common (64% vs 20%).

In 2014, Nelson et al⁸ reported the third comparative study. They retrospectively compared the thickness of the squamous temporal bone and the zygoma in 50 patients with either spontaneous CSF leaks or preoperative temporal bone c scans for planned cochlear implants (obese and nonobese control groups). The calvarium of patients with confirmed spontaneous CSF leaks was found to be 23% thinner than in the other groups. There was no difference in the calvarium thickness of the nonobese and obese control groups. The zygoma, serving as an internal control, was not significantly different among the 3 groups. The diagnosis of OSA was found in 5.8% of each control group and in 46.2% of the group with spontaneous CSF leaks. There was no difference in the skull thickness of patients with a spontaneous CSF leak and OSA compared with those with a spontaneous CSF leak without OSA.

Two case series were found to report on spontaneous CSF leaks and OSA.^{3,7} In 2015, Nelson et al⁷ reported the incidence of spontaneous CSF leaks and OSA diagnosis. They retrospectively reviewed the health care database to include 1218 patients who underwent craniotomies to repair spontaneous CSF leaks. They also evaluated 61 patients at their local institution. They found OSA rates of 14.8% in patients with spontaneous CSF leaks nationally and 37.1% at their institution. The second case series³ investigated the use of a lumbar catheter for CSF pressure monitoring. In 2014, Xie et al³ retrospectively reviewed medical records for 25 patients who underwent endoscopic endonasal repair of spontaneous CSF rhinorrhea. The mean BMI was 38.5, and 8 of 25 patients (32%) had OSA. Finally, 1 case report¹⁰ described spontaneous CSF rhinorrhea after increasing the pressure of their CPAP treatment from 5 to 7 cm H₂O.

Discussion

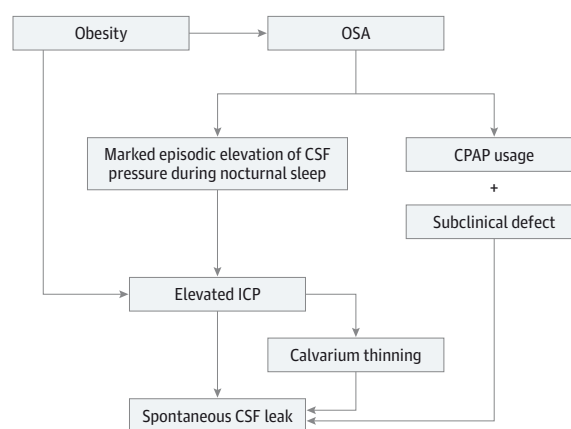
The literature on the association between OSA and spontaneous CSF leaks is limited to retrospective studies. In these studies, the cumulative reported prevalence of having OSA in 1376 patients with spontaneous CSF leaks was 16.9%. The comparative studies demonstrated that these patients were 2.85 to 4.73 times more likely to have OSA and spontaneous CSF leaks than their control counterparts (Figure 2).

In adults, CSF is produced at a rate of 0.3 mL/min, which approximates 450 mL/24 hours.¹ Adults have a total volume of 150 mL; therefore, CSF is turned over 3 to 4 times a day. Cerebrospinal fluid is mainly absorbed by arachnoid villi granulations, which extend into the dural venous sinuses. The venous flow is pressure dependent, and the cerebrovascular hemodynamics can be altered by episodes of hypoxia and hypercapnia in patients with OSA, resulting in elevated ICP levels.^{3,4} Repetitive ICP elevations during sleep may lead to an overall increase in ICP (Figure 4). Intracranial hypertension could also occur owing to the presence of other risk factors for OSA, such as obesity.¹² Central obesity can lead to increased intra-abdominal pressures and decreased venous return from the brain, resulting in increased ICP. This may confound the relationship between OSA and spontaneous CSF leaks.

Elevated ICP over time erodes the skull base, causing bone deformities that can lead to CSF leaks. Nelson et al⁸ demonstrated that patients with symptoms of OSA had thin skulls, but they were unable to establish a casual role between OSA and calvarial thinning. This may be due to the study's low power or individuals with thicker skulls being able to tolerate high ICP levels, whereas patients with thinner skulls developed spontaneous CSF leaks.

To investigate the association between OSA and spontaneous CSF leaks, Fleischman et al¹¹ and Levay and Kveton⁶ selected patients with nonspontaneous CSF leaks as their comparative control group. The relationship was significant only with spontaneous CSF rhinorrhea. Fleischman et al¹¹ demonstrated that the odds of having OSA and spontaneous CSF rhinorrhea were 2.57 times ($P = .04$) more likely than the odds of having OSA and nonspontaneous CSF leaks. The association

Figure 4. Summary of Discussed Mechanisms



It is currently hypothesized that the marked elevation of cerebrospinal fluid (CSF) pressure during apneic events in patients with obstructive sleep apnea (OSA) may lead to spontaneous CSF leaks. CPAP indicates continuous positive airway pressure; ICP, intracranial pressure.

of OSA and spontaneous CSF otorrhea reported by Levay and Kveton⁶ was not significant.

The heterogeneous patient population prevents firm conclusions about the association between OSA and spontaneous CSF leaks. Higher BMI, male sex, and increased age are risk factors for developing OSA.¹³ The increased prevalence of OSA in the spontaneous leak group noted by Fleischman et al¹¹ could be due to increased age (approximately 10 years) and increased BMI (overweight vs obese). Levay and Kveton⁶ found a significantly higher mean BMI in the spontaneous CSF group. Because obesity has a well-known relationship with the development of both OSA and spontaneous CSF leaks, it is difficult to conclude whether OSA is independently a risk factor for spontaneous CSF leaks. However, Nelson et al⁸ found that the odds were 13.71 times ($P = .03$) more likely for OSA in patients with spontaneous CSF leaks than in a matched obese control group with cochlear implants. Fleischman et al¹¹ also found a significantly higher rate of females in the groups with spontaneous CSF leak. Specific demographics of the patients diagnosed as having OSA were not reported across all studies.

Dynamic CSF pressure monitoring may help in further understanding of the pathomechanism of OSA in the development of spontaneous CSF leaks. This prevents the use of static opening pressures, which could be artificially elevated owing to physiologic responses (Valsalva maneuver). Xie et al³ used a CSF pressure-monitoring system to help determine the need for further ICP-lowering treatments. If OSA were a contributing factor to intracranial hypertension and spontaneous CSF leak, one would expect a rise in ICP after the CSF leak is repaired because the patient's OSA would remain untreated. Unfortunately, Xie et al³ did not discuss the CSF pressure results after repair for patients with OSA.

It is unknown if the pathomechanism of spontaneous CSF leaks is associated with CPAP use. Bernstein et al¹⁰ presented a case report that suggested the spontaneous CSF leak occurred when the CPAP pressure was elevated. Administration of CPAP

at higher pressure levels (12 cm H₂O) has been shown to significantly increase CSF pressure and central venous pressure in healthy volunteers.¹⁴ Providing CPAP therapy improves oxygenation and can reduce apnea events, thereby reducing ICP elevations.¹⁵ An additional case report suggested that CPAP may uncover a subclinical defect. Future studies¹⁶ should investigate the incidence of spontaneous CSF leaks in CPAP users.

The current review is not without limitations. Many of the reports did not correlate the severity of OSA with polysomnography, nor was it offered to patients with OSA symptoms (snoring, excessive daytime sleepiness, and fatigue).^{6-8,11} The lack of formal polysomnograms in all patients with spontaneous CSF leaks may have underestimated the incidence of OSA. Nelson et al⁷ investigated spontaneous CSF leaks that were repaired with CPT codes for craniotomies, and it is possible to

have missed common transnasal approaches. The studies included in this review are limited by their retrospective nature and are therefore at higher risk for confounding factors. The pooled data should be interpreted in the context of the lack of prospective controlled studies.

Conclusions

The association between OSA and spontaneous CSF leaks demonstrated by retrospective studies is confounded by heterogeneous patient characteristics. Large prospective controlled studies that include polysomnography and ICP measurements are required to further evaluate the relationship between OSA and spontaneous CSF leaks.

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Study concept and design: All authors.

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