Lax Eyelid Syndrome, Obstructive Sleep Apnea, and Ocular Surface Inflammation

Clayton Kirk, Mackenzie Becker M.D., Ramsudha Narala M.D., Sunita Kumar M.D., Charles Bouchard M.D.
Department of Ophthalmology

Abstract

Purpose: **Aim 1:** To establish the incidence of lax eyelid syndrome (LES) in patients with newly diagnosed sleep apnea. Lax eyelid syndrome is the association of distensible eyelids (in conjunction with metalloproteinase induced elastin deficiency) with a chronic papillary conjunctivitis. **Aim 2:** To determine the presence of matrix-metalloproteinases in the tear film of patients with LES, as elevated metalloproteinase may be responsible for the ocular surface inflammaiton in LES; **Aim 3:** To compare current methods for grading the severity of eyelid laxity with a newly designed "Laxometer" and to correlate these findings with the severity of OSA.

Methods: All patients referred for an initial sleep study were asked to participate in the study. Those patients consenting to the study then underwent ocular examination including visual acuity, color vision, pupils, intraocular pressure, slit lamp exam, matrix metalloproteinase-9 tear film assays. Measurements of the degree of eyelid laxity was determined using the following four methods: 1) degree of tarsal conjunctiva exposure; 2) ease of upper eyelid eversion; 3) degree of medial canthal tendon laxity; and 4) distensibility of the "laxometer".

Results: **Aim 1:** Nine patients (18 eyes) have been included in the study thus far, 7 of which were determined to have sleep apnea (77.8%). Eight of nine patients were determined to have lax eyelids, and seven patients with LES were diagnosed with OSA. **Aim 2:** 14 of 16 eyes (89%) with LES had a positive MMP assay (p< .001). **Aim 3:** We found a correlation between the average laxometer measurements and the severity of sleep apnea (22.4 m in nonexistent OSA, 23.3 mm in mild OSA, and 26.5 mm in moderate OSA).

Discussion: Numerous studies have reported an association between LES and OSA. Lax eyelids, as a clinical sign, is associated with sleep apnea, but appears to be under diagnosed. This observation was confirmed in a large Loyola data mining study of 12,000 patients with sleep apnea in which only 4% of patients with sleep apnea seen in the eye clinic had a diagnosis of lax eyelids. The results of our study thus far, as well as our clinical experience, suggest a much stronger association between OSA and LES. OSA, which is strongly associated with obesity, is a significant marker of increased morbidity through its association with a wide variety of systemic diseases including: cardiovascular disease, hypertension, pulmonary hypertension, and congestive heart failure. OSA patients have also been shown to exhibit a wide variety of ocular neurovascular diseases, including glaucoma, ischemic optic neuropathy and retinal vein occlusion. The higher association of LES and OSA reported here will allow the eye care community to gain better awareness and seek appropriate referral for a sleep study.

Previous attempts to grade LES severity have been suggested and are included in this study as well. Although our data set is currently small, the laxometer data thus far is the first to suggest an association between the severity of LES and the severity of OSA. Additionally, the MMP assays also indicate there may be a strong connection with MMP and the pathophysiology of the papillary conjunctivitis associated with LES, although ongoing data collection will further characterize this relationship. As our data collection is ongoing, the early trends noted above will be further described in hopes to better understand the relationship between LES and OSA.

Introduction

Floppy eyelid syndrome (FES) was first described by Culbertson and Ostler in 1981, initially referring to rubbery, lax upper eyelids with tarsal papillary conjunctivitis seen in young obese men (1). Several studies have described this phenomenon since then, including Van den Bosch (6) and Fowler (2).

Obstructive sleep apnea (OSA) is a disease that affects predominantly overweight individuals, with a reported incidence of 15-25% in males (3). It is characterized by interruption of ventilation for more than 10 seconds due to airway collapse (13). This chronic hypoventilation places the individuals at high risk for significant systemic morbidity including cardiovascular and ocular ischemic disease (Glaucoma, ischemic optic neuropathy, and retinal vein occlusion). LES and its association with obstructive sleep apnea (OSA) has been reported in numerous studies (2, 5, 16, 17) and a positive correlation between severity of OSA and LES outlined by Acar et al., as in Table 1. (22, 5).

Clinical Finding	Control No OSAS	Mild OSAS	Moderate OSAS	Severe OSAS	Sig (p<.05)
FES	23.1%	41.7%	66.7%	74.6%	p<0.01
OSDI	12.57 +/- 17.64	22.90 +/- 16.78	45.94 +/- 22.03	56.68 +/- 22.5	p<0.01
Schirmer (mm)	10.76 +/- 3.58	9.83 +/- 2.53	7.73 +/- 2.42	6.97 +/- 2.15	p<0.01
TBUT (sec)	10.53 +/- 3.64	9.46 +/-2.40	7.29 +/-2.13	6.82 +/-2.20	p<0.01
Corneal Stain	0.26 +/- 0.60	0.40 +/- 0.71	0.98 +/- 0.72	1.14 +/- 0.90	P<0.01

Table 1. Acar et al.

The etiology of LES has also not been clearly determined. Netland et al demonstrated a decreased concentration of elastin in the tarsal plate of patients with LES (7). Decreased elastin may be a result of a higher concentration of matrix metalloproteinases, particularly MMP-7 and MMP-9, in these affected individuals (8). The possibility of a systemic elastin deficiency with elastin deficiency in the soft palate as a potential cause of OSA has not been reported. Furthermore, Taban et al found elevated plasma leptin levels in patients with LES. Leptin was proposed to trigger the inflammatory cascade by up-regulating MMP-9 resulting in the breakdown of elastin (9). In this study, we investigate the presence of MMP-9 in the tear film of patients with LES to determine the significance of its role in the pathophysiology of the disease.

We will also document the presence and severity of LES in patients with mild, moderate and severe obstructive sleep apnea. We will use several reported techniques for quantitating the severity of eyelid laxity as well as introduce a new method for grading eyelid laxity, the laxometer. We will then determine if the severity in FES correlates with the severity of OSA.

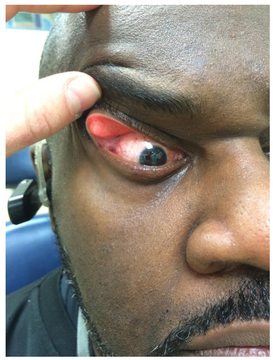


Figure 1. Severe tarsal conjunctival exposure upon lateral upper eyelid lateral traction. (22)

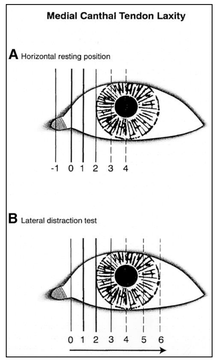


Figure 5. Measuring degree of medial canthal tendon laxity as described by Olver et al. (21)

Methods and Statistical Analysis

Laxometer development

A modified wire speculum that measures distensibility of the eyelid in millimeters using a constant spring-loaded force was developed through Katena® for use in this study (Figure 2).

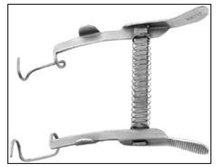


Figure 2. The Laxometer device

Patient evaluation and data collection

Patients were identified for participation in the study at their initial sleep study appointment at the Loyola Pulmonology Sleep Apnea clinic. Those patients agreeing to participate in the study then underwent ocular examination consisting of visual acuity, color vision, pupils, intraocular pressure, slip lamp exam, and matrix metalloproteinase-9 tear film assays (InflammaDry).

Measures of the degree of eyelid laxity were also determined using four different methods: 1) degree of tarsal conjunctiva exposure (Figure 1); 2) duration of upper eyelid eversion; 3) degree of medial canthal tendon laxity; and 4) distensibility of the "laxometer". Tarsal conjunctiva exposure was graded as described by Acar et al (22). Duration of upper eyelid eversion, as described by Beis et al, was measured in seconds while the eyes were in the inferior gaze position (20). The third method of grading medial canthal tendon laxity was performed as described by Olver et al (21). The horizontal position of the lower punctum was measured at rest and at lateral distraction with minimal pressure. Laxometer measurements were obtained as demonstrated in Figure 3.

Figure 3. Eyelid distensibility as measured by the novel laxometer introduced in this study. The distensibility was measured in millimeters as the distance between the upper and lower specula bars.

Sleep study results were also recorded, including the apnea-hypopnea index (AHI), which is defined as the number of episodes of apnea or hypopnea in a one house sleep period (14). OSA has been clinically defined as an AHI of great than or equal to five in a person with excessive daytime sleepiness. The severity of OSA is graded into mild (AHI 5-14), moderate (AHI 15-30), and severe (AHI >31).

All data was recorded and stored in REDCap, a secure electronic research database.

Statistical analysis was completed on the preliminary data collected thus far, although the study is still ongoing. A one-sample binomial test allowed us to test whether the proportion of cases identified with LES were MMP-9 positive differed from a hypothesized expected value of 14%, which was the previously cited amount of positive InflammaDry MMP-9 assays in mild dry eye syndrome (**35**). A nonparametric Kruskal-Wallis test was used to assess whether eyelid elasticity correlated with the degree of sleep apnea severity, and whether eyelid elasticity as measured by the laxometer correlated with other methods of grading eyelid laxity (medial canthal tendon laxity, duration of eyelid eversion, and degree of tarsal conjunctiva exposure).

Results

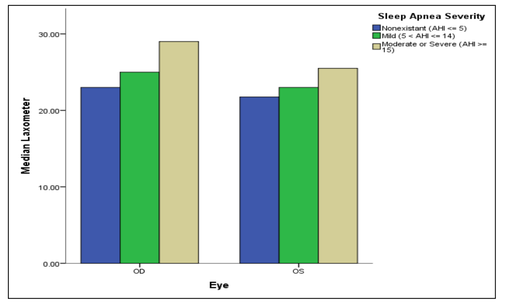
Data collection is still ongoing, however our preliminary results included nine patients (18 eyes). Of these patients, 7 were determined to have sleep apnea (77.8%). Eight patients were determined to have LES, and seven of these patients were diagnosed with OSA. The observed proportion of cases with LES (89%) using the MMP-9 assay was significantly higher than the expected proportion (14%) identified by Schargus et al ($p < .001$) (35). We found that as severity of sleep apnea increases, the degree of eyelid elasticity as measured by the laxometer also increased (Table 1). This is also demonstrated in Figure 4. However, this correlation was not statistically significant (p>0.05). There was no significant association between degree of eyelid elasticity and medial canthal tendon laxity (both $p = 0.16$) or degree of tarsal conjunctiva exposure (both p>0.05). There was a small but non-significant positive association between laxometer measurement and duration of eyelid eversion ($\tau = 0.16$, $p = .29$). Conversely, there was a small but non-significant negative association between laxometer measurement and duration of eyelid eversion ($\tau = -0.19$, $p = .25$).

Table 1: Elasticity of eyelid as a function of sleep apnea severity, stratified by eye

	AHI ≤ 5 (n = 2)	5 < AHI ≤ 14 (n = 5)	AHI ≤ 15 (n = 2)	Total (N = 9)	*p*
OD Laxometer	23.00 (20.00 – 26.00)	25.00 (24.00 – 25.00)	29.00 (28.00 – 30.00)	25.00 (24.00 – 26.00)	.12
OS Laxometer	21.75 (20.00 – 23.50)	23.00 (22.50 – 25.00)	25.50 (25.00 – 26.00)	23.50 (22.50 – 25.00)	.30

Note: Medians are tabled with the interquartile range in parentheses. N = The number of valid cases used to compute the estimate. OD = oculus dexter (right eye) and OS = oculus sinister (left eye). AHI = Apnea-Hypopnea Index. Significance (*p*) is determined using the nonparametric Kruskal-Wallis test.

Figure 4. Elasticity of eyelid as a function of sleep apnea severity, stratified by eye



Conclusion

One of the most well-known systemic associations of LES is sleep apnea. Woog was the first to describe a relationship between obstructive sleep apnea and LES in 1990 (2). In 1997, McNab described 17 patients with LES, of which 8 were referred for a sleep study (16). All eight patients were diagnosed with OSA. Bouchard et al reported an association of LES of only 4% in 11,975 patients with OSA in a Loyola data mining study, suggesting that lax eyelid syndrome is underdiagnosed and its implications under-recognized (5). However, the results of our study thus far, as well as our clinical experience, suggest a much stronger association between OSA and LES.

OSA is a significant cause of both ocular and systemic morbidity and mortality. The resultant absence of ventilation and hypoxemia as a consequence of this disease predisposes these individuals to cardiovascular disease, congestive heart failure, pulmonary hypertension, stroke, and many other life threatening illnesses (4). LES has also been found to be associated with additional systemic manifestations including hypertension, diabetes mellitus, and ischemic heart disease (4). According to a 2010 report by the Harvard Medical School Division of Sleep Medicine, the prevalence of moderate to severe sleep apnea in the US was about 25 million patients with 82% of patients (19 million) undiagnosed (34). The total cost for managing the sleep apnea, and other comorbidities was on the order of $100 billion (34). The higher association of LES and OSA reported here will help the eye care community to gain better awareness and seek appropriate referral for a sleep study.

Additionally, 89% of the patients in this study with LES had positive tear film MMP-9 assays. MMP-9 is a well-known inflammatory marker present in patients with dry eye syndrome. The statistically significant (p<.001) high association between MMP-9 and LES strongly supports the role of MMP-9 in the pathophysiology of the disease, as well as their predisposition to ocular surface diseases such as dry eye syndrome, phlyctenular disease, superior limbic keratoconjunctivitis, neurotrophic keratitis, and many other non-infectious ocular inflammatory diseases.

This study also sought to standardize a method of grading eyelid laxity and comparing it with the severity of sleep apnea. Our preliminary data does suggest that with an increase in sleep apnea severity, there is also an increase in the eyelid laxity as measured by the laxometer (seen in Figure 4). However, these results failed to show statistical significance because our sample size is small and underpowered. As our data collection is ongoing, we hope to further characterize this relationship. Our results so far have failed to show a correlation between laxometer measurements and the three previously described methods of eyelid laxity grading (tarsal conjunctiva exposure, duration of eyelid eversion, and medial canthal tendon laxity).

References

1. Culbertson W, Tseng S. Corneal disorders in floppy eyelid syndrome. Cornea 1994; 13 (1): 33-42
2. Fowler A, Dutton J. Floppy Eyelid Syndrome as a Subset of Lax Eyelid Conditions: Relationships and Clinical Relevance (an ASOPRS Thesis). Ophthal Plast Reconstr Surg 2010; 26 (3): 195-204.
3. Diaper CJ. Wake up to floppy eyelid syndrome. Br Journal of Ophthalmology. 2013; 97 (12): 1363-1364.
4. Yaggi HK, Concato J, Kernan, WN, Lichtman JH, Brass LM, Mohsenin V. Obstructive Sleep Apnea as a Risk Factor for Stroke and Death. The New England Journal of Medicine 2005; 353:2034-41.
5. Bouchard C, Mali S, Undevia N, Gaynes B, Price R, and Valdez D. The Association of Systemic and Ocular Disease and the Under Diagnosis of Floppy Eyelid Syndrome in Patients with Obstructive Sleep Apnea. Invest Ophthalmol Vis Sci 2014; 55: E-Abstract 1465.
6. Van Den Bosch WA, Lemij, HG. The lax eyelid syndrome. British Journal of Ophthalmology. 1994; 78: 666-670.
7. Netland PA, Sugrue SP, Albert DM, Shore JW. Histopathologic features of floppy eyelid syndrome. Involvement of tarsal elastin. Ophthalmology. 1994; 101 (1):174-181.
8. Schlötzer-Schrehardt U, Stojkovic M, Hofmann-Rummelt C, Cursiefen C, Kruse FE, Holbach LM. The Pathogenesis of Floppy Eyelid Syndrome Involvement of Matrix Metalloproteinases in Elastic Fiber Degradation. Ophthalmology 2005; 112 (4): 694-704.
9. Taban M, Taban M, Perry JD. Plasma leptin levels in patients with floppy eyelid syndrome. Ophthalm Plast Reconstr Surg. 2006; 22(5): 375-377.
10. Ezra DG, Beaconsfield M, Collin R. Floppy Eyelid Syndrome: Stretching the Limits. Surv Ophthalmol 2010; 55 (1): 35-46.
11. Culbertson WW, Tseng SC. Corneal disorders in floppy eyelid syndrome. Cornea. 1994 Jan;13(1):33-42.
12. Abdol H, Pizzimenti JJ , Purvis CC. The eye in sleep apnea syndrome. Sleep medicine 2006; 7 (2): 107-115.
13. De Torres-Alba F, Gemma D, Armada-Romero E, Rey-Blas JR, Lopez-de-Sa E, and Lopez-Sendon JL. Obstructive Sleep Apnea and Coronary Artery Disease: From Pathophysiology to Clinical Implications. Pulmonary Medicine 2013; 2013: 1-9.
14. Myers KA, Mindrzada M, Simel DL. Does this patient have obstructive sleep apnea: The rational clinical examination systematic review. JAMA. 2013; 310 (7): 731-741.
15. Karger, RA, White WA, Park W, Rosales AG, McLaren JW, Olson EJ, Wrogg JJ. Prevalence of Floppy Eyelid Syndrome in Obstructive Sleep Apnea–Hypopnea Syndrome. Ophthalmology 2006; 113 (9): 1669-1674.
16. McNab AA. Reversal of floppy eyelid syndrome with treatment of obstructive sleep apnoea. Clinical and Experimental Ophthalmology 2000; 28: 125-126. Muniesa MJ, Hueva V, Sanchez-de-la-Torre M, Jorjo C, Barbe F. The relationship between floppy eyelid syndrome and obstructive sleep apnea. Br J Ophthalm. 2013. 97 (11): 1387-1390.
17. Chantler J, Lalli S, Hubbard J, Erhardt C, Ruppert E, Schroder C, Malan A, Bouvier T, Bourgin P. Floppy eyelid syndrome is associated with obstructive sleep apnea: a prospective study on 127 patients. J Sleep Res. 2012; 21(3): 308-315.
18. Acar M, Firat H, Yucesoy M, Ardic S. Long-term effects of PAP on ocular surface in obstructive sleep apnea syndrome. Can J Ophthalmol. 2014; 49 (2): 217-221.
19. Beis PG, Brozou CG, Gourgoulianis KI, Pastaka C, Chatzoulis DZ, Tsironi EE. The Floppy Eyelid Syndrome: Evaluating Lid Laxity and Its Correlation to Sleep Apnea Syndrome and Body Mass Index. ISRN Ophthalmology 2012: 1-4.
20. Olver J, Sathia PJ, Wright M. Lower eyelid medial canthal tendon laxity. Ophthalmology 2001; 108 (12): 2321-5.
21. Acar M, Firat H, Acar U, Ardic S. Ocular surface assessment in patients with obstructive sleep apnea-hypopnea syndrome. Sleep Breath. 2013. 17: 583-588.
22. Atanian H, Viola-Saltzman M, Jay WM. Ophthalmic and neuro-ophthalmic complications of obstructive sleep apnea. Neuro-ophthalmology. 2011; 35(5-6): 236-241.
23. Cheung N, Wong TY. Obesity and Eye Diseases. Survey of Ophthalmology 2007; 52 (2): 180-195.
25. Ezra DG, Beaconsfield M, Sira M, Bunce C, Shah-Desai S, Verity DH, Uddin J, Collin R. Long-term Outcomes of Surgical Approaches to the Treatment of Floppy Eyelid Syndrome. Ophthalmology 2010; 117 (4): 839-846.
26. Fernandez B, Ferreras A, Calvo P, Abadia B, Fogagnolo P, Wang Y, Marin JM, Lester M. Retinal sensitivity is reduced in patients with obstructive sleep apnea. Invest Ophthalm Vis Sci. 2014; 10(9).
27. Leibovitch I, Selva D. Floppy eyelid syndrome: Clinical features and the association with obstructive sleep apnea. Sleep Medicine 2006; 7: 117–122
28. Liu DT, Di Pascuale MA, Sawai J, Gao Y, Tseng SCG. Tear Film Dynamics in Floppy eyelid syndrome. Invest Ophthalmol Vis Sci. 2005; 46 (4): 1188-1194.
29. Madani M, Madani F. Epidemiology, Pathophysiology, and clinical features of Obstructive Sleep Apnea. Oral Maxillofacial Surg Clin N Am 21 2009: 369-375.
30. Parunovic A. Floppy eyelid syndrome. British Journal of Ophthalmology 1983; 67; 264-266.
31. Pihlblad, MS, Schaefer D. Eyelid Laxity, Obesity, and Obstructive Sleep Apnea in Keratoconus. Cornea. 2013; 32 (9): 1232–1236.
32. Robert PY, Adenis JP, Tapie P, Mellon B. Eyelid hyperlaxity and obstructive sleep apnea (O.S.A.) syndrome. Eur J Ophthalm. 1997; 7(3): 211-215.
33. Yeung AM, Agrawal S, Ghosh YK, Kyprianou I, Ahluwalia HS. Floppy eyelid syndrome: the Coventry experience. Orbit. 2014; 1-7.
34. The Price of Fatigue: The surprising economic costs of unmanaged sleep apnea. Harvard Medical School Division of Sleep Medicine, 2010.
35. Schargus M, Ivanova S, Kakkassery V, Dick HB, Joachim S. Correlation of Tear Film Osmolarity and 2 Different MMP-9 Tests With Common Dry Eye Tests in a Cohort of Non-Dry Eye Patients. Cornea. 2015 Jul;34(7):739-44.