



## FLOPPY EYELID SYNDROME AND OBSTRUCTIVE SLEEP APNEA

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### SUMMARY

In this concise review, some essential characteristics of a relatively rare ocular disorder, floppy eyelid syndrome, are described. A special emphasis is made on the close relationships between this eye disease, on the one hand, and obstructive sleep apnea designed as a common and socially significant pathology of modern society, on the other hand. Along with conservative drug treatment, a variety of effective surgical techniques for the treatment of floppy eyelid syndrome are presented. A closer collaboration between ophthalmologists and sleep medicine specialists is needed to solve the problems of obstructive sleep apnea-related floppy eyelid syndrome.

**Keywords:** floppy eyelid syndrome, diagnosis, treatment, obstructive sleep apnea, comorbidity,

### INTRODUCTION:

Floppy eyelid syndrome, first reported in 1981 by Culbertson and Ostler [cited in 1], is recognized by a loose upper eyelid that readily everts by pulling it upward, a soft, rubbery tarsus that can be easily folded [2], and chronic papillary conjunctival response [3]. This syndrome represents a condition in which the upper eyelids easily evert with upward traction [4]. This leaves the eye susceptible to discomfort and visual symptoms related to exposure. Floppy eyelid syndrome is a distressing condition that can cause significant morbidity and vision loss [5].

It has been postulated that a genetic predisposition, like genetic abnormalities in collagen, elastin, or both, associated with age and sleeping patterns, would cause this syndrome [6, 7]. According to another hypothesis, there is a common underlying connective tissue disorder in obstructive sleep apnea and floppy eyelid syndrome and redundancy of tissue in the tarsal plate of lateral canthal tendons might contribute to the development of this syndrome, like the excess of oropharyngeal tissues found in obstructive sleep apnea cause upper airway obstruction specially when the person is sleeping [8]. Inflammation can also be a contributing factor to floppy eyelid syndrome. Since it and blepharochalasis share many of the same ocular findings and present with significant chronic inflammation, a theory of a common inflammatory pathway has been launched. Inflammation would cause generalized atrophy and attenuation of muscles, tendons and ligaments.

In the second phase of Shahroud Eye Cohort Study performed in 2014 with 4737 participants aged 45 to 69 years, 11.3% of the participants (6.7% of men and 14.6% of women) present with floppy eyelid syndrome in at least one eye [9]. Its prevalence decreases with age. Floppy eyelid syndrome symptoms of grades 1, 2, and 3 are observed in 72.8%, 21.6%, and 0.6% of the cases, respectively. Body mass index  $\geq 25$  kg/m<sup>2</sup> (odds ratio=1.65, 95% CI: 1.25-2.18), meibomian gland dysfunction (odds ratio =1.47, 95% CI: 1.18-1.81), and arterial hypertension (odds ratio =1.84, 95% CI: 1.46-2.31) are statistically significantly associated with floppy eyelid syndrome.

Obstructive sleep apnea is a common sleep disorder characterized by repetitive upper airway collapse during sleep with consequent oxygen desaturation, frequent arousals, and sleep fragmentation [10]. This is a major challenge for physicians and healthcare systems throughout the world. Its high prevalence and impact on daily life oblige clinicians to offer effective and acceptable treatment options [11]. The results from the population-based Study of Health in Pomerania, Northeast Germany, demonstrate that in a cohort of 1208 individuals aged between 20 and 81 years (at a median age of 54 years), the estimated obstructive sleep apnea prevalence is 46% (59% in men and 33% in women) for an apnea-hypopnea index  $\geq 5\%$ , and 21% (30% in men and 13% women) for an apnea-hypopnea index  $\geq 15$  [12].

### Diagnosis of floppy eyelid syndrome

Physicians caring for patients with suspected and/or known obstructive sleep apnea may identify floppy eyelid syndrome by asking about symptoms of ocular discomfort. Patients generally complain of non-specific irritation, foreign body sensation, mucoid discharge, dryness, redness, photosensitivity, eyelid swelling and decreased vision [7]. These symptoms are usually worse on awakening in the morning, and the affected side seems to correspond to the side the patient usually sleeps [3].

Normal eyelids measure approximately 5-1- mm, while in floppy eyelid syndrome, the eyelids measure 10-25 mm [13].

The histology in floppy eyelid syndrome reveals decreased elastin content and increased matrix metalloproteinase activity in eyelid connective tissue, demonstrating a similar connective tissue weakness [4]. Eyelid histol-

ogy also reveals chronic inflammation with absent tissue atrophy.

Within a case-control study of 107 patients, corneal biomechanical properties are determined in 72 eyes of 37 patients with floppy eyelid syndrome and in 136 eyes of 70 control subjects [14]. Mean corneal hysteresis is statistically significantly lower in floppy eyelid syndrome patients than in control subjects ( $9.51 \pm 1.56$  versus  $11.66 \pm 9.11$ ;  $p < 0.001$ ). Mean corneal resistance factor is  $10.02 \pm 2.08$  in the first group and  $11.21 \pm 5.36$  in second one ( $p = 0.001$ ) while mean corneal-compensated intraocular pressure is  $17.7 \pm 4.8$  and  $16.3 \pm 4.4$ , respectively ( $p = 0.036$ ).

A 52-year-old man with floppy eyelid syndrome presenting with redness and irritation of the left eye as well as with redundant, wrinkled eyelid skin bilaterally with a greater amount on the affected side is reported [15]. There is ptosis of the left upper eyelid. The upper eyelashes are inverted and in contact with the cornea, which shows chronic inflammatory changes such as diffuse, punctate epithelial defects after fluorescein staining of the cornea. Slit-lamp examination shows papillary conjunctivitis. The left upper eyelid is easily distracted and everted.

### **Floppy eyelid syndrome and obstructive sleep apnea - a common comorbidity paradigm?**

Floppy eyelid syndrome is not completely understood yet. It may be associated with many systemic and ophthalmic diseases such as obesity, obstructive sleep apnea, arterial hypertension, ischemic heart disease, skin and collagen pathologies, corneal and eyelids abnormalities and glaucoma [1] as well as with diabetes mellitus, hypercholesterolemia, osteoarthritis, bronchial asthma, gastroesophageal reflux disease, chronic renal failure, and schizophrenia [16]. However, many of these conditions are directly or indirectly linked with obesity, which may represent a confounding factor.

Obstructive sleep apnea is associated numerous eye disorders including floppy eyelid syndrome, optic neuropathy, glaucoma, non-arteritic anterior ischemic optic neuropathy and papilledema secondary to raised intracranial pressure [17].

Obstructive sleep apnea is the most frequent systemic disease that is associated with floppy eyelid syndrome [18]. Its prevention in floppy eyelid syndrome patients may be as high as 96%. The prevalence of this syndrome in obstructive sleep apnea patients is between 2% and 33% [5,7]. According to these authors, floppy eyelid syndrome is often associated with diabetes mellitus, arterial hypertension, hyperlipidemia, and ischemic heart disease.

In obstructive sleep apnea patients, floppy eyelid syndrome is caused by mechanical trauma to the eyelids during sleep. This syndrome is associated with many eyelid and corneal pathological conditions ranging from dry eyes to corneal ulceration and infection (Skorin).

The prevalence of floppy eyelid syndrome in 114 subjects consecutively admitted for obstructive sleep apnea evaluation and the presence of obstructive sleep apnea in 45 floppy eyelid syndrome patients are investigated [19].

Eyelid laxity measurement, slit-lamp examination and polysomnography are performed. Eighty-nine patients present with obstructive sleep apnea. Of them, 14 patients (15.73% of the cases) have floppy eyelid syndrome. Obstructive sleep apnea is diagnosed in 38 out of the 45 floppy eyelid syndrome patients (in 84.44% of the cases).

The association between obstructive sleep apnea syndrome and floppy eyelid syndrome is analyzed in 127 patients aged 25-75 years referred to the Strasbourg University Sleep Clinic with suspicion of obstructive sleep apnea syndrome [20]. Diagnosis is based on overnight ambulatory respiratory polygraphy, comprehensive ophthalmological examination and completed standard sleep questionnaires. Floppy eyelid syndrome is diagnosed in 15.8% of the subjects without obstructive sleep apnea syndrome and 25.8% of the total obstructive sleep apnea syndrome population as its frequency is significantly increased (up to 40%) in patients with severe sleep apnea syndrome population (apnea-hypopnea index  $> 30$  events/hour). There is a strong correlation between obstructive sleep apnea syndrome severity and floppy eyelid syndrome after adjustment for age, sex and body mass index. Severe obstructive sleep apnea syndrome might be an independent risk factor for floppy eyelid syndrome.

The analyses of the current literature reveal associations of floppy eyelid syndrome and other eye diseases with obstructive sleep apnea [21].

Three meta-analyses and several cross-sectional cohort and case-control studies retrieved from *PubMed* and the Brown University Library Collection reveal the association between obstructive sleep apnea and floppy eyelid syndrome and prove that obstructive sleep apnea affects the eye and ocular adnexa [1]. A more aggressive attention to ocular symptoms in patients with sleep apnea is needed to prevent vision-threatening complications.

A comprehensive literature search of *PubMed*, *EMBASE*, and the *Cochrane Library* databases reveals six studies with 767 participants devoted to the prevalence of floppy eyelid syndrome in obstructive sleep apnea syndrome [22]. The results from the meta-analysis demonstrated that floppy eyelid syndrome is statistically significantly more prevalent in obstructive sleep apnea syndrome patients than in non-obstructive sleep apnea syndrome subjects ( $Z = 4.98$ ;  $p < 0.00001$ ). The incidence of floppy eyelid syndrome in obstructive sleep apnea syndrome increases along with obstructive sleep apnea syndrome severity as indicated by increased odds ratios = 2.56, 4.62, and 7.64 for mild, moderate, and severe obstructive sleep apnea syndrome.

The results from a systematic review and meta-analysis of observational studies retrieved from *PubMed*, *EMBASE* and *Scopus* databases demonstrate that relative to non-obstructive sleep apnea subjects, obstructive sleep apnea patients have increased odds of diagnosis with floppy eyelid syndrome (pooled odds ratio = 4.157;  $p < 0.001$ ) [23]. Screening for obstructive sleep apnea should be considered in patients with floppy eyelid syndrome.

Lax eyelid syndrome is defined as the association of distensible 'floppy' eyelids and chronic papillary con-

junctivitis [24]. This syndrome is also found in obstructive sleep apnea patients who have systemic elevation of inflammatory markers, including matrix metalloproteinases.

### Floppy eyelid syndrome management

Treatment of floppy eyelid syndrome can be conservative or surgical. In most cases, the patient is chronically treated with topical therapeutic agents with no response. Treatment of OSA may help floppy eyelid syndrome, halt progression of associated glaucoma or optic neuropathy, and reduce intracranial pressure in patients with associated papilledema [17].

An obese 44-year-old smoker with history of diabetes mellitus and multiple presentations of floppy eyelid syndrome, i.e. left red eye, tearing, burning, itching, gritty feeling as well as of obesity (body mass index of 38 kg/m<sup>2</sup>), snoring, daytime sleepiness and polysomnographically proved severe obstructive sleep apnea (Epworth Sleepiness Score is 20/24 and apnea/hypopnea index is 32) undergoes conservative management [25]. It consists in lubricating ointment application and taping the eyelid shut at night, while continuous positive airway pressure combined with weight loss and smoking cessation improves the obstructive sleep apnea symptoms.

Although conservative treatments can sometimes be effective, a wide variety of surgical treatments to tighten the upper eyelid have been described [5].

In a modified technique with a temporally placed, modified back tapered wedge resection and advancement flap, a wound and scar is created that satisfactorily falls within or more nearly parallel to the eyelid crease and camouflages it [26]. This technique uses the relaxed skin tension lines to tighten the lids in an aesthetically minded reconstruction. Its application in five patients provides excellent long-term structural wound integrity with a potentially more acceptable camouflaged scar, relief of symptoms and good cosmetic and functional results as well.

In a cross-sectional study of 78 floppy eyelid syndrome patients, four different forms of surgical treatment are encountered [27]. Thirty-three full-thickness wedge excision procedures are done in 26 patients; 43 upper lid lateral tarsal strip procedures - in 31 patients; 19 medial canthal and lateral canthal plication procedures - in 15 patients, and six medial tarsal strip procedures - in six patients. There is failure in 44 procedures. Superior long-term survival outcomes over the full-thickness wedge excision are established in both plication procedures ( $p=0.003$ ) and upper lid lateral tarsal strip ones ( $p=0.001$ ).

In 24 patients, 18 males and six females at a mean age of 56 years with floppy eyelid syndrome, a new surgical technique for medial eyelid laxity correction based on the medial upper eyelid stretching is applied [28]. A complete relief of ocular symptoms and good functional and cosmetic results are established in all cases after 18 months of follow-up.

Surgical intervention in floppy eyelid syndrome is the most effective treatment of choice [29]. There are nu-

merous blepharoplasty techniques such as full-thickness wedge excision of the tarsus, medial and lateral canthal ligament ligation, conchal cartilage graft, lateral tarsal strip with flap, and lateral tarsorrhaphy.

Within a prospective controlled trial of 62 patients with mild or moderate obstructive sleep apnea, 35 patients of which 21 (60%) with floppy eyelid syndrome undergo anterior palatoplasty while 27 ones of which 15 (55,5%) with floppy eyelid syndrome refuse surgery [30]. Floppy eyelid syndrome ratio decreases down to 25.71% after the third postoperative month ( $p=0.007$ ). After successful surgery, the preoperative-postoperative oxygen desaturation index and preoperative-postoperative lowest oxygen saturation values are  $11.755\% \pm 9.037\%$  and  $6.77\% \pm 5.362\%$  ( $p=0.04$ ) and  $86.1\% \pm 3.89\%$  and  $87.8\% \pm 2.85\%$ , respectively ( $p=0.124$ ).

In 16 patients with floppy eyelid syndrome, a total of 18 procedures (on 36 eyelids) of combined medial canthopexy and lateral tarsal strip are performed from 2009 to 2013 [31]. In eight patients, there is pre-existing diagnosis of obstructive sleep apnea. Two patients experience some degree of floppy eyelid syndrome recurrence without return of symptoms during an average follow-up of 124 days. This combined intervention is a safe and effective technique for the treatment of floppy eyelid syndrome.

A 62-year-old man presents with complaints of foreign body sensation, burning, tearing and redness in both eyes [32]. An easy eversion of the upper eyelids is accomplished with minimal manipulation. Another 70-year-old man presents with similar symptoms. There is a spontaneous eversion of the right upper eyelid when he closes his eyes. Both patients are previously diagnosed with obstructive sleep apnea syndrome. A 30-year-old man with bilateral floppy eyelid syndrome (more prominent in the left eye) and progressive keratoconus has corneal collagen crosslinking in both eyes [33]. There are no intraoperative or early postoperative complications. Topographic examination after this crosslinking reveals a continuous increase of the keratometric values in the left eye, indicating keratoconus progression as a signs of corneal collagen crosslinking failure. A third case of congenital combined eyelid imbrication syndrome, an extremely rare, benign, transient, self-limiting eyelid malposition disorder, and floppy eyelid syndrome in a healthy neonate that is resolved within a week with conservative treatment is reported [34]. A rare case of a 16-year-old male with floppy eyelid syndrome is described [35]. This represents one of the youngest patients reported in the literature.

**CONCLUSION:** The associations between obstructive sleep apnea and several eye diseases including floppy eyelid syndrome highlight the need for ophthalmologists to consider obstructive sleep apnea in their patients and recommend future research studies, especially whether therapies for obstructive sleep apnea can be effective for ocular disorders, too [36]. Further interdisciplinary research is needed to more completely clarify the essential features of floppy eyelid syndrome.

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