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Technicians & Nurses Program

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Lax Eyelids, Obstructive Sleep Apnea (OSA), and Ocular Disease

Obstructive Sleep Apnea/Hypopnea Syndrome (OSAHS)

1. Overview
   a. Repetitive episodes of upper airway occlusion
   b. Loss of normal orpharyngeal tone-soft palate and base of tongue
   c. 30% reduction in airflow
   d. 3-4% oxygen desaturation and/or arousal
   e. Apnea/hypopnea index: (AHI) average number of episodes/hour
   f. Respiratory disturbance index (RDI): Number of arousals/hour

2. Epidemiology (USA)
   a. $115 Billion Total Annual Costs
      i. Less than: Cancer, Diabetes and Coronary Artery Disease
      ii. More than : Stroke, Hypertension, Asthma
   b. 25 Million Patients Affected
   c. 82% (19 Million) Undiagnosed

3. Symptoms
   a. Snoring
   b. Excessive daytime sleepiness or fatigue
   c. Witnessed apneas by bed partner
   d. Morning headaches
   e. Waking up choking or short of breath
   f. Insomnia

4. Physical Exam Features
   a. Floppy Eyelids
   b. Obesity
   c. Large neck circumference
d. Tonsillar hypertrophy
e. Retrognathia

5. Pathophysiology
   a. Elastin Deficiency? (Present in lids of patients with floppy eyelid syndrome)
   b. Hypoxia from ischemia-reperfusion injury

6. Genetic Predisposition?
   a. + Family history of OSA with use of CPAP

7. Associated Systemic Diseases (Loyola study: 562,585 patients, 11,975 with OSA)
   a. Obesity (OR 20.2)
   b. Hypertension (OR, 9.4)
   c. Complications of organ transplant (GVHD?) (OR, 6.7)
   d. Diabetes Type 1 (OR, 5.2)
   e. Rosacea (OR, 3.8)

8. Associated Ocular Diseases
   a. Floppy (Lax) Eyelids (OR, 27)
   b. Chiasm disorders (OR, 9.2)
   c. Dry Eye Disease (OR 4.6)
   d. Glaucoma (OR, 4.5)
   e. Blepharitis (OR, 4.2)
   f. Rosacea Conjunctivitis (OR, 4.1)
   g. Papilledema (OR, 3.8)
   h. Keratoconus (OR, 3.6)
   i. Benign intracranial hypertension (OR, 3.3)

9. Management
   a. Continuous positive airway pressure (CPAP)

**Lax Eyelids (LEL), Lax Eyelid Syndrome (LES) and Floppy Eyelid Syndrome (FES)**

i. **Overview**
   a. Very common yet unrecognized disease
   b. Often managed (mismanaged) as dry eye disease
   c. Elevated ocular surface matrix metalloproteinases (MMPs)
   d. Strong association with obstructive sleep apnea (OSA)
      i. OSA associated with significant systemic and ocular morbidity
   e. Significant opportunity to benefit patients by recognizing FES and making referral for sleep study
ii. **Definitions** (Fowler AM et al, OPRS, 2010)
   a. Floppy eyelid syndrome (FES) (Culbertson et al, 1981, AJO)
      i. Rubbery, malleable, upper tarsus
      ii. Associated with papillary conjunctivitis
      iii. Obese males
   b. Lax Eyelid and Lax Eyelid Syndrome (LES) (Van den Bosch (1994, BJO)
      i. Distensible eyelids with Normal body mass index (BMI)
      ii. Relationship between LES and OSA not yet determined
      iii. Lower lid laxity atypical of the FES originally described
      iv. Lax eyelid as clinical feature rather than syndrome?
      v. Need to evaluate in all patients
   c. More severely affected eye: more severe symptoms
      i. Sleep preference side
      ii. Higher tear evaporation rate
      iii. Shorter tear break up time (TBUT)
      iv. Higher skin temperature, Higher skin evaporation rate
   d. Grading of upper eyelid laxity
      i. Horizontal distraction (Movement of lower punctum (mm))
      ii. Proportion of upper tarsal conjunctiva exposed with traction (Liu et al 2005)
      iii. Strain gauge (Karger 2006)
      iv. Bouchard-Fowler Laxometer (Katena, Inc.)

iii. **Clinical Features**
   a. Ocular Associations
      i. Eyelid
         1. Easily everted upper eyelid
         2. Skin hyperpigmentation
         3. Dermatochalasis
         4. Aponeurotic blepharoptosis
         5. Eyelash Ptosis
         6. Ectropion
         7. Blepharitis, rosacea blephartiis
         8. Demodex brevis
         9. Meibomianitis
      ii. Cornea
         1. Punctate keratopathy
         2. Scarring
3. Neovascularization
4. Filamentary keratitis
5. Recurrent corner erosion
6. Ulcerative microbial keratitis, bilateral?
7. Thinning, perforation-rare
8. Keratoconus
   a. Often but not always same side of sleep preference
   b. Criteria of KCN unclear in several articles
   c. Association might be underestimated

iii. Tear Film
1. Lipid tear film deficiency
   a. Kinetic tear interference imaging
2. Vertical lipid spread
3. Deficient lipid
4. Uneven spread
5. Punctate keratitis

iv. Infrared thermometry
1. Higher ocular (and mouth) skin temperature

v. Conjunctiva
1. Chronic papillary conjunctivitis
   a. Traumatic
   b. Nocturnal eversion
      ➢ Epithelial and stromal changes
   c. Non specific
   d. Chronic exposure?
   e. Non specific findings lead to delay in diagnosis
2. Other conjunctivitis
   a. Allergic
   b. Mechanical: Associated with rubbing?

vi. Globe
1. Luxation of the Globe

b. Systemic Associations (reported)
   i. Obstructive Sleep Apnea-Hypopnea Syndrome (OSAHS)
      1. OSAHS as causative factor
         a. Artifact of sample bias, questions about the etiology of disease
      2. FES resolving with CPAP as therapy?
3. OSAHS associated with significant morbidity
   a. Cardiovascular
   b. Cerebral sequelae
   ii. Diabetes
   iii. Arterial Hypertension
   iv. Obesity
   v. Hyperlipidemia
   vi. Chronic Bronchitis
   vii. Psoriasis
   viii. Hyperglycemia
   ix. Paraparesis
   x. Schizophrenia
   xi. Pachydermoperiostitis
   xii. Eye rubbing
   xiii. Cocaine use
   xiv. Severe learning disabilities
   xv. Epibulbar nodular fasciitis
   xvi. Congenital cataracts
   xvii. Facial dysmorphism neuropathy

iv. Treatment
   a. Medical
      i. Shield at bedtime
      ii. Lid taping
      iii. Nocturnal lubrication
      iv. Topical steroids
      v. Lid scrubbing
      vi. CPAP for OSAHS
         a. Therapeutic? (McNab 2000)
   b. Surgical
      i. Punctual plugs
      ii. Lid tightening procedures
         1. Full thickness wedge excision (FTWE)
            i. Dutton 1985
         2. Medial FTWE with blepharoplasty
            i. Valenzuela 2005
         3. Lateral FTWE
            i. Periman 2002
4. Large FTWE with vertical shortening of tarsal plate
   i. Madjilessi 2000

5. Lateral tarsorrhaphy
   i. Permanent or temporary
      ➢ Bouchard 1992

6. Lateral Tarsal Strip (LTS)
   i. Tensely 1977 first described
   ii. For FES
      ➢ Gerner 1984
      ➢ Burkett 2005
   iii. Bilateral upper lid, lower lid LTS with posterior advancement flaps

7. Lateral canthal tendon plication
   iii. Long term follow up/recurrence
       1. Recurrence (Moorefield's)
       2. 42% since 1995

v. Pathology
   a. Culbertson 1981
      i. Conjunctival scrapings
      ii. Tarsoconjunctival biopsy
         1. Non specific keratinization
         2. Inflammatory papillary reaction
      iii. Tarsal extra cellular matrix (ECM)
         1. Normal structures (TEM)
         2. Stains normal
            i. Elastin and collagen
   b. Gonnering and Sonneland 1987
      i. Meibomianitis
      ii. TEM: tarsal lipomatous atrophy
      iii. Demodex brevis
      iv. High incidence of Demodex folliculorum
   c. Netland et al 1994
      i. Conjunctival inflammation (not in the tarsus)
      ii. Conjunctival keratinization
      iii. No glycosaminoglycans, amyloid, or proteoglycans abnormalities
      iv. Decrease quantity of elastin
         1. Not uniform distribution
         2. Thick elastin network around meibomian glands

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3. Decrease in orbicularis endomysium
4. Controls not age matched in study
d. Schlotzer-Schrehardt 2005
   i. Conjunctival keratinization
   ii. Widened meibomian gland ducts
   iii. Subepithelial inflammation
   iv. Meibomian gland poor areas
      1. Absence of elastin
   v. Meibomian gland rich areas
      1. Elastin around gland acini
   vi. Eyelid skin
      1. Reduction in elastin around ciliary roots
      2. ? explanation for lash ptosis
   vii. Matrix metalloproteinases (MMP)
      1. MMP-2 in conjunctival epithelium (EP)
e. FES as subset of Ehlers Danlos Syndrome (EDS)
   i. 6 subtypes (1997)
   ii. Collagen V mutation
   iii. Classic EDS
   iv. Functional Implications
      1. Elastic tissue recoil, compliance
      2. Fibrillation collagen
      3. Tensile strength
      4. Comparison with cutix laxa, loose and inelastic
      5. Collagen disorders, EDS gives rise to elasticity
vi. **Etiological Hypotheses**
   a. Mechanical
      i. Symptoms common on side of sleeping preference
      ii. Symptoms of discomfort
      iii. Worse on awakening
      iv. Eye rubbing disorders
      v. Similar to KCN
   b. Poor Globe Apposition
      i. Not well supported
      ii. Sleeping side preference not 100%
      iii. Some tarsal degeneration leads to upper lid laxity
   c. Ischemia Reperfusion Injury
      i. Support by FES and OSAHS association
ii. OSAHS associated with low nocturnal PaO₂

iii. Pressure induced ischemia on sleep preference side

iv. Reperfusion
   1. Release free radicals
   2. Tarsal stromal damage
   3. PMN migration
   4. Conjunctivitis
   5. ? Ectatic changes

vii. Conclusions
   a. FES is a multisystem disease with protean manifestations and associations
   b. Eyelid laxity should be routinely examined
   c. FES on the differential diagnosis of patients with chronic conjunctivitis
   d. Patients with a diagnosis of FES would benefit from a referral for sleep study

**Obstructive Sleep Apnea and Glaucoma**

1. Glaucoma
   a. Overview
      i. Progressive optic neuropathy with slow progressive degeneration of retinal ganglion cells and their axons
      ii. Most common cause of irreversible blindness in the world
   b. Classification
      i. Categorized into large groups- Primary and Secondary and Open angle vs Closed angle
   c. Characteristic findings
      i. Cupping of ONH
      ii. Visual field defect
      iii. Thinning of RNFL
      iv. Increased IOP is one of main contributing factors
   d. Pathophysiology
      i. Elevated IOP is thought to compromise retinal ganglion cell axons and lead to degeneration and cell death
      ii. Other processes may contribute to the death of retinal ganglion cells and optic nerve fibers
      iii. Dysfunctional blood flow autoregulation leading to ischemia and hypoxia oxidative stress with the formation of inflammatory cytokines and free radicals

2. OSA and glaucoma
a. Overview
i. Several studies have examined the prevalence of OSA in patients with POAG and vice versa
ii. The prevalence of OSA in patients with POAG or NTG ranged from 20% to as high as 57%.
iii. Conversely, studies of patients with OSA have an estimated POAG and NTG prevalence that ranges from 2% to 27% (General population is 2%)
iv. The severity of glaucoma was related to the severity of OSA (apnea/hypopnea index as well and RDI)

b. Pathophysiology
i. Several proposed pathophysiologic mechanisms may link OSA to glaucoma, although most theories have not received adequate scientific testing.
ii. Direct hypoxic injury to the nerve
iii. Disrupted autoregulation of blood flow to the optic nerve from periods of hypoxia and hypercapnia
iv. Disruption of blood flow from periods of hypotension during apneas.
v. Some have theorized that increased IOP was associated with apnea

c. Treatment
i. Lowering IOP
   1. Drops
   2. Lasers
ii. Surgery
iii. Neuroprotection?
   1. Brimonidine
   2. Ca channel blockers- minimal, if any benefit
   3. Memantine- failed to prove effective

d. Treatment of OSA
i. Several studies have shown benefit of CPAP treatment in patients with both OSA and glaucoma

Obstructive Sleep Apnea and Other Optic Neuropathies

1. Non-ischemic optic neuropathy
   a. Sudden painless onset of unilateral visual loss.
   b. Visual loss is typically irreversible and may deteriorate further during the course of days or weeks.
   c. Clinical findings include nerve fiber bundle field defects, relative afferent pupillary defect, and optic disc edema
   d. Pathology-
      i. Exact pathogenesis is unknown but is believed to be related to vasculopathic occlusion causing infarction.
ii. microvascular disease
iii. optic disc crowding
iv. optic disc compartment syndrome
v. systemic nocturnal hypotension, and nocturnal hypoxia.

e. Relation to OSA
i. The risk ratio was 4.9 in patients with OSA compared with the general population

f. Mechanism
i. impaired optic nerve head blood flow autoregulation secondary to the direct effects of repetitive apneic episodes, apnea-induced blood pressure variations
ii. an imbalance between nitric oxide, a vasodilator, and endothelin, a vasoconstrictor.
iii. direct hypoxic effects on the optic nerve
iv. episodic increases in intracranial pressure (subsequently transmitted to the eye via the cerebrospinal fluid within the optic nerve sheath), associated with hypercapnia during apneic episodes, may act on the optic nerve head either through direct compression or impaired circulation.

g. Treatment
i. No effective treatment is available for NAION and no studies have shown that treating OSA reduces the risk of NAION

2. Papilledema
a. Refers specifically to bilateral optic disc swelling in the setting of increased ICP
b. occurs when the elevated ICP is transmitted to the eye through the optic nerve sheath.
c. The elevated pressure mechanically disrupts axoplasmic flow within the optic nerve, leading to swelling of the axons and leakage of water, protein, and other cellular contents into the extracellular space
d. When a cause of increased ICP cannot be found, it is referred to as idiopathic intracranial hypertension.
e. Pathology in relation to OSA
i. Studies have found large increases in the ICP during sleep that correlated with apneic events.
ii. The degree of increase in ICP correlated with the duration of the apnea and the decrease in oxyhemoglobin saturation.
iii. Secondary to transient hypercapnia and the resultant transient increases in ICP.
f. Treatment
i. Acetazolamide
Some reports of improvement with CPAP and treatment of OSA

3. **Conclusion**
   a. Many optic nerve diseases including glaucoma, NAION and papilledema may be related to OSA. Therefore, testing patients with these findings for OSA may be beneficial as well as having patients with OSA screened for glaucoma and warned about the higher risk of other optic neuropathies.
References


24. Osborne NN. Recent clinical findings with memantine should not mean that the idea of neuroprotection in glaucoma is abandoned. Acta Ophthalmol. 2009 Jun;87(4):450-4


