

## Dry Eye Syndrome



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**Abstract :** Dry eye is not a disease but it is rather an annoyance, which may be because of varied causes including genetics. Dry eyes, eyelid abnormalities, nasolacrimal drainage pathologies, neurological causes, corneal disorders, irritation of lashes and hypersecretion of tears are some the known causes. The article deals with the diagnostic, prevention and treatment paradigms for the same. Recent advances related to the cause and target oriented treatment of the tears have also been discussed. Dry eye syndrome is not very uncommon especially in old age. Depending on etiology varied treatment modalities are decided. Meticulous diagnosis is required for better management of the dry eye syndrome. The knowledge of influence of sex hormones on the etiology of tears in old age has opened new avenues for research, to find out specific treatment measures. (Gupta *et al.*, 2005).

**Keywords :** Tears, old age, epiphora, dry eyes

### I. Introduction

Overflow of tears, is usually caused by insufficient drainage of the tear film from the eye (epiphora). The most common cause is a blockage of the lacrimal (tear) ducts located next to the nose, but the condition may also result from the excessive production of tears. Epiphora is a symptom rather than a disease and may be caused by a variety of conditions.

The function of tears is to lubricate, nourish, and protect the eye from dust and other irritants thus preventing infections. Spread by blinking (about every six seconds), tears keep the surface of the eye optically clear and smooth. Tears flow into the eye through ducts from tiny glands located under the upper eyelids and drain from the eye through small openings near the nose (the puncta).

### II. Dry Eye

The cause of dry eyes is an imbalance in the composition of the tears, decreased tear production or excessive tear evaporation. Like skin and hair, tear production tends to dry up as one gets older. When the tear production decreases, eyes become easily irritable. The medical term for this condition is *keratoconjunctivitis sicca*.

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Although dry eyes can affect both men and women at any age, the condition is more common among women (about 80%), especially after menopause (before menopause 36%; 64% at or after menopause). The causative factors are unknown, most likely due to hormonal changes. Damage to the tear glands from inflammation or radiation can hamper tear production. Nevertheless, this condition may also be genetic (autosomal or recessive) and may be congenital or familial. Dry eyes are also associated with medical conditions such as rheumatoid arthritis, lupus, scleroderma and Sjogren's syndrome (Gupta and Pushkala, 2005). The common medications used by geriatric population can also cause dry eyes. These include, diuretics (drugs commonly used to treat high blood pressure), antihistamines, decongestants, sleeping pills, tricyclic antidepressants, isotretinoin-type drugs for treatment of acne, opiate-based pain relievers such as morphine. In addition to these it is also associated with collagen disorders.

**(A) Blink rate :** Something as innocuous as a blink can make the difference between maintaining the integrity of the ocular surface and leaving the eye open to the ravages of dry eye. In fact, researchers have shown that a blink facilitates the distribution and formation of the pre-corneal tear film across the cornea (Carney and Hill, 1982). Factors influencing blinking :

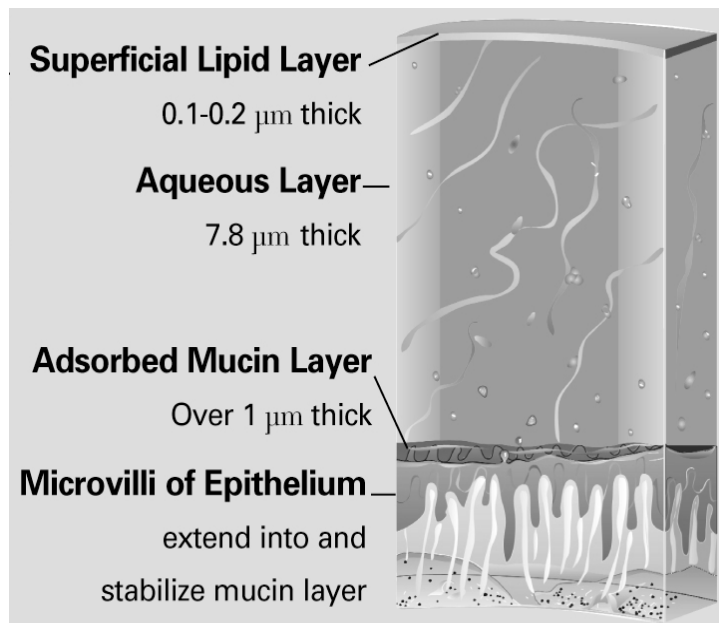
- (i) Environmental :** Alterations in temperature, humidity, lighting and airflow can have a profound effect on blink rate. There are conflicting studies evaluating blink rate at different lighting levels (Tinker, 1949), but this may be due to difficulties in accurately measuring blink rate. Factors that either directly or indirectly affect the ocular surface, such as wind, significantly affect blink rate (Nakamori *et al.*, 1997).
- (ii) Activity-related :** Engaging in conversation can increase blinking, while intently concentrating on a visual task can cause it to drop. One study showed that blink rate went from 17 blinks/min at baseline to 26 blinks/min during conversation, and dropped to as low as 4.5 blinks/min during reading (Bentivoglio *et al.*, 1997)
- (iii) Psychological :** Though the neural pathways that control blink rate and how they are affected by mental processes aren't completely understood, it's apparent that blink rate changes during cognitive function. Blinking increases with excitement, frustration and anxiety, decreases with guilt, reading and occurs when mental load is at its lowest. Most blinks occur with ocular saccades analogous to line

changes while reading (Nakamori *et al.*, 1997). The neurotransmitter dopamine and its levels in the central nervous system have been found to be associated with blink rates (Ponder and Kennedy, 1928).

- (iv) **Physiopathological** : Age, gender and muscular tension and certain disease seem to have effects on blink rate however not all physiological factors appear to have a significant effect. There appears to be no significant difference between the blink rate of males and females (Orchard and Stern, 1991). However, alterations in eye position (*i.e.*, looking up or down) may affect blink rate (Karson, 1988; Nakamori *et al.*, 1997) The neurotransmitter dopamine and its levels in the central nervous system have been found to be associated with blink rates (Ponder *et al.*, 1928) As mentioned, Parkinson's and schizophrenia, decrease and increase blink rate respectively ( Hall, 1945).

**(B) Tear Film** : The eyelids spread tears across the surface of the eyes in a continuous thin film. Studies have suggested that the pre-corneal tear film is composed of three layers composed of oil, water and mucus (Lemp and Wolfey, 1998) Problems with any of these layers can cause dry eye symptoms (Figure1).

- (i) **Oil** : The outer layer, produced by small glands on the edge of the eyelids (meibomian glands), contains fatty oils . These smooth the tear surface and slow evaporation of the middle watery layer. When the oil layer is abnormal, the watery layer evaporates at faster rate. Dry eye symptoms are common in people whose meibomian glands are clogged. Meibomian dysfunction is more common in people with inflammation along the edge of their eyelids. It may also be due to skin disorders such as rosacea and others.
- (ii) **Water** : The middle layer, which makes up about 90 percent of tears, is mostly water with a little bit of salt. This layer, produced by the lacrimal glands, cleanses the eyes and washes away foreign particles or irritants. A shallow water layer can predispose to tear film instability. If the eye produces only small amounts of water, the oil and mucus layers can touch and cause the stringy discharge.
- (iii) **Mucus** : The inner layer of mucus allows tears to spread evenly over surface of the eyes. Dry spots form easily in any part of the cornea that has patchy loss of the mucus layer.



**Fig. 1 : The tear film is made up of 3 substances as mucous, aqueous and oily layers.**

The interaction of the time between blinks (the inter-blink interval, or IBI) and tear film break-up time (TFBUT) regulate ocular surface integrity. A protected surface exists when the TFBUT matches or exceeds the IBI. In contrast, the surface is unprotected when TFBUT is less than the IBI. This is clinically relevant, since intermittent exposure of a tear-film-deficient cornea leads first to ocular discomfort, then to clinical signs of keratitis and redness (Ousler and Abelson, 2001) The development of an ocular protection index quantifies the interaction between the IBI and TFBUT, and seems to be useful in assessing the factors that cause dry eye.

As TFBUT decreases in dry eye (Yolton *et al.*, 1994) blink rate increases, (Al-Abdulmunem, 1999; Yap, 1991) and pathological conditions such as dry eye worsen. It is shown that subjects experienced discomfort shortly after break-up occurred (Cho *et al.*, 1997) Research has shown that an increase in corneal sensitivity is directly proportional to blink rate (Tsubota *et al.*, 1996; Nakamori *et al.*, 1997) and this may be a driving force behind blink rate.

**(C) Eyelid Abnormalities :** Since it is pointing inward toward the lacrimal lake, an observer looking directly toward the eyelid cannot see the

punctum. Malposition or eversion, more commonly, is an acquired anomaly in older individuals with eyelid laxity and senile ectropion (outward turning of eyelid margin) where the punctum is rotated vertically away from the globe. If the punctum is visible with the slit lamp without manipulating the eyelid, medial or punctual ectropion exists. Many patients with medial ectropion complain of tearing because of failure of the punctum to capture tears in the lacrimal lake. Long-standing medial ectropion and punctual eversion lead to stenosis or occlusion of the lower eyelid punctum, which is another cause of epiphora. Conjunctiva in the area may become injected, thickened, or keratinized due to chronic irritation. In most patients with lower eyelid punctual malposition, the cause is excessive horizontal lower eyelid laxity.

Ectropion may be mild or severe and may involve all or part of the eyelid margin. It progresses from punctal eversion to generalized ectropion. Horizontal laxity of the eyelid may be assessed by the snap back test. This test is performed by placing a finger on the inferior orbital rim and pulling the lower eyelid down. The eyelid is pulled away from the globe and released. If it fails to “snap back” into approximation with the globe without a blink, the test is considered positive, that is, horizontal laxity of the lower eyelid is present. If the eyelid snaps back against the globe without a blink, the test is considered negative. The lower eyelid is also considered lax if it can be passively stretched more than 6 mm from the globe (Liu and Strasior, 1983). Lower eyelid laxity due to laxity of the LCT (lateral canthal tendon) may be diagnosed by directing gentle digital pressure in a nasal direction along the center of the lower eyelid. If this draws the lateral canthal angle closer to the temporal limbus, LCT laxity is present. In a similar manner, MCT (medial canthal tendon) laxity may contribute to overall laxity of the lower eyelid and may be diagnosed by directing lateral digital pressure on the eyelid. If the lower punctum is displaced temporally, MCT laxity is present. Medial ectropion or punctal eversion is a subset of involutional ectropion and is often the first sign of impending generalized involutional ectropion. Medial ectropion is manifest by ectropion of the medial one third of the lower eyelid.

**(D) Nasolacrimal Drainage System Pathology :** True lacrimal obstruction or dacryostenosis, is much more common in elderly. As much as 3% of the patients visiting the clinic are thought to be related to this problem (Colin *et al.*, 1978). It has been recognized that acquired dacryostenosis is a problem of elderly persons and that women are affected

four times more often than men (Linberg and Mc Cormick, 1986) The exact pathogenesis of primary nasolacrimal duct obstruction remains unclear, although chronic inflammation with secondary fibrosis of mucosal tissue seems to be an important factor. Obvious stenosis of the puncta or the canaliculus due to senility, inflammations or tumor can cause obstruction in the drainage path of the tears. The fact that the basal rate of tear secretion progressively diminishes after age of 40 years (Henderson and Prough, 1950) suggests that many patients probably have complete lacrimal obstruction but no epiphora owing to their small tear volume.

Inflammation of the canalicular system can occur secondary to dacryocystitis, but isolated bacterial infections of the canaliculus are rare. Perhaps the most common infection is caused by *Streptomyces*, *Actinomyces israelii*, or *Arachnia propionica* (previously mislabeled as *Streptothrix*). Fungus infections (Jordan, 1997) with organisms such as *Candida albicans*, *Aspergillus niger*, *Nocardia* and *Pityrosporum pachydermatis* (Romano et al., 1978) have been reported. However, action-mycotic infection is by far the most common (Richards, 1975; Jordan, 1997). In the clinical presentation, the lower canaliculus is usually involved and the patient complains of epiphora, Swelling and inflammation of the lid medially are noted. The punctum is swollen and red, with mucoid or mucopurulent discharge, irrigation may or may not be possible through the canaliculus, and a small probe may encounter gritty resistance. Diagnosis is made on expressing yellow-tinged concretions from the canaliculus. On cytological examination, they show Gram-positive branching filaments. If the classic symptoms are absent, high-resolution ultrasonic examination (transducer frequency of 20 MHz) of the lacrimal drainage system demonstrates concretions (sulfur grains), measuring 1-2 mm in diameter (Tost et al., 2000)

When there is a stenosis of nasolacrimal duct patients may present with symptoms of chronic epiphora, conjunctivitis, and low-grade infections or with acute dacryocystitis. The clinical syndrome is most common in elderly Caucasian women. Stones in the lacrimal sac usually are not of fungal etiology. Studies have revealed inflammation, vascular congestion, and edema of the nasolacrimal duct in the early phases and, ultimately, fibrosis with complete occlusion of the nasolacrimal duct's lumen in the late phases (Linberg and Mc Cornick, 1986). The specific cause that triggers this sequence of events is not known. Nonetheless, it is reasonable to postulate that inflammation with partial ductal obstruction leads to accumulation of cellular debris, which further aggravates the ongoing inflammation and

creates a vicious cycle that leads to permanent cicatrization of the nasolacrimal duct lumen. Generalized or localized stenosis of the nasolacrimal duct can result from involutional changes or occur secondary to bouts of infection, stones, topical medications, or other sources of inflammation. Involutional changes may produce a nasolacrimal system that appears open to irrigation, but due to lid laxity and poor lacrimal pump function, will not drain tears through the system properly.

**(E) Neurological :** The commonest neurological cause is Bell's palsy which is an acquired weakness of one side of the face, due to an injury to the facial nerve. The symptoms on the affected side typically include inability to close the eye, to smile, wrinkle the forehead and whistle. Speech may be mildly slurred. Tearing occurs because the eye does not close completely. Taste sensation may be diminished on the front half of the tongue. Sounds may appear louder on the affected side (hyperacusis) — this may be caused by paralysis of the stapedius muscle but also occurs independently. The incidence of Bell's palsy is 20 to 30 cases per 100,000 people per year (Hauser *et al.*, 1971); it accounts for 60 to 75 percent of all cases of unilateral facial paralysis (Adour *et al.*, 1978). The sexes are affected equally. The median age at onset is 40 years, but the disease may occur at any age (Katusic *et al.*, 1986). The incidence is lowest in children under 10 years old, increases from the ages of 10 to 29, remains stable at the ages of 30 to 69, and is highest in people over the age of 70. The left and right sides of the face are involved with equal frequency. Most patients recover completely, although some have permanent disfiguring facial weakness (Peitersen, 1982). Poor prognostic factors include older age (Hauser, 1971), hypertension (Adour and Wingerd 1974), impairment of taste (Diamant *et al.*, 1972), pain other than in the ear, and complete facial weakness (Cawthorne and Wilson, 1963). In the first three days, electrical studies reveal no changes in involved facial muscles, whereas a steady decline in electrical activity is often noted on days 4 to 10. When excitability is retained, 90 percent of patients recover completely; in the absence of excitability, only 20 percent of patients recover completely (Campbell *et al.*, 1962; Richardson, 1963).

Other causes of acquired peripheral facial weakness are much less common. Associated conditions include diabetes mellitus, hypertension, HIV infection, Lyme disease, the Ramsay Hunt syndrome (See. Gupta and Pushkala, 2005), sarcoidosis, Sjögren's syndrome, parotid-nerve tumors, eclampsia, and amyloidosis. Peripheral-facial-nerve palsy has also been

reported among recipients of inactivated intranasal influenza vaccine (Mutsch et al., 2004).

Bell's palsy rarely recurs. Recurrent or bilateral facial palsy should prompt consideration of myasthenia gravis or lesions at the base of the brain, where the facial nerve exits the pons; such types of palsy occur in lymphoma, sarcoidosis, and Lyme disease (Keane, 1994). In rare cases, patients with inflammatory demyelinating polyneuropathy (Guillain-Barré syndrome) present with bilateral facial palsy but relatively little weakness of the extremities however, in immunocompetent people, the Ramsay-Hunt syndrome is neither recurrent nor bilateral.

**(F) Corneal Disorders :** Age-related changes in the cornea can affect the ability of the cornea both to protect the internal structure of the eye and to refract incoming light for vision.

Loss of corneal sensitivity to mechanical stimuli occurs with increasing age as the central cornea retains its sensitivity longer than other areas (Skuzza, 1971). Measurement of the corneal touch threshold (CTT) in healthy people of different ages by stimulating the cornea with nylon microfilaments of various lengths indicates that the CTT remains almost the same between ages 7 and 40 years (Millidot, 1977). Beginning in the fifth decade of life, the CTT becomes significantly higher and continues to increase with age, such that by 80 years, the CTT is almost twice that of a 10-year-old (Millidot, 1977). The cause of the decline in corneal sensitivity may be attributed to the thickening of the fibrous structure of the cornea, to a decrease in water content, or to an atrophy of nerve fibers (Millidot, 1977). Moreover, Various corneal degenerations affecting the anterior surface of the cornea will cause irritation and reflex tearing.

**(G) Irritation from Lashes :** Trichiasis is a posterior misdirection of eyelashes. Owing to constant corneal irritation, it can give rise to persistent reflex tearing, discomfort, recurrent infections, corneal ulceration, and pannus formation.

In some individuals, the tarsal glands may be totally or partially absent. When this is the case, they are often replaced by an abnormal row of cilia, which invariably turn inward to abrade the cornea, a condition known as distichiasis (Dayal et al., 1968). Long-standing inflammatory disease of the lid margins may result in the tarsal glands assuming such a hair-bearing function, known as acquired distichiasis. The latter condition usually does not involve all four eyelids, and the newly acquired eyelashes are usually

short and nonpigmented, or they may be lie crumpled along the epithelial surface of the eyelid margin (Scheie and Albert,1966).

**(H) Hypersecretion of Tears :** Sometimes, tears will result from hypersecretion. This can be caused by ocular inflammation, corneal irritation, gustatory tearing, thyroid problems or nasal irritation. Because of its rarity, hypersecretion is primarily a diagnosis of exclusion.

### **III. Management of Dry Eye's**

**(A) Diagnosis :** Tears in old age though not very uncommon is not a grave problem, nor does it indicate any impending permanent harm to the eye and its structures. When an elderly patient presents with complaints of excessive tearing, the possible causes are as listed above. Differential diagnosis doesn't have to be difficult, though. By paying close attention to the complaint, and following a stepwise approach, you can get to the root of the problem and manage better.

**(a) The History :** Patients with severe dry eye typically complain of foreign body sensation, burning, itching and conjunctival redness. The symptoms will be less intense when the patient wakes up in the morning, and become worse in the afternoon or evening. Reading, wind and smoke may make the symptoms worse. Patients with very severe disease may have complaints of blurred vision, pain and photophobia. When there is no obvious infections or other outward signs to explain the symptoms, a thorough description of the problem should be obtained. Important points which suggest the diagnosis are:

- If the tears does not actually overflow the lid margins and run down the face, than excessive reflex tearing secondary to dry eyes is considered.
- If the tears overflow the lid margins and run down the face obstruction (complete or partial) of the lacrimal ducts system (drainage system) is the possible cause.
- Environmental factors like fumes, pollutants, etc which trigger the reflex tearing should also be ruled out.
- History of any injury in the facial region should be sorted as damage to the nerves of the face may cause tear problems.
- Also, history of head or neck tumor is also important. A mass in the area of the lacrimal sac can result in partial obstruction of tear drainage.

**(b) The Examination :**

- *Examination of the tear meniscus* : In aqueous deficiency, the meniscus will be miniscule or absent, and lots of debris will be present. If the lacrimal drainage system is not in working order, a much larger than normal tear meniscus will be seen. In blepharitis, there will be some froth on the tear meniscus due to excess oil in the tears. If the tear meniscus is thick and sticky, and the lids stuck together upon waking, suspect a chronic infection secondary to a lacrimal obstruction. In such patients, some crusty deposits stuck to the lashes and in the corners of the eye.
  - *Examination of the area around the lacrimal sac* : Looking for tumors in this area and palpating this area for tenderness may point towards a diagnosis.
  - *Schirmer test should be performed* : This is the test to diagnose the severity of dry eyes and confirms excessive tearing.
- (c) Determination of the extent and location of an obstruction** : If nasolacrimal system obstruction is found to be a cause than the diagnosis of the site of obstruction can be made by dye disappearance test, lacrimal irrigation, lacrimal probing, nasal endoscopy and dacryocystography.

**(B) Treatment for various causes dry eyes :**

**(a) Treatment of dry eye**

- (i) House-hold remedies* : Several aspects are to be considered while treating dry eye patients.
- Like controlling the humidity by using a humidifier in the living and working areas, particularly the bedroom. Ideally, the humidity should remain at 40 to 50 percent.
  - Four drops of preservative free artificial tears in each eye every day.
  - Reduction or discontinuation of systemic drugs for allergies, insomnia and nervous disorders.
  - As in mild dry eye good lid hygiene should be advised.
  - As suggested by MacKeen *et al.* (1996), washing the faces with a Turkish face cloth twice a day, followed by a 30-

second warm tap-water compress using a face cloth over both closed eyelids, also benefits such patients. After the warm (as opposed to hot) tap-water compress, the lower lid margin of each eye should be wiped once with a tightly wound dry cotton-tipped applicator. The heat and mild friction created with a single wipe from side to side removes excess oils, mucous and debris from the lower lid margin (MacKeen *et al.*, 1996). Also, this will draw reflex tearing from the lacrimal gland, if it's available. Even a small amount of reflex tearing will decrease the need for artificial tear solutions.

- Moist chamber spectacles (Hart *et al.*, 1997) can also be considered when patient compliance is not a problem.

(ii) *Tear Replacement Therapy* : The replacement of newly identified tear components to maintain tear-film stability on the ocular surface represents an important innovation. An eye drop with low osmolarity, in turn, inverts the osmotic gradient between the tear film and the ocular surface. By lowering tear-film osmolarity and reversing the gradient, these substitutes rehydrate the dehydrated tissue and don't pull water out of the surface of the eye (Gilbard, 2000).

Many of the new substitutes are preservative-free and contain viscoelastic materials (hypromellose, methyl cellulose, etc.) targeting the role of mucin on tear-film. These newly formulated drops allow adsorption to the ocular surface, increasing retention time. Further, preservatives are known to alter the normal electrolyte balance of the tear film and eliminating them will be not disturb this electrolyte balance.

(iii) *Interventional Therapies* :

- Blocking the puncta with silicone plugs. If these plugs fall out more than once, suturing the punctum closed with 10-0 nylon is recommended.
- Lid tarsoraphies can be opted when there is a threat of impending corneal damage due to dry eye secondary to neurological causes.

(iv) *Challenges of Future Therapies* : As the number of available treatment strategies for dry-eye and ocular-surface disorders increases, it's becoming difficult to determine the potential value

of a therapeutic approach. Additionally, the diagnostic tests to evaluate success must be more accurate. Additional tear components being evaluated as tear substitutes include lactoferrin, a protein secreted by the lacrimal glands; lipocalin, a lipid binding protein; and waxes. Additionally, researchers have identified two components of meibomian gland secretion, phosphatidylethanolamine and sphingomyelin, that are decreased in obstructive meibomian gland dysfunction. Replacing these lipids may lead to increased stability of the lipid layer, minimizing evaporative tear loss. New tools such as fluorophotometry, confocal microscopy and lactoferrin analysis may assist researchers in understanding what's being measured and determining normative values for a population. Furthermore, the formulation of topical agents that address tear-film deficiencies, stimulate secretory processes or suppress inflammatory activities may result in products with multiple active ingredients.

**(C) Eyelid Abnormalities :** Punctal ectropion can be corrected by horizontal eyelid tightening procedures (*viz.* lateral tarsal strip procedure, blepheroplasties, transconjunctival tightening and rotation procedures, etc). These tightening procedures restore adequate horizontal tension to the lower eyelid and often correct any punctal ectropion. All these procedure are used in combination also.

**(D) Nasolacrimal Drainage System Pathology :**

- (a) *For puctal stenosis :* Wide dilatation, punctoplasty (*viz.* one snip procedure) and silicone tube implantation are advocated.
- (b) *For canalilculitis :* After a cytological examination or a high-resolution ultrasonic examination, curettage and debridement through the dilated punctum followed by antibiotic lavage is performed. Large diverticuli are excised or marsupialized.
- (c) *For Nasolacrimal duct blocks :* Dacryocystorhinostomy (DCR) is the treatment in which a passage is created surgically between the nasal cavity and the lacrimal sac.

**(E) Neurological Causes :** If there are no central neurological lesions with facial palsy and no apparent cause (Bell's palsy), and is diagnosed within one week after the onset of symptoms, than no tests are indicated unless other cranial-nerve deficits develop (indicating more widespread disease). If there is no recovery three to six weeks after the onset of symptoms, or a facial

twitch or spasm preceded Bell's palsy than that indicates continuous facial-nerve irritation suggestive of a tumor. Short course of Steroids (prednisone) within 2 to 14 days after the onset of symptoms is the treatment of choice. Because Bell's palsy is associated with HSV infection, antiviral treatment may help. If complete facial paralysis is still present after one week of medical treatment, electroneurography should be performed. If electroneurography documents 90% nerve degeneration, than surgical decompression may be considered. Finally, for patients with permanent facial paralysis, various surgical procedures exist for dynamic reconstruction of the facial nerve.

**(F) Corneal Disorders :** If there is corneal insensitivity due to neurological cause than the treatment should be as described above. In mild loss of sensitivity lubricating tear supplements are the preferred mode of therapy.

**(G) Irritation from Lashes :** For trichiasis several modalities of treatment exist which include epilation, electrolysis, cryotherapy, argon laser thermoablation (Sharif *et al.*, 1991; Bartley and Lowry, 1992; Ghabrial *et al.*, 1994; Sahni and Clark, 2001) and full thickness pentagonal resection with primary closure (may be considered with the trichiasis confirmed to a segment of the eyelid only).

Management of distichiasis is difficult and often unsuccessful. In localized cases, a wedge resection with primary closure may be effective. Cryotherapy can be used after splitting the posterior lamella. The excised area may be replaced with full-thickness mucous membrane grafts.

#### **IV. Recent Advances**

**Tear-film dysfunctions**, collectively diagnosed as dry-eye syndromes, are classified into two major types: aqueous-deficient and evaporative (Lemp, 1995).

Aqueous-deficient dry eye is due to a lack of tear secretion from the lacrimal gland. An example is Sjögren's syndrome, an autoimmune disease. The disease is associated with an extensive inflammation in lacrimal tissue, an immune-mediated destruction and/or dysfunction of epithelial cells, and a precipitous decrease in aqueous tear output (Sullivan *et al.*, 2002). Sjögren's syndrome may be either primary (*i.e.*, no associated connective tissue disease) or secondary (*e.g.*, patients with systemic lupus erythematosus or rheumatoid arthritis). Evaporative dry eye is typically caused by meibomian gland dysfunction and lipid insufficiency, leading to increased evaporation

and reduced stability of the tear film (Sullivan *et al.*, 2002). It's estimated that meibomian gland disease, which also occurs in Sjögren's syndrome, may be a contributing factor in more than 60 percent of all dry-eye cases (Shimazaki *et al.*, 1995).

The majority of dry-eye sufferers are women, and female gender has been identified as a risk factor for dry-eye development (Schaumberg *et al.*, 2001; Caffery *et al.*, 1996). This sex-related prevalence is not surprising, given that more than 90 percent of the individuals with primary or secondary Sjögren's syndrome are women, and that these autoimmune disorders are among the most frequent causes of aqueous-deficient dry eye.

Numerous published studies document that sex and sex steroids exert a significant impact on the health and well-being of the eye (Gupta *et al.*, 2005). Sex-associated differences have been identified in the lacrimal gland, meibomian gland, conjunctiva, goblet cells, cornea, anterior chamber, iris, ciliary body, lens, vitreous and retina. Many of these differences appear to be due, in part, to the action of sex steroid hormones (*i.e.*, androgens, estrogens and progestins).

The recognition of these sex-related differences, and the determination of their underlying basis (*e.g.*, sex steroid action), is extremely important. Such understanding may lead to new insights into the physiological control of ocular tissues, as well as the development of novel therapeutic strategies to treat diverse eye disorders.

Androgens are known to regulate structure and function of lacrimal tissue in a variety of species. Androgen receptors are located almost exclusively in nuclei of epithelial cells and the density of androgen receptors is far higher in males, as compared to females. The distribution of the androgen binding sites in lacrimal tissues is under the influence of gender and endocrine system (Rocha *et al.*, 2003).

Androgen receptors has been reported to be present in the meibomian gland of human, rat and rabbit (Rocha *et al.*, 2000; Wickham *et al.*, 2000; Auw-Haedrich and Feltgen, 2003). The meibomian gland is also a target organ for androgen (Sullivan *et al.*, 2000). Production of fatty acid, total and neutral lipids in the meibomian gland is regulated by the hormone action. The changes in lipid contents affect the stability of the tear. Chronic androgen deficiency is associated with meibomian gland dysfunction, which results in dry eye, a common disease both in males and females. The onset of dry eye is very common during menopause and may result from the loss of hormonal

support. In human tear production is correlated with serum prolactin and sex steroids hormones levels prior to and during menopause (Mathers *et al.*, 1998). Androgen has been shown to elevate a secretory activity of production of the tears in the lacrimal gland of rats (Sullivan and Allansmith, 1987; Sullivan *et al.*, 1990). Estrogens may or may not be inhibitory to the androgen effect (Varma *et al.*, 1994). Lacrimal fluid peroxidase has cyclic variation during the menstrual cycle (Madia *et al.*, 2001). Thus an altered hormonal balance at menopause may affect tear production. Recently it has been shown that premature ovarian failure women show more symptoms of dry eye than age matched controls (Smith *et al.*, 2004). These on-going researches may lead to a discovery of new specific modalities for tears related problems.

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