Age-Related Eyelid Diseases

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Abstract: Although aging is natural and acceptable process by most people, it has become a major problem with increased life expectancy and socio-cultural levels. The eyelid protects eyes from dryness, environmental exposure and trauma. It is important that the eyelid is to be robust and in the proper position for eye health.

Keywords: Aging, ectropion, entropion, eyelid, ptosis, tumor.

1. INTRODUCTION

Some natural changes may occur in the eyelids as a result of age, and the incidence of serious diseases that affect the quality of vision may increase with age. To treat diseases associated with aging and the desire to look younger, many people resort to medical and surgical methods. As a result, cosmetic products that promise rejuvenation have become a big business, and surgical procedures are constantly being renewed. In order to be able to offer better treatment options, it is necessary to understand and know about the anatomical changes that occur as a result of aging [1].

The three basic structures required for periorbital stability are skin, soft tissue and bone. Loss of elastic fibers and relaxation in the skin are mainly a result of aging [2]. However, a number of studies have shown that changes in fat and muscle tissue are effective in developing age-related appearance [3]. A study reported that the volume of the fat packages in the nasal passages increased more than those at the center, and that this should be taken into consideration during surgery [4].

There are different explanations for the changes that occur in the eyelids and those occurring in the orbicularis muscle. Some authors indicate that the orbicularis muscle is not responsible for the changes that occur with aging, and that it is unnecessary to touch this muscle during surgery. According to other authors, reduction in the tissue fibers of the muscles and weakening of connections between the bands play a major role in eyelid aging [2, 5].

In this review we aim to discuss more common age related eyelid changes and diseases.

2. ENTROPION

Entropion refers to the inward rotation of the lid margin [6]. The subtypes include congenital, cicatricial, involutional and spastic entropions. The most common age-related type is the involutional entropion [1].

The lid margin and lashes may touch the cornea and cause corneal erosion (Figure **1a**). Chronic blepharitis, chronic conjunctivitis, dry eye syndrome and superficial punctate keratitis may then occur [6]. These conditions have been observed to occur more frequently in the lower eyelid. The main reason for this is lateral canthal tendon laxity, which is a type of horizontal laxity. Disinsertion of the lower eyelid retractors is one of the reasons for vertical laxity [6].

Eyelid laxity is measured by the "pinch test" and the "snapback test." For the pinch test, the eyelid is compressed and pulled. If it elongates more than 6mm, this means that the eyelid is loose. The snap test determines whether there is a sound as the eyelid returns to its anatomical position after the pinch test; this shows adequate elasticity [7].

In a study showed that a decrease in collagen and elastin fibers in the extra cellular matrix of the eyelid is responsible for eyelid looseness. The study also revealed that collagen acting on contractile force and elastic fibers is responsible for flexibility and elasticity [6]. In another study, it was reported atrophy of the orbital fat tissue and a decrease in the orbital contents due to the weakening of the orbital ligaments that occurs with aging. Axial ocular globe projection was lower in eyes with entropion that were measured with Hertel exophthalmometry [8]. One study has also reported that overlapping preseptal orbicular muscle on the pretarsal component and the orbital fat tissue that directs forward to the orbital rim contributes to the development of entropion [9].

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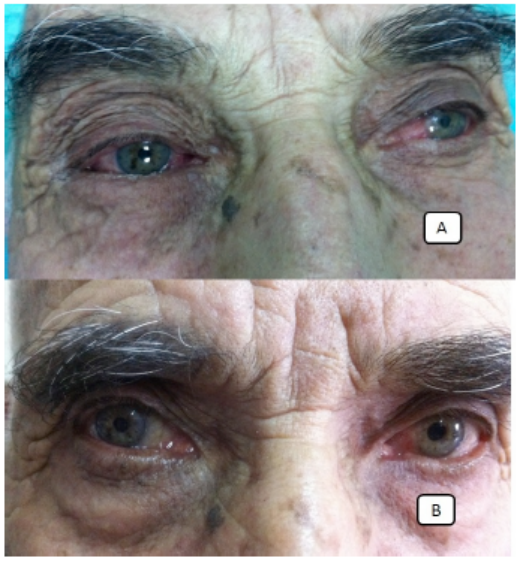

Figure 1a: Entropion. **b:** Postoperative second months appearance.

Moisturizers are used until surgical treatment (Figure **1b**), and the eyes are closed if this is necessary [9]. One of the best surgical methods for treating entropion is Quickert-Rathburn full thickness rotational sutures. This is a temporary technique that is used for inoperable patients, such as those with bleeding diathesis [1]. However, the most commonly used eyelid shortening surgery is the lateral tarsal strip. This surgery involves first creating a lateral stripe with canthotomy and cantholysis; then the tarsus is shortened and sutured to the orbital rim [1]. The Weis procedure is the other method that is used for horizontal lid laxity. After making a horizontal full thickness incision on the lower lid, it is sutured by passing through the pretarsal muscle and skin. The Quickert method can also include using the full thickness tissue resection along with the Weis method [9].

In recent years, transconjunctival entropion surgery has been performed because it results in less scarring, fewer complications and a lower recurrence rate [10].

It has been injected 0.1 cc botulinum toxin A into the lower eyelid orbicular muscle of patients who had age related entropion, demonstrating that this temporary method is safe and effective [11]. As a result, treatment for entropion is now performed as an interventional procedure.

3. ECTROPION

Ectropion describes the outward rotation of the lid margin. The prevalence of ectropion is about 4.8%. It is more common in men. The differences between the tarsal sheet sizes and axial ocular globe projections of men and woman are the reason for this [6].

The subtypes of ectropion are congenital, paralytic, cicatricial, mechanical and involutional (Figure **2b**). The most common type is involutional ectropion (2.9%), which usually occurs in the lower eyelids due to gravity [1].

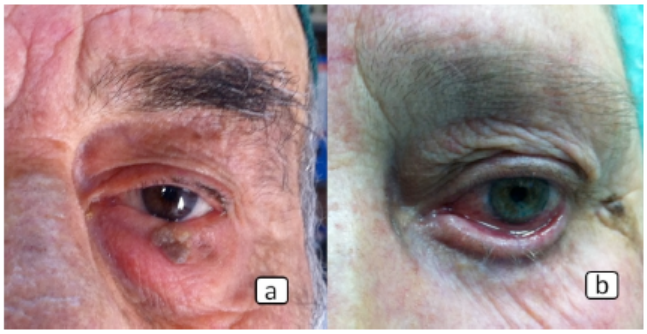

Figure 2a: Actinic keratosis. **b:** Ectropion.

Horizontal eyelid laxity and atrophy and disinsertion of the lower eyelid retractors are the causes of ectropion. The lateral canthus is generally affected. Punctual occlusion and epiphora may also occur if the medial canthal tendon is affected [1]. Ocular irritation, ulceration, chronic conjunctivitis, recurrent infections, punctate keratitis, corneal scarring and vision loss can be seen in untreated patients [1]. Pinch and snap tests can be performed to diagnose ectropion. The inferior scleral appearance is also helpful in the diagnosis [8, 9].

A study showed a reduction in collagen and elastic fibers of the extracellular matrix among patients with horizontal eyelid laxity and involutional ectropion [8]. Another report stated eyelid orbicular muscle degeneration and atrophy in patients with ectropion [9]. Another study found the axial ocular globe projection to be smaller in involutional ectropion. Ocular adipose tissue atrophy, which causes enophthalmos with aging, has been shown to be a reason for this. This value was lower than for entropion [6].

In addition to continued observation, topical moisturizers can be used in cases that are asymptomatic and where the punctum is not affected. It should be taken into consideration for surgery that involutional ectropion occurs mainly as a result of canthal laxity and weakness of the eyelid retractors [8, 9].

Pentagonal resection, tarsorrhaphy, lateral or medial canthopexy, lazy-T, the Kuhnt-Szymanowski technique and the Smith modification of the Kuhnt-

Szymanowski technique are generally used during surgery [8, 9]. In some involutional ectropion cases, carbon dioxide or argon laser conjunctivaplasty can be done to create cicatricial entropion [12].

Consequently, although some patients who have involutional ectropion and are asymptomatic can be treated with artificial tears, the general approach is to correct the eyelid through surgical procedures.

4. DERMATOCHALASES

Dermatochalasia means having more skin tissue in the upper and lower eyelids [13]. The eyelid is the thinnest tissue in the human body and, because of its thin nature, blinking, which is a normal activity, can eventually lead to prolongation of the eyelid [14]. (Figure **3a**) Patients may complain of heavy eyelids, loss of peripheral visual fields and frontal headaches. The marginal reflex distance (MRD) is the distance from the pupillary light reflex to the upper eyelid. If this value is less than 2.5mm, it may require blepharo-plasty [14].

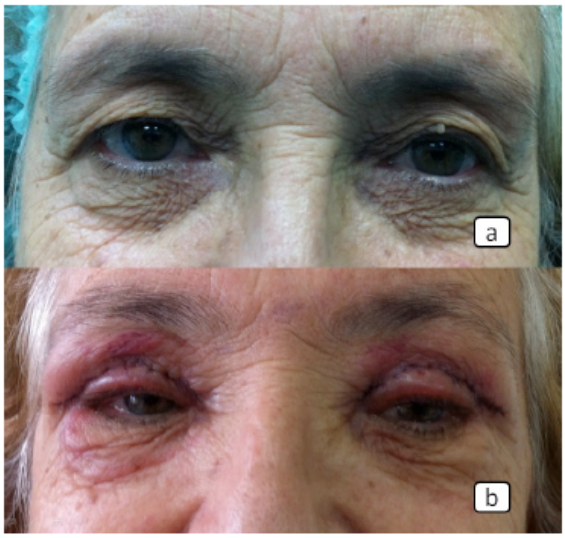

Figure 3a: Dermatochalases. **b:** Postoperative first day apperence.

One study compared the biopsies of patients who received blepharoplasty for dermatochalasis or other reasons. The authors compared the patients' lymphatic dilatation, loss of elastic fibers, collagen degradation and increases in the number of macrophages in the dermatochalasia samples to those of a control group. This study suggests that the sub clinical inflammation through macrophages caused the elastolysis, then the lymphostasis and finally the dermatochalasis [15].

With aging, the free movement of orbital fat pads and herniation can be seen as a result of weakness of the eyelid and orbital soft tissues and the loss of supporting tissues. Fat tissue herniation, which increases with standing and generally occurs later in the day, may be accompanied by dermatochalasis, which is formed by a similar mechanism [16].

It was performed Humphrey visual field (HVF) testing on 3 patients with dermatochalasis who had been referred to them or had complaints of peripheral visual field loss. Bitemporal hemianopia was detected in these patients. Magnetic resonance imaging (MRI) revealed no chiasm defects. Although superior or superotemporal visual field losses have been seen in patients with dermatochalasis, it was found that the bitemporal hemianopia that mimics the pathology of chiasm can be detected with the Humphrey device [17].

Age-related upper eyelid dermatochalasis is usually treated by resection of the excess dermal tissue between the two lines on the eyelid (Figure **3b**). It has been demonstrated that the sutures that are discarded by this method thicken the skin and change the appearance. To avoid this, they suggest making the incision under the eyebrows so that the eyebrow is close to the wound and a more natural look can be achieved [18].

Frowning, squinting and trying to lift the eyebrows may cause forehead wrinkles, the formation of crow's feet and sagging skin. Patients with subclinical dermatochalasis may develop visible dermatochalasis by doing these activities. Botulinum toxin can help to restrain these activities and prevent the dermatochalasis from becoming visible. However, if blepharoplasty is performed in these cases, the latent dermatochalasis might be omitted and skin sagging may re-occur after surgery [19].

Also, in recent years, ultra pulse CO_2 laser has been applied to the upper eyelids, over the eyebrows and to the periorbital region in patients with dermatochalasis. Regeneration and collagen remodeling is expected to increase with beam damage [20].

5. APONEUROTIC PTOSIS

Ptosis occurs when the upper eyelid becomes lower than its normal level (Figure **4a**). There are 4 types, including myogenic, neurogenic, mechanical and aponeurotic. Eyelid ptosis can be mild (1-2mm), moderate (3-4mm) and severe (>4mm). After some time, patients develop head positions in which the jaw is raised upward. Patients then raise the eyebrows and may complain of headaches [21].

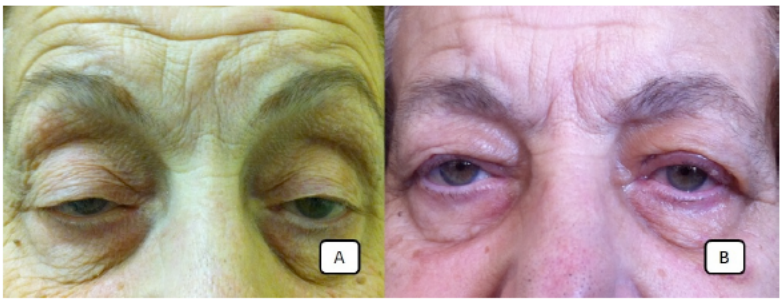

Figure 4a: Aponeurotic ptosis. **b:** Postoperative second week's apperence.

Aponeurotic ptosis develops as a result of age related weakness of the aponeurosis, which is part of the levator muscle that adheres to the upper eyelid. Aponeurotic defects occur in the form of dehiscence and disinsertion disorders. In addition to the natural processes related to aging, rubbing the eyelids, using contact lenses and undergoing cataract surgery may cause dehiscence between the levator and the tarsus and lead to weakening and elongation of the aponeurosis and Muller muscle [22].

The aim in treatment is to repair the aponeurosis defect or to improve dehiscence aponeurosis onto the tarsus [22]. (Figure **4b**) It is recommended that ptosis surgery be performed with local anesthesia. This is aimed at achieving more accurate results by being able to communicate with the patient during surgery [23]. It has been suggested that skin resection be done during ptosis surgery because elderly patients with involutional blepharoptosis usually also have dermatochalasis [23].

It was shown that there is no significant difference in aponeurotic ptosis surgery that is performed with a small incision and minimal dissection according to conventional methods in terms of the eyelid height and contour. In this study the authors also stated that this method is much faster [24].

Transconjunctival blepharoptosis methods, which were described previously, are used in aponeurotic blepharoptosis patients as well. A study suggested strengthening the levator aponeurosis through the transconjunctival approach without Muller muscle resection in aponeurotic ptosis treatment. They have found that this method may be a good approach for patients who do not want to risk complications such as scarring or who do not have excess skin, since skin incision is not required. The authors also showed that the operation is shorter with this method and the patients regain their normal anatomy and function more quickly [25].

6. ACTINIC KERATOSIS

Actinic keratosis (AK), also called solar keratosis or senile keratosis, is a common skin disorder seen in areas of the body that are exposed to the sun, such as the head, neck, hands and forearms (Figure **2a**). AK does not protrude from the skin surface, as dry squamous lesions do [26]. The ultraviolet (UV) that is emitted from the sun causes excessive proliferation of keratinocytes in the epidermis. Excessive exposure to UV leads to inflammation, immunosuppression and the failure of apoptosis [26]. Immunosuppressive, cardiac and diuretic drugs have also been shown to lead to AKs. The symptoms include pain and itching, and bleeding and ulceration can be seen as well. Generally, elderly people and light-skinned men are affected [27]. The lesions may disappear with spontaneous remission, may remain stable over many years or may transform into invasive squamous cell carcinoma (SCC) that is capable of metastasis [27, 33]. It was indicated that AK is associated with SCC (58%), basal cell carcinoma (BCC) (30%), melanoma *in situ* (12%) and invasive melanoma (6%). These diseases should be considered in the differential diagnosis [27].

Cryotherapy and carbon dioxide laser ablation may be used in the treatment. Topical 5-fluorouracil (FU), imiquimod, diclofenac or ingenol mebutate preparations are medical treatments. Photodynamic therapy can also be performed in patients who are resistant to topical therapy or have recurrent lesions. In recent years, plastic surgeons generally prefer excisional biopsy and pathological confirmation (62%), especially for lesions that are smaller than 2mm. Other methods include determining the limit with a frozen section, consulting about the Mohs technique and using liquid nitrogen to manipulating and locating within the form [28].

7. SEBORRHEIC KERATOSIS

Seborrheic Keratosis (SK) is a benign keratinocytic lesion. It is usually seen on the face, chest, back and

limbs in elderly people. It has sharp limits and an irregular and swollen surface. It also looks as if it has been glued onto the skin. The lesions can be yellow, brown or black [29].

Excessive growth of squamous epithelium due to proliferation of basal cells can be observed in histology specimens, and lesions such as comedones and milialike cysts can be seen in dermoscopy. These lesions are called pseudo-melanocytic criteria [30]. SK is the second most common benign tumor of the eyelid (26%), after squamous cell papillomas [29]. SK can be confused with basal cell carcinoma, nevi or melanoma. However, in SKs the basal membrane is intact [31]. Cryotherapy and carbon dioxide laser treatment have been applied successfully. Surgical excision and histopathological confirmation is also required when a diagnosis is not definite and for functional and cosmetic reasons [31].

In a recently conducted study, basal keratinocyte proliferation and an increased turnover were detected using all-trans retinoic acid-loaded micro needle patches. It was recommended that this method can be used in cases of SK [32].

8. BASAL CELL CARSINOMA

BCC is the most common malignancy among humans, and accounts for 90% of eyelid malignancies [33]. The most important predisposing factor is exposure to sunlight for long periods. As a result, it is usually seen in elderly people [34]. Ionizing radiation, arsenic exposure and defects in DNA repair genes, such as xeroderma pigmentosum, are among the risk factors of younger patients for developing BCC [33, 34]. Neoplastic cells originate from the basal cells of the epidermis and move toward to dermis. Such tumors are locally invasive and rarely metastasize. BCC is observed most frequently in the lower eyelid after exposure to sunlight. Then, in order of frequency, the medial canthus, the upper eyelid and the lateral canthus are affected [33].

The nodular type of BCC is the most common. Nodular-ulcerative (rodent ulcer) and infiltrative BCC (morpheaform) (Figure **5a**) are other types that are frequently found. Basosquamous, cystic, adenoid (plexiform) and solid types are less common types of BCC [35]. It is known that recurrent BCC is the most aggressive [33].

Orbital invasion is rare and seen in approximately 2% of cases. It occurs most frequently in BCC with recurrence tumors, large lesions, sclerosing types and those settled in the medial canthus, as well as in patients over the age of 70. It also requires orbital exenteration [36].

Primary treatment is excision of the tumor, and it is important not to leave any tumor cells in the intact tissue (Figure **5b**). In order to determine the margin of surgery as accurately as possible, intraoperative Mohs micrographic surgery (MMS), frozen section control and paraffin section verification methods are used. In the Mohs micrographic surgery technique, recurrent excision is necessary until the intact margin is determined. In a study performed on excised eyelid tumors in patients who have BCC with 3-mm clinical limits, the authors have performed frozen sections or

Figure 5a: Basal cell carcinoma. **b:** Postoperative first month apperence. **c:** Squamous cell carcinoma **d:** Postoperative 5. Days apperence.

paraffin section confirmation in infiltrative tumors because they could not be sure from the border. The defects have primarily been closed. After 5-year follow up, the recurrence rate was found to be very low (0.26%) in both the primary and the recurrent tumors [37]. According to some authors, there was no significant difference between BCC types and localization in primary and recurrent BCC. They have noted that the main cause of recurrence is insufficient surgical removal [33].

Cryotherapy, radiation, photodynamic therapy, electrodissection and curettage, topical 5-fluorescein and topical imiquimod are other treatment options. Vismodegib is an oral treatment that has been used in recent years to treat BCC. This treatment inhibits signal pathways that play a role in the pathogenesis of BCC. Currently, vismodegib was used in 7 patients with eyelid BCC and it was observed full recurrence in 2 patients and an 80% reduction in tumor size in the other 2 patients [38]. Interferon alpha 2b eye drops has been used for an 88-year–old patient who had eyelid BCC but did not want surgery. The patient was given 1 million IU / ml of IFN 4 times a day for 4 months. The tumor reduced in size and has remained stable for 3years [39].

9. SQUAMOUS CELL CARCINOMA

SCC is the second most common eyelid malignancy after BCC and accounts for approximately 5-10% of eyelid malignancies [40]. The most common location is the lower eyelid. SCC also affects the medial canthus, upper eyelid and lateral canthus [41]. SCC is more common in fair-skinned elderly men who have had chronic exposure to sunlight. Radiation, chemo-therapyinduced immunosuppression, human papilloma virus (HPV), xeroderma pigmentosum, scars and burns are the risk factors for SCC [40]. SCC is more aggressive than BCC and may metastasize to regional lymph nodes. It can spread to trigeminal, oculomotor and facial nerve branches through perineural routes. Hematogenous and distant metastases are rare but possible. Fast-growing, large, recurrent and unresec-table tumors spread more frequently than others [40].

Orbital invasion is seen in approximately 2-4% of cases. When the tumor is detected, CT or MRI should be performed to look for any metastasis [41]. Because the clinical types are variable, they can be difficult to diagnose. The horn shape can be seen in the nodular, ulcerative and cutaneous types [42].

SCC is formed by an abnormal proliferation of squamous cells in the layers of the epidermis. Central keratinization and keratin pearl formation are also possible [41]. (Figure **5c**) SCC can occur spont-aneously as primary or from the floor of AK. One study reported that squamous carcinoma *in situ* or Bowen disease, which is known as squamous intraepidermal carcinoma, transforms into SCC in about 19% of cases [41].

Staging of the tumor is based on the TNM (tumor, node, and metastasis) staging system. Treatment is regulated accordingly [43]. The primary treatment for the tumor is clear margin excision with the Mohs or frozen section method (Figure **5d**). If there is invasion, orbital exenteration may be required, followed by radiotherapy [40].

The surgeons have observed that the patients underwent radical radiotherapy were functionally and cosmetically inoperable and did not want surgery. This study shows that radical radiotherapy is a good option in advanced T-stage, but that patients should be followed up frequently for local invasion [44].

When there is perineural invasion, radiotherapy and chemotherapy with multi-agents should be used. Cryotherapy, systemic retinoids, topical 5-fluorouracil and imiquimod are also used as an alternative to surgery [40].

CONCLUSION

In conclusion, there are a lot of diseases that may be considered malignant or benign eyelid and surrounding areas with aging. We share our approach and methods of treating these diseases in our clinical experience and accordance with the literature. Generally, treatment of these diseases make by surgical methods. If patients don't want to surgery, convansiyonel treatment (e.g. artificial eye drops and gel) may be use. Approach to these diseases should be established in line with the experience of the surgeon and proper patient selection.

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