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Review Article

Expression of Matrix Metalloproteinase-9, Transforming Growth Factor Beta and Fibroblast in The Simblefaron Due to Alkali Burn: Literature Review

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ABSTRACT

Simblefaron is one of the most challenging complications in the late stages of an alkali burn. Symblepharon characteristically resembles connective tissue or bands that protrude from the eyelid's interior surface (palpebral conjunctiva) to the surface of the eyeball (bulbar conjunctiva). This literature review was conducted to see the molecular mechanism of symblepharon formation. Matrix metalloproteinase (MMP-9), transforming growth factor (TGF-β), and Fibroblast played a significant part in the healing of conjunctival wounds. MMP-9, TGF-β, and fibroblast overexpressed are suspected to cause excessive inflammation and fibrosis, which results in symblepharon. By knowing this, it is hoped that it can become a basis for developing appropriate management for the occurrence of simblepharon.

Keywords: Symblepharon, Alkali, Burn, Conjunctiva.

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INTRODUCTION

Simblefaron is one of the most challenging complications in the late stages of an alkali burn. A symblepharon is characterized by bands or connective tissue that run from the surface of the eyeball (bulbar conjunctiva) to the inside of the eyelid (palpebral conjunctiva). Restrictive disorders of eye movement, abnormalities during blinking, entropion, ptosis, and corneal injury leading to reduced visual acuity are among the consequences. Simblefaron is quite difficult to diagnose, but in the United States in 2012 there were 0.8 million cases of simblefaron with ocular cicatricial pemphigoid (OCP), 0.2 million cases of Steven-Johnson syndrome (SJS), and 0.2 million other causes. million. Meanwhile, another study stated that 46.87% of the causes of simblefaron were burns, especially chemical trauma.[1,2]

Despite a number of medicinal attempts, simblepharon development and recurrence have not been shown to be prevented with adequate outcomes. The mechanism of simblepharon, particularly the molecular mechanism of simblepharon synthesis, still needs further study. Several methods have been used to create therapies for simblepharon. Several treatments have been tried, including immunosuppressants, systemic steroids, and harsher medicines to stop inflammation on the surface of the eye. Following symblepharon lysis, the open tissue has been closed using tissue replacement materials such as conjunctival grafts, amniotic membrane, oral mucosa, and nasal mucosa. Several additional methods have also been developed to prevent re-adhesions, such as the use of symblepharon rings, silicone, mitomycin (MMC), anchoring sutures, bevacizumab, and beta irradiation.[3,4]

One way to apply preventive therapy is to target cells that help generate symblepharon as soon as an injury occurs. Transforming growth factor-β (TGF-β) is thought to play a role as the main regulator of fibrosis in the conjunctiva. However, the role of TGF-β in the mechanism of simblepharon formation is not yet clearly known. The process of fibrosis formation also induces the expression of fibroblasts and matrix metalloproteinase-9 (MMP-9). Excessive levels of fibroblasts and MMP-9 can increase ECM degradation, resulting in scar tissue formation.[5,6]

Research examining the molecular mechanisms of simblepharon formation is still very limited. It is anticipated that the knowledge gained from this review will aid physicians in learning about this area, which could lead to improved patient outcomes. By knowing this, it is hoped that it can become a basis for developing appropriate management for the occurrence of simblepharon.

Overview of Ocular Alkali Burn

An ocular emergency that results in the corrosion towards corneal tissue is chemical harm to the cornea and conjunctiva. It is present in between 11.5% and 22.1% of all cases of ocular injuries. Nearly two-thirds of chemical damage to the cornea occurs in young men.[8] The majority of them are the consequence of industrial mishaps, with only a small percentage coming from attacks or mishaps at home. Alkali injuries accounted for a greater portion of all injuries than acid injuries[7].

Alkali was responsible for 60% of the chemical damage to the cornea brought on by different compounds including potassium hydroxide, ammonia, lime, magnesium hydroxide, and lye. All these substances can be found in multiple daily products such as cleaning agents, fertilizers, refrigerants, caustic potash, drain cleaners, airbags, firework sparklers, flares, plaster, mortar, cement, and whitewash. Because alkali agents are lipophilic

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and can penetrate ocular tissue more easily than acid agents, they are more hazardous than acid agents[8].

Damaged tissues release proteolytic enzymes that may break down more cells and tissues, resulting in further harm. Numerous symptoms, including extreme pain, epiphora, decreased visual acuity, and blepharospasm, are caused by alkali chemical damage. Based on their severity, alkali chemical injuries are categorized into four grades. Roper Hall categorized corneal burns into four stages according to the prognosis, the extent of damage to the cornea, and the conjunctiva.[9,10].

Irrigation is the first course of treatment for this trauma to help recover corneal pH to physiological pH. The subsequent actions are taken in accordance with the corneal burn grading system. Since grade I and II corneal ulcers have a good prognosis, medical treatment alone may be sufficient to treat them. Antibiotics, cycloplegic drugs, artificial tears, and steroid drops are all part of medical treatment. When burns are severe enough to necrotize tissues, surgery should be performed to remove them. This is because prolonged inflammation can prevent re-epithelization. Surgical methods that might be applied include transplantation of amniotic membrane, debridement of necrotic epithelium, transplantation of limbal stem cells, Boston keratoprosthesis, and transplanting oral mucosal epithelial cells that have been cultivated.[11,12]

Simblepharon

Fuchs used the term "symblepharon" for the first time in 1982 in a book entitled Cicatrical adhesion of the conjunctiva of the eye and the eyelid. The characteristic of a symblepharon is that it resembles bands or connective tissue that extends from the surface of the eyeball to Bulbar conjunctiva, the interior of the palpebral conjunctiva on the inner of the eyelid.[13,14]

The anterior portion of the eyeball and the posterior portion of the eyelid are covered by the conjunctiva, a thin, transparent mucous membrane. One tissue that can combine to generate the symblepharon is the conjunctiva. The conjunctiva consists of three parts, namely the bulbar conjunctiva which covers the anterior part of the eyeball, the palpebral conjunctiva which covers the posterior part of the eyelid and the fornix conjunctiva which is found between the palpebral conjunctiva and the bulbar conjunctiva.[15]

Simblefaron can be caused by exogenous and endogenous causes. Exogenous causes include chemical trauma and burn trauma. Meanwhile, endogenous causes include Steven-Johnson syndrome (SJS), ocular cicatricial pemphigoid (OCP), mucous membrane pemphigoid (MMP), and dry eye disease. Simblefaron can also result from side effects from drug reactions or can also occur after glaucoma filtering surgery (GFS) as a result of changes in the surface of the conjunctival epithelium. Simblefaron itself is quite common. Based on studies in the United States in 2012, there were 0.8 million cases of symblepharon in OCP, 0.2 million cases of SJS, and 0.2 million other causes.[16]

The conjunctival fornix makes up the conjunctiva from the limbus to the lid border. The ability of the surface of the eyeball to stay healthy is a benefit of having a deep fornix. The fornix shortening is one indicator of simblepharon development. Shortening of the fornix can be caused by continuous scar formation. Shortening of the fornix can inhibit the movement of the eyeball and block the outlet of the tear duct from the lacrimal gland, thereby causing dry eye disorders. This can also result in microtrauma due to friction from continuous eye blinking, cicatricial entropion, blinking disorders, limited Bell phenomenon, and visual defects due to restriction of eye movement and ptosis.[17]

The severity of symblepharon can be determined from the shortening of the fornix in the affected eye and compared with the depth of the upper and lower fornix in the normal eye and the distance from the intercanthus, and compared with normal values based on age and gender.[18]

Kheirkhah et al assessed the severity of symblepharon using a scoring system of length, width, and inflammatory activity. Based on length, simblepharon is divided into levels I, II, III, and IV. Length is defined as the shortest distance between the edge of the eyelid to the limbus, grade I simblepharon has a length equal to or greater than normal palpebral conjunctiva. The length of the level II symblepharon is shorter than the normal palpebral conjunctiva but has a normal tarsus length. Grade III is shorter than normal tarsus, and grade IV has a length close to zero. Based on width, it is defined as the longest horizontal distance compared to length. Grade 'a' if one-third of the length of the eyelid is covered by the simblepharon, 'b' if two-thirds of the length of the eyelid is covered, and 'c' if more than two-thirds of the eyelid is covered by the simblepharon. Based on the level of inflammation, simblepharon is classified into several degrees, namely grade 0 if there is no hyperemic conjunctiva, grade 1+ for mild simblefaron, grade 2+ for moderate simblefaron and 3+ for severe simblefaron.[19]

TGF-Beta Role in Fibrosis

Transforming growth factor (TGF-β) is the most powerful growth factor involved in wound healing. One of the most significant profibrogenic cytokines in the conjunctival wound healing process is TGF-β, which is produced by platelets, fibroblasts, lymphocytes, and macrophages. It promotes collagen synthesis and the migration and proliferation of human Tenon's fibroblasts. Inhibiting TGF-β is an effective way to prevent postoperative scarring.[20]

Fibroblasts are the primary cellular effectors of the fibrotic response, and TGF-β is one of its main activators. TGF-β's involvement in tissue fibrosis is suggested by research on cell biology, trials using animal models, and clinical data. In several studies, it was found that, in fibrotic tissue, TGF-β was overexpressed. Immunohistochemical studies showed TGF-β was upregulated in conjunctival scar tissue. It was also found that there was a significant increase in the TGF-β isotype in filtration surgery performed on animals and humans.[21]

Because it causes fibroblasts to transdifferentiate into myofibroblasts, which are defined by the production of alpha-smooth muscle actin (α-SMA), TGF-β is crucial for wound healing, stimulating proliferation, migration, and collagen production. TGF-β is intrinsically involved in the balance between TIMPs and MMPs that controls extracellular matrix degradation and deposition. Excessive activation of TGF-β causes fibrosis in eye tissue, which can disrupt vision and ocular tissue homeostasis.[22]

MMP- 9 Role in Fibrosis

A calcium- and zinc-dependent endopeptidase, matrix metalloproteinase (MMP) breaks down several extracellular matrix (ECM) constituents. MMP is produced by neutrophils, stromal fibroblasts, and epithelial cells. Numerous non-ECM molecules, including growth factors, integrins, and receptors, can also be broken down by these proteases. Based on their cellular location, the 25 discovered MMPs are divided into two primary groups. In addition, MMPs are categorized into six classes based on their structure and substrate specificity: membrane types, stromelysins, matrilines, collagenases, and gelatinases.[23]

MMP-9, one of them, is engaged in cellular remodeling pathways and is present on the surface of the eye. MMP-9 molecules are overly produced in the extracellular matrix in response to pathogenic stimuli, which speeds up cell turnover and sustains an inflammatory state. MMP-9 is involved in wound remodeling and has the capacity to break down components of the extracellular matrix, so it is widely expressed in

the remodeling phase. Regular MMP-9 activity is essential for normal wound healing. However, high MMP-9 activity can cause damage to the basement membrane and matrix. Excessive MMP expression due to IL-1, TNF-a, and TGF b can cause scarring. NF-kB, IL-1, TGF-b, and PAF are pro-inflammatory mediators that increase MMP-9 expression in response to injury on the surface of the eyeball, chemical injuries, and infections. Tissue inhibitors of metalloproteinases act to inhibit MMP-9, and the MMP-9/TIMP balance is important in determining the degree of collagen proteolysis.[24]

Fibroblast Role in Fibrosis

Fibroblasts are necessary to promote healthy wound healing, engaged in crucial procedures such dissolving fibrin clots, producing fresh extracellular matrix (ECM), and forming collagen structures to support other cells necessary for efficient wound healing, in addition to causing the wound to contract. The first fibroblasts develop at the site of damage 24 to 48 hours after the injury, marking the end of the inflammatory phase and the start of the proliferation phase in the healing process.[25]

Once at the wound site, fibroblast migration activity uses many integrins to break down the fibrin clot and wound bed, which is affected by the ECM composition. In order to eliminate denatured proteins and transient matrix-related components that are not required for the healing wound, they start to multiply and produce MMPs and other proteinases, like seperinase. In order to eliminate denatured proteins and transient matrix-related components that are not required for the healing process, they start to multiply and produce MMPs and other proteinases, like seperinase. Tissue metalloproteinase inhibitors (TIMPS), which are also made by fibroblasts, carefully regulate these proteinases. They also create a new extracellular matrix (ECM) at the same time, which is initially quite high in fibronectin, hyaluronic acid, and collagen III. It is still unclear how fibroblast populations are regulated and undergo apoptosis. The role of fibroblasts is very important in the formation of fibrosis, contracture, or keloid and hypertrophic scar tissue.[26]

Non-operative Therapeutic Management on Simblefaron

In 1950, a preventive technique was developed to prevent the occurrence of symblepharon by creating a barrier separating the damaged conjunctival surfaces so as not to cause adhesions. This effort uses a glass layer that can separate the simblepharon manually. Another alternative is to use therapeutic soft contact lenses and conformers which are placed in the fornix for around two weeks to stop a simblepharon from forming. Contact lenses and conformers are used to keep the surfaces of the palpebral conjunctiva and bulbar conjunctiva separate until re-epithelialization occurs, but this is not effective in symblepharon which occurs due to severe chemical trauma.[27]

The use of silicone spacers can also be considered to temporarily reduce complaints, however, if the silicone spacers are removed then simblefaron can occur again. Some medications such as steroid therapy are also sometimes chosen, but the use of steroids can often cause systemic side effects such as diabetes or infection. Several therapies such as the use of mitomycin C (MMC), bevacizumab, nylon foil-anchored polytetrafluoroethylene (Gore-Tex), and postoperative applications using gamma-irradiation have been developed, but the recurrence rate is still quite high, ranging from 6.2% to 40%.[28]

Operative Therapeutic Management on Simblefaron

The development of the latest therapy for the treatment of simblefaron continues. Some of them are operative management using lamellar keratoplasty, amniotic membrane transplantation (AMT), autologous conjunctival, and oral mucosal transplantation. The use of autologous conjunctival graft taken from the neighboring eye is used to save damaged conjunctival tissue. However, damage due to chemical trauma or severe burns which often involve the entire cornea and conjunctiva require more mucosa for reconstruction of the surface of the eyeball. The use of allogeneic conjunctiva often results in rejection reactions from the immune system. As an alternative option, nasal mucosa can also be used as a substitute for the use of conjunctival mucosal tissue. However, the use of nasal mucosa is not complemented by the presence of limbal stem cells, and the recurrence rate of symblepharon is quite high.[29]

The prognosis for burn and chemical trauma has significantly improved with the use of amniotic membranes. However, the use of amniotic membranes in chemical trauma or severe burns is not yet effective. While amniotic membranes can be used as a patch to cover injured conjunctival tissue, their use is still insufficient in cases of significant stromal thinning and approaching perforation. Severe symblepharon often has many complications such as extensive conjunctival deficiency, eyelid malformation, stem cell destruction, corneal opacification, and corneal thinning. Some of these complications are related to each other, so complicated surgical techniques and several types of surgery are needed, such as reconstruction of the conjunctival sac, corneal transplantation, and stem cell transplantation, to obtain more effective surgical results. Current therapeutic management has not yet achieved effective and satisfactory results, because areas in the deep fornix cannot be reached completely. So there are still conjunctivas that stick together and cause shallowing of the fornix.[30]

CONCLUSION

Understanding how symblepharon forms at the molecular level will facilitate treatment development. Matrix metalloproteinase (MMP-9), transforming growth factor (TGF-β) and fibroblast had an important role in the conjunctival wound healing process. MMP-9, TGF-β, and fibroblast overexpressed are suspected to cause excessive inflammation and fibrosis, which results in symblepharon. Preventative therapies may be possible by targeting symblepharon progenitor cells immediately after injuries.

AUTHOR'S CONTRIBUTION

The study's concept, design, literature search, statistical and data analysis, manuscript preparation, and manuscript review are all under the purview of DM. LA is in charge of the study's concept, literature search, and manuscript evaluation. SF is in charge of the study's concept and manuscript production. R is in charge of the study's design and manuscript editing. PL is in charge of the data analysis.

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CONFLICTS OF INTEREST

There isn't any potential conflict of interest in this review article.

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ETHICAL CLEARANCE

Not applicable.

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