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Progress in the Treatment of Dry Eye

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Abstract: ***Dry Eye Disease (DED) is a chronic ocular surface disease caused by multiple factors, characterized by decreased tear film stability, ocular surface inflammation, and abnormal neural sensation. With the increasing use of electronic devices, an aging population, and environmental factors, its global prevalence continues to rise. This article systematically discusses the etiology, pathogenesis, epidemiological characteristics, pain mechanisms, and the latest advancements in pharmacological and non-pharmacological treatments of dry eye. It also provides an outlook on current controversies and future research directions.***

Keywords: Dry eye, Tear film stability, Inflammation, Neuropathic pain, Artificial tears, Meridian theory**.**

1. Introduction

Dry eye is a common ocular surface disease, whose main clinical manifestations include dryness, foreign body sensation, burning sensation, and fluctuating vision. In severe cases, it can lead to corneal damage and even loss of vision. Long-term ocular discomfort can also significantly affect patients' quality of life, work efficiency, and psychological state [1]. According to the 2020 Chinese Dry Eye Expert Consensus, dry eye is defined as "a multifactorial disease caused by abnormalities in the quality, quantity, or dynamics of tear fluid, leading to decreased tear film stability, accompanied by ocular surface inflammation, tissue damage, and neural abnormalities" [2]. In recent years, research on the pathogenesis of dry eye has been continuously deepening. To reveal its complexity and heterogeneity, researchers' treatment approaches have evolved from the past single artificial tear supplementation to multi-target intervention, individualized treatment, and integrated traditional Chinese and Western medicine models, forming a more systematic and comprehensive diagnosis and treatment strategy.

2. Epidemiological Characteristics of Dry Eye

Globally, the prevalence of dry eye ranges from approximately 5% to 50%, with statistical variations due to different regions and diagnostic criteria. The incidence rate is relatively high in Asia, where epidemiological surveys indicate a prevalence rate of over 30% [3]. There is a significant gender difference, with female patients significantly outnumbering male patients. Additionally, age is a notable independent risk factor. Due to factors such as natural decline in lacrimal gland secretion and age-related systemic diseases, the prevalence of dry eye significantly increases in the elderly population. As a populous country, China has also seen an upward trend in the prevalence of dry eye in recent years, driven by changes in lifestyle and environmental factors [4]. Multiple epidemiological studies on the Chinese population have shown that the prevalence of dry eye ranges from approximately 21% to 30%. In addition to age and gender, risk factors such as prolonged use of video terminals (using electronic screens for more than 2 hours per day), insufficient sleep, diabetes, autoimmune diseases (such as Sjögren's syndrome and rheumatoid arthritis), history of allergic diseases, and ocular surgeries such as refractive and cataract surgeries are closely associated with the occurrence of dry eye [5]. A study conducted by Li Jiao and colleagues on 1,216 subjects found that diabetes, smoking, and using electronic screens for more than 2 hours per day are independent risk factors for dry eye. These findings provide valuable reference for the prevention and control of dry eye in China.

3. Etiology and Pathogenesis

3.1 Abnormalities in Tear Film Structure and Function

A stable tear film is essential for maintaining the health of the corneal and conjunctival epithelium. The tear film consists of a lipid layer, an aqueous layer, and a mucin layer, arranged from the outer to the inner layer, forming a precise "sandwich" structure. Any abnormality in the quality or quantity of any layer may lead to instability and premature rupture of the entire tear film [6]. The lipid layer is mainly secreted by the meibomian glands, whose primary function is to prevent excessive evaporation of tears. Therefore, structural or functional abnormalities of the meibomian glands have become the primary cause of evaporative dry eye.

3.2 Inflammation and Immune Mechanism

Inflammation has been widely recognized as the core mechanism underlying the pathogenesis of dry eye disease [7]. Regardless of the initial etiology, it may ultimately lead to ocular surface damage through an immune inflammatory response. The hyperosmolar state of ocular surface tears is considered a key link in initiating the inflammatory response. It can activate multiple intracellular signaling pathways, including the MAPK and NF-κB pathways, thereby promoting the release of various pro-inflammatory cytokines (such as IL-1β, TNF-α, IL-6, etc.) [8]. These inflammatory factors can induce apoptosis of ocular surface epithelial cells and goblet cells, leading to reduced mucin secretion, further disrupting the stability of the tear film, and forming a positive feedback vicious cycle of "inflammation-ocular surface damage-instability of the tear film-higher osmolarity" [9]. Recent studies have found that the effector mechanisms of innate immunity, such as the activation of neutrophil extracellular traps (NETs) and the cytoplasmic DNA sensing pathway cGAS-STING, also play an important role in the chronic inflammation associated with dry eye disease.

3.3 Neural Regulation and Pain Mechanism

Many patients with dry eye syndrome not only experience dryness but also often suffer from varying degrees of ocular pain, such as burning sensation, stabbing pain, foreign body sensation, and even severe pain that does not match the physical signs. A significant portion of these patients can be classified as having neuropathic pain. The mechanism involves sensitization of the trigeminal nerve endings on the ocular surface (peripheral sensitization) and functional remodeling of the pain signal transmission pathway and sensory integration area of the cerebral cortex (central sensitization) [10]. Abnormal activation and expression changes of ion channels such as transient receptor potential vanilloid 1 (TRPV1) and melatonin-related member 8 (TRPM8) have been shown to be closely related to abnormal pain perception in dry eye syndrome. Furthermore, it cannot be ignored that psychological and emotional factors such as depression and anxiety can also exacerbate the subjective symptoms of dry eye syndrome through a complex neuro-immune-endocrine network, forming a complex situation of psychosomatic interaction.

3.4 Hormonal and Metabolic Factors

Sex hormone levels regulate the maintenance of the function of lacrimal and meibomian glands. For example, perimenopausal and postmenopausal women are at high risk of developing dry eye due to decreased estrogen levels. Androgens play a crucial role in maintaining the morphology and function of meibomian glands, and low androgen levels are significantly associated with meibomian gland dysfunction [11]. In addition, systemic diseases such as diabetes can exacerbate or cause dry eye by inducing peripheral neuropathy and microcirculatory disorders, which affect the autonomic nervous function controlling the lacrimal glands and the blood supply to ocular surface tissues.

4. Traditional Chinese Medicine's Understanding of Dry Eye

Traditional Chinese Medicine categorizes dry eye as "Bai Se Zheng" (dry and itchy syndrome) and "Shen Shui Jiang Ku" (the vital fluid is about to dry up), believing that its core pathogenesis is the deficiency of body fluid and the loss of nourishment to the eyes, which is closely related to liver and kidney yin deficiency, lung yin insufficiency, and qi and blood not nourishing the eye orifices. The essence of this disease is deficiency, and superficial excess can be accompanied by dryness-heat, qi stagnation, and blood stasis. Common syndrome differentiation types include lung yin insufficiency, liver and kidney yin deficiency, qi and yin deficiency, liver meridian stagnant heat, and persistent pathogenic heat. Constitutional research shows that people with yin deficiency and qi stagnation constitution are more prone to dry eye [12].

4.1 Syndrome Differentiation and Internal Treatment Principles

Traditional Chinese Medicine (TCM) emphasizes a treatment philosophy that integrates "disease-syndrome-constitution", with internal administration of traditional Chinese herbs as the primary means of holistic regulation:

- Deficiency of lung yin syndrome is characterized by dry eyes and dry nasopharynx. The treatment is to nourish yin and moisten the lungs, with the prescription of Baihe Gujin Decoction modified as appropriate;
- Deficiency of liver and kidney yin syndrome: characterized by dry eyes, blurred vision, soreness in the waist, and dizziness. The treatment involves nourishing the liver and kidneys, and the prescription is based on the modified Qijudihuang Pill;
- Deficiency of both qi and yin syndrome, accompanied by fatigue and weakness, dry mouth without desire to drink, treated with nourishing qi and yin, using Shengmai Powder combined with Zengye Decoction as the prescription;
- Liver meridian stagnation and heat syndrome, accompanied by burning sensation in the eyes and hypochondriac pain, restlessness, and bitter taste in the mouth, treated by soothing the liver and clearing heat, with the prescription of modified Danzhi Xiaoyao Powder;
- Syndrome of persistent pathogenic heat: Presently, the eyes are red, dry, and painful, and the urine is yellow and red. The treatment is to clear heat and dispel pathogenic factors, using a modified version of Sangbaipi Decoction.

4.2 External Treatment and Characteristic Therapies

The external treatment methods of traditional Chinese medicine directly act on the eyes and meridians, offering the advantages of rapid efficacy and minimal side effects [13]:

- Chinese medicine atomization and eye steaming: Select herbs such as chrysanthemum, goji berries, and scutellaria to decoct into a soup and atomize it to improve the ocular surface microenvironment;
- Acupuncture treatment: Commonly used acupoints include Jingming, Cuanzhu, Hegu, and Sanyinjiao, which promote tear secretion by regulating inflammatory factors, sex hormone levels, and neural reflexes [14];
- Muscle-tendon therapy: It focuses on loosening the "muscle-tendon nodules" in the head and neck region, improving local blood circulation and neural regulation function;
- Auricular point application: Selecting acupoints such as those for the liver, kidney, and eyes for continuous stimulation to regulate visceral functions.

4.3 The Value of Integrated Traditional Chinese and Western Medicine Treatment

The characteristics of holistic regulation in traditional Chinese medicine (TCM) exhibit unique advantages in the treatment

of mild to moderate dry eye, refractory hormone-related dry eye, and neurogenic dry eye. The integrated traditional Chinese and Western medicine model can synergize and enhance efficacy, such as the combination of nourishing yin and clearing heat in traditional Chinese medicine with basic treatment of artificial tears, and acupuncture and moxibustion assisting in relieving neural pain. Clinical practice has shown that this model helps reduce the dosage of western medicine and improve patients' quality of life, especially for chronic dry eye patients who require long-term management [15].

5. Treatment Progress

5.1 Pharmacotherapy

5.1.1 Artificial tears and lubricants

Artificial tears are currently the first-line basic medication for treating various types of dry eye. Their purpose is to replace and supplement natural tears, alleviate dryness symptoms, and provide epithelial protection to the ocular surface. Common ingredients include sodium hyaluronate, polyvinyl alcohol, and sodium carboxymethylcellulose, which have good water-retaining properties. New artificial tears have been continuously optimized in their formulations [16], such as adding lipid components to simulate the lipid layer of normal tear film, incorporating vitamin A to promote epithelial repair, or containing bioactive ingredients such as epidermal growth factor (EGF), in order to achieve more active ocular surface repair functions on the basis of lubrication.

5.1.2 Anti-inflammatory drugs

Given the central role of inflammation, anti-inflammatory treatment is key to controlling moderate to severe dry eye [17].

- NSAIDs (Non-Steroidal Anti-Inflammatory Drugs): such as Pranoprofen and Diclofenac Sodium Eye Drops, which reduce the synthesis of prostaglandins by inhibiting cyclooxygenase (COX), are used to alleviate mild to moderate ocular surface inflammation and discomfort. Due to their potential ocular surface toxicity, long-term use is generally not recommended.

- Immunosuppressants: 0.05% cyclosporine A and 0.1% tacrolimus are widely used anti-inflammatory treatments for dry eye globally. They control inflammation at the immune source by inhibiting T lymphocyte activation and inflammatory factor release, making them suitable for long-term use to maintain disease stability.

- Glucocorticoids: They can nonspecifically inhibit various inflammatory pathways and have rapid onset of action, often used for short-term control of acute and severe ocular inflammation. However, due to their potential side effects such as increased intraocular pressure (steroid-induced glaucoma), cataracts, and secondary infections, they must be used under close medical supervision for short-term periods and follow the principle of tapered withdrawal.

5.2 Non-pharmacological Therapy

5.2.1 Physical therapy

- Meibomian gland massage and hot compress: This is the basic physical therapy for treating meibomian gland dysfunction (MGD)-related evaporative dry eye. By applying hot compress to soften the coagulated lipids within the meibomian glands, and then assisting their drainage through massage, the stability of the tear film lipid layer can be restored, thereby improving the situation of excessive tear evaporation.

- Intense Pulsed Light (IPL): IPL technology acts on the eyelid skin through light energy of specific wavelengths, producing photothermal effects and photobiomodulation, which can seal abnormal capillaries, kill microorganisms, reduce inflammation, and promote the recovery of meibomian gland function. It has become an important treatment method for MGD.

- Lacrimal puncta embolization: By temporarily or permanently blocking the punctum or canaliculus, it reduces the drainage of tears from the nasolacrimal duct, thereby prolonging the residence time of the natural or artificial tears on the ocular surface. It is particularly suitable for aqueous deficiency dry eye.

5.2.2 Surgical Treatment

For refractory dry eye that is extremely severe and ineffective to medication and conventional physical therapy, surgical treatment may be considered.

- Submandibular gland transplantation: The autologous submandibular gland is transplanted to the temporal region, utilizing its continuous secretion of saliva-like fluid to moisten the ocular surface. It is primarily used for end-stage dry eye with absolute lack of tear production, such as patients with severe Sjögren's syndrome.

- Corneal nerve transplantation: For nerve paralytic dry eye or neurotrophic keratitis caused by corneal nerve damage, healthy nerve tissue is surgically transplanted to restore corneal sensation and nutritional regulation. This technique is currently still in the exploratory and research phase.

5.2.3 External treatment methods of traditional Chinese medicine

- Chinese medicine atomization and eye fumigation: After decocting Chinese herbs with the effects of clearing heat, detoxifying, nourishing yin, and improving vision (such as chrysanthemum, wolfberry fruit, scutellaria, etc.), an atomization device is used to vaporize and fumigate the medicinal liquid onto the eyes, directly acting on the ocular surface to moisturize, reduce inflammation, and promote circulation.

- Acupuncture treatment: By stimulating specific acupoints such as Jingming, Cuanzhu, Taiyang, Hegu, and Sanyinjiao, research has shown that it can regulate the body's endocrine and immune status, affect the

levels of inflammatory factors, and promote lacrimal gland secretion through the neural reflex arc, thereby improving dry eye symptoms.

- Meridian muscle therapy: Based on the meridian muscle theory of traditional Chinese medicine, it involves loosening the "muscle nodules" (trigger points) in the head and neck region, especially around the eyes, through manual techniques or acupuncture instruments. This is done to alleviate local muscle tension, improve blood circulation and neural regulation functions, thereby indirectly improving ocular conditions.

6. Pain Mechanism and Management Strategies

Dry eye-related pain often manifests in a variety of forms, including burning, stabbing, foreign body sensation, and even sensitivity to light and wind (photophobia and wind allergy). Its mechanism is far more complex than simple tissue damage. Peripheral sensitization refers to the decrease in threshold of ocular surface trigeminal nerve endings due to continuous inflammatory stimulation, resulting in the generation of pain signals even for normal harmless stimuli (such as blinking). Central sensitization refers to the plastic changes in pain signaling pathways and the central nervous system, which amplify and maintain pain perception, even after the original stimulus has been eliminated, resulting in persistent pain [18]. In addition, psychological factors such as anxiety, depression, and catastrophizing thinking can significantly exacerbate the perception of pain and the degree of suffering by affecting the descending inhibitory pathway [19].

For dry eye-related pain, especially the neuropathic pain component, a multidimensional management strategy is required:

- Pregabalin/Gabapentin: As calcium channel modulators, they are first-line drugs for the treatment of neuropathic pain, which can alleviate allodynia by inhibiting abnormal excitation in the central nervous system.

- Low-dose naltrexone: By briefly blocking opioid receptors, it feedback-promotes the secretion of endogenous endorphins and regulates the activity of microglia, exhibiting unique anti-inflammatory and neuromodulatory effects, making it suitable for chronic pain management.

- Cognitive Behavioral Therapy (CBT): A psychological treatment method that assists patients in identifying and modifying negative thought patterns and behavioral patterns related to pain, while fostering positive coping strategies. It has been shown to be effective in alleviating pain distress and enhancing quality of life.

7. Efficacy Evaluation and Disputes

7.1 Efficacy Evaluation Indicators

The efficacy evaluation of dry eye requires a combination of subjective and objective indicators to comprehensively reflect the patient's condition:

- Subjective indicators: The Ocular Surface Disease Index (OSDI) questionnaire is used to assess symptom frequency and impact on quality of life; Visual Analogue Scale (VAS) is used to quantify the severity of pain and discomfort.

- Objective indicators: Schirmer test measures tear secretion; breakup time (BUT) evaluates tear film stability; corneal fluorescein staining observes epithelial defects; tear osmolarity measurement reflects the degree of increase in tear osmolarity; in addition, the detection of tear inflammatory factors (such as MMP-9) is also gaining increasing attention.

7.2 Disputes and Challenges

- Inconsistent diagnostic criteria: Dry eye symptoms (subjective feelings) often do not fully align with clinical signs (objective examination). For instance, in patients with "symptom-dominant dry eye" or "neurogenic ocular pain", symptoms may be pronounced, yet objective examination reveals only mild abnormalities, posing challenges to diagnosis and disease classification.

- Significant variation in treatment response: Due to the heterogeneity and multifactorial nature of dry eye, there is significant individual variation in patients' responses to the same treatment, emphasizing the necessity of individualized treatment strategies.

- Long-term medication safety: Some drugs, such as cyclosporine A, may cause irritating symptoms such as a burning sensation in the eyes; the risk of side effects from long-term use of glucocorticoids still needs to be vigilant [20].

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