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Review Article

Advances in Artificial Intelligence in Dry Eye Disease

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ABSTRACT

Dry eye is the most common ocular surface disease except refractive error, which is often manifested as dryness, foreign body sensation, itching sensation, accompanied by blurred vision, eye acidity, visual fatigue, etc., mild to moderate dry eye has become the most common ocular disease that affects people's daily work, study and life and severe dry eye seriously affects the quality of patients' life and visual quality and may even lead to blindness. At present, the diagnosis of dry eye is relatively subjective and lacks the only certain diagnostic criteria, mostly relying on the rich experience of clinicians and a variety of auxiliary examinations; its treatment mostly relies on topical medication, long-term use of drugs has side effects and the efficacy of the treatment is inconsistent. Therefore, in the new era, in order to help precision medicine, more accurate diagnosis and treatment of dry eye, artificial intelligence came into being, artificial intelligence in dry eye research has made some progress, this paper on the application of artificial intelligence in the field of dry eye to review, in order to form a highly efficient, economical and accurate diagnosis and treatment mode in the future clinical work.

Keywords: Dry eye disease; Ocular surface disease; Artificial intelligence; Deep learning

INTRODUCTION

Dry Eye Disease (DED) is a global health problem with a prevalence of approximately 5%-50% and the prevalence of DED is projected to continue to increase with the aging of the population, prolonged screen time and contact lens wear [1,2]. Inflammatory and immunological factors play an integral role in the pathogenesis of dry eye, which often manifests itself in varying degrees of dryness, foreign body sensation, itching, burning, irritation and visual fatigue and may lead to potential damage to the cornea and conjunctiva or even loss of vision [3,4]. Dry eye affects a wide range of people and the resulting economic burden is high, but the diagnosis and treatment of DED remains a great challenge. Therefore, there is an urgent need for a diagnostic test that can objectively reflect the underlying immune activation, the severity of inflammation and the stability of the tear film, so that even if the clinical signs are not obvious, a clear diagnosis at the microscopic level can still effectively guide the treatment and avoid the use of long-term medication, thus reducing the side effects of medication and the economic burden.

With the advancement of technology and the rapid development of the Internet industry, new and emerging production tools have been born, mainly Artificial Intelligence (AI), big data and block chain. In AI, machine learning refers to a class of algorithms that are able to learn from data, rather than being programmed using explicit rules. Artificial intelligence and machine learning in particular, is increasingly becoming an integral part of the healthcare system, transforming traditional models of care. The subfield of machine learning known as deep learning i.e., deep artificial neural networks has received increasing attention in recent years, particularly for its image and text recognition capabilities and is widely used to solve a variety of medical problems, such as the diagnosis and personalized treatment of cancers, the application of gastroenteroscopy and endoscopy, anaesthesia and perioperative management, assisted reproductive medicine, diagnosis of retinal effusions, retinal splits, macular tears, retinal detachments and pathological high myopic choroidal neovascularisation [5-10]. In the field of ophthalmology, AI initially focused on posterior segment eye diseases such as macular degeneration and diabetic retinopathy and more and more studies have begun to use AI to assist in the

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diagnosis and management of ocular surface disease problems by segmenting the region of interest in an image, automatically diagnosing and predicting the development of the disease [11,12]. In this paper, we describe the application of AI in the field of dry eye, with a view to diagnosing and treating DED more accurately, improving the quality of vision and quality of life of patients and improving work and study efficiency. Powerful machine learning techniques can be used to understand the nuances in the patient's data and in the medical images, aiming at a consistent diagnosis and grading of the severity of the disease.

LITERATURE REVIEW

AI for the diagnosis of DED

Currently, there is a lack of a unique diagnostic index for dry eye and its diagnosis relies on the results of several manual tests, the extensive experience of the clinician and questionnaires in order to avoid as much as possible misses and misdiagnoses, which is more time-consuming and labour-intensive; in other words, the diagnosis of DED is carried out through a combination of tests, some of which are invasive, non-repeatable and lack accuracy [13,14]. When diagnosing DED, most tests are limited to specifying tear deficiency as a sign and fail to detect an underlying inflammatory response, such as the Schirmer test and Tear Break-up Time (TBUT). The Ocular Surface Disease Index (OSDI), on the other hand, is completely subjective as it is a questionnaire. It has been shown that positive corneoconjunctival sodium fluorescein staining is associated with the expression of inflammatory cytokines in dry eye, but some patients may have positive clinical findings without significant conjunctival and corneal staining; therefore, there is a need to explore new perspectives for the diagnosis of dry eye and the use of Artificial Intelligence (AI) technology in ocular surface diseases has many advantages, such as continuous learning, high reliability, automation and good correlation with manual measurements.

Tear break-up time

Tear film instability is one of the pathogenic mechanisms of dry eye, therefore, the correct assessment of tear film stability is crucial for the diagnosis of dry eye; Tear Break-up Time (TBUT) is an important indicator of tear film stability, which is of great significance for the diagnosis of DED [15]. However, traditional TBUT testing methods rely on the subjective judgement of doctors and are susceptible to interference by human factors. AI technology can automatically calculate TBUT values by analyzing video images of the tear film before it breaks up, improving the accuracy and reproducibility of the test.

Vyas, et al. [16], proposed a Tear Film Break-up Time (TBUT)-based dry eye disease detection method using a Convolutional Neural Network (CNN) to detect TBUT videos, which not only diagnosed dry eye but also assessed its severity, with an accuracy of up to 83% and a correlation with ophthalmologist's judgement of 90%.

Tear Meniscus Height (TMH) and Tear Inflammatory Factor (TIF)

The Tear Meniscus Height (TMH) is an indicator of whether tear secretion and drainage are in balance. TMH increases when the tear punctum is narrowed or the tear duct is obstructed and decreases when tear secretion is reduced or evaporation is too strong. Therefore, by detecting the height of the tear river can help clinicians determine whether they are suffering from diseases such as dry eye. A study proposed a tear river height measurement method based on deep learning and image processing, aiming to solve the problems of traditional manual or semi-automatic measurement methods, such as susceptibility to subjective factors, time-consuming and labour-intensive, etc., and achieved accurate segmentation of the tear river through the improved DeepLabv3 architecture, with a high degree of consistency and a correlation coefficient of 0.94 compared to the manual results, which is capable of achieving automatic measurement of tear disc height to assist clinicians in the diagnosis of dry eye [17].

In addition to this, dry eye itself is an inflammatory disease and the detection of inflammatory factors in the tear fluid has an auxiliary role in the diagnosis of dry eye. Professor Lu, et al. [18], team developed a wireless and convenient tear sensor based on Deoxyribonucleic Acid (DNA) nanotechnology, which enables the simultaneous measurement of multiple inflammatory factors (Matrix Metalloproteinases (MMP)-9, Tumor Necrosis Factor (TNF)-α, Interferon (IFN)-γ, Interleukin (IL)-6) in a trace amount of tear fluid (3 μl) at a high sensitivity (detection limit 0.1 pg/ml) and it has been demonstrated that IL-20 is a potential target for the treatment of dry eye disease, the TNF-α blocker HL036337 administered topically at a dose of 1 mg/mL was effective in improving corneal erosion caused by dry eye and topical TNF-α blockers were effective in suppressing lacrimal gland and corneal inflammation by inhibiting IFN-γ, IL-21 and IL-6; therefore, the detection of low concentrations of inflammatory factors in a limited amount of tear fluid could provide a precise diagnosis of dry eye disease provides a new tool [19-21].

Tear osmolarity

The core mechanism of dry eye pathogenesis is the imbalance of tear film homeostasis. Tear film instability caused by various reasons can lead to increased tear osmolarity and high tear depth activates the inflammatory pathway of the ocular surface and promotes the secretion of inflammatory mediators, which causes damage to the ocular surface, which in turn leads to tear film instability and further aggravates tear hyperosmolarity, forming a vicious cycle. Therefore, it is particularly important to detect and interrupt this vicious cycle in a timely manner [22]. Basal tear osmolality can be used as an indicator for assessing the severity of dry eye; therefore, accurate measurement of tear osmolality can effectively guide clinical medication and assess prognosis [23].

Cartes, et al. [24], found that tear osmolarity was significantly higher in the dry eye group by measuring tear osmolarity in dry eye patients and healthy controls and classifying them using machine learning techniques and that the machine learning algorithm was effective in distinguishing between dry eye and healthy states.

Meibomian gland infrared photography and blepharography

The Meibomian Gland (MG) plays a key role in the health of the ocular surface by secreting lipids into the tear film to slow down the rate of tear evaporation and Meibomian Gland Dysfunction (MGD) is the most common cause of dryness in the eyes [25]. AI techniques can provide new perspectives for the diagnosis of DED by analyzing the health of meibomian glands through the analysis of meibomian gland infra-red photography and blepharography images. blepharography images to assess the health of the blepharoplasty glands and provide new perspectives for the diagnosis of DED. Blepharography is the photographic documentation of the meibomian glands in the eyelids using transmitted light or infrared light and is commonly used in dry eye clinics for the diagnosis, treatment and management of MGD.

The relative size of the area of blepharosphenoid atrophy or the area of gland loss is an important clinical indicator for assessing the severity of blepharosphenoid dysfunction. Visual lid gland monitoring is important for assessing the risk of lid gland dysfunction, identifying active pathological changes and tracking treatment outcomes. Blepharoplasty, the photographic recording of the *in vivo* blepharoplasty using transmission or infrared imaging, is now commonly used in the diagnosis, treatment and management of clinical blepharoplasty dysfunction. An automated artificial intelligence method for segmenting individual blepharoplasty regions in infrared blepharoplasty images and analyzing their morphological features, including local contrast, length, width and tortuosity of the gland, was introduced in a study [26].

Wang, et al. [27], collected 706 blepharoplastogram images with corresponding lid scores and annotated each image with eyelid and atrophic areas, according to which the proposed deep learning method automatically segmented the entire eyelid and blepharoplast atrophic area and calculated the percentage of atrophy with high accuracy and consistency of the algorithm, which has a very high performance. Accuracy rates of 97.6% and 95.4% were achieved for the eyelid area and atrophy area, respectively, which provided quantitative information on the severity of glandular atrophy based on the blepharoplasty images.

It follows that the health and morphology of the meibomian glands may be related to the quality of the lipid layer and the stability of the tear film. If these detailed morphological features can be obtained and quantified quickly and accurately, this would provide a reference point for clinicians to confirm the diagnosis of dry eye. In the long term, the proposed diagnostic tool could make a significant contribution to improving the diagnosis, treatment and long-term management of tear film instability and hyper-evaporative dry eye.

Anterior Segment-Optical Coherence Tomography (AS-OCT)

The key benefits of Anterior Segment Optical Coherence Tomography (AS-OCT) include rapid, non-contact, *in vivo* and quasi-histological imaging of corneal structures, which can provide cross-sectional images of the lacrimal meniscus as well as quantitative assessment of lacrimal parameters, such as the height and area of the lacrimal meniscus, which may be useful in the diagnosis and treatment of DED.

Chase, et al. [28], evaluated and found that the accuracy of the AS-OCT deep learning model was significantly better than corneal conjunctival staining and the Schirmer test in the diagnosis of dry eye disease ($P<0.05$), which achieved an accuracy of 84.62%, a sensitivity of 86.36% and a specificity of 82.35% in the diagnosis of dry eye disease, but compared with the diagnostic accuracy of OSDI and TBUT did not differ significantly. In addition, another scholar applied AS-OCT to measure the thickness of corneal epithelium and found that the epithelial cells were significantly thinner in the DED group compared with the control group and the diagnostic algorithm had high sensitivity (86.4%) and specificity (91.7%), suggesting that the integration of OCT corneal epithelial specimen measurement data into the diagnostic algorithm using AI may improve the reliability of DED diagnosis [29].

In Vivo Confocal Microscopy (IVCM)

In Vivo Confocal Microscopy (IVCM) is an emerging non-invasive technique for real-time observation of ocular surface tissues and microstructures, which is widely used for observing the microscopic morphology of the cornea at the cellular level. The ICVM of patients with dry eye is often characterized by the disordered arrangement of nerve fibers under the corneal epithelium and the loss of parallelism. The ICVM of dry eye is often characterized by the disordered arrangement of nerve fibers under the corneal epithelium, loss of parallelism, large nerve curvature and many branches. The ICVM of dry eye patients often shows that the sub-epithelial nerve fibers of the cornea are disarranged and lose parallel alignment and the nerves have large curvature and many branches. Some researchers have assessed the corneal nerve morphology and the number of Langerhans Cells (LC) in DED by IVCM, which used the Corneal Nerve Segmentation Network (CNS-Net), a deep learning model for measuring corneal nerves, i.e., combining the Pentacam, IVCM and Oculus corneal maps to assess the individual ocular status of DED and the results showed that the AI techniques obtained changes in corneal nerve morphology (i.e., mean density and maximum length) were significantly correlated with intrinsic corneal aberrations. Jing, et al. [10], team similarly combined the Oculus corneal topographer, IVCM and Pentacam HR system to analyses and investigate the changes in sub-corneal nerve morphology and corneal intrinsic refractive error in patients with DED and found that there was a significant correlation between LC and corneal intrinsic refractive error, especially higher-order refractive errors in patients with DED with reduced sub-corneal nerve density and maximum length.

Currently, there are fewer clinical trials on the use of ICVM for the diagnosis of dry eye and large-scale clinical testing remains to be performed.

DISCUSSION

With the continuous development of artificial intelligence technology, its application in dry eye diagnosis and treatment has become increasingly widespread. This paper mainly describes the research progress of applying AI to diagnose dry eye in recent years. Artificial intelligence can achieve efficient and accurate diagnosis of dry eye by analyzing information such as patients' symptoms, signs and eye images. The application of AI in the diagnosis and treatment of dry eye is promising, showing the possibility of using deep learning methods for clinical diagnosis of ocular surface diseases. New investigations can be realized through automated and quantitative assessments, opening up many exciting opportunities for targeted medical and drug discovery. However, further research and exploration is needed to improve its accuracy and reliability to provide better diagnostic and therapeutic options for dry eye patients.

CONCLUSION

Although AI has shown great potential in DED diagnosis and treatment, it still faces some challenges and limitations. Firstly, the training of AI models requires a large amount of data support and the current data on DED is not yet abundant enough; secondly, the interpretability of AI models needs to be improved. Finally, the application of AI technology needs to meet the requirements of ethics and laws and regulations to ensure patient privacy and data security. Looking forward, with the continuous development and improvement of AI technology, its application in the diagnosis and treatment of DED will be more extensive and in-depth. Through interdisciplinary cooperation and technological innovation, we are expected to overcome the current challenges and limitations and provide more accurate and personalized diagnosis and treatment services for DED patients. At the same time, the development of AI technology will also promote the progress and innovation of ophthalmology, providing more possibilities for the prevention and treatment of ocular surface diseases.

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