

Dry eye disease caused by viral infection: review

Olho seco causado por infecções virais: revisão

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ABSTRACT

Dry eye disease and ocular surface disorders may be caused or worsened by viral agents. There are several known and suspected virus associated to ocular surface diseases. The possible pathogenic mechanisms for virus-related dry eye disease are presented herein. This review serves to reinforce the importance of ophthalmologists as one of the healthcare professional able to diagnose a potentially large number of infected patients with high prevalent viral agents.

Keywords: Dry eye syndromes/diagnosis; Eye infections, viral; Eye infections

RESUMO

A síndrome do olho seco e as doenças de superfície ocular podem ser causadas ou agravadas por agentes virais. Diversos vírus são causadores ou tem associação suspeitada com as doenças de superfície ocular. Esta revisão apresenta os possíveis mecanismos patogênicos envolvidos no olho seco causado por infecções virais e reforça a importância do oftalmologista como um dos profissionais de saúde capazes de diagnosticar um grande número de pacientes infectados por agentes virais altamente prevalentes.

Descritores: Síndromes do olho seco; Infecções oculares virais; Infecções oculares

INTRODUCTION

Dry eye disease (DED) and ocular surface disorders may be caused or worsened by viral agents. There are several known and suspected virus associated to DED⁽¹⁻³⁾. The pathogenic mechanisms and therapeutic approach for virus-related DED are reviewed herein.

The ocular surface comprises a unique and vital component of vision. The interface composed by cornea transparency and the tear film is a major refractive surface of the visual system⁽⁴⁻⁶⁾. All components of the ocular surface are intrinsic linked by the continuity of the epithelia to the tear film and by the reflex innervation and the endocrine, vascular and immune systems. The synergic function of the ocular surface components and the harmonic influence of the sensory and motor nerves, hormones and fluids are responsible for the maintenance of a regular, comfortable and perfect refractive surface⁽⁷⁻⁹⁾. In this context, viral infections might cause direct damage to the ocular surface, such as herpes virus or indirectly through interference in lacrimal gland function.

DED is a widely prevalent and multifactorial disorder involving multiple interacting mechanisms and a great range of signs and symptoms. Dysfunction of any component of the ocular surface and/or tear film can lead to dry eye causing lower tear secretion, alterations in its composition and distribution and eventually leading to epithelial damage and inflammation⁽⁴⁾.

Sjögren syndrome is one of the most complicated forms of DED. It is a chronic disease affecting exocrine glands, mainly lacrimal and salivary ones, but also organs and systems can be involved. It is characterized by an aggressive lymphocytic infiltration and circulating autoantibodies that lead to damage and dysfunction of glands and target organs⁽¹⁾. Although the pathogenesis of Sjögren Syndrome

is considered a multifactorial process, it has been postulated that some viral infection could play a significant role on initiating and/or perpetrating the autoimmune response⁽¹⁰⁾.

Viruses can trigger autoimmune reactions through several mechanisms affecting different tissues in both animal models and humans. Virus infection can induce neoantigen expression due to molecular mimicry between viral and host antigens resulting in the production of autoantibodies, cytotoxic T-cell or both directed to different host tissues⁽¹¹⁾. Once the innate immune response is initiated in glandular and dendritic cells there is an up-regulation of adhesion proteins and an increased production of chemokines that become activated and start acting as antigen-presenting cells. Those events could eventually lead to overproduction of immunoglobulins, autoantibodies and memory lymphocytes and subsequently tissue damage and dysfunction due to apoptosis and inflammation⁽¹²⁾.

The occurrence of Sjögren syndrome-like illness, reported as dry eye symptoms or signs, in patients having confirmed viral infections, such as human T-cell lymphotropic virus (HTLV), human immunodeficiency virus (HIV), Epstein-Barr virus (EBV), and hepatitis C virus (HCV), as well as the beneficial effect of anti-viral treatment, brings circumstantial evidence that their mechanism maybe pathogenically associated^(3,13).

The aim of this review is to summarize the knowledge on the role of virus infection in the pathogenesis of DED, plausible mechanisms and implications for diagnosis and therapeutic strategies.

VIRAL INFECTIONS RELATED DO DRY EYE

The best-studied viral agents related to systemic infection and DED manifestation are HTLV, HIV, HCV and EBV. Table 1 shows major characteristics of those viruses.

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The potential pathogenic mechanisms to DED associated to the viral infection in the lacrimal gland are the following:

HTLV

The human T-cell lymphotropic virus (HTLV) infection is endemic in Japan, the Caribbean basin, Central and South America and Africa. It is transmitted through sexual intercourse, breast-feeding, blood transfusion and sharing of contaminated syringes and needles. HTLV is characterized by asymptomatic infection in most of seropositive cases. Although 90% of the approximately 20 million infected people worldwide remain asymptomatic carriers during their lives, HTLV infection is also associated with systemic and ocular complications⁽¹⁴⁾.

HTLV infection is etiologically linked to two potential fatal diseases: 1) the malignant proliferation of T cell causing the adult leukemia/lymphoma (ATL) and 2) a neuromyelopathy known as tropical spastic paraparesis (TSP). ATL is considered an aggressive lymphoproliferative malignancy with short survival in its acute form, occurring in less than 5% in HTLV infected people. TSP is a chronic meningomyelitis in the spinal cord, with demyelination and axonal degeneration leading to the development of a slowly progressive spastic paraparesis, high impairment of gait, autonomic dysfunction and profound repercussions on abilities and quality of life of the patients^(15,16). HTLV also causes dermatitis, pneumonia, polymyositis, thyroiditis and Sjögren's like syndrome⁽¹⁶⁾.

HTLV ocular lesions may present as uveitis, dry eye, keratitis and retinal vasculitis⁽¹⁷⁾. The prevalence of uveitis is controversial in different parts of the world. In Japan, for instance, a 35.4% prevalence of uveitis in patients infected with HTLV was observed, while in Martinique, the prevalence was 14.5%⁽¹⁸⁾. The incidence of dry eye in seropositive patients was 36.4% in study conducted in the region of highest prevalence of HTLV infection in Brazil. Moreover, 54.4% of DED in TSP patients and 20.3% in asymptomatic seropositives. In those patients immunophenotyping analysis shown high levels of both CD4+ and CD8+⁽¹⁹⁾. Another study, evaluating 200 infected patient found 37% of DES accompanied by lymphoplasmocytoid infiltration of secondary salivary gland^(20,21).

Serological studies demonstrated the prevalence of antibodies to HTLV in Sjögren patients ranging from 23-36%, significantly higher

than that among blood donors. Salivary IgA antibodies to HTLV were found in seropositive HTLV patients with SS^(22,23). Indeed, two independent studies confirmed the presence of HTLV genome in salivary glands samples from patients with Sjögren^(24,25).

HIV

HIV (human immunodeficiency virus) infection may present with a large variety of primary and secondary (caused by opportunistic infections) ocular manifestations, some of those have threatening potential to vision and life quality. The incidence and presentation of the AIDS epidemic and its correlated complications have dramatically changed since the introduction of the potent antiretroviral therapies (also know as highly active antiretroviral therapy, or HAART), but remains as a dramatic public health in very low income countries.

DED appears to be much more prevalent among individuals with AIDS (21.4-38.8% of HIV-infected men, 16.9% of HIV-infected women) than in the general population^(13,26,27). Burtin et al. evaluated the ocular surface and DED complains in a group of HIV positive patients. According to this study, 70% of them had complained of DED symptoms, 85% present at least one clinical sign of ocular surface dysfunction tested through Schirmer test, tear break-up time and lissamine stain and the impression cytology revealed a decrease in the number of dendritic cells⁽²⁸⁾.

Geier et al. showed that decreased tear production occurs in approximately 20% to 25% of patients with HIV infection without correlation with the CD4+v lymphocytes blood count, or to the severity of HIV disease, in a group of 144 HIV patients⁽²⁹⁾. Although the entire pathogenesis of the aqueous tear deficiency in HIV-infected remain unclear, it may be associated with lymphocytic infiltration and destruction of the lacrimal gland acini and ducts.

In fact, a Sjögren's syndrome-like picture may be present in HIV-infected patients who develop the diffuse infiltrative lymphocytosis syndrome (DILS). Thus, it is an exclusion criteria for individuals under investigation for Sjögren syndrome⁽³⁰⁾. DILS is a disorder in patients with HIV infection that is characterized by the enlargement of salivary and lacrimal glands and a varying intensity of DED symptoms. In addition, DILS is accompanied by persistent circulating and infiltration of CD8-positive lymphocytes. DILS may mimic Sjögren's syndrome in

Table 1. Major characteristics of virus associated to dry eye disease

Virus	Type	Major clinical manifestation	Major ocular manifestation	Transmission
HTLV	Retrovirus (Oncornavirus)	Adult T-cell leukemia/lymphoma Neuromyelopathy	Uveitis Dry eye	Blood and blood products transfusion, breastfeeding; sexual intercourse
HIV	Retrovirus (Lentivirus)	Acquired immunodeficiency syndrome	Dry eye	Sexual intercourse; blood and blood products transfusion; maternal fetal; injection drug users;
HCV	RNA virus (Flavivirus)	Hepatitis Cirrhosis Liver failure Hepatocellular carcinoma Extrahepatic manifestations (e.g. glandular, renal, dermatological, hematological, joints)	Retinopathy Scleritis Keratitis Dry eye	Injection drug users; blood and blood products transfusion; needlestick injuries in health care settings; sexual intercourse (rare); maternal fetal (rare); contaminated needles and instruments (tattoo, piercings)
EBV	DNA virus (Herpesvirus)	Infectious mononucleosis Burkitt's lymphoma Nasopharyngeal carcinoma	Dry eye	Exchanging of saliva Direct contact
HSV-1	DNA virus (Herpesvirus)	Mucocutaneous lesions (typical oral and skin watery blisters) Meningitis, encephalitis, Bell's palsy	Keratitis Blepharitis Conjunctivitis Uveitis Retinitis	Direct contact

HTLV= human T-cell lymphotropic virus; HIV= human immunodeficiency virus; HCV= hepatitis C virus; EBV= Epstein-Barr virus; HSV-1= herpes simplex virus-1.

terms of symptoms and parotid and lacrimal glands involvement. On the other hand, it differs by the high frequency of extra glandular sites of lymphocytic infiltration, such as lungs, muscles and liver, scarcity or absence of serum autoantibodies and the nature of infiltrating lymphocytes. While in Sjögren syndrome presents lymphocytic infiltration of CD4+ and in DILS it is a CD8+ lymphocytes and anti-Ro and anti-La are seen less frequently^(2,31). The prevalence of DILS had dropped significantly after the introduction of HAART, indirectly inferring that the HIV infection contributes to DILS pathogenesis.

HEPATITIS C

Hepatitis C virus (HCV) is frequently associated with autoimmune features and extra hepatic manifestations, especially with chronic infection⁽³²⁾. The prevalence of HCV infection in patients with primary SS have been analyzed in different studies and its is comparatively higher than in the general population although varying geographically^(3,33,34).

Ocular manifestations such as retinopathy, scleritis and keratitis have been well documented⁽³⁵⁾. Cacoub et al. evaluating a group of 312 HCV patients found xerostomia and/or xerofthalmia symptoms in 10%⁽³⁶⁾ which makes the ocular surface one of the most important sites of manifestations in HCV infected patients⁽³⁷⁾.

Both entities, Sjögren syndrome and HCV, are characterized by B-cell hyperactivity although related to different etiologies, autoimmune and infectious respectively. HCV have demonstrated capability to infect and replicate in the salivary and lacrimal gland tissues leading to lymphocytic infiltration, signs and symptoms of SS. Patients with Sjögren syndrome associated to HCV infection have demographic, immunological and clinical different profiles. Comparatively, Sjögren syndrome-HCV patients are older aged, higher incidence of extra glandular manifestations, especially cryoglobulinemia, and have negative Ro/La antibodies and hypocomplementemia.

Again the American European criteria for Sjögren syndrome, exclude Sjögren diagnosis in patients who are HCV positive⁽³⁰⁾.

EBV

EBV (Epstein Barr virus) is herpes virus that infects epithelial cell located in oropharyngeal tissues, salivary glands and B-lymphocytes. The virus occurs worldwide and most people become infected with EBV during the first two decades of life. In the United States, as many as 95% of adults between 35 and 40 years of age have been infected. Primary EBV infection is usually asymptomatic and resolves spontaneously. Occasionally, EBV infection may cause infectious mononucleosis characterized by fever, pharyngitis and general lymphadenopathy⁽³⁸⁾. After the primary infections it remains latent and occasionally reactivates in salivary glands⁽³⁹⁾. EBV infection of B cell activates intrinsic pathway that results on continuous cellular division and consequently lymphoproliferation.

There is increasing evidence suggesting that EBV infection may be related to lacrimal gland lymphocytic proliferation of Sjögren syndrome, which leads to decreased aqueous tear production and severe DED^(40,41). Many studies have reported primary Sjögren syndrome development immediately after serological confirmation of infectious mononucleosis⁽⁴²⁻⁴⁴⁾. EBV genome has been amplified from the majority of lacrimal gland biopsies of Sjögren patients postulating that EBV may be considered a risk factor for the lacrimal gland pathologic mechanisms of Sjögren syndrome⁽⁴³⁾. Salivary and lacrimal glands differ in the type of EBC infection observed in biopsies from Sjögren patients. Minor salivary gland shows CD4 T cells infiltration and less severe inflammation. On the other hand, in lacrimal gland biopsies the infiltrating cell type is predominately B-lymphocytes and EBV antigen and EBV DNA are detected in ductal epithelia associated high levels of lymphoproliferation surrounding infected ducts or foci replacing secretory acini⁽⁴⁵⁾.

HSV AND OCULAR SURFACE

HSV-1 (herpes simplex virus-1) ocular infection is a common cause of ocular surface disorder. It can present in a broad range of manifestations from primary blepharconjunctivitis to recurrent forms of keratitis and even intraocular involvement as that seen in retinitis and uveitis^(46,47). Although there is no evidence of HVS direct infection in the lacrimal gland it has been demonstrated that corneal sensation and tear production are significant lower in patients with ocular herpetic disease^(48,49).

CONCLUSIONS

Circumstantial evidence suggests that systemic and ocular viral infections, along with many environmental and other risks factors, may play an important role in the pathogenesis of dry eye disease. Patients with moderate to severe dry eye disease and other clinical manifestations should be investigated by serology of mentioned viral systemic infections. Many studies confirmed the association of viruses and lacrimal gland dysfunction and many others have been addressed efforts to the understanding its mechanisms. Future research should characterize this subpopulation, the application of diagnostic tools and the possible benefits of specific antiviral treatment as a therapeutic approach for dry eye disease.

Finally, the present review reinforces the importance of ophthalmologists as one of the healthcare professional able to diagnose a potentially large number of infected patients with high prevalent viral agents. Moreover, it may contribute to make more widely known the possible association between viral infections and dry eye disease and the importance of including an ophthalmologic evaluation as part of the medical approach to patients infected with specific chronic viral infections.

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