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Treatment and non-treatment related ocular manifestations in patients with chronic hepatitis B or C

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Abstract. – BACKGROUND: Worldwide, 480-520 million people are chronically infected with hepatitis B or C virus. In addition to their effects in the liver, chronic hepatitis viral infections may have serious extra hepatic manifestations. These manifestations have been more widely studied in chronic HCV infection, where they are more frequently described, but they have been also reported chronic HBV infection.

AIM: Among those, of great interest are the ocular manifestations caused by the HBV or HCV infection or induced by chronic hepatitis therapy. These we attempted to review.

MATERIALS AND METHODS: A PubMed search was conducted using the terms hepatitis, ocular, eye.

RESULTS: This article describes the ocular symptoms related to HBV and HCV hepatitis such as xerophthalmia, Mooren's ulcer and retinopathy as well as other rare manifestations caused by either the infection or the therapy.

CONCLUSIONS: The ocular manifestations of HCV infections best supported by the literature include a dry eye syndrome similar to Sjögren's syndrome, and ischemic retinopathy caused by either HCV-induced vasculitis or treatment with interferon. There are no serious ocular manifestations of HBV infection other than dry eye syndrome. Special consideration should be held for possible connection between HBV vaccine and uveitis.

Key Words:
Ocular manifestations, Hepatitis B, Hepatitis C, Eye, Interferon.

Introduction

Viral hepatitis B and C are contagious liver diseases caused by hepatitis B virus (HBV) and hepatitis C virus (HCV), respectively. HBV is a 42-nanometer, partially double-stranded DNA virus classified in the Hepadnaviridae family while HCV is a 55-nanometer, enveloped, positive-strand RNA virus classified as a separate genus, Hepacavirus, in the Flaviviridae family[1].

The global epidemic of hepatitis B and hepatitis C is a serious public-health problem. Worldwide, about 1 in 12 persons (480-520 million people) are chronically infected with HBV or HCV although a vaccine against HBV exists since 1981. Hepatitis B and C kill approximately 1,5 million people in the world each year[2].

The current treatment option for chronic HCV infection consists of a combination of pegylated interferon-alpha (peg-IFN-alpha) and ribavirin. Unfortunately, these limited treatment options often produce significant side effects, and currently, complete eradication has not yet been achieved for the majority of chronically HCV-infected individuals. There are two types of drugs available to treat chronic hepatitis B virus (HBV) infection: interferons that boost the immune system, and antiviral or nucleoside analogues that are designed to interfere with HBV DNA to prevent its replication. However, hepatitis B treatment only rarely leads to "cure", although very effective at controlling or suppressing the hepatitis B virus.

Apart from liver disease, these viral infections are known to be associated with a wide spectrum of extra hepatic manifestations like the possibility to infect not only hepatic but also lymphatic cells and to associate with extra hepatic disorders of an autoimmune and/or lymphoproliferative nature. These characteristics have been more widely studied in the case of chronic HCV infection, where they are more evident, but have also been described in HBV. Among the best-reported extra hepatic complications of HCV infection are cryoglobulinemia, glomerulonephritis, high titer of autoantibodies, idiopathic thrombocytopenic purpura, lichen planus, Mooren's corneal

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ulcer, Sjögren's syndrome, porphyria cutanea tarda and necrotizing cutaneous vasculitis, while hepatitis B virus has been well recognized as causing a variety of manifestations including skin rash, arthritis, arthralgia, glomerulonephritis, polyarteritis nodosa, and papular acrodermatitis. The precise pathogenesis of these has not been determined, although the majority represents the clinical expression of autoimmune phenomena[3,4]. Although no pathognomonic manifestation of HCV infection in the eye has been demonstrated, associations between HCV infection and various ocular syndromes have been reported in small case series and individual patients. The ocular manifestations of HCV infections best supported by the literature include dry eye syndrome similar to Sjögren's syndrome and ischemic retinopathy caused by either an HCV-induced vasculitis or treatment with interferon[5]. While HBV infection has not been directly associated with ophthalmic disease there is a well-documented connection between interferon therapy and ischemic ocular diseases as well as a hypothesis of hepatitis B vaccine and uveitis association[6]. In this review the main ocular manifestations of hepatitis infection are described and therapeutic implications discussed (Table I).

Ocular Manifestations in Chronic HCV Patients

Anterior Segment

Dry Eye

Severe ocular surface damage and signs of dry eye are commonly present in patients affected by hepatitis C[7]. Complicated immunological mechanisms leading to focal lymphocytic infiltration of the lacrimal glands seem responsible[8]. This inflammation procedure probably results in decreasing tear production. Several studies address this issue.

Gumus et al[9] showed that patients with hepatitis C scored significantly worse in all parameters used for xerophthalmia testing (Schirmer's test with and without anesthesia, tear film break up time, corneal and conjunctival lissamine green staining scores) while advanced stages of hepatic fibrosis correlated to significantly lower values of tear film breakup time and worse Ocular Surface Disease Index (OSDI) scores. Similar conclusions were reached by Jacobi et al[10] who used Jones test to measure tear production and Abe et al[11] who studied tear lactoferrin concentration levels as means of investigating the dry eye condition in patients with chronic Hepatitis C.

Standard of care in HCV infection is interferon alpha plus ribavirin. Studies [12,13] have documented an impairment of tear dynamics and squamous metaplastic changes on the ocular surface of patients under treatment. It has been also observed that these alterations may persist even 6 months after its discontinuation.

Mooren's Ulcer

Mooren's ulcer is a rare, idiopathic disease characterized by progressive, circumferential, peripheral, stromal ulceration. The exact etiology is uncertain. The presence of an autoimmune process directed against a specific target antigen in the corneal stroma is hypothesized.

Various case reports associate Mooren's ulcer with HCV infection[14-18]. First in 1993 Wilson et al[14] reported 2 chronic HCV patients suffering from severe bilateral corneal ulceration. HCV treatment with interferon alpha 2b led to symptomatic and objective improvement, followed by resolution of the corneal disease. The probability of two consecutive patients coincidentally affect-

Table I. Ocular manifestations of viral hepatitis

	Anterior segment	Posterior segment
HBV	• Dry eye • Uveitis (possible relation with HBV vaccine)	Age related maculopathy
HCV	• Dry eye • Mooren's ulcer • Peripheral ulcerative keratopathy and scleritis • Trichomegaly of eyebrows • Myasthenia Gravis	• Retinopathy HCV correlated or treatment induced • Central vein thrombosis • Cystoid macular edema • Nonarteritic anterior ischemic optic neuropathy (NAION) • Optic neuropathy • VKH (Vogt-Koyanagi-Harada)

ed by Mooren ulcer and HCV was estimated to 1:10,000. Cunningham and Wilson[16] acknowledged 14 similar patients who responded to hepatitis treatment. Jain et al[19] concluded that there is no need for screening asymptomatic chronic HCV patients for corneal ulceration.

Mechanisms suggested for inducing keratitis in HCV patients include antigenic mimicry in which host immunity against hepatitis C antigen cross reacts with epitopically similar autoantigens and immune complexes deposition in the cornea. The concentration of HCV RNA is higher in the tear fluid than in the plasma, so the exposure of the ocular surface to a relatively higher viral antigen load is possible[20, 21].

Other Rare Manifestations

One case of necrotizing scleritis and peripheral ulcerative keratopathy (PUK) associated with HCV related cryoglobulinemia, probably as first manifestation of small vessel vasculitis, has been described. The patient responded to steroids combined with pegylated interferon alpha 2b and ribavirin[22]. Ku and Sharma[23] reported a single case of posterior subcapsular cataract in a patient with confirmed hepatitis, during treatment. It is notable that the patient had no ocular history including trauma, no other past medical history and was not on any medications such as steroids that would account for the development of cataract. An unusual adverse effect during treatment of hepatitis C is eyelashes trichomegaly[24-32]. It is attributed mostly to interferon and seems dose defendant and there is no proposed mechanism. Even after discontinuation of the therapy trichomegaly remained. There are rare cases of ocular myasthenia presenting with ptosis and diplopia during pegylated interferon and ribavirin treatment[33-35]. Discontinuation of the therapy led to rapid improvement in most cases.

Posterior Segment Manifestations

Retinopathy Correlated with HCV Infection

Ischemic retinopathy is commonly seen in patients infected with HCV and many consider it a manifestation of systemic vasculitis induced by the infection.

Abe et al[36] first reported HCV-associated retinopathy in 1993 and described patients with retinal hemorrhages and cotton-wool spots typical to ischemic retinopathy. In 1995 the Authors expanded their study[37] through a prospective randomized clinical trial in which 85 untreated patients with chronic hepatitis C were compared to 100 matched control subjects. They reported a prevalence of idiopathic retinopathy in chronic HCV patients of 31.8% in at least one eye, compared with 6% in the control group ($p < 0.001$). Binocular retinopathy in the study group occurred in 51.9% of cases. In these patients the most common lesions reported were posterior pole retinal hemorrhages, followed by cotton-wool spots and peripheral retinal hemorrhages. Myers et al[38] reported a single case of Purtscher-like retinopathy in a chronically infected HCV patient with type II mixed cryoglobulinemia. Ophthalmoscopy revealed peripapillary cotton-wool spots and superficial retinal whitening in the macula.

Possible mechanism suggested for the appearance of retinopathy in HCV infection is a pathogenic sequence in which microemboli from complement-tagged immune complexes result in vaso-occlusion. The complement mediated immune pathway may lead to granulocyte aggregation within the retinal vasculature, which, in turn, leads to the release of inflammatory mediators and ischemia[39].

Interferon treatment, used routinely against HCV, has been known to induce unilateral or bilateral retinopathy. Several clinical studies have evaluated the prevalence of ocular complications associated with the use of interferon for the treatment of HCV.

First it was recognized in 1990 when Ikebe et al[40] reported a 39 year old patient who developed retinal hemorrhages and cotton wool spots following intravenous administration of interferon. The reported frequency varies from 18 to 86%[41-44], depending on the study design, with higher rates in those including a high induction dose of IFN[41,4]. Interferon monotherapy is associated with a prevalence of retinopathy of 24-58%[26,42,45] while interferon-ribavirin combination with a prevalence of 16%-64%[46-50]. The first retinal lesions were recognized in the first weeks after initiation of treatment. They were small and in most cases resolved spontaneously after cessation of treatment. Diabetes mellitus is an independent risk factor in the development and progression of interferon associated retinopathy[41,42,44], while age and hypertension remain important risk factors whether it is induced by IFN or not[26,41,42,44,51]. Its appearance seems dose dependent with various reports showing an increased frequency in patients on higher and more frequent doses[43].

Retinopathy, as well as other ophthalmic complications, is infrequent in children treated for hepatitis C (2-3%) as it is shown in the PED-C trial[52].

The exact pathogenesis is not known but is presumably related to the disturbance in retinal microcirculation[53,54], thus, preexisting arteriosclerosis that affects microcirculation may promote interferon induced retinopathy. Guyer et al[55] speculated that IFN-alpha therapy may cause deposition of immune complexes in the retinal vasculature. This leads to leukocyte infiltration with subsequent retinal ischemia which itself leads to capillary non perfusion, retinal hemorrhage and cotton wool spots formation. Additional studies, using a rat model of retinal microcirculation, proposed that interferon, after activating leucocytes, increased leukocyte adherence to the vascular endothelium, trapping these cells in the retinal capillaries. These activated leukocytes and the toxic substances generated result in the capillary infarction observed during interferon associated retinopathy[56,57].

IFN induced retinopathy is of benign nature, rarely symptomatic and may resolve spontaneously or after cessation of interferon. Therapy may usually be continued in asymptomatic patients as long as there is careful fundoscopic examination[58].

Vascular Manifestations

Isolated cases of decreased or even complete loss of vision after retinal vascular thrombosis, optic neuritis, macular edema or papilledema have been reported during chronic HCV treatment with pegylated interferon[59].

Retinal vein and artery thrombosis is a rare complication described in HCV patients treated with interferon. Interferon therapy is known to induce a number of thrombogenic autoantibodies, including cryoglobulins, anti-nuclear, anti-smooth muscle, anti-liver microsomal, antithyroglobulin and anti-phospholipid antibodies which are thought to play a role in the pathogenesis of a hypercoagulable state[60-64].

There are three published cases of cystoid macular edema accompanied by visual loss in HCV patients while in treatment[65,66,67].

Anterior Ischemic Optic Neuropathy (AION) has been reported in patients treated for HCV[68-71]. In these cases therapy was discontinued and prednisolone was initiated. A single case of bilateral Nonarteritic Anterior Ischemic Optic Neuropathy (NAION) in an HCV infected patient which remained unaffected by the successful treatment of the viral infection was reported in 2008[72].

Optic neuropathy has been described to occur in 20.3% of patients under treatment, as proved by prolonged visual evoked potential[73].

Other Rare Posterior Segment Manifestations

VKH (Vogt-Koyanagi-Harada)-like disease during interferon therapy is another, rare, ocular manifestation affecting HCV patients. To our knowledge only ten cases of VKH in patients with HCV infection under an IFN-a course have been reported in the literature[70,74-80]. It is an autoimmune disorder involving the eyes causing mainly granulomatous panuveitis associated with exudative retinal detachments as well as skin, hair (vitiligo, poliosis and alopecia), ear and meninges (meningitis, cranial nerve palsy, focal signs, dysacusis, hearing loss) symptoms. The diagnosis is confirmed by retinal fluorescein angiography that shows typical pin-points and bilateral serous retinal and pigmented epithelial detachments. In all the cases of VKH associated with hepatitis C, the intraocular inflammation responded to systemic corticosteroid treatment plus discontinuation of antiviral agents.

Ocular Manifestations of HBV Infection

Hepatitis B virus can be detected in the eye as a number of studies have reported the detection of HBsAg in tears and aqueous humor of HBsAg seropositive patients[81,82]. Temel et al[81] noted that 7 of 10 HBsAg-seropositive patients also tested positive for HBsAg in tear and aqueous humor samples on the day of cataract surgery[80]. Similarly, Koksal et al[82] found that 85% of HBsAg-positive patients also tested positive for HBsAg in tear samples. There have been also reports of HBV detection in aqueous humor using PCR[83]. Although these findings make ocular manifestations of chronic hepatitis B infection possible, extensive review of the literature did not reveal many such reports. Sicca syndrome or dry eye has been positively associated with chronic HBV infection in two studies. Thus, Wang et al[84] reported that 12,007 patients, seeking care for dry eye symptoms, when compared with 36,021 randomly selected patients in the comparison group, without dry eye disease, were more likely to have chronic hepatitis B infection with an Odd's ratio of 1.64. Likewise sicca syndrome was also observed among other extrahepatic manifestations of chronic HBV infection in the Cacoub et al[85] multicenter, retrospective, cross-sectional study involving 190 HBsAg-positive patients.

Another interesting study by Roh et al[86] determines HBV infection as a distinct risk factor for age-related maculopathy. After adjusted multivariate analysis for socioeconomic factors such as education level and monthly income in this study, HBsAg ($p < 0.001$; OR 2.736; 95% CI 1.588-4.714) and anti-HBc antibody ($p < 0.05$; OR 1.475; 95% CI 1.092-1.992) were significantly associated with age-related maculopathy. The statistical significance of both HBs antigen and anti-HBc antibody in age-related maculopathy suggest that there is less opportunity than that this association is by chance alone ($1/20 \times 1/20 = 1/400$). There is a biologic plausibility underlying this association. First, HBs Ag is found in subretinal fluids with an increased detection rate of antibodies to S-antigen in healthy virus carriers, increasing thus the risk for uveoretinal pathology[87,88]. This inflammatory process may induce drusen formation. Secondly, molecular mimicry between retinal S-antigen and Hepatitis S antigen can induce cross reactivity which can predispose to uveoretinal inflammation[89,90]. Furthermore, as viral hepatitis is associated with decreased level of complement C3, C4 and complement factor H related protein 1[91], this may activate the alternative complement pathway, thereby increasing the risk of drusen formation[92]. Finally past studies trying to demonstrate implication of chronic HBV infection in the aetiology of uveitis did not prove any such connection[93,94].

Current treatment for chronic HBV infection consists of interferon or nucleos(t)ide analogues. Ocular side effects of interferon therapy are discussed extensively in another part of this article while no major ophthalmologic complications have been reported after nucleos(t)ide analogue therapies.

Hepatitis B vaccination can prevent hepatitis B virus infection and its serious consequences. Serious side effects after hepatitis B vaccination are very uncommon. Ophthalmological complications seen following hepatitis B vaccination consist of optic neuritis, uveitis, acute placoid pigment epitheliopathy, multiple evanescent white dot syndrome, and central vein occlusion as reported by various case reports[6,95-103]. Fraunfelder et al[6] especially reviews thirty-two case reports of uveitis occurring after hepatitis B vaccine appearing in various databases. The mean age of the patients was 29 years (1-57 years), with 8 male and 24 female patients. The mean number of days until uveitis was reported after vaccination was 3 days (1-15 days). Uveitis was reported to occur after the first vaccination in 15 patients, after the second vaccination in 3 patients, and after the third vaccination in 3 patients; the duration of time to occurrence of uveitis was not reported for 9 patients. One patient had recurrent uveitis after both the second and third doses of vaccine. One patient had recurrent uveitis after the first and second doses of vaccine. The conclusion is that there is a possible connection with immune complex deposition and adjuvant effects as potential pathogenic mechanisms.

Conclusions

Although no pathognomonic manifestation of HCV infection in the eye has been demonstrated, associations between HCV infection and various ocular syndromes have been reported in small case series and individual patients. At this time, the ocular manifestations of HCV infections best supported by the literature include a dry eye syndrome similar to Sjögren's syndrome, and ischemic retinopathy caused by either an HCV-induced vasculitis or treatment with interferon. Patients with diabetes seem to be more susceptible to interferon retinopathy and to subsequent permanent visual loss. Most of the reported ocular complications were mild and reversible but there have been several irreversible (severe) cases of ophthalmopathy associated with IFN treatment of chronic hepatitis C. Some studies propose that patients on interferon therapy should be offered ophthalmological examination before the initiation of therapy, during and after the end of treatment[4]. Such guidelines have not been issued and with the current data ophthalmologic examination should be reserved for patients complaining of visual symptoms or for those with predisposing factors such as diabetes mellitus. Interferon treatment may usually be continued in asymptomatic patients as long as there is careful fundoscopic examination even if evidence of ophthalmopathy can be found. Recommended ophthalmic examinations for patients on interferon include visual acuity, color vision examination, slit lamp microscopy and ophthalmoscopy[54,104].

Screening for HCV should be considered in patients with risk factors for HCV infection who suffer from unexplained ischemic retinopathy or dry eyes.

No correlation between hepatitis genotype, RNA/DNA levels or therapeutic outcome and ocular symptoms was established in any of the studies.

Presently an in vitro model of ocular tissue derived cells infected with HCV is missing. The establishment of such in vitro models would be helpful to better understand the mechanisms through which HCV induces optical pathologies in order to specifically target the causes of ocular disease[105].

There are no serious ocular manifestations of HBV infection other than dry eye syndrome. Special consideration should be held for possible connection between HBV vaccine and uveitis. Until now there have been only small case series suggesting this hypothesis and further research on this subject is needed.

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