

Clinical & Refractive Optometry is pleased to present this continuing education (CE) article by Dr. Amy Lam and Dr. Steven Ferrucci entitled **Interferon Retinopathy Associated with Hepatitis C**. In order to obtain 1-hour of COPE-approved CE credit, please refer to page 208 for complete instructions.

Interferon Retinopathy Associated with Hepatitis C

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ABSTRACT

Background: Hepatitis C is a blood borne pathogen made up of a single stranded RNA virus that attacks and damages the liver, a vital organ that filters toxin and waste products. It is the leading cause of liver transplant in the United States and produces 8,000 deaths per year. In accordance to the National Institute for Clinical Excellence, combination therapy of pegylated interferon alpha and ribavirin is the most successful treatment of hepatitis C. Unfortunately, this antiviral treatment poses numerous systemic as well as ocular complications. Although a majority of these ocular side effects are benign and asymptomatic, ocular changes should be monitored cautiously. **Case Report:** A 44-year-old male undergoing treatment for hepatitis C with pegylated interferon alpha and ribavirin, presented in the eye clinic for an annual comprehensive eye evaluation. A dilated fundus exam revealed bilateral cotton wool spots without any accompanying retinal hemorrhages. The retinopathy was associated with interferon therapy from hepatitis C. The ischemic changes resolved upon discontinuation of the medication, without any permanent vision loss. **Conclusion:** Interferon is used to treat multiple systemic disease, including chronic hepatitis B, C, and D, multiple sclerosis, and various types of carcinoma. Ocular complications have been associated with the usage of interferon alpha. Side effects range from asymptomatic cotton wool spots to severe vision loss with optic nerve edema. Although most reported retinopathy is reversible, patients being treated with

interferon should be monitored closely, as there are reported cases of ocular complications resulting in debilitating vision loss.

INTRODUCTION

Approximately 123 million people worldwide, including 4 million Americans, are infected with the hepatitis C virus (HCV), surpassing the human immunodeficiency virus type 1 (HIV-1) by five times.^{1,2} This blood borne pathogen is capable of sufficiently reducing the liver's function so as to cause chronic liver damage. Nearly 20% of those infected with HCV will experience cirrhosis of the liver (end stage liver disease).³

Hepatitis C is characterized by two significant stages, the first being the acute phase. Many cases are undetected at this early stage secondary to its asymptomatic and quiescent onset, with roughly 25% to 35% developing mild symptoms such as anorexia, malaise, or fatigue.¹ Fifteen percent of those infected will spontaneously recover by clearing the blood completely of the virus. Approximately 85% infected neglect to recover and will go on to develop chronic hepatitis. The primary treatment of chronic hepatitis C is interferon alpha, which can be taken either alone or in combination with ribavirin. Once treatment is started the patient needs to be monitored closely due to interferon's multitude of systemic and ocular side effects.

CASE REPORT

A 44-year-old Hispanic male came to the eye clinic for an annual comprehensive eye exam with a chief complaint of itchy eyes secondary to seasonal allergies. The patient had been seen twelve months prior, with best corrected visual acuities of 20/20 (6/6) OD and 20/20 (6/6) OS. A dilated fundus exam at that visit revealed unremarkable retina and optic nerves, with no diabetic retinopathy. His current medical history was positive for neuropathy, hepatitis C, hypertension, paranoid schizophrenia, and diabetes mellitus type 2. It is suspected that the patient contracted the HCV through intravenous drug use. Ocular history was unremarkable. Current medication included clonazepam, hydroxyzine, risperidone, temazepam, and trihexyphenidyl for depression and anxiety; insulin, metformin/rosiglitazone and glimepiride for diabetes; valsartan for hypertension; and fenofibrate for high cholesterol. Pegylated interferon

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This article was originally published in *Clinical & Refractive Optometry*, Vol. 17, No. 8, August 2006.

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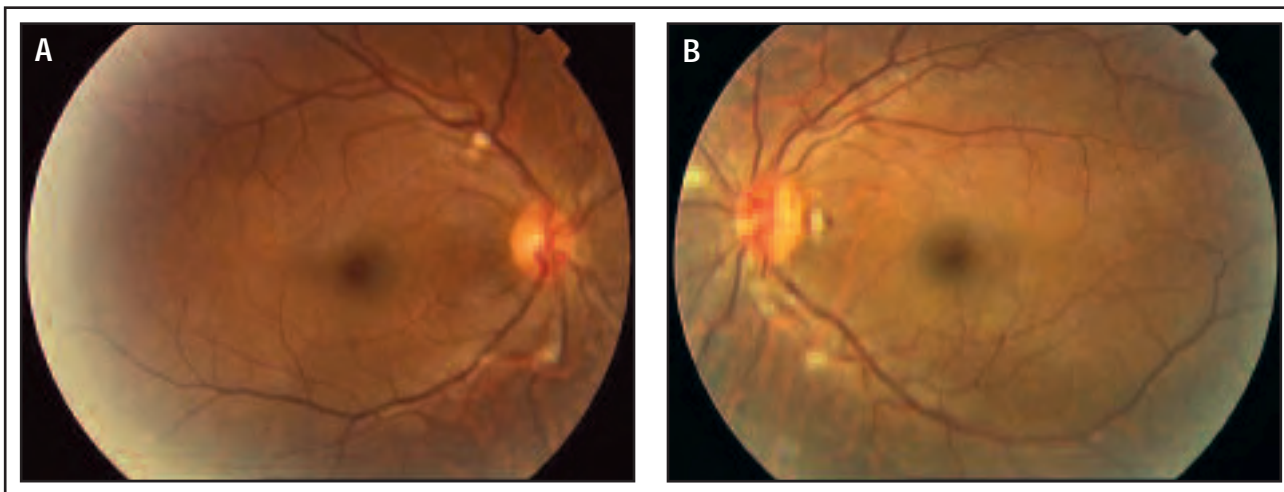


Fig. 1 (A) Fundus photograph of multiple cotton wool spots in the posterior pole of the right eye (OD), secondary to interferon therapy **(B)** Fundus photograph of multiple cotton wool spots in the posterior pole of the left eye (OS), secondary to interferon therapy

alpha and ribavirin for treatment of hepatitis C were added by his internist one month ago.

Best corrected visual acuity was 20/20 (6/6) OD and 20/20 (6/6) OS with a correction of $-1.25 -0.75 \times 170$ OD, $-1.75 -2.50 \times 10$ OS with a $+1.00$ add. Pupils were equal round and reactive to light without an afferent pupillary defect. Extraocular motilities showed full and smooth movements OD and OS, and a gross visual field screening revealed full fields OU. Anterior segment examination was remarkable for pinguecula in both eyes. Intraocular pressures of 14 mm Hg OD and 13 mm Hg OS were measured with Goldmann applanation tonometry. A dilated fundus exam revealed multiple cotton wool spots in both eyes without any accompanying hemorrhages in the posterior pole and no evidence of macular edema or neovascularization (Fig. 1A,B). The cup to disc ratio of the optic nerves was symmetrical, with measurements of 0.2 in the right eye and 0.2 in the left eye with healthy neural retinal rim tissue OU. The vitreous was clear. Arteries and veins were normal with an artery to vein ratio of 2 to 3. The peripheral retina was without holes, tears, or detachment 360 degrees OU. The retinopathy was credited to interferon treatment for hepatitis C. The patient was advised to return to the eye clinic in one month for a follow-up dilated fundus exam. The internist was also informed about the patient's ocular manifestation from interferon treatment to ascertain if an adjustment in medication was indicated.

The patient returned to the clinic in 8 weeks for a follow-up visit. By this time the patient had self-discontinued both interferon and ribavirin medication secondary to intolerable psychiatric side effects. A dilated fundus exam revealed one resolving cotton wool spot in the right eye and no retinopathy in the left eye (Fig. 2A,B).

DISCUSSION

The hepatitis C virus (HCV) was first discovered in 1975 when a non-A, non-B hepatitis virus was discovered. Fourteen years later, the genome of HCV was finally identified, and is currently the leading cause of chronic liver disease worldwide.^{2,4} Africa and Asia have the highest prevalence of HCV infection; the countries with the lowest prevalence are North America, Europe, and Australia.² Those typically infected are middle aged individuals, 30 to 49 years of age, with low socioeconomic income. The highest rate of HCV infection is among African Americans, followed by Hispanics and Caucasians.^{5,6}

Transmission of hepatitis C is commonly spread through blood or blood products, with a lesser means of infection through mucous membrane exposure. High-risk groups include intravenous drug users, those with a history of blood transfusion or organ transplant before 1992, those practicing unprotected sex, infants born by infected mothers, and health care workers frequently exposed to needles.⁶

In 1990, new routine testing was introduced to measure antibodies against HCV (anti-HCV) in donated blood supplies, and in 1992 a more sensitive test was created. This helped to significantly reduce the transmission of hepatitis C via the method of blood transfusion, from 5% in 1993 to less than 1% at present.⁶ Other studies have also shown transmission of the blood borne pathogen with even small amounts of infected blood. Therefore, it is important to be cautious when sharing implements such as toothbrushes and razors, which can carry small amounts of blood, when living with household members infected with HCV.⁶

In a hospital setting, the risk of infection from an accidental needle injection ranges from 0 to 10%.



Fig. 2 (A) Fundus photograph of a single resolving cotton wool spot in the right eye (OD) after discontinuation of interferon therapy **(B)** Fundus photograph without any signs of retinopathy in the left eye (OS) after discontinuation of interferon therapy

However, this depends on the size of the inoculum as well as the surface area of the needle exposed.⁶ The “rule of three” states that when a person is accidentally infected with a needle contaminated with HBV (hepatitis B virus), there is a 30% risk of transmission, with HCV a 3% risk of transmission, and if the needle is contaminated with HIV there is a 0.3% risk of infection.⁶

A single small study confirmed the presence of hepatitis C virus RNA in both tears and aqueous humor. However the risk of infection via tears was not studied. A complete disinfection of tonometer tips and contact lens is highly suggested before use. A five minute soak in 3% hydrogen peroxide followed by a rinse with cold water has proven to be the best method of disinfecting tonometer tips after contamination with HCV.^{7,8} Further, it is strongly recommended that corneal donors be screened for hepatitis C, in fear of infection via corneal transplant.^{7,8}

DIAGNOSIS

A detailed history of the individual is useful in determining if the patient is at a risk for HCV infection. If it is suspected that the person has been exposed to HCV, they should then be tested for antibodies to HCV (anti-HCV). The third generation enzyme immunoassay (EIA-3) is commonly used first as a screening test to detect for anti-HCV, because of its inexpensive, reproducible, and automated features. Occasionally, the EIA-3 produces a false-positive. When this occurs, or if a positive EIA needs to be confirmed, testing for HCV RNA can be helpful, using a polymerase chain reaction (PCR) based assay.⁹⁻¹¹ PCR testing is a more sensitive test for HCV, and is useful in detecting low levels of RNA in serum, as well as detecting the virus sooner than the standard EIA test.

Patients with chronic hepatitis C may develop elevated alanine aminotransferase (ALT) by an average of five

times greater than normal (ranging from 2 times to 20 times above normal). However, an elevated ALT is not pathognomonic of hepatitis C, especially since in some cases normal ALT serum level has been detected in hepatitis C patients. Close monitoring of ALT levels has proven useful, as studies reveal a close relationship between ALT and the progression of the disease.¹¹

Liver biopsy remains the gold standard in determining the stage of the disease. Although a biopsy is the most accurate approach in detecting the activity of the disease, it is not always used because of its potential risk for damaging other neighboring organs. This procedure provides information on the fibrosis and inflammatory stage of the disease. Treatment seems to respond best in those with a mild degree of fibrosis, and worse in those with advance fibrosis.¹⁰

The hepatitis C virus consists of 6 different genotypes and 50 subtypes. This wide genetic diversity of HCV poses an obstacle in creating an efficient treatment to eradicate the disease completely. Defining the precise genotype can help predict the chance a patient will respond to antiviral therapy. For example, studies show that patients with genotypes 2 and 3 are two to three times more likely to respond to interferon-based therapy than patients with genotype 1.^{10,11} The duration and dosage of treatment may also be adjusted based on the genotype of the virus. A patient's genotype does not change during the course of its infection, so testing is performed only once.

TREATMENT

The course of hepatitis C consists of an acute and chronic phase. Most patients with an acute infection are commonly undetected because of its asymptomatic presentation. Typically, by the time the disease is recognized, the infection has progressed to its chronic stage.¹⁰ Malaise,

weakness, jaundice, and anorexia are common symptoms in 30% to 40% of those with acute infection. The body does not generate antibodies to hepatitis C until approximately three months after infection.⁹ If infection is suspected, the earliest test that can be performed is one that measures HCV RNA. The RNA virus is present in blood before the onset of symptoms and within one to three weeks after initial infection. Liver cell injury can be detected as early as 50 days after infection, and this is identified by elevated ALT levels.¹¹ Approximately 15% of those with acute hepatitis C are self limiting. This small group will completely recover and eradicate all detectable viruses in the blood without treatment.

The remaining 85% of those with acute infection will develop chronic hepatitis C, which occurs when the virus remains in the blood six months after initial exposure to the pathogen.¹¹ The chronic stage progresses at a slow rate in the first two decades. A small percentage of patients can develop non-specific symptoms during the chronic phase of the disease, such as malaise and fatigue. Approximately 20% of those with chronic hepatitis C will develop cirrhosis between the first and second decade.¹¹ During chronic hepatitis, inflammation and dead liver cells may lead to fibrosis. The stage of the disease can be determined by the extent of the fibrosis. Severe fibrosis and inflammation marks the beginning of cirrhosis, and complications secondary to liver failure will arise such as jaundice, ascites, variceal hemorrhage and encephalopathy. Cirrhosis can develop rapidly in patients with excessive use of alcohol.¹¹

A multitude of randomized studies have been performed to determine the most effective and safest treatment of hepatitis. The most recent advancement is the development of pegylated interferon alpha 2a, a 40-kd (kilodaltons) molecule covalently attached to interferon alpha. The addition of polyethylene glycol moiety to interferon produced a drug with a longer half life, sustained absorption, and better pharmacokinetics than the natural molecule interferon alpha 2a.^{12,13} The pegylated interferon alpha allows for a more convenient dosage, a subcutaneous injection once a week compared to the unmodified interferon alpha which requires an injection every other day. This innovative treatment does not only improve compliance, but is also more effective.

A combination of peginterferon alpha 2b and ribavirin has the highest rate of success in treating hepatitis C. In 1990, clinical trials of ribavirin for the treatment of hepatitis C initiated after discovery of its ability to fight against RNA and DNA virus. Ribavirin monotherapy has proven to reduce ALT levels in half the patients, but does not absolve the hepatitis C virus.¹⁴ As a result, ribavirin was approved for treatment but only in combination with pegylated interferon alpha. Therefore, the current optimal treatment of hepatitis C is a combination of weekly injections of pegylated interferon alpha along with oral ribavirin according to guidelines set by the American Association for the Study of Liver Diseases

(AASLD).¹⁰ Unfortunately, using a second drug also places the patient at a higher risk for toxicity.

Although there have been great strides in the treatment of hepatitis C, an estimate of 40% to 50% of patients are either non-responders (HCV RNA levels will remain stable with treatment) or relapsers (HCV RNA levels are absent during treatment but will reappear once treatment is discontinued).¹⁰ Therefore a more effective, less expensive, and more tolerable medication is still needed.

Interferon alpha has been used widely to treat several systemic diseases such as high-risk cutaneous melanoma, Kaposi sarcoma, hemangiomas, renal cell carcinoma, leukemia, lymphoma, and hepatitis C.^{15,16} Historically, for a brief period, interferon was believed to be beneficial in treating age-related macular degeneration based on studies demonstrating its antiangiogenic activity preventing proliferation of endothelial cells. Unfortunately, it has since been shown to be futile in treating choroidal neovascular membrane in numerous studies.^{17,18}

OCULAR TOXICITY

Interferon alpha, pegylated interferon alpha and ribavirin, the most commonly used medications for hepatitis C, are associated with several systemic side effects. Interferon, being the most difficult to tolerate, may present with systemic complications including flu-like symptoms, rash, hypotension, peripheral neuropathy, neutropenia, depression, hypothyroidism, hyperthyroidism, irritability, memory disturbance, headaches, muscle aches, nausea, vomiting, insomnia, hearing loss, tinnitus, interstitial fibrosis, and thrombocytopenia.^{10,17} Adverse systemic effects typically associated with ribavirin include fatigue, birth defects, rash, sinusitis, and hemolytic anemia. Hemolytic anemia is the most significant reason for discontinuation of ribavirin.¹⁴

Ocular complications such as retinopathy, optic neuropathy, and vision loss, although uncommon, have nonetheless been reported as adverse side effects associated with interferon therapy. The most common presentation of interferon retinopathy is cotton wool spots and retinal hemorrhages, representing ischemic retinopathy. A majority of these cases usually are self limiting without any visual significance. However, there are reported cases of patients with permanently impaired vision secondary to interferon therapy. These ocular complications can appear unilateral or bilateral, and as early as two weeks after initiation of therapy. Other ocular complications include vascular occlusion, capillary non-perfusion, trichomegaly (increased number of lashes), macular edema, ischemic optic neuropathy, subconjunctival hemorrhage, and epiretinal membrane.^{15,17-25}

Although most occurrences of interferon-associated retinopathy in patients with HCV are benign and reversible, reported events of permanent ocular damage have been documented. Schulman et al presented a case of a 46-year-old man treated with interferon alpha 2b for hepatitis C who developed permanent monocular visual

field defect. It is suggested that optic nerve ischemia was responsible for the peripheral monocular scotoma in this patient.¹⁷ In 1993, Guyer et al reported more serious ocular side effects in ten patients treated with interferon for diagnoses other than HCV. One of the cases described a 33-year-old woman treated with high-dose interferon alpha for metastatic renal cell carcinoma. The patient developed symptomatic vision loss after one month of therapy with best corrected visual acuity of 20/100 (6/30) OD and 20/400 (6/120) OS. A dilated fundus exam revealed multiple cotton wool spots and retinal hemorrhages; in addition, a fluorescein angiography demonstrated arteriolar occlusion in both eyes. Ocular complications improved after discontinuation of medications, but once interferon was restarted, the vision loss recurred.¹⁸

According to one prospective case study, 69% of hepatitis C patients treated with interferon demonstrated ocular manifestation. Other studies have demonstrated the incidence of interferon retinopathy ranging from 18% to as high as 86%. Associating factors such as systemic conditions, dosage of interferon, and the frequency of follow-up eye examination is believed to be the cause for large variability in incidence of retinopathy in each study. In a majority of the cases, ischemic retinopathy was shown to resolve during the course of therapy and discontinuation of medication was not required.

The pathogenesis of ischemic retinopathy from interferon is unknown, but various theories have been proposed. One theory proposes that the antiviral agent deposits immune complexes in the retinal vessels causing ischemic retinal changes.¹⁸ Other studies hypothesize a process similar to diabetic retinopathy in which the microvasculature becomes damaged, leading to retinal non-perfusion and ischemia.²⁶ Still others propose that thrombocytopenia, an adverse effect of interferon, as well as alteration of endothelial cells, may be related to retinopathy.²⁵ Other researchers suspect a pathogenesis similar to Purtscher's retinopathy in which an increased level of plasma activated complement 5 occurs in patients treated with the antiviral therapy. It is suggested that plasma activated complement 5, a potent aggregator of platelets, can cause retinopathy in the form of cotton wool spots and retinal hemorrhages.^{27,28}

Ischemic retinopathy also has been reported in untreated patients infected with hepatitis C. Khouri et al described a hepatitis C patient with an isolated cotton wool spot detected during a routine eye examination. The asymptomatic patient had no other significant systemic condition associated with ischemic retinopathy. Cotton wool spots, an infarction of the retinal arteries, is frequently recognized in diabetic patients, and is also observed in patients diagnosed with hypertension, blood disorders, collagen vascular disease, carotid vascular disease, intravenous drug abuse, anemia, leukemia, and HIV. The author proposed that HCV infection causes immunoglobins to be

deposited in ocular vasculature leading to increase viscosity of blood serum producing microinfarct in the nerve fiber layer. Therefore, they suggest that hepatitis C needs to be added as a differential diagnosis when isolated cotton wool spots are discovered.²⁹

In 1995 a randomized clinical study to determine the prevalence of retinopathy in untreated hepatitis C was undertaken. The study concluded 31.8% of hepatitis C patients presented with idiopathic retinopathy in at least one eye versus 6% in the control group.^{30,31} Other studies found no incident of retinopathy in untreated hepatitis C patients. Schulman and associates suggest the presence of a potent variant genomic HCV strain, which might explain the reason why Japanese studies report a higher rate of retinopathy in untreated patients.

Patients with a history of diabetes and hypertension commonly have a weaker retinal vasculature, placing them at a greater risk of developing interferon retinopathy.³²

Studies have confirmed that retinal changes due to interferon therapy were higher among diabetic and hypertensive patients. One study examined 63 patients with chronic hepatitis C before and during treatment, 14 of which were diagnosed with diabetes and/or hypertension. In this study, 92% of the diabetic patients and 80% of the hypertensive patients showed retinal abnormalities. Comparatively, only 49% of patients without these diseases developed retinopathy.²⁵ While this is statistically significant, it is important to remember that the sample size in this particular study is small.

The relationship between dosage of interferon and incident of retinopathy is unclear. One study reported a 60% incidence of interferon retinopathy in those treated with interferon at a dosage of 9x10⁶ U/day, 6 times per week, whereas those treated with a lower dosage 3x10⁶ U/day showed a lower frequency of developing retinal changes, 23%.³³ Other studies using dosages ranging from 7 to 593 U/day showed no correlation between dosage of interferon alpha and retinopathy.³³

A second study reported no correlation between the incidence of retinopathy and the duration of interferon treatment (24 versus 48 weeks).²⁶ In the study, a majority of retinopathy occurred within 16 weeks of treatment and those treated for a longer of period time, 48 weeks, did not have a higher rate of retinal change. Nonresponders and relapsers appear to have the highest risk of developing retinopathy. Relapsers are characterized as patients with absent RNA during treatment but in whom, upon completion of treatment, the virus reappears.

FOLLOW-UP

Guidelines for the proper follow-up care in patients treated with interferon therapy are non-existent. Establishing suitable rules and procedures in eye care may be difficult because of the conflicting results in various studies. The

incidence of interferon associated retinopathy in the literature is variable, ranging from 14% to 85%. Further, the incidence of retinopathy can be influenced by the dosage, pre-existing systemic disease such as diabetes or hypertension, frequency of follow-up care, abnormal blood count, and concomitant usage of additional drugs such as paroxetine (serotonin reuptake inhibitor).¹⁵

One small study concluded that screening hepatitis C patients during therapy is unnecessary on a routine basis. This study revealed only a small percentage, 4 out of 25 patients (16%), developed retinal changes, with all four completing therapy without permanent visual side effects. However, three of the four patients developing interferon associated retinopathy were either diabetic or hypertensive.³⁴

Severe vision loss is uncommon in patients undergoing interferon therapy. Nonetheless, case studies of permanent vision impairment have been documented in those treated with interferon. Several studies suggest close monitoring of ocular side effects in patients receiving interferon therapy. These studies recommended a comprehensive eye exam before treatment is administered, for baseline. A dilated fundus exam should be repeated two months after the initiation of therapy. If retinopathy is present, close follow-up dilated fundus exams should be performed until the retinopathy resolves completely. In addition, the internist should be notified regarding the patient's ocular condition. This protocol is highly recommended in patients with additional systemic disease, such as diabetes and hypertension, as well as in those taking high dosage of interferon alpha for the treatment of high-risk melanoma, for example. If severe retinopathy develops it is recommended that interferon dosage be lowered or discontinued with the approval of the internist. It is important to work with the internist to prevent irreversible retinal damage from interferon treatment.

CONCLUSION

Interferon treatment is associated with various side effects; one of specific importance is retinopathy. Retinal changes can present in various forms, most commonly documented as cotton wool spots and retinal hemorrhages. A majority of these ocular side effects are temporary and asymptomatic. Frequently these ocular side effects may never be reported due to its quiescent characteristic and early onset presentation.

Although there is no agreement in the literature, it is generally recommended that a comprehensive eye exam be performed before treatment is initiated, with a repeat fundus exam two months after the start of therapy. If retinopathy is present, dilated fundus exams should be performed until retinopathy resolves. In addition, the internist should be notified regarding the patient's ocular condition. This is especially important in patients with additional systemic disease, such as diabetes and hypertension, which have higher rates of associated interferon retinopathy. □

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