

Latest updates on chronic delta hepatitis

Kronik delta hepatiti ile ilgili son güncellemeler

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ABSTRACT

The hepatitis D virus was shown for the first time in 1977 by Rizzetto and friends. The HDV genome and the cloning of sequence were made in 1986. HDV is the first animal virus with circular RNA genome which is seen only in plant viruses. HDV is an RNA virus with the known smallest viral genome in animal viruses. It is classified as *Deltavirus* genus depending on the type of virus by ICTV in 1996. HDV is classified as the sole example of delta virus in this genus.

Chronic delta hepatitis is the least common form of chronic viral hepatitis due to hepatotropic viruses. In contrast, the virus is highly pathogenic and can cause serious consequences. Today, prevalence of delta hepatitis has been shown to decrease. However, the delta hepatitis continues to be an important health problem in some parts of the world. In our country, especially in Eastern and Southeastern Anatolia, hepatitis D is a serious and important health problem and still maintains its importance as a health problem. In Turkey, still there is a significant number of patients with HDV infection despite a documented decrease in HDV infection.

The recommended treatment for chronic HDV infection in the current guidelines is the treatment with peginterferon alfa given once a week for 48 weeks. Treatment is indicated for patients who has compensated disease with active infection. In patients with advanced form of disease, the expected benefits of the peginterferon must be well balanced against the potential side effects and low response rate. An oral antiviral can be recommended in patients who has high levels of serum HBV DNA. In contrast, the control of HBV infection does not seem to change the natural history of HDV related disease.

Keywords: Delta hepatitis, Treatment, Prognosis

ÖZ

Hepatit D virüsü ilk kez Rizzetto ve arkadaşları tarafından 1977 yılında gösterilmiştir. HDV genomunun klonlanması ve sekanslanması ise 1986 yılında yapılmıştır. HDV sadece bitki virüslerinde görülen sirküler RNA genomuna sahip ilk hayvan virüsü ve hayvan virüsleri içinde de bilinen en küçük viral genoma sahip RNA virüsüdür. 1996 yılında ICTV tarafından *Deltavirus* cinsine bağlı bir virüs olarak sınıflandırılmıştır. HDV, delta virüs cinsi içinde, bu cinsin tek örneği olarak sınıflandırılmıştır.

Kronik delta hepatiti, hepatotrop virüslere bağlı kronik viral hepatitlerin en seyrek görüleni, buna karşılık yüksek derecede patojenik ve sonuçları itibarı ile en ciddi seyredenidir. Günümüzde delta hepatit prevalansının azaldığı, özellikle İtalya'dan yapılan çalışmalarda gösterilmişse de, dünyanın bazı bölgelerinde delta hepatit önemli bir sağlık sorunu olmaya devam etmektedir. Ülkemizde özellikle Doğu ve Güneydoğu Anadolu'da delta hepatit önemli ve ciddi bir sağlık sorunu olarak hala önemini korumaktadır. Son yıllarda Türkiye genelinde HDV enfeksiyonu azalmasına rağmen hala ciddi oranlarda HDV pozitifliği devam etmektedir.

Kronik HDV hastalığı için güncel kılavuzlarında önerdiği ve etkinliği kanıtlanmış tek tedavi şekli, 48 hafta süreyle haftada bir verilen peginterferon alfa tedavisidir. Aktif kompanse HDV hastalığı olan hastalarda tedavi endikedir. İlerlemiş hastalığı olan hastalarda, tedavinin beklenen yararları peginterferonun sirotik hastalarda potansiyel yan etkilerine ve düşük yanıt oranına karşı dengelenmelidir. Anlamlı HBV DNA serum titreleri bulunan hastalarda bir hepatit B virüs antiviralinin kullanılması önerilebilir ama HBV'nin kontrol altına alınması HDV karaciğer hastalığının doğal seyrini değiştiriyor gibi görünmemektedir.

Anahtar kelimeler: Hepatit D, Tedavi, Prognoz

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Introduction

Hepatitis D virus (HDV) is a distinctive human pathogen, which depends on hepatitis B virus (HBV) for infection [1].

Patients co-infected with HDV and HBV have a higher rate of progression of severe liver disease and cirrhosis than patients infected with only HBV.

Virology

HDV is a unique RNA pathogen which proliferates by 'rolling circle mechanism' that is unknown in other animal viruses. HDV is dependent on the presence of HBV to cause infection and can replicate in patients who have surface antigen of the hepatitis B (HBsAg) virus. HBsAg is required function for HDV. Infection with HDV does not correlate with HBV DNA level. HDV genome contains one ribosome and codes two proteins: S-HDAg and L-HDAg. S-HDAg supports replication and L-HDAg provides virion packaging while inhibiting the replication [2].

Contrary to conventional RNA viruses, HDV cannot code its own replication and entirely depends on host replication mechanism for its synthesis [2]. HDV replicates in the liver cell with rolling circle mechanism, using DNA dependent RNA polymerase I, II and III [3]. Briefly, HDV replication starts with viral attachment. Delta virus, similar to HBV, connects to hepatocyte membrane with L-HBsAg and enters. After the virus peels off in cytoplasm, remaining ribonucleoprotein passes to nucleus. Genome heads towards the nucleus, with the help of nuclear localization signals located in delta antigen. Transcription and replication of HDV genome, display a unique property. Finally, virus leaves the cell after viral assembly is completed. Leaving the host hepatocyte requires HBsAg.

Epidemiology

There are nearly 350 million chronic HBV carriers worldwide [4]. Approximately 5% of HBsAg carriers have HDV infection. Nearly 15 million of these cases have serological evidences of HDV exposure [5-7]. Prevalence rates show differences in Europe; Eastern Europe rates range between 14% and 39%, while Central Europe and Western Europe have rates lower than 6% [8].

Current HDV infection rate of HBsAg carriers is nearly 10% in Italy [9] and roughly 11% in Turkey [10]. However, HDV is still responsible for nearly half of liver cirrhosis and hepatocellular carcinoma cases in Southeastern Turkey [11]. Latest studies from Turkey indicate HDV prevalence between 0.9-16.2% in asymptomatic HBV carriers, 2.5-21.8% in acute HBV infections, 9-51.7% in chronic liver disease patients and 23-74% of cirrhosis patients [10,12-14].

Transmission

Fundamental principles of protection against HDV are vaccination against Hepatitis B in uninfected or unimmunized patients, and education for risk factors such as sexual transmission and use of contaminated needles. HDV is transmitted by parenteral route [15], and potentially sexually transmitted [16,17]. Perinatal transmission and patients who undergo hemodialysis are low because of routine testing for HBV, and this varies depending on the country.

Hepatitis D virus genotypes

Eight different HDV genotypes were identified [19]. Genotype 1 is the most commonly seen genotype worldwide and is commonly seen in Europe, Middle East, North America, Africa and India. It has been shown that the genotype of delta virus seen in Turkey is genotype 1 as well [20]. While Genotype 2 is common in Far East, Genotype 3 is only found in Northern countries of South America. Genotype 4 is found in Taiwan and Japan and Genotype 5-8 are identified in African patients, also they are in relation with A-E genotypes of HBV. Genotype 1 HDV infection has a versatile clinical course and Genotype 2 infection is generally characterized by a slowly progressive disease. Genotype 3 is the most different and aggressive genotype and generally causes a fulminant disease via microvesicular steatosis and eosinophilic degeneration in a cytopathic noninflammatory liver [21].

Pathogenesis

Most of the acute HBV/HDV co-infections are healed with the clearing of HBV. Typically, an HDV super-infection over a preexisting HBV infection becomes chronic. While the indicators for HBV replication are positive in a co-infection, they are often negative in a super-infection.

The pathogenesis of delta hepatitis is not fully understood. HDV affiliated hepatocyte damage is a result of immunologic response. In these cases, there is proliferation in CD4+ T cells and in the contrary there is a weakening in the CD8+ T-cell response. Fulminant delta hepatitis with microvesicular steatosis cases are noticed in Northern side of South America, and another feature that attracts attention is the lack of inflammation.

HDV's transmission risk is determined by the HBsAg status of the person [22]. HDV cannot infect HBsAg negative people. 95% of acute HBV/HDV co-infection cases result in clearance of HBV, same with conventional acute hepatitis B [23]. Hepatitis D cannot continue its existence after the HBV elimination and as a result, hepatitis D has a self-limiting attribute.

Diagnosis

Identifying antibodies against hepatitis D antigen

All HBsAg positive patients with liver disease and especially HBsAg positive drug users must be tested in terms of anti-HD [24]. Total anti-HD is commercially available. Anti-HD appears after the first couple weeks of infection and stays at high levels in HBsAg carriers with progressed chronic HDV infection [25]. IgM anti-HD is the indicator of liver damage related to HDV.

Identifying RNA of hepatitis D virus

Patients with positive anti-HD must be tested for serum HDV RNA levels. PCR is the most effective method [26-29]. HDV RNA levels do not correlate with the severity of infection but can be useful for evaluating the treatment efficiency [28]. The best evidence of active infection is HDV RNA levels. HDV RNA positive patients must be tested for underlying liver diseases.

Natural course and clinical characteristics

In a patient with Hepatitis B infection, delta infection usually presents itself in two ways: Patient receives HDV with hepatitis B virus simultaneously (Co-infection) or delta infection gets combined with preexisting hepatitis B infection afterwards (Super-infection). Both infections forms have different clinical presentations and natural courses.

Acute delta hepatitis (Co-infection)

HBV/HDV co-infection generally results in an acute, self-limiting hepatitis [7]. It can be distinguished from acute hepatitis B by biphasic peak aminotransferase elevation. Transaminases display two elevations within 2-5 week interval. Generally the first elevation is associated with the HBV infection while the second one with the HDV infection. The chronicity risk of a co-infection is roughly 2-7%.

Hepatitis D virus super-infection

HDV super-infection generally results in a severe hepatitis in HBsAg carriers. Clinically acute hepatitis are seen in 50-70% of super-infections that are developed in HBsAg carriers. The biphasic course that is seen in co-infection may not occur in super-infection. In most HDV patients, HDV disease becomes chronic; and in most cases (around 90%) it leads to cirrhosis. Chronic disease has a more progressive and severe course than HBV mono-infection [31]. In patients with HBV/HDV/HCV triple infection, HDV is generally the dominant virus and inhibits the replication of both viruses. HIV infected patients with HDV has a higher risk to develop cirrhosis.

Primary HDV super-infection leads to severe hepatitis [18].

If the patient's HBsAg status is unknown, Hepatitis D with super-infection can be similar to acute hepatitis B infection or it can mimic the reactivation of the underlying chronic hepatitis B virus infection [18].

Chronic hepatitis D virus infection

A progress towards chronic hepatitis D after super-infection is common [18]. HDV generally inhibits HBV replication. However, it takes a more severe and progressive route that goes towards cirrhosis in patients with HBV or hepatitis C virus (HCV) that leads to liver failure and death. A range of autoantibodies can accompany the chronic hepatitis delta infection, the most specific ones are 'liver-kidney' (LKM antibody, type 3) antibodies. Pathogenic roles of LKM and other autoantibodies in delta hepatitis are unknown. Unlike HBV, it only infects the hepatocyte and extrahepatic virus replication is not seen. In acute HDV infection, microvesicular steatosis and granular eosinophilic necrosis are commonly seen.

A European research published in 2000 showed that HCC risk was 3 times greater in patients with HDV than patients with HBV mono-infection [22,31]. But in other studies it is not clearly seen that HDV provides any meaningful increase to this risk [32]. In another study, it was shown that HBV/HDV co-infection was with a higher risk of hepatocellular carcinoma than mono-infected with HBV patients or uninfected people [33]. Drug users are under the risk of both HDV and HCV, furthermore, HBV/HDV/HCV triple infection is commonly seen in these patients. Chronic hepatitis D seems as it takes an accelerated course in patients with HIV.

Treatment

Developing antiviral treatment against HDV is insufficient for these reasons:

- Absence of a specific enzymatic target,
- HDV's diminishing prevalence in the Western World,
- Need of attention to two viral targets because of infection's synchronous nature.

First research about standard interferon showed that 6-12 months of treatments decrease the liver enzymes in roughly 20-25% of patients with HDV [34]. With the peginterferon alfa treatment, up to 47% high virologic response rates (HDV RNA serum that can not be identified 6 months after the end of treatment) are observed [35]. In patients treated with antiviral drugs against HBV, a significant virologic or clinical recovery of HDV disease is not observed.

Pretreatment Response and Toxicity Predictors

Low basal HBsAg and HDV RNA levels can predict response to treatment [28,29]. Genotype 1 HDV can be affiliated with a reduced response [36]. It is shown that HDV RNA kinetic indicates the response throughout the treatment [37]. IgM anti-HD reduction can indicate a response to antiviral treatment [38].

Treatment of hepatitis delta and HIV co-infection

Treatment should be always considered based on the high probability of HDV's poor prognosis. Because of lower effectiveness and high toxicity with peginterferon in patients co-infected with Hepatitis B virus (HBV)/HIV [39] using peginterferon is advised only on HBV/HIV co-infected patients who have positive response predictors and do not get antiretroviral treatment [40]. Similarly, treatment only should not be considered in patients co-infected with HBV/HDV/HIV if the risk of complications in the liver is greater than the benefits of peginterferon treatment [36].

Liver transplantation

End stage liver disease is an indication for liver transplantation because of its excellent results [41,42]. Hepatitis B immunoglobulin and its prophylaxis with antiviral treatment should be given to all transplanted patients in order to prevent reinfection.

Current treatment strategies

Generally, it is suggested that HDV-infected people with a compensated disease should be treated with peginterferon for 48 weeks [5,43]. Use of oral antiviral agents can be suggested for patients with significant HBV DNA levels. Extending the treatment beyond 12 months can be effective for patients with partial virologic and biochemical responses.

New treatments

Hepatitis D antigen undergoes various post-translational procedures such as prenylation, acetylation, phosphorylation and methylation that present new potential targets for new treatments [5]. Prenylation has a key role in HDV morphogenesis. It is shown that prenylation inhibitors cause clearance of HDV RNA [44]. Studies about gene treatments made with anti-sense oligonucleotides which inhibit viral gene expression and replication without affecting host protein synthesis, or ribosomes that cause the division of target RNA by specifically binding with the target RNA's molecules, are still ongoing. Little interfering RNAs that target the messenger RNA, which codes Hepatitis D antigen, can effect the HDV replication [45].

Primary care physicians who diagnose HDV infection in patients with HBV infection should refer patients to a hepatologist because of the lack of available data and consensus on the optimum treatment procedure and period based on solid evidence.

Vaccination

Hepatitis B vaccination is an effective prophylaxis against HDV. Lifelong protection against HBV provides protection against HDV [46]. HBsAg carriers should be informed about the risks of super-infection from carriers co-infected with HDV, and should be educated on the subjects of protective/preventive practices.

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