Research Article

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Investigating the Prevalence of Hepatitis Delta and Assessment of Treatment Response

Delta Hepatit Sıklığının Araştırılması ve Tedavi Yanıtının Değerlendirilmesi

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ABSTRACT

Objectives: The purpose of this study was to investigate the seroprevalence of delta virus, assess the treatment outcomes of patients receiving treatment.

Materials and Methods: The files of patients diagnosed with chronic hepatitis B followed up between 01.01.2015 and 31.12.2019 were examined. For the patients positive for delta antibody, demographic information, hepatitis delta virus (HDV)-RNA levels, treatment information and treatment outcomes were recorded from the files. Undetectable HDV-RNA levels after treatment was considered as total virologic response.

Results: There was a delta antibody positivity in 2.9% (n=74) of the 2,548 patients positive for hepatitis B surface antigen (HBsAg). The HDV-RNA tests of 60 patients found to be positive for delta antibody could be accessed. HDV-RNA was positive in 33.3% (n=20/60) of these patients, while 60% among the positive ones (n=12) received treatment. Among the patients who received treatment, 58.3% (n=7) were male, 41.7% (n=5) were female, and their median age was 53 (31-69) years. There was virologic response in 50% of the patients who received treatment, while no patient displayed HBsAg seroclearance.

Conclusion: At similar rates to those in other studies conducted in Turkey, hepatitis delta seroprevalence, virologic response rate were found to be low.

Keywords: Hepatitis delta, prevalence, treatment

ÖZ

Amaç: Bu çalışmanın amacı kronik hepatit B tanılı hastalarda delta virüs seroprevalansını araştırmak, tedavi alan hastaların tedavi sonuçlarını değerlendirmekti.

Gereç ve Yöntemler: 01.01.2015-31.12.2019 tarihleri arasında takip edilen kronik hepatit B tanılı hastaların dosyaları incelendi. Delta antikor pozitif olan hastaların demografik bilgileri, hepatit delta virüsü (HDV)-RNA düzeyleri, tedavi bilgileri ve tedavi sonuçları dosyalardan kayıt edildi. Tedavi sonrası HDV-RNA saptanamaz düzeyde olması virolojik tam yanıt olarak değerlendirildi.

Bulgular: Hepatit B yüzey antijeni (HBsAg) pozitif 2.548 hastanın %2,9'unda (n=74) delta antikor pozitifliği saptandı. Delta antikor pozitif tespit edilen 60 hastanın HDV-RNA testine ulaşıldı. Hastaların %33,3'ünde (n=20/60) HDV-RNA pozitif tespit edilmiş olup bu hastaların %60'ına (n=12) tedavi uygulanmıştı. Tedavi uygulanan hastaların %58,3'ü erkek (n=7), %41,7'si (n=5) kadın olup yaş ortanca 53 yıl (31-69) yıldı. Tedavi gören hastaların %50'sinde virolojik yanıt gözlenirken hiçbir hastada HBsAg seroklirensi gözlenmedi.

Sonuç: Türkiye'de yapılan diğer çalışmalara benzer oranda delta hepatit seroprevalansı, virolojik yanıt oranı düşük saptanmıştır.

Anahtar Kelimeler: Delta hepatit, prevalans, tedavi

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Introduction

The hepatitis delta virus (HDV) is an RNA virus, which causes a hepatitis delta infection in only hepatitis B surface antigen (HBsAg)-positive individuals. The virus was detected for the first time in Italy in 1977 by Rizzetto et al. (1), (2). While delta virus infection prevalence changes from country to country, it is estimated that 15 million people around the world are infected with HDV (3). Although HDV infections are endemic in Turkey, their seroprevalence varies from region to region (4,5).

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Its form of contagiousness is similar to that of the hepatitis B virus (HBV) infection, and it is transmitted by contaminated blood and blood products, infected body fluids, vertically from the mother to the infant and horizontally. Hepatitis delta progresses with two different clinical pictures as coinfection and superinfection. When someone is infected by HDV and HBV at the same time, a co-infection develops, and the clinical condition is more severe. Superinfection develops when an individual already infected with HBV receives HDV later and the clinical picture is milder. The only agent that is still used in treatment is alpha interferon (6).

Our purpose in this study was to investigate the seroprevalence of hepatitis delta in patients diagnosed with hepatitis B who had been followed up at our polyclinic for the last five years and to assess the treatment responses among the patients who were treated.

Materials and Methods

The data of 2548 HBsAg-positive patients who visited our polyclinic between 01.01.2015 and 31.12.2019 were retrospectively examined. In addition to delta antibody positivity, the treatment responses of the patients who received treatment due to hepatitis delta infection were investigated. HBsAg, anti-HDV studied with the ELISA method and HDV-RNA values measured by the polymerase chain reaction method. In addition to IV drug user, men who have sex with men (MSM), human immmunodeficiency virus (HIV)/HCV co-infection, whether their partners had HDV infection or not, the patients were also evaluated in terms of co-infection, superinfection, fulminant hepatitis, cirrhosis and hepatocellular carcinoma. Assessment of the treatment response was performed based on the Turkey 2017 Clinical Practice Guidelines on Hepatitis Delta Virus Infection Diagnosis, Monitoring, Management and Treatment (7). Total virologic response was accepted as undetectable levels of HDV-RNA. Hepatitis B e antigen (HBeAg)/anti-HBe, alanine aminotransferase (ALT), HBV-DNA, alpha-fetoprotein, abdominal imaging and liver pathology tested at the beginning of the treatment and HDV-RNA, HBV-DNA, ALT, HBsAg/anti-Hbs tested after the treatment were examined.

The study was approved by the Ethics Board of the İstanbul Medeniyet University, Göztepe Training and Research Hospital (decision no: 2020/0032, date: 21.01.2020). The study was carried out in compliance with the principles of the Declaration of Helsinki.

Statistical Analysis

Utilizing the SPSS IBM 22.0 (SPSS Inc., Chicago Il) software, the data was processed. The distribution of the data was evaluated by Kolmogorov-Smirnov test. The descriptive variables are presented as frequency, percentages, mean and standard deviation, while non-normally distributed variables are expressed as median (minimum-maximum). Using chi-squared test and Fischer's exact test, comparisons were made. A p-value of smaller than 0.05 was accepted as statistically significant.

Results

Delta antibody positivity was determined in 2.9% (n=74) of the 2548 HBsAg-positive patients. 50% of the patients (n=37) were male, 50% (n=37) were female, and their median age was 51 (23-80) years. The HDV-RNA tests of 60 patients with positive delta antibody could be accessed. HDV-RNA was positive in 33.3% (n=20/60) of these patients, while 60% among the positive ones (n=12) received treatment. Eight patients had not received treatment due to reasons such as pregnancy, being of foreign nationality and not being able to receive treatment or not coming for follow-up. Among the patients who received treatment, 58.3% (n=7) were male, 41.7% (n=5) were female, and their median age was 53 (31-69) years. The patients received at least 48 weeks of pegylated interferon (Peg-IFN) treatment. 66.7% (n=8) of these patients received interferon only the treatment by itself, while 33.3% (n=4) received a nucleoside/nucleotide analogue alongside with interferon. There was virologic response in 50% of the patients who received treatment, while no patient displayed HBsAg seroclearance or seroconversion. Fulminant hepatitis was not observed in this study, but hepatocellular carcinoma developed in one patient who received treatment and was being monitored for a long time with negative HDV-RNA. The pre-treatment and post-treatment data of the patients who received treatment, the treatment that they received and treatment durations are shown in Table 1.

Discussion

In HBsAg-positive individuals, delta infection is a condition that always needs to be kept in mind and monitored. Especially individuals born in places with high HDV endemicity, those using intravenous drugs, MSM, HCV- or HIV-infected individuals, those with multiple partners or previous history of sexually transmitted disease and individuals with high ALT values alongside low or undetectable HBV-DNA are under the risk of HDV infection (8). While none of our patients had intravenous drug use, MSM history or HIV and/or HCV positivity but the spouse of one patient had a diagnosis of hepatitis delta. Also one of our patient came from a foreign country.

In the course of HDV infection, acute hepatitis, chronic hepatitis, fulminant hepatitis, cirrhosis and hepatocellular carcinoma may appear (2,9). Fulminant hepatitis was not observed in any of our patients examined in this study, while it was determined that hepatocellular carcinoma developed in one patient who received treatment and was being monitored for a long time with negative HDV-RNA (Table 1, patient no: 10). Rates of becoming chronic following superinfection are 70-90%, while there are much higher in comparison to rates after coinfection (7,10,11). None of our patients had acute coinfection, in all patients delta positivity was determined during their monitoring.

Turkey is a moderately endemic region in terms of delta infection, while the positivity rates show differences between the east and the west of the country (12). In the meta-analysis by Değertekin et al. (4), when the data of studies conducted after 1995 were examined, it was shown that the anti-HDV positivity rate in the west of Turkey was 4.8%, while it was 27.1% in the east. In their study conducted in 2019 in İstanbul, Yolcu et al. (13) reported the anti-HDV positivity rate as 4.1%. The delta positivity rate in this study was 2.9%, and it was lower than those in eastern provinces and similar to those in western ones.

Studies have shown a decrease in the HDV prevalence in Turkey throughout the years. Ayaz and Sarı (14), in their study covering the period of 2012-2017, determined anti-delta positivity as 4.4%, and

Table 1. Data of treated patients before and after treatment

Patient no	Gender	Age	Before treatment HBV-DNA (IU/mL)	Before treatment HBeAg/anti-HBe	Before treatment ALT	Before treatment Alfa Feto Protein	Before treatment imaging	Before treatment (HAI*, Fibrozis)	Treatment	Treatment duration (week)	After treatment HDV-RNA	After treatment HBV-DNA	After treatment ALT	After treatment HBsAg/anti-HBs
1	Male	1969	3.109.096	-/+	249	1.81	Hepatosteatosis	7/2	Pegile interferon alfa 2b, 100 mcg	48	Negative	88	23	+/-
2	Male	1969	12.098	-/+	63	4.21	Hepatosteatosis	Did not performed	Pegile interferon alfa 2b, 150 mcg	48	Positive	106	145	+/-
3	Female	1979	6.017	-/+	26	1.62	Within normal range	6/0	Pegile interferon alfa 2a, 180 mcg + entekavir 0.5 mg	48	Negative	Negative	20	+/-
4	Male	1959	3.778	-/+	36	2.06	Hepatosteatosis	11/4	Pegile interferon alfa 2b, 100 mcg	48	Negative	7.091	6	+/-
5	Female	1972	32	-/+	46	6.14	Fine granular pattern	13/2	Pegile interferon alfa 2b, 120 mcg	96	Positive	Negative	19	+/-
6	Female	1962	4.729.680	+/-	96	3.23	Fine granular pattern	Did not performed	Pegile interferon alfa 2b, 120 mcg + entekavir 0.5 mg	48	Positive	Negative	86	+/-
7	Female	1989	51.161	-/+	121	2.69	Fine granular pattern	6/1	Pegile interferon alfa 2a, 180 mcg	48	Positive	14.000	71	+/-
8	Male	1965	1.931.073	+/-	56	1.57	Minimal granular appearance	6/3	Pegile interferon alfa 2b + tenofovir disoproksil fumarat 245 mg	96	Positive	Negative	76	+/-

Table 1 contiuned

9	Male	1954	Negative	-/+	28	4.3	Within normal range	Did not performed	Pegile interferon alfa 2a, 180 mcg	48	Positive	Negative	23	+/-
10	Male	1951	Negative	-/+	102	6.04	Hepatomegaly granular pattern	12/3	Pegile interferon alfa 2a, 180 mcg	96	Negative	38	25	+/-
11	Male	1985	Negative	-/+	49	2.39	Within normal range	Did not performed	Pegile interferon alfa 2b, 80 mcg	96	Negative	38	25	+/-
12	Female	1957	70.240	-/+	46	2.85	Hemangioma in the liver	Could not be performed	Pegile interferon alfa 2a 180 mcg + tenofovir disoproksil fumarat 245 mg	48	Negative	Negative	45	+/-

*HAI: Histological activity index, HBV: Hepatitis B virüs, HBeAg: Hepatitis B e antigen, ALT: Alanine aminotransferase, HBsAg: Hepatitis B surface antigen

they reported that this rate was 8.52% in their study covering the period of 2002-2004 (14,15). Eser-Karlıdağ (16) found the delta positivity in Elazığ in eastern Turkey as 8.8% and reported that this ratio was lower in comparison to those reported in previous studies in the region. It is an ordinary outcome that, with the addition of hepatitis B vaccination to the national vaccination program in 1998, there has been a decrease in the prevalence of chronic hepatitis B, therefore, the prevalence of hepatitis delta, among young adults. Despite this, as hepatitis B infections have not been eradicated, HDV still continues to be a public health problem.

While studies are going on regarding new agents including the hepatocyte entry inhibitor myrcludex B, farnesyl transferase inhibitor lonafarnib, nucleic acid polymers and Peg-IFN-λ, the only option in treatment today is still Peg-IFN-α (17,18). The primary target in treatment is to lower the HDV-RNA value to an undetectable level. HBsAg clearance and seroconversion are the ultimate goal, while it is highly difficult to reach this goal. Without regards to treatment response, PEG-IFN treatment must continue for 48 weeks. While reaching undetectable levels of HDV-RNA and continuation of these 6 months after the end of the treatment are desired, low rates of sustainable HDV suppression are reached after treatments of 48-96 weeks (19). For this reason, the HDV-RNA negativity we obtained 6 months after the end of the treatment cannot be considered as permanent virologic response, but biochemical and virologic monitoring is recommended. In the 5-year follow-up study of HIDIT-1 by Heidrich et al. (20), at least one positivity was determined in the follow-ups of 9 of 16 patients whose HDV-RNA was determined as negative 24 weeks after the end of the treatment. Rather than IFN monotherapy, combined treatment studies are also conducted to increase the success of treatment. In the randomized controlled HIDIT-1 and HIDIT-2 studies conducted by Wedemeyer et al. (21) , (22), no significant difference could be found in the treatment responses between patients receiving IFN treatment and those receiving IFN and tenofovir disoproxil treatment. There are also other studies showing that usage of nucleoside/nucleotide analogues as monotherapy or in combination with PEG-IFN does not have an additional benefit (23,24,25). Combined treatment may be recommended in patients with diagnosis of chronic hepatitis B needing treatment in addition to HDV infection. While HBV-DNA was negative after treatment in all 4 patients we gave combined therapy, only 2 patients were found to have negative HDV-RNA values.

In the review by Yurdaydin and Idilman (26), virologic success was reported as 14-50% in controlled studies conducted on patients using IFN and 17-47% in studies conducted with PEG-IFN. In our study, virologic response was determined at a rate of 50%, which was similar to those reported in studies conducted in Turkey and around the world.

As eradication is out of the question as long as the presence of HBsAg continues, the necessity of HDV-RNA monitoring is clear. During the treatment of HDV which is generally dominant in HDV coinfection, HBV-DNA monitoring of patients should also be conducted (27).

Study Limitations

The limitation of the study is that it is a retrospective study, so all patient datas were not available.

Conclusion

The primary way of preventing delta infection development is to achieve protection of under-risk individuals by applying effective vaccination programs and eradicating hepatitis B infection by raising awareness in all parts of the society. All patients positive for HBsAg should be screened in terms of HDV, and patients with HDV viremia should be treated. While IFN is still the only preferred option in treatment, a more effective antiviral agent is needed.

Ethics

Ethics Committee Approval: The study was approved by the Ethics Board of the İstanbul Medeniyet University, Göztepe Training and Research Hospital (decision no: 2020/0032, date: 21.01.2020).

Informed Consent: Since our study was retrospective, informed consent was not used.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: P.E., F.Y.K., Ö.A., Design: P.E., Ö.A., Data Collection or Processing: P.E., Analysis or Interpretation: F.Y.K., Literature Search: Ö.A., Writing: P.E., F.Y.K.,

Conflict of Interest: Authors declare no conflict of interest.

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