Turk J Gastroenterol 2006; 17 (1): 25-34

The prevalence of hepatitis delta virus infection in acute and chronic liver diseases in Turkey: An analysis of clinical studies

Türkiye'de akut ve kronik karaciğer hastalıklarında hepatit delta virus infeksiyon prevalansı: Yapılmış klinik çalışmaların analizi

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Background/aims: *The objective of this study was to review the studies on hepatitis D virus-related liver diseases and to evaluate the national and regional outcomes in order to identify the hepatitis D virus infection in Turkey.* ***Methods:*** *This retrospective study included 2182 acute viral hepatitis, 6613 inactive HBsAg carriers, 5961 chronic hepatitis B, 1264 liver cirrhosis and 748 hepatocellular carcinoma cases, who were evaluated for anti-hepatitis D virus positivity at several centers in Turkey since 1980's. ELISA method was used and the results were statistically evaluated.* ***Results:*** *The anti-hepatitis D virus positivity was 3.0% in 1416 acute viral hepatitis and 8.1% in 766 acute hepatitis B cases. This ratio was significantly higher in Diyarbakir than in Istanbul and Ankara for acute viral hepatitis (p<0.001). The mean anti-hepatitis D virus was 4.9% in inactive HBsAg carriers and significantly decreased from 1980 to 2005 (4.1% and 2.9%, respectively p<0.001). The anti- hepatitis D virus was 20% in chronic hepatitis B and 32.5% in liver cirrhosis cases. The positivity were significantly lower in Istanbul and İzmir compared to Diyarbakır and Van (p<0.001). Anti-hepatitis D virus positivity was decreased in all regions for the last two decades (p<0.001). The rates decreased from 31% to 11% for chronic hepatitis B and from 43.3% to 24% for liver cirrhosis (p<0.001). The mean anti-hepatitis D virus was 23% in hepatocellular carcinoma cases, which was significantly lower in Istanbul and Izmir compared to Diyarbakır and Elazığ (p<0.0001).* ***Conclusions:*** *The hepatitis D virus infection is a critical problem in our country, particularly in the Eastern and Southeastern Anatolia. In recent years, the hepatitis D virus infection is decreasing countrywise, however the rate still remains to be critical.*

Anahtar kelimeler: Hepatitis D virus, hepatitis B virus, chronic hepatitis D, liver cirrhosis, hepatocellular carcinoma

Amaç: *Bu çalışmada Türkiye'de hepatit D virusu infeksiyonunun önemi araştırılmış, çeşitli karaciğer hastalıklarındaki anti-hepatit D virusu seroprevalansı çalışmaları gözden geçirilmiş, genel ve bölgesel sonuçlar değerlendirilmiştir.* ***Yöntem:*** *Ülkemizde 1980'lerden günümüze kadar anti-hepatit D virusu pozitifliği aranan 2182 akut viral hepatit, 6613 inaktif HBsAg taşıyıcısı, 5961 kronik B hepatiti, 1264 karaciğer sirozu ve 748 hepatoselüler karsinoma vakası retrospektif olarak incelendi. Tetkiklerde ELİSA yöntemi kullanıldı. Sonuçlar istatistiksel yöntemlerle değerlendirildi.* ***Bulgular:*** *Anti-hepatit D virusu, akut viral hepatitte %3, akut B hepatitinde %8.1'di. ABH'de anti hepatit D virusu, Diyarbakır'da Ankara ve İstanbul'a göre anlamlı yüksek bulundu (p<0.001). İnaktif HBsAg taşıyıcılarında anti-hepatit D virusu %4.9'du. Pozitifliğin 1980'den 2005'e anlamlı azaldığı izlendi (%4.1 ve %2.9, p<0.001). Anti-hepatit D virusu pozitifliği 5961 kronik B hepatitlilerde %20, 1264 karaciğer sirozluda % 32.52'di. Pozitiflik İstanbul ve İzmir yörelerinde, Diyarbakır ve Van yöresine göre anlamlı şekilde düşüktü (p<0.001). Ancak tüm bölgelerde anti-hepatit D virusunun 20 yılda azaldığı, oranların kronik B hepatitte %31'den %11'e, karaciğer sirozu da %43.3 ten %24'e indiği saptandı (p<0.001). Hepatoselüler karsinomalılarda anti-hepatit D virusu %23 bulundu. Bu oranın İstanbul ve İzmir'de Diyarbakır ve Elazığ'a göre anlamlı düşük olduğu görüldü (p<0.0001).* ***Sonuç:*** *Hepatit D virusu infeksiyonu ülkemizde özellikle Doğu ve Güneydoğu'da ciddi bir sorundur. Son yıllarda ülke genelinde hepatit D virusu infeksiyonu azalmaktadır, ancak hala ciddi oranlarda pozitiflik devam etmektedir.*

Key words: Hepatit D virusu, hepatit B virusu, kronik hepatit D, karaciğer sirozu, hepatoselüler karsinoma

INTRODUCTION

It is well known that the viral hepatitis are the most important causes of chronic liver diseases in Turkey. All related studies carried out since the 1980's have ranked the hepatitis B virus (HBV) in-

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Manuscript received: 12.01.2005 **Accepted:** 28.06.2005

fection first for all regions, followed by hepatitis C virus (HCV) and hepatitis D virus (HDV) infections in the western regions, and by HDV and HCV in Eastern and Southeastern Anatolia. The HDV infection is also remarkably common in the western regions in addition to the Eastern and Southeastern regions (1-3).

Although the infection of HDV appears to have some geographical differences, it is a severe disease with very low, low, moderate and high endemicity worldwide (4-9). However, in recent years it has been reported that the prevalence of HBV infection is decreasing in western countries and other countries struggling with HBV, together with the prevalence of HDV infection (10, 11).

The scientific data reported in our country is similar to these findings (1, 2, 12-14). However, currently and continuing into the near future, HBV and HDV infections will retain their place in our scientific agenda. Therefore, it is critical to know about HDV infection, which also has a great importance, as well as HBV infection, in the diagnosis and treatment of liver diseases in our country.

In this study, we retrospectively reviewed the anti-HDV seropositivity related with cases of acute viral hepatitis (AVH), inactive HBsAg carriers, chronic hepatitis B (CHB), liver cirrhosis (LC) and hepatocellular carcinoma (HCC) in Turkey. All studies carried out since the 1980's were reviewed, and the anti-HDV positivity in several liver diseases, the regional differences of HDV infection and the change from the 1980's until today were evaluated. It is thought that the results may contribute to the better recognition of HDV infection, which remains a critical problem in some of the regions.

MATERIALS AND METHODS

In this study, we retrospectively reviewed all studies about anti-HDV seroprevalence in cases of adult AVH, inactive HBsAg carriers, CHB, LC and HCC carried out by several centers, mainly university and specialized hospitals, between 1980 and 2005.

For this purpose, all related scientific journals, and the bulletins of the Turkish Gastroenterology and National Hepatology Congresses, Viral Hepatitis Symposiums and other related meetings, particulary the book Viral Hepatitis 2003 by the Association of Viral Hepatitis Campaign, were all reviewed.

The study included a total of 22,499 AVH, 6,613 inactive HBsAg carrier, 5,961 CHB, 1,264 LC and 748 HCC cases.

It was checked and confirmed that the AVH, inactive HBsAg carriage, CHB, LC and HCC were diagnosed clinically, biochemically, and serologically in all cases and histopathologically in some cases. The total anti-HDV positivity was studied by ELISA method. The results were assessed statistically using Pearson's chi-square and Student's t tests.

RESULTS

Acute Viral Hepatitis

The anti-HDV was studied in a total of 2,249 AVH cases from the 1980's to 2005. The distribution of the studies by centers, years and researchers is shown in Table 1. It appears that the results differ between the centers as well as between the researchers working in the same centers. When the mean value is taken into consideration, the anti-HDV positivity was found as 3.0% in 1,416 AVH cases without any type differentiation and as 8.8% in 833 cases with acute hepatitis B (AHB) diagnosis.

The results of anti-HDV positivity in AHB cases differed between three centers located in different regions of the country. It was found as 6.9% in İstanbul, which is located in the western part of the country, with 117 reviewed cases; as 11.2% in Ankara, which is located in the central part of the country, with 229 reviewed cases; and as 22.5% in Diyarbakır, which is located in the Southeastern part of the country, with 159 reviewed cases. It appears that the result was significantly higher in Diyarbakır (Table 2, $p<0.001$).

Inactive HBsAg Carriers

The anti-HDV positivity results from a total of 6, 613 HBsAg carriers collected from several centers since the 1980's are shown in Table 3. It is important to note that the results are similar in centers with a higher number of cases, while the anti-HDV rates for HBsAg carriers differ even in the same center in our country. When all cases are taken into consideration, the positivity was determined as 4.9%.

When the change in the anti-HDV positivity of HBsAg carriers over time was reviewed, it appears that the positivity was 4.1% between 1980 and 1990, and regressed to 2.9% after 2001 (Table 4, $p<0.01$).

Table 1. Studies related with anti-HDV positivity for AVH in Turkey

Region	Year	Researcher	Group	No.	Anti HDV+ (%)
Western Anatolia					
İstanbul	1988	Badur et al. (1)			11.0
"	1988	Ökten et al. (1)	AHB	27	7.0
"	1991	Çavuşlu et al. (1)	AHB	63	6.3
"	1996	Mert et al. (1)	AHB	27	7.4
"	1996	Göktaş et al. (15)	AVH	428	0.7
İzmir	1994	İsler et al. (16)	AVH	333	2.9
"	1996	Kurultay et al. (17)	AVH	230	0.4
"	1996	Sivrel et al. (18)	AVH	127	0.0
Central Anatolia					
Ankara	1989	Emri et al. (1)	AHB	16	2.5
"	1991	Erbaş et al. (19)	AVH	37	0.0
"	1995	Eyigün et al. (20)	AHB	80	3.8
"	1996	Bayındır et al. (1)	AHB	82	17.9
"	2003	Çolpan et al. (22)	AVH	75	1.3
Eskişehir	1999	Us et al. (1)	AHB	152	2.5
Kayseri	1992	Doğan et al. (1)	AHB		12.5
"	1996	Kılıç et al. (23)	AVH		2.5
Eastern and Southeastern Anatolia					
Diyarbakır	1989	Kankılıç et al. (1)	AHB	49	23.0
"	1991	Değertekin et al. (24)	AVH	120	15.0
"	1995	Turfan et al. (1)	AHB	110	22.0
Elazığ	1994	Felek et al. (1)	AHB	41	7.3
Gaziantep	1997	Alkan et al. (1)	AHB	50	4.0
Adana	1994	Dündar et al. (1)	AHB	39	2.5
"	1996	Güler et al. (25)	AHB	30	2.6
"	1996	Tasova et al. (26)	AVH	66	4.5
Total			**AVH**	**1416**	**3.0%**
			AHB	**833**	**8.8%**

AVH: Acute viral hepatitis, AHB: Acute hepatitis B

Table 2. Anti-HDV positivity in AHB in several centers in Turkey

Center	No. of Cases	Anti HDV+
İstanbul (1,15)	117	6.9%
Ankara (1,19-22)	229	11.2%
Diyarbakır (1,24)	159	22.5%

The results from Diyarbakır were statistically significant compared to results from Istanbul and Ankara, p<0.001, AHB: Acute hepatitis B

Chronic Hepatitis B

The anti-HDV positivity was studied in 5,961 CHB cases from the 1980's until today by several researchers (Table 5). It seems that even in the same center, the results were different at various time points. Based on these results, the following should be highlighted:

a. When all cases were considered, the anti-HDV positivity was 20.0% in CHB cases.

b. The anti-HDV positivity was significantly different in various regions with higher series of cases (Table 6).

The anti-HDV rate was similar in the cities of Western Anatolia such as İstanbul and İzmir, at 16.5% and 14.0%, respectively, which is lower than the average value for Turkey (p=0.001, p<0.001).

The anti-HDV rate in CHB was 28.0% in Ankara, which is located in Central Anatolia, and it was significantly higher than the average value for Turkey (p<0.001).

The anti-HDV positivity was 33.3% and 38.0% in Van and Diyarbakır, respectively, which are located in Eastern and Southeastern Anatolia. These are significantly higher than the mean value for Turkey and the results of other regions (p<0.001, p<0.001).

c. The change in the anti-HDV positivity of CHB from the 1980's until today is shown in Table 7. The positivity of 31.0% between 1980 and 1990 decreased to 19.4% in 1991-2000, and to 11.0% in 2001-2005, which was found significant (p<0.001).

d. The change in the anti-HDV positivity of CHB over time can also be seen with the regional results (Table 8). The anti-HDV positivity rate in İstanbul in Western Anatolia was 34.2% between 1980-1990, while it decreased to 19.6% between 2000 and 2005 (p<0.001). Similarly, the rate in Diyarbakır in Southeastern Anatolia was 38.8% between 1991 and 2000, decreasing to 32.1% between 2001 and 2005, which was also significant (p<0.001).

Table 3. Anti-HDV positivity in inactive HBsAg carriers in Turkey

Region	Year	Researcher	No	Anti HDV (%)
Western Anatolia				
İstanbul	1985	Batur et al. (1)		2.1
"	1988	Ökten et al. (1)	42	2.4
"	1989	Söyletir et al. (1)		5.5
"	1991	Çavuşlu et al. (1)	477	1.0
"	1992	Doğan et al. (1)		11.2
"	1996	Mert et al. (1)	162	2.5
"	1997	Ökten et al. (27)	372	4.8
"	1988	Özaras et al. (28)	511	1.6
Bursa	1988	Töre et al. (1)	106	9.0
İzmir	1999	Topalak et al. (29)	132	1.0
"	2001	Akarca et al. (30)	1016	0.5
Central Anatolia				
Ankara	1990	Balık et al. (1)		5.8
"	1991	Oğuz et al. (31)	49	4.0
"	1991	Erbaş et al. (9)	167	2.4
"	1992	Hacıbektaşoğlu et al. (1)	117	16.2
"	1993	Balcı et al. (1)	120	15.6
"	1998	Senel et al. (1)	282	1.4
"	2000	Karakuş et al. (32)	387	2.6
"	2000	Görenek et al. (33)	72	1.4
"	2000	Baylan et al. (21)	95	5.3
Eskişehir	1997	Us et al. (1)	729	7.5
"	1999	Us et al. (1)	50	2.0
Kayseri	1992	Doğan et al. (34)		11.2
Eastern and Southeastern Anatolia				
Diyarbakir	1995	Turfan et al. (1)	98	3.0
"	1998	Değertekin et al. (1)	736	4.0
"	2001	Yıldırım et al. (35)	132	3.2
"	2003	Yalçın et al. (36)	224	2.0
Elazığ	1994	Felek et al. (1)	142	8.5
Malatya	1993	Tecimer et al. (37)	103	2.9
Gaziantep	1997	Alkan et al. (1)	140	8.5
Erzurum	2003	Kacar et al. (36)	301	1.2
Van	1998	Berktaş et al. (1)	246	3.3
"	1998	Turkdogan et al. (38)	67	9.8
"	2003	Türkdoğan et al. (36)	135	5.0
Sivas	1991	Poyraz et al. (1)	92	9.8
Adana	1989	Aksu et al. (1)		7.0
"	1991	Oğuz et al. (1)	49	2.0
"	1994	Dündar et al. (1)	106	0.9
"	1994	Güler et al. (1)	106	0.9
Mersin	2000	Kandemir et al. (39)	66	6.0
Total			**6613**	**4.9%**

Liver Cirrhosis

a. The mean anti-HDV positivity was 32.5% in a total of 1,264 cases studied throughout the country.

b. Similar to CHB cases, there were regional differences in LC cases.

Table 4. Change in the anti-HDV positivity in inactive HBsAg carriers over time in Turkey

Years	No. of Cases	Anti HDV+
1980-1990	659	4.1%
1991-2000	5162	5.4%
2001-2005	792	2.9%

p<0.01

The anti-HDV rates in İstanbul and İzmir in Western Anatolia were 26.9% and 24.0%, respectively; however, these similar rates were significantly lower than the mean value for Turkey ($p<0.05$, $p<0.01$). This rate is 44% in Ankara in Central Anatolia. Based on the limited number of cases, it is not significant compared to the mean value for Turkey ($p>0.01$) (Table 6).

In Eastern and Southeastern Anatolia, the rates were 30.0% and 59.4% in Van and Diyarbakır, respectively. The result in Diyarbakır was significantly higher than the mean value for Turkey ($p<0.001$), while the result in Van was significantly higher than the results obtained for the western regions ($p<0.001$) and is close to the mean

Table 5. Anti-HDV positivity in chronic liver diseases in Turkey

Region	Year	Researcher	Group	No	Anti HDV (%)
Western Anatolia					
İstanbul	1988	Badur et al. (1)	CHB		20.0
"	1988	Ökten et al. (1)	CHB	25	28.0
	1988	Ökten et al. (1)	LC	73	34.2
"	1988	Özdemir et al. (40)	CHB	100	36.0
"	1991	Çavuşlu et al. (1)	CHB	28	32.4
"	1996	Mert et al. (1)	CHB	116	14.6
"	1997	Ökten et al. (1)	CHB	526	4.5
"	1999	Aksoy et al. (41)	CHB	35	2.8
"	2001	Tabak et al. (42)	CHB	423	7.0
"	2003	Ökten et al. (13)	CHB	296	2.9
"	2003	Ökten et al. (13)	LC	316	19.6
Bursa	1997	Nak et al. (43)	CHB	579	3.5
			LC		17.4
İzmir	1984	Bilgiç et al. (1)	LC		23.0
"	1985	Batur et al. (1)	CHB		40.9
"	1985	Batur et al. (1)	LC	110	41.0
"	1996	Akarca et al. (1)	CHB		22.0
"	1996	Kuruüzüm et al. (1)	LC	107	14.0
"	1999	Ersoz et al. (44)	CHB	1551	4.7
"	1999	Topalak et al. (29)	CHB	104	6.0
"	1999	Topalak et al. (29)	LC		18.0
"	2001	Akarca et al. (30)	CHB	526	6.1
"	2001	Akarca et al. (30)	LC	141	25.8
Manisa	2001	Tosun et al. (45)	CHB	180	3.2
Central Anatolia					
Ankara	1989	Emri et al. (1)	CHB	18	34.5
"	1989	Emri et al. (1)	LC	59	44.4
"	1990	Balık et al. (1)	CHB		32.7
"	1991	Erbaş et al. (19)	CHB	191	31.5
"	1992	Okçu et al. (46)	CHB	51	21.8
"	1993	Özyılkan et al. (1)	CHB	123	28.4
"	2000	Görenek et al. (33)	CHB	89	8.6
"	2000	Baylan et al. (21)	CHB	36	38.9
Eskişehir	1999	Us et al. (1)	CHB	77	15.6
Kayseri	1989	Akın et al. (1)	CHB		23.0
Eastern and Southeastern Anatolia					
Diyarbakır	1989	Değertekin et al. (1)	LC	60	74.0
"	1991	Göral et al. (47)	CHB	45	53.4
"	1995	Turfan et al. (1)	CHB	54	51.7
"	1995	Turfan et al. (1)	LC	50	58.0
"	1994	Canoruç et al. (48)	CHB	100	30.0
"	1998	Değertekin et al.(49)	CHB	120	20.0
"	2003	Yalçın et al. (36)	CHB	168	32.1
"	2004	Yalçın et al. (36)	LC	179	46.3
Elazığ	1994	Felek et al. (1)	CHB	17	41.2
"	1999	Bahçecioğlu et al. (36)	CHB	55	9.0
"	2001	Yalnız et al. (36)	CHB	209	16.5
"	2003	Akbulut et al. (36)	LC		6.7
"	2004	Koca et al. (50)	CHB	62	16.1
"	2004	Koca et al. (50)	LC	120	30.0
Erzurum	1996	Kaya et al. (51)	CHB		6.3
"	2001	Polat et al. (36)	CHB		8.0
Gaziantep	1989	Alkan et al. (1)	CHB	10	20.0
Malatya	1999	Aladağ et al. (52)	CHB	120	2.5
"	2002	Karıncaoğlu et al. (36)	LC		4.0
Van	1989	Türkdoğan et al. (38)	CHB	21	33.3
"	2001	Tuncer et al. (53)	LC	115	20.8
"	2003	Türkdoğan et al. (36)	CHB	148	33.3
"	2003	Türkdoğan et al. (36)	LC	75	45.3
"	2004	Uygan et al. (54)	LC	157	23.0
Sivas	2000	Turkay et al. (55)	CHB	21	3.2
Adana	1991	Oğuz et al. (1)	CHB	69	33.3
"	1994	Dündar et al. (1)	CHB	55	9.0
"	1994	Güler et al. (25)	CHB	55	9.9
Mersin	2000	Kandemir et al. (39)	CHB	54	20.3
Total			**CHB**	**5961**	**20.0%**
			LC	**1421**	**32.0%**

CHB: Chronic hepatitis B, LC: Liver cirrhosis

Table 6. Anti-HDV prevalence in CHB and LC cases in different regions of Turkey

Center	CHB		LC	
Western Anatolia				
İstanbul	1524	16.5%	389	26.9%
İzmir	2181	14.0%	358	24.0%
Central Anatolia				
Ankara	508	28.0%	59	44.4%
Eastern-Southeastern Anatolia				
Diyarbakır	487	38.0%	289	59.4%
Van	169	33.3%	347	30.0%
Mean value for Turkey	**596**	**20.0%**	**1421**	**32.0%**

References: Table 5.

Turkey vs İstanbul:	p=0.001	Turkey vs İstanbul:	p<0.005
Turkey vs İzmir:	p<0.001	Turkey vs İzmir:	p<0.01
Turkey vs Ankara:	p<0.001	Turkey vs Ankara:	p>0.05
Turkey vs Diyarbakır:	p<0.001	Turkey vs Diyarbakır:	p<0.001
Turkey vs Van:	p<0.001	Turkey vs Van:	p>0.05

CHB: Chronic hepatitis B, LC: Liver cirrhosis

value for Turkey, where the difference is insignificant (p>0.05).

c. The change in the anti-HDV rate from the 1980's until today in LC cases all over the country was similar to that of the CHB cases, and it was significant (Table 7). The positivity rate of 43.5% between 1980 and 1990 decreased to 26.1% from 1991-2000 and to 24.0% from 2001-2005 (p<0.001).

d. Similar reductions were observed in the western and eastern-southeastern parts of the country. The rate of 34.2% in İstanbul between 1980 and 1990 decreased to 19.6% between 2001 and 2005 (p<0.001) (Table 8). Similarly, the rate was 74.0% between 1980 and 1990 in Diyarbakır, and this decreased to 58.0% from 1991-2000 and to 19.6% from 2001-2005 (p<0.001).

Hepatocellular Carcinoma

The number of studies on anti-HDV infection in HCC is limited in our country (Table 10). In a total of 748 cases studied since the 1980's until today, the mean anti-HDV positivity was 23%. When the study by Emri et al. in Ankara was disregarded due to the restricted number of cases, it appears that the positivity in the western parts of the country, between 4.2% and 15% (mean value 9%), was lower than the rate in Elazığ and Diyarbakır, with 37.5% to 45% (mean value 42%), and the difference was significant (p<0.001) (Table 9).

Table 7. Change in anti-HDV positivity in CHB and LC cases in Turkey by years

Years	Group	No. of Cases	Anti HDV+ (%)
1980-1990	CHB	204	31.0
1991-2000	CHB	4271	19.4 (p<0.001)
2001-2005	CHB	1486	11.0
1980-1990	LC	302	43.3
1991-2000	LC	157	26.1 (p<0.001)
2001-2005	LC	805	24.0

References: Table 5
CHB: Chronic hepatitis B, LC: Liver cirrhosis

Table 8. Change in anti-HDV positivity for CHB and LC cases in İstanbul between 1980 and 2005

Year	CHB	Anti HDV+	LC	Anti HDV+
1980-1990	125	28%	73	34.2%
1991-2000	705	12%	--	--
2001-2005	719	5%	316	19.6%
References: Table 5		p<0.001		p<0.001

CHB: Chronic hepatitis B, LC: Liver cirrhosis

Table 9. Change in anti-HDV positivity for CHB and LC cases in Diyarbakır between 1980 and 2005

Years	CHB	Anti HDV+	LC	Anti HDV+
1980-1990	---	---	60	74.0%
1991-2000	319	38.8%	110	58.0%
2001-2005	168	32.1%	179	46.3%
References: Table 5		p<0.001		p<0.001

CHB: Chronic hepatitis B, LC: Liver cirrhosis

Table 10. Anti-HDV positivity for HCC cases in Turkey

Center	Researcher	Year	No.	Anti HDV+
Western Anatolia				
İzmir	Batur et al.(1)	1985		6.0%
İstanbul	Özdemir et al.(56)	1993	54	11.0%
İstanbul	Özyılkan et al.(57)	1996	47	4.2%*
İstanbul	Ökten et al.(58)	2001	66	15.0%
İstanbul	Ökten et al.(13)	2003	66	7.6%
Central Anatolia				
Ankara	Emri et al.(1)	1989	6	33.3%
Eastern-Southeastern Anatolia				
Elazığ	Koca et al.(1)	2004	23	43.5%
Diyarbakır	Kadıköylü et al.(59)	1994	32	37.5%**
Diyarbakır	Yalçın et al.(36)	2003	110	45.0%
Total			748	23.0%
Overall Turkey	Uzunalimoğlu et al.(14)	2001	69	18.8%

Compared to overall Turkey *p<0.001 **p<0.0001
HCC: Hepatocellular carcinoma

DISCUSSION

The results of a retrospective study related with HDV seroprevalence in AVH, CHB, LC and HCC cases from the 1980's until today in Turkey indicate the significance of HDV infection (Table 11).

The anti-HDV studies of AVH and AHB produced relatively different outcomes (1, 15-26) (Table 1), which may result from the disparity in the centers and number of cases. However, the majority of studies except for those in Southeastern Anatolia

Table 11. Anti-HDV positivity in several liver diseases in Turkey (1980-2005)

Group	No. of Cases	Anti HDV+
Acute Viral Hepatitis	1416	3.0%
Acute Hepatitis B	766	8.1%
Inactive HBsAg Carrier	6613	4.9%
Chronic Hepatitis B	5961	20.0%
Liver Cirrhosis	1264	32.5%
Hepatocellular Carcinoma	748	23.0%

produced similar results, like 0.0% - 4.5% in AVH cases and 2.5% - 7.4% in AHB cases, with the exception of the three higher results reported from Ankara and Kayseri as 17.9%, 12.5% and 20.7% (Table 1). The three results from Diyarbakır in the Southeastern Anatolia were quite high and comparable to each other, at 15%, 22% and 25%. When all results are considered, it seems that the anti-HDV positivity was 3.0% in 1, 416 AVH cases and 8.8% in 833 AHB cases, which was significantly high. The most important and significant finding was the higher results in Southeastern Anatolia both in AVH and AHB cases compared to the results of the western regions (Table 2, $p<0.001$). This indicates the significance of HDV infection, and verifies the information about high HDV infection, which is common for the chronic liver diseases in those regions. However, lack of any new studies related with this subject in Southeastern Anatolia raises concerns about the latest status of the anti-HDV positivity for AVH in this region. It would not be surprising to determine that HDV infection had decreased throughout the country in recent years.

There are many studies on anti-HDV for inactive HBsAg carriers (1, 27-39) (Table 3). The results are somewhat similar except for a few studies reported from İstanbul, Ankara and Kayseri, which are higher than the expected (Table 3, 11.2%, 16.5%, 15.6% and 11.2%). Furthermore, three studies from Diyarbakır had similar reports. When all studies are considered, there appears to be a mean of 4.9% positivity in 6, 613 inactive HbsAg carriers throughout Turkey, and there is no difference between the regions in that sense. The overall rate verifies the low endemicity in our country.

On the other hand, the change in the anti-HDV positivity of inactive HBsAg carriers over time provided interesting results. As shown in Table 4, the posivity rate of 4.1% in the 1980's and 5.4% in the 1990's significantly declined to 2.9% in the 2000's ($p<0.01$). This is most likely due to better recogniton of HBV and consequently HDV, carriers becoming more conscious and to the impact of overall precautions. This trend can be expected to continue in the coming years.

Many studies were carried out in Turkey about HDV in chronic hepatitis and liver cirrhosis (1, 19, 29, 30, 33, 34, 36-55). Some of them provided particularly interesting outcomes (Table 5). The same center, and even the same researcher, produced different results, which might have been due to the disparity in the patient groups and number of cases. However, in studies with low anti-HDV rates, it was likely that anti-HDV was not studied in all HBV-positive cases. In groups of CHB or LC cases, the limited number of cases studied for anti-HDV was mistakenly considered valid for the whole group and this naturally produced lower results. Anti-HDV positivity should only be compared to the total number of cases studied for anti-HDV. Just as in all HbsAg-positive cases, serious prospective trials studying anti-HDV produced similar results.

When all reported results are considered, it appears that the anti-HDV positivity is 20.0% in CHB cases (5991) and 32.0% in LC cases (1421). Thus, 1/5 of CHB patients and 1/3 of cirrhosis patients have HDV infection, which is compliant with the mean endemicity in our country compared to the European and Western countries (9).

A detailed analysis of the results indicates the regional differences for anti-HDV positivity (Table 6). In western cities like İstanbul and İzmir, the positivity was found very similar (16.5% and 15.4% for CHB, and 26.9% and 24.0% for LC, respectively). These rates are lower than the mean values for Turkey, 20% and 32% ($p=0.001$, $p<0.001$, $p<0.05$, $p<0.01$). However, the rates for CHB and LC become increasingly high in Central Anatolia (28% for CHB in Ankara), particularly in Eastern and Southeastern Anatolia (33.3% and 38.0% and 59.4% in Van and Diyarbakır). These results were significantly higher than others ($p<0.001$, $p<0.001$, $p<0.001$).

On the other hand, the change in anti-HDV positivity over time produced interesting outcomes (Table 7). Anti-HDV positivity has shown significant reduction both in CHB and LC since the 1980's. The positivity declined from 31.0% to 19.4% and 11.0% in CHB and from 43.3% to 26.1% and 24.0% in LC ($p<0.001$ and $p<0.001$). This overall result supports that the course previously ob-

served in European and Western countries continues in Turkey as well and that HDV infection decreases.

The regional results reveal that HDV infection is common in each region (Tables 8, 9). However, the reduction is more prominent in the western part of the country (28%, 12% and 5% for CHB and 34.2% and 19.6% for LC in İstanbul), while it was lower in Southeastern Anatolia (38.2% and 32.1% for CHB and 74.0%, 58.0% and 46.3% for LC in Diyarbakır). Nevertheless, HDV infection is still high in Eastern and Southeastern Anatolia and sudden reductions should not be expected in the near future. However, due to mass immigration from the east to the west, particularly to the big cities in our country, it has been verified that the profile of the patients with liver disease has altered in the large cities.

The number of studies on anti-HDV positivity in HCC cases is restricted in our country (1, 36, 13, 56-60) (Table 10). The overall anti-HDV positivity in Turkey was 23% on average in a total of 748 cases, which is close to the result of the first and single study by Uzunalimoğlu et al. (14) (18.8%) carried out country-wide and to the result of a multicentered (60) study which was performed in Eastern and Southeastern Anatolia (25%). The latter found that the overall mean was lower than the expected due to cities like Erzurum, Malatya and Gaziantep with rare HDV infections, whereas significantly higher values (40.0%) were obtained in Elazığ and Diyarbakır with frequent HDV infection (1, 36, 59). The study by Yalçın et al. (60) highlighted the significance of HDV, with 61.4% HDV positivity in 57 HBV-positive HCC cases. When the study by Emri et al. was excluded due to its limited number of cases, the anti-HDV positivity was 4.2%-15% in the western part of the country, but 40% in Elazığ and Diyarbakır, and the difference was significantly high ($p<0.0001$). This complies with the high anti-HDV rate in the other liver diseases in those regions.

Our results from inactive HBsAg carrier, CHB and LC cases were parallel to the study performed by Sagnelli et al. (10) demonstrating the reduction in HDV endemicity in Italy. They found significant reduction in the anti-HDV positivity in healthy HBsAg carriers, and CHB and LC cases studied for anti-HDV seropositivity between 1987 and 1992. It was shown that the anti-HDV positivity was 23.4% in 1987, declining to 14.4% in 1992. This was explained by the overall reduction in HBV infection in the country and the consequent decrease in chance of horizontal contagion, by the fight against HIV, the common availability of vaccine for HBV and overall health precautions.

Despite reductions country-wide in recent years, high HDV endemicity, particularly in Eastern and Southeastern Anatolia, is likely a result of the high prevalence of HBV infections in our country, multi-membered family structure with close contact, unavailability of HBV vaccine, use of common injectors in the rural areas, poor circumcision and lack of health services and sanitation. This is reminiscent of the previous status of countries like Italy and Greece years ago.

In conclusion, the significance and role of HDV infection in chronic liver diseases throughout the country, particularly in Eastern and Southeastern Anatolia regions, are remarkable. Furthermore, better recognition of HDV infection, which is gradually decreasing in the European and Western countries but remains significant in Turkey, will help us in the struggle against HBV and HDV.

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