

CLINICAL STUDIES

Seropositivity for delta hepatitis in patients with chronic hepatitis B and liver cirrhosis in Turkey: a meta-analysisHalil Değertekin¹, Kendal Yalçın², Mustafa Yakut² and Cihan Yurdaydin³

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Abstract

Background: Recent reports suggest a decline of delta hepatitis (DH) in the West as well as in the Far East. **Aim:** To study the DH seroepidemiology in Turkey. **Methods:** Statistical power analysis was utilized based on data available in a recent article using prevalence figure estimates. Binominal distribution was applied in order to assess the number of samples required to estimate the prevalence with a given precision. **Results:** Out of 62 studies in the original study, 32 were eliminated because of insufficient power. A total of 6734 patients (5231 with chronic hepatitis and 1503 with cirrhosis) were analysed. Anti-HDV seropositivity among patients with chronic hepatitis B (CHB) and hepatitis B-induced cirrhosis was lowest in the west of the country and highest in the southeast (5 vs. 27%, $P < 0.0001$ and 20 vs. 46%, $P < 0.0001$) respectively. Compared with data obtained before 1995, after 1995, DH prevalence in patients with CHB and cirrhosis decreased from 29 to 12% ($P < 0.0001$) and from 38 to 27% ($P = 0.03$) in central and southeast Turkey and from 38 to 20% ($P < 0.0001$) and from 66 to 46% ($P < 0.002$) in west and southeast Turkey respectively. **Conclusion:** Despite the decrease of its prevalence in Turkey, DH remains a significant health problem in parts of the country with low socio-economic level.

Hepatitis B, C and D are the three hepatotropic viruses that can lead to chronic liver disease. Among these three hepatotropic viruses, hepatitis B virus (HBV) and hepatitis C virus infections are the most important and common causes of chronic liver disease in Turkey in parallel to the rest of the world. These infections are a major cause of morbidity and mortality. Almost forgotten is the impact of the third virus, the hepatitis D virus (HDV), on the burden of chronic liver disease. The hepatitis delta virus (HDV) leads to liver disease through the helper function of the HBV (1). Chronic delta hepatitis (DH) is significant in the context that it is associated with the most severe form of chronic viral hepatitis (1). In the 1990s, a number of reports have indicated a decline in the prevalence of HDV infection in the West as well as in the Far East (2–4); however, it needs to be seen and assessed whether the trend is similar in other areas of the world.

Turkey is a hepatitis B endemic country where studies in blood donors reported an HBsAg carrier rate between 4 and 5% with striking differences in prevalence rates between the west and the east of the

country (5). This variance in prevalence between west and east Turkey is also reflected in studies on HDV prevalence. A major limitation is that these studies (6–8) either were presented only in abstract form or were published in Turkish and thus are practically not available for the rest of the world liver community.

A retrospective analysis of data on antiHDV seropositivity rate in chronic hepatitis B (CHB) and liver cirrhosis (LC) patients from different regions of Turkey has recently been published (9). The time period of interest was between 1980 and 2005. In the current study, the above mentioned study was re-analysed with the aim of reaching a more objective epidemiological estimate of the DH burden in Turkey. The prevalence of HDV in the setting of both chronic hepatitis and LC was analysed separately. Regional differences as well as potential chronological changes were investigated.

Patients and methods

The study by Değertekin *et al.* (9) forms the base of the current meta-analysis. In the study by Değertekin

et al., all published material indexed in the Turkish Medical Index had been searched for the key word DH. Further, all abstract books within the time period 1980–2005 from National Gastroenterology and Hepatology Meetings were investigated. Through this intensive search, data from 20 health centres (19 university hospitals and one state hospital) located in west, central, east and southeast Turkey had been analysed. This study had information on a total of 7225 patients with chronic HBV infection, of whom 5961 had a diagnosis of CHB and 1264 had a diagnosis of LC. The diagnosis of chronic hepatitis was based on liver biopsy whereas diagnosis of LC was based on either liver biopsy or clinical findings consistent with LC. Clinical findings included related findings observed at physical examination, ultrasound and upper gastro-intestinal endoscopy. Both HBsAg and antiHDV had been looked for with available commercial serological assays.

In the current study, the study by Değertekin *et al.* (9) was re-analysed with the aim of reaching a more objective epidemiological estimate of the DH burden in Turkey using reasonable scientific logic. We used statistical power analysis based on data available in the data set using prevalence figure estimates. Because prevalence figures appeared to change according to region and time (before and after 1995), these two variables were taken into consideration when using prevalence figure estimates for power analysis. Binomial distribution was used in order to assess the number of samples required to estimate the prevalence with a given precision:

$$Q = \sum_{i=\text{round}[n(p-\delta)]}^{\text{round}[n(p+\delta)]} \binom{n}{i} p^i (1-p)^{n-i}$$

In this equation, p is the expected prevalence, δ is the arbitrary tolerance range for the estimate of p , n is the total number of random samples and Q is the probability of finding the prevalence in the range $p \pm \delta$. This equation was solved numerically for n by setting $Q=90\%$, for a given set of values of δ and p . With this approach, in an area and time frame where the prevalence of DH was approximately 30%, the number of patients required to estimate prevalence figures of $30 \pm 10\%$ with $> 90\%$ precision was calculated. The same calculation was made for prevalence figures of $5 \pm 2\%$, $10 \pm 5\%$ and $20 \pm 7\%$ with $> 90\%$ precision. Accordingly, 50, 80, 120 and 230 patients were required for $30 \pm 10\%$, $20 \pm 7\%$, $10 \pm 5\%$ and $5 \pm 2\%$ prevalence figures respectively. Out of 62 studies, 32 were eliminated because of insufficient statistical

power and the current study contains data analysis of 30 studies with 'acceptable' statistical power. Of these 30 studies, eight had been published in peer-reviewed *Turkish Gastroenterology or Infectious Diseases Journals*, 11 had been published in the form of symposia proceedings and 11 were from presentations made at National Gastroenterology, Hepatology or Viral Hepatitis Meetings (obtained from abstract books of the relevant meetings).

The χ^2 test was used for group comparisons. A P value of < 0.05 was considered as statistically significant.

Results

A total of 6734 patients were analysed. Of them, 5231 had chronic hepatitis and 1503 had LC. As expected, DH was more frequent in patients with LC compared with patients with chronic hepatitis. The analysis showed that striking geographical differences exist in the prevalence of DH in Turkey and where analysis was possible it showed that DH is decreasing in Turkey but not at the magnitude seen, for example, in Italy.

Prevalence of DH in patients with CHB is shown in Table 1. DH prevalence was around 5% in western Turkey where all analyses had been performed in the last decade. The prevalence was highest in southeast Turkey (around 30%), followed by east Turkey and central Turkey. Data on the prevalence of DH in patients with hepatitis B-induced LC are shown in Table 2. Data of the last decade suggest a prevalence of DH around 20% in western Turkey, whereas in southeast Turkey the prevalence of DH is around 45%. The differences in prevalence rates in different regions of Turkey are shown in Table 3a and b for patients with CHB and hepatitis B-induced cirrhosis respectively. In these latter tables, comparison between different regions was made by taking into account only studies performed after 1995.

Comparisons of the prevalence of DH before and after 1995 are shown in Table 4. Accordingly, the prevalence of DH among CHB cases decreased from 29 to 12% and from 38 to 27% in central and southeast Turkey respectively ($P < 0.001$ and $P < 0.001$). In patients with hepatitis B-induced LC, the contribution of DH decreased from 38 to 20% and from 66 to 46% in west and southeast Turkey respectively ($P < 0.001$ and $P < 0.001$).

Discussion

The results of this meta-analysis indicate that DH continues to be an important medical problem in Turkey. Several issues emerge from the meta-analysis:

Table 1. AntiHDV positivity in patients with chronic hepatitis B in Turkey

Region	Year	Researcher	No.	Anti-HDV	
				(%)	<i>n</i>
West Turkey					
Istanbul	1997	Ökten <i>et al.</i> (6)	526	4.5	24
Istanbul	2001	Tabak <i>et al.</i> (10)	423	7.0	30
Istanbul	2003	Ökten <i>et al.</i> (8)	296	2.9	9
Bursa	1997	Nak <i>et al.</i> (11)	579	3.5	20
Izmir	1999	Ersöz <i>et al.</i> (12)	1551	4.7	73
Izmir	2001	Akarca <i>et al.</i> (13)	526	6.1	32
Total			3901	4.8	188
Central Turkey (< 1995)					
Ankara	1991	Erbaş <i>et al.</i> (14)	191	31.5	60
Ankara	1992	Okçu <i>et al.</i> (15)	51	21.8	11
Ankara	1993	Özyılkan <i>et al.</i> (6)	123	28.4	35
Total			365	29.0	106
Central Turkey (> 1995)					
Ankara	2000	Görenek <i>et al.</i> (16)	89	8.6	8
Eskişehir	1999	Us <i>et al.</i> (6)	77	15.6	12
Total			166	12.1	20
Southeast Turkey (< 1995)					
Diyarbakır	1994	Canoruc <i>et al.</i> (17)	100	30.0	30
Diyarbakır	1995	Turfan <i>et al.</i> (6)	54	51.7	28
Total			154	37.7	58
Southeast Turkey (> 1995)					
Diyarbakır	1998	Değertekin <i>et al.</i> (18)	120	20.0	24
Diyarbakır	2003	Yalçın <i>et al.</i> (19)	168	32.1	54
Total			288	27.1	78
East Turkey					
Elazığ	2001	Yalınz <i>et al.</i> (19)	209	16.5	35
Elazığ	2003	Türkdoğan <i>et al.</i> (19)	148	33.3	49
Total			357	23.5	84

(i) DH is more prevalent in the east and the southeast of the country compared with the west; (ii) DH is decreasing in Turkey; (iii) despite this, more than a quarter of CHB cases and almost half of cirrhotic cases are caused by HDV in southeast Turkey, underlining the importance of DH in Turkey.

The original study (9) had put together all available data on the sero-epidemiology in DH in Turkey. The current study, in contrast, tried to be 'selective'. Most studies subject to this re-analysis were of retrospective origin, and it appeared that none had used strict scientific epidemiological random sampling methodology. These retrospective studies of course bear the pitfalls and deficiencies of being retrospective. Because we felt that 'suboptimal data' is better than 'no data', the aim in this study was to put forward 'the better' studies in this set of 'suboptimal' data collection to have a more reliable estimate of the DH burden in Turkey. In order to differentiate between 'more' vs.

'less' reliable data, statistical power analysis was used based on data available in the data set using prevalence figure estimates in the original study. This 'selection' process appears to have been successful in the context that it led to the avoidance of striking differences seen in different reports from the very same region in the original study.

More data were available, expectedly, from big centres in the west of the country compared with the east of the country. This can lead to a certain bias in the context of overrepresentation of some regions. We therefore refrained from giving 'total numbers' and 'overall prevalence figures' in Tables 1 and 2.

This study is based on serological testing, and confirmation of ongoing HDV infection by PCR testing of HDV RNA is lacking. The impact of this lack of information is that patients with and without active delta infection cannot be differentiated, which is beyond the scope of this study.

Table 2. AntiHDV positivity in patients with liver cirrhosis in Turkey

Region	Year	Researcher	No.	Anti-HDV	
				(%)	<i>n</i>
West Turkey (< 1995)					
Istanbul	1988	Okten <i>et al.</i> (6)	73	34.2	25
Izmir	1985	Batur <i>et al.</i> (6)	110	41.0	45
Total			183	38.3	70
West Turkey (> 1995)					
Izmir	1996	Kuruüzüm <i>et al.</i> (6)	107	14.0	15
Izmir	2001	Akarca <i>et al.</i> (14)	141	25.8	36
Istanbul	2003	Okten <i>et al.</i> (11)	316	19.6	62
Total			564	20.0	113
Central Turkey					
Ankara	1989	Emri <i>et al.</i> (6)	59	44.4	26
Southeast Turkey (< 1995)					
Diyarbakir	1989	Degertekin <i>et al.</i> (6)	60	74.0	44
Diyarbakir	1995	Turfan <i>et al.</i> (6)	50	58.0	29
Total			110	66.4	73
Southeast Turkey (> 1995)					
Diyarbakir	2004	Yalcin <i>et al.</i> (19)	179	46.3	83
East Turkey					
Elazig	2004	Koca <i>et al.</i> (20)	120	30.0	36
Van	2001	Tuncer <i>et al.</i> (21)	115	20.8	24
Van	2003	Turkdogan <i>et al.</i> (19)	75	45.3	34
Van	2004	Uygan <i>et al.</i> (22)	157	23.0	36
Total			467	27.8	130

Table 3. Prevalence of delta hepatitis according to geographical region in patients with chronic hepatitis B is shown in Table 3a and in patients with hepatitis B-induced cirrhosis in Table 3b

Region	Total <i>n</i>	Delta (+) <i>N</i> (%)
3a		
West Turkey	3901	188 (4.82%) ^{1,2}
Central Turkey	166	20 (12.1%) ^{3,4}
East Turkey	357	84 (23.5%)
Southeast Turkey	288	78 (27.1%)
3b		
West Turkey	564	113 (20.0%) ^{5,6}
East Turkey	467	130 (27.8%) ⁶
Southeast Turkey	179	83 (46.3%)

¹*P* < 0.0001 vs. central Turkey.²*P* < 0.0001 vs. east and southeast Turkey.³*P* = 0.0032 vs. east Turkey.⁴*P* = 0.0003 vs. southeast Turkey.⁵*P* < 0.0042 vs. east Turkey.⁶*P* < 0.0001 vs. southeast Turkey; all data are from studies reported after 1995.

The accumulation of DH to the east and southeast of the country can be linked to the lower socio-economic status of these regions, which represent the poorest parts of Turkey. The decline in DH prevalence in the last 10 years may be compared with the reports of a decline in DH prevalence reported from the West,

Table 4. Change in delta hepatitis prevalence among patients with chronic hepatitis B in different regions of Turkey

Disease group	Prevalence		<i>P</i> value
	< 1995 <i>n</i> (%)	> 1995 <i>n</i> (%)	
Central Turkey CHB	106/365 (29.0%)	20/166 (12.1%)	< 0.001
Southeast Turkey CHB	58/154 (37.7%)	78/288 (27.1%)	< 0.001
Western Turkey LC	70/183 (38.3%)	113/564 (20.0%)	< 0.001
Southeast Turkey LC	73/110 (66.4%)	83/179 (46.4%)	< 0.001

CHB, chronic hepatitis B; LC, liver cirrhosis.

especially Greece and Italy (2, 3, 23) and from the Far East (4). However, a decrease in prevalence of DH in western countries is not a universal finding owing to new migration routes as a recent report suggests (24). On the other hand, the decline in Turkey, especially in southeast and east Turkey, is less striking and in these regions prevalence figures are still high and a reason for concern. The introduction of disposable syringes in 1990 in Turkey is likely to have contributed the most to this decline whereas public awareness of transmission routes and preventive measures may have had less

effect because of low socio-economic and educational level. The effect of universal HBV vaccination, which started in 1995 in Turkey, is expected to affect prevalence figures in the years to come.

In summary, DH continues to be a significant health problem in southeast and east Turkey and this should without doubt not be confined to the Turkish borders. It indicates that DH should also be a major health problem for neighbouring countries of southeast Turkey such as Iran, Iraq and Syria. A study from Iran reporting anti-HDV positivity in roughly half of patients with chronic liver disease supports these assumptions (25). The same line of reasoning also applies to the impact of DH in east Turkey and the countries that border east Turkey, namely Azerbaijan and Armenia. It is thus hoped that this study will refresh the awareness of the burden of delta virus not only at the national but also at the international level.

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