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Prevelance of hepatitis D co-enfection in children with hepatitis B infection: Cross-sectional analyses from Western Turkey

Funda ÖZGENÇ, Çiğdem ÖMÜR ECEVİT, Gülin ERDEMİR[1], Rüçhan SERTÖZ, Raşit Vural YAĞCI

Department of Pediatric Gastroenterology, Ege University School of Medicine, İzmir

Background/aims: *Effective hepatitis B virus control has warranted a decline in hepatitis B virus prevalence over the world with a relevant reduction in hepatitis B virus-associated delta hepatitis. However, despite the dramatic decline in hepatitis D virus infection rate, no further decrease was recorded after 2000. This cross-sectional study aims to investigate: I- The prevalence of hepatitis D virus co-infection in children with hepatitis B virus infection in Western Turkey; II- The influence of neonatal hepatitis B virus vaccination on hepatitis D virus co-infection rate; and III- The impact of co-infection on prognosis of liver disease.* ***Materials and Methods:*** *Serological markers of hepatitis B virus and hepatitis D virus infections were determined by ELISA in patients with chronic hepatitis during immune tolerance, immunoactive, HBeAg-negative chronic, and inactive carrier state. Delta co-infection rate was evaluated in two groups, children born before and after the national neonatal mass vaccination has started (before and after 2000). Viral load, serum alanine aminotransferase, and histological grade were evaluated in co-infected cases.* ***Results:*** *Overall hepatitis delta virus infection rate was 1,76% (3/170); two patients with eAg-negative chronic hepatitis B and one patient in the immunoactive phase were infected with hepatitis D virus. Mean fibrosis score of hepatitis D virus -infected cases and hepatitis B virus -infected counterparts were 4±1,7 and 1,3±1, respectively (p: 0,006). Hepatitis D virus infection was detected in 2 out of 158 children born before and in 1 of 12 born after the neonatal vaccination program. Hepatitis B e-antibody was detected in two patients with delta co-infection (11 and 6 years old), and all mothers of delta hepatitis cases were chronically hepatitis B virus-infected.* ***Conclusions:*** *Delta hepatitis is rare among hepatitis B virus-infected children in the Western region of Turkey. Despite the success of the national vaccination program, delta hepatitis is not a vanishing disease and it has a grave prognosis due to development of early cirrhosis.*

Key words: Hepatitis B, delta hepatitis, children

Hepatit B enfeksiyonu olan çocuklarda hepatit D ko-enfeksiyonu sıklığı: Türkiye'nin batı bölgesinden kesitsel analiz

Giriş ve Amaç: *Hepatit B virüsünün kontrolü ile dünyada gerek hepatit B virüsü ve gerekse delta hepatiti prevalansında azalma sağlanmıştır. Ancak; ilk zamanlarda delta hepatiti sıklığında izlenen dramatik düşüş 2000'li yıllardan sonra izlenmemiştir. Bu kesitsel çalışmada şunlar hedeflenmektedir: I- Türkiye'nin batı bölgesinde hepatit B virüsü enfeksiyonlu çocuklarda delta hepatiti ko-enfeksiyon sıklığını belirlemek II- Yeni doğan hepatit B virüsü aşı programının delta hepatiti ko-enfeksiyon sıklığına etkisini belirlemek III- Karaciğer hastalığının prognozu üzerine delta hepatiti'nin etkisini belirlemek.* ***Gereç ve Yöntem:*** *Kronik hepatit B virüsü enfeksiyonunun immun toleran, immunoaktif, HBeAg negatif ve inaktif taşıyıcılık fazında olan olgularda hepatit B virüsü ve delta hepatiti serolojisi ELİSA yöntemi ile çalışıldı. Ulusal yeni doğan aşılamasından önce ve sonra doğanlar olmak üzere 2 grupta delta hepatiti ko-enfeksiyon sıklığı değerlendirildi. Viral yük, serum alanin aminotransferaz ve histolojik derecelendirme delta hepatiti ko-enfeksiyonu olan ve olmayan olgularda karşılaştırıldı.* ***Bulgular:*** *Tüm olgularda delta infeksiyonu sıklığı 1,76% (3/170) bulundu. HBeAg negatif kronik hepatitli 2 hasta ve immunoaktif 1 hastada delta hepatiti enfeksiyonu tespit edildi. Sadece hepatit B enfeksiyonu ve delta hepatiti dual enfeksiyonu olan hastalarda ortalama fibrosis skoru sırasıyla 1,3±1 ve 4±1,7 bulundu (p: 0,006). Hepatit delta sıklığı aşılama öncesi ve sonrası doğan çocuklarda sırasıyla, 2/158 (%1,2) ve 1/12 idi. Hepatit e antikoru (anti-HBe) delta hepatiti tespit edilen olguların 2'sinde pozitifti ve tüm çocukların annelerinde kronik hepatit B enfeksiyonu mevcuttu.* ***Sonuç:*** *Türkiye'nin batı bölümünde, hepatit B virüsü ile enfekte çocuklarda delta hepatiti sıklığı düşüktür. Ulusal aşı programına rağmen, delta hepatiti ortadan kaldırılamamıştır ve bu olgular erken yaşta siroza ilerlemektedir.*

Anahtar kelimeler: Hepatit B virusu, delta hepatiti, çocukluk çağı

Address for correspondence: Funda ÖZGENÇ
Ege University, Department of Pediatric Gastroenterology, İzmir, Turkey
E-mail: funda.ozgenc@ege.edu.tr

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INTRODUCTION

The hepatitis D virus (HDV) is endemic worldwide, but the prevalence of infection varies in different geographical areas. Since the super-infection of hepatitis B virus (HBV) carriers represents the major mechanism of acquisition of defective HBV-dependent HDV, it is particularly prevalent in endemic areas for HBV infection (1). Mass vaccination and sanitary measures have warranted a decline in the number of HBV infection and a relevant decline in HBV-related HDV. In Turkey, HDV prevalence in inactive HBsAg carrier adults diminished from 7,4% to 4,4% and 1,4% for the years 1980, 1990 and 2000, respectively (2-5). This progressive decline in HDV designated a clear age-dependent pattern with prevalence distinctly higher in carriers over 50 years of age reflecting past rather than recent infection (6). On the contrary, a recent Italian survey has documented a trend to higher anti-HD prevalence in HBeAg-positive carriers suggesting recent infection (7). Moreover, despite the dramatic decline in HDV infection rate and the hope for eliminating the disease, no further decrease was recorded after 2000. Longitudinal epidemiologic surveys might enlighten the ongoing arguments in the future. However, pediatric population concerning the children before and after mass HBV vaccination program may serve as a good model to predict the HDV risk in the future.

Hereby, this cross-sectional study aims to investigate: I - the prevalence of HDV co-infection in children with HBV infection in the Western part of Turkey; II - the influence of national infant HBV vaccination on HDV co-infection rate; and III - the impact of HDV co-infection on prognosis of liver disease.

PATIENTS and METHODS

Serum samples of 170 children with HBV infection were evaluated for the detection of total anti-HDV. Serological markers of hepatitis B infection (HBsAg, HbeAg, anti-HBe) were measured by enzyme-linked immunosorbent assay (ELISA), and HBV DNA levels were determined by solution hybridization technique before 2002 and, thereafter, by quantitative polymerase chain reaction (PCR) assay with a detection limit of 100 copies/mL. Total anti-HDV antibody levels were measured by ELISA in the 170 patients. Liver enzymes were analyzed and the phase of HBV infection was defined as follows: immune tolerance [HBeAg +, normal alanine aminotransferase (ALT), HBV-DNA level more than 10^4 copies/mL, hepatic activity index (HAI) less than 5], immunoactive (elevated ALT, HBV-DNA level more than 10^4 copies/mL, HAI more than 5), HBeAg-negative chronic HBV (elevated ALT, HBV-DNA level more than 10^4 copies/mL, HAI more than 5, HBeAg -, anti-HBe +), and inactive carrier state (normal ALT, HBV-DNA less than 10^4 copies/mL, normal liver histology, anti-HBe +), screened at 3-month intervals for at least 1 year (8). There was no child with decompensated liver disease and liver biopsy was performed in 85 (89.5%), 6 (75%), and 34 (64.2%) children in the immunoactive, HBeAg-negative chronic HBV, and immune tolerance phase, respectively. Liver biopsy was taken after 2 years of follow-up for screening ALT flare in immune tolerant patients according to the local protocol. Histopathologic evaluation was made according to the Knodell (HAI) scoring system, and after 2005 - according to the modified Knodell scoring system; cirrhosis was defined by fibrosis stage greater than 5. Delta co-infection rate was evaluated and another comparison was applied between the two groups, children born before and after the national neonatal mass vaccination has started (before and after 2000). Viral load, serum ALT, and histological grade were evaluated in co-infected cases.

RESULTS

Overall delta virus infection rate was 1,76% (3/170); two patients with eAg-negative chronic hepatitis B and one patient in the immunoactive phase were infected with HDV. Patient characteristics of the study group are shown in Table 1. Mean fibrosis score of HDV-infected cases and HBV-infected counterparts were 4±1,7 and 1,3±1 (p: 0,006). HDV was detected in 2 out of 158 children born before the neonatal HBV vaccination program and in one patient of 12 born after the millennium. Hepatitis B hyperimmunglobulin (HBIG) and three doses of HBV vaccine were administered in one child whose mother was known to be infected with HBV before labor. Index cases were mothers in all HDV cases and acute hepatitis was defined in one patient (Table 2). Low viral DNA with advanced fibrosis was observed in all dual infections. The characteristics and histological scoring of HDV-infected patients are shown in Table 3.

DISCUSSION

Universal HBV vaccination, better public health standards, and effective human immunodeficiency

Table 1. Patient characteristics and HDV infection rate of the patient group

	Immune tolerant Cases (n: 53)	Immunoactive HBV (n: 95)	eAg-negative chronic HBV (n: 8)	Inactive carrier (n: 14)
Mean ALT±SD (U/L)	38±22	94,6±88,9	135,5±131,5	30,6±11,2
Mean HBV DNA level ±SD pg/mL (n*)	1679,2±6683,4 (n: 41)	1861,8±1319,2 (n: 74)	3802,4±3620 (n: 8)	471,6±397,5 (n: 6)
Copies/mL (n**)	$2,2x10^7$±$2.4x10^8$ (n: 12)	$1,9x10^7$±$2,5x10^8$ (n: 21)	-	$3x10^3$±$1,4x10^4$ (n: 8)
Mean HAI score ±SD	3,8±1,6	8,8±3,4	8,4±4	-
Mean fibrosis score ±SD	0,6±0,5	1,6±1	2,8±1,8	-
Anti-HDV-positive patients (n,%)	∅	1/95 (1,05%)	2/8 (25%)	∅

* Number of patients evaluated with solution hybridization, **Number of patients evaluated with HBV-DNA PCR.

Table 2. History of HDV infected cases

Patient ID	Age (years)	HBV index case in the family	HBV Vaccination	Acute hepatitis history
OO	17	Mother	∅	∅
SK	12	Mother	∅	∅
MHK	6	Mother	Three doses	(+)

Table 3. Patient characteristics of HDV-infected cases

Patient ID	OO	SK	MHK
ALT (U/L)	71	74	69
HBsAg	(+)	(+)	(+)
HBeAg	(+)	(-)	(-)
HBV-DNA (copies/mL)	$8.9x10^2$	1.4x10	(-)
Interface hepatitis	2	4	3
Inflammation	2	4	4
Fibrosis	6	6	5
Grade/Stage	6/6	6/6	5/6

virus (HIV) control have eventuated in a decline in the number of HBV infection and a relevant decline in HBV-related HDV infection. However, it remains an important problem in Turkey since HDV is the second cause of liver disease in adults in the Eastern regions and the third cause in the Western parts of the country (4, 5). There are no data on neither the prevalence of HDV nor the acquisition age and route of the infection among children in Turkey. In the present study, HDV prevalence among chronically HBV-infected children was 1.76%. This observation well correlates with 1.4% prevalence after the millennium among adults in Turkey (3, 8). Attention was drawn to the children born after the national neonatal HBV vaccination program, and HDV was demonstrated in a child born from a HBV-infected mother. He was vaccinated and HBIG was also administered. His HBV was suspected to be a surface antigen mutant, but a mutation analysis was not held. All three children were HBeAg-positive and HDV existed despite HBV vaccination. Our observations counter with the observations of Sakugawa et al. (6) that HDV prevalence increases with age and may also shed insight against the expectation of HDV elimination.

All three children infected with HDV had mothers as index cases in their family. Childhood viral transmission is acquired mainly from the family. So, HDV prevalence concordant with the adult population is an expected result. Longitudinal surveys of case series would better define the transmission route and acquisition age of the two viruses; however, two epidemiologic analyses from the Western part of Anatolia have reported that horizontal contamination with higher risk after 10 years of age is the major way of HBV acquisition (8). In our patients with HDV, patients' age corresponded with expected HBV contagion age in two children, but the last child acquired the virus perinatally. Since all three mothers were infected with HBV and HDV, it is not possible to suggest if HDV presented as dual infection or superinfection; however, history of hepatitis in the youngest child may be suggestive of HDV superinfection.

Dual infection with hepatitis B and delta virus is a significantly more severe condition evolving to cirrhosis (9, 10). Higher prevalence of HDV infection is found in the more severe form of HBV infection suggesting that HDV infection increases the severity of HBV infection (11). Among our group, all 3 cases co-infected with HDV had cirrhosis on biopsy. The third child in our group presented with acute hepatitis a year ago and cirrhosis was documented at very young age. This may correspond with the observation that the prevalence of histological cirrhosis showed a linear increase over the years after acute delta hepatitis episode, reaching 23% (10/43), 41% (9/22), and 77% (9/13) after 10, 20 and 30 years, respectively (12). Rapid progression to cirrhosis within 2 years has been also reported in up to 10-15% of delta hepatitis cases; however, cirrhosis in early age of our third case may also be attributable to perinatal acquisition of HBV.

In conclusion, delta hepatitis is rare among HBV-infected children in the Western region of Turkey. Despite the success of the national vaccination program, delta hepatitis is not a vanishing disease, and it has a grave prognosis due to development of early cirrhosis.

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