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Coinfection of Hepatitis B and Hepatitis Delta Virus in Belgium: A Multicenter BASL Study. Prospective Epidemiology and Comparison With HBV Mono-Infection

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Epidemiological data on hepatitis delta virus (HDV) infection in Belgium are lacking. A multicenter questionnaire-based registry on HDV infection was collated between March 1, 2008 and February 28, 2009. It consisted of patients coinfected with hepatitis B virus (HBV) and HDV. The data samples were compared to those of a concurrent registry on HBV infection. Prospective data of patients with HBV–HDV coinfection were collected. Active HBV replication is defined as HBeAg positivity or HBV DNA $>$ 2,000 IU/ml. Forty-four patients from 15 centers were registered. A comparison of 29 patients infected with HDV (registered in the concurrent HBV registry) was made against 785 HBV mono-infected patients. The seroprevalence of patients coinfected with HBV and HDV in Belgium is reported to be 3.7% (29/785), consisting solely of the HBV–HDV coinfected patients in the HBV registry. This rises to 5.5% (44/800) if all patients infected with HDV from the two registries combined are included. The patients coinfected with HBV and HDV had higher ($P < 0.05$) ALT values and more advanced liver disease (Metavir score $\geq$F2), but had less active HBV replication and lower HBV DNA titers when compared with the patients infected only with HBV. Additionally, the majority of HBV–HDV coinfected patient was male, and 13.6% (6/44) of the patients that were coinfected HBV and HDV were also infected with HCV. In conclusion, this study provided much needed epidemiological data on the current state of HDV infection in Belgium. ***J. Med. Virol. 85:1513–1517, 2013.*** © 2013 Wiley Periodicals, Inc.

KEY WORDS: hepatitis D virus; hepatitis B virus; prevalence; registry; Belgium

INTRODUCTION

Hepatitis delta virus (HDV) is an RNA virus discovered by Rizzetto et al. [1977]. HDV requires the hepatitis B virus (HBV) surface protein (HBsAg) to replicate and a high rate of HBV infection to achieve endemicity. This was determined to be the case at the time of HDV discovery in the Mediterranean [Rizzetto et al., 1977] and other geographical areas.

Worldwide vaccination efforts to control chronic infection with HBV [Chang, 2003], the companion virus of HDV, and reports of declining anti-HDV antibody prevalence in a large group of HBsAg positive patients in Italy throughout the 1990s [Ciancio and Rizzetto, 2002], have led to the common belief that HDV infection was vanishing and subsequently reduced interest in the virus among health

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professionals. However, renewed interest emerged in the mid-2000s when Wedemeyer et al. [2007] showed a sustained prevalence of HDV in Central Europe. Further reports from Cross et al. [2008] and Le Gal et al. [2007] also showed similar findings in the UK and France, respectively. Both reports suggested that migration of individuals was an important factor in the persistence of chronic hepatitis delta infection.

There is currently a lack of epidemiological data on HBV–HDV coinfection in Belgium. However, the discovery of sustained HDV in geographically close areas such as central Europe, the UK, and France, and the established severity of HBV–HDV super infection in patients [Yurdaydın et al., 2010] necessitate a need for an epidemiological survey of HDV in Belgium. Therefore, the aim of this study was to provide epidemiological data on the prevalence and clinical characteristics of HDV infection in patients chronically infected with HBV in Belgium.

METHODS

Survey Design and Participants

A 1-year prospective, questionnaire-based registry was performed from March 1st, 2008 until February 28th, 2009 under the aegis of the Belgian Association for the Study of the Liver (BASL). Participating in the study were gastroenterologists and hepatologists from different Belgian University hospitals and large non-university hospitals. The questionnaires were standardized forms, with inquiries towards basic characteristics of the patients, HBV, HCV, and HIV status, liver disease parameters, histological parameters, and treatment modalities. Hepatic histological activity (A) and liver fibrosis (F) were measured using the Metavir score (A0-3, F0-4) [Bedossa and Poynard, 1996]. Active HBV replication was defined as when a patient was positive for HBeAg, or when HBV DNA was >2,000 IU/ml if HBeAg was determined to be negative. All questionnaires were accompanied by informed consent forms. The questionnaires were sent out to participating hepatologists and gastroenterologists throughout Belgium.

This study was undertaken in compliance with the relevant laws and institutional guidelines and in accordance with the ethical standards of the Declaration of Helsinki. The registration study was approved by the Committee of Bio-ethics of the Antwerp University Hospital. A signed informed consent form was obtained from all included patients.

Data from this registration study were compared to data from the concurrent Belgian HBsAg registry from Deltenre et al. [2012], which was conducted in the same timeframe and was made with data from approximately the same participating centers in Belgium.

Serological Analysis

Patient samples were sent to the Belgian Scientific Institute of Public Health (Brussels, Belgium), the St. Luc, UCL University Hospital (Brussels, Belgium) or the St. Pierre University Hospital (Brussels, Belgium) for HDV serologic testing. HDV serology was performed in all laboratories by detection of total anti-HDV antibodies in serum using the commercially available ETI-AB-DELTAK-2 enzyme immunoassay (DiaSorin S.p.A. Turin, Italy), in accordance to the instructions of the manufacturer.

Statistical Analysis

Data were tabulated in SPSS [version 19, IBM Inc., 2010]. Statistical analysis was performed using the Mann–Whitney *U*-test for continuous variables and the Chi-square test for categorical variables. $P < 0.05$ was considered to be statistically significant.

RESULTS

In total, 15 centers participated in the study. Forty-four patients were registered in the HDV registry as having HBV–HDV coinfection. Half of the patients (22/44) were Caucasians, 34.1% (14/44) were Black Africans, 9.1% (4/44) were from Asia and 6.8% (3/44) were from another ethnic origin. The risk factors for HBV–HDV coinfection in these patients were uncertain or unknown in the majority of the cases (56.8%, 25/44); however, in a small number of cases, intravenous drug use (11.4%, 5/44), and sexual contact (13.6%, 6/44) were identified as important risk factors. Of patients coinfected with HBV and HDV, 29.5% (13/44) tested HBeAg positive, 13.6% (6/44) had a HBV DNA level of 2,000 IU/L and 15.9% (7/44) had HBV DNA level above that. Most of the patients were untreated, only 16 were reported to have been treated with interferon or pegylated interferon and two patients underwent liver transplantation. The survey also examined HCV and HIV infection in all the patients with HBV–HDV coinfection and found that 13.6% (6/44) were also infected with HCV, but none of the patients were infected with HIV.

When comparing data from the concurrent HBsAg registry compiled by Deltenre et al. [2012], amongst the 785 patients in that registry tested for HDV antibodies, 29 patients were registered as having HBV–HDV coinfection. Fifteen more patients were entered in the HDV registry in the same centers. During the concurrent time period, these patients were not formally entered in the aforementioned HBV registry. Thus, the suspected seroprevalence in Belgium of HBV–HDV coinfection is 3.7–5.5% (29/785–44/800).

Numerous parameters were compared between (a) the patients infected with only HBV and (b) the patients infected with HBV and HDV (Table I). Patients coinfected with HBV and HDV had significantly higher ALT values. These patients presented more advanced liver disease according to the Metavir score, with significantly less HBV active replication and lower HBV DNA titers when compared with the

TABLE I. Comparison of Variables Between Patients Infected Only With Hepatitis B Virus (HBV) and Patients Co-Infected With HBV and Hepatitis Delta Virus (HDV)

Variable	HBV patients[a]	HBV–HDV patients[a]	Statistical significance
Continuous[b]			
Age	40.00(median)	38.00(median)	$P > 0.05$
HBV viral load (lU/ml)	726.00(median)	100.00(median)	$P = 0.028$
Categorical[c]			
Gender: male	67.90% (514/757)	79.31% (23/29)	$P = 0.195$
Race: non-Caucasian	48.40% (364/752)	48.28% (14/29)	$P > 0.05$
HBV active replication[d]	49.56% (336/678)	23.08% (6/26)	$P = 0.008$
Anti-HCV antibody positivity	2.55% (19/746)	7.14% (2/28)	$P = 0.142$
Anti-HIV antibody positivity	1.56% (11/707)	0% (0/28)	$P > 0.05$
ALT > 2N	13.66% (103/754)	34.48% (10/29)	$P = 0.002$
Fibrosis F3F4[e]	36.46% (144/395)	76.19% (16/21)	$P = 0.000$

[a]Total patients differ due to missing data.
[b]Analysis with Mann–Whitney *U*-test.
[c]Analysis with cross tabulation and Chi-square test.
[d]HBV active replication: HBeAg positive or HBV DNA >2,000 lU/ml if HBeAg negative.
[e]Metavir fibrosis score F3 or F4 [Bedossa and Poynard, 1996].

patients infected only with HBV from the HBsAg registry.

DISCUSSION

The large volume of research on viral hepatitis, in particular hepatitis B and more recently hepatitis C, is in stark contrast with the relative lack of interest in hepatitis delta. Therefore, this report aims to provide epidemiological data, including prevalence, of HBV–HDV coinfection in Belgium by compiling a HDV registry and comparing it with the concurrent HBsAg registry.

In the HDV registry, 44 individuals coinfected with HBV and HDV were registered over the course of 1 year. However, the concurrent HBsAg registry by Deltenre et al. [2012] found only 29 patients coinfected with HDV. This discrepancy between these two registries illustrates the inherent inaccuracy of cross-sectional registration which could be caused by the fact that the population of patients examined in both registries are not the same even though both registries compiled data from largely the same centers and time period (March 2008–March 2009) in Belgium. Despite this, the reported suspected range of seroprevalence concurs with data found in the literature and may be a better reflection of the actual seroprevalence of HBV–HDV coinfection in Belgium.

A large proportion of patients coinfected with HBV and HDV originated from outside Western Europe (Table I). Although 50% (22/44) of the patients were of Caucasian descent, only eight were confirmed from Belgian descent. Four patients were from Italy, and the remaining 10 were from Eastern Europe. Previous studies from the UK [Cross et al., 2008], Germany [Erhardt et al., 2010], and France [Le Gal et al., 2007] also reported a large proportion of HBV and HDV infected patients originating from outside Western Europe. Cross et al. [2008] studied the prevalence of hepatitis delta in the south of London and reported a seroprevalence of 8.5%. This percentage was lower (7.1%) when only UK residents were included. A significant portion of subjects were from regions of high HBV endemicity (28.1% from South and Eastern Europe, 28.6% from Africa). A retrospective study, by Erhardt et al. [2010], in Germany where the seroprevalence of 1,307 HBsAg carriers was investigated for HBV–HDV coinfection over the course of two decades (1989–2008) showed that 46.2% of subjects were immigrants from the former Soviet Union and 17.9% were from Africa. In France, an analysis of 617 patients with a novel infection with HDV from 2001 to 2006 showed a rising proportion of patients from Africa [Le Gal et al., 2007].

The Asia-Pacific region, an area known to be endemic for hepatitis B, interestingly has shown a decline in the prevalence of hepatitis delta [reviewed by Abbas et al., 2010]; most of the data incorporated in this review involved studies from the late 1990s. Recent studies from Pakistan and South Korea have revealed new and contrasting epidemiological data on HDV prevalence. Studies in Pakistan [Khan et al., 2011; Mumtaz et al., 2011] showed a high prevalence of HDV; Mumtaz et al. [2011] reported HBV–HDV coinfection at 35.2%. In addition, Khan et al. [2011] found that within Pakistan, there are significant regional differences in HDV prevalence; the Sindh area reports HBV–HDV coinfection at 67% while the Khyber Pakhtoonkhaw and Punjab areas reported 6% and 4%, respectively. In contrast to Pakistan, HBV–HDV coinfection in South Korea is reported to be very low at 0.32% (3/940 patients) [Kim et al., 2011].

Interestingly, there are certain subpopulations in the general population that maintain a high HDV prevalence. These tend to be in isolated populations that also have high hepatitis B prevalence. For example, in Greenland, there was an outbreak of hepatitis delta amongst children and adolescents 20 years old and younger [Borresen et al., 2010]. In

2006, 27% of the population in a small settlement in the west of Greenland was HBsAg positive, and 46% were 20 years old or younger; however, the percentage of HDV prevalence in that age group increased 1 year later where 68% of them were found to be anti-HDV IgG positive [Borresen et al., 2010]. A similar pattern of high HDV prevalence in isolated populations is also found in the Western Amazonian Basin [Viana et al., 2005]. Other hyper endemic regions like the southeast of Turkey also report a high prevalence of HBV–HDV coinfection (27%) [Değertekin et al., 2008].

Serological analysis in our study showed that patient coinfected with HBV and HDV have higher ALT values and generally higher fibrosis scores (Table I); this finding supports the fact that HBV–HDV coinfection tends to cause more severe liver disease [Yurdaydın et al., 2010]. However, to understand the long-term effects of HBV–HDV coinfection on patients, longer follow-up of the clinical course may be needed. One study by Romeo et al. [2009] followed 300 patients with persistent hepatitis Delta infection and found an annual cirrhosis rate of 4% and HCC rate of 2.8%. Within that study, the authors state that active HDV replication is the only predictor for liver related mortality.

Our study also demonstrated that a significant minority of patients retain active HBV infection but, at the same time, there are generally lower HBV DNA levels in patients coinfected with HBV and HDV. This observation is supported by previous findings [Jardi et al., 2001; Sakugawa et al., 2001; Erhardt et al., 2010]. Further study may be required to explain this phenomenon, for example by testing quantitative HBsAg and covalently closed circular DNA (cccDNA). Shih et al. [2008] show a correlation between HBsAg levels and HDV RNA in HBV–HDV coinfected patients with undetectable levels of HBV DNA, but not in patients with detectable HBV DNA levels. Moreover, HBV DNA levels were not correlated with HDV RNA levels. This suggests HDV replication is independent from HBV replication and that it competes with HBV for HBsAg (which both viruses require to construct infective virions). Interestingly, these findings were only partly confirmed in a study by Heidrich et al. [2009]: 258 patients coinfected with HDV and HBV were compared to 2,083 patients infected with HBV alone. Lower HBV DNA levels were detected in the coinfected patients and no correlation between HDV RNA and HBV DNA levels was found. In contrast, no difference in HBsAg level was found between coinfected patients and monoinfected patients.

A study by Pollicino et al. [2011] investigated the intrahepatic interactions of HBV and HDV, elucidating how HDV suppresses HBV. They found that, during a HBV–HDV coinfection, there is a decrease in HBV DNA and pregenomic RNA, but a persistence of HBsAg and preS/S RNA. Furthermore, HBV genomes with large deletions in the basal-core-promoter/precore regions were found in patients coinfected with HBV and HDV but not in patients infected with only HBV; this finding suggests that HDV selects HBV variants with low replicative capacity.

With regards to the control and management of HDV infection in populations, the importance of consistently testing for HDV cannot be understated. Due to the complex and changing epidemiology, inconsistent and sporadic testing may lead to underestimation of HDV prevalence. A report by Xiridou et al. [2009] proposes a mathematical model in which HBV control was studied using prevalence rates of HDV and HBV. It was demonstrated that HDV presence could potentially hamper HBV eradication—and ignoring HDV infection may produce overoptimistic estimates of HBV control. The study proposes systematic HDV testing in HBV monitoring to more effectively control HBV. While this may be open for debate, consistent HDV testing for selected HBsAg positive patients in higher HBV prevalence areas, and for patients using a combination of parameters that include low HBV DNA, detectable levels of HBsAg, elevated ALT values, or liver fibrosis, is in line with published guidelines [Lok and McMahon, 2009]. Furthermore, a recent study by Schaper et al. [2010] elucidates the complex HDV virology throughout its infective course, and supports longitudinal testing as opposed to sporadic testing of HDV viremia.

In conclusion, the study provided epidemiological data on the prevalence of HBV–HDV coinfection in Belgium, which is estimated to be from 3.7% to 5.5% (29/785–44/800). However, the relatively small sample size and the cross-sectional nature of the HDV registry did not permit an analysis of the treatment modalities of HBV–HDV coinfection.

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