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Acute Hepatitis B and Hepatitis D Co-Infection in the Stockholm Region in the 1970s and 1980s – A Comparison

Summary: The frequency and clinical features of acute hepatitis B virus (HBV) infection with and without a hepatitis D virus (HDV) co-infection was investigated retrospectively in the Stockholm region during two different time periods, September 1977–October 1978 and November 1984–October 1986. Totally, 31/229 (14%) patients with acute HBV infection had a HDV co-infection. No change in the frequency of co-infections, 12% and 15%, respectively, was observed between the 1970s and 1980s. Among the 31 HDV co-infected patients 74% were intravenous drug addicts. Totally 23/66 (35%) intravenous drug addicts with acute HBV infection had HDV co-infection. Clinically a biphasic rise of the serum levels of alanine aminotransferase and bilirubin was noted among 63% of the HDV co-infected patients but only among 8% of the solely HBV infected patients ($p < 0.001$). A clinically more severe hepatitis was seen significantly more often among the HDV co-infected patients than among the solely HBV infected.

Zusammenfassung: *Akute B-Hepatitis und Hepatitis D-Virus-Koinfektion in der Region Stockholm – Vergleich der 70er und 80er Jahre.* In einer retrospektiven Studie wurden Häufigkeit und klinische Verläufe der akuten B-Hepatitis mit und ohne Koinfektion durch Hepatitis D Virus (HDV) in der Region Stockholm während zwei verschiedener Zeitphasen, September 1977 bis Oktober 1978 und November 1984 bis Oktober 1986, untersucht. Eine HDV-Koinfektion war bei 31/229 Patienten mit akuter HBV-Infektion (14%) aufgetreten. Zwischen den 70er und 80er Jahren waren keine Unterschiede in der Häufigkeit der Koinfektionen, die bei 12% und 15% lagen, festzustellen. 74% der 31 zusätzlich mit HDV infizierten Patienten waren i. v. Drogenabhängige. Insgesamt hatten 23/66 i. v. Drogenabhängigen (35%), die an einer akuten HBV-Infektion erkrankt waren, eine HDV-Koinfektion. Bei 63% der zusätzlich mit HDV infizierten Patienten war ein zweiphasischer Anstieg von Alanin Aminotransferase und Bilirubin im Serum zu beobachten; dies war nur bei 8% der nur mit HBV Infizierten der Fall ($p < 0{,}001$). Ein schwerer klinischer Verlauf der Hepatitis fand sich bei Patienten mit HDV-Koinfektion signifikant häufiger als bei Kranken, die nur durch HBV infiziert waren.

Introduction

Hepatitis D virus (HDV) is a small, incomplete and defective RNA virus which depends on the helper function of hepatitis B virus (HBV) for its expression and replication [1, 2]. It was first discovered by *Rizzetto* et al. and found to be highly endemic in southern Italy [1, 2]. Other endemic foci are found in the Middle East, North Africa and parts of South America [3–4]. In non-endemic areas HDV infections are mainly found among polytransfused patients and intravenous drug abusers [5–8]. In Sweden HDV was introduced among intravenous drug addicts in the early 1970s [7, 8]. Infection with HDV may occur simultaneously with an acute HBV infection, a so called co-infection, or superimposed on a chronic HBV infection [9]. A biphasic course with two peaks of serum alanine aminotransferase (s-ALAT) levels is commonly noted during acute HDV co-infections [10–12]. In the following report the frequency and clinical picture of HBV and HBV with HDV co-infections in the Stockholm region of Sweden during the 1970s and 1980s are compared.

Patients and Methods

Patients: Patients with acute HBV and HBV and HDV co-infection attending the Department of Infectious Diseases, Karolinska Institute, Roslagstull Hospital, Stockholm, Sweden during two different time periods were included in the study.
Period I: During September 1977–October 1978 124 patients were included, 83 men and 41 women, with a mean age of 28.8 years (range 15–65 years).
Period II: During November 1984–October 1986 105 patients were included, 59 men and 46 women, with a mean age of 28.3 years (range 3–75 years). Five patients were below 15 years of age.
Serological methods: Sequentially obtained sera from all patients were stored frozen at – 20 °C. Sera were tested for HBsAg and the corresponding antibody (anti-HBs), for antibody to hepatitis B core antigen (anti-HBc, total and IgM) and for antibodies to HDV (anti-HDV) by commercially available RIA kits (Abbott Lab., North Chicago, Ill).
Serum bilirubin, alanine aminotransferase (s-ALAT) and normotest/thrombotest (NT/TT) were analyzed by standard techniques. Reference values were as follows: serum bilirubin 4–21 µmol/l, s-ALAT < 0.70 µkat/l and normotest (NT) > 70%.
Diagnostic criteria: The diagnosis of an acute HBV infection was based on the presence of HBsAg and IgM anti-HBc in the first available serum sample from each patient. The diagnosis of an acute HDV co-infection was based on the presence of anti-HDV in a serum drawn ≥ 3 weeks after onset of the hepatitis.
The biochemical and clinical course of the hepatitis: The biochemical and clinical course of the hepatitis was defined as *bio-*

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Table 1: Epidemiological data among 229 patients with acute hepatitis B virus infection, co-infected or not with hepatitis D virus.

		Anti-HDV			
		Positive		Negative	
	No.	No.	(%)	No.	(%)
I. v. drug addicts	66	23	(35)	43	(65)
Homosexuals	26	0		26	(100)
Heterosexual contact	52	4	(7.7)	48	(92.3)
Various or unknown types of exposure	85	4	(4.7)	81	(95.3)
Total	229	31	(14)	198	(86)

chemically severe when TT was < 30% and the serum ALAT more than 10 times the upper normal limit, as *biochemically moderate* when TT was > 30% and the s-ALAT > 5 times the upper normal limit. Patients with s-ALAT ≤ 5 times the upper normal limit were classified as having a *biochemically mild* hepatitis.

Fulminant hepatitis was diagnosed when liver failure developed with TT < 15% in connection with hepatic encephalopathy. Recovery was defined as normalization of s-ALAT and HBsAg clearance.

Statistical analyses: Group means were compared with the Mann-Whitney U-test and frequencies with the Chi-square test.

Results

Epidemiological Data

Epidemiological data among the 229 patients with acute HBV infection in the Stockholm region of Sweden during 1977–78 and 1984–86, co-infected or not with HDV, are shown in Table 1. Totally 31/229 (14%) patients were HDV co-infected, 20 men and 11 women. The majority, 23/31 (74%) of the HDV co-infected patients were intravenous drug addicts and no male homosexuals. Among patients with a heterosexual transmission route 4/52 (7.7%) were HDV-co-infected of whom three were women. Only 4/85 (4.7%) patients with various or unknown transmission routes were HDV co-infected, one a brother of an intravenous drug addict.

The overall prevalence of HDV co-infections was 15/124 (12%) during period I in the 1970s and 16/105 (15%) during period II in the 1980s. Among intravenous drug abusers a slight decrease in the prevalence of HDV co-infections from 13/29 (45%) to 10/37 (27%) was noted between the two periods (not significant).

Table 2: Mean maximum serum levels of alanine aminotransferase (S-ALAT) and bilirubin among 229 patients with acute hepatitis B virus infection, co-infected or not with hepatitis D virus. Ranges are given within brackets.

	Anti-HDV				
	Positive (no. 31)		Negative (no. 198)		P-value
Mean ALAT maximum µmol/L	44.9	(8.5-153)	36.7	(0.3-128)	NS
Mean bilirubin maximum µmol/L	253	(79-600)	147	(5-570)	< 0.001

s-ALAT normal < 0.7 µkat/l; serum bilirubin normal 4-21 µmol/l.

Table 3: Occurrence of one or two alanine aminotransferase peaks among 187 patients with acute hepatitis B virus infection co-infected or not with hepatitis D virus.

	Anti-HDV			
	Positive		Negative	
	No.	(%)	No.	(%)
Two ALAT-peaks with more pronouced clinical symptoms	11	(46)	2	(1)
Two ALAT-peaks	4	(17)	11	(7)
One ALAT-peak	9	(37)	150	(92)
Total	24	(100)	163	(100)

Biochemical and Clinical Course of the Hepatitis

Serum levels of bilirubin and ALAT among the 229 patients with acute HBV infection in the Stockholm region of Sweden, co-infected or not with HDV, are shown in Table 2. The mean maximum serum bilirubin level was significantly higher in patients with a HDV co-infection as compared to patients with an isolated HBV infection ($p < 0.001$). The mean maximum s-ALAT level was higher in HDV co-infected than in solely HBV infected patients, however, not significantly.

Jaundice was noted in all patients with HDV co-infection whereas only 20/198 (10%) patients with an isolated HBV infection were icteric ($p < 0.001$).

The number of s-ALAT peaks during the clinical course of the hepatitis was evaluable in 187 patients and is shown in Table 3. Two s-ALAT peaks were noticed among 15/24 (63%) HDV co-infected patients versus 13/163 (8%) solely HBV infected patients, respectively ($p < 0.001$). The mean time interval between the two s-ALAT peaks in HDV co-infected and solely HBV infected patients was 30 days for both groups (range 9–90 days). The s-ALAT level was highest during the first peak in 8/15 (53%) HDV co-in-

Table 4: Biochemical and clinical severity of acute hepatitis B infection among 198 patients co-infection or not with hepatitis D virus.

	Anti-HDV			
	Positive		Negative	
	No.	(%)	No.	(%)
Fulminant hepatitis*	2	(7)	1	(0.5)
Biochemically severe hepatitis*	5	(19)	5	(3)
Biochemically moderate hepatitis*	20	(74)	164	(96)
Biochemically mild hepatitis*	0	(0)	1	(0.5)
Total	27		171	

* For definitions see Patients and Methods.

fected and in 10/13 (77%) solely HBV infected patients with two s-ALAT peaks. More detailed information about the clinical and biochemical features of the hepatitis was available in 198 patients and is shown in Table 4.
Totally 3/229 (1.3%) patients had fulminant hepatitis, two HDV co-infected intravenous drug addicts and one solely HBV infected nurse. All three survived. Among HDV co-infected patients 7/27 (26%) had a fulminant or biochemically severe hepatitis with s-ALAT > 10 times the upper limit of normal and TT < 30% whereas only 6/171 (3.5%) solely HBV infected patients ($p < 0.001$). Fulminant or biochemically severe hepatitis was noted in 5/21 (24%) HDV co-infected intravenous drug addicts and in 2/39 (5%) solely HBV infected intravenous drug addicts (not significant).

Chronic Evolution of the Acute Hepatitis

Chronic evolution of the acute hepatitis was possible to evaluate in 115 patients from period I and in 100 from period II. Only one patient each from period I and II, both males, totally 2/215 (0.9%), thus developed chronic hepatitis, none with a HDV co-infection. One was a homosexual male infected with the human immunodeficiency virus who developed biopsy proven chronic persistent hepatitis after 13 months, the other a heterosexual man with biopsy proven chronic active hepatitis 7 and 21 months after onset of the acute hepatitis.

Discussion

In this study totally 14% of patients from the Stockholm region of Sweden with acute HBV infection were found to be HDV co-infected. This is in accordance with the variable but generally low rates of HDV co-infection in patients with acute HBV infection reported by others [3, 7, 13–15]. In Sweden, as in many other Northwestern European countries, the main group of patients infected with HDV is the intravenous drug addict group. 35% of our intravenous drug addicts were found to be HDV co-infected, a figure well in accordance with what has been reported from other regions of Sweden, but higher than the 3% found in Norway [7, 14]. The very high prevalence of HDV co-infection noted in southern Italy is more comparable with the prevalence we have found among chronically HBV infected intravenous drug addicts in Sweden, a high percentage [3, 8] of whom seems to be chronically HDV infected. Among homosexual men we found none to be HDV co-infected in agreement with our own previous findings among patients with chronic HBV infection in the Stockholm region [8]. Apparently HDV has not yet been introduced in the homosexual population in Stockholm. The overall frequency of HDV co-infections was found to be the same during the 1970s and 1980s. We have earlier reported that HDV has been present in Stockholm among intravenous drug addicts at least since the early 1970s [8]. In contrast to the findings in other regions of Sweden we found a slight decrease in the frequency of HDV co-infections among intravenous drug addicts in Stockholm from the 1970s to the 1980s [7].
Patients with HDV co-infection were found to have a more severe biochemical and clinical course than patients with an isolated acute HBV infection, as noted by others [10, 15, 16]. We also found a biochemically biphasic course to be more common among patients with HDV co-infection than among patients with an acute HBV infection only ($p < 0.001$), as described earlier [10, 11, 15]. Among intravenous drug addicts the finding of a more severe clinical disease associated with HDV co-infection was not as common as that reported by *Shattock* et al. [16]. All our patients with HDV co-infection had a complete recovery from acute hepatitis although two had a fulminant clinical course. A selflimiting course without an increased incidence of chronic evolution of most HDV co-infections seems to be the most likely outcome [15].
In conclusion, we have found that 1) a simultaneous HBV and HDV infection is clinically more severe than an isolated acute HBV infection, 2) that patients with acute HDV co-infections most often completely recover, and 3) that the frequency of HDV co-infection has remained unchanged in Stockholm during the 1970s through the 1980s.

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Book Review

M. S. Gottlieb, D. J. Jeffries, D. Mildvan, A. J. Pinching, T. C. Quinn, R. A. Weiss
Current Topics in AIDS (Vol. 2)
291 pages, numerous figures
John Wiley & Sons, Chichester, 1989
Price: £ 29.95

This book consists of 13 chapters describing actual topics of HIV infection like epidemiology, molecular biology of HIV-1 and HIV-2, covering vaccine development and ending with treatment. The individual chapters are written by highly qualified authors. As happened with the first volume as well, from the completion of the contributions (end 1988, sometimes beginning of 1989) until publication ot the book a long time elapsed in this quickly developing field of HIV research.

The history of AIDS and the present pandemic is described, giving suggestions for the future prevention of the spread of HIV worldwide through information and educational programmes. Heterosexual spread of HIV is discussed considering different risk groups and different geographic regions and comments are given on the various strategies of prevention. Cofactors and aspects of HIV transmission are put together in mathematical models, leading to short-term and long-term (40 years) predictions of the HIV prevalence and incidence in different populations.

Virological and clinical features of HIV-2, its biology, pathogenicity and epidemiology are briefly summarized. The replication and genomic organization, as well as the special aspect of the regulatory elements of HIV-1, and other factors such as lymphokines and other viruses are thoroughly discussed. The current knowledge of animal models for AIDS is reviewed according to data on chimpanzees infected with HIV-1 and macaques infected with SIV. Information on the prevention of HIV infection by different kinds of vaccines, like envelope subunit, peptide based, or anti-idio-type based material or inactivated HIV is put together, covering the difficulties of antigenic variation of HIV, preclinical testing of some vaccine candidates and animal models.

The immuno-pathogenesis of HIV-1 covers the replication cycle, cytopathic effect on T4 lymphocytes and monocyte/macrophages and finally brain cells. The humoral immune response to HIV-1 deals with the time course of antibodies to HIV, especially the *nef* compound, which is still ambiguously discussed, neutralizing antibodies and the validity of the p24 antigen determination.

The clinically orientated chapters describe the ophthalmic manifestations of HIV, such as microvascular changes, infectious complications and neuroophthalmic disorders. This chapter is illustrated with several colour photographs. The management of opportunistic infections focuses on the treatment of pneumocystis pneumonia, toxoplasma encephalitis, some fungal diseases and generally on cytomegalovirus infection. Mycobacteria and treponema are briefly covered. Strategies of treatment of HIV infection by virus binding, inhibition of transcription of viral RNA, of translation of viral proteins, of posttranslational modifications of virion budding is described in 15 pages.

The last chapter deals with the legal and ethical issues in AIDS, covering discrimination, confidentiality and reporting. The limits of coercion are basically discussed.

This book can be recommended for everyone unable to keep up with the huge number of original publications in this field. The subject index at the end of the book and the conclusions at the end of each chapter facilitate a general survey. The number of cited references is encouraging. Thus, this book is of value not only to scientists, but also health care workers and politicians engaged in HIV management.

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