

# Hepatitis delta infections in Toronto, Ontario

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**ABSTRACT:** This study assessed the prevalence of hepatitis delta virus infection, the relation of this infection to the clinical and histological status and to the geographic origin of 216 patients with hepatitis B virus infection in Toronto, Ontario. Evidence of delta infection was present in 13 of the 216 patients (6.0%). It was more common in patients with acute hepatitis (11.1%) and with chronic hepatitis (16.7%) than in asymptomatic carriers (3.6%). It was not present in the three patients with hepatocellular carcinoma. The clinical course of the two patients with acute hepatitis and delta markers was similar to patients with hepatitis B alone and both made a complete recovery. Of the five patients with chronic liver disease and delta markers, three had severe chronic active hepatitis. Three of the 13 patients with delta infection were born in Canada. All three patients were intravenous drug abusers. Of the 10 patients not born in Canada, eight were immigrants from countries where delta infection is endemic. The remaining two were from West Germany and China. From this study it was concluded that, in Toronto, delta infection was more common in patients with acute and chronic hepatitis B than in asymptomatic carriers. Patients with both acute hepatitis B and delta infection had a similar clinical course to patients with acute hepatitis B alone. Patients with chronic hepatitis B and delta infection frequently had severe chronic active hepatitis. In Canadian-born patients delta infection was present in intravenous drug abusers only. Most immigrants with evidence of delta infection came from countries where delta is endemic. *Can J Gastroenterol* 1988; 2(4):151-5

**Key Words:** *Clinical features, Delta infection, Prevalence, Toronto*

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THE HEPATITIS DELTA VIRUS (HDV) IS an incomplete virus requiring the helper function of the hepatitis B virus (HBV) for its expression (1,2). HDV can infect a nonimmune host simultaneously with HBV (coinfection) or infect an hepatitis B surface antigen (HBsAg) carrier causing an acute, chronic or asymptomatic illness (superinfection). Following the introduction of sensitive methods for detecting HDV antigen and its antibodies it became apparent that HDV infections originally described in southern Italians are worldwide (2,3). Endemic areas of HDV exist in the eastern Mediterranean area, the Middle East, some areas of Africa (4), among the Yucpa Indians in Venezuela (5) and in the Nauru and other islands of the western Pacific (6). In western and northern Europe and in the United States, HDV infections occur mostly in parenteral drug abusers and hemophiliacs (7-11). HDV infections are rare among Chinese, despite a high HBsAg carrier rate (12).

The aims of this study were to estimate the prevalence of HDV infection in patients with various types of HBV related liver disease in Toronto, Ontario

**TABLE 1**  
Geographic origin of 216 patients and type of hepatitis B virus liver disease

Geographic origin	Number	AS CAR	AC HEP-B	CPH-B	CAH-B	CIRR-B	HCC-B
Canada	53	26	15	3	8	1	0
Italy	46	45	0	0	1	0	0
Northern Europe	28	22	2	1	1	2	0
Southeast Asia	65	51	1	2	5	3	3
Eastern Mediterranean area	11	10	0	0	1	0	0
Africa	3	2	0	1	0	0	0
Other countries	10	9	0	0	1	0	0
Total	216	165	18	7	17	6	3

AS CAR Asymptomatic HBsAg carrier; AC HEP-B Acute hepatitis B; CAH-B Chronic active hepatitis B; CPH-B Chronic persistent hepatitis B; CIRR-B Cirrhosis B; HCC-B Hepatocellular carcinoma B

and to correlate the presence of HDV infection with the clinical and histological status of the patients and with their geographic origins.

### PATIENTS AND METHODS

Two hundred and sixteen HBsAg positive patients were included in the study (Table 1). Of the 216, 18 had acute hepatitis B, 30 had chronic liver disease, three patients had hepatocellular carcinoma and 165 were asymptomatic HBsAg carriers. Of the patients with chronic liver disease, seven had chronic persistent hepatitis, 17 chronic active hepatitis and six patients had cirrhosis.

Of the 18 patients with acute hepatitis, two were intravenous drug abusers and one of them was homosexual. All patients with chronic hepatitis, cirrhosis and hepatocellular carcinoma had liver biopsies. Histological interpretation was in accordance with the Fogarty classification (13). All the asymptomatic carriers had no clinical evidence of liver disease and had persistently normal liver function tests for at least six months.

The patients selected for study had all been referred to the Liver Study Unit at Mount Sinai Hospital, Toronto. The 165 asymptomatic carriers were selected from an HBsAg carrier clinic which has been following 600 carriers for many years. All patients who attended the clinic over a period of nine months were tested for antibody to HDV. These patients were evaluated every four months and have been followed for at least three years. The patients with acute and chronic liver disease were those seen in the liver clinic over a period of nine months. Patients with acute hepatitis were seen weekly

and those with chronic liver disease were seen monthly. Liver biopsies were performed when clinically indicated and delta determinations were done within three to six months of the liver biopsy.

**Laboratory tests:** Hepatitis B surface antigen, anti-HBsAg, anti-HB core antigen, hepatitis Be antigen, anti-hepatitis Be and IgM anti-HBc tests were done by commercially available RIA kits (Abbott Pharmaceutical, North Chicago, Illinois).

Antidelta was measured by the commercially available antidelta RIA kit (Abbott Pharmaceutical Laboratories) and by blocking RIA in the Division of Molecular Biology and Immunology, Georgetown University. The delta antigen was measured by a blocking RIA also at Georgetown University. All samples were analyzed under code.

### RESULTS

Thirteen of the 216 patients (6.0%) were found to have antidelta in their sera. The distribution of antidelta in the various types of HBV liver disease is shown in Table 2.

**TABLE 2**  
Prevalence of delta infection in various types of hepatitis B virus liver disease

Diagnosis	Number	Number with delta infection	Percentage
Acute hepatitis B	18	2	11.1
Chronic hepatitis B	30	5	
CPH	7	1	14.3
CAH	17	3	17.7
Cirrhosis	6	1	16.7
Hepatocellular carcinoma B	3	0	
Asymptomatic carriers	165	6	3.6
Total	216	13	6.0

CPH Chronic persistent hepatitis; CAH Chronic active hepatitis

**Patients with acute hepatitis B:** Of 18 patients (11.1%) with acute hepatitis B, two were found to have delta coinfection. One had delta antigen in the serum in the first week of illness and one had high levels of antidelta in the second week of the illness. Both were Canadian-born and both were intravenous drug abusers; one was homosexual. There was no difference between the clinical presentation of the two patients who were antidelta positive and the 16 who had no evidence of HDV infection. There were no chronic sequelae in either the 16 patients with acute hepatitis B or the two patients with coincident HDV infection. The only fatal case was negative for HDV infection.

**Patients with chronic liver disease:** Five of the 30 patients (16.7%) with chronic liver disease had evidence of delta infection. One of seven patients with chronic persistent hepatitis had antidelta in the serum; this patient had immigrated from Africa. Three of the 17 patients with chronic active hepatitis had antidelta in the serum; one was from Italy, one from Malta and one was Canadian-born. The Canadian-born patient was an intravenous drug abuser. All three patients had very severe chronic active hepatitis on liver biopsy. One of the six patients with cirrhosis had antidelta in the serum. This patient came from Germany, a country where HDV is not endemic. The patient denied intravenous drug abuse.

**Asymptomatic carriers:** Six of 165 carriers (3.6%) had evidence of HDV infection. Five of the six carriers were from a group of 108 who were born in areas where HDV is endemic. Two were

from Italy, one from Greece, one from Turkey and one from Africa. The other patient was from China, a nonendemic area. None of these patients were drug users.

## DISCUSSION

The prevalence of HDV infection was 6% in the 216 patients studied. The three patients in this study who had evidence of HDV infection and who were born in Canada were all intravenous drug abusers. The majority of patients (eight of 10) with HDV infection who were born outside of Canada came from countries where HDV infection is endemic. None of these were drug abusers. A previous Canadian study also found that, where HDV infection was present, it was almost exclusively in immigrants from countries where HDV infection is endemic (14). In that study, serum antidelta was done in 326 HBsAg positive patients. The group consisted of 216 Indochinese refugees, 46 patients with acute hepatitis, 39 blood donors and 25 patients at high risk for hepatitis (homosexuals, patients with hemophilia and drug abusers). Eight serum samples were positive for antidelta (2.4%). Seven were from Indochinese refugees whose samples were obtained on arrival in Canada and one from a homosexual male with no history of drug abuse. This was a serological survey only and the clinical and histological status of the immigrants was not mentioned in the report (14).

The high prevalence of antibody to HDV in the Indochinese immigrants in the aforementioned study compared to the low prevalence in the Asian group in the present study is probably due to the different areas of origin of the two groups. Almost all the Asians in the present group were from mainland China or Hong Kong rather than from Indochina. A similar finding was reported from the United States (15). Three of 70 Oriental immigrants were delta antibody positive and all were from Vietnam.

In the present study only one of the 13 patients who were positive for delta antibody was homosexual and he was a drug abuser. Homosexuals are believed to be less susceptible to delta infection than to hepatitis B (15-17).

Two of 18 patients in this study with

TABLE 3

Comparison of prevalence of delta infection in various countries

Country	Asymptomatic carriers percentage with delta	Chronic liver disease percentage with delta	Reference
Italy	6.4	52.3	(26)
France	0.0	20.0	(6)
Germany	0.3	2.7	(16)
Kuwait	NA	66.0	(4)
USA	4.3	NA	(20)
	2.0	18.0	(17)
China	0.0	2.0	(27)
Canada	3.6	13.7	(Present study)

NA Data not available

acute hepatitis B had HDV coinfection (Table 2). Both were intravenous drug abusers. Acute hepatitis due to coinfection with HDV and HBV is seen commonly in intravenous drug abusers both in countries where delta infection is endemic (7-9) as well as in countries like Canada where there is a low prevalence of HDV infection (15,18,19). In endemic areas HDV is also common in the absence of intravenous drug abuse and in these areas transmission may be by inapparent permucosal or percutaneous routes (20).

The acute illness in the patients in this study with HBV and HDV coinfection was not more severe than in the 16 patients who had hepatitis B alone and no patient in either group developed chronic hepatitis. Other studies have shown that acute coinfection with HBV and HDV does not result in chronic hepatitis more commonly than in patients who have acute hepatitis B alone (18,21). The reason for this is that when HBV and HDV infection are acquired simultaneously, the HDV infection cannot outlast the HBV infection (22). In this study, the patient with fulminant hepatitis had no markers of HDV infection. However, other studies have shown a high prevalence of delta markers in patients with fulminant hepatitis (5,23). This is not a universal finding. In a report from the Mayo Clinic none of eight patients with fulminant hepatitis had delta markers (15).

Chronic HDV infection is seen more commonly when HDV infection is superimposed on chronic HBV infections than when coinfection occurs. Superinfection in an HBsAg carrier may be subclinical

or present as acute hepatitis. It frequently causes progression of liver injury and an asymptomatic carrier or one with chronic persistent hepatitis can be converted to a carrier with chronic active hepatitis and cirrhosis (24). In patients with chronic delta hepatitis, chronic active hepatitis is the most common histological lesion seen (22,25). In the present study five of 30 patients with chronic hepatitis B had evidence of delta infection. Three of the five had chronic active hepatitis and all three had severe disease on liver biopsy (Table 2).

There is considerable difference in the prevalence of delta infection in chronic liver disease in different parts of the world (Table 3). In countries with a low prevalence of delta infection, such as West Germany (19) and China (12,26), delta infection in patients with chronic liver disease due to HBV is uncommon, while in endemic areas, such as Italy (27), it is common. The reasons for the difference in prevalence of HDV markers in patients with chronic active hepatitis in the reported studies are not known. They may be related to difference in frequency of drug abuse, the geographic origin of the patients or the extent of liver damage prior to the delta superinfection. It is evident that HDV superinfection of patients with chronic hepatitis B is an important contributor to chronic liver disease in some parts of the world but plays a negligible role in other areas.

The number of patients with cirrhosis and hepatocellular carcinoma in this study was too small to estimate the importance of HDV infection in their pathogenesis. In another study, coincident HDV infection did not appear to increase

the frequency of hepatitis B related carcinoma (28).

In the asymptomatic carriers in this study, 3.6% had HDV markers. The prevalence of HDV markers in 108 patients born in countries with a high prevalence of HDV was 4.6%. This approximates the prevalence in asymptomatic HBsAg carriers in an endemic area such as Italy (6.4%) (28). In 57 patients born in countries with a low prevalence it was only 1.7%.

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A low prevalence of HDV infection in asymptomatic carriers has been reported from France (6), Sweden (7), Germany (19), the USA (4,22) and China (12,29) (Table 3). The asymptomatic HBsAg carriers with delta superinfection had a similar clinical course to those without delta infection. All remained well during follow-up.

In summary, in Toronto, HBV infection was more common in patients with acute and chronic hepatitis B than in

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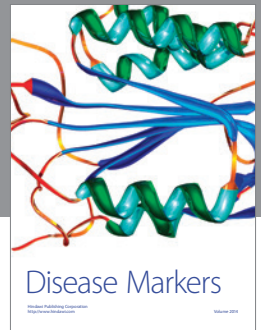
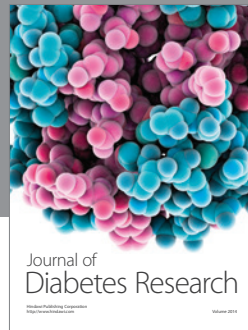
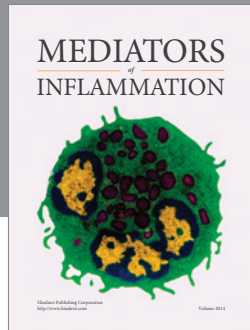
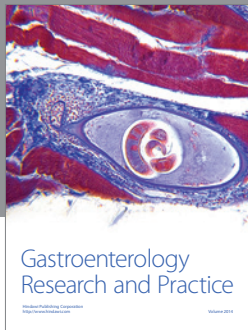
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### Les infections delta à Toronto : Prévalence et signification clinique

Cette étude évalue la prévalence de l'hépatite virale delta, la relation entre cette infection, le statut clinique et histologique ainsi que l'origine géographique de 216 patients atteints d'hépatite virale B à Toronto. Une infection de type delta a été décelée parmi 13 patients d'un groupe de 216 (6.0%). Elle était plus courante chez les patients souffrant d'hépatite aiguë (11.1%) et d'hépatite chronique (16.7%) que parmi les porteurs asymptomatiques (3.6%). Elle était absente chez les trois patients atteints de carcinome hépatocellulaire. L'évolution clinique des deux patients atteints d'hépatite aiguë et porteurs de marqueurs delta était similaire à celle des patients atteints d'hépatite B seulement et tous deux se sont complètement rétablis. Des cinq patients atteints de maladie chronique du foie avec marqueurs delta, trois souffraient d'hépatite sévère en évolution. Trois des 13 patients souffrant d'infection delta étaient canadiens d'origine. Tous trois faisaient usage de drogue par voie intraveineuse. Des 10 sujets nés en dehors du Canada, huit provenaient de pays où l'infection delta est endémique. Les deux autres venaient de l'Allemagne de l'Ouest et de la Chine. Les auteurs concluent qu'à Toronto, l'infection delta est plus commune chez les patients souffrant d'hépatite B aiguë et chronique que chez les porteurs asymptomatiques. Chez les patients atteints à la fois d'hépatite aiguë B et d'infection delta, la maladie suivait une évolution clinique semblable à celle des seules hépatites B aiguës. Les patients souffrant à la fois d'hépatite chronique B et d'infection delta avaient fréquemment une hépatite évolutive chronique sévère. Parmi les patients canadiens d'origine, l'infection delta n'était présente que chez les drogués utilisant les intravéneuses. La plupart des immigrants chez qui se manifestait une infection delta venaient de pays où elle est endémique.

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