Hepatitis delta virus infection in Northern Ireland 1970 – 1989

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SUMMARY

The incidence of hepatitis delta virus (HDV) infection in Northern Ireland (1970–1989) was tested by enzyme linked immunosorbent assay in 401 hepatitis B surface antigen (HBsAg) positive sera. Hepatitis delta antigen (HDAg) was tested in 388 patients and antibody to delta antigen (anti-HD) in 401 patients. Four patients (1.03%) were HDAg positive. Nine patients (2.24%) were positive for anti-HD and after acid pre-treatment of sera from eight of these patients, five were positive for HDAg. The overall incidence of HDV markers was 3.27%, which reflects the low incidence in HBsAg carriers in Northern Ireland (who were in high risk groups for delta hepatitis). The use of acid treatment of the sera to break up antigen/antibody complexes has been a useful technological improvement in the identification of this virus.

INTRODUCTION

The hepatitis delta virus is unique among virus-like agents. It is a defective virus that requires active helper functions from the hepatitis B virus (HBV) for its replication. The hepatitis delta virus is approximately 36nm in diameter with an RNA core and an HBsAg coat. Infection with HDV, therefore, may occur in patients with acute or chronic HBV infections and in the latter is often associated with severe and progressive liver disease, including chronic active hepatitis and cirrhosis. HDV has also been implicated in cases of fulminant hepatitis, occasionally in epidemic form. The incidence of delta virus infection in certain hepatitis B virus populations may be used as a surrogate indicator of intravenous drug use.

PATIENTS, MATERIALS AND METHODS

Four hundred and one HBsAg positive sera were stored at –20°C from 1970–89. Three hundred and eighty eight were tested for the presence of HDAg and 401 for anti-HD by enzyme linked immunosorbent assay (ELISA). These included sera from cases of hepatitis from all parts of Northern Ireland and carriers discovered by screening of blood donors and ante-natal patients by

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the Northern Ireland Blood Transfusion Service. Nineteen sera from haemophiliacs with hepatitis B antibodies (anti-HBs) were also studied and tested for anti-HD.

The Organon Teknika Hepanostika anti-Delta Microelisa test was used. The HDAg test was based on a direct "sandwich" using 6% Tween 20 and overnight incubation at room temperature. The anti-HD test was based on a competitive "sandwich" inhibition method. Sera from eight patients with anti-HD were pre-treated with 0.5N HCl as previously described for detection of HDAg. Sera which tested positive for HDAg or anti-HD were repeat tested.

RESULTS

Three hundred and eighty-eight HBsAg positive sera were tested for HDAg and 401 HBsAg positive sera and 19 anti-HBs positive sera were tested for anti-HD. The groups of patients with positive HDV markers are shown in Table I.

| Group                        | Tested | Positive | % Positive |
|------------------------------|--------|----------|------------|
|                              | HDAg   | Anti-HD  | HDAg       | Anti-HD   | HDAg   | Anti-HD   |
| Haemophiliacs                | 9      | 28*      | 0 (1)**    | 2         | 0 (11.1)%** | 7.1%     |
| Intravenous drug abusers     | 20     | 20       | 1          | 0         | 5.0%    | 0         |
| Post surgery                 | 21     | 21       | 0 (1)**    | 1         | 0 (4.8)%** | 4.8%     |
| Foreign-born adults or foreign contacts | 141   | 153      | 3 (3)**    | 4         | 2.1 (2.1)%** | 2.6%     |
| Blood donors                 | 47     | 47       | 0          | 2         | 0       | 4.3%      |

*Includes sera from 19 haemophiliacs with anti-HBs.
**Figures in brackets show additional HDAg positive sera after acid pre-treatment.

The results show that the highest incidence of HDV infection was in haemophiliacs followed by intravenous drug abusers, post surgery, foreign-born adults and foreign contacts, and blood donors. Other groups of patients including healthcare workers, recipients of multiple transfusions, sexual or perinatal contacts, the recently tattooed, antenatal patients or organ donors did not show evidence of HDV infection.

Further details of the patients positive for HDV markers are shown in Table II.

DISCUSSION

The epidemiology of HDV infection is closely linked to the epidemiology of HBV infection. There is a lower incidence of HBV infection in Northern Ireland than in the rest of the United Kingdom, and one would expect the incidence of HDV infection to be lower. In addition there has been a marked fall in HBV infections in the United Kingdom since 1984, probably due to publicity about AIDS which will further decrease the risk of HDV infection.

The highest incidence of HDV infection was seen in haemophiliacs, which correlates with their need for transfusions or blood products. HBsAg infection in these patients has not occurred since 1982, probably due to more sensitive HBsAg screening of blood.
**Hepatitis delta virus**

### TABLE II

*Patients with evidence of HDV infection*

| Date | Age | Sex | Groups | Clinical status |
|------|-----|-----|--------|-----------------|
| **HDAg Positive** | | | | |
| 1976 | 25 | M | Intravenous drug abuser (London) | Acute hepatitis (1976) |
| 1982 | 8  | M | Vietnamese | HBsAg carrier |
| 1986 | 35 | M | Laboratory worker (Guyana) | Acute hepatitis (1985) |
| 1986 | 64 | F | Hepatitis acquired 8 years previously in Greece | Chronic active hepatitis |
| **Anti-HD Positive** | | | | |
| 1974* | 21 | M | Haemophiliac | Acute hepatitis (1972) |
| 1987 | 53 | M | Haemophiliac | Acute hepatitis (1973) |
| 1982* | 59 | M | Surgery in previous 2 years | Cirrhosis |
| 1981* | 27 | M | Ethiopian | Acute hepatitis |
| 1988* | 40 | M | Iranian (previous hepatitis in Africa) | Chronic active hepatitis |
| 1983* | 27 | M | Chinese | HBsAg carrier |
| 1988 | 26 | M | Gilbert Islands citizen | HBsAg carrier |
| 1986 | 42 | F | Blood donor | HBsAg carrier |
| 1979 | —  | M | Blood donor | HBsAg carrier |

*HDAg positive after acid pre-treatment of sera.

There is a small but not negligible risk of HBV infection from HBsAg negative, HB core antigen (HBcAg) positive blood not detected by screening for HBsAg in donated blood. The risk of transmission of HDV infection in this way is even lower, and additional testing of HBsAg negative blood for HDV is unlikely to reduce this risk since HDV serum markers detected usually reflect past rather than current infection. The HBsAg positive recipient, however, is at high risk for HDV infection from HBcAg positive blood.⁴

Only 20 HBsAg positive drug abusers were available for study and one (5·0%) had HDV antigen. This patient acquired his HDV infection in London. Intravenous drug abuse is a small problem in Northern Ireland.⁵ Hepatitis associated with HDV infection was first found among intravenous drug abusers in Italy. Studies in the United Kingdom and Republic of Ireland (West of Scotland,⁶ South East London,⁷ Merseyside⁸ and Dublin⁹) have shown that HDV infection is largely confined to intravenous drug abusers and their social and sexual contacts.

The post-surgical patient with HDV markers in this study presented with cirrhosis of unknown origin. The only known risk factor was a total hip replacement two years previously. There were no apparent sources of HDV infection for the two blood donors found to be positive.

About one third of HBsAg positive patients in Northern Ireland were foreign-born or had foreign contacts, and most of these were of Chinese or Vietnamese origin.² Half of the patients with HDV markers in Northern Ireland (7/13) were foreign-born or had contact with HBV in a foreign country. In our study only two patients from the far east had evidence of HDV infection. It is not known why HDV infection is uncommon in HBsAg carriers in South East Asia and China where the

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prevalence of HBV infection is very high. Delta virus infection is endemic in certain populations and is especially common in the Mediterranean area and the middle east, the highest prevalence being reported from Kuwait and Saudi Arabia. The health care worker in our study was a laboratory worker in Jamaica and also in Georgetown, Guyana, which is proximal to known epidemic foci. There are known epidemic foci in Colombia, Venezuela and the Amazon basin, but delta hepatitis is rare in Northern Europe, the United States and most of South America. One patient in the study was from the Gilbert Islands. The incidence of HDV infection in the Western Pacific region is very low apart from high prevalence foci in Polynesia and Micronesia.

Delta virus infection can only occur in the presence of existing HBV infection, but HDV interferes with the replication of HBV. Clinically, delta virus hepatitis resembles other forms of acute and chronic hepatitis but it tends to be more severe. Acute delta hepatitis occurs in two forms. In co-infection HBV and HDV are acquired together and the clinical picture is indistinguishable from acute HBV hepatitis, but there is a higher incidence of fulminant hepatitis with a higher mortality. In superinfection, acute HDV infection occurs in a chronic HBV carrier which often leads to chronic hepatitis. Chronic delta hepatitis usually progresses from superinfection and may have a rapid course to cirrhosis. The diagnosis of acute HDV infection rests on detection of HDAg in blood in the first three or four weeks of illness, or the presence of anti-HD which appears on average more than four weeks later. Acid pre-treatment of sera containing anti-HD in our study showed that an anti-HD/HDAg complex was present. The HDAg was split off at acid pH and could then be detected, but it would not be known if it was infectious. In chronic HDV infection, HDAg may be detected in serum by immunoblotting although it may be complexed with antibody. In HDV infected HBsAg carriers, high titre IgM anti-HD is a useful indicator of chronic HDV infection and will distinguish between patients with chronic HDV infection and those with previous exposure. Comparison of five HDV assays showed that the Organon Teknika assay as used in this study was the most sensitive for HDAg detection. The use of acid treatment of the sera to break up antigen/antibody complexes has been a useful technological improvement in the identification of this virus.

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