Effect of concurrent acute infection with hepatitis C virus on acute hepatitis B virus infection

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Abstract

***Objective*—To investigate the possible interference with acute hepatitis B virus infection by coinfection with hepatitis C virus.**

***Design*—Analysis of stored sera collected for transfusion transmitted viruses study in 1970s.**

***Setting*—Four major medical centres in the United States.**

***Patients*—12 recipients of blood infected with hepatitis B virus.**

***Main outcome measures*—In 1970s, presence of antibodies in hepatitis B virus and raised serum alanine aminotransferase concentration; detection of antibodies to hepatitis C virus with new enzyme linked immunoassays.**

***Results*—Five of the 12 patients were coinfected with hepatitis C virus. Hepatitis B surface antigen was first detected at day 59 in patients infected with hepatitis B virus alone and at day 97 in those coinfected with hepatitis C virus ($p=0{\cdot}01$); median durations of antigenaemia were 83 and 21 days respectively ($p=0{\cdot}05$), and the antigen concentration was lower in the coinfected patients. Alanine aminotransferase patterns were uniphasic when hepatitis B virus infection occurred alone (range 479-2465 IU/l) and biphasic in patients with combined acute infection (no value >380 IU/l; $p=0{\cdot}0025$). Four coinfected recipients developed chronic hepatitis C virus infection. The fifth patient was followed for only four months.**

***Conclusions*—Acute coinfection with hepatitis C virus and hepatitis B virus inhibits hepatitis B virus infection in humans, and onset of hepatitis B may reduce the severity of hepatitis C virus infection but not frequency of chronicity. Alanine aminotransferase concentration showed a biphasic pattern in dual infection.**

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BMJ 1993;307:1095-7

Introduction

Studies in chimpanzees suggest that coinfection with hepatitis B and C virus may alter the course of the infection.[1-3] Hepatitis B virus infection has been reported in only two patients who received blood contaminated with hepatitis C virus.[4] Presence of hepatitis B virus was detected by the polymerase chain reaction in both cases.

Tests are now available to detect hepatitis C virus in patients receiving blood, and we re-examined stored sera obtained during the transmitted transfusion viruses study in the 1970s for this virus.[5-7] Fifteen of 1553 (1·0%) patients who received blood developed hepatitis B virus infection despite routine screening of donors for hepatitis B surface antigen. Three had been infected with hepatitis C virus infection before transfusion. Of the remaining 12 patients infected with hepatitis B virus, seven had only hepatitis B virus infection and five were infected with hepatitis B and C viruses. We investigated these 12 cases to determine the effect of hepatitis C virus coinfection on acute hepatitis B.

Patients and methods

The transfusion-transmitted viruses study was a non-interventional, prospective investigation of hepatitis associated with blood transfusion in the United States. Recipients of blood; their implicated and control donors; and hospital patients who had not had transfusions (controls) were enrolled during July 1974 to June 1979.

Blood samples were taken from patients before transfusion and during follow up at 2, 4, 6, 8, 10, 12, 15, 18, 21, 24, and 40 weeks. Additional samples were collected weekly if biochemical evidence of hepatitis was detected.

Serum samples from recipients and controls were originally tested for hepatitis B surface antigen, antibody to this antigen, and antibody to hepatitis B core antigen by radioimmunoassay (AUSRIA-II, AUSAB, and CORAB, Abbott Laboratories, North Chicago, Illinois). All blood donated was routinely screened for hepatitis B surface antigen. Serum alanine aminotransferase activity was measured by a standardised kinetic method; values ≥ 45 IU/l were defined as raised.

Hepatitis B virus infection was defined as the presence of hepatitis B surface antigen or a pattern of antibody to hepatitis B core antigen different from that seen after passive transfer from the donor. All sera collected in the study were stored at −70°C by the National Heart, Lung, and Blood Institute.[8]

We studied coded serial specimens from all 15 patients infected with hepatitis B virus after transfusion. Antibodies to hepatitis C virus were detected by enzyme linked immunoassays (ELISA; Abbott hepatitis C virus 2·0 and MATRIX).[9,10] The polymerase chain reaction was used in one patient to detect hepatitis C virus RNA by the methods described by Bukh *et al.*[11] Hepatitis B surface antigen concentrations were measured with the IMx hepatitis B surface antigen assay and a standard panel for quantitation (Abbott Laboratories).[12]

We used TRUE EPISTAT programs (Epistat Services, Richardson, Texas) for the Mann-Whitney U test. All p values are two sided. Confidence intervals were calculated by the Conover method.[13]

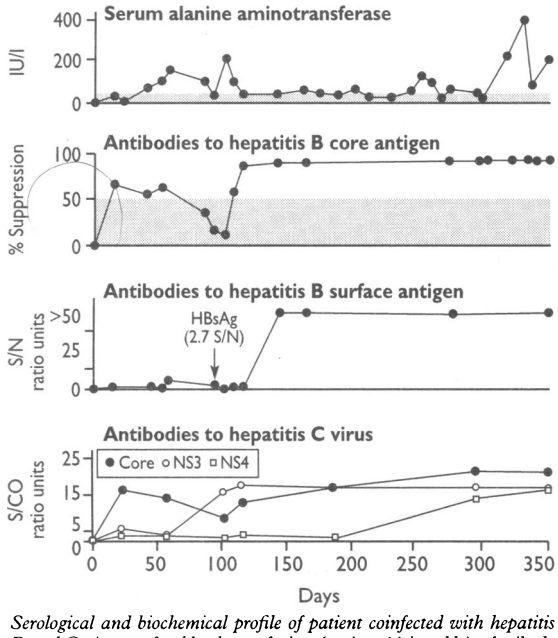
Results

The seven patients who were infected only with hepatitis B virus received 25 units of blood. None of the blood contained antibodies to hepatitis C virus. The other five patients received a total of 27 units of blood and each had one donor who was positive for

antibodies to hepatitis C virus. Four of these patients developed antibodies to hepatitis C virus within four months after transfusion and the fifth had RNA from hepatitis C virus detected by the polymerase chain reaction on days 12 to 163 after transfusion.

The figure shows data typical for a coinfected patient (case 11 in table). Alanine aminotransferase activity had two peaks in the acute phase—on days 58 and 102—and low levels of hepatitis B surface antigen were detected during the second peak. Ten to 12 months into the chronic infection alanine aminotransferase activity flared to higher levels than seen in the acute phase. The level of antibodies to hepatitis B core antigen and hepatitis C virus fell as antibodies passively transferred from the donor were eliminated and then increased as the patient responded to infection.

In patients infected only with hepatitis B virus, surface antigen was first detected a median of 59 days after transfusion compared with 97 days in coinfected patients (p=0·01, 95% confidence interval −55 to −10) (table). The antigen was detected for a median of 83 days in patients infected with hepatitis B virus only and 21 days in coinfected patients (p=0·05, 0 to 80).



Serological and biochemical profile of patient coinfected with hepatitis B and C viruses after blood transfusion (patient 11 in table). Antibody to hepatitis B core antigen is given as percentage suppression in a competitive radioimmunoassay; hepatitis B surface antigen and its corresponding antibody are expressed as the ratio of counts per minute of sample to those of the negative control (S/N) in solid phase radioimmunoassays. Antibodies to peptides from hepatitis C virus (core, non-structural region 3, and non-structural region 4) are indicated as ratio of sample absorbance to cut off value for positivity (S/CO) measured by enzyme linked immunoassays

Serological and biochemical tests in patients infected with hepatitis B and C viruses after blood transfusion in 1970s

	Hepatitis B surface antigen				Peak alanine aminotransferase	
Patient No	First detected (day)	Duration of detection (days)	Peak concentration (mg/l)	Infection with hepatitis C virus	No of days after transfusion	Value (IU/l)
Received blood negative for hepatitis C virus:						
1	55	29	10·9	No	108	2465
2	84	93	299·2	No	120	2010
3	87	29	0·6	No	121	1318
4	59	95	247·2	No	128	945
5	42	>296	154·4	No	107	701
6	71	83	0·6	No	154	593
7	37	23	0·7	No	73	479
Received blood positive for hepatitis C virus:						
8	80	18	3·5	Yes	80, 109	380
9	102	21	<0·1	Yes	49, 116	326
10	110	29	4·0	Yes	110, 146	318
11	94	15	<0·1	Yes	58, 102	256
12	97	45	<0·1	Yes†	88, 163	368

*Patient developed symptoms of hepatitis and jaundice.
†Virus detected by polymerase chain reaction.

Clinical implications

- Animal studies have shown coinfection with hepatitis C and B viruses affects multiplication of hepatitis B virus
- In this study coinfection with hepatitis C virus in humans reduced the multiplication of hepatitis B virus
- Coinfected patients showed a biphasic pattern of raised serum alanine aminotransferase activity
- Infection through blood transfusion is now unlikely but percutaneous exposures to both viruses may be seen among others, particularly intravenous drug misusers

The median peak concentrations were 10·9 and <0·1 mg/l respectively (p=0·07, −2·8 to 247·1).

Peak alanine aminotransferase activity occurred a median of 120 days after transfusion in patients infected only with hepatitis B virus and the median peak value was 945 IU/l (table). All five coinfected patients had two peaks of alanine aminotransferase activity. The median value when patients were also positive for hepatitis B surface antigen was 326 IU/l and all values were below those in singly infected patients (p=0·0025, 223 to 1754). The time from transfusion to peak alanine aminotransferase activity after hepatitis B surface antigen was detected did not differ between the two groups.

Hepatitis B surface antigenaemia resolved in all coinfected patients. Of the four patients followed for 8 to 13 months after the initial rise in alanine aminotransferase activity, three had persistently raised alanine aminotransferase activity. The fifth patient was followed for only four months and his last value was 290 IU/l.

Discussion

In our study the occurrence of simultaneous infection with hepatitis B virus and hepatitis C virus was associated with a delay in the appearance of hepatitis B surface antigen, a shortening of the duration of hepatitis B surface antigenaemia, usually a lower level of antigen, and a lower peak of alanine aminotransferase activity compared with patients who had hepatitis B virus infection alone. Coinfected patients had two peaks of alanine aminotransferase concentration, and in at least some cases this biphasic pattern may represent the sequential expression of the two viruses.[14]

The two acute infections could have been less severe because of metabolic interferences or because of nonspecific inhibition by the cytokines associated with cytolytic hepatitis C virus infection.[15] Experimental work has suggested that structural proteins from hepatitis C virus can suppress replication of the hepatitis B virus genome (C M Shih *et al*, University of California meeting on hepatitis B virus, La Jolla, California, 1992). Our series contained too few cases to permit any conclusion about an effect of hepatitis C on persistence of hepatitis B virus infection, which may be suppressed but not eliminated. Even this small number of cases, however, suggests hepatitis B does not inhibit hepatitis C virus infection from becoming chronic.

The formation of the transfusion transmitted viruses study/National Heart, Lung, and Blood Institute repository was supported by Contract No NO1-HB-42972 of the National Institutes of Health.

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(Accepted 23 August 1993)

Social deprivation and premature mortality: regional comparison across England

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Abstract

***Objective*—To investigate the pattern and size of the relationship between social deprivation in electoral wards and premature mortality for each health region in England.**

***Design*—Ecological study using 1981 census variables and data on mortality for 1981-5.**

***Setting*—14 regional health authorities in England.**

***Main outcome measure*—Mortality under the age of 65 years from all causes, coronary heart disease, and smoking related diseases in men and women.**

***Results*—Increasing deprivation was significantly associated with mortality from all causes, coronary heart disease, and smoking related diseases. The relationship was linear with no apparent threshold. Correlation coefficients were generally greater for deaths from all causes and smoking related diseases and for men compared with women. The slope of the relationship between deprivation and mortality varied among regions. Variations in mortality still existed between regions for equal levels of deprivation.**

***Conclusion*—Deprivation of an area and premature mortality are strongly linked. The effects of deprivation can be seen throughout the range of affluence and are not limited to the poorest areas. Current targets for reducing coronary heart disease mortality may be achievable if the mortality in poor areas can be reduced to the rates in affluent areas.**

Introduction

The Health of the Nation set targets for reducing mortality from coronary heart disease and advocated changes in lifestyle, particularly in smoking and diet, to meet them.[1] This strategy is potentially an important step forward for public health in England. Changes in lifestyle, however, are likely to be effected to differing degrees in different subgroups of the population. The evidence suggests that this variation may have previously resulted in increased social differences in mortality from coronary heart disease and other diseases.[2] If improvement in disease rates occurs only among the more wealthy sections of the community the health targets will be harder to achieve for the whole population and progress towards the World Health Organisation's goal of equity in health will be retarded.

Action to achieve health targets should therefore take into account social variations in disease for two reasons. Such variations may allow effective targeting of groups at higher risk, and an understanding of their causes may suggest ways of preventing them. One way to understand the causes is to examine the extent to which variations in mortality in small areas are related to socioeconomic factors. Socioeconomic status is a powerful predictor of mortality in individual people.[3-5] Social variables related to social deprivation also predict geographical variations in mortality.[6-8]

Using data from 8464 electoral wards in England, we analysed the relationship for each ward between social deprivation and premature mortality (under 65) from all causes, coronary heart disease, and smoking related disease. Our aims were to measure (*a*) the extent to which deprivation predicts mortality and (*b*) the possible benefits of improving life circumstances.

Methods

We initially used three different measures of social deprivation: the Carstairs index,[7] the Townsend index,[8] and the underprivileged area score.[9] Table I shows the variables used in these indices. Data on socioeconomic variables for each ward were obtained from the 1981 census (SASPAC)[9a] and collated; the three social deprivation indices were calculated by using transformed summated normal scores of each component as published.[7-9] Increasing scores indicate greater deprivation in all three indices.

Mortality statistics for England between 1981 and 1985 were obtained from the Office of Population Censuses and Surveys. Numbers of deaths from all causes, coronary heart disease, and smoking related

TABLE I—*Socioeconomic components of each index*

Variable	Jarman	Carstairs	Townsend
Unemployed	Yes	Yes	Yes
No car	No	Yes	Yes
Overcrowding	Yes	Yes	Yes
Social classes IV and V	No	Yes	No
Housing tenure	No	No	Yes
Unskilled*	Yes	No	No
Lone pensioner	Yes	No	No
Children under 5 years old	Yes	No	No
Lone parent	Yes	No	No
Geographical mobility	Yes	No	No
Ethnic minority group	Yes	No	No

*Socioeconomic group 11.

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BMJ 1993;**307**:1097-102