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Clinical course of hepatitis C virus during the first decade of infection: cohort study

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Abstract

Objective To determine the clinical course of hepatitis C virus in the first decade of infection in a group of patients who acquired their infections on a known date.

Design Cohort study.

Setting Clinical centres throughout the United Kingdom.

Participants 924 transfusion recipients infected with the hepatitis C virus (HCV) traced during the HCV lookback programme and 475 transfusion recipients who tested negative for antibodies to HCV (controls).

Main outcome measures Clinical evidence of liver disease and survival after 10 years of infection.

Results All cause mortality was not significantly different between patients and controls (Cox's hazards ratio 1.41, 95% confidence interval 0.95 to 2.08). Patients were more likely to be certified with a death related to liver disease than were controls (12.84, 1.73 to 95.44), but although the risk of death directly from liver disease was higher in patients than controls this difference was not significant (5.78, 0.72 to 46.70). Forty per cent of the patients who died directly from liver disease were known to have consumed excess alcohol. Clinical follow up of 826 patients showed that liver function was abnormal in 307 (37.2%), and 115 (13.9%) reported physical signs or symptoms of liver disease. Factors associated with developing liver disease were testing positive for HCV ribonucleic acid (odds ratio 6.44, 2.67 to 15.48), having acquired infection when older (at age \geq 40 years; 1.80, 1.14 to 2.85), and years since transfusion (odds ratio 1.096 per year, 1.00 to 1.20). For patients with severe disease, sex was also significant (odds ratio for women 0.38, 0.17 to 0.88). Of the 362 patients who had undergone liver biopsy, 328 (91%) had abnormal histological results and 35 (10%) of these were cirrhotic.

Conclusions Hepatitis C virus infection did not have a great impact on all cause mortality in the first decade of infection. Infected patients were at increased risk of dying directly from liver disease,

particularly if they consumed excess alcohol, but this difference was not statistically significant.

Introduction

Hepatitis C virus (HCV) is a common cause of liver disease¹ and a major health problem worldwide.² Acute infection is rarely diagnosed, and information about the clinical course of HCV infection has come largely from retrospective studies of patients with established liver disease.³ Such studies exclude people with no clinical evidence of infection, and observations are often biased towards severe disease outcomes. Opportunities for prospective studies of HCV related disease are rare, and the rate of development of chronic liver disease and hepatocellular carcinoma is poorly understood.

In early 1995, the UK Department of Health announced that they would undertake a "lookback" at people who had received blood from donors subsequently found to be infected with the virus when transfusion took place before the introduction of testing of the blood supply for antibodies to HCV.⁴ Recipients were identified from hospital records, traced, and offered counselling, serological testing, and treatment for HCV infection. Our study describes the HCV related disease and mortality seen after 10 years of infection.

Methods

Patients

At the end of 1999, 996 transfusion recipients infected with HCV had been traced during the lookback.⁵ For most patients, transfusion was the only probable route of infection, but 18 were excluded because exposure to other possible causes meant that the date they acquired the virus was uncertain. Another 54 patients were excluded because of missing or unclear key information or because initial reactivity to antibodies to HCV was not confirmed. Of the remaining 924 eligible patients, 608 (65.8%) were known to be positive for HCV ribonucleic acid and 189 (20.5%) negative for

ribonucleic acid; for 127 (13.7%) the status was unknown.

Controls

To provide a source of data on transfusion recipients who were HCV negative, all 536 recipients from the HCV lookback exercise in England who were traced and counselled and who tested negative for anti-HCV were identified.⁵ Of the 475 eligible controls, 443 (93%) were confirmed to be HCV ribonucleic acid negative; the ribonucleic acid status of 32 (7%) was not known.

Sources of data

Data were collected from patients and controls at the time of initial counselling during the HCV lookback and from death registration forms.⁵ We reviewed the text of the death certificates; deaths in which HCV related liver disease was likely to have been a direct cause of death were also identified. For this we included certificates that mentioned hepatocellular carcinoma or end stage liver disease (varices, ascites, or hepatic encephalopathy) or where liver disease was coded as the underlying and only cause of death. Death certificates for which liver disease or hepatitis C were given as contributory factors were not included in this analysis.

Data on clinical features of liver disease were available for registered patients. Features were classified as severe where there were signs or symptoms of a liver tumour or of portal hypertension; other signs or symptoms of liver disease were classified as mild.

Statistical analysis

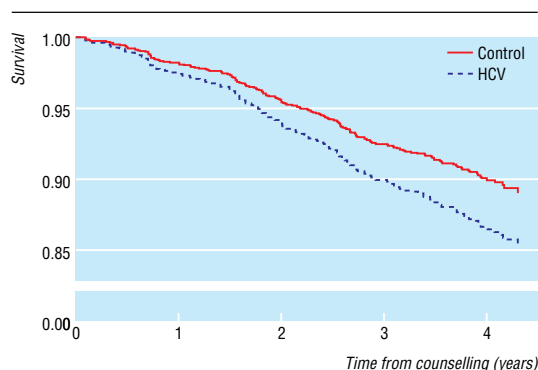
Differences in baseline data between patients and controls at counselling were assessed by using *t* tests for means or χ^2 tests for proportions. We used Cox's proportional hazards survival analysis, with survival taken from the date of counselling to death with censoring at the end of 1999. Risk factors for signs and symptoms of liver disease, within patients, were investigated by using logistic regression.

Results

All 924 eligible patients and 475 eligible controls were counselled between January 1995 and March 1999. The eligible patients did not differ significantly from the controls by age ($P=0.50$) or sex ($P=0.72$) (table 1). Ethnic group and country of birth were more often unknown for controls than for patients ($P<0.001$). Patients were more likely to report drinking ≥ 20 units of alcohol/week⁶ or to have unknown alcohol consumption at baseline than were controls ($P<0.001$). They were also more likely to have evidence of exposure to hepatitis B virus (tested positive for antibodies to hepatitis B virus core protein; $P=0.001$).

Deaths

By the end of 1999, 117 of 924 eligible patients (12.7%) had died, including 112/826 (13.6%) of the patients registered with the national HCV register. Of the 117 patients who died, 29 (25%) had one or more liver related conditions mentioned on their death certificate: hepatocellular carcinoma ($n=3$), liver encephalopathy ($n=1$), ascites ($n=1$), hepatic failure ($n=5$), cirrhosis ($n=11$), chronic hepatitis or hepatitis C ($n=20$). Of these 29, only 10 were considered to have



Survival (Cox's proportional hazards model) among HCV infected patients and controls

died directly from liver disease and they had been infected for a mean of 11 years (SE 0.77, range 8.42-15.88). Four of these 10 were known to have consumed excess alcohol. Of the controls, 43/475 (9%) had died by the end of 1999 (figure), and one (2%) had a liver related condition mentioned on the death certificate. This person died from a hepatocellular carcinoma, was known to be negative for HCV ribonucleic acid and antibodies to hepatitis B virus core protein, and was reported at counselling to consume no alcohol.

The difference between patients and controls in terms of all cause mortality was significant only at the 10% level (hazards ratio 1.41, 95% confidence interval 0.95 to 2.08, $P=0.08$). Factors that significantly

Table 1 Baseline characteristics of patients infected with hepatitis C virus and of controls who tested negative for antibodies to hepatitis C virus. Results are numbers (percentages) unless otherwise stated

Characteristic	Patients (n=924)	Controls (n=475)
Mean (range) years since exposure by end of 1999*	11.1 (8.2-20.6)	11.8 (8.3-25.0)
Mean (range) age at exposure in years	43.6 (0.0-87.2)	41.5 (0.0-84.5)
Sex:		
Male	445 (48.2)	224 (47.2)
Female	479 (51.8)	251 (52.8)
Ethnic group:		
White	783 (84.7)	325 (68.4)
Non-white	54 (5.8)	37 (7.8)
Not known	87 (9.4)	113 (23.8)
Country of birth:		
United Kingdom	740 (80.1)	333 (70.1)
Not United Kingdom	68 (7.4)	35 (7.4)
Not known	116 (12.6)	107 (22.5)
Alcohol consumption reported at counselling or first diagnosis:		
Nil	274 (29.7)	249 (52.4)
Less than 20 units/week	421 (45.6)	181 (38.1)
At least 20 units/week or alcoholism reported	125 (13.5)	29 (6.1)
Not known	104 (11.3)	16 (3.4)
Hepatitis B status at counselling or first diagnosis:		
Chronic infection†	2 (0.2)	0 (0.0)
Resolved infection‡	20 (2.2)	0 (0.0)
No evidence of current infection§	706 (76.4)	390 (82.1)
Evidence of past infection, but current status unknown¶	24 (2.6)	8 (1.7)
Not known	172 (18.6)	77 (16.2)

*Excluding those who had died before the end of 1999.

†Positive for hepatitis B surface antigen (HBsAg).

‡Negative for hepatitis B surface antigen but positive for hepatitis B core protein (Hbc) antibody.

§Negative for HBsAg or negative for Hbc antibody.

¶HBsAg unknown, but positive for Hbc antibody.

Table 2 Clinical characteristics at the time of registration of 826 patients with hepatitis C virus

Characteristic	No (%) of patients
Concentration of serum liver transaminases:	
Substantially raised*	120 (14.5)
Mildly raised†	182 (22.0)
Raised‡	5 (0.6)
Within normal range	451 (54.6)
Not known	68 (8.2)
Physical signs or symptoms of liver disease:	
Severe liver disease	34 (4.1)
Liver tumour	1 (0.1)
Varices	9 (1.1)
Ascites	7 (0.8)
Splenomegaly	17 (2.1)
Mild liver disease	81 (9.8)
No physical signs or symptoms	640 (77.5)
Not known	71 (8.6)
Results of liver biopsy§:	
Biopsy taken	362 (43.8)
Cirrhosis	35 (9.7)
Chronic hepatitis	270 (74.6)
Minimal change	23 (6.4)
Normal	26 (7.2)
Not known	8 (2.2)
Biopsy not performed	408 (49.4)
Not known if biopsied	56 (6.8)

*Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >twice the upper limit of normal.

†ALT or AST one to two times the upper limit of normal.

‡ALT or AST reported as abnormal, but degree unknown.

§Percentages are of patients who had a biopsy.

worsened survival were older age, being male, and the level of alcohol consumption. Compared with drinkers of 1-20 units, survival was worse for patients with unknown consumption and zero consumption of

alcohol (2.71, 1.58 to 4.64 and 1.76, 1.18 to 2.62, respectively) and for patients consuming ≥ 20 units/week (1.28, 0.75 to 2.18). The relation between survival and age, sex, or alcohol use did not differ between patients and controls. A significant difference in survival to death certified as liver related (30 deaths) was observed between patients and controls (12.84, 1.73 to 95.44, $P=0.013$). Survival to a death directly from liver disease (11 deaths) was greater for patients than controls but this difference was not significant (5.78, 0.72 to 46.70, $P=0.10$).

Liver function and disease

Data on the clinical features of and laboratory investigation for liver disease were available for 826 (89.4%) of the eligible patients registered between February 1998 and the end of 1999 (table 2). Some physical signs or symptoms of liver disease were reported for 115 (13.9%) of the registered patients. Twenty one (18%) patients with features of liver disease had other reported factors that may have contributed to the severity of the disease (11 alcohol, 4 iron overload, 2 cryptogenic cirrhosis, 2 congenital hepatic fibrosis, 1 β -thalassaemia major, and 1 drug induced liver abscess). In a multivariate logistic regression model, testing positive for HCV ribonucleic acid, age at transfusion, and a longer time since transfusion were associated with liver disease (table 3). Sex, smoking, and alcohol were not significantly associated with disease, but the direction of the effect was as in other studies.⁷ For patients with severe disease, sex was also significant (table 3).

Discussion

Study limitations

Our study has provided data on a group of patients infected with HCV for which the time since infection is accurately known. The median time from acquisition of the virus to cirrhosis has been estimated to be 30 years,⁷ and so the morbidity described here occurred after a relatively short observation period. Loss to follow up has been minimised by flagging all patients and controls in the NHS central registers; mortality data is complete. The use of death certification to establish cause of death is a potential information bias.^{8,9} Knowledge of HCV status is likely to influence content of the death certificate and this may partly explain the excess risk of liver related deaths among patients. By examining the text of the death certificates, however, we restricted one of our analyses to conditions likely to be clinically apparent at the time of death.

The cohort was limited to transfusion recipients who were traceable and had survived long enough to be tested in the national lookback.⁶ To reduce confounding, deaths have been compared with those in negative recipients also recruited by this mechanism.⁵ Analysis of the lookback shows that the HCV ribonucleic acid status of the source was the biggest influence on infection status and that recipient factors, like age or sex, did not differ between recipients who tested negative and recipients who tested positive for the virus.⁶ Information is also available on important confounding factors among the controls, including alcohol consumption and hepatitis B markers.

Table 3 Multivariable logistic regression analyses for signs and symptoms of liver disease in patients infected with hepatitis C virus, n=755. Values are odds ratio (95% confidence intervals)

Factor/levels	Mild or severe infection v no infection		Severe infection v no or mild infection	
	Odds ratio	P value	Odds ratio	P value
Sex:				
Male	1	0.11	1	0.019
Female	0.69 (0.44 to 1.10)		0.38 (0.17 to 0.88)	
Alcohol consumed (units/week):				
<20	1	0.13	1	0.14
None	1.20 (0.70 to 2.06)		1.97 (0.77 to 5.07)	
≥ 20	1.97 (1.10 to 3.51)		2.84 (1.09 to 7.41)	
Unknown	0.93 (0.37 to 2.36)		1.19 (0.23 to 6.16)	
Age at transfusion (years):				
0-19	1	0.028	1	0.24
20-39	1.15 (0.53 to 2.51)		2.19 (0.50 to 9.63)	
40-49	1.96 (0.86 to 4.53)		4.48 (1.00 to 20.08)	
50-59	2.76 (1.27 to 6.03)		3.52 (0.79 to 15.42)	
≥ 60	1.38 (0.65 to 2.95)		3.22 (0.79 to 13.06)	
Time since transfusion				
Years	1.096 (1.00 to 1.20)	0.045	1.098 (0.95 to 1.26)	0.22
HCV ribonucleic acid status:				
No	1	<0.001	1	0.008
Yes	6.44 (2.67 to 15.48)		4.18 (0.94 to 18.44)	
Unknown	2.06 (0.68 to 6.18)		0.94 (0.12 to 6.95)	
Smoker:				
No	1	0.35	1	0.43
Past	1.31 (0.72 to 2.39)		0.52 (0.17 to 1.58)	
Current	1.78 (0.92 to 3.44)		0.69 (0.20 to 2.34)	
Unknown	1.33 (0.75 to 2.35)		1.28 (0.53 to 3.10)	

What is already known on this topic

The clinical course of HCV infection is unclear because most information has come from studies of patients with established chronic liver disease

Studies that follow patients from disease onset are rare because most HCV infections are asymptomatic

What this study adds

HCV infection does not have a great impact on all cause mortality in the first decade of infection

Infected patients have an increased risk of dying from a liver related cause, particularly if they consumed excess alcohol

Comparison with other studies

Overall, patients who have been infected for longer tend to be more sick than patients who have been infected more recently. Some patients, however, progress rapidly to end stage liver disease, whereas others remain unaffected. This is likely to be due to individual effects (like genetic differences), as well as other risk factors such as sex, age, and alcohol intake. Male sex is independently associated with an increased risk of progressive disease,⁷ and this might explain the relatively low rate of disease seen in female cohorts.^{10 11} Acquisition of disease over 40 years of age is also associated with increased progression of fibrosis in paired liver biopsies,⁷ and mathematical models estimate annual progression rates to be 300 times greater for men aged 61-70 than for men aged 21-40.¹² Although fibrosis in men infected at younger ages initially progresses less rapidly than in older men, it may progress more rapidly as they age.¹³ The baseline prevalence of risk factors, such as excess alcohol use, may also explain the differential rates of progression observed in different cohorts. An excess of deaths from liver disease was seen in only two of the five cohorts studied by Seeff et al,¹⁴ and these were the only two cohorts not to have excluded patients with alcoholic liver disease.

Transfusion is a recognised risk factor for HCV transmission, but transfusion recipients make up a small proportion of people with known HCV infections in the United Kingdom.¹⁵ As the reason for the transfusion may be associated with reduced life expectancy, our study may have diluted the impact of the virus on morbidity and mortality.⁵ Most people with the virus in the United Kingdom have acquired infection by injecting drugs,¹⁵ and they may also have a shortened life expectancy due to factors other than HCV infection.¹⁶ The clinical course of the virus may depend on the route of infection, being less severe in patients infected by injecting drugs than by transfusion.^{17 18} A cross sectional study in the United Kingdom, however, showed no evidence of a difference in the extent of liver fibrosis between these two groups.¹⁹ Patients with a history of injecting may be infected with different HCV genotypes¹⁹ and are likely to differ in other important ways (such as age at infection and alcohol use).

Conclusions

Our study supports the view that HCV infection does not have a great impact on all cause mortality in the

first decade of infection.^{10 14 20 21} Like other studies,^{7 22 23} our results show that the influence of alcohol is independent of other factors and is exerted only at high levels of intake. If patients can keep their alcohol consumption to a minimum, their prognosis in the first decade of infection is likely to be improved. Continued observation of this cohort will determine the outcome of HCV infection in the longer term and enable us to evaluate the impact of antiviral treatment.

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