Hepatitis C virus infection in the elderly

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Summary

We studied hepatitis C virus (HCV)-related disease in older people because the treatment rationale for younger asymptomatic patients is based on the long-term prognosis of infection. Of the HCV-antibody-positive patients seen at Freeman Hospital 1990–1994, 25 were >65 years old; 24 were Caucasian and one was Afro-Caribbean. Median age at presentation was 67 years, and five were female. Nine were asymptomatic at presentation, six presented with varices, five with malaise, three with abdominal pain, one with pruritis and one with oedema. Risk factors identified were: transfusion (7), haemodialysis (1), health care worker (dentist) (1), and tattoos (2). There was no recognized risk factor for infection in 14, but five of these had done military service in areas of high HCV prevalence. Liver biopsy in 20 showed chronic hepatitis in two, cirrhosis in 12, and cirrhosis and hepatocellular carcinoma in six. Three additional patients also developed hepatocellular carcinoma. HCV genotyping was done in 19 and all were type 1 (1a, 4; 1b, 14; 1ntypable, 1). Eleven died, at median age 71 years (range 65–94 years), five of HCV liver-related deaths and two from HCV-associated non-hepatic disorders (non-Hodgkin's lymphoma and fibrosing alveolitis).

Introduction

Although hepatitis C virus (HCV) was ‘discovered’ in 1989,1 it had been endemic for many years. Studies of HCV frequency have focused on the prevalence amongst asymptomatic blood donors, which in the UK is around 0.2%,2 much lower than that reported in for example Japan (1.9%)3 or Italy (2.0%).4 In both Italy3 and Japan1 the prevalence of HCV infection increases with age; in Japan the prevalence is 0.2% in those <20 years and 3.9% in those >50 years, presumably reflecting increased exposure to recognized risk factors with advancing age.

Around 20% of infected individuals progress from mild chronic hepatitis to cirrhosis over 10–20 years, and about 10% develop hepatocellular carcinoma (HCC) over 30 years.5,6 There is some evidence that disease progression is more rapid in those acquiring the infection at an older age.3,9 However, there have been few long-term follow-up studies of HCV-infected individuals into old age, and it is still unclear which particular patients progress, and what effect HCV infection has on overall life expectancy and quality of life.

An increasing number of young asymptomatic HCV-infected patients are being identified through screening and being considered for interferon-alpha therapy, with important implications for health-care resources. Examination of the pattern of HCV-related disease in the elderly might illuminate the natural history of HCV infection and the potential benefits of treating these asymptomatic patients.

We therefore studied all patients over 65 years identified as HCV-antibody (Ab)-positive in our hospital from 1990 to 1994, to assess the severity of their disease, the associated morbidity and mortality, the risk factors for acquisition of HCV and the presence of associated diseases.

Methods

We identified 25 patients aged over 65 years, 19 of whom were attending the Liver Unit and six of whom were attending other hospital departments (Haematology, Renal and Geriatric units), from
<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Presentation and age (years)</th>
<th>RIBA bands + ve*</th>
<th>HCV-RNA</th>
<th>Genotype</th>
<th>Risk factor, age (years) exposed</th>
<th>Biopsy, age (years)</th>
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<td>Parkinson's disease</td>
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HCV in the elderly

Records held in the Microbiology Department at Freeman Hospital, Newcastle, who had been found to be HCV-Ab-positive since testing began in May 1990. From May 1990–1993, initial antibody screening was by second generation ELISA (Orthodiagnostics); subsequently screening was by UBI ELISA (Organon). Positive ELISA results were confirmed by at least two-band reactivity by recombinant immunoblot assay (RIBA) (ORTHO). Patients were interviewed whenever possible (n = 15) and/or their case-notes examined. Details specifically assessed included mode of presentation, age at presentation, sex, risk factor for acquisition of HCV infection (transfusions, occupational exposure, hospital care involving invasive procedures, lifestyle including recreational and therapeutic needle use, e.g. acupuncture, tattoos, foreign travel), time from potential exposure, results of liver function tests (LFTs) and liver biopsy, the presence of other risk factors for liver disease (e.g. alcohol consumption, hepatitis B virus (HBV) markers) concurrent diseases and follow-up data. Plasma was collected in EDTA and frozen at −80°C until analysed. Genotyping was performed by hybridization of 5’UTR PCR product to genotype-specific oligonucleotides in the INNO-LIIPA HCV kit (Innogenetics).

Results

Details of all 25 patients are given in Table 1. Median age at first presentation with liver disease was 67 years, range 50–91 years. In some patients, there was a long delay between presentation and recognition of HCV infection, as HCV Ab testing only became available in 1990. Nine were asymptomatic at presentation and HCV testing was undertaken because of a chance finding of abnormal LFTs, six presented with bleeding oesophageal varices, five with malaise, one with pruritis, three with abdominal pain and one with oedema. Five were female. No risk factor was evident in nine, and in a further five patients the only possible risk factor for exposure to HCV was service during WWII in areas with a high prevalence of HCV infection. Seven had a history of transfusion 2–11 years previously, two of whom had additional risk factors (one tattoos alone, one tattoos and war service), one had been a haemodialysis patient and one was a healthcare worker (dentist). In the two haematology patients (1 and 5) who received transfusion 2–3 years prior to detection of HCV Ab, no liver biopsy has been performed, whereas of five patients (6, 8, 9, 11 and 19) who received transfusion 10–13 years prior to assessment, all have developed cirrhosis. The two haematology patients (1 and 5) were transfused prior to routine screening of blood donors by the Blood Transfusion
Service in 1991. Evidence of previous hepatitis B virus (HBV) infection, HBcAb positivity, was present in 10/16 tested. Only 4/25 had a history of significant alcohol consumption (>40 units/week). All patients had abnormal LFTs. Liver biopsy was performed in 20, and showed chronic hepatitis in two aged 67 and 70 respectively, cirrhosis in 12 (median age 68 years, range 64–75 years) and cirrhosis with HCC in six (median age 70.5 years, range 67–76 years). In addition, three patients had ultrasound examination, which suggested cirrhosis in two and showed normal liver texture and no splenomegaly in the third. Thus at the time of first presentation, 20/25 patients showed evidence of cirrhosis (two by ultrasound alone). In addition to the six with histological evidence of HCC, a further three patients with cirrhosis developed HCC (two, both aged 75 years, were diagnosed at angiography performed because of a rising α-fetoprotein and one was diagnosed on ultrasound examination, aged 85 years).

HCV-RNA was positive in 19/20 assessed, all type 1 genotypes (14 type 1b, four type 1a and one untypeable). Genotype did not appear to be related to mode of infection or severity of disease.

Two patients suffered non-Hodgkin’s lymphoma (6 and 21), two fibrosing alveolitis (11 and 18), two carcinoma of lung (7 and 11) and two haematological disorders which pre-dated the liver disease. One haemodialysis patient (patient 16) who subsequently received a renal transplant is currently asymptomatic from his HCV infection.

Two patients received anti-viral therapy with no biochemical evidence of response. One patient (17) received a liver transplant and is currently well despite HCV recurrence in the graft. 11 patients have died, median age 71, range 65–94 years; five with HCC, one from fibrosing alveolitis, one from non-Hodgkin’s lymphoma, two from haematological disorders which necessitated transfusion, and two from carcinoma of the lung.

Discussion

Patients aged over 65 years with HCV-related liver disease accounted for 54% of patients with HCV cirrhosis seen during the study period at Freeman Hospital, Newcastle. However, of the HCV-positive patients aged <65 years with cirrhosis, 8/17 (47%) had a history of significant alcohol intake and one of haemochromatosis (data not shown). A large proportion of our elderly patients had advanced HCV-related liver disease in the absence of cofactors, because of the long natural history of HCV infection and slow progression to cirrhosis. Nine patients were asymptomatic at presentation but three of these had acquired HCV infection recently, and of the other six, only three had definite cirrhosis at first presentation.

All but one patient assessed was viraemic, agreeing with previous findings that those with more advanced disease have higher and more persistently positive HCV-RNA. All patients genotyped were genotype 1, and the majority were subtype 1b. The distribution of genotypes differed to that of patients <65 years in our hospital, in that 12/19 (63%) were genotype 1b vs. 12/40 (30%) in younger patients and none were genotype 3 or 4 vs. 9/40 (22.5%) genotype 3 and 2/40 (5%) genotype 4 in younger patients. This difference might be because infection with genotype 1b is more likely to progress to significant liver disease, but an alternative explanation might be that genotype 1b was prevalent at the time of presumed infection of these elderly patients. In addition, intravenous drug use, which is associated with infection with genotype 1a and 3 was not a risk factor for infection in any of our elderly patients.

A number of our patients had no identifiable risk factor for acquisition of HCV, so we must assume inapparent parenteral spread. In those with transfusion as the major risk factor the time between exposure and presentation with liver disease was around 10 years as previously reported. There were too few patients to comment upon whether disease progression was more rapid in elderly patients or in patients acquiring infection following transfusion as has been previously suggested but our results are compatible with this. However in two studies of the natural history of chronic HCV acquired through blood transfusion in the USA and Japan, the mean times to progression to cirrhosis were 20.6 and 21.2 years, respectively.

War service in areas known to have a high prevalence of HCV infection, such as Southern Europe and the Middle East, has never been considered to be a risk factor for HCV infection, but this was the only risk factor in five of our patients. A number of studies of ex-Far-East prisoners of war have highlighted increased morbidity and mortality, including an excess of cirrhosis and liver cancer and a high incidence of HBV markers have been reported amongst such individuals. A recent study has shown that patients with chronic hepatitis C have a greater risk of developing HCC compared to those with chronic hepatitis B, suggesting that HCV may contribute to the excess of HCC seen in prisoners of war.

In this elderly population, the majority of whom have been infected with HCV for some time, we noted a high prevalence of diseases previously reported to be associated with HCV infection. HCV has been associated with fibrosing alveolitis in an area of high endemicity of HCV but not in an area...
with a low background rate of HCV infection. In addition, HCV has been implicated in the development of non-Hodgkin's lymphoma. Studying elderly patients for HCV-related non-hepatic disease who have presumably been infected for a prolonged period may be more fruitful than looking at young patients for such associations.

Of the elderly patients in this cohort, 9/25 (36%) had histological and/or radiological evidence of hepatocellular carcinoma, five of whom have already died of this complication (the only liver-related deaths in this cohort). In addition, two patients died of this complication (the only liver-related deaths in this cohort). In addition, two patients died of disease associated with HCV infection: non-Hodgkin's lymphoma and fibrosing alveolitis. In previous reports of post-transfusional non-A, non-B hepatitis, the mortality considered to be related to underlying liver disease has varied from 15.3% to only 3.3%. It is clear from such studies that chronic HCV has a long natural history, with mean times to progression to HCC of 28–29 years.

What is the outlook in these elderly patients with HCV infection? Treatment with interferon-alpha is less likely to result in a biochemical and virological sustained response in those with established cirrhosis compared to patients with chronic hepatitis. However, a recent study has shown that interferon-alpha therapy may improve the long-term prognosis in patients with well-compensated cirrhosis, due to a reduction in the rate of development of HCC. Transplantation is a therapeutic option only in the younger fitter elderly; the one patient transplanted in our unit has had a good result in terms of quality of life, despite having evidence of HCV recurrence in the graft, the long-term consequence of which is uncertain.

The spectrum of liver disease seen in this elderly cohort, with symptomatic serious disease predominating, would support the use of anti-viral therapy to eradicate the virus and prevent progressive disease in the younger asymptomatic population. In addition, a recent study using Markov modelling to simulate the cost and outcomes of treating and not treating early asymptomatic infection indicated cost-effectiveness. However, further studies are required to identify viral and host factors which determine patients at high risk of disease progression, so that treatment can be targeted to those most likely to benefit.

Acknowledgements

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References

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