

Clinical Paper

Progression from acute to chronic hepatitis B is more common in older adults

Cara McKeating¹, Ian Cadden², Neil McDougall², Lucy Jessop³, Say Quah⁴, Michael Lavelle³, Alison Griffiths³ and Conall McCaughey¹

Accepted: 9th December 2017

Provenance: externally peer-reviewed

ABSTRACT

PURPOSE: The rate of progression of acute Hepatitis B (HBV) to chronic disease is quoted as <10%. The purpose of this study was to determine the rate of progression from acute to chronic HBV in Northern Ireland (NI), assessing the influence of age, gender and biochemical parameters.

METHODS: All “acute” HBV cases diagnosed in NI between 2011 and 2015 were reviewed. Inclusion criteria: 1). positive HBsAg and positive HBV core IgM; 2). in the absence of positive HBV core IgM, positive HBsAg with a recent negative HBsAg. Patient age, HBsAg, HBV core IgM, peak bilirubin and peak ALT were recorded, along with date and result of repeat HbsAg testing. Mann-Whitney U test was used to compare mean age, peak ALT and bilirubin between clearing and non-clearing groups. Fisher’s exact test was used to compare progression to chronicity according to gender and age less than or greater than 50yrs.

RESULTS: Of 80 identified cases, 4 incorrectly categorised cases were excluded. Of the remaining 76, (15 female (mean age 37.27yr), 61 male (mean age 47.39yr)) follow-up data was available for 71 patients (15 female (mean age 37.27yr), 56 male (48.59yr)). All female patients cleared HBV. 42 of 61 males cleared HBV (p=0.0313).

Overall the chronicity rate was 18.42% The mean age of those clearing the virus was 43.88 years, versus 55.64 years for those going on to develop chronic HBV (Mann-Whitney U test, z= -2.68, p=0.0037). Clearance rate was 83.72% in patients aged <50yrs and 63.64% in patients ≥50yrs (p=0.0068).

Mean peak ALT (U/L) and peak bilirubin (μmol/L) for the clearing group were 2130 and 174 respectively compared to 656 and 100 for the non-clearing group (z= -3.51, p=0.0002, z= -2.35, p=0.009).

CONCLUSION: Our results suggest a higher than expected rate of progression from acute to chronic HBV with a significantly higher risk for those over 50yrs. This suggests a need to revise information provided to older patients with acute HBV regarding the likelihood of progression.

Key words: Hepatitis, HBV, Acute, Chronic, Progression, Northern Ireland

INTRODUCTION

The rate of progression from acute to chronic hepatitis B in adults is typically quoted as 5-10%¹ with the rest clearing the infection. A review of Northern Ireland 2012-2013 data had suggested a higher rate, with 28% of acute cases failing to clear the virus within 6 months of diagnosis.² A retrospective review of the acute HBV cases diagnosed in NI between 2011 and 2015 was undertaken to further investigate this inconsistency. The primary objective was to determine the rate of development of chronic HBV amongst acutely infected patients and to assess the influence of age, gender and biochemical parameters on the development of chronicity. A secondary aim was to determine whether those developing chronic infection had been referred for specialist assessment.

METHODS

Case definition: World Health Organisation (WHO) criteria for laboratory diagnosis of acute hepatitis B is a positive anti-HBc IgM result.³ European Centre for Disease Prevention and Control (ECDC) criteria for differentiating acute and chronic hepatitis B define acute HBV infection by the presence of anti-HBc IgM, or detection of HBsAg or HBV-DNA with

1. Regional Virus Laboratory, Royal Victoria Hospital, Belfast HSC Trust, Belfast BT12 6BA
2. Liver Unit, Royal Victoria Hospital, Belfast HSC Trust, Belfast BT12 6BA
3. Public Health Agency, Northern Ireland, 12-22 Linenhall Street, Belfast BT2 8BS
4. Department of Genitourinary Medicine and HIV, Royal Victoria Hospital, Belfast, BT12 6BA

Correspondence to Dr Conall McCaughey

Email conall.mccaughey@belfasttrust.hscni.net



previous negative HBV markers less than 6 months ago.⁴

All new "acute" hepatitis B cases diagnosed between 2011 and 2015 were evaluated for inclusion.

The inclusion criteria in this review were: 1. positive HBsAg and positive HBV core IgM; 2. in the absence of positive HBV core IgM, positive HBsAg with a recent negative HBsAg.

For the subset of samples tested after July 2014, quantitative results for Anti-HBc IgM were still available for analysis. Anti-HBc IgM testing was determined using the Roche cobas immunoassay on an Elecsys analyser. A cutoff index (COI) of 1.0 equals approximately 100 Paul Erlich I-U/mL. Specimens with a COI \geq 1.0 are considered positive, whilst those with a COI $<$ 1.0 are considered negative. The equivocal range set by the manufacturer is 0.9-1.1.

Chronic infection was defined as a positive HBsAg at \geq 6 months from the first positive HBsAg result. This was in keeping with the widely accepted definition of chronic HBV and in accordance with ECDC criteria.³⁻⁵ The result from the first repeat HBsAg test taken at \geq 6 months was used. This period ranged from 6 months to greater than 1 year in some cases.

Data collection: Northern Ireland has a single public health agency and a single virus laboratory which performs all HBV serology tests for the region. It was therefore possible to capture all acute HBV cases diagnosed in NI during the study period. The laboratory results for each patient were reviewed. Peak bilirubin and peak ALT were recorded, along with the date and result of repeat HbsAg testing. The age and, where available, clinical details and HIV status were also recorded. Peak bilirubin and ALT were defined as the highest value in the month preceding and following the date of HBsAg positivity.

Data analysis: The overall chronicity rate, mean age of patients who cleared and did not clear the virus, mean peak ALT and mean peak bilirubin were calculated. The Mann-Whitney U test was used to determine the significance of the differences in age, peak ALT and peak bilirubin between the clearing and non-clearing groups, using all available results (ALT was unavailable for 9 of the 71 patients and bilirubin was unavailable for 4). 2x2 contingency tables were constructed and Fisher's exact test was used to compare progression to chronicity according to gender and age less than or greater than 50yrs using known outcomes (i.e. cleared and not cleared, positive and negative).

RESULTS

80 cases were identified, 4 had been incorrectly categorised as acute infections and were excluded. Of the remaining 76 patients, all but 2 patients had both positive HBsAg and positive HBV core IgM. The two exceptions met the second inclusion criterion in that there was evidence of recent seroconversion to HBsAg positivity. 75 of the 76 patients were Caucasian. 15 were female (mean age 37.27yr) and 61

were male (mean age 47.39 yr). Follow up data was available for 71 out of 76 patients (15 female (mean age 37.27yr), 56 male (mean age 48.59yr)).

Progression to chronic infection: Data is summarised in Table 1. Of the 71 patients for whom follow up data was available, 57 cleared the virus within 6 months of diagnosis. 14 patients did not clear within 6 months and were therefore deemed to have progressed to chronic HBV infection. These figures gave an overall chronicity rate of 18.42%, where $n=76$. This rose to 19.72% when the 5 patients for whom there was no follow up data were excluded from the analysis, i.e $n=71$. All 14 patients who had failed to clear the virus within 6 months had been referred for hepatology follow up. All female patients cleared HBV. 42 males cleared HBV (clearance rate female 100% v male 68.85%, $p=0.0313$).

Age: The mean age of the 76 patients was 45.39 years (range 17-75 years). The mean age of the group who cleared the virus was 43.88 years (range 17-75 years) and was 55.64 years (range 36-71 years) for the chronic group (Mann-Whitney U test, $z = -2.68$, $p = 0.0037$).

When divided into two groups according to age $<$ 50 and \geq 50, chronicity rates were 6.98% for those $<$ 50 years and 33.33% for those \geq 50 years. Clearance rates were 83.72% and 63.64% respectively, $p = 0.0068$.

ALT: Peak ALT (ALT at +/- 1 month from the date of HBsAg positivity) was available for 51 of the patients who cleared the virus and 11 of the patients who progressed to chronicity. The mean peak ALT for the cleared group was 2130 U/L. The mean peak ALT for the chronic group was 656 U/L (z score = -3.51 , p value 0.0002).

Bilirubin: Peak bilirubin (bilirubin at +/- 1 month from the date of HBsAg positivity) was available for 55 of the patients who cleared the virus and 12 of the patients who progressed to chronicity. The mean peak bilirubin was 174 μ mol/L for the cleared group and 100 μ mol/L for the chronic group (z score = -2.35 , p value 0.009).

HIV status: It was possible to determine the HIV status for 64 out of 76 patients. 58 patients were HIV negative. 6 patients were HIV positive at the time of their acquisition of HBV. Of these 6 patients 4 cleared HBV and 2 progressed to chronic infection. Out of the overall 14 patients who progressed to chronic HBV infection, HIV status was unknown for 2.

HIV positive individuals were less likely to clear HBV with a higher chronicity rate of 33.33% versus 17.24% in HIV negative individuals. However, the overall number of HIV positive patients was small and the difference was not found to be significant (p value 0.5896).

Clinical picture: 12 patients did not have symptoms of acute hepatitis. From the information available, the majority of these cases appear to have been picked up through screening or follow-up of recent risk of exposure. There were 5 patients who did not have any information available regarding clinical



TABLE 1:
HBV clearance rates by gender, age, HIV status and clinical presentation

	Number	HBV cleared	HBV not cleared	Unknown	Clearance rate (%)	Chronicity rate (%)
Male	61	42	14	5	68.85	22.95
Female	15	15	0	0	100	0
Age <50	43	36	3	4	83.72	6.98
Age ≥50	33	21	11	1	63.64	33.33
HIV positive	6	4	2	0	66.67	33.33
HIV negative	58	44	10	4	75.86	17.24
Symptomatic	57	48	5	4	84.21	8.77
Asymptomatic	12	4	8	0	33.33	66.67
Complex presentation	2	1	1	0		
Unknown	5	4	0	1		

presentation. 2 patients had complex clinical presentations and therefore symptoms of acute hepatitis were difficult to differentiate.

All other patients (57) had either an acute symptomatic illness or were clinically jaundiced. All except for 3 had a bilirubin >20 µmol/L. Of the 3 exceptions, 2 did not have any clinical information available with the remaining patient describing an acute illness following a clear risk-associated incident.

Symptomatic individuals had a HBV clearance rate of 84.21% versus 33.33% in the asymptomatic group (p value 0.0001).

In terms of the quantitative data for anti-HBc IgM in the subset of 26 cases presenting after July, one case had a negative anti-HBc IgM with the highest recorded value for this case being 0.23 COI. This case however met the second of the inclusion criteria, having had a recent negative HBsAg and went on to demonstrate clearance.

The range of positive values was 2.05 – 57.28 COI. The mean anti-HBc IgM value was 27.7. Of the 26 cases with quantitative anti-HBc IgM results, three failed to clear HBsAg. Two of these cases had anti-HBc IgM values above the mean. One had a low anti-HBc IgM result at 2.31. However this value was still well above the equivocal range. The next recorded anti-HBc IgM for this case, three months later, was negative.

DISCUSSION

The geography of Northern Ireland and the structure of its health care system make it ideally placed for a survey of acute hepatitis B infection. It has one public health agency, one virology laboratory and one hepatology service. The Hepatitis B and C Managed Clinical Network (MCN) brings together the leads from each of these specialties and coordinates joint working between the specialties. It is therefore possible to capture and follow all new diagnoses of acute hepatitis B infection. This work was initiated by the MCN and stemmed from a routine audit of acute hepatitis B cases carried out by the network.² It has revealed a number of interesting findings.

The incidence of acute hepatitis B in Northern Ireland in the period 2011-2015 was estimated to have been 1.03 per 100,000 (population of NI 1,851,600 at 30th June 2015).⁶ This is slightly higher than the incidence of 0.83 per 100,000 reported in England in 2015, but lower than the incidence in London (1.53 per 100,000). The highest incidence of acute HBV in England was observed in men aged 45-54.⁷ This review of Northern Ireland's data has shown the highest frequency in men aged 55-64, possibly suggesting a higher incidence of older men becoming infected with HBV in NI.

Firstly, our results suggest that between 2011 and 2015 the rate of progression to chronicity was higher than expected. A widely cited literature review looking at 10 studies of generally healthy adults reported a range of 0-12.1% chronicity following acute hepatitis B infection. The pooled incidence of chronicity was 4% in the 7 studies of initially uninfected populations.¹ In view of this, the rate of progression from acute to chronic hepatitis B is usually cited as less than 10%. The result in our survey was 18.42%.

Secondly, as far as we are aware, this is the first report of an increased rate of development of chronic HBV in an older Caucasian population. Our results suggest that, the risk of progression to chronicity was significantly higher in patients aged over 50yrs (6.98% vs 33.33% p = 0.0068). Whilst a recent review of HBV infection in the elderly has suggested that the rate of developing chronic infection may be as high as 59%⁸ this figure appears to be based on a single report of a 1993 outbreak in a Japanese nursing home.⁹ The average patient age in this study was 77.4 years.⁹ With the exception of this study, the possible association of increased risk of progression to chronicity with increasing age has not been widely described, nor has it been described in a Caucasian population. Another study, carried out in Shanghai and focusing on the viral determinants of progression from acute to chronic infection, found that progression was commoner with genotype C2 than genotype B2 and that patients with HBV C2 were more likely to be older men. However, age and gender were not found to be independent risk factors

for chronicity.¹⁰ Neither genotype B nor C is prevalent in the UK and our study did not gather genotype data. Other studies have looked at different aspects of hepatitis B infection in older age groups. Findings include an increased prevalence of chronic hepatitis B infection in those aged ≥ 50 years than in younger individuals¹¹, lower peak serum bilirubin and ALP levels¹² and a higher spontaneous HBsAg seroclearance rate in elderly adults with chronic HBV.¹³ However, these studies did not specifically address chronicity rates following acute hepatitis B infection.

Other results from our study agree with previously established concepts including the observation that males had an increased rate of developing chronic infection (22.95% v 0% $p = 0.0313$). Whilst this is recognised⁵, it may be partly explained by the increased age amongst the male group in our study. Additionally, those clearing the virus, and therefore not developing chronic infection developed significantly higher peak levels of ALT (2130.49 v 656.18 $p = 0.0002$) and bilirubin (174 v 99.75 $p = 0.009$). The influence of LFTs in predicting progression is well accepted in practice, with those experiencing a more active hepatitis being at lower risk of developing chronic infection.

Regarding HIV, the numbers in this survey give a chronicity rate of 33.33% in HIV/HBV coinfecting patients. The prevalence of HIV/HBV coinfection is thought to be 5-7% in HBV low-endemic countries¹⁵. Patients with HIV have been found to be at increased risk of developing chronic hepatitis B after an acute infection. It has been suggested that this increase may be as great as six times that of HIV seronegative patients^{16,17}. The numbers in this survey give a chronicity rate of 33.33% in HIV/HBV coinfecting patients, 1.8 times higher than the overall chronicity rate. However, the small number of coinfecting patients makes it impossible assess significance from this survey.

A potential weakness of our data is that although we have used an internationally accepted case definition for acute HBV, using anti-HBc IgM as the key marker, it is possible that low levels of anti-HBc IgM can occur in chronic HBV infection following hepatic flares. Hence a new diagnosis of a previously unrecognised case of chronic HBV undergoing such a flare could potentially be misconstrued as an acute HBV infection. It would be useful to analyse quantitative anti-HBc IgM results to investigate this but these values were only available for 26 cases. From this limited data no cases had results close to the cut-off for anti-HBc IgM and 2 of the 3 cases that did not clear infection in this dataset had anti-HBc IgM values greater than the mean thus giving some reassurance with regard to this potential criticism.

The association between older age and increased rates of progression to chronicity is not hitherto well established in the literature. The findings of this study suggest that clinicians may need to revise the information provided to patients regarding the likelihood of development of chronic HBV following acute infection dependent on the patient's age.

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