Decline in hepatitis B infection in sickle cell anaemia and β-thalassaemia major

I Al-Fawaz, S Ramia

Abstract
Seventy-five Saudi children, 55 with sickle cell anaemia and 20 with β-thalassaemia major, who were negative for all hepatitis B virus (HBV) markers five years ago were recently investigated for exposure to HBV and hepatitis C virus (HCV) infection. Of the 55 patients with sickle cell anaemia and 20 with β-thalassaemia major, 20 and five patients respectively had been vaccinated against HBV earlier and all of them still had protective antibody (anti-HBs 42-96 IU) 3-5 years after vaccination and there was no vaccine failure. Among the non-vaccinated children the exposure rates to HBV were 14-3% among those with sickle cell anaemia and 26-7% among those with β-thalassaemia and this was not statistically significant when compared with the exposure rate to HBV among the general paediatric population (20-1%). Anti-HCV positivity among those with β-thalassaemia major and sickle cell anaemia was 70% and 18-2%, respectively, and this was significantly higher than anti-HCV positivity among the control group (0-8%). Anti-HCV positivity was directly related to the amount of blood transfused and to the duration of transfusion. The results of the study show that although the exposure rates to HBV among patients with sickle cell anaemia and β-thalassaemia major were not significantly different than that among the general paediatric population, infection with HBV still takes place among non-vaccinated patients despite strict precautionary measures taken. Hence early vaccination against HBV would probably be the only effective way of controlling HBV infection. For HCV infection, and because a vaccine against HCV is still not available, preventive measures such as blood screening for anti-HCV before transfusion and stringent infection control measures are crucial steps to be implemented for the control of spread of HCV among these groups of patients.

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Hepatitis C virus (HCV) was recently identified as the major causative agent of transfusion non-A, non-B hepatitis and diagnosis of infection has been made possible by the development of an anti-HCV assay. Groups at high risk of infection with HCV are those who receive multiple blood transfusions such as haemophiliacs, patients on haemodialysis, and those with thalassaemia.

In addition to HCV, multitransfused patients are also at a high risk of acquiring hepatitis B virus (HBV) infection. Previously we have shown that multitransfused Saudi patients with sickle cell anaemia and thalassaemia have a high exposure rate to HBV. Because of this, strict measures were implemented at our hospital to control the spread of HBV infection. These included improved infection control, vaccination against HBV, and using third generation techniques for screening for hepatitis B surface antigen (HBsAg). This report is concerned with the prevalence of HBV infection in the above-mentioned two groups of Saudi patients five years after implementation of the control measures and also with the prevalence of anti-HCV using the recently available screening and confirmatory second generation enzyme immunoassay techniques.

Patients and methods

PATIENTS STUDIED
Fifty-five Saudi children with sickle cell anaemia (30 boys, 25 girls; age range 2-5-14 years) and 20 Saudi children with β-thalassaemia major (11 boys, nine girls; age range 1-14 years) who attended the haematology clinic at King Khalid University Hospital, Riyadh, were included in this study. The diagnosis was confirmed by haemoglobin electrophoresis on cellulose acetate at pH 8-6 and citrate agar at pH 6-0. Adult and fetal haemoglobin values were estimated by the elution method and alkaline denaturation respectively as described earlier. Routine screening for HBsAg and antibody to HBsAg (anti-HBsAg) were done on each patient on the initial visit to the clinic. No screening for antibody to HCV (anti-HCV) was performed as the test was not available then. Among the 55 children with sickle cell anaemia and the 20 children with β-thalassaemia major, 20 (36-4%) and five (25%), respectively, were already vaccinated (three doses) against HBV. Those who were vaccinated were the only ones whose parents accepted the theoretical risk from a plasma derived vaccine. Genetically derived HBV vaccine became available only recently at our hospital.

CONTROL GROUP
The control group consisted of 120 Saudi children (60 boys, 52 girls; age range 1-12 years) who were investigated in another research project regarding the age specific prevalence of HBV markers among Saudi
Table 1  HBV markers and antibody to HCV (anti-HCV) in multitransfused Saudi patients with sickle cell anaemia and \( \beta \) thalassaemia major

<table>
<thead>
<tr>
<th>No (%) HBV markers positive</th>
<th>HbsAg</th>
<th>Anti-HbC alone</th>
<th>Anti-HbC and anti-Hbs positive</th>
<th>Anti-Hbs positive</th>
<th>Anti-HCV positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls (n=120)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sickle cell anaemia (n=55)</td>
<td>7 (5-8)</td>
<td>1 (0-8)</td>
<td>14 (11-7)</td>
<td>3 (2-5)</td>
<td>1 (0-8)</td>
</tr>
<tr>
<td>( \beta ) Thalassaemia major (n=20)</td>
<td>0</td>
<td>0</td>
<td>5 (14-3)*</td>
<td>20 (36-4)†</td>
<td>10 (18-2)</td>
</tr>
</tbody>
</table>

*These patients had no history of vaccination against HBV.
†These patients were vaccinated (three doses) against HBV.

SEROLOGY STUDIES
All sera were tested for HBV markers (HbsAg; total antibody to HBsAg (anti-Hbs); total antibody to hepatitis B core antigen (HbcAg) (anti-Hbc), and to hepatitis B e antigen (HbeAg)) by the enzyme linked immunosorbent assay (ELISA) from Organon Teknika NV, Belgium and for anti-HCV by ELISA from Abbott Laboratories, North Chicago, Illinois, USA. All anti-HCV positive samples were confirmed by the Abbott HCV enzyme immunoassay supplemental assay. Specimens from children who were vaccinated against HBV were tested by ELISA from Organon Teknika and an anti-Hbs titre of 10 mIU was considered positive. The procedures followed in all assays were as stated by the manufacturer.

SERUM ALANINE AMINOTRANSFERASE
Alanine aminotransferase activities were considered abnormal if they were at least 5 times the normal value (0-56 IU).

STATISTICAL ANALYSIS
Fisher’s exact test and \( \chi^2 \) test were used in the comparison of proportions. Mean values were compared using Student’s t test.

Results
Prevalence of HBV markers and anti-HCV among multitransfused Saudi patients with sickle cell anaemia and \( \beta \) thalassaemia major is shown in table 1. Seven (5-8%) of the controls were HbsAg positive and none of the patients was a carrier. Among the 35 patients with sickle cell anaemia and who were not vaccinated against HBV five (14-3%) were exposed to HBV (anti-Hbc and anti-Hbs positive) compared with 25 patients (14 anti-Hbc and anti-Hbs positive, one anti-Hbc positive, three anti-Hbs positive, and seven HbsAg positive) among the control group; this was not statistically significant (p=0.535). Among the 15 patients with \( \beta \) thalassaemia major who were not vaccinated against HBV four (26-7%) had evidence of exposure to HBV (anti-Hbc and anti-Hbs), which also was not statistically significant compared to the exposure rate to HBV (20-8%) among the control group (p>0.815). There was no vaccine failure against HBV among the 25 patients vaccinated and the anti-Hbs titre range was 42-96 IU 3-5 years after vaccination.

Anti-HCV positivity among patients with \( \beta \) thalassaemia major was 70% compared with 18-2% among patients with sickle cell anaemia and 0-8% among the control group (table 1). Anti-HCV was significantly higher in those with \( \beta \) thalassaemia major than in those with sickle cell anaemia (p<7×10^{-7}) and among the control group (p<10^{-8}). Furthermore, anti-HCV positivity among the patients with sickle cell anaemia was significantly higher than that among the control group (p<4×10^{-5}). Among patients with sickle cell anaemia as well as among those with \( \beta \) thalassaemia major anti-HCV positivity was directly related to the amount of blood transfused (table 2). In addition to the amount of blood transfused, the duration of transfusion, particularly among the thalassaemias, influenced the rate of anti-HCV positivity (table 2).

Discussion
Our earlier data from the Riyadh area showed an exposure rate to HBV of 30-8% in the general paediatric population compared with 45-3% and 79-4% in sickle cell anaemia and \( \beta \) thalassaemia major patients, respectively. The results of this study show clearly that the exposure rate to HBV has been reduced drastically in the same groups of patients who were not vaccinated against HBV. This reduction is most probably due to the use of the most sensitive third generation techniques for screening HbsAg in all blood donors during the past five years in addition to the strict precautionary measures applied at our hospital against spread of HBV infection. However, although the exposure rate among our patients was not different from that among the general paediatric population, infection with HBV still takes place among unvaccinated patients with thalassaemia and sickle cell anaemia. This infection is most probably due to frequent exposure to blood in these patients but intrafamilial spread cannot be ruled out. In all of our exposed patients, the infection was subclinical. The finding of no vaccine failure against HBV among our 25 vaccinated patients underscores the importance of vaccinating all patients with thalassaemia and sickle cell anaemia who have not been exposed to HBV. Early vaccination of these patients would probably be the only effective way of controlling HBV infection as HbsAg free blood cannot completely safeguard against HBV.

Table 2  Comparison of patients with sickle cell anaemia and \( \beta \) thalassaemia major who were positive or negative for anti-HCV

<table>
<thead>
<tr>
<th>Sickle cell anaemia</th>
<th>( \beta ) Thalassaemia major</th>
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<tbody>
<tr>
<td>Positive (n=10)</td>
<td>Positive (n=14)</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>10-1 11-0 &gt;0.05</td>
</tr>
<tr>
<td>Amount of blood transfused/year (units)</td>
<td>4-6 5-4 &lt;2×10^{-6}</td>
</tr>
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infection.\textsuperscript{15, 16} Vaccination against HBV is now a part of the Expanded Programme of Immunisation in Saudi Arabia.\textsuperscript{17}

In contrast to the situation with HBV our patients, and particularly those with $\beta$ thalassaemia major, are highly exposed to HCV (70%). This is much higher than what has been reported earlier\textsuperscript{7} where the first generation enzyme immunoassay test for anti-HCV was used. Hence, earlier data on anti-HCV have to be interpreted with caution in the light of relative insensitivity\textsuperscript{18, 19} and specificity\textsuperscript{20, 21} of this first generation immunoassay. A similarly high exposure rate to HCV infection has recently been reported among Saudi patients on haemodialysis using a second generation immunoassay (S Huraib \textit{et al}, personal communication). Whether some of these second generation assay results are false positive still awaits the development of more reliable confirmatory tests. The finding that only 15% of our anti-HCV positive patients had raised alanineaminotransferase activities and none of them was anti-HBC positive indicates that these surrogate markers are not reliable for predicting HCV infection and is in agreement with our earlier observation\textsuperscript{22} and those of others.\textsuperscript{23} Higher frequency hospital admission and hence blood transfusion in thalassaemics compared with patients with sickle cell anaemia may explain the difference in exposure rate to HCV found among the two groups.

In conclusion, it seems therefore that until a vaccine against HCV becomes available, preventive measures such as blood screening for anti-HCV before transfusion and stringent infection control measures are crucial for the control of spread of HCV among these categories of patients. This is particularly important as recent evidence indicates that HCV does not illicit long term immunity and reinfection with a homologous strain is possible.\textsuperscript{24}