Prevalence of Hepatitis (C) Virus among Thalassemic Children in Sulaymani

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ABSTRACT

Background and Objective: Thalassemia, one of the most dangerous diseases, is an inherited impairment of hemoglobin production, in which there is partial or complete failure of the globin chain synthesis. To evaluate the prevalence of hepatitis C in multi-transfused children with thalassemia major.

Materials and methods: From February 2014 to September 2014, 200 patients with thalassemia major were studied retrospectively. Data regarding their age, sex, number of blood transfusions, use of chelating agents, and history of splenectomy were obtained. Serum was used for detection of antibodies against HCV, HBsAg and HIV. In addition, the liver enzymes AST and ALT were checked.

Results: Eighty-eight (44%) patients were found to be HCV seropositive. The prevalence correlated with gender, history of splenectomy, and number of blood transfusions. No significant differences were found between age groups or chelating agents. Liver enzymes were significantly higher in seropositive patients.

Conclusion: Multi-transfused patients with thalassemia have a high risk of HCV infection, and more accurate techniques of blood screening are recommended.

Keywords: Prevalence, Thalassemia, Hepatitis C.
Introduction

Thalassemias are a heterogeneous group of genetic disorders, resulting in a reduced synthesis rate of the hemoglobin alpha or beta chain (1). The imbalance of globin chain synthesis results in red cell damage and destruction in the marrow (ineffective erythropoiesis) and peripheral circulation (hemolysis) (2). The hemoglobin molecule has two protein chains, alpha and beta, and both can be affected (3), resulting in alpha- or beta-thalassemia, respectively (4). The most common type is beta-thalassemia (5). Alpha-thalassemia is the reduction or absence of the alpha chain synthesis and it is common in South East Asia. Because there are two alpha-globin gene loci in chromosome 16 (6), each individual carries four genes, two from the paternal and two from the maternal chromosome. This results in four possible genotypes with different clinical syndromes each (7). If one gene is deleted, the individuals become silent carriers of alpha-thalassemia, with no clinical effects. If two are deleted, the patient exhibits a mild hypochromic anemia, the feature of alpha-thalassemia trait (8). Beta-thalassemia is an autosomal recessive disorder characterized by reduced or absent beta-globin chain synthesis, caused by one of the 180 possible mutations in the gene coding for the hemoglobin beta chain (9). The beta-globin gene is located on chromosome 11 (10).

Hepatitis C virus (HCV) is a blood-borne virus. Most epidemiological studies have focused on groups with HCV infection risk due to multiple blood transfusions, such as patients with thalassemia. Moreover, HCV is considered the main cause of post-transfusion hepatitis worldwide (11). The risk of acquiring HCV infection after a transfusion is approximately 10% (12). It was reported that HCV is responsible for at least 90% of transfusion-related non A–non B hepatitis (13). Repeated blood transfusions are necessary for the survival of patients with thalassemia, but such transfusions increase their exposure, not only to HCV but also to other blood-borne viruses, such as hepatitis B (HBV), hepatitis G (HGV), and the human immunodeficiency virus (HIV) (14). Liver disease, due to blood-borne viral hepatitis, is the second most common cause of death in patients with thalassemia major over 15 years of age (15). Interestingly, more studies showed that patients on long-term transfusion therapy have a risk of infection with HCV, with a prevalence ranging from 12.2% to 16% (16). Furthermore, the infection with HCV may not induce immunity, and multiple distinct episodes of acute hepatitis, and re-infection with a different strain, were observed in multi-transfused patients with thalassemia (17).

The aims of the study were:
1- To identify the prevalence of anti-HCV antibodies in patients with thalassemia major, who received multiple blood transfusions, and who were regularly attending the thalassemia center of the Sulaymani Teaching Hospital.
2- To investigate changes in this prevalence during the last 10 years.

Materials and Methods

Patients and Methods:

From February 2014 to September 2014, 200 beta-thalassemia major (Cooley’s anemia) patients, aged 1 to 17 years, were studied retrospectively. These patients represented approximately 20% of the beta-thalassemia major population of the Sulaymani province. The diagnosis of
thalassemia was confirmed by hemoglobin electrophoresis. The patients’ age, sex, number of blood transfusions, chelating agents received, and history of splenectomy were obtained. Blood samples were obtained and the following serological tests were performed using standard methods:

1- Anti-HCV antibodies were screened using a third generation ELISA.
2- HBsAg and anti-HIV antibodies were screened using a quantitative third generation microparticle enzyme immunoassay.
3- HCV seropositive cases were confirmed by polymerase chain reaction (PCR).
4- Serum liver enzymes alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels were measured according to the International Federation of Clinical Chemistry standards.

Statistical analysis

The seroprevalence for infection was calculated and the chi-squared test was used to assess the correlation of prevalence and age, sex, number of blood transfusions, receiving chelating agents and splenectomy. A T-test was used to compare the mean liver enzymes levels between the HCV seropositives and a control group of 50 seronegative, non-thalassemic patients, matched for age and sex. P values of less than 0.05 were considered significant.

Results

The demographic data of the 200 patients included in this study is shown in table 1. There were 106 males and 94 females. Twenty-six patients were less than 5 years old, 22 were between 5 and 12 years old, and 152 were more than 12 years old. Forty patients received blood more than 20 times after the initial diagnosis, whereas 160 patients received blood less than 20 times. Ninety-four patients were splenectomized. The seroprevalence of HCV, HBV, and HIV among the studied group is shown in table 2.

Eighty-eight of the 200 patients (44%) were HCV seropositive, six were HBsAg seropositive, and none tested positive for HIV. The prevalence of HCV seropositives by age group, gender, number of blood transfusions, splenectomy, and type of chelating agents is shown in tables 3, 4, 5, 6 and 7, respectively.

Of the 88 seropositive patients, 54 were males and 34 were females, ten patients were less than 5 years old, eight were between 5 and 12 years old, and 70 were 12 years old or more. Twenty-four patients received blood more than 20 times after the initial diagnosis. Forty patients were on Desferal® as a chelating agent, and 26 had splenectomy. The mean levels of the ALT and AST liver enzymes of the 88 HCV seropositive patients and the control group, are shown in table 8. The levels were significantly higher among seropositive patients, in comparison with the seronegative (p= 0.01).
Table 1. Sociodemographic characteristics of multi transfused thalassemic patients.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Number of patients (n=200)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>106</td>
</tr>
<tr>
<td>Female</td>
<td>94</td>
</tr>
<tr>
<td>Splenectomy</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>94</td>
</tr>
<tr>
<td>No</td>
<td>106</td>
</tr>
<tr>
<td>Number of blood transfusion</td>
<td></td>
</tr>
<tr>
<td>More than 20 times</td>
<td>40</td>
</tr>
<tr>
<td>Less than 20 times</td>
<td>160</td>
</tr>
<tr>
<td>Age group (years)</td>
<td></td>
</tr>
<tr>
<td>Less than 5 years</td>
<td>26</td>
</tr>
<tr>
<td>5-12 years</td>
<td>22</td>
</tr>
<tr>
<td>More than 12 years</td>
<td>152</td>
</tr>
</tbody>
</table>

Table 2. Prevalence of viral infection in multi transfused thalassemic patients (n=200).

<table>
<thead>
<tr>
<th>Serology test</th>
<th>Number of positive results</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-HCV</td>
<td>88</td>
<td>44</td>
</tr>
<tr>
<td>Anti-HBV</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Anti-HIV</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Discussion

Before the introduction of routine testing for HCV antibody in donated blood, the risk of exposure to HCV depended directly on the number of transfused blood units, and on the prevalence of HCV in the blood donor population (20). Consequently, patients affected with hemoglobinopathies such as thalassemia major, being the most transfused with packed red blood cells, were frequently infected by HCV, with prevalence varying geographically from 23% to 72% (21). The results of this study show that 44% of thalassemic children were HCV seropositive, 3% were HBsAg seropositive, and none of them was HIV seropositive. These values were lower than the HCV seropositivities reported in Arabian countries such as Egypt, Bahrain, and Saudi Arabia, and in China, where HCV seropositivities were 44%, 40%, 70%, and 34%, respectively (22). However, in USA, since the introduction of screening of blood products, transfusions account for less than 5% of new hepatitis C cases (23). The difference in the results among different countries could be explained by the use of different screening methods, including first and second generation ELISA, which have variable sensitivity and specificity, and may give false positive results (24). In addition to HCV, multi-transfused patients with thalassemia are at risk of acquiring HBV. Fortunately, our study revealed HBsAg prevalence rate of 3%, which is low in comparison to a study done in Saudia Arabia in 1993, where the exposure rate of thalassemic children to HBV was 26%. This low prevalence rate may be due to the use of third generation ELISA technique for the screening of donated blood, which started
several years ago. In addition, the strict preventive measures employed at hospitals against the spread of HBV infection, and the inclusion of hepatitis B vaccine in the immunization schedule may have contributed to the low prevalence of HBV (25). In our study, the HCV prevalence rate was directly related to the number of blood transfusion units: 60% of patients who received blood more than 20 times were seropositive, compared to 40% of patients who received it less than 20 times. The same trend was also recorded by Ibrahim et al. in Sulaymani in 2005, by Tareef et al. in Diyala in 2009, by Abdul Kareem et al. in the Al-Kadhimia Teaching Hospital Baghdad in 2013, by Al-Zamili et al. in the Al-Diwania Teaching Hospital in 2009 and by Baydaa et al. in the Ibn-Albalady Teaching Hospital Baghdad in 2010 (28,29,30,31,32). These similar results can be explained by the increasing risk of transmission with the increasing number of transfused blood units (21,22,23).

Table 3. Prevalence of positive HCV-antibody according to several factors

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Total number of patients</th>
<th>Sero(+) patients and %</th>
<th>Sero(-) patients and %</th>
<th>Chi-square</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 5</td>
<td>26</td>
<td>10 (38%)</td>
<td>16 (62%)</td>
<td>1.083</td>
<td>0.298036</td>
</tr>
<tr>
<td>5-12</td>
<td>22</td>
<td>8 (36%)</td>
<td>14 (64%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>More than 12</td>
<td>152</td>
<td>70 (46%)</td>
<td>82 (54%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>106</td>
<td>54 (51%)</td>
<td>52 (49%)</td>
<td>4.4128</td>
<td>0.035671</td>
</tr>
<tr>
<td>Female</td>
<td>94</td>
<td>34 (36%)</td>
<td>60 (64%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of blood transfusions</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; than 20 times</td>
<td>40</td>
<td>24 (60%)</td>
<td>16 (40%)</td>
<td>5.1948</td>
<td>0.022654</td>
</tr>
<tr>
<td>&lt; than 20 times</td>
<td>160</td>
<td>64 (40%)</td>
<td>96 (60%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Splenectomy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>94</td>
<td>62 (66%)</td>
<td>62 (66%)</td>
<td>34.7036</td>
<td>0.00</td>
</tr>
<tr>
<td>No</td>
<td>106</td>
<td>26 (24%)</td>
<td>26 (24%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chelating agent</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>desferal</td>
<td>60</td>
<td>40 (66%)</td>
<td>20 (34%)</td>
<td>17.8726</td>
<td>2.4</td>
</tr>
<tr>
<td>exjade</td>
<td>140</td>
<td>48 (34%)</td>
<td>92 (66%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ALT: liver enzymes test in patients with Sero(+),(-) and in order 75.5±16, 44.8±17 (p-value< 0.05)

AST: liver enzymes test in patients with Sero(+),(-) and in order 68.1±17, 32.7±17 (p-value< 0.05)

We found a significant difference of HCV seropositivity prevalence between males and females, which was expected as the virus transmission occurs mainly through blood transfusion and drug injection, rather than other routes. This result was
similar to those of Tareef et al 2009 and Al-Zamili et al 2009.

The prevalence of HCV infection was higher in the group aged more than 12 years (46%), as compared to the observed in the age group of less than 5 years old, and between 5 and 12 years old (38% and 36%, respectively). This is attributed to number of transfused blood units increasing as the children were getting older, the development of antibodies to red blood cells, and to the possibility of developing hypersplenism. This result was compatible with studies from different countries, but it was not significant (23,24,25).

In thalassemic children with splenectomy, the prevalence of HCV infection was 62%, significantly higher than in non-splenectomized patients, where it was 26%. This difference could be due to a decrease in the clearance of microorganisms and particulate antigens from the blood, decrease in the synthesis of immunoglobulin G (IgG), and decrease in the removal of abnormal red blood cells. In contrast, other studies reported no significant difference in the prevalence of HCV infection between splenectomised and non-splenectomised children (24,25,26).

There was no significant difference in the prevalence of HCV infection in patients receiving the chelating agent Desferal® from those receiving oral Exjade® (27).

Comparing our results with the study done by Ibrahim et al, 2005 in Sulaymani, there was an increase from 24% to 44% in the prevalence of HCV seropositives, and this could be due to insufficient methods to prevent the HCV infection.

Conclusions

1- The prevalence of anti-HCV antibodies in thalassemia patients is still relatively high, which carries high risk for development of chronic liver disease.
2- Screening of blood donors is vital for the control of HCV infection.
3- All patients with thalassemia should be screened for HCV infection every 6 months.
4- The availability of ELISA tests, that detect antibody rather than antigen after 14–16 weeks after the onset of infection (20–22 weeks after the blood transfusion), may result in false negative results. Therefore, it is best to employ a PCR, which detect viral antigens as early as 1-2 weeks after the onset of infection.
5- To educate the population, providing information regarding the disease and the importance of screening tests.

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