Frequency of Hepatitis B and C Sero Markers Among Hemophiliacs and Von Willebrand's Disease in Alkut, Iraq. (2017)

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Abstract
Objective: Blood-borne infections, such as the hepatitis B and C, are major problems in patients receiving blood products. The aim of this study was to determine the frequency of occurrence of hepatitis B and C viruses among hemophiliacs in AlKut city, Iraq. Methods: A cross sectional study of 50 patient having hemophilia and VWD registered in hematology center in Al Karama hospital in AlKut city, Was it state, Iraq , in 2017. And evaluated for the presence of hepatitis B surface antigen (HBsAg), hepatitis C virus antibody (HCV-Ab). Demographic data of patient's age at time of diagnosis, sex, ABO blood group and type of treatment were also recorded and analysed .Results: 50 patients presented with bleeding disorder, 41 patients diagnosed as hemophilia [ 100% in male] and 9 patients diagnosed as von wille brand's disease [33.3% are male and 66.7 % was female] . 66% of them have proved to have +ve family history, and 16% have –ve family history, and 18% not yet proved. 42.9% (15 patients) of all investigated patients (35 patients) was sero positive for hepatitis B& C. 8.6% (3 patients) and 31.4% (11 patients) had hepatitis B and C respectively. 2.9% (1 patient) had both of them. 53.3% (8 patients) of patient with +ve hepatitis infection had diagnosed to be having coagulopathy (hemophilia & von will e brand's disease when they was below 10 years, 26.7% (4 patients) between 10 – 20 years and 20% (3 patients) was above 20 years. 4 VWD patients underwent viral screen , 50% of them were +ve for hepatitis C and 50% were ve for all hepatitis types. 31 hemophiliac patients underwent viral screen, 41.9% were +ve { 9.7 % (3 patients) had hepatitis B, 29% (9 patients) had hepatitis C, and 3.2% (1 patient) had both of them} .patients with coagulopathy receive treatment as cryoprecipitate and factor VIII and IX . 66.7% of hepatitis B sero positive patients had received cryoprecipitate, 90.9% (10 of all 11 patients) of hepatitis C sero positive patients had received cryoprecipitate, and the patient who had both types of hepatitis also receive cryoprecipitate. Conclusion: Management of transfusion of blood and blood products should account for the underlying prevalence of infectious agents, And the risk of getting these infections increased with increasing the period and frequency of exposure to them.

Introduction
Inherited bleeding disorders (IBDs) are caused by quantitative and qualitative alterations of either platelets or plasma proteins involved in coagulation and fibrinolysis. Hemophilias are the most frequent IBDs, However Various studies have reported that VWD is the most common congenital bleeding disorder in the population [¹,²,³]. Hemophilia is a disease characterized by serious bleeding symptoms due to a deficiency of factor VIII for hemophilia A and factor IX for hemophilia B (Christmas disease)⁴. VWD has recently been classified into types 1, 2 and 3. Type 1 VWD is caused by low levels of functionally normal protein (10% to 50% of normal values), Type 2 is caused by variable amounts of functionally abnormal VWF, Type 2 is further subdivided into type 2A, in which the larger protein multimers are missing; type 2B, in which VWF has increased affinity for platelets; type 2M, in which there is a
normal protein multimer pattern; and type 2N, in which the protein has markedly decreased affinity for factor VIII. Type 3 is the result of the virtual absence of VWF. Bleeding episodes were previously treated with whole blood transfusions. The management of haemophilia has dramatically improved in the last 25 years to be clotting-factor concentrates in the form of Factor VIII & Factor IX infusion, and VWD treatment also improved to involve desmopressin acetate (DDAVP Ferring Inc, Canada), transfusion with plasma concentrates that contain VWF and antifibrinolytic agents.

However, these therapies based on human properties have always been associated with the risk of microbiological transmission, especially viral infections such as human immunodeficiency virus (HIV), hepatitis C virus (HCV), and hepatitis B virus (HBV). A potential risk of virus transmission by these blood products persists because the serological screening of blood donors cannot detect all potential infections. As a result, screening blood donors for HIV-1, HBs Ag and HCV RNA by means of nucleic acid amplification was introduced in 1999 in developed countries to identify donations made during the window period before seroconversion. Besides, patients with haemophilia & VWD remain at risk of contamination by non-inactivated products such as cryoprecipitate and/or nosocomial infections. Specifically, much attention has been drawn to the safety issues of handling blood and blood products after the worldwide accidental viral contamination among haemophilia patients. Thus, the purpose of the current study was to investigate the seroepidemiology of these infections (hepatitis B & C) transmitted by blood and blood products.

Patients & Methods

A cross-sectional study of the medical records of 50 patients, who were physician-diagnosed haemophilia A or B and VWD and registered in haematology center in Al Karama teaching hospital in the city of Al Kut, the state of was it, Iraq. The data collected on April 2017. Data collected included sex, age at diagnosis and registration, blood group, type of treatment received by the patients, and family history of coagulopathy. The following

age groups were considered: <10 years old, 10–20 years, and >20 years. Age and sex specific frequency of sero positive hepatitis B & C observed were computed. Descriptive statistics were performed using the SPSS statistical software. The comparative study of the demographic variables was performed. Data are presented as mean ± SD and range for quantitative variables. Categorical data are presented as numbers and percentages. For comparison, the t test and the chi square test was used for qualitative variables, and were considered statistically significant when p<0.05

Results

50 patients with coagulopathy in haematology center in Al Kut were enrolled in the study (44 male, and 6 female, mean age 9.4 years, range 1 to 25 years, standard deviation 7.5). 70% (35 patients) had haemophilia A, 12% (6 patients) haemophilia B and 18% (9 patients) had VWD, as shown in (fig. 1). The age at time of diagnosis and registration is divided into 3 age groups, as shown in (Table 1).

All haemophiliacs were male. 57.1% (20 patients) of haemophilia A had proved +ve family history of the disease, 20% (7 patients) of them had proved –ve family history of the disease, and 22.9% (8 patients) are not yet proved to be +ve or –ve family history of the disease. 83.3% (5 patients) of haemophilia B had proved +ve family history of the disease, while 16.7% (1 patient) are not yet proved to be +ve or –ve family history of the disease. 66.7% (6 patients) of VWD were male & 33.3% (3 patients) were female, 88.9% (8 patients) had proved +ve family history of the disease, while 11.1% (1 patient) had proved –ve family history of the disease. 35 patients (31 male & 4 female) underwent viral (HBV & HCV) screen, the seroprevalence of HBV was 8.6% (3 of the 35 patients), while the seroprevalence of HCV was 31.4% (11 of the 53 patients), 2.9% (1 patient) had both of them, and 57.1% (20 patients) were seronegative for both viruses. Frequency of hepatitis in patients with coagulopathy according to their type of
coagulopathy are shown in (Table. 2), and according to their sex are shown in (Table. 3). 53.3% (8 patients) who were sero positive for either HBV, HCV or both, were diagnosed and registered as having coagulopathy when they were below 10 years old, as shown in (Table. 4). 25 patients with coagulopathy receive cryoprecipitate, 52% of them (13 patients) were sero positive for either HBV, HCV or both, as shown in (Table. 5). 7 patients with coagulopathy receive Factor VIII, 14.3% of them (1 patient) were sero positive for HCV. 3 patients with coagulopathy receive Factor IX, 33.3% of them (1 patient) were sero positive for HBV. The history of receiving whole blood transfusion is unknown for all patients. 66.7% (4 of all the 6 patients) of patients with A+ blood group were sero positive for HCV. 66.7% (4 of all the 6 patients) of patients with A+ blood group were sero positive for Either Hbv, HCV or both, as shown in (Table. 6).

Fig. 1: frequency of coagulopathy in hematology center in Alkut city.

Table 1: Pattern of coagulopathy according to age groups at time of diagnosis

<table>
<thead>
<tr>
<th>Age group</th>
<th>Hemophilia A</th>
<th>Hemophilia B</th>
<th>VWD</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency</td>
<td>percentage</td>
<td>Frequency</td>
<td>percentage</td>
<td>Frequency</td>
</tr>
<tr>
<td>&lt; 10</td>
<td>19</td>
<td>5</td>
<td>6</td>
<td>30</td>
</tr>
<tr>
<td>10 – 20</td>
<td>7</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>&gt; 20</td>
<td>8</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Unknown</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>35</td>
<td>70</td>
<td>6</td>
<td>12</td>
</tr>
</tbody>
</table>

Table 2: Distribution of hepatitis infection according to type of coagulopathy

<table>
<thead>
<tr>
<th>Type of coagulopathy</th>
<th>Hepatitis B</th>
<th>Hepatitis C</th>
<th>Hepatitis B+C</th>
<th>-ve</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency</td>
<td>percentage</td>
<td>Frequency</td>
<td>percentage</td>
<td>Frequency</td>
<td>percentage</td>
</tr>
<tr>
<td>Hemophilia A</td>
<td>2</td>
<td>5.7</td>
<td>9</td>
<td>23.6</td>
<td>1</td>
</tr>
<tr>
<td>Hemophilia B</td>
<td>1</td>
<td>2.9</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>VWD</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>5.7</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>3</td>
<td>8.6</td>
<td>11</td>
<td>31.4</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 3: Distribution of hepatitis infection according to sex of patients

<table>
<thead>
<tr>
<th>Gender</th>
<th>Hepatitis B</th>
<th>Hepatitis C</th>
<th>Hepatitis B+C</th>
<th>-ve</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency</td>
<td>percentage</td>
<td>Frequency</td>
<td>percentage</td>
<td>Frequency</td>
<td>percentage</td>
</tr>
<tr>
<td>Male</td>
<td>3</td>
<td>8.6</td>
<td>9</td>
<td>25.7</td>
<td>1</td>
</tr>
<tr>
<td>Female</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>5.7</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>3</td>
<td>8.6</td>
<td>11</td>
<td>31.4</td>
<td>1</td>
</tr>
</tbody>
</table>
Discussion

Hemophilia and von Willėnbrand’s disease are congenital bleeding disorder due to quantitative or qualitative deficiency of coagulation factors IX, VIII respectively. The severity is generally related to the degree of the underlying defect. Rapid and reliable identification of these diseases is important to allow the adoption of appropriate substitutive or supportive therapies.

In Iraq, consanguineous marriage are frequent, there for autosomal recessive coagulation disorders reach a higher prevalence than in many other countries. Beside, genetic diseases do not receive any public health support because they are considered to be rare conditions with low prevalence. Furthermore, actual statistics on the demography of genetic diseases in the Iraqi population are largely unavailable.

In hematology center in Al Kut , the commonest IBDs was hemophilia A affecting 35 patients (of the all 50 patients), followed by VWD affecting 9 patients, followed by Hemophilia B affecting 6 patients. This result reflects that hemophilia is the most frequently encountered IBDs. Few published studies in Saudi Arabia, Jordan and Egypt describe the distribution of IBDs in the population [10,11,12].

They obtained the distribution of IBDs resembling what has already been established by western countries. They reported that VWD was the second most common cause of IBDs with the exception of increased platelet disorders, mostly due to the increased rate of consanguinity in the community. Although our results may be inaccurate to describe the frequency of IBD in Al Kut due to some degree of under...
diagnosis of the less severe forms of hemophilia and VWD, or registration in other center outside Al Kut, but it may be related to different ethnic and racial groups too. For age presented at diagnosis, 68.6% (24 patients) of hemophilia patients diagnosed when they was below 10 years old 25 % of them was below 1 year, while 66.7% (6 patients) of all VWD diagnosed when they was below 10 years old. The age at diagnosis was determined from the case papers.

The problems with management of hemophilia in developing countries and the priorities in establishing hemophilia services have been discussed. This study highlights that hemophilia & VWD services are needed during their infancy, and identifies some areas of intervention that would improve the treatment available to patients. The need to extend hemophilia services as well as increase awareness not only among practitioners, but also among family members, becomes obvious.

A second area of intervention, which is of minimum importance at the current time, is the need to collect genetic information from families. These data would form the basis for genetic counseling, a feature that currently has very low priority. Before the introduction of substitution therapy the cause of deaths among IBDs was the almost inevitable bleeding. The low number of deaths due to all types of bleeding, except cerebral hemorrhage, proves the improvement and the effectiveness of the provided care.

Nowadays, hemophiliacs are growing older and survive to experience diseases of the elderly like cancer and ischemic heart disease. However, these have not yet become the commonest causes of death because of the appearance of transfusion transmitted viral diseases which is a major co-morbid condition among patients with IBDs who received non-virus-inactivate or insufficiently inactivated large-pool clotting factor concentrates or cryoprecipitate.

In the present study, 22% (11 patients) of all screened patients had serological evidence of hepatitis C and 6% (3 patients) had serological evidence of hepatitis B virus, and 2% (1 patient) had both of them. 53% of sero positive hepatitis found in patients who diagnosed to have coagulopathy when they was below 10 years age, this is related more frequent transfusions than older patient till the time of screening.

Already from 1975, 77% of poly transfused Greek hemophiliacs were infected by the hepatitis B virus giving cause to the fears expressed in previous studies. Prevalence of HCV-Ab sero positivity in other studies published in Iran was 76.6% and 77% and 81.8%. Prevalence of HCV-Ab sero positivity in other countries was 80% in hemophilic children in Poland, 42.4% in Morocco, 42.4% in Japan and 92.2% in Italy. Sero positivity for HBs Ag in Iran was reported to be 26.7%. Additionally, since hemophiliacs infected by HIV, HBV and HCV are not uncommon, more deaths due to combined infections may be expected for the near future.

The risk of hepatitis virus infection is great if the non-inactivated factor concentrates are used for patient treatment. In addition blood and blood products transfusion carry the same risk if the donor was in the open window phase i.e. before antibodies appearance. Regarding blood transfusions, multivariate analysis showed that patients who received more than 160 transfusions had a 10.7-fold (95% CI: 2.0-57.5) greater risk of HCV positivity compared to subjects who received less than 50 transfusions. In the last decade there have been significant advances in the therapy of coagulopathy.

The technological evolution of the processes of purification and viral inactivation has allowed the marketing of new plasma-derived concentrates, while progress with the production of factor VIII (FVIII) and factor IX (FIX) in animal cells by recombinant DNA technology has enabled the progressive elimination of human and animal proteins from various stages of the manufacturing process. Some recombinant products have, therefore, been replaced by newer generation products and other innovative molecules are currently in an advanced experimental or registration stage. Beside, for blood products it may be safe to encourage blood bank to implant molecular techniques as nuclear amplifications technique for screening of mini pool of blood and blood products for safety of blood transfusion. A
more strict policy for blood product usage, universal HCV screening and HBV vaccination is needed to abolish those disease in patients with IBDs.

Conclusions
The most frequent coagulopathy in our locality is hemophilia A followed by VWD, and there is a high sero prevalence for hepatitis viruses, vaccination against HBV, continues screening for HCV, and continuous follow up to detect asymptomatic patients is highly recommended.

Acknowledgment
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References


