

Outcomes of Congenital Bleeding Disorders

Galila Zaher, MD, FRCPath* Soheir Adam, MD, FRCPath*

Background: Hemophilia is an x-linked inherited bleeding disorder that requires lifelong medical support.

Objective: To evaluate the prevalence, presentation and management of inherited bleeding disorders.

Setting: Hematology Department, King Abdulaziz University, Saudi Arabia.

Design: Retrospective study.

Method: Sixty-four patients with inherited bleeding disorders were included in the study from January 2000 to January 2011. Clinical, baseline coagulation screen, factor assay and serological testing were collected.

Result: Thirty-one patients (48.4%) were diagnosed with hemophilia A, eighteen patients (28.1%) had von Willebrand disease, eleven patients (17.9%) had Hemophilia B and four patients had other factor deficiencies. Eleven patients with Hemophilia A and one patient with Hemophilia B had severe disease. The prevalence of hepatitis C virus infection was 5%. All patients were negative for hepatitis B S Ag and human immune deficiency virus antibodies.

Conclusion: The distribution of hereditary bleeding disorders reported in this study is similar to other studies; however, the prevalence of von Willebrand disease was lower than expected. We believe there is under-representation of bleeding disorders in our referral population due to lack of awareness and diagnostic expertise in remote areas of the Western region.

Furthermore, the implementation of rigorous donor screening and the adoption of nationwide hepatitis B vaccination have successfully reduced transfusion-transmitted viral infections among Saudi patients.

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* Assistant Professor
Hematology Department
King Abdulaziz University
Saudi Arabia
Email: gailazaher@yahoo.com

Hemophilia is an x-linked inherited disease that requires lifelong medical support¹. Hemophilia A (HA) and Hemophilia B (HB) are caused by deficiency of coagulation factor VIII and IX respectively. Clinical picture of hemophilia is variable and depends on the level of coagulation factor. Factor levels <1U/dl is severe hemophilia, 1-5 U/dl is moderate and >5 U/dl is mild. The disease is characterized by bleeding in early childhood including hemarthrosis, soft tissue bleeding and less commonly intracranial bleeding. Delayed or insufficient treatment can cause musculoskeletal complications within the joints leading to chronic synovitis and severe joint hemarthropathy². In the past, those diagnosed with hemophilia were crippled by the time they reached adolescence and seldom reached adulthood².

Due to the chronic nature of the disease and the high cost of therapy, hemophilia management presents a challenge to the health care system in Saudi Arabia³. To improve care for persons with hemophilia, comprehensive treatment centers for all bleeding disorders should ideally be introduced to all regions. This will ensure early diagnosis, treatment and prophylaxis to prevent disease complications including joint bleeding and consequent arthropathy¹⁻³.

The aim of this study is to evaluate the prevalence, presentation and management of inherited bleeding disorders.

METHOD

Data were collected from medical records after obtaining an informed consent and obtaining approval of the Hospital Ethical Committee at KAUH.

Sixty-four patients with inherited bleeding disorders have been registered from January 2000 to January 2011. Mild cases are seen annually or biannually, while severe ones are seen three times a year.

Clinical examination, family history and coagulation study were performed for each patient. Laboratory screening tests include prothrombin time (PT-BC thrombin time) and activated partial thromboplastin time (APTT -BC Pathromtin SL). Immediate and 2 hours post incubation mixing studies are used for identification of inhibitors.

Factor levels are measured using one stage clot based assay on BCS as described⁴⁻⁶. Von Willebrand disease (vWD) is diagnosed using initial screening tests (PT, APTT and Platelets function analyzer PF-100) supplemented by confirmatory tests (VWF ristocetin cofactor activity and VWF antigenic assay)⁷. Bethesda assay is used to quantify inhibitor level^{2,5}.

During the study period, Hepatitis C virus (HCV) was identified by the antibodies to HCV (anti HCV) through enzyme linked immune-sorbent assay (ELISA) and the confirmatory recombinant immunoblot analyses (RIBA). On the other hand chemiluminescent micro particle immunoassay (CMIA) was used to identify hepatitis B virus (HBV) infection.

The treatment includes recombinant factor concentrates, virally inactivated plasma derived factor concentrates, fresh frozen plasma and cryoprecipitate. All donors are screened for the human immunodeficiency virus type 1&2 (HIV-1/HIV-2), Hepatitis B surface antigen (HBS Ag) and

hepatitis C virus antibody (HCV Ab). The preparation of cryoprecipitate involves slow thawing of FFP at 4°C to 6°C. Each concentrate is prepared from a single donor unit of plasma⁸.

Statistical analysis was performed using SPSS version 16@IBMprogram.

RESULT

Sixty-four patients wereregistered, aged 1-37 years (mean 12.9 years). Thirty-one (48.4%) patientshad HA, eighteen (28.1%) had vWD, eleven (17.9%) had HB and four (6.3%) hadother factors deficiencies(one factor VII deficiency, one combined factor V and VIII and two factor X deficiency). Thirty (46.9%) patientswere Saudi patients; other nationalities include Yamani, Egyptian, Lebanese and Afghani. Eleven patients with HA were severe, while one with HB was severe. Eleven patients (35.5%) patients with severe HA are on secondary prophylaxis. Out of vWD, eleven patients (61.1%) patientswere females, seetable 1.

Table 1: Sex Distribution between vWD and Rare Inherited Bleeding Disorders

	vWD	Others
Male	7 (38.9)	2 (50)
Female	11 (61.1)	2 (50)

No death related to hemophilia has been reported in our study. Three of 31 (9.7%) patients with HA had factor VIII inhibitors, see table 2.The three patients had severe HA; two of them had brothers with similar factor levels, but with no evidence of inhibitors. Immune tolerance induction was offered with success to two patients using the Bonn protocol. Recombinant activated factor VII was used effectively for the management of intracranial hemorrhage in one patient with HA and factorVIII inhibitor.

Table 2: Prevalence of Inhibitors among Patients with Hemophilia

Inhibitors	Present	Total
HA	3	31
HB	0	11
Total	3	42

Forty-six (72%) patients have been tested for HBV, HCV and HIV infections. All our patients tested negative for HBV and HIV infections, while three patients (4.7%) tested positive for HCV infection, see figure 1. Three out of total 31 patients with HA developed inhibitors(9.7%), which account for 27.2% of the eleven patients with severe HA.

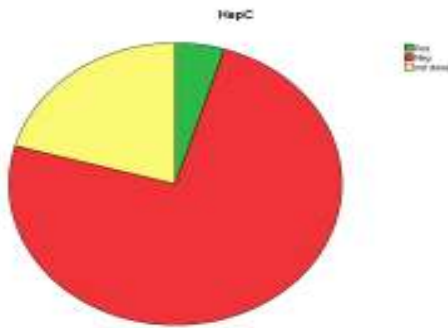


Figure 1: The Prevalence of Hepatitis C in Patients with Inherited Bleeding Disorders in Western Saudi Arabia

DISCUSSION

Acute hemarthrosis is the hallmark of hemophilia. The introduction of coagulation factor concentrate has doubled the life expectancy of such patients^{1,2,9}. Major factors that influence hemophilia management are lack of diagnostic and counseling support and insufficient supply of factor concentrates^{4,9}. Demographic data are extremely valuable tools in healthcare⁹. Unfortunately, there is no epidemiological data on inherited bleeding disorders in Saudi Arabia. Country-specific prevalence is calculated based on various prevalence rates available worldwide. Therefore, in Saudi Arabia with a population of 25,795,938, the expected number of individuals with HA is 1,896 and 37 new cases diagnosed annually. Based on a population of 3.2 million, the expected number of individuals with HA in Jeddah is 236¹⁰.

Few studies on inherited bleeding disorders were performed from different parts of the kingdom of Saudi Arabia⁹⁻¹⁴. Two studies came from the Eastern Province, while the largest study was from Central Province¹¹⁻¹³. This is the first report on inherited bleeding disorders in the Western Province of Saudi Arabia. The prevalence of HA in this study is much lower than the calculated prevalence, that might be due to the lack of awareness and patchy medical access in various areas of the Western region¹⁰.

Prophylaxis is widely recommended for the management of severe HA. Evidence showed that persons receiving early secondary prophylaxis demonstrated a lower incidence of arthropathy^{1,2,15}. Cryoprecipitate should not be used as a replacement therapy for HA^{1,2}. All severe cases with HA in this study have been receiving home-based secondary prophylaxis. Patients with mild to moderate hemophilia are receiving factor concentrate to treat acute bleeding episode. A minority of patients with HA at KAUH is treated with cryoprecipitate or fresh frozen plasma where limited resources make this the only available option⁴.

The risk of blood-borne virus infection is generally low; however, the cumulative risk in hemophilia patients treated with cryoprecipitate or fresh-frozen plasma over a lifetime could be significant⁹. Hepatitis C infection is an important public health problem worldwide¹⁶. It can cause liver damage and liver cirrhosis, whilst co-infection with HIV reduces life expectancy. An earlier report of HCV infection prevalence in healthy Saudi population was 5%, which is five times than

that reported from Western Europe and USA¹⁷. Previous study among Saudi patients showed that 78% of patients who had hemophilia had HCV infection¹⁸.

Given the high level of HCV infection and the possibility of serious complications, routine HCV screening of blood donors became mandatory since 1990 in Saudi Arabia. Recent epidemiological data have shown that the incidence of HCV in Saudi Arabia is low (0.17%)¹⁹. The rate of seropositivity for HCV (5%) in this study is lower than the rate seen in earlier studies, which emphasizes the efficacy of rigorous screening policies of blood donors and the provision of virally inactivated blood products in the form of factor concentrates.

Saudi Arabia is also endemic for HBV infection. The prevalence of HBV infection among blood donors in Saudi Arabia is 11-28%^{17,20}. Arif et al showed that HBV infection in Saudi population with congenital bleeding disorders to be 11.1%²¹. A nationwide vaccination program has been adopted since 1990²⁰. Forty-six (71.9%) patients tested negative for Hepatitis S antigen.

The prevalence of acquired immunodeficiency syndrome (AIDS) is nearly 1% in hemophiliac patients²². Our results are similar to other studies; however, twenty-eight percent were not tested for hepatitis S antigen, hepatitis C antibody and for HIV-1/HIV-2, which reflect lack of adherence to written protocols.

The development of inhibitor antibodies complicates the management of hemophiliac patients^{1,2,5}. Review by the University of Sheffield showed overall prevalence of inhibitors in unselected hemophilic populations to be 5-7%, with the cumulative inhibitor risk varying from 0% to 39%²³. Similar prevalence was obtained in this study (9.6%).

vWD was the second commonest inherited bleeding disorder in this study; these findings are similar to other studies from SA, but it is not the most common inherited bleeding disorder^{7,11-13}. However, the fact that the majority of patients with vWD are mild, and the complexity of diagnosis may explain this discrepancy⁷. A survey showed that below one-third of the expected vWD patients within the population had been diagnosed with the disease²⁴. Eighteen patients were diagnosed as vWD: two sisters (11.1%) had a type III (severe form), one patient diagnosed as type 2B and the majority were diagnosed as type 1a where they had a mild clinical course. All patients with type 1 vWD had DDAVP for the management of mild bleeding episodes.

CONCLUSION

The prevalence of hereditary bleeding disorders in this study is similar to other parts of the kingdom; however, the number of vWD patients is lower than expected. This may be due to under-representation of bleeding disorders because of the lack of awareness and diagnostic expertise in remote areas of the Western region.

All severe cases with HA at our center have been receiving home-based secondary prophylaxis, which proved to be a successful approach. Furthermore, the introduction of hepatitis B vaccination has effectively reduced the prevalence of hepatitis B viral infection in patients with hemophilia.

National registry for hemophiliac patients would be an ideal channel to obtain more data on the prevalence, complications and outcome of inherited bleeding disorders. Furthermore, there is a need to develop blood transfusion services within comprehensive care centers to ensure timely and appropriate care for this patient population in various parts of the Kingdom.

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