ORIGINAL ARTICLE

Clinical characteristic and management of haemophilia patients in Malaysia: A single centre experience

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ABSTRACT

Introduction: Haemophilia is one of the commonest inherited bleeding disorders which may lead to long term disabilities if not treated properly. Our aim of study is to understand the clinical characteristic, treatment and complications of adult haemophilia patients in our centre.

Materials and Methods: A retrospective cross-sectional review of all adult haemophilia A (HA) or haemophilia B (HB) patients who received treatment in Hospital Pulau Pinang from January 2021 to December 2022 was conducted. Data was retrieved from patients' medical records.

Results: A total of 75 haemophilia patients (64 HA and 11 HB) were included in this study with median age of 37 years (range 19 70). 42 of them had severe haemophilia (50% of HA, 91% of HB). All HB and 93.8% of severe HA patients were on prophylaxis. Six severe and one mild HA patients developed inhibitor with four of them currently on non-factor prophylaxis. 24 patients (32%) had prior hepatitis C infection and all of them have been successfully treated. The mean annual bleeding rate for severe haemophilia patients were 1.77 (SD ±3.6). Target joints were observed in 9.3% of patients with ankle joint (71.4%) being the most affected joint. More than one quarter (26.7%) of our patients have comorbidities with majority of them having hypertension (17/20), followed by diabetes mellitus (5/20) and ischemic heart disease (5/20).

Conclusion: Our study showed that a significant number of adult patients with haemophilia have comorbidities. Apart from optimising factor replacement therapy, future planning should include improvement in screening, risk modification and prevention of cardiovascular disease.

KEYWORDS:
Haemophilia, Malaysia, comorbidities

INTRODUCTION

Haemophilia is a group of inherited bleeding disorders caused by deficiency or dysfunction of the coagulation proteins factor VIII and factor IX which lead to haemophilia A (HA) and haemophilia B (HB) respectively. Haemophilia is a X-linked recessive disorder, affecting mainly males. Both, factors VIII and IX genes are located on the X chromosome in which factor VIII gene is large and more complex (26 exons) as compared to factor IX gene (eight exons).[1] Since the discovery of factor VIII gene sequencing, a large number of mutations that cause HA, have been identified. The most common genetic defect in severe HA is intron 22 inversion and intron one inversion which occurred 45% and 4% of patients, respectively.[2] HB is also genetically heterogenous and predominantly due to missense mutation in contrast to inversions in the factor VIII gene. The prevalence is around 17.1 and 3.8 per 100,000 male births for HA and HB globally.[3] Based on the report of the Annual Global Survey 2022 by World Federation of Haemophilia, the prevalence of people with haemophilia in Malaysia is 1048, with 899 (85.8%) haemophilia A and 149 (14.2%) haemophilia B.

Patients with moderate to severe haemophilia are prone to spontaneous bleeding, mainly into joints and muscles. Historically, the bleeding episodes of haemophilia were treated with fresh frozen plasma and cryoprecipitate in the 1960's to 1970's and replacement therapy with plasma derived clotting factors in the 1980's onwards. However, multiple transfusion of blood products has been linked to higher risk of transfusion-transmitted infections due to lack of strict screening of blood and its components in the past.

With the advances in clotting factor concentrates, development of specialised haemophilia treatment centres and usage of factor prophylaxis, the number of severe haemorrhages has decreased. Advances in management of haemophilia have also led to significant improvements in life expectancy. Haemophilia patients are experiencing higher numbers of medical conditions associated with aging such as cardiovascular disease. The health burden of the current generation of adult haemophilia patients are due to both the haemophilia-related complications and increasing age-related comorbidities.

Our aim of study is to understand the demographic, comorbidities, treatment and complications of haemophilia patients in our centre. We hope this study will help to improve our understanding about adult haemophilia patients and help in future planning and management of this group of patients.

MATERIALS AND METHODS

This is a single centre, retrospective cross-sectional study of all adult patients with HA and HB who received treatment in Hospital Pulau Pinang, Malaysia from January 2021 to December 2022. Demographic data, clinical characteristics, comorbidities, treatment history, complications and factor consumption were retrieved from patients' medical records

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and data were collected using a standardised form. Transfusion-transmitted infections (hepatitis B, hepatitis C, human immunodeficiency virus infection) and comorbidities (hypertension, diabetes mellitus, dyslipidaemia, cardiovascular disease, chronic kidney disease, liver cirrhosis and malignancy) were obtained.

Severity of haemophilia was defined as: a) Mild: clotting factor level between 5 to 40% of normal factor activity, b) Moderate: clotting factor level between 1 to 5% of normal factor activity and c) Severe: clotting factor level less than 1% of normal factor activity. Target joint is defined as the joint with 3 or more spontaneous bleeds that have occurred within a consecutive 6-month period. Annual bleeding rate was defined as the total number of reported bleeding events for each patient for 1 year.

Data were analysed using Statistical Package for Social Sciences software (version 21.0). Categorical data were expressed as frequencies and percentages. Wilcoxon signed rank test were used to compare dependent variables and p value <0.05 was considered as statistically significant.

RESULTS

Patient Characteristics

A total of 75 haemophilia patients were included in this study with median age of 37 years (range 19 to 70). Majority of them were Chinese (50.7%) followed by Malay (36%) and Indian (13.3%). There were 64 patients diagnosed with HA (50% of them had severe haemophilia) and 11 patients were diagnosed with HB (91% with severe haemophilia B) (Table I). All severe HB patients and 93.8% of severe HA patients were on prophylactic factor replacement therapy, respectively (Table II). Besides, there were eight mild and moderate HA patients on prophylaxis therapy due to recurrent bleeding episodes and antiplatelet therapy for various underlying comorbidities.

Comorbidities

More than one quarter (26.7%) of our patients have comorbidities with majority of them having hypertension (17/20). They were diagnosed with hypertension at median age of 42 years (range 29 to 61). Five patients (6.7%) have ischemic heart disease and diabetes mellitus respectively (Table III). Two patients died during the study period due to cardiovascular event and hepatocellular carcinoma respectively.

Clinical Characteristics

Plasma-derived factor concentrate is the main treatment for our haemophilia patients without inhibitor, except for one patient who is receiving recombinant factor concentrate due to allergic reaction towards plasma-derived factor concentrate. The mean prophylaxis dose for haemophilia A and B was 59.8 ± 28.1 IU/kg/week and 48.5 ± 16.2 IU/kg/week, respectively.

The mean annual bleeding rate for severe haemophilia patients were 1.77 (SD ±3.6). Target joints were observed in 9.3% of patients with ankle joint (71.4%) being the most affected joint. There was a significant number of patients (41.3%) who developed haemophilic arthropathy. Among those with haemophilic arthropathy, 58.1% had single-joint involvement and knee joints were the most commonly affected (Table IV).

Hepatitis C infection (32%) was the commonest blood-borne infection among our study population. All of them successfully cleared the virus either with treatment (13/24) or spontaneous seroconversion (11/24). None of our study population had hepatitis B or human immunodeficiency virus (HIV) infection.

Seven patients (9.3%) developed inhibitor and six of them were severe HA and one was a mild HA. The patient with mild HA was exposed to intensive treatment with factor VIII concentrate for haemothorax requiring cardiothoracic surgery. The incidence of inhibitor among HA patients who were on demand and prophylaxis factor replacement therapy were 4.2% (1/24) and 15% (6/40), respectively (Table V). This was not statistically significant (p = 0.241). Among the patients with inhibitor, four of them are currently on non-factor prophylaxis therapy. Four of the patients with inhibitor have factor VIII gene mutation (intron 22 inversion and large deletion) that are commonly associated with inhibitor development. Besides, two of these patients are siblings.

DISCUSSION

With the advancement in haemophilia care, life expectancy of people with haemophilia (PWH) is now approaching that of the general population. There are a number of complications of haemophilia such as inhibitor development, joint disease and cardiovascular disease (CVD) which are increasing with aging.[4-6]

Transfusion-transmitted infection is one of the serious complications of haemophilia patients. Older haemophilia patients who were exposed to fresh frozen plasma and cryoprecipitate prior to availability of viral inactivation techniques were infected with hepatitis C and HIV.[7] These infections occurred more often before 1985. Majority of the infected patients do not suffer any acute symptoms and cleared the infection spontaneously, the remaining patients become chronic carriers. These older haemophilia population have higher risk of liver cirrhosis and hepatocellular carcinoma.[8] In our study, hepatitis C infection was the commonest transfusion-transmitted infection and was found in 32% of our haemophilia patient. Another study on haemophilia patients in Malaysia by Boo YL et al, reported almost similar rate of hepatitis C infection (30%) among their study cohort.[9] Almost half of our haemophilia patients with hepatitis C infection had cleared the virus spontaneously and the remaining were started on anti-viral treatment and all of them were cured from hepatitis C infection.

Musculoskeletal bleeding is the most common haemorrhagic manifestation among haemophilia patients. Haemarthrosis mainly affects large joints such as knees, elbows, ankles and more frequently involve the dominant side of weight-bearing joints as child begins to walk. Repeated haemarthrosis will lead to synovial hyperplasia and angiogenesis with further

Table I: Demographic and clinical characteristics of patient with haemophilia

	Mild	Moderate	Severe	Total
Haemophilia A				
Severity, n (%)	16	16	32	64
Age distribution, n (%)				
15-24	1	1	3	5
25-34	3	4	11	18
35-44	4	3	11	18
45-54	3	6	6	15
55-64	4	1	0	5
65-75	1	1	1	3
Ethnicity, n (%)				
Malay	5	2	16	23
Chinese	11	10	12	33
Indian	0	4	4	8
Haemophilia B				
Severity, n (%)	0	1	10	11
Age distribution, n (%)				
15-24	0	0	1	1
25-34	0	1	5	6
35-44	0	0	3	3
45-54	0	0	1	1
55-64	0	0	0	0
65-75	0	0	0	0
Ethnicity, n (%)				
Malay	0	0	4	4
Chinese	0	0	5	5
Indian	0	1	1	2

Table II: Treatment characteristic of patients with haemophilia

	Mild	Moderate	Severe	Total
Haemophilia A				
On demand, n (%)	15	9	2	26
Prophylaxis, n (%)	1	7	30	38
Inhibitors				
Yes, n (%)	1	0	6	7
No, n (%)	15	16	26	57
Haemophilia B				
On demand, n (%)	0	1	0	1
Prophylaxis, n (%)	0	0	10	10
Inhibitors				
Yes, n (%)	0	0	0	0
No, n (%)	0	1	10	11
Mean prophylaxis dose (IU/kg/week)				
Haemophilia A	59.7 ± 28.1			
Haemophilia B	48.5 ± 16.2			

Table III: Comorbidity of patients with haemophilia

Comorbidity	n = 20 (26.7%)
Diabetes mellitus	5
Hypertension	17
Dyslipidaemia	4
Ischemic heart disease	5
Chronic kidney disease	3
Chronic liver disease	3
Stroke	2

Table IV: Complications of patients with haemophilia

Complications	Value
Inhibitor	
Yes, n (%)	7 (9.3)
No, n (%)	68 (90.7)
Blood-borne infections	
Hepatitis B	
Yes, n (%)	0 (0)
No, n (%)	75 (100)
HIV	
Yes, n (%)	0 (0)
No, n (%)	75 (100)
Hepatitis C	
Yes, n (%)	24 (32)
Treated	13
Not treated	11
No, n (%)	51 (68)
Musculoskeletal	
Haemophilic arthropathy	
Yes, n (%)	31 (41.3)
Single joint	18 (58.1)
Multiple joints	13 (41.9)
No, n (%)	44 (58.7)
Chronic synovitis	
Yes, n (%)	4 (5.3)
No, n (%)	71 (94.7)
Target joint	7 (9.3)
Yes, n (%)	
Knee, n	1
Ankle, n	5
Elbow, n	1
No, n (%)	68 (90.7)
Annual bleeding rate (Severe haemophilia)	1.77 ± 3.6
Surgery	
Yes, n	6
Major	3
Minor	3

Table V: Characteristics of haemophilia patients with inhibitor

	Presence of inhibitor		P value
	Yes	No	
Factor replacement therapy			
On demand	1	23	0.241
Prophylaxis	6	40	

bleeding occurring in the friable and thickened synovium.[10] Eventually, these will result in chronic synovitis and progressive chronic haemophilic arthropathy. The gold standard in prevention of bleeding and its complication is the prophylaxis with clotting factor replacement. Almost all our severe haemophilia patients were on prophylactic factor replacement therapy currently. However, there is still a significant number of our patients (41.3%) who developed haemophilic arthropathy. This was mainly due to lack of access or non-compliance to prophylaxis factor replacement therapy previously. There are other factors contribute to the development and progression of arthropathy in haemophilia patients, such as genetic susceptibility and environmental factors.[11] Gene polymorphisms associated with an increased expression of pro-inflammatory cytokines such as tumour necrosis factor (TNF)-α and thus lead to more rapid joint damage progression. Overweight and obesity is associated with increased joint weight loading, decreased range in motion of joints, accelerated loss of joint mobility and involved in progression of haemophilic arthropathy in patients with haemophilia.[12] According to the World Health Organisation, the prevalence of obesity has tripled since the 1975 and the concerns this trend raises for managing the health of all patients. Several epidemiological data in United States and Europe suggest that the prevalence of overweight and obesity in haemophilia patients is comparable with the general population.[13] A study in Taiwan showed that obesity had a positive correlation with annual joint bleeding rate and thus leads to higher rate of haemophilic arthropathy.[14]

The development of inhibitors remains one of the most serious challenges in haemophilia patient care. This has been associated with significant morbidity and results in deterioration in quality of life (QoL) as well as with increased healthcare cost.[15] A European multicentre study evaluated the orthopaedic complications and QoL in severe haemophilia patients with or without inhibitors, they reported that higher number of patients with inhibitors suffered joint pain, reduced mobility, orthopaedic

complications and poor QoL as compared to those without inhibitors.[16] In addition, severe studies show the similar results and haemophilia patients with inhibitors experienced more bleeding complications and haemophilic arthropathy.[17-8]

Besides, there are emergence of age-related comorbidities, and these poses additional challenges in providing optimal care for this aging population of patients. Previously, there is little attention on cardiovascular disease (CVD) prevention in PWH. Several studies reported lower risk of CVD among PWH as compared with general male population due to perception that they are protected from thrombus formation by their hypocoagulability.[19-21] However, CVD in particular are increasingly being reported among PWH recently. A study by Pocoski et al. showed that cardiovascular comorbidities are more prevalent among PWH and they appear earlier in life in comparison to the general male population in United States.[22] Another study by Wang JD et al, reported prevalence of CVD among PWH was comparable to that of general population but appeared at earlier age among PWH.[23] In our study, there were five patients (6.7%) with ischemic heart disease and two patients (2.7%) had developed non haemorrhagic stroke. Hypertension is the commonest comorbidities among our study cohort. These results are consistent with ARCHER study, which included the largest Canadian cohort of PWH, in which 31.3% of them has hypertension and 10.5% has diabetes mellitus.[24] Besides, the prevalence of hypertension in PWH were also reported to be higher compared to the general population in several studies.[25-26] It was also highlighted that hypertension starts at younger age among PWH as compared to the general population, therefore blood pressure monitoring should be part of standard care in haemophilia patients.

There were several limitations in the present study which include being a single centre study and small sample size. Due to the small sample size, it is difficult to made a significant comparison of prevalence of comorbidities between our haemophilia patient with the general male population.

CONCLUSION

With the increasing age of adult haemophilia patients, management of this population will become more complex. Our study showed that a significant number of adult patients with haemophilia have comorbidities, in which majority of them have hypertension. Management of these age-related comorbidities in haemophilia patients remains a challenge due to its complexity and lack of evidence-based guidelines on usage of antithrombotic and antiplatelet agents in this condition. Therefore, future planning should include implementation of strategies on improvement in screening, risk modification and prevention of cardiovascular disease.

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DECLARATION OF CONFLICTING INTEREST

The authors declare that there is no conflict of interest.

APPROVAL

Ethical approval of this study was obtained from Malaysia Medical Research & Ethics Committee (NMRR ID-23-01195-HTS).

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