RESEARCH ARTICLE

Haemophilia care in Iraq; a multi-centre study

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Abstract

Objective: To evaluate the level of care available for haemophilia patients.

Method: The descriptive, retrospective analytical study was conducted from December 15, 2020, to March 1, 2021, after approval from the Mustansiriyah University, Baghdad, Iraq, and comprised data from 3 haemophilia treating centres in Iraq participating in the World Bleeding Disorders Registry. The data collected related to patients with haemophilia A and B enrolled in the registry since March 2018, and included age at diagnosis, type of haemophilia, disease severity, age at first bleed and at first joint bleed, type of replacement therapy and outcome. Data was analysed using statistical package of social sciences (SPSS) version 20.

Results: Of the 638 patients with mean age 16.2±4.3 (range: 9-29 years), 581(91%) had haemophilia A, 57(8.9%) had haemophilia B, 385(60.5%) had severe haemophilia, 126(19.8%) moderate and 125(19.7%) mild. Further, 259(41%) patients had been diagnosed for <1 year. There were 1354 bleeding events, and haemarthrosis accounted for 959(70.8%) of them. The mean annualised bleeding rate for severe patients was 2 ± 0.6(range 0-4), while the mean annualised joint bleeding rate was 4 ± 1.3(range :2-8). There were 256(32.3%) patients who were tested for inhibitors, and 62(24.3%) were positive. Among 426(73.3%) haemophilia A patients with a treatment history, 248(58%) were on prophylactic therapy, and the corresponding value among 37(65%) haemophilia B patients was 17(46%).

Conclusions: Access to treatment was found to be limited, and patients were found to be suffering from high bleeding rates and joint damage.

Key Words: Haemophilia A and B, Hemarthrosis, Health Services, Acuity

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Introduction

Haemophilia is a rare X-linked recessive inherited bleeding disorder due to deficiencies in factor VIII haemophilia A (HA) or factor IX haemophilia B (HB). The prevalence is 17.[1] and 3.8 cases per 100,000 males for HA and HB, respectively,1 with a 3-fold increase in the number patients with haemophilia (PWHs) over 20 years; from72,629 in 1999 to 210,454 in 2018.[2]

Patient registries can provide a real-world setting to improve PWH care, including clinical therapies.[3] It enables haemophilia treatment centres (HTCs) to assess modalities of therapies, drug safety and quality of care provided.[4]

In Iraq, the estimated total number of PWH in 2019 was 2,416.[5] There is insufficient data on haemophilia epidemiology and outcome in Iraq, including regional and HTC based data.[6,7]

The current study was planned to assess the level of care available to PWHs in Iraq.

Patients and Methods

The descriptive, analytical study was conducted from December 15, 2020, to March 1,2021, after approval from the Mustansiriyah University, Baghdad, Iraq, and comprised data from 3 haemophilia treating centres in Iraq participating in the World Bleeding Disorders Registry (WBDR)[8]. The participating hospitals were the National Centre of Haematology (NCH) at Mustansiriyah University, the Child Welfare Hospital (CWH) at the Medical City Teaching Hospital, Baghdad, and the Centre for Hereditary Blood Diseases (CHBD), Basra.

The WBDR is a prospective, longitudinal, observational registry which provides a platform for HTCs to collect data on PWHs. It is a privacy-protected web-based data entry system, providing a clinical profile for each PWH; both HA and HB.[8] The sample size was not formally calculated but all haemophilic patients visiting the three centres during the study period were recruited.

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Inclusion criteria:

1-All patients with haemophilia A with or without inhibitors.

2-All patients with haemophilia B with or without inhibitors.

Exclusion criteria:

1-Patients with von Willebrand disease.

2- All patients with other factors deficiencies as factor I, V, VII, X, or XIII.

All patients or their caregivers provided written informed consent for participation in the study. The data retrieved included date of birth, age at diagnosis, age at WBDR, type of haemophilia, disease severity, age at first bleed and age at first joint bleed.

Type of episodic versus prophylactic replacement therapy and outcome of patients in terms of inhibitor development and joint arthropathy were also noted.

The severity of haemophilia was classified depending on plasma levels of factor VIII (FVIII) or IX (FIX) activity: severe if <1%, moderate 1-5% and mild if >5-< 40% of normal.[9]

Annualized bleeding rate (ABR) and annualised joint bleeding rate (AJBR) were calculated based on the total number of bleeds reported at follow-up visits divided by the observation period in days and multiplied by 365.25.[10]

Target joint was defined as 3 or more spontaneous bleeds into a single joint within a consecutive 6-month period.[9] Episodic (on-demand) replacement therapy was given at the time of clinically evident bleeding, while prophylactic replacement therapy was given to prevent bleeding.[9] Inhibitors, the neutralising antibodies against the infused factor, were either low-titer and low-responding inhibitors (<5 Bethesda units [BU]/mL), or high-titer inhibitors with inhibitor titers of 5BU/mL or higher.[11]

Data was expressed as frequencies and percentages or as the mean±SD. The Statistical Package of the Social Sciences (SPSS) version 20 was used for data tabulation and statistical analysis (IBM Corp., Armonk, N.Y., USA).

Results

Of 638 PWHs with mean age 16.2±4.3 range (9-29) years, 137(21.5%) were from NCH, 343(53.7%) from CWH and 158(24.8%) from CHBD. were followed for a mean of 16.2±1.4 months (range: 5-30 months) There were 581(91%) patients with HA and 57(8.9%) with HB, while 385(60.3%) had severe haemophilia, 126(19.7%) moderate and 125(19.6%) had mild disease (Table 1). A total of 330(51.7%) PWHs, and 193(50.1%) of these with severe disease were aged <18 years. The paediatric: adult ratio for all PWHs was 1.07:1.

Table-1: Demographic characterestics of PWH.

Variable	All PWH (N. 638)	Severe (N. 385)
Type of haemophilia		
Haemophilia A	581 (91.1%)	366 (95.1)
Haemophilia B	57 (8.9%)	19 (4.9%)
Severity of haemophilia		
Mild	125 (19.7%)	
Moderate	126 (19.8%)	
Severe	385 (60.5%)	
Age of PWH (Years)		
Mean Age ± SD (Range)	16.2±4.3 (9-29)	17.3±4.1 (10-29)
<18	330 (51.7%)	193 (50.1%)
≥18 years	308 (42.3%)	192 (49.9%)
Age at diagnosis		
Mean ±SD	20.7± 19.1	12.2±10.9
in months(Range)	(7-117)	(6-56)
0–12 months	259(40.6%)	199(51.7%)
1–4 years	153(24%)	92(23.9%)
5–17 years	139(21.8%)	64(16.6%)
18+ years	87(13.6%)	30(7.8%)
Age at first bleed		
Age at first bleed, ** months, Mean±SD(Range)	9.4 ±2.4 (5-16)	7.3 ± 1.2 (5-11)
Age at first joint bleed***, months, Mean ±SD (Range)	15.9±5.1 (12-36)	13.8 ± 0.6 (12-24)

* Based on 636 PWH

**Based on 625 PWH with data on joint bleeds and 385 with severe disease

***Based on 430 PWH with data on joint bleeds and 309 with severe disease

The mean age at diagnosis was 20.7 ±19.1 months (range 17-117 months), while for severe homophilic patients, it was 12.2±10.9 months (range: 6-56 months). Diagnosis at aged <1 year was in 259(40.6%) cases, and the corresponding value for those with severe disease was 199(51.7%).

The mean age at first bleed was 9.4 ±2.4 months (range: 5-16 months) for all PWHs, and 7.3 ± 1.2 months (range : 5-11 months) for those with severe disease. For first joint bleed, the mean age was 15.9±5.1 months (range: 12-36 months) for all PWHs, and 13.8 ± 0.6 months (range:12-24 months) for those with severe disease.

The total bleeding events for the 30 months of follow-up were 1354 for all patients, and 1061 for severe patients. Of them, 959(70.8%) had haemarthrosis. The average number of bleedings per patient in all PWHs was 2.1±0.8, while the average number of bleedings per patient in severe disease was 2.7±0.7. The mean ABR for severe patients was 2±0.8 (range: 0-4), while median AJBA was

Table-2: Clinical data of PWH.

Variable	All PWH (N. 638)	Severe PWH (N. 385)
Total bleeding events, n	1354	1061
Average number of bleeds per patient	2.1±0.8	2.7 ±0.7
ABR, mean ± SD (range)*	0±0.7 (0-4)	2 ± 0.6(0-4)
AJBR, mean ± SD (range)**	2±0.8 (0-4)	4 ± 1.3(2-8)
Location of bleeds, n (%)		
Joint	959 (70.8%)	821(77.4%)
Muscle	62 (4.6%)	40 (3.8%)
Central nervous system	5 (0.4%)	1(0.1%)
Other location	328 (24.2%)	199 (18.6%)
Number of pts with ≥1 target joint***	274 (43%)	234 (61%)
Hospitalization		
N. (%) of unique PWH hospitalized	58 (9%)	34 (9%)
Total Hospitalization, N. (%)	59 (9.2%)	34 (9%)
Days per hospitalization, median	4 (2-10)	4(2-10)

* 634 PWH and 333 with severe disease

** 298 PWH and 165 with severe disease

***based on 632 PWH with data on target joints and 381 with severe disease.

4(3.1) (range: 2-8). The number of patients with one or more target joint were 234(61%) in severe patients, while it was 274(43%) for all PWHs. Among severe HA, 58 (32%) of paediatric patients had more than one target joint compared 165 (92%) in adults.

The frequency of hospitalisation was 259(9.2%) for all PWHs and 34(9%) among those with severe disease, with a mean duration of 4 days (range:2-10) (Table 2). Joint bleeding with or without muscle bleeding 8(13%), intracranial haemorrhage 8(13.5%) and surgery 9(15%) were among the main causes of hospitalization.

Overall, 256(32.3%) PWHs and 129(33.5%) with severe disease were tested for inhibitors, because of unavailability of relevant facilities. The frequency of positive inhibitors was 62(24.3%) for the tested PWHs, and 131(34.1%) for those with severe disease. The majority of the cases, 34 (81%) had high-titer inhibitors.

Table-3: Treatment Data.

Treatment Indication Haemophilia A	Total N. 426	Total N. 327
Prophylaxis	248 (58%)	232 (71%)
On-demand	253 (59%)	169 (52%)
Prophylaxis and add-on treatment	86 (20%)	80 (24%)
Haemophilia B	Total N. 37	Total N. 17
Prophylaxis	17 (46%)	14 (82%)
On-demand	26 (70%)	9 (53%)
Prophylaxis and add-on treatment	8 (22%)	7 (41%)

Among 426(73.3%) HA patients, 248(58%) were on prophylactic therapy, and the corresponding values among 37(65%) HB patients was 17(46%) (Table 3).

Discussion

Among 29 countries across the world, 53 HTCs with 4166 PWHs are participating in the WBDR programme, and 888(21%) of the PWHs are from the Eastern Mediterranean region, with Iraq being one of the countries with the highest number of HTCs and highest number of participating patients.[10]

The current study found 60.3% PWHs having severe disease; 63% in HA and 33.3% in HB cases. The finding is comparable to a previous study in Baghdad (63.4%).[6]

However, these frequencies are higher than that observed as an average result of all HTCs in the WBDR 2019 Report; 51% in HA and 43% in HB. However, frequencies for mild cases were comparable.10 In neighbouring countries, Syria has reported 31.5% and 17% severe disease in HA and HB patients, 12 while Iran has reported severe, moderate and mild HA in 47%, 33% and 20% respectively.[13]

Iraqi population exceeds 40 million, therefore, it is expected that there are cases not yet diagnosed or not registered, especially of the mild and moderate variety.

The median age of the registered PWHs was 16 years in the current study, with more than half being in the paediatric age group. The median age was lower than that of all PWHs included in WBDR,10 but was higher than that reported in India (14 years),14 and the paediatric patients accounted for 45% in WBDR HTCs,10 and 61.96% in India.[14]

The time of diagnosis is of particular importance, especially concerning orthopaedic prognosis because of the risk of developing arthropathy is increased with delayed prophylaxis initiation.[15]

The mean ages at diagnosis for the current PWHs and for those with severe disease were 20.7±19.1 and 12.2±10.9 months, respectively, with 48.3% of patients with severe disease having been diagnosed beyond the first year of life. The WBDR reported a median age at diagnosis of 14 months for PWHs, and 11 months for severe disease groups in upper middle-income countries to which Iraq belongs.[10]

The mean ages at first bleed for the current PWHs was 9.4 ±2.4 months, and for those with severe disease7.3 ± 1.2 months, while for the first joint bleeds, the median ages were 15.9±5.1 and 13.8±0.6 months, respectively. The

reported first age at bleed and first joint bleed among all PWHs in WBDR were 10 and 24 months, respectively. 10 Van Dijk et al. in the Netherlands reported a median age of 20 months for first joint bleed in patients with severe haemophilia (range: 13-31 months), and the age at first joint bleed was inversely related to treatment requirement and arthropathy, and that may indicate the clinical phenotype.[16]

The mean ABR in severe haemophilic patients was 2 ± 0.6, and the mean AJBR in all PWHs was 2±0.8 and it was 4±1.3 in severe patients. An inverse relationship between ABR and Gross National Income (GNI), has been reported with higher ABRs in low-income countries (LICs), and lower ABRs in high-income countries (HICs).[10]

Joint bleeds accounted for 70.8% PWHs and 77.4% of those with severe disease.

These figures are comparable to that reported worldwide.[17]

The frequencies of target joints were 43% in all PWHs and 61% in severe PWHs.

Although these figures are comparable to that reported for the Eastern Mediterranean region (47% and 59%),10 the findings illustrate that patients in the current study had a high prevalence of joint damage. The higher frequency of target joints among adults can be explained by the fact that prophylactic therapy was started at 2010 in Iraq, leading to a smaller number of target joints in paediatric patients.

Inhibitor antibodies occur in approximately 30% of patients with HA and 5% of those with HB.[17] Because of limited laboratory resources in Iraq, only patients with poor response to factor concentrate were tested for mixing study and BUs. Analysis of data in the current study showed that only 72% of all PWHs were tested for inhibitors, with 81% having high-titre inhibitors. Inhibitors significantly increase the cost of care, and have a negative effect on disease morbidity and mortality as it makes bleeding episodes more difficult to treat.[11]

Prophylactic therapy is regarded as a PWH standard of care, and it has to begin in childhood to avoid the long-term homophilic arthropathy. Barriers to prophylaxis implementation include the need for venous access, high cost, and difficulties with home nursing or clinic visits.[18]

The current PWHs were treated using standard recombinant factors, distributed freely by the Ministry of Health (MOH). The data showed that 58% of all HA and 71% with severe disease received prophylactic therapy, but 20% of all HA and 24% of those with severe disease needed add-on therapy. Similar findings were also noted among HB patients. This indicated that the prophylaxis programme was not sufficient. The doses should be increased and/or should be done more frequently along with regular inhibitor testing which was found lacking.

Registries help understand the variations in treatment as they may describe care patterns, including delivery and quality of care appropriateness, disparities, and may identify the factors that influence prognosis, quality of care, and provide evidence regarding resource utilisation.[19]

Conclusion

Access to treatment was found to be limited, and quality of care needed improvement as the patients were found to be suffering from high bleeding rates and joint damage.

The use of WBDR data for improvement of quality of care for PWHs in Iraq is recommended for defining the needs, developing policy and effectively managing the available resources.

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