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CLINICAL RESEARCH

Clinical profile and outcome of children with haemophilia A: The Royal Hospital, Oman's experience

Anood AlRawahi, Ibrahim AlGaithi, Fatma Al Riyami, Maather Al Abri, Hajer Al Shukaili, Abdulhakim Al Rawahi

Background: Data on clinical characteristics and bleeding outcome of Omani children with haemophilia A (HA) is limited. This study aims to describe the clinical profile and outcome of Omani children with HA at the Royal Hospital from 2006 to 2019. **Methods:** This is a retrospective study including all Omani children (< 13 years) with HA at the Royal Hospital. Data included age at presentation, factor VIII (FVIII) level, treatment, complications, and bleeding episodes. **Results:** Forty-four males were included; mean age was 1 year ± 1.7 years at presentation. Mean period of follow-up was 7.9 ± 3.6 years. The most common complaints at presentation were muscle bleeds (29.5%) and post-circumcision bleeding (11.4%). Two (4.5%) had mild HA, 29 (66%) had moderate HA, and 13 (29.5%) had severe HA. Twenty-eight (63.6%) were on regular prophylaxis, ten (22.7%) developed at least one target joint, and six (13.6%) developed FVIII inhibitors. The mean annualised bleeding rate was 1.8 ± 2.3, 4.6 ± 0.4, and 4.6 ± 8.6 for the persons with mild, moderate, and severe HA, respectively. **Conclusion:** The clinical phenotype of Omani children is milder compared to other studies but with similar clinical outcomes.

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A study of over 40 Omani children with haemophilia A notes a milder phenotype but similar clinical outcomes to other studies

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Haemophilia A (HA) is an X-linked congenital bleeding disorder caused by the deficiency of coagulation factor VIII (FVIII) [1]. Based on the activity level of FVIII, HA is classified as severe (< 1%), moderate (1% to 5%), or mild (> 5% to < 40%) [2,3]. Haemophilia is prevalent worldwide regardless of race and socioeconomic status [4]. Clinical manifestations of do not exclusively appear in males; females with FVIII levels of < 40% are classified as people with mild, moderate, or severe haemophilia [5]. A recent report on the global prevalence of haemophilia showed that the prevalence of HA of all severities and of severe cases was 17.1 cases per 100,000 males and 6 cases per 100,000 males, respectively [6].

Bleeding is the main clinical manifestation of haemophilia; other manifestations are bleeding complications [4]. Reported bleeding sites in newborns include intracranial and extracranial haemorrhage and bleeding after circumcision [4]. Bleeding into joints and muscles are more common in older children and adults [7]. People with severe haemophilia may bleed spontaneously, while those with mild or moderate haemophilia usually bleed after significant trauma or a surgical procedures [8,9]. Recurrent haemarthrosis (bleeding into joints) leads to the development of target joints and arthropathy [4]. Arthropathy is characterised by joint deformities, reduced range of motion, chronic pain, and impaired daily life [4,10]. Bleeding can occur into any joint; however, 80% of bleeding occurs in knees, ankles, and elbows [10].

FVIII concentrate can be administered during an episode of bleeding (on-demand therapy) or to prevent spontaneous bleeding (prophylaxis) [11]. The standard of care of HA management is the administration of prophylactic FVIII concentrate, which has significantly improved clinical outcomes [12,13]. However, around 30% of people with haemophilia develop FVIII inhibitors (anti-FVIII antibodies) after frequent exposure to FVIII concentrate [14]. Emicizumab, a novel non-factor replacement therapy, was introduced to overcome the limitation of FVIII concentrates, particularly inhibitor formation and frequent intravenous administration. It showed good efficacy in preventing/reducing bleeding episodes in children of all ages, including newborns, regardless of inhibitor status [15].

There is scarce data on the clinical profile and bleeding outcome of children with HA in Oman. The availability of such data can assist healthcare providers and policymakers in improving their management. The aim of this study was to describe the clinical profile and outcome of Omani children with HA at the Royal Hospital, the largest referral centre in Oman, from 2006 to 2019.

METHODS

A retrospective descriptive cohort study was conducted, including all Omani children, younger than 13 years old, diagnosed with HA, and followed up at the Royal Hospital from 2006 to 2019. Data were retrieved from the electronic chart system, Al-Shifa, which is a comprehensive healthcare information management system implemented by the Ministry of Health. Collected data included: demographic characteristics (sex, age at presentation, nationality, city of origin), bleeding sites, number of bleeding episodes (recorded by paper diaries), FVIII level, and treatment modalities (on-demand and prophylaxis). The local prophylaxis protocol is based on the Malmo Protocol, where 20-40 IU/kg per dose are administered three times a week, usually starting after the first clinically evident joint bleed or after one year of age. The evaluated outcomes were mean annual bleeding rate (ABR) and complications (FVIII inhibitor development, CNS complications, joint arthropathy). ABR was defined as the number of bleeding events occurring per year and was calculated for the whole study population. Based on plasma factor level, persons with haemophilia were classified as mild (> 5 to < 40 IU/dL), moderate (1-5 IU/dL), or severe (< 1 IU/dL). According to the International Society on Thrombosis and Haemostasis (ISTH), a target joint is defined as a joint in which three or more spontaneous bleeds occur within a consecutive six-month period [16].

Exploratory analyses were carried out to describe the study population where categorical variables were described using frequencies and percentages, and continuous variables were described using means and standard deviations (SD). Statistical analysis was performed using SPSS 24.0 (SPSS, Inc, Chicago, Illinois). Ethical approval was obtained from the Ethical Committee of the Royal Hospital, Oman.

RESULTS

Forty-four male children diagnosed with congenital HA were identified. Their age ranged from 1 day to 9 years, with a mean of 1 $\pm$ 1.7 years. The mean period of follow-up was 7.9 $\pm$ 5.6 years. Twenty (45.5%) were diagnosed during a screening test performed in response to positive family history. The two most common complaints at presentation were muscle bleeds (29.5%) and post circumcision-bleeding (11.4%). Two had mild HA (4.5%), 29 moderate HA (66%), and 13 (29.5%) severe HA, respectively. The mean ABR was 1.8 $\pm$ 2.3, 4.6 $\pm$ 0.4, and 4.6 $\pm$ 8.6 for children with mild, moderate, and severe HA, respectively. Most

Table 1: Clinical characteristics of children with haemophilia A treated at the Royal Hospital, Oman

VARIABLE	TOTAL	MILD HAEMOPHILIA A	MODERATE HAEMOPHILIA A	SEVERE HAEMOPHILIA A
Number of persons, n (%)	44 (100%)	2 (4.5)	29 (66)	13 (29.5)
Presentation, n (%)				
Joint bleeding	3 (6.8)	0 (0)	3 (10.3)	0 (0)
Muscle bleeding	13 (29.5)	0 (0)	10 (34.5)	3 (23.1)
Mucosal bleeding	4 (9.1)	1 (50)	3 (10.3)	0 (0)
Screening with positive family history	20 (45.5)	0 (0)	12 (41.4)	8 (61.5)
Post-circumcision bleeding	5 (11.4)	1 (50)	2 (6.9)	2 (15.4)
Intracranial bleeding	1 (2.3)	0 (0)	1 (3.4)	0 (0)
Post-operative bleeding	2 (4.5)	0 (0)	1 (3.4)	1 (7.7)
Clinical profile, n (%)				
Joint involvement	37 (84.1)	1 (50)	26 (89.7)	10 (76.9)
At least one target joint	10 (22.7)	0 (0)	7 (24)	3 (23)
Muscle involvement	17 (38.6)	0 (0)	12 (41.4)	5 (38.5)
CNS involvement	2 (4.5)	0 (0)	1 (3.4)	1 (7.7)
Mucosal involvement	5 (11.4)	0 (0)	5 (17.2)	0 (0)
Treatment, n (%)				
On-demand	16 (36.4)	1 (50)	10 (34.5)	5 (38.5)
Prophylaxis	28 (63.6)	1 (50)	19 (65.5)	8 (61.5)
Other treatments	5 (11.4)	1 (50)	2 (6.8)	2 (15.4)
Complications, n (%)				
Inhibitor development	6 (13.6)	0 (0)	3 (10.3)	3 (23.1)
CNS complications	1 (2.3)	0 (0)	1 (3.4)	0 (0)
Joint arthropathy	24 (54.5)	0 (0)	17 (58.6)	7 (53.8)
ABR, mean ± SD	4.4 ± 0.4	1.8 ± 2.3	4.6 ± 0.4	4.6 ± 8.6

ABR: Annualised bleeding rate; CNS: Central nervous system; SD: Standard deviation

were on regular prophylaxis (63.6%) with a mean ABR of 1.8 ± 4.5. The mean ABR for those who were not on prophylaxis was 4.6 ± 8.6.

Ten (22.7%) chlidren developed at least one target joint and six (13.6%) developed FVIII inhibitors. The majority with moderate (89.7%) and severe (76.9%) HA had joints affected by their haemophilia. Around half of those with moderate or severe HA developed joint arthropathy (Table 1).

DISCUSSION

The aim of this study was to explore the clinical profile and outcome of children with HA in one of the largest referral centres in Oman. The proportions of those with mild, moderate, and severe HA in our study were 4.5%, 66%, and 29.5%, respectively. A Jordanian study showed that 17%, 15.7%, 67.3% of the included cohort had mild, moderate, and severe HA, respectively [17]. Although this could be a random finding due to small sample size, disease severity is important for identifying bleeding patterns and treatment options. Severe HA is associated with serious spontaneous bleeding in joints, muscles, soft tissues, and life-threatening intracranial haemorrhage [18,19]; moderate HA causes bleeding after trauma [11]. Mild HA may go undiagnosed and only be diagnosed due to because of excessive haemorrhage postoperatively or after a trauma [20]. Easy and spontaneous bruising is the most obvious and early sign of haemophilia. This was not reported since the study analysed a hospitalised cohort.

A review article reported that around 70% of people with haemophilia have a positive family history [21]. In our study, around half were diagnosed after screening due to positive family history. The activity of FVIII is strongly related to inherited genetic variants. Advanced techniques in genetic analysis in haemophilia has become available in recent decades, allowing faster and more accurate data interpretation. This highlights

that adequate carrier detection and genetic counselling are essential to ensure appropriate diagnosis and management; guidelines for the interpretation and classification of gene variants have been established [22].

Comparing the clinical profile of subgroups in our cohort showed that joint, muscle, and mucosal involvement was more commonly reported in children with moderate HA than those with severe HA. This may indicate that factors other than the level of FVIII may interfere in the clinical phenotype. Further studies are required to identify these factors and establish their correlation with bleeding rate and HA clinical manifestation.

Most children in our study were receiving prophylaxis. Conversely, results from studies in Iraq and Saudi Arabia showed that the majority of people with haemophilia received on-demand treatment [23,24]. A randomised clinical trial comparing prophylactic with on-demand treatment demonstrated the effectiveness of prophylaxis in young boys with severe HA; 93% of those in the prophylaxis arm had normal joints by the age of six compared with 55% in the on-demand arm [12]. Prophylaxis in children has shown better outcomes when initiated at early age [25]. Early administration of continuous prophylaxis may decrease the risk of inhibitor formation, reduce the number of bleeding events, and reduce physical impairment due to arthropathy. Consequently, this may lead to improved quality of life [26]. However, in our cohort, a considerable proportion of children with severe HA (39%) were not receiving prophylactic treatment, mostly due to family decisions. In our institution, prophylactic treatment is initiated for people with moderate HA after developing recurrent bleeds, especially joint bleeds. A subgroup comparison of the percentages of patients with arthropathy and target joints among those receiving prophylaxis or on-demand therapy showed comparable results. However, a definitive conclusion cannot be derived because of the small sample size and number of events.

Haemarthrosis (bleeding into joints) is one of the clinical hallmarks of HA and occurs particularly in knees, elbows, and ankles [3]. Our findings showed that 84% of our cohort had HA with joint involvement (bleeding and/or arthropathy). The proportion with at least one target joint (22.3%) was lower than that reported by a study carried out in six West European countries (50.3%) [27]. Around half of our cohort developed joint arthropathy, of whom 60% had moderate HA. This finding is uncommon. A cross-sectional study from Netherlands reported that 20% of children with moderate haemophilia had joint impairment [28]. However, a systematic literature review reported a prevalence of 15-77% of overt arthropathy in people with moderate haemophilia [29]. Variability in the reported results among studies from different countries may be explained by whether or not national management protocols recommend early prophylaxis. Moreover, people with moderate haemophilia may manifest with heterogenous bleeding phenotypes. In other words, some people with moderate HA may clinically experience severe bleeding events leading to the development of joint arthropathy. This indicates that modulators other than factor level may interfere in bleeding phenotype [26]. Haemophilic arthropathy is associated with chronic joint deformity, pain, muscle atrophy, impaired mobility and disability, and consequently a poor quality of life [4,10]. Early prophylaxis with recombinant FVIII can prevent joint damage and decrease the frequency of joint bleeding [12]. The introduction of a novel non-factor agent, emicizumab, has provided more protection and preservation of joints health and improved patient's quality of life and treatment adherence [30,31].

We reported that around 13% of the cohort developed inhibitors; those who developed inhibitors were equally distributed between moderate and severe groups. A previous study aiming to screen for the prevalence of inhibitor development among Omani persons with severe HA reported a prevalence of 35% [32]. Many patient-related factors (e.g., genetic factors, immune response, ethnicity, history of preceding surgical procedure, and massive bleeding) and treatment-related factors (e.g., duration and intensity, age at the first exposure, and product types) influence the development of inhibitors [32,33]. Controlling the factors that are manageable may improve patient management, as inhibitor development remains a challenge with significant morbidity.

Limitations

Being a single-centre study might limit the representability of our data to the general HA population. In addition, it was not possible to ascertain how many of the study participants were related. This may have accounted for the relatively high occurrence of moderate HA in the study cohort based on screening bias in relation to positive family history. The retrospective design of the study might affect the quality of the collected data. For instance, it was not possible to determine the mean age of first bleed or first joint bleed. As our hospital is a referral centre and

the majority of patients were referred from peripheral hospitals, such data were not available in a retrospective context. Similarly, data on activities, participation in daily activities, quality of life, and data on joint imaging results and pain scales were not available for all patients retrospectively. Moreover, data on Hemophilia Joint Health Score according to treatment modalities were not available as this is not included within our health information system. The study site is one of the major referral centres in Oman and is known for its good record-keeping. However, the documentation of bleeding events may be underestimated since those occurring outside of the hospital setting may not be accurately recorded. Recording the frequency of bleeding episodes in paper diaries is another limitation.

CONCLUSION

The clinical phenotype of Omani children with HA is milder compared to other studies but with similar clinical outcomes. Most of the children in this single-centre study have moderate HA, receive prophylactic treatment, and show joint arthropathy. Exploring the clinical characteristics of children with HA may help in improving diagnostic algorithms and disease management, thus improving patient care and clinical outcomes.

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Ethical considerations

Informed consent was obtained from the parents of the children who participated in the study for the publication of the cases present. An informed assent was also obtained from the participating children.

Declaration of funding

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Conflict of interest

IAG has received fees for lectures from the Oman Medical Specialty Board.

The other authors declare having no conflict of interest and financial or other relationships.

Author contributions

All authors were involved in the conception and design, analysis and interpretation of the data; the drafting of the paper revising it critically for intellectual content; and the final approval of the version to be published; and agree to be accountable for all aspects of the work.

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