Original Article

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Demography, annual incidence, and risk factors of inhibitors for pediatric hemophilia A in Basra Center for Hereditary Blood Diseases

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ABSTRACT

Background: Hemophilia A is a rare X-linked congenital bleeding disorder characterized by a tendency to bleed. This is the primary tendency of the disorder, with most of the bleeding occurring internally into the joints. A significant complication of hemophilia treatment is the development of neutralizing antibodies against factor VIII replacement therapy, known as inhibitors. **Aim**: This study aimed to investigate the demography of pediatric hemophilia A patients at the Basra Center for Hereditary Blood Diseases and assess the annual incidence of positive inhibitors and their associated risk factors. **Methods**: A descriptive, retrospective, registry-based study was conducted for hemophilia A patients registered at the Basra Center for Hereditary Blood Diseases from October 2018 to October 2023. A total of 110 males aged < 1 year to ≤ 15 years, with a median age of 8.7 ± 3.8 years, were included in this study. Patient Information collected included the date of birth, age at diagnosis, severity of disease, symptoms at diagnosis, quantitative inhibitor levels, and risk factors for inhibitor development. **Results**: In this study, 46 patients (42%) were ≥10 years old, and 53 patients (48.1%) were diagnosed between 1–5 years. Among the hemophilia A patients, between one year and five years, 48 (43.7%) had moderate severity. The primary symptom at diagnosis was postoperative bleeding in 29 patients (26.3%), followed by mucocutaneous bleeding in 26 patients (23.7%). A total of 22 out of 110 (20%) patients developed inhibitors, with 21 of these (95.5%) classified as high-titer, predominantly in severe hemophilia A patients with factor VIII levels < 1 (12/22 patients, 54.5%). The annual incidence of inhibitors decreased over the last five years from 46 to 13 (registered patients/year) and from 18 to 2.7 (examined patients/year). Severity of disease, family history of positive inhibitors, age at first exposure to factor VIII therapy, history of intensive factor VIII treatment, and type of factor VIII replacement were statistically significant correlates of inhibitor development. **Conclusions**: The annual incidence of inhibitor development has decreased over the last five years. Severity of disease, family history of positive inhibitors, age at first exposure to factor VIII therapy, history of intensive factor VIII treatment, and type of factor VIII replacement are significant risk factors for inhibitor development.

Keywords: Basra, hemophilia A, inhibitor, risk factors.

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INTRODUCTION

Hemophilia A (HA) is a rare X-linked congenital bleeding disorder characterized by a deficiency of coagulation factor VIII (FVIII).[1] Approximately 30% of all cases result from spontaneous genetic variants. Reports indicate that more than 50% of individuals newly diagnosed with severe hemophilia have no prior family history of the condition.[1-3] The best estimates of the prevalence of hemophilia, based on reliable national patient registry

data and recent World Federation of Hemophilia annual global surveys, suggest that the expected number of males with hemophilia worldwide is 1,125,000, the majority of whom remain undiagnosed, including an estimated 418,000 males with severe hemophilia.[1]

The characteristic phenotype of hemophilia is a bleeding tendency. Most bleeding occurs internally into the joints or muscles. Joint bleeding, regardless of volume, can lead to inflammation and increased iron concentration in the synovium, triggering joint damage and promoting recurrent bleeding.[4] Some bleeds can be life-threatening and require immediate treatment.[5]

Disease severity is determined by residual factor activity. In mild hemophilia, 5%–40% of normal factor activity is retained, with bleeding mostly occurring after major trauma or surgery. In moderate hemophilia, 1% to < 5% of factor activity is present, leading to occasional spontaneous bleeding episodes or prolonged bleeding triggered by trauma or surgery. Severe hemophilia manifests clinically with spontaneous bleeding episodes with < 1% factor activity retention.[6]

To prevent joint destruction, the current standard of care for children with severe HA is primary prophylaxis through regular infusions of FVIII, initiated at the time of the first episode of joint bleeding or earlier.[2] For severe, life-threatening hemorrhage, FVIII is administered to achieve the desired FVIII level of 100%; for mild to moderate hemorrhage, FVIII is administered to achieve a desired FVIII level of 30%–50%. Other pharmaceutical adjuvant therapies for HA include desmopressin, tranexamic acid, epsilon aminocaproic acid, and non-factor replacement therapy. Prophylactic FVIII concentrate infusions for patients with severe HA have benefits in preventing spontaneous bleeding, and modifying severe hemophilia to a milder form by maintaining FVIII levels above 1% of normal.[1,7]

Various complications can arise in patients with hemophilia, including hemophilic arthropathy, viral infections, and the development of inhibitors, which decrease the efficacy of factor infusions and also the psychosocial impacts on affected individuals.[8]

Complications related to treatment with FVIII concentrates, whether derived from human plasma or produced via recombinant factor concentrate, include the development of neutralizing antibodies against these products, known as inhibitors. This mostly occur within the first 50 days of exposure. Inhibitors can jeopardize the patient's life and complicate therapeutic management, with an incidence of 15%–35% among children with severe HA. Several genetic and non-genetic risk factors for inhibitor development have been identified, with the main non-genetic factors related to the modalities and circumstances of replacement therapy. These include age at treatment initiation, the FVIII product used, treatment intensity, prophylaxis regimen, major bleeds, and surgical procedures.[3]

PATIENTS AND METHODS

A descriptive, retrospective, registry-based study was conducted for children with HA registered in Basra Center for Hereditary Blood Diseases (BCHBD) from October 2018 to October 2023.

A total of 110 males with congenital HA, aged < 1 year to ≤ 15 years, with a median age of 8.7 ± 3.8 years were included in the study. Patient information including date of birth, age at diagnosis, symptoms at diagnosis, and severity of disease, is classified as mild, moderate, or severe according to FVIII levels at diagnosis.[9] Quantitative inhibitor levels were assessed, with a cut-off point for positivity set at > 0.5 Bethesda units (BU),[10] high-titer defined as > 5 BU, and low-titer as < 5 BU.[1,11-13] Risk factors for inhibitor development included family history of positive inhibitors, history of infection, vaccination, trauma, surgery before inhibitor development, age at first exposure to FVIII therapy, type of treatment (periodic or prophylaxis), history of intensive FVIII treatment, and type of FVIII replacement therapy (all replacement therapy was recombinant factor concentrate of the second and third generation). In this study the patients received either the second or third-generation products or a combination of both, depending on drug availability. All information was obtained from the center's registry data after obtaining permission from the Basra Health Directorate - Iraq Ministry of Health to review patient data.

Aims of study

1. To study the demographics of pediatric HA patients in Basra Center for Hereditary Blood Diseases.
2. To assess the annual incidence of positive inhibitors and their risk factors.

Statistical analysis

Statistical analysis was performed using SPSS version 19. Categorical variables were presented as percentages. Logistic regression analysis was conducted to analyze different risk factors. A P-value of ≤ 0.05 was considered significant.

RESULTS

A total of 110 patients with HA were included in the study. Table 1 reveals that the highest age group in this study was 10 to ≤ 15 years with 46 patients (42%) while the main age group at diagnosis was one to five years, accounting for 53 (48.1%). A total of 48 patients (43.7%) had moderate severity, followed by a mild type in 41 in-patients (37.3%). The primary presenting symptom at diagnosis was postoperative bleeding in 29 patients (26.3%), with circumcision being the most common procedure (23/29, 79.3%), followed by mucocutaneous bleeding in 26 patients (23.7%).

Regarding inhibitor titers (Table 2), 22 out of 110 patients (20%) had positive inhibitors. High-titer inhibitors were present in 21 out of 22 patients (95.5%), primarily in severe cases of HA (11/22 patients, 50%), followed by moderate cases (9/22 patients, 40.9%). The annual incidence of inhibitors at BCHBD decreased in the last five years from 46 to 13 (registered patients/year) and from 18 to 2.7 (examined patients/year), as shown in (Fig. 1). There is a statistically significant association between the development of inhibitors and the severity of HA, family history of positive inhibitors, age at first exposure to factor VIII therapy, history of intensive factor VIII treatment, and type of factor VIII replacement, with a P-value 0.000, 0.000, 0.010, and 0.000, respectively (Table 3).

Table 1: Demography of pediatric hemophilia A patients.

Item	Sub-items			No.	%	Total
Age of patients	< 5 years			21	(19)	110
	5–10 years			43	(39)	
	10 – ≤ 15 years			46	(42)	
Age at diagnosis	< 1 year			45	(41)	110
	1–5 years			53	(48.1)	
	5 years – ≤ 15			12	(10.9)	
Severity of Haemophilia A	Mild (FVIII > 5%)			41	(37.3)	110
	Moderate (FVIII 1%–5%)			48	(43.7)	
	Severe (FVIII < 1%)			21	(19)	
Symptoms at diagnosis	Skin bleeding			24	(21.9)	110
	Mucocutaneous bleeding			26	(23.7)	
	Musculoskeletal bleeding	Muscle		3	(2.7)	
		Hemarthrosis		4	(3.7)	
	Central nervous system bleeding			3	(2.7)	
	Trauma			11	(10)	
	Post-operative bleeding	Circumcision	23 (79.3%)	29	(26.3)	
		Neurosurgery	2 (6.9%)			
		Orthopedic	4 (13.8%)			
	Post-vaccination bleeding			1	(0.9)	
	By investigation due to a positive family history			9	(8.1)	

Table 2: Inhibitors, titer, and disease severity

Severity of Haemophilia A	Number & % of positive inhibitor					
	High titre ≥ 5 BU			Low titre < 5 BU		
	No.	% /22 pt*	% /110 pt**	No.	% /22 pt *	% /110 pt**
Mild	1	(4.5)	(0.9)	0	(0)	(0)
Moderate	9	(40.9)	(8.1)	0	(0)	(0)
Severe	11	(50)	(10)	1	(4.5)	(0.9)
Total	21	(95.5)	(19.1)	1	(4.5)	(0.9)

*Total number of positive inhibitor HA patients, **Total number of HA patients included in the study.

Table 3: Correlation between positive inhibitor and different variables.

Variable			Correlation	P-value
Severity of hemophilia A			− .471	0.000
Family history of positive inhibitor			.384	0.000
History of infection			− .048	0.619
Vaccination			− .109	0.257
Surgery			− .120	0.211
Trauma			.012	0.903
Age of first exposure to FVIII			.245	0.010
Treatment	Periodic		− .019	0.847
	Prophylaxis	Regular	.062	0.521
		Irregular	− .090	0.349
History of intensive FVIII treatment			.415	0.000
Type of FVIII replacement therapy			.675	0.000

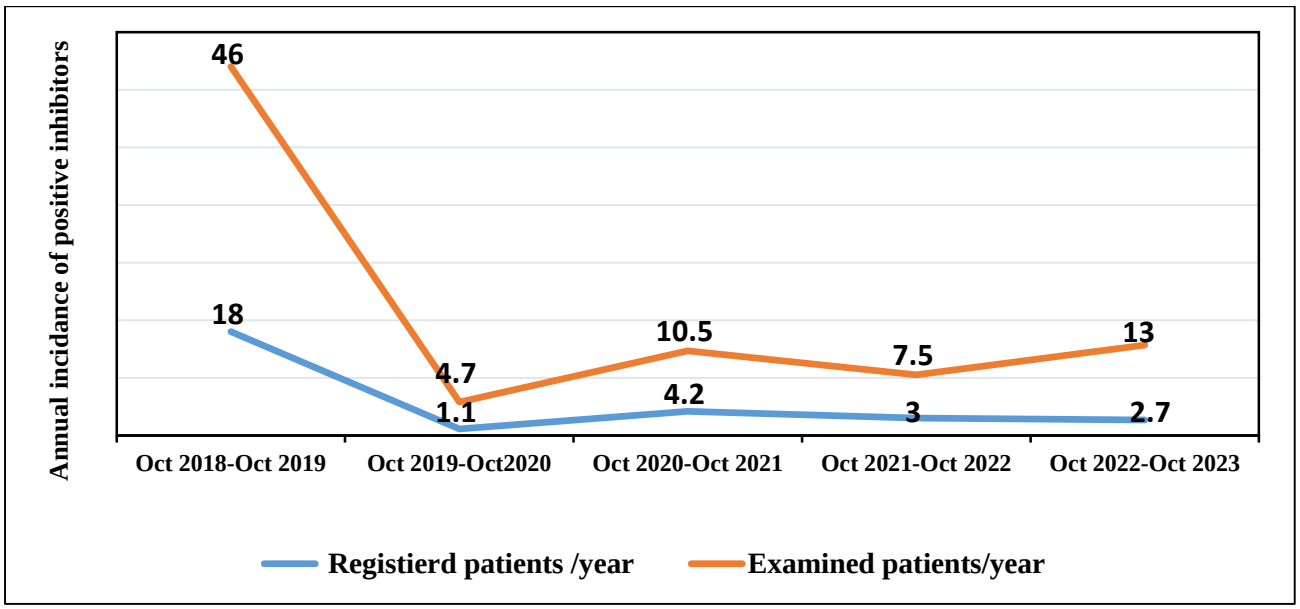

Figure 1: Annual incidence of positive inhibitor.

DISCUSSION

There is insufficient epidemiological data on hemophilia in Iraq. Valuable information on the prevalence of hemophilia in Iraq is primarily based on estimates from the World Federation of Hemophilia. Few Iraqi studies have been published, focusing mainly on the clinical aspects of the disease.[14] In Iraq, there is a hereditary blood diseases center in each governorate, except in Baghdad, where there are three centers.[15]

This study shows that 46 patients (42%) were ≥ 10 years old, which contrasts with findings from a study by Kadhim et al. in Baghdad, where only 28.4% were in the 5–13 years age group,[14] and another study by Mohammed Ali et al. in Karbala,[16] which reported 17.8% in the 11–20 years age group. This discrepancy may be because this study focused solely on the pediatric population, but it aligns with a study conducted by Lateef et al[17] in Diyala, where 36 patients (55.8%) were younger than 16 years

The median age of patients included in the study was 8.7 ± 3.8 years) and the majority (53 patients, 48.1%) were diagnosed between 1–5 years. These findings contrast with those of Owaidah et al., who reported that most patients were diagnosed at < 1 year old (75.5%),[18] and Lateef et al., whose median age at diagnosis was six months, with 50% diagnosed within the first six months of life.[17]

Among the patients, 48 (43.7%) had moderate severity, which differs from the study by Mohammed et al. where 57 patients (63.3%) had severe hemophilia,[16] and Kadhim et al., where 337 patients had severe hemophilia,[14] which may be related to the inclusion of an older age group in their study.[15] However, it is similar to a study conducted in Bangladesh where 25 (56.8%) and 19 (43.2%) had moderate and severe hemophilia, respectively.[19]

The first presenting symptoms were postoperative bleeding in 29 patients (26.3%), with the majority occurring post-circumcision (23 patients, 79.3%), followed by mucocutaneous bleeding in 26 patients (23.7%). This finding is consistent with the results of Mohammed et al. where the most common first bleeding was post-circumcision (22 patients),[16] and with Youssef AL Tonbary et al., where 37 patients (51%) experienced post-circumcision bleeding.[20]

In this study, 22 out of 110 patients (20%) developed inhibitors, a percentage higher than reported in other studies conducted in Iraq and neighboring countries,[14] and even higher than the 18.6% found in a 2016 study at the same center.[15] This may be due to an increase in the number of screened patients, but it is lower than the 29.3% reported by Owaidah et al. The majority of patients with positive inhibitors had severe hemophilia (12 out of 110 patients, 10.9%),[18] which is consistent with findings of Mohammed Ali IM et al.[16] and Lateef IA et al.[17] Their results were 10% and 11% of severe HA patients with inhibitors, respectively. Most patients with positive inhibitors had high-titer levels (21 out of 22 patients, 95.5%), similar to findings by Oudat R et al.[21] and Taresh AK et al., who found 82% of high titre.[15]

The annual incidence of inhibitors decreased over the last five years, from 46 to 13 (registered patients/year) and from 18 to 2.7 (examined patients/year). This decline may be attributed to the education regarding the importance of regular prophylaxis therapy, the introduction of new generations of FVIII therapy that reduced the risk of inhibitor development, the disappearance of transient low-titer inhibitors for 5/110patients (3.6%) in this study), and successful immune tolerance therapy. This finding aligns with the observations of Thachil J et al.[9]

This study found a significant association between the development of inhibitors and the severity of hemophilia, with inhibitors developing in 12 out of 22 patients (54.5%) with severe type compared to one out of 22 patients (4.5%) with mild hemophilia. This is similar to Oudat R et al., who reported 18 out of 111 severe HA patients (16.2%) and two out of 26 moderate HA patients (7.6%)[21] with inhibitors, although Owaidah et al. found an insignificant role.[18]

There is a statistically significant association between the development of inhibitors and family history of positive inhibitors, age of first exposure to FVIII replacement (indicating that older age at first exposure correlates with a higher risk of positive inhibitor development), treatment intensity, and type of factor replacement (with switching among products associated with an increased risk of positive inhibitor development). These findings are similar to those of Oudat R et al.,[21] but differ from those of Mohammed et al.[16] and Owaidah et al.,[18] who found no significant association between inhibitor development and treatment regimen.

CONCLUSIONS

The majority of pediatric HA patients at BCHBD were of moderate severity. Positive inhibitors were primarily present in severe HA cases and were predominantly high-titer. The annual incidence of inhibitor

development has decreased in the last five years. The severity of the disease, family history of positive inhibitors, age at first exposure to FVIII therapy, history of intensive FVIII treatment, and type of FVIII replacement are significant risk factors for inhibitor development.

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Authors' contribution

OAN wrote the abstract, methods, results (Tables 1, 2, and 3; Fig. 1), conclusions, and references of the manuscript, contributed to writing the discussion, and conducted all statistical analyses. AMM wrote the introduction and discussion and contributed data for Table 3. Both authors reviewed the final manuscript.

REFERENCES

1. Srivastava A, Santagostino E, Dougall A, Kitchen S, Sutherland M, Pipe SW, et al. WFH guidelines for the management of haemophilia panelists and co-authors. Haemophilia. 2020 Aug;26(6):1-158. doi: 10.1111/hae.14046
2. Gouw SC, van der Bom JG, Ljung R, Escuriola C, Cid AR, Claeyssens-Donadel S, et al. PedNet and RODIN study group. FVIII products and inhibitor development in severe haemophilia A. N Engl J Med. 2013 Jan 17; 368(3):231-9. doi: 10.1056/NEJMoa1208024
3. Calvez T, Chambost H, Claeyssens-Donadel S, d'Oiron R, Goulet V, Guillet B, et al. Recombinant FVIII products and inhibitor development in previously untreated boys with severe haemophilia A. Blood. 2014 Nov 27;124(23):3398-408. doi: 10.1182/blood-2014-07-586347
4. Roosendaal G, Jansen NW, Schutgens R, Lafeber FP. Haemophilic arthropathy: the importance of the earliest haemarthroses and consequences for treatment. Haemophilia. 2008 Nov; 14(6):4-10. doi: 10.1111/j.1365-2516.2008.01882.x
5. Srivastava A, Brewer AK, Mauser-Bunschoten EP, Key NS, Kitchen S, Llinas A, et al. Treatment guidelines working group on behalf of the World Federation Of Haemophilia. Haemophilia. 2013 Jan;19(1):e1-47. doi: 10.1111/j.1365-2516.2012.02909.x.
6. Coffin D , Gouider E , Konkle K, Hermans C, Lambert C, Diop S, et al. The World Federation of Haemophilia World Bleeding Disorders Registry: insights from the first 10,000 patients. Res Pract Thromb Haemost. 2023;7(8):102264.
7. Salen P, Babiker HM. Hemophilia A. 2023 Jul 17. In: StatPearls. StatPearls Publishing; 2024 Jan.
8. Azhar AAM, Raj AA, Izam F, Mokhtar MD, Zakaria NAIA, Banerjee KG. The key complications of hemophilia and recent advancements in their management: an update. Int J Res Med Sci. 2021;9(6):1800-1807. doi: 10.18203/2320-6012.ijrms20212258
9. Thachil J, Connors JM, Mahlangu J, Sholzberg M. Reclassifying haemophilia to include the definition of outcomes and phenotype as new targets. J Thromb Haemost. 2023;21:1737-40. doi:10.1016/j.jtha.2023.03.016
10. Batty P, Riddell A, Kitchen S, Infirri SS, Walker I, Woods T, et al. FVIII/IX inhibitor testing practices in the United Kingdom: results of a UKHCDO and UKNEQAS national survey. Haemophilia. 2021;27:505-10. doi:10.1111/hae.14158
11. Reipert B, Van Helden PM, Schwarz H.-P, Baumgartner CK. Erratum: mechanisms of action of immune tolerance induction against FVIII in patients with congenital haemophilia A and FVIII inhibitors. Br J Haematol. 2007;136:12-25. doi: 10.1111/j.1365-2141.2006.06426.x
12. Carcao M, Goudemand J. Inhibitors in hemophilia: a primer fifth edition [Internet]. World Federation of Hemophilia, 2018. p. 7.
13. Franchini M, Mannucci PM. Inhibitors of propagation of coagulation (factors VIII, IX and XI): a review of current therapeutic practice. Br J Clin Pharmacol. 2011 Oct;72(4):553-62. doi: 10.1111/j.1365-2125.2010.03899.x
14. Kadhim KA, Al-Lami FH, Baldawi KH. Epidemiological profile of hemophilia in Baghdad-Iraq. Inquiry-J Health Car. 2019;56. doi: 10.1177/0046958019845280
15. Taresh AK, Hassan MK. Inhibitors among patients with hemophilia in Basra, Iraq - a single center experience. Niger J Clin Pract. 2019 Mar;22(3):416-421. doi: 10.4103/njcp.njcp_388_18
16. Mohammed Ali IM, Hussein AA, Al-Musawi IMS, Hillawi SSH, Kadhim NS, Jasim AA. Epidemiological profile of hemophilia A in Karbala-Iraq. J Med Life. 2023 Nov;16(11):1611-1614. doi: 10.25122/jml-2023-0218
17. Lateef IA, Hamood HJ, Khaleel OA. Spectrum of haemophilia in Diyala-Iraq. Diyala Journal of Medicine. 2016;10(1):53-58.
18. Owaidah T, Al Momen A, Alzahrani H, Abdulrahman A, Alkasim F, Tarawah A, et al. The prevalence of FVIII and IX inhibitors among Saudi patients with hemophilia: results from the Saudi national hemophilia screening program. Medicine. 2017 Jan;96(2):e5456. doi: 10.1097/MD.0000000000005545
19. Islam MN, Biswas AR, Nazneen H, Chowdhury N, Alam M, Banik J, et al. Clinical profile and demographic characteristics of moderate and severe hemophilia patients in a tertiary care hospital of Bangladesh. Orphanet J Rare Dis. 2022 Jul 8;17(1):254. doi: 10.1186/s13023-022-02413-7
20. Tonbary YA, Elashry R, Zaki Mel S. Descriptive epidemiology of hemophilia and other coagulation disorders in Mansoura, Egypt: retrospective analysis. Mediterr J Hematol Infect Dis. 2010 Aug 13;2(3):e2010025. doi: 10.4084/MJHID.2010.025
21. Oudat R, Al-Maharmeh M, Al-Ghrayeb R, Ogeilat T, Mustafa MK. Prevalence of FVIII inhibitors among children with hemophilia a: experience at the jordanian royal medical services. Med Arch. 2020 Jun; 74(3):187-190. doi: 10.5455/medarh.2020.74.187-190
22. Peyvandi F, Kavakli K, El-Beshlawy A, Rangarajan S. Management of haemophilia A with inhibitors: a regional cross-talk. Haemophilia. 2022 Nov; 28(6):950-961. doi: 10.1111/hae.14638