Journal of Chemical Health Risks

www.jchr.org

ORIGINAL ARTICLE

Frequency of Iron Deficiency and Iron Deficiency Anemia among Hemophilia Children in Babylon Hereditary Blood Disease Center /Iraq

Ahmed Shemran Mutlaq Al-Wataify[*1], Hussain Naji Al-Shammary[2], Amna Ganem Abdul-hussain[3], Qasim Fakher Alhussainy[4]

[1]*Professor of Pediatric, Deptartment of Pediatric, Collage of Medicine, University of Babylon, Hilla, Iraq FRCP, CABP, FICMS pediatric*

[2]*Associate Professor of Hematology, College of Medicine, Babylon University, General Pathology, Hematology, Hilla, Iraq, MB.Ch.B. FICMS, Hematology*

[3] *Pediatrition, Babylon Health Directorate, Iraqi Mministryof Health, Hilla, Iraq, M.B.CH.B, F.I.C.M.S.*

[4] *Pediatrition, Babylon Health Directorate, Iraqi ministry of health. Hilla, Iraq, M.B.CH.B, F.I.C.M.S.*

(Received: 5 August 2021 Accepted: 25 November 2021)

KEYWORDS

Arthropathy;
Hemophilia;
Iron deficiency anemia;
Iron deficiency joint bleeding;
Serum ferritin

ABSTRACT: Objective: to evaluate the frequency of iron deficiency with or without anemia among hemophilia patients with its correlation with other factors including age, address, type and severity of hemophilia. Study design: Cross sectional study, it was conducted at Babylon hereditary blood disease center at Babylon Government/Iraq. For a period of 10 months, from 1st of February to end of November 2019. Methods: The study included 60 patients of hemophilia classified into: hemophilia A (40) patients and hemophilia B (20) patients; all of them were males; age ranged from 6 months to 15 years. All patients were sent for white blood cells count, Hb, Red blood cells indices, serum ferritin level, ESR, C-reactive protein and virology screening. Results: The study reveals IDA occurred in 28.3% and 58.3% of patients developed ID. There was more declined in mean ferritin level among patients with IDA reached 3.7 ± 1.4 ng ml^{-1} , compared to 5.7± 1.4 ng ml^{-1} in ID and in those with sever deficiency. Higher percentage of ID and IDA occurred in complicated hemophilia and those were lived in rural areas. Conclusion: Iron deficiency and IDA are common among hemophilia patients.

INTRODUCTION

Hemophilia is hereditary X-linked recessive complaint with features of VIII factor decrease or IX coagulant action [1]. The public congenital bleeding disease in clinical practice occurs in males, while females are commonly carriers [2]. The classification of severity depend on factor activity into “mild (6- 40%), moderate (1-5%) and severe (<1%)”[3]. Insufficient FVIII levels consequence in the inadequate generation of thrombin by the FIXa besides FVIIIa compound in the essential trail [2]. The hallmark of hemophilia was episodes of bleeding and their extent depends on the severity of the disease and the presence/absence of inhibitors (neutralizing anti-factor VIII antibodies); recurrent bleeding in muscles and joint are common in patients treated on demand, primarily as a result of bleeding into the joints, which can result to long-term hemophilia arthropathy [3, 4]. both Iron deficiency and iron-deficiency anemia are common conditions seen in daily clinical practice; (we have different stages of iron deficiency progress from prelatent stage , latent , to pre-anemia and lastly anemia stage but a

*Corresponding author: dr.ahmedshemranwataify@gmail.com (A. Sh. Mutlaq Al-Wataify)
DOI: 10.22034/JCHR.2022.688197

significant part of these patients may never progress to overt anemia as in Table 1) , although the percentage of iron deficiency anemia has somewhat recently reduced, iron-deficiency anemia has a great effect on the lives of young children and premenopausal women in both developing and developed countries [5]. The diagnosis and treatment of anemia could clearly be improved. Iron is basic to many biologic functions, as respiration, production of energy , DNA synthesis, and cell proliferation [6]. Hemophilia is a lifetime hemorrhage illness, the clinical sequence of which conquered by equally overt and covert hemorrhage [7]. Frequent external bleeding from openings, the skin and epithelial wounds lead to iron deficiency [7]. Sever cases of hemophilia suffered from recurrent internal bleeding inside the joints, lead to accumulation of iron in the synovium [7]. Mediators release of inflammatory response leading to crippling synovitis besides arthroplasty [7]. So, high synovial store of iron in patients with hemophilia increased synovial iron stores in hemophiliac patients cannot possibly recompense for the iron lack resulting from outside bleeding and the reduction of normal storing organs like liver and the bone marrow [8]. Iron deficiency might increase the morbidity in hemophilia, the iron deficiency mostly due to presence of occult blood loss in the urine and stools or due to the iron deposition in the synovial membrane through recurrent episodes of bleeding [9]. The diagnosis and treatment of iron deficiency might help to improve their quality of living [10]. Aims of study to assess frequency of iron deficiency and iron deficiency anemia among hemophilia patients, its correlation with other factors including age, address, type and severity of hemophilia.

Table 1 . Different stages of iron deficiency [11].

	Pre-latent	**Latent**	**Pre-anemia**	**Anemia**
Hb	normal	normal	Often decreased but within normal range	decreased
B.M iron	decreased	decreased	zero	zero
S. ferritin	decreased	< 50-70	< 30	<15
Transferrin saturation	Normal > 30%	Normal 20-30%	15-20%	< 15%
Serum transferrin receptor	normal	normal	Often raised	raised
Symptoms	May present	common	Common and may be disabling	Classical symptoms of anemia

MATERIALS AND METHODS

A cross sectional study was conducted at Babil hereditary blood disease center in Babil Maternity and Children Hospital at Babil province /Iraq. For a period of 10 months, from 1st of February to end of November 2019. We continued with this process after receiving informed oral agreement from the patients or their parents. It included 60 patients of hemophilia classified into: hemophilia A (40) patients and hemophilia B (20) patients; all of them are males; their age ranged from 6 months to 15 years with a mean age 9.5 ± 3.3 years. The hemophilia patients were diagnosed clinically and confirmed by factor assay at the time they recorded in the center. All studied patients presented with bleeding problem or as prophylactic therapy; we evaluating evidence of anemia clinically and confirmed by Hb and PCV and other RBC indices include MCV ,MCHC ,blood film morphology, reticulocyte count and serum ferritin. In addition, we sent them for ESR and CRP to evaluate for presence of acute infection or inflammation.

Inclusion criteria: hemophilia A and B patients with age from 6 months up to 15 years, those patients should not received blood transfusion in the last 3 months, no evidence of acute infection and inflammation and negative screen for HBV, HCV and HIV.

Those patients with elevated ESR, CRP and WBCs count are excluded from the study because this indicates acute infection or inflammation. The data was collected including demographic profile (age, sex, type of hemophilia and its severity, presence of inhibitors or not). We aspirate 5cc of blood and separated into: 2cc of blood in EDTA tube for WBCs, Hb, PCV%, MCV, MCHC, blood film morphology and the other 3cc were sent in

plain tube for estimation of serum ferritin. Iron study was determined by S. ferritin analysis that was measured by MINIVIDAS technique using a sandwich immunodetection method [12]. (Normal level of serum ferritin is between 7-150 ng ml^{-1}). Iron deficiency (ID) suggested by decreased level of serum ferritin with normal MCV, MCHC, PCV and Hb.

While iron deficiency anemia (IDA) is suggested by the followings:

1. Hypochromia, microcytosis
2. Piokilocytosis (variation in shape).
3. Anisocytosis (variation in size).
4. Pencil shaped RBCs.
5. Low Hb and PCV.
6. Low serum ferritin.

MCV: mean corpuscular volume (normal value 81-96 fL) can be directly measured by automated hematology analyzer, collected through EDTA tube.

MCHC: mean corpuscular Hb concentrate (normal value 31.8-35.4g dl^{-1}).

Hb: (hemoglobin level: - normal level 11-15 gm dl^{-1} equal 6.8266 -9.309mm l^{-1}).

(Each 1 gm is equivalent to 0.6206)

Normal reticulocyte count is 0.5-1.5 %.

Data was collected and analyzed by statistical package of social sciences (SPSS version 24). Discrete variables presented as number and percentage, were analyzed using chi square such as in comparison according to age, address and severity, the P-value <0.05 is significance.

RESULTS

75% (45/60 patients) have low ferritin of less than 7 ng ml^{-1} in patients with both ID and IDA but 58.4% (58.3%) (35/60) of total patients developed iron deficiency and 28.3% (17/60) developed iron deficiency anemia (10 patients had low Hb ,MCV, MCHC and low s. ferritin, where 7 patients had low Hb, MCV and MCHC but serum ferritin of more than 7 ng ml^{-1}) as in Table 2.

Table 2. Cases distribution according to the analysis of parameters:

Variable factors	Level	No.	Percentage%
Serum ferritin ng ml^{-1}	<7 ng ml^{-1} (ID + IDA)	45	75%
	≥7	15	25%
Iron deficiency(ID)	Low ferritin of < 7 ng ml^{-1} with normal Hb	35	58.3%
Iron deficiency anemia	Low ferritin of <7ng ml^{-1} with low Hb<11gm dl^{-1}	10	16.66%
	ferritin of ≥ 7 ng ml^{-1} with low Hb <11gm dl^{-1}	7	11.66%
		17	28.3%
RBC indices (red blood cell indices)	Low MCV<81fl	17	28.3%
	Low MCHC < 31.8 gm dl^{-1}	17	28.3%

Serum ferritin level showed that it decreased in IDA 3.7± 1.4 in compared to 5.7± 1.4 in ID without anemia, and in hemophila with arthropathy 7.3± 6.4 in comparism to those with no complication .also there were decreased level of all MCV, MCHC and Hb in IDA and hemophilia with complications, compared to ID and hemophilia without complication respectively. Statistically were significant in all parameter except in MCHC when compared between patients with complications and no complications as seen in Table 3.

It showed that Percentage of low ferritin level, RBC indices & anemia increased with increased severity of hemophilia from mild in 46.6%, 13.3%, 13.3% to severe form 95.4%, 40.9% 40.9% respectively as in Table 4.

Statistically significant between patients with normal and abnormal level of all blood parameter including ferritin level, MCV, MCHC and Hb as in Table 5.

There were increasing number of patients with low level

of serum ferritin, RBC indices and Hb with age of more than 6 years in compared to those with age below 6 years as in Table 6.

There were increasing percentage of low serum ferritin, RBC indices and Hb in rural patients, compared to urban patients and statistically were significant as in Table 7.

Table 3. Mean level of blood indices among hemophilia patients:

	Serum ferritin ± SD	MCV ± SD	MCHC ± SD	Hb ± SD
ID	5.7 ± 1.4	85.3 ± 2.1	34.4 ± 2.3	12.5 ± 1.2
IDA	3.7 ± 1.4	75.8 ± 2.4	26.2 ± 1.9	9.2 ± 1.2
p-value	< 0.05	<0.02	<0.01	<0.01
With complications (10 patients: arthropathy)	7.3 ± 6.4	81.7 ± 6.1	31.8 ±7.21	10.3±1.2
Without complications (50 patients)	19.2 ± 3.1	89.04±4.2	32.7 ± 4.9	12 ± 2.7
P- Value	<0.001	<0.001	0.6	<0.05

Table 4. Distribution of blood parameters according to severity of hemophilia and Cases distribution according to type of hemophilia with severity:-

Severity	Parameters		
	Low S.ferritin	Low MCV & MCHC	Low Hb
Mild (15 patients)	46.66% (7 patients)	13.3% (2 patients)	13.3% (2 patients)
Moderate (23 patients)	73.91 (17 patients)	26.03% (6 patients)	26.03% (6 patients)
Severe with inhibitor(22patients)	95.4% (21 patients)	40.90% (9 patients)	40.90% (9 patients)
Total (60 patients)	45	17	17

Type of hemophilia	Severity	S. ferritin<7ng ml^{-1} in ID	Low RBC Indices	Hb <11gm dl^{-1} in IDA
H. A	Mild (16)	4 25%	1 6.25%	1 6.25%
	Moderate (12)	8 66.6%	4 33.3%	4 33.3%
	Severe + inhibitors (12)	12 100%	7 58.33%	7 58.33%
Total	(40)	24 60%	12 30%	12 30%
H. B	Mild (2)	2 100%	1 50%	1 50%
	Moderate (11)	3 (27%)	2 18.18%	2 18.18%
	Severe (7)	6 (85.7%)	2 28.57%	2 28.57%
Total	(20)	11 55%	5 25%	5 25%

Table 5. Cases distribution according to mean level of blood parameters.

Factors	Level	Patients no.	%	Mean ± SD	P- value
Total low ferritin	< 7 ng ml^{-1}	45	75	4.5± 1.8	**0.002**
Normal ferritin	≥7 ng ml^{-1}	15	25	35± 7.2	
Ferritin in ID		35	58.3	5.7± 1.4	**0.04**
Ferritin in IDA		17	28.3	3.7± 1.4	
MCV	<81 fl	17	28.3	75.8± 2.4	**0.001**
	≥ 81fl	43	71.7	85.3 ± 2.1	
MCHC	< 31.8 gm dl^{-1}	17	28.3	26.2± 1.9	**0.001**
	≥ 31.8 gm dl^{-1}	43	71.7	34.4± 2.3	
HB	< 11 gm dl^{-1}	17	28.3	9.2± 1.2	**0.001**
	≥ 11 gm dl^{-1}	43	71.7	12.5± 1.3	

Table 6. Cases distribution according to the age of the patients.

Age	S. ferritin <7 ng ml^{-1} in ID	Low RBC indices	Hb <11gm dl^{-1} IDA
< 3 years (3 patients)	0 (0%)	0 (0%)	0 (0%)
≥3-<6years (11 patients)	7 (63.6%)	3 (27.27%)	3 (27.27%)
≥6 -<11 years (22patients)	13 (59%)	5 (22.7%)	5 (22.7%)
≥11 – 15 years (24patients)	15 (62.5%)	9 (37.5%)	9 (37.5%)

Table 7. Distribution of blood parameters according to address of patients.

Address	Low S. ferritin in ID	Low RBC indices	Low Hb IDA
Rural	17	11	11
23 patients	(73.91%)	47.82%	(47.82%)
Urban	18	6	6
37patients	(48.64%)	16.21%	(16.21%)
P-value	0.04	0.003	0.003

DISCUSSION

The study results reveals 75% (45/60 patients) had low ferritin, where 58.3% (35/60 patients of them) developed iron deficiency (suggested by low serum ferritin of less than 7 ng ml^{-1} with normal MCV, MCHC and Hb) and 28.3% (17/60 patients) have iron deficiency anemia (suggested by low Hb, RBC indices with more reduction of s. ferritin in 10 patients and low Hb , RBC indices and s. ferritin of more than 7 ng ml^{-1} in 7 patients only). Higher results of both ID and IDA are resulting from recurrent bleeding episodes either as external bleeding from orifices (as epistaxis, the skin, epithelial tissues and occult blood from both gastrointestinal and genitourinary system) or from frequent internal bleeding most commonly inside the joint and infrequently from internal organs like abdomen or brain [8]. The iron deposit produces as stimuli for delayed macrophage influx, macrophage release range mediators in inflammation and angiogenesis [13]. The iron get released from Hb which initially binds to ferritin while unbound iron have direct toxic effects on tissue modulate inflammatory and

immune function [13]. Our results of iron deficiency are compatible to the results done in North Nigeria [8] and India [13] showing 48.7% and 59.4% respectively , while the current study results are too much lower than those done in Dhaka, Bangladesh which reveals 86.6% developed IDA [14]. This higher results in Bangladesh can be explained by using fresh frozen plasma as on demand therapy only for bleeding attack especially in severe form of hemophilia, while in our patients, we usually used prophylactic therapy of Factor VIII or IX (that given in a dose of 20-40 unit /kg 2-3 times /week in type A and 1-2 times/week in type B) associated with more reduction in spontaneous hemorrhage and on demand therapy during episode of bleeding. In general, the ID is three times common as IDA in children [15] as iron storage are gradually and progressively depleted from prelatent stage to anemic stage if no treatment and no correction of the risk factors [11] where s.ferritin is just reduced in prelatent stage and continue to decline gradually to reach very low level in anemic stage [11] (in this study shows low mean serum ferritin 5.7 ± 1.4 ng ml^{-1} in the prelatent stage described as iron deficiency to reach to 3.7 ± 1.4 ng ml^{-1} in anemic stage described as iron deficiency anemia and statistically was significant). This is indicated that, there was a good correlation between serum ferritin and body iron store, which mean the serum ferritin, is more sensitive and more specific for diagnosis of iron deficiency with or without anemia [11], it is considered as first biochemical variable to change in ID. but the ferritin is considered an acute phase reactant and has pseudo elevation in infection and inflammation which is commonly happened in hemophilia patients with arthropathy (7 patients 11.6% in our study reveal low Hb with normal serum ferritin) and this is explained why frequency of ID is higher than IDA [15] in spite of early reduction of ferritin level and late reduction of Hb (ID is 58.3% compared to 28.3% in IDA). In the current study, the parameter mean level showed that, there was increased frequency of low level of serum ferritin and Hb with increased severity from mild 46.66%, 13.3% to severe form 95.4%, 40.90% respectively. The increased frequency of low ferritin and anemia indicates more frequent spontaneous accidental bleeding episodes. This results are similar to those done by Paranthaman Poongavanam in india [13]. The association between harshness of hemophilia and ID established earlier estimate and is consistent with severe [8]. There was no increment in the percentage of ID and IDA with increasing the age of the patients (from 6 months until 15 years except to those younger than 3 years of age) in both types of hemophilia. This can be explained by either small sample size or the same risk factors exposed in different age groups [16]. Also the frequency of ID and IDA are increased to those patients who developed complications and those lived in rural areas and statistically were significant.

CONCLUSIONS

1. Iron deficiency with or without anemia are common among patients with hemophilia, and it´s frequency was increased among severe form of hemophilia, which lived in rural areas and those patients with complications, but not related to the age and type of hemophilia.
2. Serum ferritin is highly sensitive and specific for detection ID but may be raised as false elevation among patients with chronic hemophilia arthropathy and condition with chronic inflammation.

CONFLICT OF INTERESTS

None of authors have any conflict of interest.

REFERENCES

1. Ghosh K., Ghosh K., 2016. Management of haemophilia in developing countries: challenges and options. Indian Journal of Hematology and Blood Transfusion. 32(3), 347-355.
2. Tantawy A.A., 2010. Molecular genetics of hemophilia A: Clinical perspectives. Egyptian Journal of Medical Human Genetics. 11(2), 105-114.
3. Young G., 2012. New challenges in hemophilia: long-term outcomes and complications. Hematology 2010. The American Society of Hematology Education Program Book. 2012(1), 362-368.
4. Klamroth R., Pollmann H., Hermans C., Faradji A., Yarlas A. S., Epstein J.D., Ewenstein B.M., 2011. The relative burden of haemophilia A and the impact of target joint development on health related quality of life: results from the ADVATE Post Authorization Safety

Surveillance (PASS) study. Haemophilia.17(3), 412-421.

5. McLean E., Cogswell M., Egli I., Wojdyla D., De Benoist B., 2009. Worldwide prevalence of anaemia, WHO vitamin and mineral nutrition information system, 1993–2005. Public Health Nutrition. 12(4), 444-454.

6. Scott J., Montgomery R., 2010. Hemorrhagic and thrombotic disorder. Saunder. Philadelphia.

7. Nieuwenhuizen L., Schutgens R., Van Asbeck B., Wenting M., Van Veghel K., Roosendaal G., Biesma D., Lafeber F., 2013. Identification and expression of iron regulators in human synovium: evidence for upregulation in haemophilic arthropathy compared to rheumatoid arthritis, osteoarthritis, and healthy controls. Haemophilia. 19(4), e218-e227.

8. Ahmed S.G., Kagu M.B., Ibrahim U.A., Bukar A.A., 2015. The frequency of iron deficiency among patients with haemophilia-A in northern Nigeria: correlation with the disease severity and clinical implications. The Egyptian Journal of Haematology. 40(2), 85.

9. Kosiakova I.A., Davydkin I., Zorenko V.I., 2014. Mechanisms of comorbidity in hemophilia patients. Terapevticheskii Arkhiv. 86(3), 78-82.

10. Ibrahim U.A., Ahmed S.G., Kagu M.B., Abjah U.A., 2017. Impact of intestinal helminths on the risks of gastrointestinal haemorrhage and iron deficiency among haemophilia patients in northern Nigeria. J Haem Pract 4 (1),1-8.

11. Soppi E., 2019. Iron deficiency without anemia–common, important, neglected. Clin Case Rep Rev. 5, 1-7.

12. Bhatnagar N.D., Haematology L.P., 2017. By BJ Bain, I. Bates and MA Laffan. British Journal of Haematology. 178, 652–652.

13. Poongavanam P., Nandakumaran J., Shanmugam M., Pachuau H., 2017. The Frequency of Iron Deficiency among Patients with Hemophilia. IOSR Journal of Dental and Medical Sciences. 16, 4-9.

14. Haque R., Biswas D.A., Quraishi S.A., 2018. Study of anemia among hemophilia patients. Bangladesh Journal of Medical Science. 17(4), 573-575.

15. Özdemir N., 2015. Iron deficiency anemia from diagnosis to treatment in children. Turkish Archives of Pediatrics/Türk Pediatri Arşivi. 50(1), 11.

16. Janus J., Moerschel S.K., 2010. Evaluation of anemia in children. American Family Physician. 81(12), 1462-1471.