

Research Article

Iron Deficiency in Haemophilia- Severity, Correlation and Clinical Profile- A Cross Sectional Study from South India

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Received: 15.02.26, Revised: 20.03.26, Accepted: 25.04.26

ABSTRACT

Haemophilia is an inherited X-linked recessive disorder caused by deficiency of Factor VIII or Factor IX which is required for the generation of Thrombin in the intrinsic pathway of coagulation. India has the second highest burden of haemophilia in the world. Iron deficiency is expected in these vulnerable population due to either presence of occult blood loss in urine/stool or deposition of iron in the synovium during the repeated episodes of bleeding. This study was to estimate the proportion of iron deficiency and to determine the association of severity of Haemophilia with the stage of iron deficiency in individuals with Haemophilia and to determine the clinic aetiological and haematological profile of iron deficiency in haemophiliac patients. Methods: The patients confirmed with Factor VIII/IX deficiency attending the Haemophilia OPD of Government Medical College, Kottayam during a period of 1 year were recruited. They were classified as mild (6-40%), moderate (1- 5%) and severe(<1%) based on their factor levels. Data collection was done using a case report form which included clinical characteristics of patients along with targeted blood investigations. The analysis was done using SPSS software. The data were summarized using descriptive and correlational statistics. Results: The proportion of iron deficiency in individuals with Haemophilia was found to be 27.1%. Of those with iron deficient erythropoiesis 66.7% had severe Haemophilia A and 9.5% had Haemophilia B. Of those with iron deficiency anemia 57.1% had severe Haemophilia A and 42.9% had severe Haemophilia B. Of the patients with low ferritin were 75% found to have iron deficient erythropoiesis while 25% were found to have iron deficiency anemia. The most common symptom associated with iron deficiency was muscular pain, joint pain, palpitations and shortness of breath .The most common sign associated with iron deficiency anemia was papillary atrophy of the tongue.

Conclusion: The proportion of iron deficiency in individuals with Haemophilia was found to be 27.1%. The more the severity of Haemophilia, the higher was the stage of iron deficiency of the patient.

Keywords: Haemophilia, Iron Deficiency, Serum Ferritin, Severe Disease.

INTRODUCTION

Haemophilia is an inherited X linked recessive disorder characterised by deficiency of Factor VIII (Haemophilia A) and Factor IX (Haemophilia B) required for the generation of thrombin in the intrinsic pathway of coagulation.¹Iron deficiency in haemophiliacs occurs either due to presence of occult blood in urine/ stool or deposition of iron in the synovium following bleeding into the joint.² Inadequate nutrition, intake of drugs or foods impairing iron absorption as well as coexisting parasitic infections are other factors that add on to anaemia. Iron deficiency affects healing of the wound, immunity and mental development which in turn affects the overall wellbeing of a haemophilia patient.³ Early

identification of iron deficiency is important in the management and clinical outcome of a Haemophilia patient. Identification of iron deficiency in this vulnerable population can thus help in modification of dietary habits and initiation of iron supplementation which will help to ameliorate some of the debilitating effects of iron deficiency like crippling arthropathy.² Iron is essential for all living beings, since it plays a major role in numerous vital processes like cellular oxidative mechanisms to tissue oxygen transport. Iron homeostasis is regulated by iron absorption more than excretion. The serum iron level reflects the balance between the amount of iron absorbed and the amount that the body uses.⁴

Iron deficiency gradually progresses till anemia occurs causing negative iron balance occurs. In iron deficiency there is depletion of the iron stores causing subsequent iron deficiency. Ferritin levels fall however no functional abnormalities occur at this point of time. Serum iron levels fall with decline in transferrin saturation and increased total iron-binding capacity. Negative iron balance leads to anemia. With increase in severity of anemia, haemophilia patients experience increased frequency of spontaneous bleed. Internal joint bleeds become frequent which results in iron accumulation in the synovium of their joints and causes local inflammatory changes.⁴ In the joints, chondrocytes and the synoviocytes generate tissue factor pathway inhibitors, aggravating bleeding tendency and causing recurrent bleeds which increasing chances of synovial iron deposition pathologically leading to debilitating synovitis and hemophilic arthropathy. The increased stores of synovial irons cannot be accounted and does not make for the losses of bone marrow or liver iron stores because of external and internal bleeding.

They progress to the development of further iron deficiency and iron deficiency anemia.⁴ There is an existing gap in the literature on the data from South Indian population on the epidemiology and effect of anemia in hemophilic patients. This study was conducted with objectives to estimate the proportion of iron deficiency, determine the association of severity of haemophilia with the stage of iron deficiency in individuals with Haemophilia and to determine the aetiological and haematological profile of iron deficiency in haemophilic patients.

MATERIALS AND METHODS

This was a cross sectional study done for a period of 12 months from February 2023 to January 2024 at Regional Haemophilia Centre ,Medical College Kottayam in central Kerala . After getting Institutional Review Board clearance (IRB no-52/2023 dated 24/1/2023), informed written consent was obtained from the patients or legally acceptable representatives. Patients were assessed for symptoms and signs of iron deficiency.

Haemoglobin concentration and red cell indices were determined using automated blood analysers (Mindray). Iron stores of the studied patients were assessed by serum ferritin analysis using the ELISA technique. The demographic profile (age), clinical features, haematological parameters, serum ferritin and Factor levels of each patient were recorded in a structured proforma. On the basis of Factor VIII and Factor IX levels, patients were categorized as having severe (Factor levels <1%), moderate (Factor levels 1-5%) or mild (Factor levels 6-40%) Haemophilia. From the haematological data obtained, the proportion of iron deficiency in the study population was determined. The association of severity of Haemophilia with the stage of iron deficiency and the clinic aetiological profile of Haemophilia patients was estimated. Based on 48.7% prevalence of iron deficiency in hemophiliacs in a study by Ahmed et al., sample size was calculated were 101.⁵Inclusion criteria included patients diagnosed with Haemophilia A or Haemophilia B attending as out patients in Haemophilia regional centre, Medical College, Kottayam. Exclusion criteria included patients with bleeding disorders other than haemophilia, liver disease, fever or any evidence of infection, patients who have received packed red cell transfusion in the last three months. A semi structured proforma was to collect the data from the participants. The data were entered in excel and analysed using SPSS software.

RESULTS

Among the patients who presented to the Haemophilia OPD in Government Medical College, Kottayam during the study period, a total of 103 patients who met the inclusion criteria were enrolled into the study. Eight (7.7%) were below 20 years, 68 (66%) were between 21 and 40 years, 22 (21.3%) were between 41 and 60 years, 4 (3.8%) were between 61 and 80 years and 1(0.9%) was above 80 years. Out of the 103 patients 85.4% (88) had Haemophilia A and 14.5% (15) had Haemophilia B. Severe Haemophilia A was seen in 71.8% and 11.7% had severe Haemophilia B as shown in Fig 1.

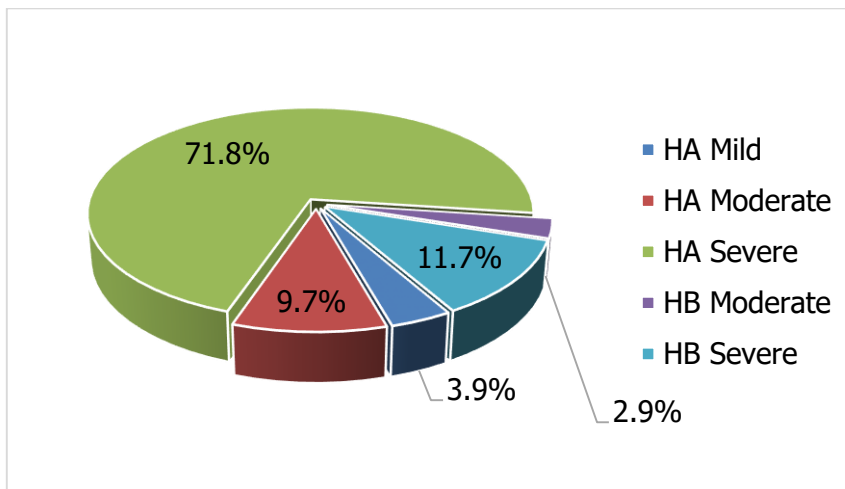


Fig 1: Severity of Haemophilia

Out of 103 patients, 28 (27.1%) had iron deficiency. Twenty eight (27.1%) had ferritin levels lower than 30ng/ml. Out of these 28 patients, 18(64.2%) had severe Haemophilia A, 5(17.8%) had severe Haemophilia B, 4(14.2%) had moderate Haemophilia A and 1(3.5%) had moderate Haemophilia B. Mean serum ferritin levels were lower in severe Haemophilia B (139.7) and severe Haemophilia A (161.5). None of the patient with mild Haemophilia A were found to have ferritin levels lower than 30ng/ml.

As depicted in Fig 2, the major symptoms of iron deficiency in haemophilia were muscular and joint pain 30.1% followed by dry skin 21.4%. The most common symptoms in Haemophiliacs with low ferritin were muscular and joint pain (28.6%) followed by palpitations, shortness of breath and dry skin (25%). In those with low ferritin the main symptoms included muscular and joint pain (28.6%) followed by palpitations, shortness of breath and dry skin (25%).

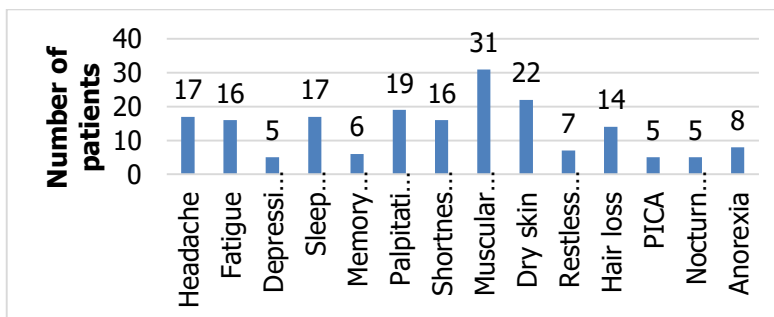


Fig 2: Symptoms of Iron Deficiency Anemia in Patients with Hemophilia

The most common sign associated with iron deficiency anemia among Haemophiliacs was found to be papillary atrophy of the tongue (100%) followed by pedal edema (71.4%) and cheilitis (42.9%).

Out of the 28 iron deficient patients, 21 (75%) had iron deficient erythropoiesis while 7(25%) had iron deficiency anemia. Out of the 21 patients with iron deficient erythropoiesis, 14 (66.7%) had severe Haemophilia A, 4(19%) had moderate Haemophilia A, 1 (4.8%) had moderate Haemophilia B and 2 (9.5%) had severe Haemophilia B. Out of the 7 with iron deficiency anemia, 4(57.1%) had severe

Haemophilia A and 3 (42.9%) had severe Haemophilia B.

DISCUSSION

In this study conducted on 103 Haemophiliacs majority had Haemophilia A 71.8% being severe Haemophilia A. More than a quarter, 27.1% had ferritin less than 30ng/ml. Mean serum ferritin levels were found to be lower in severe Haemophilia B and severe Haemophilia A. In Haemophiliacs with low ferritin, the most common symptom of iron deficiency was muscular and joint pain followed by palpitations, shortness of breath and dry skin. In those with iron deficiency anemia, the most

common symptoms were palpitations and shortness of breath and the most common sign was papillary atrophy. Out of the 28 Haemophiliacs with low ferritin, 75% were found to have iron deficient erythropoiesis and 25% were found to have iron deficiency anemia.

A retrospective study by Ahmed et al in Northern Nigeria revealed an overall frequency of iron deficiency to be 48.7% in Hemophilia A. Of the total patients, 61.5% had severe Haemophilia A. 66.7% of those with severe Haemophilia A had a significantly higher frequency of iron deficiency when compared to those with non-severe Haemophilia A.⁵ A cross sectional study conducted by Wataify et al in Babylon showed that iron deficiency occurred in 58.3% and iron deficiency anemia in 28.3% of patients.⁶ They pointed out that there was more decline in mean ferritin level among patients with iron deficiency anemia ($3.7 \pm 1.4 \text{ ng ml}^{-1}$) as compared to those with iron deficiency ($5.7 \pm 1.4 \text{ ng ml}^{-1}$). Higher percentage of iron deficiency with or without anemia occurred in complicated hemophilia and those who lived in rural areas.⁶ A prospective observational study by Haque et al done in Bangladesh revealed 58.33% patients with hemophilai were moderately anemic, 25% cases to be mildly anemic and 3.33% cases to be severely anemic.⁷

A cross sectional study by Poongavanam et al in Chennai revealed that 78% had severe disease. 68% had microcytic hypochromic blood picture while 32% had a normal blood picture. 72% had haemoglobin less than 13mg/dl. The lowest Ferritin level was 21ng/ml, the highest being 89ng/ml. The mean ferritin level was within the lower limits of normal in all the patients.⁸

According to a study by Buchanan et al in Texas, haemoglobin values were commonly below the mean normal values for age in hemophiliacs. Frank anemia was present in 31% of patients of mild severity.⁹ This study showed a lower proportion of iron deficiency among haemophiliacs in comparison with other studies. The proportion of iron deficiency was found to be higher in those with severe forms of the disease as consistent with previous studies. Soppi et al., stated that A serum ferritin concentration of $<30 \mu\text{g/L}$ a very sensitive and specific test for the identification of iron deficiency in patients with or without anemia.¹⁰ There are however every chance that the patients could be iron deficient even at much higher concentrations of ferritin.

Iron deficiency without anemia remains a clinical challenge especially in the hemophiliacs. Comorbidities range from hypothyroidism to depression to chronic fatigue syndrome. Estimation of serum ferritin concentration and a meticulous medical history with a keen look out for differential diagnosis is the key to its early detection. Patients could need oral or parenteral iron. In hemophiliacs this correctable deficiency could add on to the decline in quality of life and additional costs.

The main limitation of this study is that it is a single centre cross sectional study. More studies which are multicentric and longitudinal with follow ups and more details on management of patients with iron deficiency and iron deficiency needs to be planned in the future

CONCLUSION

The proportion of iron deficiency in individuals with Haemophilia was found to be 27.1%. Majority of those with iron deficient erythropoiesis had severe Haemophilia A and 9.5% had Haemophilia B. The more the severity of Haemophilia, the higher the stage of iron deficiency the patient was in. Three quarter of patients with low ferritin were found to have iron deficient erythropoiesis while a quarter of patients were found to have iron deficiency anemia. Proper guidelines regarding screening of iron deficiency should be established and attempts made for correction by iron or dietary supplementation in haemophiliac patients.

Acknowledgement: We thank the staff of department of Medicine GMC, Kottayam and Regional Centre of Haemophilia, GMC, Kottayam. We thank Dr Dhanya Sasidharan Palappallil, Professor CAP Pharmacology for helping in editing this manuscript.

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