



ISSN Print: 2394-7500  
ISSN Online: 2394-5869  
Impact Factor: 5.2  
IJAR 2016; 2(4): 196-200  
www.allresearchjournal.com  
Received: 24-02-2016  
Accepted: 25-03-2016

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## Study of arthropathy in haemophilia a

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### Abstract

**Introduction:** Haemophilia is the most common inherited X linked severe bleeding disorder. Screening and early detection of haemophilic arthropathy along with prophylactic factor and physiotherapy decreases complication and disability. Hence this study was conducted to detect arthropathic changes and its severity in haemophilic children.

**Aims and Objectives:** To study cases of arthropathy and to assess the severity of arthropathy in Haemophilia A patients.

**Methodology:** Diagnosed cases of Haemophilia A Patients who came to Dr. D.Y. Patil Medical College, Pune were enrolled during study period i.e. October 2013 to September 2015 who fulfilled the inclusion criteria.

A standard proforma was used to get the detailed history and the examination findings along with X ray Knee and MRI Knee were evaluated and statistically analysed.

**Results:** Out of 50 subjects majority 84% were symptomatic & 16% were asymptomatic. Pain was the major complaint in 84%, followed by swelling 80% and restriction of movement in 44% cases. X ray findings in the study group, 58%- normal x ray findings, 16%- widened intercondylar notch in knee joint, 20%- minimal knee joint effusion, 2%- hyperdense expansion of the joint capsule with bony erosion & 4%- epiphyseal enlargement. MRI findings in study group, 34%- findings s/o haemophilic arthropathy, 28%- diffuse siderotic synovitis with minimal knee joint effusion, 26%- normal MRI finding, 8%- pigmented villonodular synovitis & 4%- findings s/o inflammatory arthritis.

**Conclusion:** All symptomatic cases had findings suggestive of haemophilic arthropathy on MRI; even 1 asymptomatic patient had findings suggestive of haemophilic arthropathy on MRI. MRI revealed findings suggestive of arthropathy in many cases where X ray findings were normal. This showed that MRI is a more sensitive tool than X ray to detect arthropathic changes.

**Keywords:** Haemophilia A, Arthropathy, X ray, MRI

### Introduction

Haemophilia is the most common X-linked inherited disorder of clotting factor deficiencies. The genes for factors VIII and IX are located on the X chromosome and display a recessive inheritance pattern [1]. Bleeding into a joint (hemarthrosis) is the most common clinical consequence of haemophilia. Hemarthrosis is the single most important risk factor for the development of haemophilic arthropathy [2]. In nearly half of all children with severe haemophilia, the initial joint hemorrhage occurs during the first year of life, and 90% of children with severe disease experience at least one joint hemorrhage before the age of 4.5 years [3]. Knee joint is most commonly affected. Bleeding into the joints may be induced by minor trauma; many hemarthroses are spontaneous [4].

Physiotherapy has shown many benefits in the prevention & improvement of acute joint injuries, as well as in the management of hemarthrosis in patients with haemophilia. Approximately 50% of patients with haemophilia develop permanent changes in the target joint. If arthropathy is diagnosed at an early stage, disability can be delayed or prevented to some extent MRI is more sensitive and diagnostic tool for detection of arthropathy compared to conventional methods like X ray etc. Screening and early detection of haemophilic arthropathy along with prophylactic factor and physiotherapy decreases complication and disability. Hence this study was conducted to detect arthropathic changes and its severity in haemophilic children.

### Aim and Objectives

To study cases of Arthropathy in Haemophilia A patients aged 2-12years.

To assess the severity of arthropathy in Haemophilia A patients aged 2-12years.

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**Materials and Methods**

Study Design: - Cross-sectional study.  
 Place of study: - Dr. D.Y. Patil Medical College, hospital and Research Centre, Pimpri, Pune  
 Period of study: - October 2013 to September 2015.  
 Institute Ethics committee approval was obtained before the start of study.  
 Sample size: - 50 cases.  
 Inclusion criteria: All diagnosed patients with haemophilia A aged between 2 – 12 years

**Methods**

During the study period total 50 cases of diagnosed haemophilia A were enrolled in this study, who attended Dr D Y Patil medical college, hospital and who fulfilled inclusion criteria. Appropriate consent in a prescribed format was obtained and duly signed by the parents. After inclusion in the study in each case a thorough history was taken followed by a detailed examination and the observations were recorded in a prescribed proforma. Detailed history about age at diagnosis, episodes of active bleeding, prophylactic factor replacement, physiotherapy and chief complaints related to joint involvement were recorded. Family history, socioeconomic status, dietary history, developmental history was noted. Physical Examination was done subsequently patient was subjected to routine test, blood investigation, X ray and MRI of joints.

**Imaging Study:-** All cases were subjected to imaging studies for screening of arthropathy.

**X RAY:** Radiographs of both knee joints were taken in anteroposterior and lateral view which assist in defining the extent of articular changes.

**MRI:** MRI of both knee joints of all patients were done to evaluate the cartilage, synovium, and joint space & to check severity of disease and graded according to Denver scale. MRI was done using MAGNETOM Avanto – Siemens Healthcare (1.5 T)

**Statistical Analysis**

Data analysis was done using the SPSS (Statistical Package for the Social Science) Version 17 for window. Graphs were made using Microsoft excel.

**Result**

**Table 1:** Chief complaints regarding joint involvement in study group Pain was the major complaint in 42 (84%) cases, followed by swelling 40 (80%) cases and restriction of movement in 22 (44%) cases. 32 patients were with one joint involvement & 8 patients with two joint involvement.

Chief complaints	No of cases	Percentage
Pain	42	84
Swelling	40	80
Restriction of movement	22	44
No of joint involved		
One (Knee)	32	
Two (Knee, elbow)	8	

**Table 2:** Treatment history in study group

Treatment history	No of cases	Percentage
Accessibility of treatment	28	56
Factor with Physiotherapy	17	34
Factors without Physiotherapy	33	66

The above table shows treatment history in study group. In this study 56 % cases had easy accessibility of treatment, 34 % cases had taken factor VIII with physiotherapy and 66% cases received only factor VIII.

**Table 3:** X-ray findings in study group

X- ray findings	No of cases	Percentage
Epiphyseal Enlargement	2	4
Hyperdense Expansion of the Joint Capsule with bony erosion	1	2
Minimal Knee Joint Effusion	10	20
Widened Intercondylar Notch in Knee Joint	8	16
Normal	29	58
Total	50	100

The above table shows X-ray finding in study group. The majority 29 (58%) cases had normal x ray findings, 8 (16%) had widened intercondylar notch in knee joint, 10 (20%) had minimal knee joint effusion, one (2%) cases had hyperdense expansion of the joint capsule with bony erosion & two (4%) cases had epiphyseal enlargement.

**Table 4:** MRI findings in study group

MRI findings	No of cases	Percentage
Diffuse Siderotic Synovitis With Minimal knee joint effusion	14	28
Findings S/O Haemophilic Arthropathy	17	34
Findings S/O Inflammatory Arthritis	2	4
Pigmented Villonodular Synovitis	4	8
Normal	13	26
Total	50	100

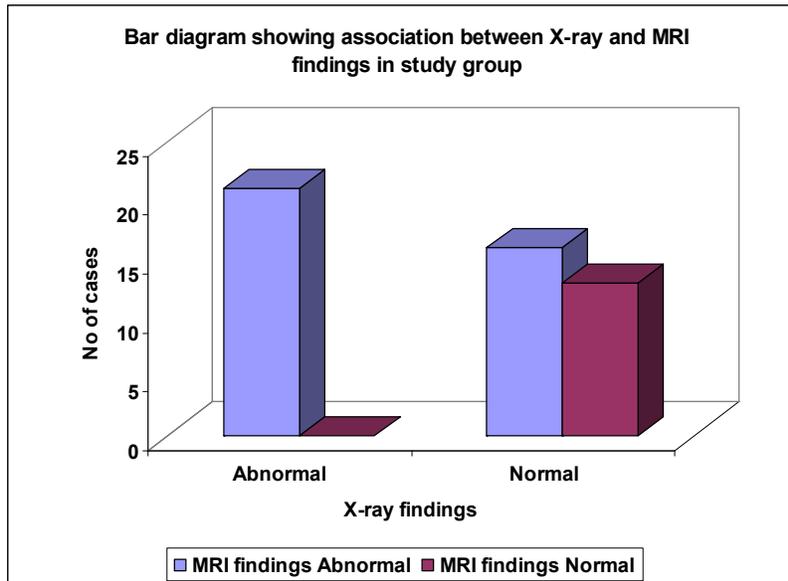
The majority 17 (34%) cases had findings s/o haemophilic arthropathy, 14 (28%) cases had diffuse siderotic synovitis with minimal knee joint effusion, 13 (26%) cases had normal MRI finding, 4 (8%) cases had pigmented villonodular synovitis & two (4%) cases had findings s/o inflammatory arthritis

**Table 5:** Association between X-ray and MRI findings in study group

X-findings	MRI findings		Total
	Abnormal	Normal	
Abnormal	21	0	21
Normal	16	13	29
Total	37	13	50

Chi-square = 7.07, P<0.05 Accuracy = 68%

The above table shows statistically significant association between X-ray and MRI findings in study group



**Table 6:** Association between X-ray and MRI findings in study group

X-ray findings	MRI findings					Total
	Diffuse Siderotic Synovitis With Minimal knee joint effusion	Finding S/O Haemophilic Arthropathy	Finding S/O Inflammatory Arthritis	Pigmented Villonodular Synovitis	Normal	
Epiphyseal Enlargement	0	0	2	0	0	2
Hyperdense Expansion of the Joint Capsule with bony erosion	0	0	0	1	0	1
Minimal Knee Joint Effusion	10	0	0	0	0	10
Widened Intercondylar Notch in Knee Joint	0	8	0	0	0	8
Normal	4	9	0	3	13	29
Total	14	17	2	4	13	50

Out of 50 cases 10 patients who had X-ray findings suggestive of Minimal Knee Joint Effusion had Diffuse Siderotic Synovitis with Minimal knee joint effusion on MRI, 8 patients with MRI findings suggestive of Haemophilic Arthropathy had X ray finding of Widened Intercondylar Notch in Knee Joint, 29 patients had Normal X ray among them 9 patients MRI Findings were suggestive of Haemophilic Arthropathy, 4 patients with Diffuse Siderotic Synovitis with Minimal knee joint effusion, 3 patients with Pigmented Villonodular Synovitis, rest 13 patients had both x ray and MRI normal.

**Table 7:** Severity of disease by Denver in study group

Severity of disease	No of cases	Percentage
0	16	32
I	13	26
II	13	26
III	8	16
Total	50	100

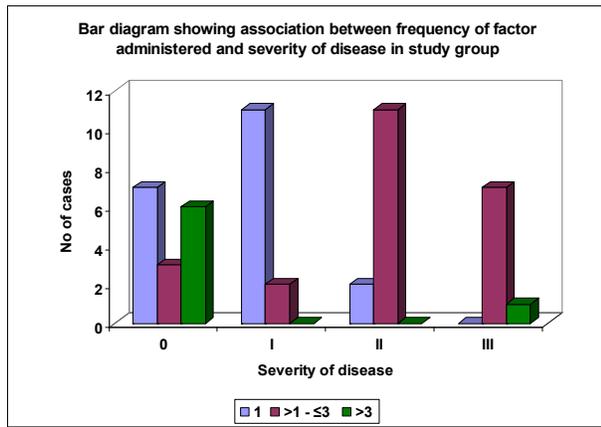
Severity of disease as follows Grade I 13 cases (26 %), II 13 cases (26 %), III 8 cases (16 %) & normal in 16 cases (32%).

**Table 8:** Association between frequency of factor administered and severity of disease in study group

Freq. of factor administered	Severity of disease				Total
	0	I	II	III	
1	7	11	2	0	20
>1 - ≤3	3	2	11	7	23
>3	6	0	0	1	7
Total	16	13	13	8	50

Chi-square = 34.10, P<0.0001

There was statistically significant association between frequency of factor administered and severity of disease in the study group.

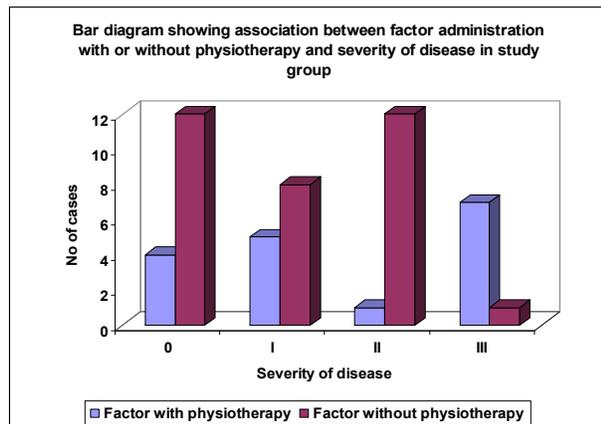


**Table 9:** Association between factor administration with or without physiotherapy and severity of disease in study group

factor administration with or without physiotherapy	Severity of disease				Total
	0	I	II	III	
Factor with physiotherapy	4	5	1	7	17
Factor without physiotherapy	12	8	12	1	33
Total	16	13	13	8	50

Chi-square = 14.91, P<0.005

There was statistically significant association between factor administration with or without physiotherapy and severity of disease in the study group.



**Discussion**

Not much of Indian data is available for comparing the study. So we have analysed the study in a descriptive manner. In this study pain was the major complaint in 42 cases (84%), swelling in 40 cases (80%) followed by restriction of movement in 22 cases (44%). One joint involvement was found in 32 cases and more than one joint involvement was found in 8 cases. Pain was present in all symptomatic cases. Studies conducted in 2007 by Raffini L54 *et al.* found that acute pain, swelling and decreased range of motion were the most common complaints. In a study conducted by Sébastien Lobet *et al.*, [6] it was found that pain onset and local discomfort were the most common signs indicating that bleeding has started. It was observed that the chief complaints of the present study matches with above mentioned studies and knee joint is the most common joint affected.

In the present study 34 % cases had taken factor VIII with physiotherapy and 66% cases received only factor VIII.

In this study 29 cases (58%) had normal X ray findings, 8 cases (16%) had widened intercondylar notch in knee joint, 10 cases (20%) had minimal knee joint effusion, & 2 cases (4%) had epiphyseal enlargement and 1 case (2%) had hyperdense expansion of the joint capsule with bony erosion. A study conducted by, Manco-Johnson *et al.* [7] in 2007 found radiographic evidence of joint damage by age 6 years in some of the subjects who had no or only a few clinical evident hemarthroses.

Bagnolesi P *et al.* [8] in 1993 described classification of the grades of disease generally relies upon X-ray findings which, although reliable in the advanced stages of the disease, appear inadequate in the early stages. In fact, synovial hypertrophy, cartilage erosions and initial subchondral cysts are most often missed on X-ray films.

In this study 17 cases(34%) had finding suggestive of haemophilic arthropathy, 14 cases (28%) had diffuse siderotic synovitis with minimal knee joint effusion, 13 cases(26%) had normal MRI finding, 4 cases(8%) had pigmented villonodular synovitis and 2 cases(4%) had finding s/o inflammatory arthritis. A study conducted by Pergantou H [9] *et al.* in 2006 performed MRI on children with haemophilia who had no obvious signs of arthropathy. They demonstrated early changes in the soft tissues (e.g., synovium and cartilage). These MRI findings indicate that incipient joint damage may occur after very few bleeding episodes. A study by Kilcoyne RF, Nuss R. proves that MRI allows evaluation of soft tissue changes that precede cartilage and bone destruction.

Out of 13 cases with normal MRI, 8 cases were symptomatic and 5 were asymptomatic. Eight cases were less than 5 years of age, 5 cases were more than 10 years of age. Although patients were of more than 10 years age group no MRI findings of arthropathy were present inspite of being symptomatic because of regular factor replacement once in a month in all five cases. Regular factor replacement can help decrease the severity of the disease.

In this study there was statistically significant association between X-ray and MRI findings. Out of 50 cases 10 patients who had X-ray findings suggestive of Minimal Knee Joint Effusion had Diffuse Siderotic Synovitis with Minimal knee joint effusion on MRI, 8 patients with MRI findings suggestive of Haemophilic Arthropathy had X ray finding of Widened Intercondylar Notch in Knee Joint, 29 patients had Normal X ray among them 9 patients MRI Findings were suggestive of Haemophilic Arthropathy, 4 patients with Diffuse Siderotic Synovitis with Minimal knee joint effusion, 3 patients with Pigmented Villonodular Synovitis, rest 13 patients had both X ray and MRI normal. A study conducted by Sierra Aisa C *et al.* [10] in 2014 observed a good positive correlation between X ray and MRI in detecting and locating synovial hyperplasia and erosion of margins in patients with haemophilia. Study conducted by Tamer Özüiker [11] in 2011 *et al.* where they assessed the role of Magnetic Resonance Imaging (MRI) and X-Ray in the evaluation of response to radiosynovectomy (RS) in patients with hemophilic arthropathy & concluded that MRI is a more sensitive tool than plain radiography for evaluating and follow-up of joint disease in persons with hemophilia. In the present study early changes of arthropathy which were missed on X ray were picked up on MRI, so MRI serves as an important tool in screening arthropathy in hemophiliacs.

In this study according to Denver classification, severity of disease was found as follows Grade I 13 cases (26 %), II 13 cases (26 %), III 8 cases (16 %) & normal in 16 cases (32%).

R F Kilcoyne, B Lundin & H. Pettersson<sup>[12]</sup> in 2006 with the establishment of MRI as the imaging method of choice in many cases of hemophilia, the need for an MRI grading system to quantify joint damage has become apparent.

In the present study, all the patients received factor VIII at varied intervals. When frequency of factor administration was compared with severity of disease it showed statistically significant association. Frequent factor administration helps in preventing severity of arthropathy. A study conducted by Karin Knobe and Erik Berntorp<sup>[13]</sup> in 2011 regular replacement therapy with clotting factor concentrates (prophylaxis) is effective in preventing recurrent bleeding episodes into joints and muscles.

Gringeri *et al*<sup>[14]</sup> in 2011 compared the efficacy of prophylaxis with episodic therapy in preventing hemarthroses and image-proven joint damage in children with severe hemophilia A (factor VIII <1%) over a 10-year time period. Hence, this randomized trial has confirmed the efficacy of prophylaxis in preventing bleeding which leads to arthropathy in children with hemophilia, particularly when it is initiated early in life.

In the present series 66% of the patients received only factor VIII without physiotherapy and 34% patients were on both factor VIII and physiotherapy. When these parameters were compared with severity of disease it showed statistically significant association. Physiotherapy along with prophylactic factor administration may prevent the complications in the joints.

A study conducted by Karin Knobe and Erik Berntorp<sup>[15]</sup> in 2011 demonstrated that treatment for haemophilia is frequently prophylactic (particularly in moderate or severe disease) and aims to reduce the frequency and severity of bleeding.

A study conducted by Khriesat *et al*<sup>[16]</sup> in 2000 evaluated the outcome of “on demand” factor VIII replacement with physiotherapeutic intervention in the prevention and treatment of recurrent knee hemarthrosis. In the study all patients received Factor VIII concentrate for 5 days, followed by physiotherapy (PT) program including the quadriceps strengthening exercise. They were followed up for fifteen months, focusing on function, range of motion (ROM), and number of bleeding episodes in the target joint. They concluded Prompt “on demand” therapy with F VIII concentrate with quadriceps strengthening exercise will reduce frequency and complications of knee hemarthrosis and allow full recovery of function.

### Conclusion

All patients of haemophilia are prone for arthropathy so all patients of haemophilia should be screened for arthropathy. In present study it was found that MRI is a more sensitive tool than X ray to detect arthropathic changes. So all patients of haemophilia should undergo MRI.

Frequent factor administration and physiotherapy showed less severe trend of arthropathy.

Severity of arthropathy was less in patients receiving frequent factor administration and physiotherapy. Regular factor administration and physiotherapy reduce the morbidity and disability as complications and disability can be reduced or prevented by early intervention.

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