International Journal of Multidisciplinary and Current Educational Research (IJMCER)
ISSN: 2581-7027 ||Volume|| 5 ||Issue|| 5 ||Pages 26-34 ||2023||

Epidemiological Study of Bleeding Disorders with Orthopaedic Problems, Speed of Haemophilic Arthropathy Progression and Pattern of Joint Involvement

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BACKGRAOUND: Bleeding disorders affects the joint very often. The aim is to assess joint involvement and haemophilic arthropathy of the patients with haemophilia as part of an epidemiologic study from a specialized unit of combined orthopaedics and haematology clinis

METHODS: A retrospective review of the medical records involving the radiological and clinical data over 12-year of follow-up, included adult patients with a moderate or severe bleeding disorder. Osteoarthritis degree and progression of haemophiliac arthropathy was also assessed and checked if any pattern of joint involvement.

RESULTS: A total of 155 patients were included; 130 haemophilia A and 25 B. Most commonly affected joints were knee and ankle, and most common operations were knee arthroplasty and ankle fusion. There was a strong correlation between severity of disease and number of joints affected (Spearman's:0.352, $p < 0.0001$). The time of Kellgren-Lawrence scale progression to next scale was a mean of 34.58 months for knees, 44.46 for ankles. There appeared to be a pattern of joint involvement and the order was ankle first, followed by elbow and knee.

CONCLUSİONS: Bleeding disorders affect the joints frequently and require expensive prophylactic treatment. It appears that there is an order of joint involvement in hemophilia disorder. An increase in regular prophylactic treatment and monitoring could provide significant health care and economic benefits.

I. INTRODUCTION :

Haemophilia, an x-linked condition associated with the deficiency of factors VIII or IX, is the most common bleeding disorder Rizzo et al.[1)], White and Lee[2)], Fijnvandraat et al.[3)] Most common complication is musculoskeletal bleeding. In moderate to severe cases, haemophilia often leads to recurrent bleeding into the joints Liddle and Rodriguez-Merchan.[4)] The severity of haemophilia is graded according to the amount of the deficient coagulation factor present in the circulation White et al. [5)] When the concentration is between 1 and 5%, moderate, below 1%, it is a severe disease Liddle and Rodriguez-Merchan [4)], White et al. [5)]

Haemarthrosis may occur spontaneously or arise subsequent to trauma. The presence of blood in an affected joint provokes a synovial tissue reaction, leading to damage to the cartilage. This eventually causes a progressive and irreversible arthropathy Rizzo et al.[1)], Manco-Johnson et al.[6)] Recurrent, painful and destructive bleeds into the same joint are a characteristic feature of 'target joint', Napolitano et al.[7)] At advanced stages, arthropathy is characterised by presence of pain, a reduction in the range of motion, malalignment, instability and severe functional impairment Rizzo et al.[1)] In the diagnosis of arthropathy, standard X-rays might show local osteoporosis, subchondral irregularities and cysts, joint-space narrowing, loss of the physiological axis, and osteophytes, Rizzo et al.[1)], Petterson et al.[8)] Kellgren - Lawrence (KL) classification system is most commonly used clinical diagnostic tool for diagnosis of OA with high inter-observer correlation especially for knee, Kohn et al.[9)] Ultrasonography can be used to detect hypertrophy of the synovium. Magnetic resonance

imaging is, however, the gold standard for diagnosis, Rodriguez-Merchan and Valentino. [10] The early recognition of bleeding episodes is essential, and the mainstay of treatment in haemophiliac arthropathy (HA) is to prevent or treat hemarthroses for avoiding inflammatory response and joint distruction, Liddle and Rodriguez-Merchan,[4] Napolitano et al.[7] Haematological prophylaxis, lifestyle modification, and physical and medical therapy may be useful for prevention of arthropathy, Carulli. [11] Patients with chronic synovitis may be treated effectively by radiosynovectomy (RS), Vanderhave.[12] Intra-articular injections are generally useful, Carulli et al., [13] when non-operative treatment is not enough, surgery is needed, which includes synavectomy, soft-tissue release for contracture, arthroplasty and joint fusion, Rizzo et al.[1], Liddle and Rodriguez-Merchan; [4] however, these are associated with a high risk of bleeding and infection, and must be performed in tandem with factor replacement therapy, Rodriguez-Merchan and Valentino. [10]In the literature, there is a lack of epidemiological studies on bleeding disorders with orthopaedic involvement reviewing prophylaxis monitoring, with only two studies found – one from India, one from Egypt, Tonbary et al, [14], Kar et al.; [15] neither of these were relevant to the group under investigation in this study. Also, to our knowledge, there is no study on progression of hemophilic arthropathy and pattern of joint involvement in the literature.

Given the potential to reduce the incidence and severity of the orthopaedic conditions, the primary aim of the study was to assess and explore joint involvement and haemophilic arthropathy of the patients with haemophilia as part of an epidemiologic study from a specialized unit of combined orthopaedics and haematology clinics. This was achieved by assessing the medical records in a specialised haematology service unit in a university hospital in the UK.

II. MATERİALS AND METHODS

Study Design : This was a retrospective observational review of the medical records of existing patients attending a specialised unit in a university hospital involving over 12 years of follow-up data. Ethical approval was obtained from the local committee. The inclusion criteria were any adult patient, aged over 18 years, with moderate or severe bleeding disorder and an orthopaedic condition. The sample size was 140 patients with haemophilia A and 45 patients with haemophilia B (total = 185 patients). Patients with inadequate data were excluded (30 patients).

Data collected included type and severity of hemophilia, prophylaxis use, concomitant diseases, affected joints, severity of osteoarthritis, athropathy progression, type of orthopaedic operations and regular x-ray record of especially knees and ankles for more than 10 years. However, we did not include any details of treatment changes, rehabilitation or outcome scores as this was not aim of the current study. The centre had a joint clinic between haematology and orthopaedics which included clinical examination and radiological evidence, orthopaedic treatments and at least yearly regular follow-up. All those records and electronic data were used for this study. Kellgren - Lawrence (KL) classification was used for radiological assessments of osteoarthritis grade using the descriptions in table 1, Schiphof.[16] The same researcher assessed all the x-rays to have consistency in KL scale assessment.

We also assessed joint involvement and the progression of haemophiliac arhtropathy over the years using patients' initial symptoms and x-rays related to the relevant joints. When assessing the prevalence of joint involvement, we analysed all the clinic letter including symptoms and all x-rays in the hospital intranet system from the patients regular clinic attendance to decide which joint involved first, second and so forth. When assessing progression arthropathy, for each individual, all the pre-operative xray analysed by using KL table, the interval between one KL grade to the next one was calculated in months. This gave us progression of KL grade approximately for each osteoarthritis degree. All of the patient identifiers were removed, and the patient data were anonymised. The data were transferred to an Excel spreadsheet for statistical analysis.

Statistical Analysis : For the statistical analysis, Social Science Statistics, Social Science [17] was used. Descriptive statistic was used to assess demographic data, evaluation of joint involvements, frequency of x-rays taken, Spearman's correlation test was used to analyse the correlation between KL scale progression and prophylaxis treatment and Pearson's test was used for correlation between number of joints affected and number of operations.

III. RESULTS

Ten patients with haemophilia A and 20 patients with haemophilia B were excluded from the study due to their inadequate records, leaving 130 patients with haemophilia A and 25 patients with haemophilia B included in the study. In the haemophilia A group, there were 20 (15.4%) moderate and 110 (84.6%) severe cases, and in

haemophilia B group, there were nine (36%) and 16 (64%) moderate and severe cases respectively. Table 2 shows demographic data. The greater number of patients diagnosed with haemophilia A compared to haemophilia B was expected. The gender split was consistent with the genetic factors associated with haemophilia. Among all of the patients, there was only one female with haemophilia B, the rest being male. HCV and HIV were the conditions most frequently observed in patients with haemophilia and orthopaedic involvement. The mean number of joints involved in patients with haemophilia A was 2.41. In haemophilia B patients, there was a lower incidence of involvement, at 2.14 joints. The most frequently affected joints were knee in haemophilia A patients, and ankle in haemophilia B patients. The wrist had the lowest involvement consistently across both groups (table 3). Most frequently performed procedures were TKR and ankle fusion. THR was equally as common as ankle fusion among the haemophilia B patients. However, hip involvement was disproportionate in prevalence compared to the ankle, with 16% compared to 44%, respectively (table 4).
An average of 38% of the patients had undergone an orthopaedic operation between both groups of patients, which translated to 36.9% and 44% for the haemophilia A and B patients, respectively.

X-ray Assessments: All the patients (155) included in the study had x-ray for their affected joints. The patients with regular preoperative x-rays were analysed for the purpose of arthropathy progression (only for knee and ankle). There were 32 patients who had longer-term regular x-rays for their 59 ankle and or knee joints Many patients with moderate and severe haemophilia showed advanced arthritis (table 5). This table shows Kellgren - Lawrence (KL) grades of both Haemophilia A and B patients with affected knee and ankle joints and the number of the joints in each KL scale. The 2nd and 3rd rows includes all the patients with knee and ankle joints and last x-rays of the patients just before the operation if they were operated and last x-rays in the x-ray system if they were not operated. Patients were followed up with x-ray for a minimum of 24 months and a mean of 60.98 months(24-122). X-rays were taken one for nearly every year for each joint. The frequency x-rays taken was one in every 13.3 months for knee and 14.6 months for ankle (table 6). These figuresincluded only pre-operative x-rays, not included the postoperative x-rays.

Arthropathy progression : For the knees, KL progression to next scale took a mean of 34.58 months (10-58) when considering all the scales and the median was 32 months. For the ankles, this figure was 44.46 months (9-108), median was 48 months. For each scale progression, table 6 shows the details. For the patients who were not on prophylaxis, the duration of KL progression to next scale was shorter with a mean of 29.25 months (median 24), comparing to the patients on prophylaxis, which was a mean of 47.48 months (median 47.25). However, there was no meaningful correlation between KL scale progression and prophylaxis treatment (Spearman's: rs = 0.32913, p (2-tailed) = 0.12514), possibly due to low number of patients who were not prophylaxis (16.66%).

26 out of 32 patients who had longer-term regular and multi-joint involvements and very regular follow-up, we noticed a pattern orsequence of involvement of the joints(table 7). Ankle was the first affected joint mostly in those who had multi-joint involvement. According to the table, 2. mostly affected joints were knee and elbow. However, elbow involvement was mostly before knee involvement. The number of the hip involvement was not enough to draw any conclusion on this. Despite the limitation in the number of cases, it appears that there is an order in the involvement of the joints appeared in haemophilia patients for the mostly affected 3 joints. According to this, it appears that haemophilia is affecting ankle joint first, followed by elbow, and then the knee in our patient group. Table 7 shows that there was also a strong correlation between severity of the disease and the number of the affected joints for haemophilia A but not between the number of the joints affected and the number of the operation for affected joints. On the other hand, there was a moderate correlation between the number of the joints affected and the number of the operation for affected joints for haemophilia B.

Prophylaxis : 97 patients (74.6%) were recorded as being treated with prophylaxes for haemophilia A, as per recommendations of the World Federation of Hemophilia, Srivastava.[18)] Nineteen patients (76%) were recorded as being treated with prophylaxis for haemophilia B. Prophylaxis were Advate®, Refacto®and Novoeight®most commonly used for haemophilia A and Benefix® for haemophilia B patients. Usual dose was 25 to 40 units/kg of body weight three times per week. However, this was tailored according to the severity or needs of the patients (weight of the patients x the rise wanted by clinician) / 2. The rise wanted depended on the clinical situation and the severity. For example, a severe patient pre surgery or muscle bleed could be a rise of 100% needed. A person with 10% normal circulating levels might be a 90% rise. For surgery, the immediate dose would be as above pre op, dropping to a half of that dose post op, depending on clinical circumstances.

IV. DİSCUSSİON

Bleeding disorders (haemophilia , vWD) are classified according to their severity – mild, moderate and severe. Replacement of the deficient factor is the mainstay of treatment for bleeding episodes, according to the type and severity of the bleed. Patients with bleeding disorders require expensive prophylactic treatment. In our study, this was recorded in only 74.6% of haemophilia A patients and 76% of haemophilia B. Patients with bleeding disorders commonly attend orthopaedic clinics with secondary complications. Certain studies have described such orthopaedic complications and the epidemiology of bleeding disorders with orthopaedic involvement; however, there were no subcategories in these epidemiological studies or measure of prophylaxis use.

Joint involvement : A prospective study based on European countries reported the involvement of a total of 1376 target joints, with 58.2% of patients reportedly diagnosed with one or more target joints. Target joints exclusively in the lower body were the most commonly reported (n = 371 patients, 52.3%). Our study showed a mean of 2.48 joint involvements in the cases analysed, mainly lower limb with 66.7%.

There was limited information in the literature on the ratio of orthopaedic operations in hemophiliac patients with joint involvement. A large study of European countries showed more than four in 10 patients who had undergone one surgery, or more, on a target joint, O'Hara.[19)] However, that study included joint aspiration (arthrocentesis) in the number of surgeries, and this was the most common procedure (200 patients, 28% of the target-joint cohort) O'Hara.[19)] Meanwhile, this should be avoided in patients with allo-antibody inhibitors due to the increased risk of bleeding complications, and before aspiration, adequate factor replacement therapy should be administered Napolitano et al.[7)] In our series, we did not count aspiration in the number of operations. An average of 38% of the patients had undergone an orthopaedic operation, in total, which was 36.9% and 44% for haemophilia A and B patients, respectively, and these patients had moderate or severe disease as we excluded the patients with mild disease. We believe that this operation rate is low for moderately and severely diseased haemophiliac patients. According to Napolitano et al., [7)] the descending order of incidence of effects was knees (contributing more than 50% to all bleeding events), elbows, ankles, shoulders and wrists. In our study, the knee was followed by the ankle, then elbow, hip and wrist (Table 2).

In the current study, the most common operations were TKR and ankle fusion, followed by arthroscopy and debridement in haemophiliac patients. For ankle problems, RodriguezMerchan stated that the first line of treatment should be radioactive synovectomy (RS), Rodriguez-Merchan.[20)] Radioactive and chemical nonsurgical synovectomies are currently used in developing countries more commonly, where the required clotting factor replacement concentrates are not available, Napolitano et al.[7)] In our hospital, clotting factor replacement concentrates were readily available and there was no documentation of RS in our data. The second line of treatment was reported to be arthroscopic synovectomy and, in advanced cases, arthrodiastasis, arthrodesis or ankle replacements were recommended, Rodriguez-Merchan.[20)] For knee involvement, similar approachesto those used for the ankle were employed, starting with RS and arthroscopic debridement and progressing to TKR, Rodriguez-Merchan.[20)] In another case-series, with 80 patients, the most had TKR (43/59), followed by THR (15/16) and arthroscopic synovectomy (13/15), but no ankle fusion was reported, Hirose et al. [21)] In a study from the Italian Hemophilia Centre, Tagariello [22)] showed that the patients with haemophilia A had a three-fold higher risk of undergoing joint arthroplasty when compared to haemophilia B. In terms of knee replacement, our study showed this ratio to be 20% for the patients with haemophilia A and 14 % for haemophilia B. Also, the initial part of the current study which was previously published showed high ratio of bilateral knee replacement in the same group of patients, Bayam et al. [23)]

KL Scale : For assessment of knee arthritis and TKA indications, plane x-rays are sufficient mostly Rizzo et al.[1)], Petterson et al.[8)] [1 8][1, 8]. KL classification system is most commonly used clinical diagnostic tool for diagnosis of OA and inter-observer correlation for knee is quite high Kohn et al.[9)] KL degree 4 is the end stage of the disease, Guermazi et al. [24)] and described as established loss of joint space, cartilage deformation, osteophytes and sclerosis, Kohn et al.[9)] This classification was accepted by the World Health Organisation (WHO) as the radiological definition of OA for the purpose of epidemiological studies Schiphof. [16)]

There was no literature on speed of progression of arthropathy either in normal population or hemophiliac patients and no order of joint involvement for hemophiliac patients. General approach in the literature was to describe the most commonly involved joints. In the current study, on x-ray assessment, KL progression speed to the next scale was less than 3 years for the knees (34.58 months) and less than 4 years (44.46 months) for the ankles. It might be expected to have faster deterioration of arthropathy in hemophiliac patients when comparing with the normal aging osteoarthritis population, due to recurrent intraarticular bleeding especially when it is not

well-controlled with prophylaxis. According to Napolitano and colleagues, the most commonly affected joint is the knee and this is followed by elbow, ankle, shoulder and wrist with decreasing order Napolitano et al.[7] Similarly, Knope et al.'s figures were knees (45%), followed by the elbows (30%), ankles (15%), shoulders (3%), and wrists (2%) for the patients not treated with prophylaxis. However, they observed that the ankle joint accounts for the most common site of bleeding for the patients on prophylaxis, Knobe and Berntorp. [25] Another study also shared the same conclusion about the ankle being more common affected joint but they added that elbow was more frequently affected than the knee, Stephensen et al. [26] [26]. In our study, we did not look at only the frequency of joint involvement but also the order of involvement since the beginning of the disease by analysing our long term data.

Prophylaxis : In developed countries, since the introduction of prophylaxis, orthopedic problems related to haemophilia have been reduced, Tobase et al., [27] and the development of factor concentrates has resulted in prolonged life expectancy in haemophilia patients Hirose et al.[21] As a separate matter, during TKR, the application of intra-articular tranexamic acid has been reported to give satisfactory results in controlling bleeding Rodriguez-Merchan.[20] A study showed the ratio of prophylactic treatment in haemophiliac patients to be 29%, based on a study in the Netherlands of 75 patients with moderate haemophilia, den Uijl et al. [28] Another study, analysing the US Hemophilia Treatment Center Network and the Centers for Disease Control and Prevention surveillance registry, including more than 6000 individuals, revelealed that prophylaxis treatment had increased from 31% overall in 1999 to 59% in 2010 and rates of joint bleeding in participants on prophylaxis had fallen 22%, from a mean of 3.03/6 months in 1999 to 2.36 in 2010, Kruse-Jarres.[29] A prospective observational study in severe haemophilia A and B patitents across five European countries (France, Germany, Italy, Spain, UK), undertaken in 2015, and with a total of 1376 target joints, found that the amount of patients receiving treatment prophylactically was 58% (n = 708, 57.7%), O'Hara.[19] Prophylaxis that can convert severe haemophilia into a moderate condition is important in preventing long-term complications, Manco-Johnson et al, [6] Rodriguez-Merchan. [30] Our results show that approximately 75% of all patients in both groups included in the study had been prescribed prophylaxis, but we included only moderate to severe haemophilia patients.

Limitations: This was a retrospective study of existing patient records. The electronic records and clinical letters had a lack of accurate documentation related to the patients' background and sport activities. Follow-up period were not perfectly regular. Therefore, the arthritis progression could be considered only as preliminary result and a study with higher number of patients in each group are needed to draw definite conclusion on the progression period of arthropathy and the order of the joint involvement. This study did not include patients with mild hemophilia because this condition has much less frequency of joint involvement.

Strengths: This study was based on records from a regional centre for hemophiliac patients, with well-established documentation, providing a relatively large number of case series.

There were no conflicts of interest attached to this study.

In conclusion, we believe this study revealed valuable information on joint involvement in the patient with hemophilia. It appears that there is an order of joint involvement which is ankle first, followed by elbow and then knee. Progression of arthropathy in hemophilia patients is probably much faster than normal population.
The study showed that the severity of the disease correlated with the number of joints affected. The rate of hemophilia prophylaxis in our study was relatively higher than documented in the literature. We believe that our operation rate was low for moderate and severe hemophiliac patients, and a high percentage of patients treated with prophylaxis might have helped prevent a higher incidence of joint involvement and this may indicate the importance of prophylaxis. In return, this could provide a significant contribution to patient care.

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Table 1: Kellgren - Lawrence (KL) classification, Schiphof.[16)]

Kellgren - Lawrence (KL) classification	Changes	Description
Grade 0	none	definite absence of x-ray changes of osteoarthritis
Grade 1	doubtful	doubtful joint space narrowing and possible osteophytic lipping
Grade 2	minimal	definite osteophytes and possible joint space narrowing
Grade 3	moderate	moderate multiple osteophytes, definite narrowing of joint space and some sclerosis and possible deformity of bone ends
Grade 4	severe	large osteophytes, marked narrowing of joint space, severe sclerosis and definite deformity of bone ends

Table 2: The demographic data associated with the sample of 155 patients affected by haemophilia A or B, and the rate of associated disease (HCV and HIV). (N: number of the patients)

Table 2. Demographic Data and Associated Disease		
	Haemophilia A	Haemophilia B
Number of patients	130	25
Age (years)	41 (16–81)	46.2 (21–76)
HCV (N)	33.1% (43)	56% (14)
HIV (+) (N)	13.1% (17)	8% (2)

Table 3: The proportion of commonly affected joints(haemophilic arthopathy) in haemophilia A and B patients and mean number of affected joints in the patients . (IQR: interquartile range, SD : Standard deviation)

Table 3. Commonly affected joints in haemophiliac patients							
	Knee	Ankle	Elbow	Shoulder	Hip	Wrist	Mean number of joints
Haemophilia A: % (number of patients)	37.7% (49)	36.9% (48)	30.8% (40)	10.8% (14)	9.2% (12)	1.5% (2)	2.41 (median:2, IQR:2)
Haemophilia B: % (number of patients)	40% (10)	44% (11)	28% (7)	12% (3)	16% (4)	4% (1)	2.14 (SD: 1.19)

Table 4: Orthopaedic procedures of the joints carried out on the patients with haemophilia A and B.

Table 4. Commonly performed orthopaedic operations in haemophiliac patients				
	Knee	Ankle	Hip	Elbow
Haemophilia A: % (number of patients)	TKR 20% (26)	Fusion 13.8% (18)	THR 5.4% (7)	Replacement 1.5% (2)
	Arthroscopy 1.5% (2)	Arthroscopy 1.5% (2)	0	Arthroscopy 1.5% (2)
	Synovectomy 0.75% (1)	Debridement 0.75% (1)		
	Revision TKR 0.75% (1)			
Haemophilia B: % (number of patients)	TKR 14% (4)	Fusion 12% (3)	THR 12% (3)	0
		Arthroscopy 0.75% (1)		

Table 5: The number of the joints in each Kellgren - Lawrence (KL) Scale. Raw 2 and 3 : last KL Scales of all the knees and ankles.

KL Scale/joint	Grade 4	Grade 3	Grade 2	Grade 1	No preoperative x-ray	Total number of joints
last x-rays of the knee	24	7	6	4	18	59
last x-rays of Ankle	15	22	10	10	2	59

6: Frequency of the x-rays taken for knee and ankle

Frequency of X-rays (knee – ankle)	Ankle	Knee
Mean (months)	14.6	13.3
Median (month)	15	12
Mode (month)	12	12
Standard Deviation (SD)	3.84	3.79
Interquartile range	5.55	3.75

Table 7: The correlation between the severity of haemophilia disease, the number of affected joints and number of operation

Table 7. Correlation between haemophilia A or B and number of joints affected		
Relationship	Between severity of disease and number of joints affected (Spearman's)	Between number of joints affected and number of operations (Pearson's)
Haemophilia A	R = 0.352, p = 0.00007	R = 0.477 R^2 = 0.227
Haemophilia B	R = 0.278, p = 0.19	R = 0.655 R^2 = 0.429
Significance	Strong for haemophilia A, weak for haemophilia B	Weak for haemophilia A, moderate for haemophilia B