Clinical and functional evaluation of the joint status of hemophiliac adults at a Brazilian blood center

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Background: *Hemophilia is a potentially disabling condition as hemophilic arthropathy develops early in life and is progressive, especially in patients treated in an on-demand regime.*

Objective: *This study aimed to describe the structural joint status and the functional independence score of hemophiliac adults and correlate structural damage with the functional deficits found in these patients.*

Methods: *Hemophiliacs at the Juiz de Fora Regional Blood Center – HEMOMINAS Foundation, aged 18 years and over and treated in an on-demand regime, were clinically evaluated in respect to structural joint damage using the World Federation of Hemophilia Physical Examination Scale (WFH-PE) and functional deficits using the Functional Independence Score in Hemophilia (FISH). The Spearman rank test was used to evaluate the correlation between the two scores.*

Results*: Thirty-nine patients were evaluated. The mean age was 36.8 years. Target joints were detected in 69.2% of patients studied. The mean Physical Examination Scale and Functional Independence Score were 16.87 and 25.64, respectively. Patients with mild hemophilia showed no significant joint involvement. Patients with severe or moderate hemophilia had similar results regarding structural damage (p-value < 0.001) and functional deficits (p-value = 0.001). There was statistical significance in the correlation between the two scores (r = -0.850; p-value = 0.01).*

Conclusions*: The World Federation of Hemophilia Physical Examination Scale and Functional Independence Score in Hemophilia may be useful to clinically assess structural joint damage and functional deficits in hemophiliacs as the tools are inexpensive and easy to administer and may be able to detect hemophilic arthropathy, which results from recurrent hemarthrosis and is common in the population studied.*

Keywords*: Hemophilia A; Hemophilia B; Joint diseases; Disability evaluation; Hemarthrosis/rehabilitation*

Introduction

Hereditary hemophilia is the result of genetic alterations that cause deficiencies in clotting factors VIII or IX, hindering the process of hemostasis and predisposing hemophiliacs to spontaneous or post-traumatic bleeding. The main clinical manifestation is intra-articular bleeding (hemarthrosis), which begins even in childhood[1-3]. After an episode of hemarthrosis the joint can return to its normal functional state. However commonly there is a recurrence of bleeding, causing inflammatory and enzymatic changes in the synovial membrane[4]. The joints evolve to a state of fibrosis and contracture, with loss of mobility[5], causing deformities and disabilities in patients even within the first decades of life[6].

The treatment of hemophilia is based on the intravenous replacement of the deficient clotting factors. Infusions can be administered as prophylaxis, preventing bleeding episodes and reducing the incidence of arthropathies[7-10], or on demand, i.e., after each bleeding episode. Due to the high cost of clotting factor products, only in late 2011 did the Ministry of Health announce the implementation of primary prophylaxis in Brazil, benefiting children up to 36 months of age with severe hemophilia (or moderate, with a level of clotting factor VIII or IX less than 2%)[11].

Since, under the episodic treatment regime, the development of arthropathy seems inexorable[6,12], rehabilitation measures and methods to assess the clinical condition of the joints are essential to monitor the progression of the arthropathy, to establish or modify treatment protocols, and to assess the effectiveness of therapeutic interventions[13-15]. In this context, the present study aimed to clinically evaluate the major joints of adults with hemophilia with regard to structural damage and functional deficits, and to correlate these findings.

Methods

Study design and data collection

This was an observational, cross-sectional study, conducted at the HEMOMINAS Foundation, Regional Blood Center of Juiz de Fora (HRJF), Minas Gerais after approval by the institution's Research Ethics Committee. Informed consent was obtained from

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all patients. The inclusion criteria were: male, aged 18 years or older, and a level of clotting factor VIII or IX less than or equal to 30%. Of the 60 patients eligible for the study, one was excluded before the start of the study due to severe cognitive impairment resulting from a central nervous system hemorrhage; 13 were not located due to outdated records and seven refused to participate in the study. Thus, between June and November 2011, 39 patients with hemophilia were evaluated, all treated under the on-demand protocol.

For the purposes of this study, patients were interviewed about demographic and socioeconomic data (age, race, education, marital status, main occupation, personal and family income, receipt of social security benefits) and from medical records, data were collected on hemophilia and comorbidities (type and severity of hemophilia, presence of a clotting factor inhibitor, presence of infection with hepatitis B virus, hepatitis C, and human acquired immunodeficiency virus, target joints) and on the treatment of the coagulopathy (age at diagnosis, participation in the emergency home infusion program, physical activity habits, physical therapy and clotting factor consumption in the previous 12 months).

Participants were evaluated according to the recommendations of the World Federation of Hemophilia (WFH). The WFH Physical Examination Score (WFH-PE) and the Functional Independence Score in Hemophilia (FISH) were applied by a single duly qualified examiner.

World Federation of Hemophilia physical examination scale

This scale is an instrument developed in the 1980s to evaluate hemophilic arthropathy. It is still widely used[16] because it is easy to perform and capable of providing an extensive musculoskeletal assessment[4]. A tape measure and a goniometer are used in the examination of the knees, ankles, elbows, and hips for the presence of edema, atrophy, crepitus, flexion contractures, axial deformities, loss of range of motion and instability; points are assigned to each finding, according to severity and are summed. A score of zero denotes normal joints; 68 points corresponds to the worst level of arthropathy[17,18].

Functional Independence Score in Hemophilia

This score was developed to measure the functional independence of people with hemophilia. FISH is based on observing the performance of daily life activities. Patients are assessed for their ability to perform eight tasks, divided into three categories: self-care (eating, grooming, bathing and dressing), transfers (chair and squatting) and mobility (walking, going up stairs and running). The activities were clearly defined by the authors of the instrument to reduce inter-observer variance and graded from 1 to 4, according to the assistance required to perform the task as follows: 1) the individual is unable to perform the activity; 2) assistance or adaptation is needed to perform the activity; 3) the activity is performed, but the individual has discomfort; and 4) the activity is performed normally. The scores achieved in each task are summed giving a total from 8 to 32 points with 32 indicating the highest level of functional independence[19,20].

The purpose of including 'running' was to increase the detection capabilities of the assessment tool, especially for patients with less severe joint damage[20]. However, in this study carried out at the HRJF, it was not possible to assess the participant's capacity to run as the examination was performed in a doctor's office. In an attempt to compensate for this obstacle, patients were shown an expanse of 50 meters in the area outside the blood center, and were asked if they could cross it running, presenting them the four performance options described in the tool. The patients responded without hesitation.

Statistical analysis

Initially, the Kolmogorov-Smirnov test with Lilliefors correction was performed, which revealed the non-normality of the data. So the non-parametric Mann-Whitney U test was applied to compare the mean WFH-PE and FISH scores according to the severity of hemophilia. Spearman correlation analyses were conducted to evaluate the relationship between WFH-PE, FISH, patient age, and consumption of clotting concentrate in the previous 12 months. Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS, version 15) program.

Results

Thirty-nine patients were evaluated. Participant ages ranged from 18 to 79 years [mean = 36.8; standard deviation (SD) = 16.8 years]. Other demographic and socioeconomic characteristics of the patients are shown in Table 1.

Table 1 - Demographic and socioeconomic characteristics of patients with hemophilia at the Regional Blood Center of Juiz de Fora

Variable	n	%
Age		
18 to 29 years	17	43.6
30 to 59 years	17	43.6
60 years or over	5	12.8
Self-reported skin color		
White	23	59.0
Brown/ light-brown/ mulatto	11	28.2
Black	3	7.7
Indigenous	2	5.1
Distance between home and blood center		
0 to 30 km	18	46.2
More than 30 km	21	53.8
Schooling		
0 to 4 years	9	23.1
5 to 8 years	9	23.1
9 to 11 years	14	35.9
12 years or more	7	17.9
Occupation*		
Student	13	
Employed formally / informally	11	
Retired (age or due to illness)	24	
Without declared occupation	1	
Social security benefits due to hemophilia		
Yes	20	51.3
No	19	48.7

*some patients belonged to two or more groups.

Patient health conditions and characteristics of the treatment received

Of the 39 participants, 33 had hemophilia A and 6 had hemophilia B. In eight cases (20.5%) the hemophilia was classified as mild (level of factor VIII or IX between 5 and 30%), in 16 (41%) as moderate hemophilia (level of factor VIII or IX between 1 and 5%) and in 15 cases (38.5%) as severe hemophilia (level of factor VIII or IX < 1%).

Age at diagnosis ranged from 0 to 67 years with the diagnosis being made after three years of life in 58.8% of the cases. Comorbidities reported by patients were: asthma (10.3%), arthritis (2.6%), cancer (2.6%), heart disease (2.6%), depression (12.8%), hypertension (17.9%), chronic lower back pain (15.4%) and smoking (28.9%); 66.7% were considered sedentary and 15.4% had a body mass index greater than 25 kg/m^2.

The records of four patients (10.5%) registered seropositive for human immunodeficiency virus (HIV), 22 (57.9%) for hepatitis B virus (HBV), and 22 (57.9%) for hepatitis C virus (HCV). Of 29 participants who had up-to-date test records, the presence of clotting factor inhibitor was detected in only one patient with hemophilia A and in no patients with hemophilia B.

Among the 33 patients with hemophilia A, the consumption of clotting factor VIII concentrate in the previous 12 months was quite variable as shown in Table 2. Of the 31 patients with severe or moderate hemophilia, 22 (70.96%) were participating in the home infusion program of clotting factor concentrates in emergency situations.

Table 2 - Consumption of factor VIII concentrate in patients with hemophilia A in the previous 12 months

Severity of hemophilia	Consumption of factor VIII concentrate (IU)		
	Minimum	Maximum	Mean
Mild (n = 7)	0	25,500	4,321.43
Moderate (n = 14)	0	198,250	51,625.00
Severe (n = 12)	14,750	174,250	63,683.33

IU: international units

Clinical evaluation of structural joint status and functional independence

In 69.2% of the patients, target joint presence was detected (87.1% of the patients with severe or moderate forms of coagulopathy), which indicates, at least, the first stage of hemophilic arthropathy[5]. However, only eight participants in this study (20.5%) had received physiotherapy sessions in the previous 12 months even though the benefits of physical therapy for the rehabilitation of these patients have been demonstrated[11]. When the other 31 participants were asked about the reasons that led them not to seek physiotherapy, 16 (51.6%) considered the approach unnecessary, four (12.9%) believed that physical therapy could worsen the joint symptoms, another four said they did not have free access to a physiotherapy service in the area where they lived, two (6.45%) claimed that there had been no medical recommendation and five patients (16.1%) cited other reasons or did not know how to respond.

The mean WFH-PE score was 16.87 (standard deviation 9.49). Table 3 presents the clinical findings in the joints assessed using the WFH-PE scale. Patients with mild hemophilia showed no resulting joint damage from hemophilia. Three of them (18.75%) were scored only on the crepitus on motion item, which, alone, is not indicative of hemophilic arthropathy. Table 4 shows the results of the evaluation using the WFH-PE scale according to the severity of hemophilia.

Table 4 - Joint assessment using the World Federation of Hemophilia Physical Examination Scale (WFH-PE) by severity of hemophilia

Severity of hemophilia	Valid n	Minimum	Maximum	Mean	Standard deviation
Severe	15	15	34	20.67	6.70
Moderate	16	4	29	20.19	7.54
Mild	8	1	6	3.13	1.72
Total	39	1	34	16.87	9.49

There was no statistically significant difference in the mean WFH-PE scores between patients with moderate and severe hemophilia (15.47 vs. 16.50; p-value = 0.752) but there was a significant difference when comparing the average scores achieved in the structural joint damage assessments of patients with mild hemophilia to the average of the other patients (4.81 vs. 23.92; p-value < 0.001).

The score of the WFH-PE tool showed significant statistical correlation with the age of the patients with moderate (r = 0.51; p-value = 0.04) or severe (r = 0.54; p-value = 0.03) hemophilia, but not with the age of the patients with mild hemophilia (r = 0.41; p-value = 0.30), nor with the consumption of clotting factor in the previous 12 months regardless of the severity of hemophilia.

The mean score of the FISH instrument was 25.64 (SD: 6.09). Seven out of eight patients with mild hemophilia achieved the maximum functional independence score. Only one elderly patient reported that he would find running and bathing uncomfortable. Additional results from the FISH assessment are shown in Tables 5 & 6.

There was no statistically significant difference between patients with severe and moderate hemophilia in terms of the mean functional independence score (16.37 vs. 15.66; p-value = 0.827), yet the assessment results for patients with mild hemophilia were significantly better when compared to those of the other participants (32.25 vs. 16.84; p-value = 0.001).

FISH showed a good correlation with the age of patients with severe (r = -0.63; p-value = 0.01) and moderate (r = -0.55; p-value = 0.02) hemophilia, but not with the age of patients with mild hemophilia (r = -0.08; p-value = 0.84) nor with the consumption of clotting factor concentrate in the previous 12 months regardless of the severity of hemophilia.

The Spearman correlation coefficient between the WFH-PE and FISH scores was -0.850 (p-value = 0.01).

Table 3 - Clinical joint findings of patients with hemophilia using the World Federation of Hemophilia - Physical Examination Scale (WFH-PE)

Joint	Severity of hemophilia											
Finding	**Severe n = 30 n (%)**	**Moderate n = 32 n (%)**	**Mild n = 16 n (%)**	**Severe n = 30 n (%)**	**Moderate n = 32 n (%)**	**Mild n = 16 n (%)**	**Severe n = 30 n (%)**	**Moderate n = 32 n (%)**	**Mild n = 16 n (%)**	**Severe n = 30 n (%)**	**Moderate n = 32 n (%)**	**Mild n = 16 n (%)**
Swelling												
None	24 (80)	22 (68.7)	16 (100)	26 (86.7)	25 (78.1)	16 (100)	26 (86.7)	25 (78.1)	16 (100)	-	-	-
Present	6 (20)	10 (31.3)	0	4 (13.3)	7 (21.2)	0	4 (13.3)	7 (21.9)	0	-	-	-
Muscle atrophy												
None or minimal	13 (43.3)	21 (62.6)	16 (100)	23 (76.7)	23 (71.9)	16 (100)	16 (53.3)	21 (65.6)	15 (93.7)	-	-	-
Present	17 (56.7)	11 (34.4)	0	7 (23.3)	9 (28.1)	0	14 (46.7)	11 (34.4)	1 (6.3)	-	-	-
Axial deformity												
Normal	9 (30)	7 (21.9)	13 (81.2)	-	-	-	9 (30)	11 (34.4)	7 (43.7)	-	-	-
Minimal	12 (40)	18 (56.2)	3 (18.8)	-	-	-	18 (60)	21 (65.6)	9 (56.3)	-	-	-
Severe	9 (30)	7 (21.9)	0	-	-	-	3 (10)	0	0	-	-	-
Crepitus on motion												
None	6 (20)	9 (28.1)	10 (62.5)	14 (46.7)	16 (50)	16 (100)	7 (23.3)	8 (25)	13 (81.2)	-	-	-
Present	24 (80)	23 (71.9)	6 (37.5)	16 (53.3)	16 (50)	0	23 (76.7)	24 (75)	3 (18.8)	-	-	-
Range of motion												
Loss of < 10%	8 (26.7)	9 (28.1)	15 (93.7)	14 (46.7)	14 (43.7)	16 (100)	3 (10)	4 (12.5)	14 (87.5)	-	-	-
Loss of 10 - 33%	8 (26.7)	10 (31.2)	1 (6.3)	13 (43.3)	13 (40.6)	0	3 (10)	5 (15.6)	2 (12.5)	-	-	-
Loss of > 33%	14 (46.6)	13 (40.7)	0	3 (10)	5 (15.7)	0	24 (80)	23 (71.9)	0	-	-	-
Flexion contracture												
≤ 15 º	23 (76.7)	26 (81.2)	16 (100)	-	-	-	26 (86.7)	29 (90.6)	16 (100)	30 (100)	31 (96.9)	16 (100)
> 15 º	7 (23.3)	6 (18.8)	0	-	-	-	4 (13.3)	3 (9.4)	0	0	1 (3.1)	0
Instability												
None	29 (96.7)	30 (93.7)	16 (100)	30 (100)	32 (100)	16 (100)	30 (100)	32 (100)	16 (100)	-	-	-
Present without interference	1 (3.3)	0	0	0	0	0	0	0	0	-	-	-
Functional deficit or requires bracing	0	2 (6.3)	0	0	0	0	0	0	0	-	-	-

Table 5 - Assessment of functional independence of patients with hemophilia

Activities	Functional Independence Score in Hemophilia n (%)			
	1	2	3	4
Eating and grooming	0	3 (7.7)	2 (5.1)	34 (87.2)
Bathing	0	3 (7.7)	8 (20.5)	28 (71.8)
Dressing	0	13 (33.3)	2 (5.1)	24 (61.6)
Transfers – sitting	0	12 (30.8)	4 (10.2)	23 (59.0)
Transfers – squatting	16 (41.0)	1 (25.6)	6 (15.4)	16 (41.0)
Going up a step	0	14 (35.9)	5 (12.8)	20 (51.3)
Walking	0	4 (10.2)	18 (46.2)	17 (43.6)
Running	15 (38.5)	3 (7.7)	4 (10.2)	17 (43.6)

Scores from 1 to 4 in each area:

1. The subject is unable to perform the activity, or needs complete assistance to perform the activity
2. The subject needs partial assistance/aids/modified instruments/modified environment to perform the activity
3. The subject is able to perform the activity without aids or assistance, but with slight discomfort. He is unable to perform the activity similar to his healthy peers
4. The subject is able to perform the activity without any difficulty similar to his healthy peers

Table 6 - Functional Independence Score in Hemophilia by severity of hemophilia

Severity of hemophilia	Valid n	Minimum	Maximum	Mean	Standard deviation
Severe	15	14	32	24.20	6.10
Moderate	16	16	32	23.94	5.74
Mild	8	30	32	31.75	1.72
Total	39	14	32	25.64	6.09

Discussion

The WFH-PE and FISH assessment instruments proved useful in the clinical evaluation of structural joint status and functional independence of adults with hemophilia. Both are easily performed, inexpensive and able to detect the principle types of damage caused by recurrent hemarthrosis, which is quite evident in the population of this study.

Of the 31 patients with severe or moderate hemophilia, 27 (87.1%) showed at least the first stage of hemophilic arthropathy[5] and 20 (64.5%) were dependent on social security benefits due to complications from hemophilia, although the average age of this subgroup was only 35.1 years. Twenty-two patients (70.9%) participated in the home infusion program, indicating reasonable coverage by the program, as an attempt to minimize the inconvenience caused by transferring patients to the blood center.

It is noted that physical therapy, in general, is not viewed by patients as an integral part of coagulopathy treatment. They consider it necessary only in extreme circumstances such as injuries that cause acute immobility. Thus, disabilities that set in gradually continue to be neglected by the patients themselves, and, unlike what was shown in an audit by the Brazilian Court of Audit[21], it was not difficulty to access rehabilitation services that was primarily responsible for this lapse in treatment of HRJF patients, but the lack of information about the importance of physiotherapy in the prevention or treatment of injuries.

Among patients with mild hemophilia who do not generally exhibit spontaneous hemarthrosis, no significant change in the joint structure or functional clinical assessment was seen. What is noteworthy is that the structural joint damage and functional disabilities in patients with severe hemophilia and in those with moderate hemophilia are very similar. In 2011, Den Uijl et al. demonstrated the high clinical variability in this latter group of patients[22] which was corroborated in this study not only by the clinical findings but also by the variability in the consumption of clotting factor concentrate. This variability in the consumption of blood products among patients with coagulopathies of equal severity was so high that possible explanations extend beyond the medical field, extrapolating to psychological or accessibility issues. The assessment of joint conditions of patients who had consumed larger amounts of blood products in the previous 12 months was also quite variable and no cause-effect relationship between the factor 'consumption of blood products' and severity of arthropathy can be suggested as this was a cross-sectional study.

Conclusion

The WFH-PE and FISH instruments may be extremely useful in the clinical practice in the absence of imaging exams such as magnetic resonance imaging (MRI), which are considered very sensitive to detect early joint damage, but at a cost that makes them relatively inaccessible.

The prevalence of clinically detected joint structural lesions is high, as are deficits that impair functional independence in patients with severe or moderate forms of hemophilia at the HRJF.

Pending the implementation of primary prophylaxis in Brazil, the diagnosis of coagulopathies early in life becomes imperative. Due to the severity of arthropathies found in patients with moderate hemophilia, it is suggested that these individuals should be evaluated in a personalized way with respect to the more precise and accurate laboratory classification of the severity of hemophilia, to facilitate the recommendation of appropriate prophylaxis for these children.

For adults and adolescents (the latter not included in this study, but also not benefiting from proposed prophylaxis) there is current relevance in the guidelines regarding measures to prevent joint damage and on the fundamental importance of rehabilitation measures aimed at social reinsertion.

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