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ORIGINAL RESEARCH

Real-World Evidence on Joint Condition in Non-Severe Hemophilia A Patients: A Multicenter Study

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Purpose: Patients with non-severe hemophilia A (PwnSHA) may be at risk for joint damage (JD), yet data remain scarce. Our aim was to evaluate the joint condition in PwnSHA in a real-world setting.

Patients and Methods: A nationwide, multicenter, cross-sectional study was conducted. To mitigate the impact of discrepancies between factor VIII (FVIII) assays, baseline FVIII levels were determined using chromogenic and one-step clotting assays. Mutation in F8 gene, baseline FVIII levels, thrombin generation and age were assessed. The joint condition was described using the HEAD-US score by trained specialists at each participating hospital.

Results: One hundred and twenty-four patients were recruited, 84 of them with an available HEAD-US evaluation, who were finally included in our analysis. The median age was 38.4 years (18.3–48.5). Twenty percent (16/84) had moderate hemophilia (MoH) with FVIII levels of 4.0 IU/dL (2.6–4.6), and 80% (68/84) had mild hemophilia (MiH) with FVIII levels of 14.8 IU/dL (10.4–19.9), ($p< 0.001$). JD (HEAD-US>0) was observed in 50% (8/16) of MoH patients (HEAD-US= 6.5 [5.5–8.5]) and in 40% (27/68) of those with MiH (HEAD-US= 3.0 [2.0–6.5]), p=0.198. In the moderate group, JD was primarily observed in ankles (44%), while in the MiH group, knees were the most affected (31%). MoH patients reported a hypocoagulable thrombin generation profile compared to MiH patients ($p<0.05$).

Conclusion: Near half of PwnSHA had JD. A worse joint health and a lower thrombin generation was observed in MoH population. These patients can benefit from an early prophylaxis and prevent further joint deterioration. Future research should explore additional variables that might influence joint condition.

Keywords: mild hemophilia A, moderate hemophilia A, joint damage, HEAD-US, assay discrepancies, real-world data

Introduction

Hemophilia A, a disorder characterized by an inherited factor VIII (FVIII) deficiency, is classified into three categories, according to baseline FVIII activity, as severe (FVIII < 1 IU/mL), moderate (MoH, FVIII = 1–5 IU/mL), and mild (MiH, FVIII >5-40 IU/mL).[1] In general, the severity of the disease is inversely related to the FVIII levels, with lower concentrations indicating a more severe manifestation of the disease.[1] In severe hemophilia, joint deterioration is

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a debilitating outcome, deeply impairing the individual's quality of life as well as their ability to integrate effectively into social and professional environments.[1–3] Recent evidence suggests that patients with non-severe hemophilia A (PwnSHA) are also at risk of developing progressive joint damage (JD).[2]

The etiological factors contributing to JD in PwnSHA remain poorly understood. However, these factors are thought to be linked to recurrent, often undetected, episodes of minor bleeding that incrementally compromise joint integrity.[4,5] Additionally, discrepancies between chromogenic and one-stage clotting assays for FVIII levels detection can significantly challenge an early and accurate diagnosis of hemophilia, mainly in PwnSHA. This may, therefore, delay the initiation of personalized treatment strategies, potentially influencing the development of JD.[6]

This study evaluates joint condition in PwnSHA and elucidates the impact of FVIII-assay discrepancies and other factors, including age, thrombin generation, mutation in F8 gene and baseline FVIII levels on the development of JD in this population, through a meticulous evaluation of joint health in real-world clinical settings.

Materials and Methods

Study Design

A national, multicenter, cross-sectional study was conducted after receiving approval from the ethics committee of the Hospital Universitario Dr. Balmis (Alicante, Spain) and ratification by the ethics committees of each participating hospital. All patients provided signed informed consent prior to inclusion. The study was conducted in accordance with the basic principles of the World Medical Association Declaration of Helsinki and complied with the standards described in the European Union Guidelines for good clinical practice.

Subjects

Participants included male PwnSHA who were 12 years or older and had never received regular prophylaxis. Prior to the study visit, patients underwent a washout period of at least five half-lives following their most recent hemophilia treatment. Individuals with other hemostatic or inflammatory disorders, conditions that could impair joint health unrelated to hemophilia, or a history of inhibitors were excluded.

Samples

Blood samples were collected in trisodium-citrate-anticoagulated Vacutainer® tubes (BD Diagnostics, Spain). Plasma was obtained by double centrifugation at 1,500×g for 15 minutes at room temperature and stored in aliquots at −80°C until processing. The samples were defrosted at 37 °C for 10 min prior to analysis. All samples were processed and analyzed at the Hospital Universitario Dr. Balmis (Alicante, Spain).

Baseline FVIII Levels

Baseline FVIII activity was determined using a two-step chromogenic assay (FVIII-Chr) and a one-stage clotting assay (FVIII-Clot) in an ACL TOP 750 system (International Laboratory, Boston, USA). Hemophilia severity was determined using FVIII chromogenic assay. The ratios FVIII-Clot/FVIII-Chr ≥ 2 (classic discrepancy) and its inverse ≤ 0.5 (inverse discrepancy) were used for discrepancy identification and classification, following the criteria of Bowyer et al.[7]

Thrombin Generation Assay (TGA)

TGA is a global assay that reflects the hemostatic capacity in thrombotic and bleeding disorders. In this study, TG was analyzed using the Genesia® analyzer and the STG®-Bleedscreen kit (Diagnostica Stago, Paris, France), based on the fluorometric method described by Hemker.[8] When testing, a new calibration test, 2 levels of quality control (low and normal) and a reference plasma to normalize parameters were assessed. The STG®-Bleedscreen kit contains a mixture of phospholipids and a low picomolar concentration of human recombinant tissue factor. TG was measured in PPP samples thawed in a 37ª water bath for 3 minutes. TGA provides information on the following parameters: 1) Lag time (LT minutes) describes the time from starting the reaction until thrombin is first created; 2) Endogenous thrombin potential (ETP, nM/min) or total amount of thrombin generated, ie the area under the curve; 3) The peak of thrombin concentration

(Max peak, nM), correlates with the maximum thrombin generation; 4) The time to reach the maximum peak of thrombin (TTP, minutes); 5) Start tail (ST, minutes) corresponds to the time at which thrombin generation is ended and the generated thrombin has been inhibited; 6) Velocity index is indicative of the slope of thrombin generation between the LT and TTP. In patients with bleeding disorders, a reduced Max peak and ETP, and a prolonged LT and TTP compared to a reference plasma is usually found, reflecting a decreased hemostatic capacity. However, in patients with thrombotic disorders, a shorter LT and time to reach the peak of thrombin generation and an increased Max peak and ETP is described.[9]

HEAD-US Score

The HEAD-US index, a scoring system for detecting early arthropathy in hemophilia using ultrasound,[10] was applied by experienced specialists at each participating hospital. This approach appraises each joint for signs of synovitis and damage to cartilage and osteochondral structures through a streamlined scoring system designed to effectively manage the intricacies of hemophilia-related clinical data. The cumulative score for each patient was derived by adding the individual scores from the elbows, knees, and ankles. Similarly, a comparative additive system to assess the grade of synovitis and cartilage and subchondral bone damage separately in elbows, knees, or ankles was employed. A HEAD-US score > 0 defined the presence of JD.

Mutations in F8 Gene

Genomic DNA was extracted from peripheral blood in EDTA. All patients were first screened for intron 22 and 1 inversions by the long-distance polymerase chain reaction method.[11] In people found to be negative for intron 22 and 1 inversions, next-generation sequencing (NGS) assay was performed.[12] NGA is a new technology for DNA and RNA sequencing and variant/mutation detection. This technology combines the advantages of unique sequencing chemistries, different sequencing matrices, and bioinformatics technology. This combination allows a massive parallel sequencing of various lengths of DNA or RNA sequences or even whole genome within a relatively short period of time. Briefly, following blood sample extraction, the amount of DNA and RNA is determined, using a spectrophotometer. A sequencing library from RNA or DNA sample is required and involves 2 steps: 1) amplification to yield a pool of appropriately sized target sequences, and 2) the addition of sequencing adapters that will later interact with the NGS platform. If RNA is the starting template, an additional step is needed in which the RNA is first converted to cDNA by reverse transcription. Then, once DNA sequencing is performed, there is an alignment to a reference genome and data analysis.[12,13] HGVS nomenclature was use for describing F8 gene mutations.[14]

Statistical Analysis

Numerical variables were reported using the median and interquartile range (IQR), while categorical variables were described using percentages. Group comparisons were conducted with statistical tests suited to the data distributions. In our analysis, multiple logistic regression was applied to assess the impact of FVIII assay discrepancies, TG, age, and baseline FVIII levels on the occurrence of JD. For this analysis, the HEAD-US was designated as the dependent variable, categorized as 0 (no JD) or 1 (presence of JD). Independent variables included age, baseline FVIII levels, and the presence or absence of assay discrepancies (categorized as 0 = no discrepancy, 1 = presence of discrepancy). A p-value of < 0.05 was considered statistically significant.

Results

Patients

A total of 124 PwnSHA were recruited; however, only 84 underwent the HEAD-US evaluation and were finally included in the analysis. Median age of participants was 38.4 years (18.3–48.5), and hemophilia severity was notably skewed towards milder forms of the condition. Specifically, 80% (68/ 84) of them, were classified as MiH, with FVIII of 14.8 IU/dL (10.4–19.9). In contrast, a smaller fraction, 20% (16/84) of PwnSHA, were identified as MoH, with significant lower baseline FVIII levels (4.0 IU/dL (2.6–4.6)) ($p< 0.001$).

Table 1 HEAD-US Evaluation in MoH and MiH Patients

Severity	Joint	N (%)	HEAD-US synovial	HEAD-US cartilage	HEAD-US subchondral bone	HEAD-US total	p-value
MoH	Elbows	1 (6)	3	0	0	3	N/A
MiH		10 (15)	0.5 [0.0–1.0]	0.0 [0.0–1.0]	1.0 [0.0–1.0]	2.0 [1.0–3.0]	
MoH	Knees	6 (38)	2.0 [0.0–2.0]	2.5 [1.0–3.0]	0.5 [0.0–2.0]	4.5 [2.0–5.0]	0.057
MiH		21 (31)	1.0 [0.0–1.0]	1.0 [0.0–2.0]	0.0 [0.0–1.0]	2.0 [1.0–3.0]	
MoH	Ankles	7 (44)	2.0 [0.5–2.0]	2.0 [1.5–2.5]	0.0 [0.0–0.5]	4.0 [3.0–4.0]	0.087
MiH		17 (25)	0.0 [0.0–1.0]	1.0 [0.0–1.0]	0.0 [0.0–1.0]	2.0 [1.0–3.0]	

Abbreviations: N, number of patients evaluated; N/A, not applicable; MoH, moderate hemophilia; MiH, mild hemophilia; p-value, comparison between HEAD-US total.

HEAD-US Evaluation

JD was observed in 50% (8/16) of the MoH patients, with a median HEAD-US score of 6.5 (5.5–8.5). By contrast, 40% (27/68) of the MiH patients showed JD, presenting a lower median HEAD-US score (3.0 (2.0–6.5)); however, the difference was not statistically significant (p=0.198). In Table 1, JD was reported by joint and possible affected areas (synovial, cartilage, and subchondral bone) in both patient groups. Although damage in all three areas was greater in patients with MoH, the statistical analysis did not reveal significant differences between the two groups. Based on the frequency of JD occurrence in each joint, we observed that the ankle was the most affected joint in MoH patients (44% of them), followed by the knee (38%) and elbow (6%). In contrast, in patients with MiH, the knee was the most commonly affected joint (31%), followed by the ankle (25%) and the elbow (15%).

In Table 2, we included patients with no JD (HEAD-US score of 0). The authors provided data in both MiH and MoH patients, in particular TG parameters, baseline FVIII-Clot and FVIII-Chr levels and age. MiH patients were older than

Table 2 MiH and MoH Patients without and with JD

MiH and MoH patients without JD (HEAD-US=0)								
N=55	**Age (Years)**	**FVIII coagulant (IU/dL)**	**FVIII chromogenic (IU/dL)**	**ETP%***	**Peak of thrombin%***	**TTP (Minutes)**	**LT (Minutes)**	**ST (Minutes)**
MiH (n=47)	42.3 (36.8–46.4)	22.8 (13.6–33.2)	21.3 (12–28)	73.01 (55.8–81.4)	57.6 (37.4–66.7)	1.44 (1.29–1.62)	1.19 (1.02–1.36)	1.34 (1.17–1.46)
MoH (n=8)	29.4 (15.4–41.1)	4.2 (1.2–5)	3.6 (1.1–5)	70.01 (48.5–74.3)	56.8 (26.7–74.8)	1.57 (1.24–1.92)	1.29 (0.91–1.6)	1.56 (1.2–1.93)
P value	0.041	0.0006	0,0005	0.746	0.958	0,19	0.388	0.069
MiH and MoH patients with JD (HEAD-US over 0)								
N=88	**Age (years)**	**FVIII coagulant (IU/dL)**	**FVIII chromogenic (IU/dL)**	**ETP%***	**Peak of thrombin%***	**TTP (minutes)**	**LT (minutes)**	**ST (minutes)**
MiH (n=56)	45.6 (30–59.4)	26.7 (14.8–36.3)	31.8 (13–45)	75.16 (50.1–100.9)	61.5 (41.7–72.1)	3.81 (1.17–1.682)	1.35 (1.11–1.48)	1.71 (1.07–1.44)
MoH (n=13)	40.04 (23.4–48.3)	4.8 (3.3–5)	4.6 (4–5)	47.78 (30.6–75.3)	29.8 (19.8–37.8)	1.58 (1.38–1.83)	1.16 (0.85–1.25)	1.47 (1.25–1.61)
P value	0.351	0.0004	0.0068	0.0024	0.001	0.626	0.155	0.795

Abbreviations: MiH, mild hemophilia; MoH, moderate hemophilia; ETP, endogenous thrombin potential (in %, compared to a reference plasma); TTP, time to peak (minutes); LT, lag time (minutes); ST, start tail (minutes).

MoH patients, while no other statistical significance in TG and FVIII levels were reported. The same data have been reported in patients with JD (HEAD-US score over 0). In this last group, the authors observed a lower ETP and peak of thrombin in the MoH population compared to MiH patients ($p<0.05$). Age was similar in both groups.

Discrepancies in FVIII Assays

A total of 19% of PwnSHA exhibited discrepancies in FVIII assays. Among these, 69% (n=11) were considered classic discrepancies, with FVIII-Clot levels of 18.0 [13.6–23.2] IU/dL and FVIII-Chr levels of 4.0 [1.5–6.2] IU/dL ($p = 0.03$). Patients with inverse discrepancies (n=6) showed FVIII-Clot levels of 3.8 [3.3–4.3] IU/dL and FVIII-Chr levels of 9.0 [9.0–10.0] IU/dL ($p = 0.043$). In Table 3A and 3B, patients with classic and inverse discrepancies were described, including mutation in F8 gene, TG parameters (in particular ETP and peak of thrombin % compared to a reference plasma), HEAD-US score, FVIII-Clot, FVIII-Chr and age.

Table 3 Data Reported in Classic (Table 3A) and Inverse Discrepancies (Table 3A)

Classic Discrepancy								
F8 gene mutation	**Frequency**	**FVIII-Clot (UI/dL)**	**FVIII-Chr (UI/dL)**	**Peak (%)**	**ETP (%)**	**Severity depending on F8 mutation**	**HEAD-US**	**Age**
c.1492G>A (p.Ala498Thr)	1	16.1	7.0	23.5	42.7	Mild/moderate/severe	0	36.5
c.1648C>T (p.Arg550Cys)	1	11.0	5.3	40.1	63.4	Mild	0	35.2
c.1834C>T (p.Arg612Cys)	1	23.8	10.0	35.8	55.8	Mild/moderate	0	59.1
c.2043G>A (p.Glu681=)	1	17.0	5.0	29.0	57.9	Mild	0	47.8
c.5144G>A (p.Arg1715His)	1	75.3	0.7	98.9	78.3	Mild	0	66.3
c.5425A>T (P.Lys1809Ter)	1	8.4	2.0	12.9	27.8	Moderate	0	45.0
c.5428T>C (p.S1810P)	3	18.0	4.0	23.4	37.5	Mild	8	21.7
c.5428T>C (p.S1810P)		18.1	4.0	27.8	49.2	Mild	6	15.7
c.5428T>C (p.S1810P)		22.6	11.0	63.2	84.9	Mild	10	24.8
c.5879G>A (p.Arg1960Gln)	1	5.0	1.0	33.2	60.0	Mild/moderate	0	20.4
c.6622C>G (p.Gln2208Glu)	1	33.5	1.0	170.5	158.1	Mild	0	42.4
Inverse Discrepancy								
F8 gene mutation	**Frequency**	**FVIII-Clot (UI/dL)**	**FVIII-Chr (UI/dL)**	**Peak (%)**	**ETP (%)**	**Severity depending on F8 mutation**	**HEAD-US**	**Age**
N/A	1	3.2	9.0	24.5	39.2	N/A	0	40.9
c.1764C>A (p.Asn558Lys)	1	4.5	13.0	35.4	82.0	Mild	7	68.3
c.5123G>A (p.Gly1708Glu)	1	31.2	96.0	51.1	102.7	Mild	8	73.6
c.5399G>A (p.Arg1800His)	2	3.3	7.0	20.0	33.5	Mild/moderate/severe	2	48.3
c.5399G>A (p.Arg1800His)		3.8	10.0	40.2	70.9	Mild/moderate/severe	9	47.1
c.6419G>T (p.Gly2140Val)	1	4.3	9.0	65.3	84.7	Not listed in EAHAD database	5	23.4

Abbreviations: FVIII-Clot, one-stage FVIII clotting assay; FVIII-Chr, two-step FVIII chromogenic assay; ETP, endogenous thrombin potential (in %, compared to a reference plasma); N/A, not available.

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Discussion

The results of this study provided a detailed view of the distribution of hemophilia severity among participants, crucial for understanding variations in joint conditions. The predominance of milder forms of hemophilia, with 80% of participants classified as MiH, is primarily due to the higher prevalence of MiH compared to MoH,[15] being more likely to recruit such patients. Furthermore, the significant differences in FVIII levels between MiH and MoH emphasize the need for tailored treatment and monitoring strategies adapted to the disease severity to improve health outcomes.[6]

This is clearly seen in the majority of patients with MoH suffering from JD (50%) compared to the group with MiH (40%). However, it is interesting to note that the percentage of patients with JD was not very different between groups, which suggests that FVIII levels are not the only decisive factor for the development of JD in PwnSHA.

In fact, age emerged as a risk factor of JD in all PwnSHA enrolled in our study (median age of 38.4 (18.3–48.5)), highlighting the cumulative impact of repeated bleeding episodes over time on joint health. The authors remark that the median age in both MiH and MoH with JD was over 40 years old. This points up the importance of age as a marker not just of chronological risk but as a critical factor for timely intervention to potentially arrest or reverse joint deterioration. In this setting, early prophylactic interventions tailored to mitigate these episodes have been shown to significantly reduce the progression of joint disease.[16,17]

However, in agreement with the literature, MiH patients without JD were older than MoH subjects, reflecting that the milder forms can be underdiagnosed, overall if there is no family history of hemophilia.[18]

It is important to clearly define other associated causes that may be involved in joint impairment. In our study, patients with JD and MoH patients reported a hypocoagulable state by TGA compared to the milder forms of hemophilia. In particular, a lower ETP and maximum peak of thrombin were observed. This could explain, at least partially, the more severe bleeding phenotype described in the moderate population with JD.

The risk of bleeding associated with the patient's physical activity, spontaneous and traumatic joint bleeding history, or the type of treatment and medical advice according to the patient's bleeding phenotype, may influence in the joint integrity. Obesity and metabolic syndrome are associated with high release of proinflammatory cytokines, contributing to destructive effects of joint cartilage and subsequently, inducing JD.[19] These factors should be considered with the aim of achieving healthy joints and an optimal quality of life derived from an appropriate disease management.[18] Weight loss management and regular physical activity are essential factors to preserve an adequate joint health.[19] From the treatment perspective, an individualized treatment should be administrated, depending on the bleeding phenotype and patient's daily activity. This could include the proposal of conducting guided and suitable physical activity to strengthen the musculoskeletal system, providing joint stability, reducing the risk of microbleeds, and thereby potentially increasing the patient's quality of life.[1,16,17]

Recent data have shown that one third of patients with MiH present JD.[15] Our results corroborate this, revealing JD presence in 50% and 40% of patients with MoH and MiH, respectively. In MoH, the ankles and knees were the most affected joints, with the ankles experiencing the greatest degradation in synovium and cartilage. The knees showed lesser changes in these areas. Minor subchondral bone damage was noted in both joints, with the elbow being the least injured. In MiH, the knee was the most affected joint, followed by the ankle, mainly in the cartilage. The elbow was the least impacted. This suggests that asymptomatic joint microbleedings might progressively affect joint condition, a phenomenon previously observed in severe hemophilia.[20,21]

Discrepancies between FVIII one-stage clotting and two-stage chromogenic assays significantly influence treatment outcomes due to their impact on an early accurate diagnosis and tailored treatment.[7] These inconsistencies can lead to undertreatment, posing risks such as inadequate protection against bleeding, and contributing independently to JD over time.[22] In our study, different TG profiles and baseline FVIII levels have been observed, even in patients with the same F8 mutation. On top of that, some patients with the same F8 mutation had discrepancies and others not: c.1648C>T (p. Arg550Cys), c.1834C>T (p. Arg612Cys), c.5144G>A (p. Arg1715His), c.5879G>A (p. Arg1960Gln), c.5399G>A (p. Arg1800His). Therefore, this study addresses the importance of resolving these discrepancies to enhance the precision of therapeutic interventions in PwnSHA and reveals the complexity of an appropriate approach in hemophilia.

This aligns with observations that joints previously affected by bleeding are more susceptible to subsequent injuries and degenerative changes.[23] Our findings suggest that baseline levels of FVIII are less critical in predicting JD compared to other markers such as age. This shift highlights a growing recognition that while baseline factor levels are important for the diagnosis of hemophilia and for guiding initial treatment proposals, they do not strongly correlate with long-term joint outcomes. This points to the need for a more holistic approach to patient assessments.

The main limitation of our study relies on the exclusion of some initially recruited participants from the final analysis. Our experience shows that not all centers have trained and experienced staff available to conduct the HEAD-US assessment, which underlines the importance of exploring alternative methodologies for determining JD, such as the identification of biomarkers as well as the use of artificial intelligence to predict JD from less complex determinations.[24,25] This approach could potentially overcome the barriers presented by the specialized nature of the HEAD-US and ensure broader applicability and inclusivity in clinical assessments.

Our study, however, has several strengths, particularly the large sample size of patients, the participation of 12 Spanish hospitals, and the representation of "real-life" clinical practice.

Conclusion

The significant incidence of JD among PwnSHA patients urges the formulation of comprehensive guidelines for the diagnosis, management, and ongoing surveillance of JD in PwnSHA. Further tools for an easier evaluation of JD, enabling more targeted and effective management strategies in this group of patients are required.

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Disclosure

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