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ORIGINAL ARTICLE

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Can we compare haemophilia carriers with clotting factor deficiency to male patients with mild haemophilia?

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Abstract

Introduction: Certain haemophilia carriers demonstrate an increased bleeding tendency, mainly related to clotting factor deficiency. No study has so far formally compared the bleeding phenotype of women and girls with mild FVIII or FIX deficiency and associated management with that of male patients affected by mild haemophilia A and B.

Material and methods: We retrospectively evaluated 44 women and girls with mild FVIII or FIX deficiency (FVIII or FIX 0.05-0.5 IU/mL) and 77 male patients with mild haemophilia A or B and compared them with respect to clotting factor level, age at and trigger for diagnosis, as well as treatment modalities.

Results: After excluding gender-related haemorrhagic symptoms, haemophilia carriers with plasma factor levels in the mild haemophilia range and male patients affected by mild haemophilia present a comparable haemorrhagic profile, mainly characterized by mucocutaneous and postinjury bleeding. Haemophilia carriers with clotting factor deficiency, however, distinguish themselves in terms of later age at diagnosis, higher mean factor levels and trigger for diagnosis.

Conclusions: Women and girls with mild FVIII or FIX deficiency should be considered as mild haemophilia patients and have access to care and management inspired from male haemophilia patients while integrating differences and specificities. Larger international studies comparing the clinical presentation and treatment modalities of mild clotting FVIII and FIX deficiencies in both haemophilia males and females should be encouraged.

KEYWORDS

bleeding phenotype, carriers, FIX, FVIII, mild haemophilia

1 | INTRODUCTION

Haemophilia is an inherited gender-linked bleeding disorder caused by clotting factor VIII (FVIII; haemophilia A) or IX (FIX; haemophilia B) deficiency. It is a rare disease, with a worldwide frequency of 1 in 5000 live male births for haemophilia A (HA) and 1 in 30 000 live male births for haemophilia B (HB).[1] With a X-linked recessive inheritance pattern, haemophilia mostly affects males, while females are more commonly heterozygous carriers of the disease.[2]

Haemophilia carriers are expected to have a FVIII or FIX plasma concentration corresponding to half that found in healthy individuals, which is generally adequate for normal haemostasis.

However, clotting factor levels may greatly vary in carriers, ranging from very low to the upper limit of normal.[3] A number of variables have been proposed to explain clotting factor deficiency in

women and girls with haemophilia (WGH), including co-inheritance of a variant von Willebrand factor allele in carriers of HA, homozygous or compound heterozygous defect alleles of FVIII of FIX genes, structural or numerical aberrations of the X chromosome, extreme lyonization and mutation severity.[3-5]

It is known that WGH may exhibit an increased bleeding tendency related to their FVIII or FIX plasma concentration. However, some studies have suggested a possible increase in bleeding symptoms in WGH that cannot be solely explained by their coagulation factors levels.[6-8] In most cases, bleeding symptoms are described as comparable to those in males with mild haemophilia,[9] except that the WGH may additionally display obstetrical and gynaecological bleeding manifestations.[2,10]

While extensive information on the features of haemophilia in men has been accumulated, data on the clinical presentation, overall haemorrhagic diathesis and treatment modalities in female patients with clotting factor deficiency remain scarce. In spite of existing recommendations, the management of WGH is extrapolated from the evidence gathered in male haemophilia patients.[2]

This retrospective study was aimed at investigating the bleeding phenotype and haemostatic treatments in women with clotting factor activity in the range of mild haemophilia as compared to men affected by mild haemophilia followed in the same haemophilia treatment centre.

2 | MATERIALS AND METHODS

This study was conducted at the Haemophilia Treatment Centre (HTC) of the *Cliniques universitaires Saint-Luc*, Brussels, Belgium, where 249 patients with all types and severities of haemophilia have been identified. The population studied consisted of all patients with mild HA or HB (FVIII or FIX levels > 0.05 <0.4 IU/mL) and women and girls with mild FVIII (WGMHA) or FIX (WGMHB) deficiency (FVIII or FIX levels 0.05-0.5 IU/mL) who were regularly examined at the centre and for whom reliable and informative data on their clinical history were available. We have selected male patients according the definition of mild haemophilia of International Society of Thrombosis and Haemostasis (ISTH),[9] while for women we took in account the definition of normal range of FVIII or FIX to define factor deficiency. FVIII and FIX levels were measured by one-stage activated partial thromboplastin time (aPTT) in all patients and by chromogenic assay for FVIII in some selected male patients.

All patients with additional bleeding disorders or using antithrombotic medication were excluded from the analysis. The patients' data were retrieved from clinical records backwards to 2000, which was facilitated by the availability, since January 2000, of an electronic record system.

The patients' data prior to attendance at the HTC were obtained from their paper clinical records and a careful interview. The following information was collected for each patient: basal level of deficient clotting factor, age, trigger for diagnosis, age at diagnosis, desmopressin (1-deamino-8-D-arginine vasopressin; DDAVP) testing and response and haemorrhagic phenotype.

The haemorrhagic phenotype was evaluated while taking into account 12 different bleeding symptoms: (a) epistaxis, (b) cutaneous bleeding, (c) bleeding from minor wounds, (d) oral cavity bleeding, (e) haematuria, (f) bleeding associated with tooth extraction, (g) surgical bleeding, (h) menorrhagia, (i) postpartum haemorrhage, (j) muscle haematomas, (k) haemarthrosis and (l) central nervous system (CNS) bleeding. DDAVP testing was performed by administering DDAVP at dose of 0.3 μg/kg body weight diluted in 50-100 mL NaCl solution given intravenously over 30 minutes. Plasma samples were obtained prior to DDAVP administration, as well as 30, 60, 120 and 240 minutes post-DDAVP administration. Complete responders (CRs) were defined as having a FVIII level ≥ 0.5 IU/mL after DDAVP and partial responders (PRs) as having a FVIII < 0.5 IU/mL but increased at least twofold and >0.30 IU/mL. Patients who were neither PRs nor CRs were considered non-responders (NR).

2.1 | Statistical analyses

All statistical analysis was performed using GRAPHPAD PRISM 6. Continuous variables were expressed as mean and range, and categorical variables as number and percentage. Statistical analysis was performed using Student's *t* test. A *P*-value < .05 was considered statistically significant.

3 | RESULTS

3.1 | Study population

In total, 296 WGH (230 WGHA and 66 WGHB) and 101 patients with mild haemophilia (87 HA and 14 HB) were identified in the centre. Among WGH, 122 (104 HA and 18 HB) were excluded due to missing recent clotting factor levels. Clotting factor levels were available in 174 WGH (126 HA and 48 HB); however, we analysed the 44 WGMH (32 HA and 12 HB) presenting FVIII/FIX levels between 0.05 and 0.5 IU/mL. As regards male patients, we analysed 77 patients (65 with HA and 12 with HB), while twenty-four male patients were excluded because data were incomplete (20 patients), presence of cancer (3 patients) or antithrombotic therapy (1 patient).

3.2 | Demographics, clinical presentation, and phenotype

The mean age of WGMH and males was 45 years (range: 12-95 year) and 42 (range: 3-90 year), respectively. Table 1 summarizes the characteristics of the study population.

The difference in mean clotting factor levels between the two groups (0.29 ± 0.15 vs 0.19 ± 0.11 IU/mL, *P* < .0001) was statistically significant. The mean age at diagnosis in men and women was

TABLE 1 Characteristics of study population

Characteristic	HA patients	HB patients	Total	WGMHA	WGMHB	Total	*P*-value
Number of patients	65	12	77	32	12	44	
Mean ± SD FVIII/FIX level, IU/dL(range)	0.19 ± 0.12 (0.05-0.40)	0.17 ± 0.9 (0.06-0.31)	0.19 ± 0.11 (0.07-0.40)	0.29 ± 0.15 (0.06-0.49)	0.27 ± 0.17 (0.16-0.48)	0.29 ± 0.15 (0.06-0.49)	*<.0001*
Mean age ± SD, years (range)	40.72 ± 23.94 (3-90)	49.5 ± 24.90 (8-89)	42.1 ± 24.02 (3-90)	42.38 ± 20.61 (12-95)	52.10 ± 15.96 (31-79)	43.9 ± 19.19 (12-95)	
Mean age at diagnosis + SD, years (range)	16.40 ± 21.86 (1-77)	34.00 ± 26.43 (1-72)	18.20 ± 22.83 (1-77)	28.30 ± 21.50 (2-83)	39.70 ± 19.09 (6-67)	31.6 ± 21.24 (2-83)	*<.002*

Abbreviations: HA, haemophilia A; HB, haemophilia B; WGMHA, women and girls with mild haemophilia A; WGMHB women and girls with mild haemophilia B.

Italic number denotes the statistical significance.

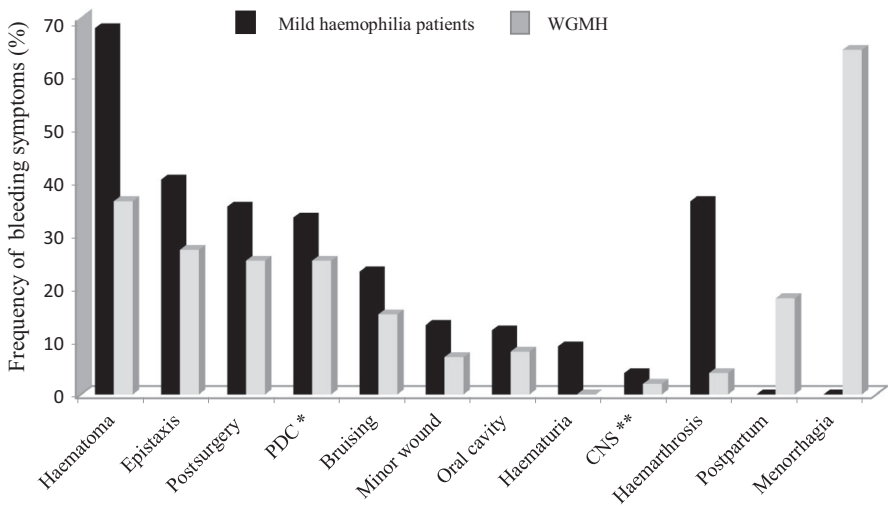

FIGURE 1 Frequency of bleeding symptoms in mild haemophilia patients and women and girls with mild haemophilia (WGMH). *PDC: bleeding postdental care; **CNS: central nervous system

19.18 years (range: 1-77 year) and 31.63 years (range: 2-83 year) ($P < .002$), respectively. The main trigger for diagnosis in WGMH was family screening in relatives (84%; 37/44), while the remaining cases were diagnosed after haemorrhagic episodes (4/44; 9%), mostly following surgical/invasive procedures (75%; 3/4), and after incidental observation of a prolonged aPTT (3/44; 7%). In male patients, the most common reason for diagnosis was onset of bleeding (32/77; 42%), mostly following trauma or surgical/invasive procedures (31/32; 96%). Furthermore, 33% (25/77) of patients were diagnosed by family screening and 26% (20/77) during workup for prolonged aPTT. The most common reported bleeding symptoms (in order of decreasing frequency) in WGMH were as follows: menorrhagia (28/44; 64%), mucocutaneous haemorrhages (34/44; 77%), bleeding following dental care and surgery (22/44; 50%) and haematoma (16/44; 34%). Postpartum haemorrhage complicated eight of 33 pregnancies (24%) (Figure 1).

In the group of men, haemarthrosis occurred in approximately one-third of patients (28/77; 36%), while mucocutaneous (63/77; 81%) and muscle (52/77; 68%) bleedings were more frequent. Haemorrhages following medical interventions were observed in more than half of men (53/77; 69%), namely in 27 (35%) after surgery and 26 (33%) after dental care. Joint bleeds were reported by 4% (2/44) of WGMH and 36% of affected men. None of the WGMH experienced haematuria, as compared to 9% (7/77) of men and CNS bleeding occurred in 4% (3/77) and 2% (1/44), respectively.

3.3 | Haemostatic treatments

All patients received on-demand therapy, except one female who was on prophylaxis for recurrent haemarthrosis. Among WGMH, 43% (19/44; 12/32 HA and 7/12 HB) received at least one treatment during the follow-up period, with a total number of 24 treatments. The two main reasons for treatment were prophylaxis for surgical/invasive procedures (17/24; 71%), including dental care (6/24; 25%). Only one patient received on-demand therapy for haemarthrosis. Among male patients, 71% (55/77; 46/65 HA and 9/12 HB) were treated at least once, with a total of 86 treatments during the follow-up period. The most frequent indication for therapy was prophylaxis for surgery/invasive procedures (35/82; 43%), followed by treatment for haematoma (16/82; 19%) and prophylaxis for dental care (11/82; 13%). Treatment was required seven times (7/82; 8%) for joint bleeds and eight times (8/82; 10%) for mucocutaneous bleeds. Male patients also required therapy for haematuria (4/82; 5%).

The haemorrhagic episodes in males were treated as follows: DDAVP (39/82; 48%), associated with tranexamic acid (TXA) in 11 cases (28%), recombinant (r-)FVIII (22/82; 27%) and r-FIX (16/82; 20%). Treatment consisted of TXA alone in four episodes (5%) and of blood transfusion on one occasion. In WGMH, four episodes (17%) required therapy with r-FVIII and nine (37%) with r-FIX (plus TXA in eight patients). DDAVP was used nine times (37%), twice in association with TXA. On two occasions, treatment consisted of TXA alone. Finally, 15 (19%) mild haemophilia patients and 12 (27%) WGMH never received replacement therapy with plasma derived (pd) or r-FVIII/FIX concentrates.

3.4 | DDAVP test infusion

A DDAVP test infusion was performed in most male patients with HA (49/65; 75%), with an overall response rate (ORR) of 92% (36/49 [73%] CR and 9/49 [18%] PR). In 9/16 (56%) of the patients, DDAVP test was not performed since it was contraindicated because of age or concomitant diseases; 7 patients refused the DDAVP test. Among WGMH, DDAVP test was performed in 22/32 (68%), with an ORR of 90.5% (19/22 [86%] CR and 1/22 [4.5%] PR). No serious drug-related adverse effects were reported in both groups.

4 | DISCUSSION

Over the last decade, the proportion of WGH receiving care has grown thanks to several community initiatives to foster screening and better awareness in HTCs.[11] According to published data, there are at least four WGH related to a single male with haemophilia and reduced clotting factor levels are found in approximately 30% of WGH.[11,12]

WGH represent the second largest group of women with inherited blood clotting defects after patients with von Willebrand disease (VWD).[13] Since WGH may present an increased bleeding tendency that is only partially related to their basal plasma factor levels, many studies have been conducted to evaluate their haemorrhagic risk in comparison with healthy women.[6,7,14]

Despite the fact that the haemorrhagic phenotype of WGH with reduced clotting factor activity has been reported in literature to resemble that of mild haemophilia patients and that the recommended treatment is the same,[2] to our knowledge, this was the first study that directly compared WGMH and males with mild haemophilia.

It is interesting that WGMH represented one-third (44/121) of the whole population affected by mild haemophilia in our study. Considering that clotting factor levels were missing in 122 WGH, our data probably underestimate the real percentage of WGMH, who may represent an emerging subgroup of mild haemophilia sufferers.

We found a significant difference in the mean age at diagnosis between WGMH and male patients that has already been reported in the literature.[10] This delay could be due to several reasons: first, an undervaluation of the personal and family haemorrhagic history by patients and/or physicians[5]; second, the lack of awareness of haemophilia in the differential diagnosis of females presenting with haemorrhagic diathesis. In addition, the main trigger for diagnosis in females was family screening, while in males it was onset of bleeding complications, mostly after injuries. This difference, however, cannot be explained by a different haemorrhagic tendency, because postmedical intervention haemorrhages were reported in a similar proportion in the two groups. Regarding gender-linked haemorrhagic symptoms, the results in our cohort are in line with existing data showing that menorrhagia is the most frequent symptom and that postpartum haemorrhages complicate 24% of pregnancies in WGMH.[15]

When removing from analysis these two feminine items, the most common bleeding symptoms were the same in both groups: mucocutaneous bleeding, postmedical intervention bleeding and haematomas. However, a major difference in the frequency of haemarthrosis was observed, which contrasts with previously published data[7,16] Differences in cohort size and study methodology might partially explain this discrepancy. Moreover, our analysis revealed a statistically significant difference in clotting factor levels between the two groups that could partially explain higher frequency of haemarthrosis in affected males.

Regarding haemostatic treatment modalities, a greater proportion of males received therapy as compared to WGMH. Although the main reason for treatment was prophylaxis for surgery in both groups, therapy was also required for other haemorrhagic symptoms (haematomas and haemarthroses) in males. The missing involvement of HCT in the management of bleeding in WGMH could partially explain this difference. It is important to consider that menorrhagia, the most common bleeding symptom in WGH, is often treated with oral contraceptives (OC), sometimes associated with TXA or DDAVP without the use of concentrates.[2,12]

As regards DDAVP infusion test, a similar ORR was seen in both groups. These results compare favourably with the few data published on the response to DDAVP and its use in WGHA,[17,18] even if a recent study suggested a decreased and less sustained desmopressin response in WGHA.[19]

This study has some limitations, namely the retrospective nature of data collection and the relatively small number of patients. Furthermore, almost all male haemophilia patients followed at the HTC were enrolled, while only WGH who had been screened for clotting factor deficiency were included.

In conclusion, our study demonstrates that, after excluding gender-related haemorrhagic symptoms, WGH with mild deficiency and male patient affected by mild haemophilia present a comparable haemorrhagic profile that is mainly characterized by mucocutaneous and postinjury bleeding.

WGH–with mild FVIII or FIX deficiency, however, differs from male mild haemophilia patients in terms of age at diagnosis, trigger for diagnosis and mean clotting factor levels.

Our conclusions are in line with the already published proposal[12] that WGH with mild clotting factor deficiency should be considered as mild haemophilia patients and have access to specific care

and management mainly inspired from mild haemophilia males, but also integrating important differences and specificities. Initiatives to support awareness, large-scale data collection and development of validated guidelines for mild haemophilia in females should be encouraged.

DISCLOSURES

The authors stated that they had no interests which might be perceived as posing a conflict or bias.

AUTHOR CONTRIBUTIONS

SR performed the research and wrote the paper; CL contributed to the data acquisition and analysis; AB contributed to data acquisition; MS and SS contributed to the paper review CH designed the research study and reviewed the paper.

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