Haemophilia A/B carriers: haemorrhagic burden of disease and open issues

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Dear Sir,

The severity and burden of symptomatic spontaneous bleeding in women with haemophilia (WwH) remains unclear. The guidelines for the management of haemophilia[1] state that most WwH are asymptomatic, but a review of literature shows that many bleeds also occur in women (**Table I**). So how should they be effectively monitored[2]? Management of bleeding should be very similar to that performed in male haemophiliacs[3]. Joint bleeding was proven to have a strong and negative impact on the quality of life of these women[4]. Prevention procedures should be put in place to avoid haemophiliac arthropathy as far as possible. Intracranial haemorrhage (ICH) is the most serious event in haemophilia. It

***Table I** - Characteristics of the studies on haemophilia carriers presenting spontaneous symptomatic bleeding*

Authors	Year	Type of haemophilia	Total patients (n)	Minor bleeds n/pts (%)	Major bleeds n/pts (%)
Plug et al.	2006	A/B	274	Gum bleeding: 164/107 (153.3) Cutaneous bleeding: 50/219 (22.8) Nose bleeds: 115/155 (74.1)	Joint bleeds: 23/271 (8.5)
Sharathkumar *et al.*	2009	B	76	Cutaneous bleeding: 5/20 (25.0) Bruising: 20/64 (31.3) Nose bleeds: 11/64 (17.2)	
Miesbach *et al.*	2011	A	46	Cutaneous bleeding: 31/46 (67.4) Gum bleeding: 2/46 (4.3) Nose bleeds: 7/46 (15.2)	
***Paroskie**	2014	A	32	Gum bleeding: 14/32 (43.8) Cutaneous bleeding: 19/32 (59.4) Nose bleeds: 2/32 (37.5)	Joint bleeds: 5/32 (15.6)
Sidonio *et al.*	2014	A/B	451	Not evaluated	Joint bleeds: 44/297 (14.8)
Di Michele *et al.*	2014	A/B	22	Cutaneous bleeding: 18/22 (81.8) Nose bleeds: 2/32 (37.5)	Joint bleeds: 20/22 (90.1) ICH: 1/22 (4.5)
Olsson *et al.*	2014	A/B	126	Gum bleeding: 15/126 (11.9) Cutaneous bleeding: 20/126 (15.9) Nose bleeds: 30/126 (23.8)	Joint bleeds: 4/126 (3.2) Large haematomas: 26/126 (20.6) GI bleeding: 6/126 (4,8) ICH: 1/126 (0.8)
Paroskie *et al.	2015	A	44	Gum bleeding: 22/44 (50.0) Bruising: 31/44 (70.5) Nose bleeds: 16/44 (36.4)	Joint bleeds: 8/44 (18.2) Large haematomas: 15/44 (34.1) GI bleeding: 5/44 (11.4)
Lambert *et al.*	2019	A/B	61	Gum bleeding: 3/61 (4.9) Bruising: 2/61 (3.3) Nose bleeds: 3/61 (4.9)	
Bryant *et al.*	2019	A	5		Joint bleeds: 3**/5 (60.0) **one TKR GI bleeding: 1/5 (20.0)
Raso *et al.*	2020	A/B (only mild haemophilia)	44	Gum bleeding: 4/44 (9.1) Cutaneous bleeding: 34/44 (77.3) Nose bleeds: 12/44 (28.0).	Joint bleeds: 4/44 (9.1) ICH: 2/44 (4.5) Large haematomas: 16/44 (36.4)

n: number; pts.: patients; ICH: intracerebral haemorrhage; GI: gastrointestinal; TKR: total knee replacement. *Some patients are included in both studies.

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mostly occurs in infants ≤2 years or in adults ≥60 years with known risk factors, such as hypertension[5]. Three different authors reported cases of ICH in haemophilia carriers (**Table I**). On the basis of this, even if cerebral haemorrhage is not a frequent event in WwH, the underlying risk factors still require careful attention. Minor spontaneous bleeding is very frequent, as reported for von Willebrand disease. However, it can be the cause of error in the initial diagnosis, thus underestimating the numbers of haemophilia carriers.

Based on these considerations, we put forward some simple and feasible suggestions to manage WwH.

- Women presenting spontaneous bleeding should be suspected as having haemophilia as well as other haemorrhagic disorders (e.g. von Willebrand disease, thrombocytopenia, etc.).
- Clinical and anamnestic data should be accurately collected, also using haemorrhagic scores.
- Plasmatic FVIII/FIX should always be assessed, while other blood chemistry and coagulation data should be evaluated to establish any possible correlation with the haemorrhagic phenotype.
- Genetic analyses should be performed to define whether the presented mutation correlates with the haemorrhagic phenotype (e.g intron 22 inversion/severe phenotype).
- The underlying diseases must be carefully evaluated and treated, especially those that could be correlated to a high haemorrhagic risk (e.g. hypertension/ICH, as reported in mild haemophilic males).
- Joint damage should be strictly monitored to prevent the onset of haemophiliac arthropathy.
- Continuous prophylaxis with coagulation factor concentrates should be considered in case of recurrent severe bleeds and/or presence of haemophiliac arthropathy.

Spontaneous symptomatic bleeding in haemophilia carriers can occur at any age, significantly worsening their quality of life. Since knowledge of the real haemorrhagic burden, treatment and outcomes has not yet been well defined in WwH, we launched the "International Registry on Haemophilia A/B Carriers" with the contribution of the Scientific and Standardization Committee of the International Society of Thrombosis and Haemostasis (SSC-ISTH) "Women's Health Issues in Thrombosis and Haemostasis" in order to respond to the unanswered questions of the scientific community.

The Authors declare no conflicts of interest.

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