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Epidemiology of bleeding symptoms and hypermobile Ehlers-Danlos syndrome in paediatrics

S. E. HICKEY^{*,†}, E. A. VARGA^{†,‡}, and B. KERLIN^{†,‡,§}

^{*}Division of Molecular & Human Genetics, Nationwide Children's Hospital, OH, USA

[†]Department of Pediatrics, The Ohio State University College of Medicine, OH, USA

[‡]Division of Hematology/Oncology/Bone Marrow Transplantation, Nationwide Children's Hospital, OH, USA

[§]Center for Clinical & Translational Research, The Research Institute at Nationwide Children's Hospital Columbus, OH, USA

Ehlers-Danlos syndrome (EDS) is characterized by tissue fragility, skin hyperextensibility and joint hypermobility [1]. Hypermobile EDS (hEDS) is generally accepted to be the most common subtype. Bleeding and bruising are common findings in patients with all EDS subtypes, affecting >90% of patients in one large cohort [2]. However, a systematic assessment of bleeding severity and frequency in hEDS has not been previously reported. Thus, in this study we sought to (i) quantify bleeding severity in children with hEDS using a validated bleeding assessment tool (BAT) [3] and (ii) screen children referred for bleeding symptom evaluation for hEDS, to assess the prevalence of hEDS within a paediatric haemostasis clinic referral population [1]. Better understanding this epidemiology may further the investigation of appropriate management of hEDS-related bleeding. In addition, improved recognition of hEDS in patients referred for bleeding symptoms may facilitate proper diagnosis and institution of appropriate hEDS-related health surveillance for musculoskeletal disease, autonomic dysfunction and other functional disorders.

Following Nationwide Children's Hospital Institutional Review Board (IRB11–0110) approval, patients were recruited through either an outpatient Genetics or Haemostasis visit between July 2011 and February 2013. Beighton scores are known to demonstrate nonspecific increased mobility in children <9 years old, making it difficult to distinguish pathologic from polymorphic hypermobility [1,4]. Thus, children aged 9–21 years were eligible for participation and were approached, prospectively, as they presented to each clinic. Patients with pre-existing haemostasis diagnoses or another hereditary disorder of connective tissue (HDCT; e.g. Marfan or Loeys-Dietz syndrome) were excluded.

The Paediatric Bleeding Questionnaire (PBQ), based upon a BAT designed for adult patient evaluation, has been validated to screen children for vWD [3,5]. Originally designed for

Correspondence: Scott E. Hickey, MD, Division of Molecular & Human Genetics, Nationwide Children's Hospital, 700 Children's Drive, Timken H235, Columbus, OH 43205, USA. Tel.: 614-722-3535; fax: 614-722-3546; Scott.Hickey@NationwideChildrens.org.

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children <18 years old, the PBQ has subsequently demonstrated specificity for adult vWD [6]. The PBQ is suspicious for vWD when ≥ 2 . Although the PBQ has not previously been applied to hEDS it provides a method to objectively quantify bleeding in paediatric settings

New patients presenting to Genetics clinic and meeting Villefranche criteria for hEDS diagnosis were eligible for recruitment [1]. The major diagnostic criteria for hEDS are (i) generalized joint hypermobility (Beighton ≥ 5), which is necessary for the clinical diagnosis, and (ii) skin hyperextensibility and/or smooth, velvety skin. Minor, diagnostic criteria for hEDS are recurring joint dislocations, chronic joint/ limb pain, and positive family history. Patients were evaluated by one of two dysmorphologists using the Villefranche criteria and objectively assigned a Beighton score by a physical therapist using a goniometer [7]. Three physical therapists (PT) were involved in the study. Substantial inter-rater reliability (IRR) was established on the first 10 patients (weighted κ -coefficient 0.79 for each pairing of 2 PTs; $P = 0.02$). Therefore, subsequent patients were assessed by only one PT. The patients were also contacted by a genetic counsellor experienced with haemostasis evaluations (EAV) to complete the PBQ. Depending on family preference, this was done either in person or by telephone. Patients with PBQ ≥ 2 were referred to the Haemostasis clinic for further evaluation at the discretion of the haematologist.

Patients referred to Haemostasis clinic for bleeding symptom evaluation were eligible for the Haemostasis arm. In addition to any clinically indicated haemostatic evaluation, one of the PTs determined a goniometric Beighton assessment, as described above. Those with Beighton ≥ 5 were referred for Genetics evaluation where the Villefranche diagnostic criteria were applied, as described above. Those with a Beighton <5 had no further participation in the study.

Seventy-three patients consented to participation, seven were excluded from the Genetics cohort because the goniometric Beighton was <5 , for a final cohort of 66 (Fig. 1). Despite high IRR between PTs using a goniometer, IRR was weak between PTs and dysmorphologists (weighted κ -coefficient 0.18; $P = 0.03$). Because the dysmorphologists did not use goniometers this may indicate that subjective hypermobility assessments are less reliable.

Thirty-four Genetics cohort patients met Villefranche criteria for hEDS (Table 1). Four subjects who did not complete the PBQ and five with pre-existing haemostasis diagnoses (all of whom had qualitative platelet dysfunction with varying laboratory characteristics) were subsequently excluded. The remaining 25 patients had a mean PBQ of 1.8 (± 2.0). Fourteen (56%) patients had a PBQ ≥ 2 , seven of whom attended their haemostasis appointment where no haemostatic abnormality was identified. Interestingly, patients with PBQ ≥ 3 were more likely to have previously been evaluated by haematology as compared to patients with PBQ ≤ 2 ($P < 0.01$). Commonly employed haemostasis assays included prothrombin time, partial thromboplastin time, thrombin time, fibrinogen, von Willebrand activity and antigen, bleeding time, and PFA-100 closure times. Some patients also had platelet aggregometry and/or electron microscopy. All assays were performed in the clinical laboratory using institutional methods and standards.

Thirty-two patients enrolled in the Haemostasis arm, nine (28%) of whom had a Beighton 5 (Fig. 1). All nine had normal haemostasis laboratory evaluations and, interestingly, they were all girls. Six of them attended their Genetics appointment, five of whom were diagnosed with hEDS. The sixth patient had dysmorphic facial features and a learning disability, so although no specific diagnosis was made; a diagnosis of EDS was not rendered. Importantly, PBQ scores were not utilized to guide their hEDS evaluation.

Although bleeding may be a common EDS feature, previous studies have noted that laboratory investigations of platelet aggregation, clotting factors, and bleeding time are usually normal [5]. Thus, although platelet dysfunction has been reported in ~26% of EDS patients and may be associated with dysfibrinectinemic EDS, there is no objective laboratory assessment for hEDS-related bleeding [8]. Describing the EDS-related bleeding phenotype has been complicated by the heterogeneity of the patient populations studied. For example, Anstey *et al.* [2] described 51 patients with five different subtypes of EDS, only five of whom had hEDS. In this study, wherein pre-existing haemostasis defects were excluded, no platelet dysfunction was identified. However, the interaction between co-morbid platelet dysfunction and hEDS remains ill-defined, as illustrated by the excluded patients. Cutaneous and menstrual bleeding symptoms were the strongest contributors to an elevated PBQ (Table 1). Heavy menstrual bleeding secondary to anovulatory cycles is commonly reported in adolescent females, but is not specifically addressed by the PBQ. Thus, the contribution of anovulatory cycles to hEDS-related bleeding remains undefined. Quantifying the bleeding tendency in patients with hEDS may facilitate studies designed to understand the physiology of hEDS-related bleeding and to determine which patients may benefit from haemostatic therapy [8].

A recent study, using the Brighton criteria for benign joint hypermobility syndrome, identified a higher prevalence of symptomatic joint hypermobility amongst an adult haemostasis cohort (24% vs. 2% of controls) [9]. This finding is consistent with our study in which nine (28%) of 32 patients referred for bleeding symptoms had evidence of joint hypermobility. Most of these patients (five of six) who underwent a formal genetics evaluation met Villefranche criteria for hEDS. This study did not assess for a potential correlation between PBQ and Beighton scores. Thus, whether hEDS severity may be correlated with bleeding severity remains unknown. Moreover, the reliance on generalized joint hypermobility (Beighton 5), to screen haemostasis referral patients for hEDS may have missed patients with benign joint hypermobility who may have met the less stringent Brighton criteria or less common types of EDS [1]. Therefore, the relationship between bleeding referral and other explanations for joint hypermobility remains incomplete.

In this study, 14 of 25 patients (56%) with hEDS were found to have a PBQ 2, a score consistent with suspected vWD in children with bleeding symptoms [3]; however, its utility for determining bleeding severity in association with hEDS requires further validation. Although the PBQ IRR has not been directly assessed, it is known to be reasonable for the BAT upon which it is based [5]; thus, direct assessment of PBQ IRR may strengthen future studies. More stringent definitions of elevated bleeding scores (3 or 4) have been proposed for adults [10]. Thus, using PBQ 3, nearly 30% of these hEDS patients would be abnormal. PBQ scores should be compared between healthy controls and children with

hEDS to better define how the PBQ may be utilized to guide haemostatic evaluation and/or intervention in childhood hEDS.

Unfortunately, seven of 14 patients with hEDS and PBQ 2 did not attend their haemostasis appointment. It is unclear if this was due to inconvenience (simultaneous genetics and haemostasis evaluations were not offered in this study because of feasibility constraints). However, patients with PBQ 2–3 had both a low rate of previous haemostasis evaluation (one of seven) and a low rate of compliance with haemostasis referral (one of six) suggesting that the patient/parents were not concerned about bleeding symptoms in this range. Similarly, three of nine patients referred from Haemostasis for Beighton 5 did not follow-up with Genetics evaluation. Thus, loss to follow-up was a major limitation of this study design. Future studies designed to capture simultaneous haemostasis and genetic evaluations may facilitate a better understanding of haemostatic comorbidities in hEDS. Such research could also be enhanced with predefined haemostasis laboratory panels.

In this study, 56% of the hEDS patients had a positive bleeding score (PBQ 2) in the absence of an identified haemostatic defect. Thus, the mechanisms underlying bleeding symptoms in hEDS deserve further investigation.

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Fig. 1.
Study cohort assignment and ultimate diagnosis.

Table 1.

Hypermobility Ehlers-Danlos syndrome participant characteristics.

A) Genetics clinic cohort characteristics				
	Total n= 25	PBQ < 2 n= 11	PBQ 2 n= 14	
Age in Years; Mean (Range)	13.2 (9–18)	12.3 (9–16)	13.9 (9–18)	
Female; n (%)	17 (68)	6 (55)	11 (79)	
Race; n (%)				
Caucasian	20 (80)	8 (73)	12 (86)	
Other	5 (20)	3 (27)	2 (14)	
hEDS Villefranche criteria [1];				
Major diagnostic criteria				
Beighton score; Mean (SD)	6.0 (1.3)	5.8 (0.8)	6.1 (1.5)	
Skin involvement; n (%) *	8 (32)	4 (36)	4 (29)	
Minor diagnostic criteria				
Recurring joint dislocations/subluxations; n (%)	13 (52)	7 (64)	6 (43)	
Chronic joint/limb pain; n (%)	16 (64)	5 (45)	11 (79)	
Positive family history; n (%)	10 (40)	2 (18)	8 (57)	
PBQ bleeding symptoms [†]				
Epistaxis; n (%)	6 (24)	1 (9)	5 (36)	
Cutaneous; n (%)	9 (36)	1 (9)	8 (57) [§]	
Bleeding from minor wounds; n (%)	3 (12)	0 (0)	3 (21)	
Oral; n (%)	3 (12)	0 (0)	3 (21)	
Tooth extraction; n (%)	4 (16)	0 (0)	4 (29)	
Gastrointestinal; n (%)	1 (4)	0 (0)	1 (7)	
Surgical; n (%)	1 (4)	0 (0)	1 (7)	
Menorrhagia; n /postmenarche [‡] (%)	7/13 (54)	0/4 (0)	7/9 (78) [§]	
Muscle hematomas; n (%)	3 (12)	0 (0)	3 (21)	
Haemarthrosis; n (%)	1 (4)	0 (0)	1 (7)	
B) Haemostasis clinic cohort characteristics				

A) Genetics clinic cohort characteristics				
	Total <i>n</i> = 32	PBQ < 2 <i>n</i> = 11	PBQ	2 <i>n</i> = 14
		Beighton < 5 <i>n</i> = 23	Beighton	5 <i>n</i> = 9
Age in Years: Mean (Range)	13.6 (9–18)	13.4 (9–17)		13.9 (10–18)
Female; <i>n</i> (%)	25 (78)	16 (70)		9 (100)
Race; <i>n</i> (%)				
White	23 (72)	16 (70)		7 (78)
Other	9 (28)	7 (30)		2 (22)

* Skin hyperextensibility and/or smooth, velvety skin.

† For definitions please see the PBQ which is available in reference #3, no postpartum or central nervous system bleeding were reported in this study.

‡ Reported only for female, postmenarche participants.

§ Fisher's Exact test *P* < 0.05.