Physician practices in evaluation and treatment of patients with generalized joint hypermobility and bleeding

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The association between bleeding and joint hypermobility may not be as diagnostically obvious in patients with milder connective tissue disorders. We surveyed members of the Hemostasis and Thrombosis Research Society regarding their knowledge, evaluation, and management practices in patients with generalized hypermobility spectrum disorder/hypermobile Ehlers–Danlos syndrome (hEDS) and bleeding symptoms. The objectives of this study were to (1) evaluate hematologists' diagnosis and management practices for patients with bleeding symptoms and generalized hypermobility spectrum disorder/hEDS and (2) determine future education and research priorities regarding bleeding symptoms within this population. Evaluate hematologists' diagnosis and management practices for patients with bleeding symptoms and generalized hypermobility spectrum disorder/hEDS. Determine future education and research priorities regarding bleeding symptoms within this population. A web-based survey was sent to Hemostasis and Thrombosis Research Society physician members. Physician demographics, preferred evaluation for hEDS, management of bleeding episodes, and referral patterns were collected and descriptive statistics were performed. Only two-thirds of respondents reported evaluating for hypermobility, despite all respondents being aware of the association with bleeding. There were significant variations in referral patterns for genetic counseling, diagnostic evaluation, and management of nonhematologic symptoms. There were also significant variations in reported medical homes for this patient population. Research prioritization included understanding the evolution of bleeding symptoms with age in this population as well as the development of functional tests to identify the molecular mechanism of bleeding and the development of novel hemostatic agents for this population. Results from 33 respondents show differing physician practices regarding the evaluation and management of bleeding in hypermobile patients. Many physicians suggested further research priorities to include studying the natural history of the disease and development of functional diagnostic testing as well as targeted therapeutic options in this patient population. *Blood Coagul Fibrinolysis* 32:591–595 Copyright © 2021 The Author(s). Published by Wolters Kluwer Health, Inc.

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Introduction

Patients with hereditary connective tissue disorders may experience significant bleeding symptoms throughout their lifetime, including easy bruising, mucosal bleeding, and heavy menstrual bleeding [1–3]. While this association is well recognized in the more severe connective tissue disorders, it is perhaps not as diagnostically obvious to healthcare providers seeing patients with milder forms such as generalized hypermobility spectrum disorder (G-HSD) and hypermobile Ehlers–Danlos syndrome (hEDS). The diagnosis of hEDS requires patients to meet specific criteria evaluating joint hypermobility, associated systemic manifestations of connective tissue dysfunction, family history, and musculoskeletal pain symptoms [4]. Most patients with generalized joint hypermobility do not meet these diagnostic criteria, but they can still have significant associated symptoms that place them in the spectrum of disorders known as G-HSD [5]. Given these subtle findings, these patients may present to a hematologist for evaluation and treatment of bleeding symptoms before receiving a diagnosis of G-HSD/hEDS.

The diagnosis of these conditions also requires the provider to understand and assess a Beighton score. The Beighton score is a validated and reproducible nine-point assessment of joint mobility that evaluates dorsiflexion of the fifth digits, apposition of the thumbs to the flexor surface of the forearms, hyperextension of the elbows, hyperextension of the knees and forward flexion of the trunk [6,7]. Recent studies show that Beighton scores can vary significantly with age, sex, and ethnicity, indicating

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Table 1 Prophylaxis and treatment strategies of respondents for typical patients with significant bleeding history and patients with generalized joint hypermobility

Medication or product	Typical prophylaxis, *n* (%)	Typical treatment, *n* (%)	Hypermobile prophylaxis, *n* (%)	Hypermobile treatment, *n* (%)
Desmopressin acetate	6 (18%)	6 (18%)	7 (21%)	9 (27%)
Antifibrinolytics	10 (30%)	13 (39%)	11 (33%)	14 (42%)
Platelets	3 (9%)	2 (6%)	2 (6%)	2 (6%)
Plasma	1 (3%)	1 (3%)	0 (0%)	0 (0%)

that different thresholds may be necessary for diagnosis [8]. The updated 2017 hEDS diagnostic criteria utilizes the Beighton score as one of its measures, with different thresholds specified for different ages [9].

As hematologists may be the first subspecialists encountered by this population, they must be aware of these diagnostic criteria as well as treatment strategies supported by current literature. The Ehlers–Danlos Society Hematology Consortium surveyed physician members of the Hemostasis and Thrombosis Research Society (HTRS) to evaluate diagnosis and management practices for this population and to determine future education and research priorities.

Methods

Survey questions were developed in consultation with members of the Ehlers–Danlos Society Hematology Consortium. A web-based survey was sent to HTRS physician members through the society mailing list, with two reminders sent out at weekly intervals. The survey remained open for 1 month. Information regarding physician demographics, preferred evaluation for hEDS, management of bleeding episodes, and referral patterns was collected. Participants were also given space to provide additional comments. Descriptive statistics in the form of mean, range, and frequency distributions were performed.

Results

Of the 385 members who received the e-mail, 33 responded. There were 12 (36.4%) adult providers, 16 (48.5%) pediatric providers, and five (15.2%) combined adult and pediatric providers. Most respondents (93.9%, $n=31$) were based in a university hospital, while the remaining (6.1%, $n=2$) were based in community hospitals. Fifteen respondents (45.5%) had more than 10 years of experience, ten respondents (30.3%) had 5–10 years of experience, and eight respondents (24.2%) had 1–5 years of experience.

All providers were aware of the relationship between bleeding and joint hypermobility but only 21 respondents (63.6%) reported always evaluating for hypermobility as part of their clinical exam. Ten respondents (30.3%) did so only if they did not establish an alternative cause of bleeding and two respondents (6.1%) reported never evaluating for hypermobility due to lack of training and minimal influence on management of reported bleeding symptoms. Approximately one-third of providers ($n=11$) endorsed using more than one method to evaluate for joint hypermobility. The most popular method of evaluation was the Beighton score (57.6%, $n=19$) closely followed by a combination of subjective assessment and patient report (48.5%, $n=16$). Most respondents did not utilize the 2017 hEDS criteria (72.7%, $n=24$) due to unfamiliarity with the checklist (48.5%, $n=16$) and lack of training in the evaluation (33.3%, $n=11$). Other reasons included time constraints ($n=2$) and lack of influence of hypermobility on management plans ($n=1$). Most respondents (63.6%, $n=21$) felt that the use of a templated checklist in the electronic medical record would encourage the use of the 2017 hEDS criteria.

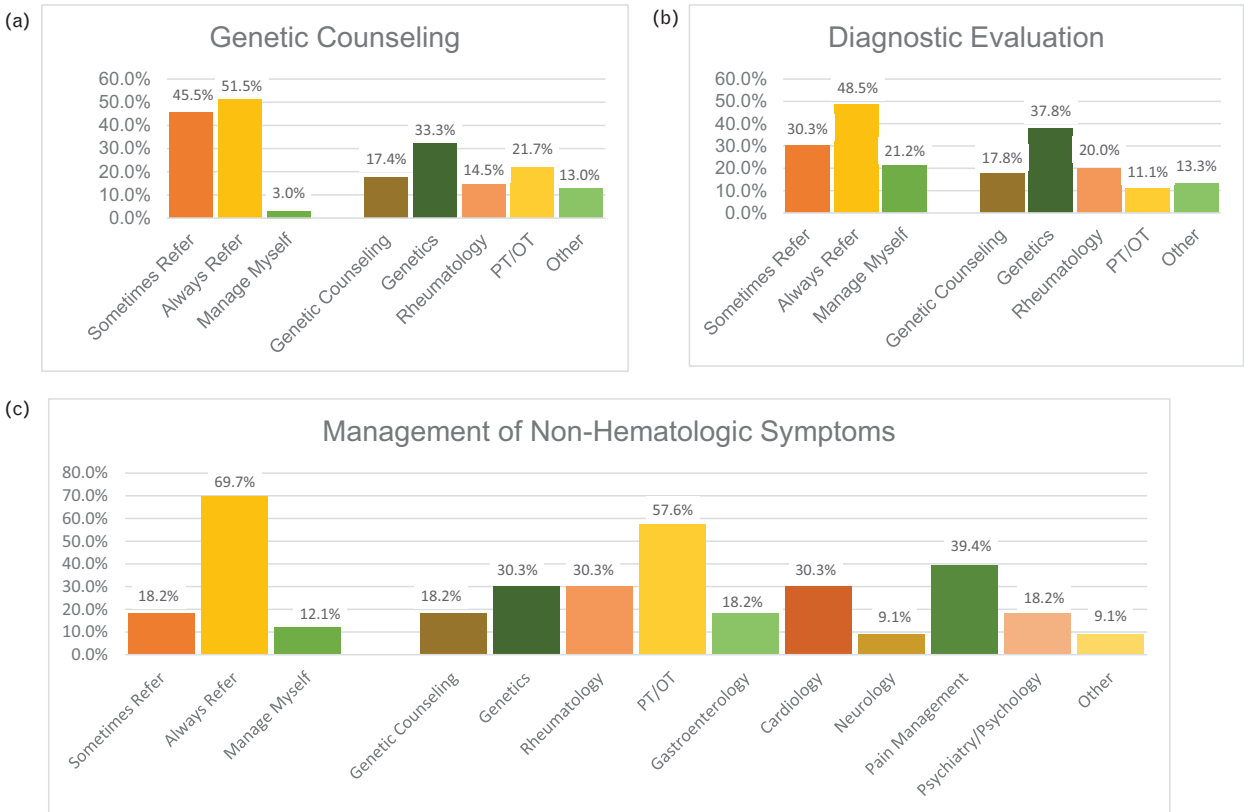
According to respondent recall, bruising (84.8%, $n=28$), uterine bleeding (66.7%, $n=22$) and epistaxis (54.5%, $n=18$) were the most frequently observed bleeding symptoms in patients with joint hypermobility.

Respondents were asked to provide their preferential prophylaxis and treatment strategies for patients with significant bleeding history, both with and without joint hypermobility. Half of respondents (51.5%, $n=17$) believed that joint hypermobility changed their management of perioperative bleeding. However, regardless of the presence of joint hypermobility, antifibrinolytics and desmopressin acetate were the agents most commonly used for both prophylaxis and treatment (Table 1).

The referral patterns of treating hematologists were also explored (Fig. 1). Referrals were placed most often for genetic testing and management of nonhematologic symptoms related to hypermobility, although the specialties to which patients were referred varied among respondents. Genetics, genetic counseling, rheumatology and physical or occupational therapy were the most common referrals placed.

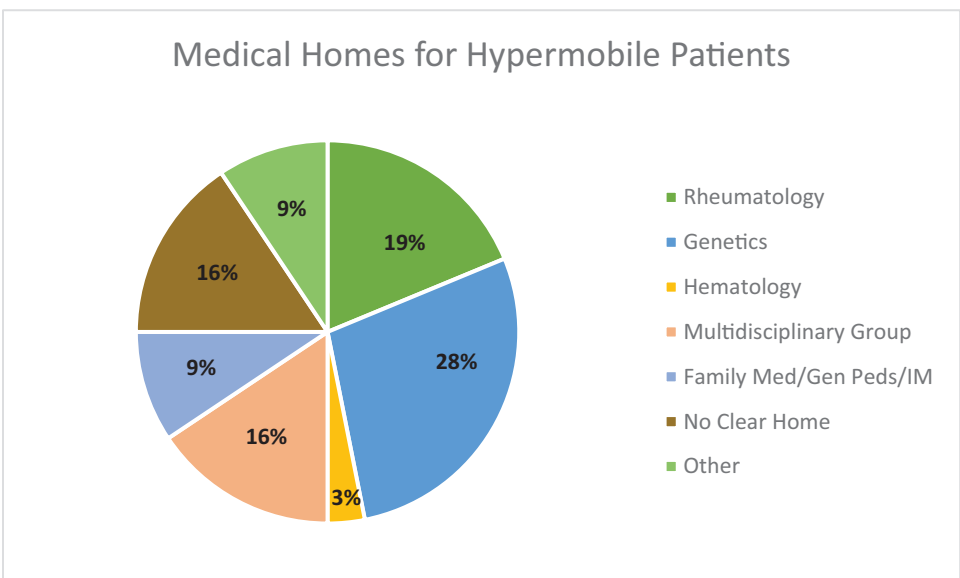
In regards to follow-up, most respondents planned follow-up every 1–2 years (66.7%, $n=22$) with fewer respondents following patients more than once per year (15.2%, $n=5$), only as needed (15.2%, $n=5$) or never (3.0%, $n=1$). Most respondents reported that these patients were followed in a Hemophilia Treatment Center (60.6%, $n=20$), followed by a general hematology clinic (36.4%, $n=12$) or another comprehensive multidisciplinary clinic (3%, $n=1$). Various clinics were described as medical homes for these hypermobile patients (Fig. 2).

Fig. 1



Referral patterns of respondents in regards to (a) genetic counseling, (b) diagnostic evaluation, and (c) management of nonhematologic symptoms, including frequency of referral and locations of referral. Regarding genetic counseling and diagnostic evaluation, 'other' includes gastroenterology, cardiology, neurology, pain management, psychology, and psychiatry. Regarding management of nonhematologic symptoms, 'other' refers to orthopedics and multiple referrals, depending on symptoms present.

Fig. 2



Variety of medical homes for hypermobile patients according to survey respondents. Other was selected to describe those with variable homes depending on additional symptoms.

Respondents were also asked to rank areas for research prioritization. The top ranked areas of research prioritization included development of a natural history cohort to understand the evolution of bleeding symptoms with age (30%, $n = 9$), followed by the development of functional tests to identify the molecular mechanism of bleeding in these patients (26.7%, $n = 8$) and the development of novel therapeutics to treat bleeding episodes in patients with joint hypermobility (25.8%, $n = 8$).

Discussion

Although this study was limited due to the challenges associated with a voluntary survey, including low response rate and self-selection of participants that may not necessarily reflect the views of hematologists across the nation, we were able to identify some important trends in this area. All respondents were aware of the relationship between bleeding and hypermobility and most routinely evaluated for joint hypermobility in their clinical assessments, though the method of evaluation differed between providers. There were wide variations in treatment regimens, referral patterns, follow-up schedules and presumed medical homes, reflecting the complex clinical needs of this patient population as well as the varied approaches to management.

In the absence of consistent hemostatic laboratory abnormalities, the Beighton score provides an important diagnostic clue in the assessment of bleeding symptoms. Despite being a major component of the 2017 hEDS diagnostic criteria, not all respondents felt they were adequately trained in the physical examination procedures required for the Beighton assessment. A study in physical therapists indicated that they were more likely to utilize these diagnostic criteria if they had received formal training in the management of this patient population [10]. Consequently, more formal hypermobility assessment and management training should be considered an integral part of education in hematology. Our survey also suggests that a templated checklist may encourage use of the diagnostic criteria. The presence of generalized joint hypermobility, however, should not deter physicians from obtaining standard coagulation screening tests in patients with significant bleeding symptoms, as patients with hEDS can have additional hemostatic abnormalities [11].

Regarding the management of bleeding symptoms, only half of respondents felt that the presence of joint hypermobility would change their treatment strategies. Antifibrinolytics and desmopressin acetate were the most common responses, irrespective of the presence of joint hypermobility (Table 1). While currently available literature supports the use of desmopressin acetate in this population, there is little evidence regarding the effectiveness of antifibrinolytics [12–15]. It seems reasonable to extrapolate the efficacy of antifibrinolytics to this population given that these medications are nonspecific agents used successfully in a wide variety of bleeding disorders. With the current recall on desmopressin acetate, our institution is currently utilizing antifibrinolytics for outpatient procedures. For inpatient or major surgeries, we may utilize a combination of intravenous desmopressin acetate and antifibrinolytics, particularly if the surgery involves mucous membranes. These patients may also require special precautions given their known issues with wound healing, including closure of wounds with minimal tension, generous use of deep sutures and delay of suture removal for twice the usual duration. The lack of a standardized management approach, despite well recognized bleeding symptoms, highlights the need for further education and research.

The wide variation in referral patterns, follow-up schedules and identifiable medical homes further emphasizes the unfamiliarity and lack of standardized approach in management of this patient population. Most of the responding hematologists follow these patients in a Hemophilia Treatment Center rather than a general hematology clinic, indicating the complexity of their associated bleeding symptoms and the need for comprehensive clinical care. The research priorities selected by respondents also reflect the lack of robust data regarding the natural history of bleeding as well as the lack of understanding regarding the pathophysiology behind these symptoms. Research within this population, however, is limited due to the absence of directed functional testing and the lack of a representative animal model. The varied responses highlight the need for a collaboration between hematologists and established multidisciplinary medical homes to better understand the course of bleeding symptoms, which could potentially lead to the development of functional tests and ultimately, the development of more tailored therapeutic options for patients with bleeding tendencies due to joint hypermobility syndromes.

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Conflicts of interest

There are no conflicts of interest.

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