Received: 21 December 2018 | Revised: 13 May 2019 | Accepted: 14 May 2019

DOI: 10.1111/hae.13800

REVIEW ARTICLE

Haemophilia WILEY

An update on the new classification of Ehlers-Danlos syndrome and review of the causes of bleeding in this population

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Funding information
Aniara Diagnostica

Abstract

It has long been hypothesized that bleeding symptoms in people with hypermobility occur as a result of abnormalities in the collagen of the vessel wall or the connective tissues. The bleeding symptoms, particularly in the skin, have been attributed to the fragility of skin and blood vessels caused by "defective collagen wickerwork" of the reticular layer of the skin. Collagen, which forms the framework of vessel walls, is altered in many patients with Ehlers-Danlos syndrome (EDS) leading to weakening of the vessel wall or the supporting tissues. Another important function of subendothelial collagen is its interaction with platelets and von Willebrand factor, which results in the propagation of a platelet plug. Thus, abnormalities in subendothelial collagen may alter its interaction with platelets and VWF. More recently, hypermobile-EDS (hEDS) has been associated with mast cell disorders, a condition independently associated with bleeding symptoms. It has also been observed that patients with mild bleeding disorders have a more severe bleeding phenotype when they have co-existing joint hypermobility.

KEYWORDS
bleeding disorder, Ehlers-Danlos Syndrome, generalized joint hypermobility, hEDS, mast cell activation disorder

1 | INTRODUCTION

Since the first description by Ehlers in 1901 of a patient with skin and joint laxity along with a tendency to haemorrhage, significant bruising has been noted to occur in patients with what is now called Ehlers-Danlos syndrome (EDS).[1] The increased bruising might be the most concerning symptom, and this may result in the haematologist being the first specialist to be encountered as patients begin their diagnostic odyssey.[2] Joint mobility is a "continuous trait." This means that for people in the general population, joint mobility falls on a spectrum from having "very tight" to "very lax" joints, measured as the extent of movement from less than normal to strikingly increased. The incidence of generalized joint hypermobility varies according to ethnicity, gender and age.[3] People who pass beyond a threshold into joint hypermobility and have other characteristic features fall into a clinical spectrum defined as Ehlers-Danlos syndrome. This is a clinically heterogeneous group of conditions where both genetic changes and particular clinical features (vascular rupture, bowel rupture, scoliosis, formation of markedly abnormal scars, among other things) have been used to define specific types.[4] This clinical entity overlaps with a syndrome rheumatologist described as joint hypermobility syndrome (JHS), in which pain that is not the result of inflammation is the primary defining feature.[5] The most common type of EDS, now referred to as hypermobile EDS (hEDS), is defined by joint mobility at the upper end of the spectrum, the presence of relatively objective signs of connective tissue dysfunction and the absence of most of the differentiating features of other types.[5,6] The genetic aetiology of hEDS is unclear. Patients with the phenotype do not have clear mutations in any candidate genes.

TABLE 1 Classification of EDS, genetic basis and clinical features.pptx

	EDS subtype	Abbreviation	IP	Genetic basis	Protein	Prominent clinical features	Importance haematological considerations
1	Classical	cEDS	AD	COL5A1 COL1A1	Type V collagen Type I collagen	• Skin hyperextensibility and fragility • GJH	• Easy bruising • Arterial rupture in patients with COL1A1 c.934C > T, p.Arg312Cys substitution
2	Classical-like	clEDS	AR	TNXB	Tenascin XB	• Similar to cEDS but different inheritance pattern	• Easy bruising
3	Cardiac-valvular	cvEDS	AR	COL1A2	Type I collagen	• Progressive cardiac-valvular disease • Skin hyperextensibility and fragility • GJH •	• Easy bruising
4	Vascular	vEDS	AD	COL3A1 COL1A1	Type III collagen Type I collagen (rare)	• Vascular rupture • Spontaneous colonic perforation • Uterine rupture in 3rd trimester • Carotid-cavernous fistula	• Easy bruising in unusual sites like cheeks or back • Early onset varicose veins • Translucent skin
5	Hypermobile	hEDS	AD	Unknown	Unknown	• Generalized joint hypermobility	• Easy bruising
6	Arthrochalasia	aEDS	AD	COL1A1 COL1A2	Type I collagen	• Congenital bilateral hip dislocation • GJH • Skin hyperextensibility	• Easy bruising
7	Dermatosparaxis	dEDS	AR	ADAMTS2	ADAMTS-2	• Extreme skin fragility with congenital skin tears • Characteristic craniofacial features • Redundant skin at wrist and ankles • Increased palmar wrinkling	• Severe bruising with subcutaneous haematomas
8	Kyphoscoliotic	kEDS	AR	PLOD1 FKBP14	LH1 FKBP22	• Congenital muscle hypotonia • Early kyphoscoliosis • GJH	• Easy bruisable skin • Rupture/aneurysm of medium-sized arteries
9	Brittle Cornea syndrome	BCS	AR	ZNF469 PRDM5	ZNF469 PRDM5	• Thin cornea • Keratoconus • Blue sclerae	
10	Spondylo-dysplastic	spEDS	AR	B4GALT7 B3GALT6 SLC39A13	β4GalT7 β3GalT6 ZIP13	• Short stature • Muscle hypotonia • Bowing of limbs • Skin hyperextensibility	
11	Musculo-contractual	mcEDS	AR	CHST14 DSE	D4ST1 DSE	• Multiple congenital joint contractures • Characteristic facies • Translucent skin	• Large subcutaneous haematomas
12	Myopathic	mEDS	AD or AR	COL12A1	Type XII collagen	• Muscle hypotonia that improves with age • Proximal joint contractures • Hypermobile distal joints	
13	Periodontal	pEDS	AD	C1R C1S	C1r C1s	• Intractable periodontitis • Pretibial hyperpigmentation	• Easy bruising

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; IP, inheritance pattern.

2 | THE NEW EDS CLASSIFICATION AND ITS IMPLICATION FOR THE HAEMATOLOGIST

Understanding of EDS has evolved over the last decades. In 1997, the Villefranche working group classified subtypes of EDS, placing most people with hypermobility and without electrophoretically evident collagen abnormalities or other distinctive physical findings in the EDSIII category.[7] The scientific community re-convened in 2017 to reclassify EDS using information from newly identified causative genes.[4] EDS has now been grouped into thirteen different subtypes (Table 1). Skin biopsies and protein electrophoresis have been replaced by gene sequencing, which simplifies the classification of an EDS diagnosis and increases the probability that patients who present to a haematologist will have a genetic diagnosis that can inform management. One or more genes are associated with twelve of the subtypes. The notable exception to this is the thirteenth EDS subtype, hypermobile EDS (hEDS). Since no genes have been identified that explain more than a few per cent of patients with hEDS,[4,5] the results of molecular genetic analysis are generally normal and not helpful. The majority of patients with EDS fall into the hEDS category. A subset of these patients with excessive bleeding may be seen by haematology. The aetiology of bleeding is complicated with potential causes including the inherent pathophysiology of hypermobility and also coagulopathies from factor deficiency, platelet dysfunction, acquired VWD and mast cell activation disease. All of these associations will be discussed below.

Without the tool of genetic analysis, the 2017 reclassification group created a new set of clinical criteria for hEDS (Figure 1). Essentially, these added a set of reasonably objective findings that are required to diagnose hEDS[4] with the expectation that using more objective criteria for hEDS will improve research to identify genes associated with the condition. Per the 2017, criteria, diagnosis with hEDS requires Criterion (1) hypermobility; Criterion (2) two of three A/B/C features; and Criterion (3) absence of another cause for symptoms. The second criterion features are (a) at least 5 of 12 objective signs of connective tissue dysfunction involving skin, subcutaneous tissue, growth and/or the heart; (b) a family history of hEDS (by these criteria) in a first-degree relative; and (c) chronic pain or joint instability.

The 12 objective signs of connective tissue dysfunction include skin findings (soft/velvety or stretchy, presence of unexplained striae); subcutaneous tissue findings (piezogenic papules, hernias, atrophic scarring, pelvic prolapse), growth anomalies (dental crowding, arachnodactyly, increased arm span-to-height ratio) and cardiac features (mitral valve prolapse, aortic root dilation). The use of a checklist assists with evaluation of hypermobile patients in the clinical setting (https://www.ehlers-danlos.com/heds-diagnostic-checklist/).

Criterion 3 requires ruling out other diagnoses. Because of the complexity of the differential diagnosis, the diagnosis of EDS has generally occurred in a genetics clinic. However, lack of clinical geneticists can make the wait for diagnosis burdensome. For reasons of expediency, it may be appropriate for trained physicians of a variety of specialties to evaluate and diagnose patients, using the well-laid out hEDS criteria. Only patients with concerning findings on examination or family history would then need to be sent to genetics for additional evaluation and testing. Some concerning findings would include true arachnodactyly, bicuspid aortic valve, high myopia or aortic dilation suggestive of Loeys-Dietz syndrome, Marfan syndrome or other connective tissue disorders; developmental delay or autism spectrum disorder suggesting Fragile X syndrome or other syndromic causes of hypermobility; and family history of early death by arterial dissection suggestive of vascular EDS or other conditions.

These criteria may be more relevant for adult than for paediatric patients, since paediatric patient may not be old enough or had enough exposures to form scars, develop pelvic prolapse or have clear dental crowding, etc Many clinicians are reluctant to diagnose hEDS in a child, but will instead counsel the family on prudent precautions and expectant monitoring.

In addition to adding objectivity to hEDS diagnosis, the reclassification re-envisioned hypermobility as a "spectrum" disorder (Figure 2).[6] A person who does not meet the more stringent A features in Criterion 2, but who has hypermobility and pain, can still be diagnosed with hypermobility on the EDS spectrum (HSD). The subtypes of HSD include generalized (G-HSD), peripheral (P-HSD) limited to hands and/or feet, localized (L-HSD) found only in a single joint or body part and historic (H-HSD) where hypermobility is no longer present.[8] People with hypermobility but not pain or other objective findings of connective tissue dysfunction are categorized as having asymptomatic joint hypermobility. This has made diagnosis more complicated, but also more precise.

3 | BLEEDING AND BRUISING IN THE HYPERMOBILE PATIENT

Traditionally, bleeding complications have been attributed to the vascular abnormalities associated with EDS. These complications are categorized into haematomas, intracranial haemorrhage, arterial dissections, arterial aneurysms, GI bleeding and perioperative haemorrhage. Bruising is often thought of as a mild symptom and is present in many patients with EDS.[9] For women, heavy menstrual bleeding is a commonly reported symptom.[10,11] However, experience suggests that it may not be possible to distinguish clinically the aetiology of haematomas, bleeding into organs and perioperative bleeding. Whether these are from vascular origin or from a haemostatic defect usually requires a detailed diagnostic laboratory evaluation. We will not differentiate bleeding symptoms arising from vascular wall abnormalities versus haemostatic abnormalities in this paper.

A recent case-control study revealed that the prevalence of symptomatic joint hypermobility/suspected collagen disorders in patients referred to a bleeding disorder clinic was higher than in the age- and gender-matched controls.[12] Conversely, most hypermobile patients report symptoms of easy bruising[13] and many have objective signs of abnormal bleeding.[14] This suggests the contribution of abnormal collagen, which is reflected in symptomatic joint

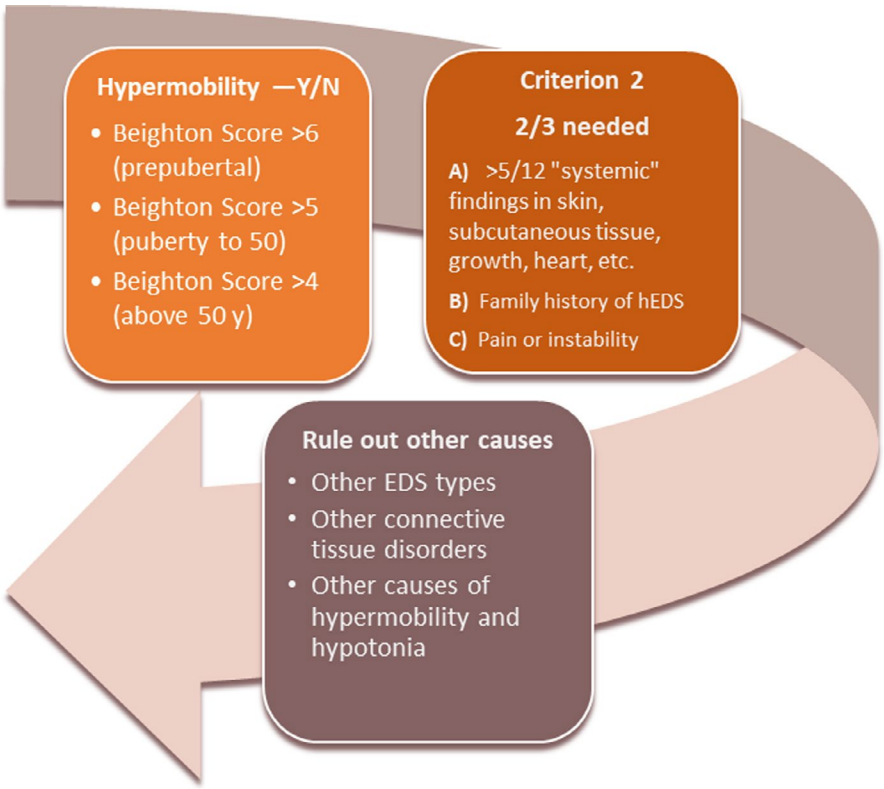

FIGURE 1 2017 hEDS diagnostic criteria. [Colour figure can be viewed at wileyonlinelibrary.com]

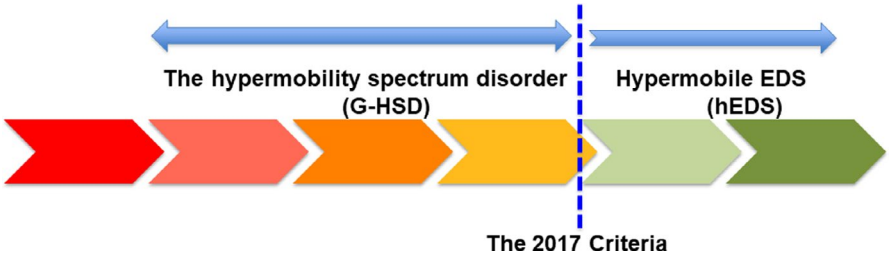

FIGURE 2 On the far left, the person is hypermobile and well with nothing else to find; on the right of the dash line are people with hEDS as defined by the new criteria. To the left of the dashed line, that is. those who do not meet the criteria (or have any other condition) we now use the term hypermobility spectrum disorder (HSD)—people with their own sets of problems due to their hypermobility but who do not have hEDS. Slide donated by Dr Alan Hakim, used with permission. [Colour figure can be viewed at wileyonlinelibrary.com]

hypermobility, to the expression of bleeding tendency. This also highlights the need for a thorough evaluation of collagen disorders as part of an assessment for patients who are being worked up for bleeding disorders.[13,15]

3.1 | Role of the collagen-VWF interaction in achieving primary haemostasis

The role of the different types of collagen appears to be twofold: to maintain the structural integrity of the blood vessels and to serve as an adsorption platform for VWF and platelets to initiate primary haemostasis when the integrity of the vessels wall is disrupted.[16] When there is a breach of endothelial integrity, there is opportunity for von Willebrand factor (VWF) to interact with different types of collagen, which is an integral part of the extracellular matrix (ECM; Figure 3). Disruption of the vessel wall exposes the ECM collagens that adhere to the VWF A3 domain. The now adhered VWF experiences shear stress that initiates a conformational change resulting in the conversion of a globular protein into a stretched protein, exposing the platelet binding site on the VWF A1 domain. VWF and platelets, which are the key components of primary haemostasis (clot initiating factors), interact with collagen type I, type III and type IV, which are in abundance in the subendothelial matrix.[17,18]

Von Willebrand factor interacts with multiple types of collagen and abnormalities in VWF that alter its collagen-binding properties have been well described. The A3 region of VWF has been shown to interact with type I and type III collagen, with the interaction with type III collagen being more clinically significant due to its higher content in the

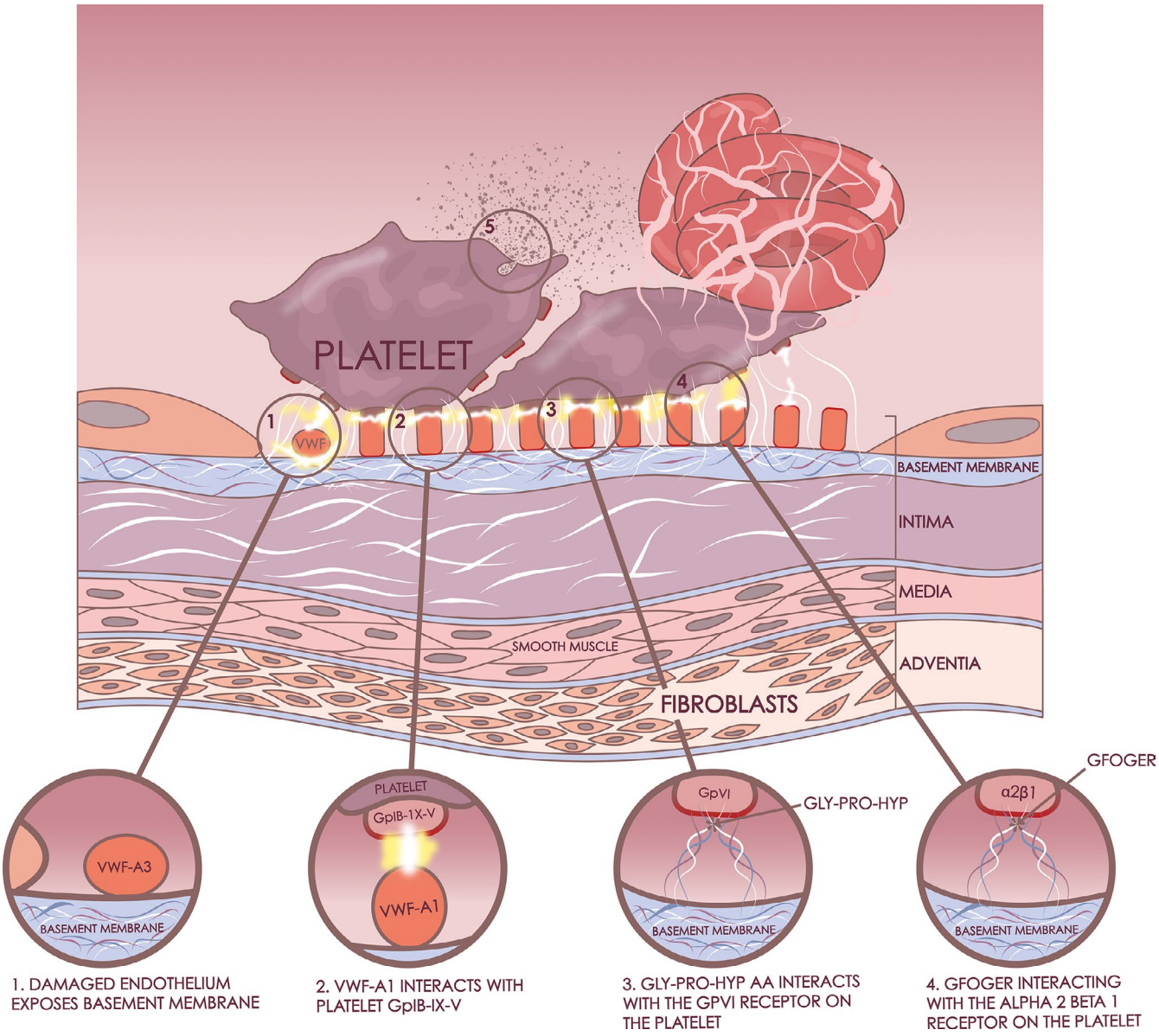

FIGURE 3 Schematic representation of collagen interaction with key players in primary haemostasis. (1) Damaged endothelium exposes basement membrane collagen to interact with VWF A3 domain. Adhered to the collagen, VWF is exposed to shear stress from flowing blood in the blood vessel and converts from a globular to more linear shape and exposing it's A1 domain. (2) The VWF-A1 domain interacts with platelet Gp1B-IX-V complex. (3,4) The above interaction enables collagen interaction with platelet receptors. (glycoprotein VI interacts with Gly-Pro-Hyp motif and the α2β1 receptor interacts with the triple-helix GFOGER motif). (5) This results in platelet activation and degranulation. [Colour figure can be viewed at wileyonlinelibrary.com]

subendothelial matrix. The site at which VWF binds to collagen III has been identified as a 9-amino acid sequence in a triple-helix domain.[19,20] The A1 domain which interacts with platelet Gp1b also interacts with collagen IV and collagen VI.[16,17,21,22] Abnormal collagen type IV has been associated with intracranial haemorrhage, although the pathogenesis has been attributed to abnormal basement membrane integrity and brain structure rather than abnormal collagen-VWF interactions.[23,24] The VWF-collagen interaction is utilized in the laboratory diagnosis of some types of VWD, and efforts have begun to better characterize this interaction so that it reflects the in vivo interaction of VWF and collagen.[18,25,26]

3.2 | Role of the platelet-collagen interaction in achieving primary haemostasis

Platelets interact with collagen via both the platelet glycoprotein VI (GPVI) and integrin α2β1. A highly specific Gly-Pro-Hyp (glycine-proline-hydroxyproline) amino acid sequence of collagen is recognized by platelet GpVI.[27] Patients with reduced or abnormal platelet GPVI show an impaired response to collagen, causing a mild bleeding tendency.[28-30] The platelet-collagen receptor integrin α2β1 recognizes a specific hexapeptide GFOGER

(glycine-phenylalanine-hydroxproline-glycine-glutamic acid-arginine) within the context of a collagen triple helix.[27,31]

It can be inferred that abnormalities in collagen can impair platelet-collagen interactions. Two independent groups have demonstrated that collagen obtained from EDS patients showed decreased platelet aggregation when compared to control collagen.[32,33] However, since EDS is now established by genetic diagnosis rather than tissue biopsy, it is unlikely that these studies will be replicated.

While collagen remains the most procoagulant subendothelial protein, the role of other subendothelial proteins continues to be elucidated. The non-collagen proteins of the basement membrane include Perlecan, Nidogen and Laminins. The role of Laminins in platelet adhesion and VWF interaction has been well described. The role of these non-collagen proteins that serve in maintaining haemostasis, however, has not been independently studied.

Another extracellular matrix protein, thrombospondin 2 (TSP2), has been shown to play a role in haemostasis in mouse model studies, and multiple mechanisms for its activity have been suggested. TSP2 null mice have disordered collagen fibrillogenesis and increased vascular density, suggesting that TSP2 modulates the adhesion and migration properties of mesenchymal cells.[34] Another study showed weak binding of VWF-coated 2-μm beads to the TSP2 knockout extracellular matrix. Similar bleeding tendencies have not been described in humans with thrombospondin 2 mutations.[35]

While there are many studies of bleeding caused by defects in platelet surface receptors and VWF, there is limited research studying the defects of collagen on bleeding symptoms. Theoretically, defects in collagen could affect the integrity of the vessel wall and fragility of connective tissue supporting the blood vessel leading to a more visible bleeding phenotype in skin and mucus membranes. It has also been speculated that bleeding disorders might originate from collagen autoantibodies; however, the presence of these antibodies in patients with EDS and bleeding has not been established. This hypothesis is based on the model of Goodpasture's syndrome where haematuria and pulmonary haemorrhage are secondary to antibodies against the NC1 domain of α3 chain of collagen type IV.[16]

3.3 | Platelet dysfunction and Ehlers-Danlos syndrome

As early as 1965, abnormalities in platelet ultrastructure in EDS were noted on electron microscopy. Although EM studies are no longer routinely used in clinical practice, this finding reflects the historical interest in identifying the aetiology of bleeding in hypermobility.[36] While platelet function defects constitute a common cause of bleeding disorders, they are usually a mild phenotype. However, platelet dysfunction in association with EDS may exaggerate the bleeding phenotype.[37,38] The specific details surrounding the role of platelet dysfunction in EDS-related bleeding have been variable. One description of EDS patients includes co-occurring joint hypermobility, thin skin, easy bruising, low factor VIII levels, low VWF and associated platelet aggregation defects.[39] More recently, it has been shown that patients with vascular EDS have a platelet dysfunction, although this was studied only in a small cohort of patients and will need to be tested in a larger group of patients.[40] A recent comprehensive study described significant platelet function abnormalities in patients with EDS and the absence of any consistent coagulation defect including thrombin generation.[14]

3.4 | Von Willebrand disease and Ehlers-Danlos syndrome

Von Willebrand (VWD) disease is a common bleeding disorder. When co-occurring in someone with EDS, it can cause more accentuated bleeding phenotype and be more likely to result in a referral to a haematologist. Recently, Hall et al described the clinical presentation of five patients with co-existing VWD and EDS and 21 patients with VWD and joint hypermobility in a retrospective chart review.[41] They believed that joint hypermobility contributed to aggravated bleeding symptoms in an otherwise mild bleeding disorder.[41] Acquired von Willebrand syndrome (AVWS) has also been reported in people with EDS with clinical manifestations likely due to the additive effect.[42] This highlights the importance of screening for EDS in patients with bleeding disorders since clarifying the diagnosis has implications in management.

3.5 | Isolated coagulation factor deficiency in Ehlers-Danlos syndrome

Patients with congenital bleeding disorders and EDS have been previously described. These include mild haemophilia A, factor XI deficiency and factor XIII deficiency. Most of these reports suggest a random association between the bleeding disorder and the hereditary collagen disorder resulting in a more profound bleeding phenotype.[39,43-45]

3.6 | Mast cell activation disorders and Ehlers-Danlos syndrome

A disease cluster of POTS, EDS and MCAD was reported by Cheung and Vadas.[46] While mast cells (MCs) are best known for their role in allergic disorders, their localization in connective tissue near the nerve fibres, blood vessels and lymphatics, could result in neuropathy and connective tissue dysfunction when MCs are dysregulated. Increased number of chymase-positive mast cells are present in the eyelid skin of patients with connective tissue disorders.[47] A subset of hEDS patients have been found to have MCAD which result in comorbidities such as functional gastrointestinal disorders, asthma, neuropsychiatric conditions and orthostatic intolerance. The key driver of these symptoms is tryptase, which is released from the MC granules, although consistently elevated levels have not been demonstrated. Symptoms of dysautonomia and connective tissue abnormalities have also been associated with increased copy number of the *TPSAB1* gene, which encodes for alpha tryptase. Tryptase causes proteolysis of the α chain of fibrinogen making it an unsuitable substrate for the action of thrombin, possibly worsening bleeding. The bleeding diathesis associated

with patients with EDS and MCAD includes AVWS, acquired disorders of primary and secondary haemostasis, and fibrinolysis.[48]

Mast cells are granulocytes that play an important role in immunology and haematology, leading to allergy and anaphylaxis symptoms. Degranulation releases histamine, heparin, vasoactive intestinal polypeptide, prostanoids, chymase, antithrombin III, tissue-type plasminogen activator, factor VIII and tryptases, which can act as pro-inflammatory mediators and also play a role in bleeding.[48-50] Excess production and accumulation of mast cells characterize a wide range of disorders, broadly termed mast cell activation disease (MCAD), which occurs from a pathologic and potentially clonal accumulation of mast cells in various organs and tissues. Organs such as the bone marrow, spleen, liver, GI tract and skin can be involved.[49]

Both mastocytosis and anaphylaxis can be seen in the EDS patient who presents with prolonged PT/PTT and unusual bleeding symptoms. Other mediators, including heparin-like compounds and antithrombin, may also contribute to bleeding symptoms in patients with mast cell disorders and EDS. This could occur in the apparent absence of an underlying congenital bleeding disorder. Interestingly, standard haemostatic management with FFP, platelet transfusion and vitamin K are often insufficient to treat bleeding related to uncontrolled degranulation of mast cells and mast cell hyperactivity. The more debilitating neurological comorbidities of hEDS have occasionally been treated with plasmapheresis, and the improvement associated with this therapy suggests that there may be an immune-mediated aetiology to some symptoms.[51]

3.7 | Common coagulation tests in Ehlers-Danlos syndrome

The abnormalities noted in diagnostic haemostatic tests are often equivocal for patients with EDS. Early studies of haemostasis showed a normal bleeding time, prothrombin time, platelet count and fibrinogen. A positive capillary fragility test also known as the Rumpel-Leede or Hess test has been observed. This pattern of results suggested an increased capillary fragility is keeping with the pathogenesis of EDS.[52] More recently, it has been shown in a small cohort that these patients have consistently elevated bleeding times.[53] Other abnormalities noted were structural or functional defects of platelets, although these abnormalities have not been consistently verified.

3.8 | New options for understanding bleeding in EDS

The use of whole exome sequencing in the diagnosis of inherited bleeding disorders (IBD) has the potential to identify pathogenic genetic variants already associated with well-defined bleeding disorders. Recent studies have identified novel defects in collagen genes in patients with IBD.[54] This highlights the importance of including an evaluation of collagen defects in a comprehensive evaluation of patients with bleeding disorders. Expanded use of whole genome sequencing (WGS) and whole exome sequencing (WES) may provide a means to discover new multifactorial mechanisms that contribute to a bleeding phenotype.[54]

3.9 | Treatment approach for patients with EDS (after excluding inherited bleeding disorders)

Some EDS experts advocate the use of cycles of vitamin C to improve collagen cross-linking, thereby reducing capillary fragility and improving mild bleeding symptoms. [22,55]

For surgical procedures and interventions, DDAVP has been used as its use is safe and may shorten the bleeding time.[53] DDAVP works by increasing VWF release from the endothelial cells, thereby improving platelet-subendothelial adhesion. There appears to be a higher incidence of bleeding complications following dental procedures in patients with hEDS (unpublished data), and it is reasonable to use DDAVP in these patients prior to the procedure. Applying sutures following dental extraction is also reasonable. It has been observed that bleeding in hypermobile patients worsens with age; however, DDAVP is a less attractive haemostatic option for older patients. This is due to the higher prevalence of comorbidities of atherosclerosis, renal failure and hypertension in the older population, which might increase the risk of complications associated with fluid retention.

For patients with a mild bleeding phenotype, it appears reasonable to allow them to undergo haemostatic challenges without any intervention. For patients with a prior history of significant perioperative bleeding or excessive bleeding symptoms, it appears reasonable to treat with DDAVP and antifibrinolytics in the perioperative period. For those hEDS patients experience tissue fragility, recommendations similar to those with classical EDS should be considered. These include closing wounds via sutures without tension; applying stitches generously and in layers and also leaving them in place twice as long as usual; and using tape to help prevent stretching of scar, but also being careful in its removal.[56] For management of heavy menstrual bleeding, care is usually individualized based on associated symptoms. If patients present with dysmenorrhoea as well, combined OCPs are appropriate. Antifibrinolytics can be used for the first 5 days of menses.

In patients with MCAD and EDS, it is imperative for the clinician to recognize that ensuring adequate haemostasis may require mast cell mediator blockers, stabilizers and steroids for acute bleeding. Maintenance treatment with these agents requires careful titration in the chronic setting to prevent reocurrence.[48,50,57]

The successful use of other agents (rVIIa[58,59] and tranexamic acid[59]) has also been reported. Again, these options should be balanced against the patient's increasing thrombosis risk with age. Our practice has been to limit the use of recombinant VIIa to life-threatening bleeds.

4 | SUMMARY

A bleeding phenotype has been a descriptor for patients with Ehlers-Danlos syndrome since it was first described and there is evidence of a wide spectrum of bleeding manifestations in patients with EDS. The aetiology for these symptoms includes mechanical weakness of

the vessel wall, defective subendothelial connective tissue supporting the vessels, mast cell defects and defective interactions between VWF, platelets and collagen. The presence of joint hypermobility in patients with bleeding symptoms and normal coagulation profile offers an explanation for the symptoms and also helps direct patients for appropriate care for their known comorbidities. If a co-existing IBD augments bleeding manifestations, bleeding can be reduced by specific treatments for the bleeding disorder. There is a paucity of data regarding management of bleeding symptoms in EDS patients without an identifiable IBD. Further studies are needed to identify the mechanisms that result in bleeding in patients with EDS, which could lead to developing newer treatments in preventing or treating acute bleeding episodes.

ACKNOWLEDGEMENTS

RJ outlined the original draft of the manuscript. RJ, CML and AC contributed to its drafting, and all authors approved the final version for publication. Figure 1 was shared by Dr. Alan Hakim. Figure 3 was created by Jump Simulation, OSF Healthcare and University of Illinois College of Medicine, Peoria.

DISCLOSURES

RJ and CML received research funding by Aniara Diagnostica. AC has no relevant conflict of interests to declare.

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How to cite this article: Jesudas R, Chaudhury A, Laukaitis CM. An update on the new classification of Ehlers-Danlos syndrome and review of the causes of bleeding in this population. *Haemophilia*. 2019;25:558–566. https://doi.org/10.1111/hae.13800