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Diagnosis of mild bleeding disorders

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Summary

The precise diagnosis of a *severe* haemorrhagic disorder is usually not too problematic. However, physicians are most often faced with individuals consulting for *mild* haemorrhagic symptoms, particularly occurring after a surgical intervention. The problem here is to evaluate whether this person really has a bleeding disorder requiring special investigations and treatments, particularly if another invasive procedure is planned. The key point is to ask the appropriate questions to discriminate bleeding occurring in normal subjects from that occurring in patients with haemostatic disorders. Recently, bleeding questionnaires allowing the calculation of bleeding scores have been proposed. Although they have some limitations, they are of help to better define and quantify the bleeding symptoms and to guide in the choice of selecting laboratory testing. This review focuses on inherited and not on acquired bleeding disorders.

Key words: haemorrhagia; mild haemorrhagic disorders; bleeding score

Introduction

If a patient suffers from *severe* haemorrhagic symptoms the diagnosis is usually not too difficult. When symptoms start in infancy, the most frequent diagnosis is haemophilia (A or B) but other rare bleeding disorders exist (e.g., platelet disorders such as Bernard Soulier or Glanzmann disease or different rare factor deficiencies such as afibrinogenaemia). When severe haemorrhagic symptoms begin in adulthood, they are usually associated with another disease (e.g., liver insufficiency) or treatment (e.g., anticoagulants). Occasionally antibodies against a coagulation factor (e.g., acquired haemophilia) may be responsible for a severe bleeding diathesis.

However, in daily practice physicians are mostly confronted with persons reporting *mild* bleeding symptoms, which can be also due to inherited or acquired bleeding disorders, table 1. These symptoms often become manifest only after trauma or surgery and in these situations they may sometimes become severe. The term "mild bleeding disorder" (MBD) is a classification based on clinical symptoms or the presence of known acquired diseases or treatments associated with bleeding, rather than the results of laboratory analysis [1]. It refers to conditions where there is an increased tendency to bleeding associated with trauma and surgery, and a tendency to easy skin bruising, epistaxis or menorrhagia, but in which spontaneous life-threatening bleeds do not generally occur. As such, discrimination between normality and a pathological bleeding tendency can be a significant challenge [2]. Indeed while the majority of such symptoms may occur in healthy persons, it is important to identify those with bleeding disorders in order to manage symptoms, to minimise the risk of bleeding in case of invasive procedures and to avoid unnecessary exposure to treatments (e.g., with their possible risks of thrombotic complications or transmission of infectious diseases).

Table 1

Main inherited and acquired causes of mild bleeding disorders.

	Inherited	Acquired
Disorders of primary haemostasis		
Von Willebrand disease	+	(+)
Thrombocytopenia	(+)	+
Some qualitative platelet disorders	+	
Pharmacological platelet inhibitors		+
Severe renal failure		+
Bone marrow disease (myeloproliferative or myelodysplastic disorder, leukaemia, plasma cell dyscrasia)		+
Disorders of coagulation/fibrinolysis		
Coagulation factor deficiency (mild haemophilia, haemophilia carrier state, coagulation factor inhibitor, hypofibrinogenaemia, etc.)	+	(+)
Vitamin K deficiency		+
Anticoagulant therapy		+
Hepatocellular failure		+

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Bleeding questionnaire and bleeding score

In order to distinguish between "normal" and "abnormal" bleeding, it is crucial to collect the data about the personal and familial medical history correctly and to interpret them with the possible help of a bleeding score.

Appropriate collection of data

Bleeding histories are subjective. Significant symptoms can be overlooked and interpreted as normal whereas minimal or trivial symptoms may be given undue consideration. If healthy individuals are asked "do you suffer from a bleeding disorder?", it has been shown in a study that up to 65% of healthy women and 35% of healthy men answer yes [3]! Clearly we need to ask more precise questions and also not to forget some crucial ones that could either decrease or increase the probability of finding a haemostatic disorder. These questions need to be guided, as evidenced by the following example: Friberg et al. [4] found that as many as 23% of Swedish girls reported three or more haemorrhagic symptoms whereas Rodeghiero et al. [5], using a questionnaire guided by a physician, observed three or more haemorrhagic symptoms in less than 1% of normal subjects. This highlights the importance of using standardised questionnaires guided by physicians.

Many questionnaires have been proposed, an example being given in table 2. This questionnaire was applied to compute the bleeding score for von Willebrand disease (VWD) in an International Multicentre study [5]. As can be seen the patient should answer questions not only on a list of bleeding symptoms, but also as to whether a medical intervention had been required. This systematic approach has a good impact on the medical education of young physicians and clearly improves the quality of data collection. Some of these questionnaires are now publicly available (see for instance http://www.med.unc.edu/isth/ssc/collaboration/Bleeding_Type1_VWD.pdf).

Interpretation of bleeding symptoms and bleeding scores

Merely collecting the data is not sufficient. The next step involves translating the information into clinical judgement. VWD can be considered as a paradigm for a MBD. Application of this questionnaire to patients with or without VWD has shown that only one of 215 control subjects had more than two haemorrhagic symptoms (specificity of 99.5%) whereas 21 of 42 obligatory carriers of VWD had more than two haemorrhagic symptoms (sensitivity of 50%). This was based only on the symptoms [5]. The next step was to establish and validate a bleeding score (BS) where for each symptom the grades of bleeding severity ranged from zero (absence of symptom) to three if there was some kind of intervention by a physician. Quantification of bleeding symptoms has many potential advantages over a binary classification system. Rodeghiero et al. [5] found that normal males had a BS below three and females below five. Using this cut-off for VWD they were able to show a better sensitivity (64.5%) with a slightly lower specificity (98.6%). The greatest benefit of using the BS rather than a much simpler criterion (e.g., more than two haemorrhagic symptoms) is the possibility of establishing the likelihood ratio for each level of BS. It has thus been demonstrated that the likelihood of VWD increases approximately in an exponential way with each unit of BS. This was done with a modified BS, where the number of possible grades for each bleeding symptom was refined, ranging from –1 (e.g., no bleeding in at least two dental extractions, or no bleeding in at least two surgical procedures) to 4 (symptoms requiring the most significant medical intervention such as administration of clotting factor concentrates or surgery to control bleeding) [6, 7]. Recently, a condensed form of the questionnaire (completed in 10 minutes), which gives similar performances and with

Table 2

Grades of bleeding severity to compute the bleeding score (adapted from reference [5]).

Symptom	0	1	2	3
Epistaxis	No or trivial	Present	Packing, cauterization	Blood transfusion or replacement therapy
Cutaneous	No or trivial	Petechiae or bruises	Haematomas	Consultation
Bleeding from minor wounds	No or trivial	Present (1–5 episodes/year)	Consultation	Surgical haemostasis
Oral cavity	No or trivial	Present	Consultation only	Surgical haemostasis/blood transfusion
GI bleeding	No or trivial	Present	Consultation only	Surgery/blood transfusion
Tooth extraction	No or trivial	Present	Suturing or packing	Blood transfusion
Surgery	No or trivial	Present	Suturing or resurgery	Blood transfusion
Menorrhagia	No or trivial	Present	Consultation, contraceptive pill use, iron therapy	Blood transfusion, hysterectomy, dilatation and curettage
Post-partum haemorrhage	No or trivial	Present, iron therapy	Blood transfusion, dilatation and curettage, suturing	Hysterectomy
Muscle haematomas	No or trivial	Present	Consultation only	Blood transfusion, surgery
Haemarthrosis	No or trivial	Present	Consultation only	Blood transfusion, surgery

a strong inverse relationship with VWF: Ag levels and BS has been proposed [8]. Indeed, the sensitivity for type 1 VWD was 100% and the specificity 87% with an excellent negative predictive value. Unfortunately, criteria for selecting VWD patients were not stringent and based solely on laboratory values, so these sensitivity and specificity figures possibly suffer from biases.

Menorrhagia is a very important and often neglected problem [9]. It is estimated that at least 5–10% of women of reproductive age will seek medical attention for menorrhagia. After having excluded various causes (such as fibroids), investigation of a possible haemostatic disorder should be discussed. Since for women as well as for physicians the perception of normal and abnormal menses varies, a BS may be of help. Higham et al. [10] proposed a pictorial assessment score in 1990. In their study a pictorial chart ≥100 was found to have a specificity and sensitivity >80% as a diagnostic test for menorrhagia. Based on the same approach Janssen and colleagues [11] refined and validated this pictorial chart method for the assessment of menstrual loss (illustrated in table 3). This study was based on 489 menstrual bleeding episodes collected by 288 women, whereas the study of Higham et al. [10] was based on only 55 menstrual cycles in 28 women. Contrary to Higham et al they did not give points for the clots since they demonstrated that the ROC curve was unchanged with or without taking them into account. Furthermore Janssen et al assessed the menstrual loss twice in 201 women. From these results, based on the ROC-curve analysis, they chose a cut-off of 185, which gives positive and negative values of 85.9 and 84.8% (sensitivity was 61.8% and specificity 95.5%). Although there is some discussion about the real sensitivity and specificity of this BS, we found this approach of real help, particularly because it forces both physicians and women to more objectivity. Recently Philipp et al. [12] found a sensitivity of 95% (95% CI, 91-99) to identify VWD and platelet disorders when they combined another pictorial assessment score with four criteria (a) duration of menses ≥7 days and either "flooding" or impairment of daily activities during periods, b) history of treatment of anaemia, c) family history of a diagnosed bleeding disorder and d) history of excessive bleeding after tooth extraction, delivery or miscarriage or surgery).

Table 3

Bleeding score in case of menorrhagia (adapted from reference 11). The numbers 1–10 represents the consecutive days of menstrual period. A total score >185 points has a positive predictive value of 85% for menorrhagia.

Pad	1	2	3	4	5	6	7	8	9	10
1 pt/pad 										
5 pts/pad 										
20 pts/pad 										
Clots (yes / no)										

Tampon	1	2	3	4	5	6	7	8	9	10
1 pt/tampon 										
5 pts/tampon 										
10 pts/tampon 										
Clots (yes / no)										

Limitations of bleeding scores

The most validated BS have been used specifically for VWD. Therefore, BS should theoretically not be extrapolated for other MBD. Whilst waiting for studies to clarify this point, in daily practice we have found that the use of BS is of help for all bleeding disorders, particularly for teaching purpose (more rigorous approach and the possibility of inter-observer comparison) but also in deciding the necessity and/or the extent of laboratory investigations. However, it has to be recognised that MBD related to platelet dysfunction is particularly difficult to score because there is a lack of standardisation in the laboratory approach to platelet function testing and thus there is not a golden standard criterion to establish whether a patient has a mild platelet disorder or not. Other limitations have to be taken into account. Firstly, BS have been designed for adults and no data are available for children. However, based on paediatric-specific symptoms, a study is ongoing. Secondly, questionnaires allowing calculation of BS may provide insufficient information for reasons other than a young age. Indeed in respect to the personal history, an individual may have been exposed to insufficient haemostatic challenges or the information may be unreliable. The family history may also not be very informative due to a lack of information (e.g., in case of an adoption or when a limited number of family members exist), the possibility that the patient has inherited a double disorder from each parent as well as the fact that other family members may have co-inherited a thrombophilic feature (e.g., factor V Leiden) that can mask a concomitant haemostatic disorder at risk for bleeding [13]. Finally, we do not have sufficient information as to whether a BS could be predictive of future bleeding, a question frequently asked [14]. This should be tested by evaluating data on prospective cohorts of patients.

It also has to be remembered that when a bleeding diathesis occurs in a person who has

never previously experienced a complication, detailed questions should be asked about any drug intake. Indeed, besides some well-known drugs such as antiplatelet agents and anticoagulants, many drugs may interfere with haemostasis, a good example being serotonin reuptake inhibitor agents [15]. Questions about over the counter drugs should also be asked since some of these preparations may lead to bleeding symptoms [16].

Physical examination

It has to be recognised that, with some exceptions, the physical examination often brings no important information, particularly as most of the time MBD only become manifest in case of surgery or trauma. However physical examination can provide some diagnostic clues and therefore should not be neglected [17]. For example, and among others, petechiae should evoke suspicion of a thrombocytopenia, mucosal bleeding a VWD or platelet disorder and haemarthrosis a possible unrecognised mild haemophilia. The search for telangiectasias should be carefully performed to exclude a hereditary hemorrhagic telangiectasia [18]. In children with a mild bleeding tendency and no overt haemostatic abnormality, hypermobility of the thumb should be searched for since it may suggest an Ehlers-Danlos syndrome [19, 20]. Ecchymotic lesions or haematomas with normal coagulation studies may raise the suspicion of battering syndrome seen not only in children but also in adults. Child abuse is well-known but domestic violence particularly affecting women and aged people may also lead to such lesions. Diagnosis is often very difficult because of denial of caring persons and because of poor cooperation on the part of the patient. Cutaneous bleeding may occasionally be self-inflicted (Munchausen syndrome). This diagnosis of exclusion should always be kept in mind, particularly when the localisation of bleeding is only in areas that can be reached by the arms of the patient. Various diseases (leukaemia, endocarditis, hypertension, scurvy, Cushing, cryoglobulinaemia, etc.) as well as complications of treatments (antithrombotic agents, steroids) may induce particular lesions with special localisations. These are not the scope of our article, which focuses mainly on inherited disorders but the reader is referred to the excellent review by Girolami et al. [17].

Laboratory investigations

We schematically divide the way we approach the investigations into two stages. However, depending not only on the bleeding symptoms but also on the family history and on various other factors (tests availability, partial work-up already performed elsewhere, attitude of the patient, geographical consideration, etc.), this order can be modified. When the suspicion of a MBD is relatively high, as indicated in table 4, there is a general consensus that a few first stage tests: platelet counts, prothrombin time (PT), activated partial thromboplastin time (aPTT) and fibrinogen [21] are carried out. Thrombin time is not systematically performed but is considered as a screening test. Increasingly often in addition to these accepted first stage assays a PFA-100 (Platelet Function Analyser) is added. The PFA-100 system mimics an artificial vessel and consists of a capillary and a biologically active membrane with a central aperture coated with two agonists, either collagen plus adenosine diphosphate (C-ADP) or collagen plus epinephrine (C-EPI). When the anticoagulated blood is aspirated, a platelet plug forms. The time to interrupt blood flow (closure time or CT) is recorded. The PFA-100 device simulates primary haemostasis at high shear and is therefore particularly sensitive to decreased von Willebrand factor (VWF) levels but also to some platelet disorders. Various studies have shown the good (although not optimal) performances of PFA-100 in detecting VWD. In the platelet function disorders, its use as a screening test is a matter of more controversy, particularly because PFA-100 is poorly sensitive to platelet secretion defects [22], which represent the most common abnormalities of platelet function. Recently Podda at al. [23] have shown a sensitivity of 51% with C-EPI for platelet function disorders but only 8% with C-ADP. Moreover the C-EPI CT was significantly associated with the levels of severity of the patient BS. Since both C-EPI and C-ADP had the same sensitivity for VWD (71%), the authors proposed a diagnostic algorithm for patients suspected of a defect of primary haemostasis starting with the C-ADP [24]. If the CT is prolonged the next test would be to test for VWD and if normal to screen for VWD and platelet function disorders. Clearly this algorithm is interesting but practically both C-ADP and C-EPI are done simultaneously. As the authors suggest the value of C-EPI in predicting the patient at risk of bleeding should be tested in a prospective study. Although the information provided is not exactly the same, this test has progressively replaced the bleeding

Table 4

An approach to laboratory investigation of mild bleeding disorder (see discussion in the text).

First stage
Basal haematocrit and platelet count
Prothrombin time
Activated partial thromboplastin time (aPTT)
Fibrinogen
Thrombin time
Platelet function analyser (PFA-100)
Von Willebrand factor assays
Factor VIII
ABO blood group
Second stage (depending on the results of the first stage investigations)
Specific coagulation factors
Mixing tests
Von Willebrand collagen binding assay
Von Willebrand factor multimers
Platelet aggregation tests / platelet secretion tests
Factor XIII
Antiplasmin
Fibrinolysis exploration

time, a test with poor sensitivity, specificity and reproductibility as has been shown many times and again by the recent study of Podda et al. [23] who found a sensitivity of 29% for VWD and 33% for platelet function disorders! Moreover, the PFA-100 has the advantage of avoiding an incision of the skin because, contrary to the bleeding time, the PFA is an *in vitro* test. Taking into consideration the high prevalence of VWD, VWF assays (ristocetin cofactor and VWF antigen as well as measurement of FVIII) are also usually performed at this stage. If not already known, ABO blood group determination is also part of this first stage approach since it is known that blood group O subjects are more prone to bleeding than subjects from other blood groups [24]. We usually also measure haematocrit level because a decrease may be indicative of the severity of the bleeding disorder, may lead to more investigations (e.g. measurement of ferritin) and finally to substitutive treatment. However, a normal haematocrit does not exclude a MBD. In case of anaemia and/or thrombocytopenia, it is recommended to perform a complete blood cell count.

When an abnormality in some of the screening tests is evidenced and depending on the importance of symptoms (with the help of the bleeding as well as the menorrhagia scores), further investigations (second stage) shown in table 4 are required. In case of prolonged PT or aPTT, mixing tests with pooled normal plasma are next performed, a correction suggesting a factor deficiency, which will be confirmed by factor assays. In the face of isolated prolongation of the aPTT not corrected in mixing studies, the search for a lupus anticoagulant has to be performed. In case of a prolonged thrombin time, reptilase time and fibrinogen antigen assay are performed. Due to the relative insensitivity to PFA-100 to mild platelet function disorders, aggregation tests (with at least ADP, collagen, arachidonic acid and ristocetin) and VWF assays (ristocetin cofactor and VWF antigen) are also performed. Platelet granule secretion assays can also be performed together with a blood smear to evaluate platelet morphology, particularly when abnormal platelet aggregation tests are suggestive. VWF assays need to be repeated at least once and multimer analysis as well as collagen binding assays should be discussed, particularly in case of a discrepancy between VW ristocetin cofactor and VWF antigen results. In women, in case of borderline VWF levels, Kouides et al. [9] advise performing VWF assays during the first three days of the menstrual cycle, when the lowest VWF are observed. A deficiency of factor XIII or antiplasmin cannot be suspected with screening assays. Therefore these tests should be performed independently of the results of PT and aPTT if there is no other explanation for the bleeding symptoms.

Many other tests can be done but before performing them (they can be very expensive and time-consuming) it should be clear that the search will be beneficial for patients (to be distinguished from research purpose). For example, many subtle platelet tests can be performed but sometimes their causative role is not demonstrated and treatment will not differ. It is also possible that global assays such as thromboelastography or thrombin generation tests [25, 26] could be of help in the understanding and investigation of MBD but at the present time data are lacking. In our eyes, these tests could be particularly useful in understanding why, with the same haemostatic abnormality, some individuals bleed whereas others do not bleed.

Finally it has to be remembered that for almost all the mentioned tests normal values have been established using the mean value and two standard deviations from a representative population. As a result 2.5% of normal subjects will have slightly prolonged clotting times, which again emphasises the difficulty in attributing a slight coagulation abnormality to the reported mild bleeding symptoms.

Conclusions

Mild bleeding disorders remain a challenge, even for specialists. These disorders are usually silent and only become manifest after trauma or surgery. In order to prevent some severe bleeding complications in a particular patient as well as for his/her family members, who may still be asymptomatic, it is important to decide whether laboratory assays should be performed, and if yes which ones. This can be done only after a medical (personal and family) history has been carefully taken. In our eyes, bleeding scores, even if designed for VWD and not for other MBDs, can be of real help, particularly as they oblige physicians to use a systematic approach in each patient and ameliorate communication between health-care providers. However physicians should use them with awareness of their limitations until full validation is performed by ongoing studies.

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