

Inherited bleeding disorders in adolescents with excessive menstrual bleeding. Should we evaluate the fibrinolytic pathway?

Trastornos hereditarios de la coagulación en adolescentes con sangrado menstrual excesivo, ¿debemos evaluar la vía fibrinolítica?

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Received: 26-12-2019; Approved: 5-4-2020

What do we know about the subject matter of this study?

Heavy menstrual bleeding (HMB) affects 40% of teenage girls and, in many cases, it may be the first symptom, making it a diagnostic opportunity. Hereditary coagulation disorders (HCD) are the most common secondary cause in this age group.

What does this study contribute to what is already known?

This study gives us an insight into the prevalence of hereditary coagulation disorders in Chilean female adolescents with HMB and explores the possible involvement of an alteration in fibrinolysis.

Abstract

Heavy Menstrual Bleeding (EMB) is a frequent problem in adolescence. The prevalence of inherited bleeding disorders (IBD) as a cause of EMB is not well established and the involvement of fibrinolytic pathway defects has been poorly explored. **Objective:** To determine the prevalence of IBD and fibrinolysis defects in adolescents with EMBs. **Patients and Method:** 93 adolescents (11 to 18 years old) were included. Personal and family history of bleeding were obtained through a standardized questionnaire. The following lab tests were performed: prothrombin time (PT), activated partial thromboplastin time (aPTT), von Willebrand factor quantification, and platelet count and function. Those patients who were not diagnosed with IBD were further evaluated with clot lysis time assay. **Results:** 41 patients (44%) were diagnosed as IBD (Von Willebrand disease n = 28, platelet function defects n=8, mild hemophilia n = 5. Decreased clot lysis time was found in 31 patients. 54% of patients diagnosed with IBD had EMB as the first hemorrhagic manifestation. **Conclusion:** These results support the need to evaluate the coagulation process, including the fibrinolytic pathway in the study of adolescents with EMB.

Keywords:

excessive menstrual bleeding; adolescents; fibrinolysis; BUC; abnormal uterine bleeding; inherited bleeding disorders; heavy menstrual bleeding

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Introduction

HMB is defined as prolonged bleeding > 7 days and/or blood loss flows higher than 80 ml¹⁻⁶. Recently in the United Kingdom, the National Institute for Health and Care Excellence (NICE) has defined it as excessive menstrual blood loss that affects women's physical, emotional, social, and material quality of life, addressing the problem more comprehensively^{7,8}.

It affects approximately 40% of adolescent girls^{1,9} causing morbidity and, in some cases, mortality, in addition to affecting daily life activities, impairing the quality of life^{4,10-12}. Good HMB diagnosis allows for the establishment of active measures promptly to reduce the risk of transfusions, chronic anemia, poor school attendance, and improve quality of life¹³⁻¹⁶.

Since 2006, the American Academy of Pediatrics and the American College of Obstetrics and Gynecology have recommended, in order to improve the HMB diagnosis, considering the menstruation characteristics as a 'vital sign' in the medical evaluation of girls and adolescents¹⁷⁻¹⁹.

The most frequent cause of abnormal uterine bleeding after the menarche period is the hypothalamic-pituitary-gonadal axis immaturity, which leads to anovulatory cycles^{2,20-22}. Published studies show variations in the prevalence of HCB, especially in the vWD ranging between 5% and 36%, and the PD between 3% and 68% of patients with HMB²³⁻²⁵.

Although HCDs have as their manifestation HMB, they are diagnosed before menarche and, in most cases, have multidisciplinary management, from early stages of life.

The biggest diagnostic challenge is mild bleeding disorders (MBD) since they may present mild or unapparent symptoms, until a hemostatic challenge occurs, such as trauma or surgery, or menstruation as in this case.

So-called mild coagulopathies or MBDs include von Willebrand disease, mild platelet dysfunctions, and mild clotting factors deficiencies.

There has been a discussion on the laboratory diagnosis of MBD²⁶, and recently diagnostic criteria have been standardized for primary hemostasis diseases, including von Willebrand disease and platelet function disorders. Our laboratory has participated in this work and its recommendations have been adopted^{14,26}.

The symptoms of MBD are mostly mucocutaneous or disproportionate bleeding according to their origin, in case of hemostatic challenges such as trauma or surgery. In order to objectify these symptoms, questionnaires such as the ISTH-SSC Bleeding Assessment Tool (BAT) have been created which is validated for the diagnosis of vWD and PD²⁷. This questionnaire consists of several items to evaluate different bleeding

symptoms, including HMB. This questionnaire is positive in children when the score is higher or equal to 3 points, which, for example, applies to those patients with HMB who have required the use of antifibrinolytics, hormonal treatment, hospitalization, or transfusions²⁷.

In this regard, it has been described that 92% of patients with HCD present HMB²⁸, therefore, we consider that menarche may be a diagnostic opportunity for these patients, allowing better management, not only for their HMB but also for future interventions such as major and minor surgery and during pregnancy and childbirth.

The role of fibrinolysis in the pathogenesis of HMB is not entirely clear, although most guidelines recommend antifibrinolytics in its management. Our laboratory has developed a global technique for the evaluation of fibrinolysis called *clot lysis time*, which we have incorporated into the evaluation of patients with mucocutaneous bleeding, especially those with bleeding of unknown cause (BUC). The objective of this study was to determine the prevalence of HCD and acceleration of clot lysis time in patients referred due to HMB to polyclinic hematology.

Patients and Method

Between April 2016 and September 2017, a descriptive and transversal study was designed that included patients aged between 11 and 18 years who consulted due to HMB at the Pediatric Hematology Polyclinic of the Pontifical Catholic University of Chile. Those patients receiving anticoagulation therapy and diagnosed with an HCD were excluded.

All patients completed the ISTH-SSC BAT questionnaire reporting personal bleeding symptoms and family history of bleeding disorders. A score of > or = 3 was considered positive.

General coagulation tests including activated partial thromboplastin time (aPTT), prothrombin time (PT), and complete blood count were applied at the first visit. We requested the vWD study which includes blood-clotting factor FVIII, vWF antigen, ristocetin cofactor, collagen-binding test, and evaluation of platelet function with platelet aggregation test. The patients were strongly requested not to present intercurrent infectious conditions and not to have used non-steroidal anti-inflammatory drugs for at least 15 days before the sample collection.

Those patients with abnormal PT-aPTT and those who had a family history of hereditary disorders were studied with clotting factors and those with abnormal platelet aggregation were also studied with platelet secretion.

Table 1. Study results

	VWD ^a	Fibrinolysis defect	Platelet function defects	ITP ^b	Clotting factors deficit	BUC ^c	Total
N	28	31	8	1	5	20	93
ISTH-BAT abnormal	20	26	6	1	4	15	72
Family bleeding history	18	19	4	0	4	10	55
Excessive menstrual bleeding as the first symptom	15	9	3	0	4	8	39
Anemia	9	16	3	0	0	7	35

a: VWD: Von Willebrand disease. b: ITP: primary immune thrombocytopenia. c: BUC: unknown cause bleeding.

If all these results were normal, the study was supplemented with the clot lysis time test to evaluate fibrinolysis. Our laboratory uses platelet-rich plasma stimulated with ristocetin or thrombin receptor agonist peptide-6 and platelet-poor plasma, evaluating the defects of the fibrinolytic system in a single technique²⁸.

Through statistical analysis performed with IBM SPSS Statistics 20.0.1 software, we were able to observe that those patients with positive ISTH-BAT scores and those with a family history of bleeding, correlated with diagnoses of coagulation disorders (vWD, blood clotting factor defects, PD and fibrinolysis defects).

This study was approved by the ethics committee of the Pontifical Catholic University of Chile, using informed consent.

Results

We included 93 patients, the median age was 14 years ranging from 11 to 18 years, 72 patients had a positive BAT questionnaire score, and, out of these, 54% had no bleeding symptoms before their menarche. 55 patients presented family history of bleeding disorders.

Regarding initial examinations, 80 patients (90%) had normal PT and aPPT, and 35 (38%) patients had anemia which was severe in 6 cases (hemoglobin < 7 g/dL).

28 patients were diagnosed with vWD, 8 presented platelet function defects, 5 with clotting factor deficiency (3 patients with factor VIII deficiency, one with factor IX deficiency, and one with factor XI deficiency), and 1 patient with primary immune thrombocytopenia. (Table 1).

In the 51 patients who presented a normal coagulation study, fibrinolysis analyses were performed where 31 of them showed an accelerated clot lysis time, which is compatible with hyperfibrinolysis. When combining patients with HCD and fibrinolysis defects, 72 patients

(77%) presented some kind of bleeding disorder. In 15 patients (75%) diagnosed with vWD, HMB was the first symptom of the disease.

There where no correlation between positive BAT score or family history and the presence of an HCD, including fibrinolysis defects.

Discussion

While this is a selected group, since it has been referred due to suspected coagulopathy or anemia, the prevalence of HCD proved to be high. This supports what is described in the literature and reinforces the idea that the possibility of an HCD should be considered when evaluating an adolescent with HMB.

Although evaluating the causes of referral was not the objective of this study, we believe that it is important for the pediatrician and adolescent health care staff to include menstrual characteristics in the evaluation and assume an active role in the diagnosis, treatment, follow-up, and referral of adolescents with HMB to a specialist, if necessary.

It is important to note that almost 90% of the patients studied had normal results in the studies most often requested to rule out bleeding disorder (PT-aPTT) which reinforces that these normal tests do not exclude the presence of coagulopathy and, if there are other mucocutaneous bleeds, family history or poor response to treatment, the patient should be referred for HCD study.

The prevalence of vWD in the general population is low (< 1%). There is an incidence between 5 and 36% in adolescents with HMB²⁶. In our study, the vWD was diagnosed in 30% of patients, and in most of them, HMB was the first symptom of the disease, therefore HMB study could be a diagnostic opportunity for these adolescents.

The reported incidence of platelet function defects

in HMB patients also shows a wide variation, ranging from 3% to 68%^{9,24,30}. In our series, 9% of patients presented platelet function defects, however, not all had platelet secretion studies, which may have added patients who have only secretion defects²⁸.

According to a study by Quiroga et al. in the Chilean population²⁸, 59.6% of patients presented BUC, which is consistent with the 54% of patients that have no HCD. We believe that these patients should be monitored, both to assess secondary repercussions of HMB and to see their behavior when facing future hemostatic challenges²⁸.

In our study, out of the patients initially classified as BUC, 60% showed a shortening of the clot lysis time which represents 33% of the total group. This suggests that the overall defects of fibrinolysis may play a role in HMB.

There is evidence that fibrinolysis is involved in the endometrial cycle. Levels of plasminogen activators, especially tissue-type plasminogen activator (t-PA) and plasminogen activator inhibitor-1 (PAI-1), increase significantly in the late secretory phase of the endometrial cycle.

There are reports of increased fibrinolytic activity in menstrual flow in patients with abnormal uterine bleeding, in contrast, women receiving hormone therapy show a decreased one^{31,32}. S. Wiewel-Verschueren et al. published a study in adult patients with HMB that measured quantitatively fibrinolytic activators and inhibitors and found no evident alterations³³. However, we think that a global test such as the one we use in our patients can better describe the interactions of the fibrinolytic system and its outcome.

Conclusion

The group studied presented a high prevalence of HCD. The HMB was the first symptom in a significant

group of patients with vWD, which reinforces the idea that HMB is a good diagnostic opportunity for HCD, even in patients with little or no other bleeding symptoms.

We believe that the high incidence of shortened clot lysis time found in this study suggests that evaluation of the fibrinolytic pathway in adolescents with EMS is necessary.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

Financial Disclosure

Authors state that no economic support has been associated with the present study.

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