Original Study

Hemostatic Abnormalities in Young Females with Heavy Menstrual Bleeding

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A B S T R A C T

Objective: To study the prevalence of hemostatic abnormalities, including bleeding disorders and risk factors, in young females referred to a multidisciplinary clinic for evaluation of heavy menstrual bleeding (HMB).
Methods: Retrospective chart review was undertaken for 131 post-menarchal girls with HMB, 7 to 17 years of age, enrolled in the institutional 'Menorrhagia Data Registry' protocol. The diagnostic approach included: (1) complete blood count, prothrombin time, partial thromboplastin time, fibrinogen, von Willebrand panel (2) platelet aggregometry, specific clotting factor assay, fibrinolytic pathway analysis, and factor XIII level as needed. The prevalence of hemostatic abnormalities and the prognostic significance of clinical variables associated with hemostatic abnormalities in young girls with HMB were evaluated.
Results: A hemostatic abnormality was identified in 69 (53%) young girls with HMB. Of these, 27 (21%) had an underlying bleeding disorder and 42 (32%) had a risk factor for bleeding, namely low von Willebrand factor activity. A larger number of girls with underlying bleeding disorder had personal history of other bleeding symptoms (48% vs 31%) and bleeding after surgical or dental procedure (25% vs 8%) when compared to females without hemostatic abnormality. Furthermore, girls with risk factor for bleeding (low vWF activity) were more likely to have bleeding after surgical or dental procedure (15% vs 8%) and family history of bleeding (79% vs 60%) than patients without hemostatic abnormality.
Conclusions: There is high prevalence of hemostatic abnormalities, including bleeding disorders and risk factors, in young girls with HMB. These findings support comprehensive and systematic hemostatic evaluation in this group of patients.
Key Words: Bleeding disorders, Young females, Heavy menstrual bleeding

Introduction

Heavy menstrual bleeding (HMB) is a common gynecologic complaint among young females.[1] In many, anovulation and immaturity of the hypothalamic-pituitary-ovarian axis are thought to be the underlying cause for heavy periods, which can often be managed with hormonal therapy. However, several studies have shown that 10%-62% of young girls with HMB have an underlying bleeding disorder that may benefit from the addition of non-hormonal therapies or may be relevant to future surgeries or pregnancies.[2–7] Bleeding disorders associated with HMB include disorders of primary and secondary hemostasis such as clotting factors deficiencies, von Willebrand disease (vWD), platelet disorders, and rare fibrinolytic pathway defects. It is important to identify female adolescents with bleeding abnormalities because the obstetric and gynecologic morbidity related to bleeding disorders go beyond troublesome heavy periods. Iron deficiency anemia, fatigue, less time spent on desired activities, and difficulty performing schoolwork are common complaints among these young women.[8] In addition, 8-18% of women with bleeding disorders have surgery for HMB and other complications including surgery for hemorrhagic ovarian cyst and hysterectomy which may be associated with significant bleeding.[9]

Despite the relatively high frequencies of bleeding disorders and risk factors in adolescents with HMB, such underlying hemostatic abnormalities are often not considered and a systematic evaluation not performed.[10–12] This is in part due to the lack of consensus regarding which patients need to be tested, difficulty in discerning 'normal' from pathologic bleeding and the lack of an optimal diagnostic approach. The aim of the present study is to evaluate the prevalence of hemostatic abnormalities in young females with HMB by utilizing a step-wise, systematic diagnostic approach. We hypothesized that hemostatic abnormalities, including bleeding disorders and risk factors for bleeding, are prevalent in a substantial number of girls with HMB and that step-wise comprehensive laboratory testing is warranted in these patients.

Patients and Methods

Data Source and Study Population

Data collected from post-menarchal young females enrolled in the institutional Menorrhagia Data Registry

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approved by the institutional review board, referred to the multi-specialty Young Women's Bleeding Disorder Clinic served by hematology and gynecology faculty and Hematology and Gynecology Clinics at Texas Children's Hospital (TCH) for evaluation of HMB from 2009 to 2011, was analyzed retrospectively for this study. HMB is defined as more than 7 days of bleeding, greater than 80 ml of blood loss per cycle, pictorial blood assessment chart (PBAC) score of more than 100, or changing pads or tampons every 1-2 hours. All patients enrolled in this registry were referred by primary care physicians and/or gynecologists. Eligibility criteria included: (1) female gender, (2) post-menarche, (3) referred to TCH for HMB, and (4) non-pregnant. Data collected included demographics, clinical history and physical exam findings, laboratory study and imaging results, therapy details, and patient outcomes. Patients underwent concurrent evaluation by gynecology for pregnancy, anatomic pelvic abnormalities, pelvic infections, and endocrine abnormalities as possible causes for HMB, and only included in our study if these tests were normal or not thought to account for heavy menses.

Definitions and Diagnostic Studies

All patients underwent complete blood count (CBC) to detect thrombocytopenia, coagulation studies for prothrombin time (PT), partial thromboplastin time (PTT), and fibrinogen to detect coagulopathy, and von Willebrand panel (vWP). Specific coagulation factor assays were done if PT, PTT, and/or fibrinogen were abnormal, to delineate specific clotting factor deficiency. Whole blood platelet aggregometry with secretion analysis was done in patients if the first level of testing was negative. In addition, fibrinolytic pathway testing, and factor XIII levels were performed to identify less common disorders for persistent, severe HMB, when deemed necessary by the treating physician.

Studies for platelet aggregation and vWP were performed by the TCH Pathology Services. The vWP performed included individual tests for factor VIII (clot based assay), von Willebrand antigen (vWF: Ag), vW ristocetin co-factor activity (vWF: RCo) and multimers (MM). vWD was diagnosed based on the criteria described in the National Heart, Lung, and Blood Institute's guideline "The diagnosis, evaluation, and management of von Willebrand disease 2008.[13]" Briefly, vWD is classified into 3 major categories: partial quantitative deficiency (type 1), qualitative deficiency (type 2) and total deficiency (type 3). Patients were diagnosed with type 1 vWD if they had vWF: Ag and/or vWF: RCo <30 IU/dL and normal MM. Those with vWF: RCo and/or vWF: Ag 30-50 IU/dL and normal MM were categorized as having low vWF activity, considered a risk factor for bleeding.

Whole blood platelet aggregometry was performed using the Chronolog Whole-Blood Lumi-Aggregometer by measuring change in electrical impedance in whole-blood. The stimulus was brought about by using platelet-aggregating agonists, including adenosine diphosphate (ADP), arachidonic acid, collagen, ristocetin, and thrombin. Adenosine triphosphate (ATP) release was measured by luminescence in whole-blood. The ATP released by the platelet dense granules binds with CHRONO-LUME™ (luciferin-luciferase, Chrono-Log Corp, Havertown, PA) and generates a light (luminescence) that is measured by a stable, high-gain photomultiplier tube. The diagnosis of platelet function defect (PFD) required detection of at least 2 abnormalities in platelet aggregation and/or secretion, as described by Hayward et al.[14]

Testing for factor XIII deficiency was done by estimation of factor XIII activity using a chromogenic assay (normal range 57%-192%; Quest Diagnostics Nichols Institute, San Juan Capistrano, CA). Fibrinolytic pathway testing was done to evaluate for congenital deficiency of plasminogen activator inhibitor type 1 (PAI-1) and alpha-2 antiplasmin. Fibrinolysis panel including testing for PAI-1 activity (1.7-15 U/mL) was performed by the University of Washington Medical Center, Seattle, WA. Alpha-2 antiplasmin testing was performed by the Blood Center of SE Wisconsin using a chromogenic activity assay (normal range 75%-126%).

Bleeding History

Data including demographic information, family history of bleeding, clinical symptoms and signs of bleeding, and laboratory test results on all patients were collected. Characteristics of menses including duration of menstrual period, number of pads and/or tampons used per day, presence and size of clots, flooding, and the PBAC score were collected. Information about other bleeding symptoms including epistaxis, gum bleeding, easy bruising, and excessive bleeding with dental procedures or other surgeries, hospitalization for management of severe menstrual bleeding and anemia and the need for red blood cell transfusions were gathered.

Study Outcomes

The primary outcome for the study was prevalence of hemostatic abnormalities, including bleeding disorders and risk factors for bleeding, in young females with HMB. The secondary outcome included the prognostic significance of clinical variables associated with HMB, namely characteristics of menstrual bleeding, other bleeding symptoms, bleeding after surgical or dental procedure, family history of bleeding or bleeding disorder, personal history of anemia, red cell transfusion or hospitalization for HMB, which may help identify girls with HMB and hemostatic abnormalities.

Statistical Analysis

The statistical analysis was performed using GraphPad Prism version 6.00 for Windows, GraphPad Software, San Diego, California, graphpad.com. Odds ratio and P values were calculated using the Fisher exact test from a contingency table. A P-value $<.05$ was considered statistically significant.

Results

Patient Characteristics

A total of 131 young females met eligibility criteria. The patients had a median age of 12 years (IQR 11-13) at the