Evaluation of the Hemostatic Disorders in Adolescent Girls with Menorrhagia: Experiences from a Tertiary Referral Hospital

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Abstract Bleeding disorders are a common cause of menorrhagia in the adolescent age group. We aimed to evaluate the incidence of hemostatic disorders, using clinical and laboratory findings of bleeding disorders in adolescent girls with menorrhagia. A retrospective chart review used to evaluate adolescent girls with menorrhagia who were referred to Yuzuncu Yil University Pediatric Hematology clinic between January 2010 and December 2014. Out of 52 patients referred for investigation, 50 patients were included in the study. The mean age and mean menarche age were 14.8 ± 1.42 (range: 12–17) and 12.47 ± 0.55 , respectively. In 42 % ($n = 21$) of patients, anemia was detected. In 22 % ($n = 11$) of patients, a bleeding disorder was detected: five cases with von Willebrand disease, two cases with acute immune thrombocytopenic purpura, one case with Bernard-Soulier syndrome, one case with Glanzmann thrombasthenia, one case with aplastic anemia and one case with factor X deficiency. The remaining 39 out of the 50 patients were finally diagnosed with dysfunctional uterine bleeding. When

compared the patients with bleeding disorders and without bleeding disorders, bleeding from other sites, including gingival bleeding or epistaxis, low platelet counts and prolonged activated partial thromboplastin time were found statistically more frequent in patients with bleeding disorders ($p < 0.05$). Menorrhagia in adolescents is frequently associated with underlying bleeding disorders. Adolescents with heavy menstrual bleeding and a history of nose or gingival bleeding should be evaluated for congenital bleeding disorders.

Keywords Adolescent gynecology · Menorrhagia · Bleeding disorders · Anemia · von Willebrand disease

Introduction

A normal menstrual period lasts from 3 to 6 days and involves blood loss up to 80 ml. An expert committee stated that normal menstruation begins between 11 and

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14 years of age and the normal length of menstrual flow is 7 days or less with no more than three to six pads or tampons required per day [1]. Menorrhagia is well recognized and defined as menstrual periods lasting more than 7 days or resulting in the loss of more than 80 ml per cycle [2]. Heavy menstrual bleeding can cause significant discomfort, anemia and decreased quality of life. Also, in severe cases it has some severe effects, such as hospitalization or repeated blood transfusions.

In reports showing the prevalence of menorrhagia in the general population has been estimated as 10–20 % but it is more frequent in the adolescent population [3]. It is reported as affecting up to 37 % of teenage girls [4]. The etiology of menorrhagia or abnormal uterine bleeding in adolescents is often attributed to anovulation due to the immaturity of the hypothalamic-pituitary-ovarian axis [5]. This is called dysfunctional uterine bleeding (DUB). DUB is a diagnosis of exclusion, so organic pathologies and systemic diseases must be excluded. It is shown that coagulation or hemostatic disorders are the second most common cause of abnormal uterine bleeding in the adolescent population. In a recent study it was suggested that up to 44 % of adolescent girls with menorrhagia may have an underlying coagulopathy [6]. Therefore, an evaluation of adolescence with abnormal uterine bleeding should include an assessment of the pelvic organs to exclude organic pathologies and if none is found, the possibility of primary hematologic abnormality should be considered before making a diagnosis of DUB. Von Willebrand disease (VWD) is the most common inherited bleeding disorder, with a prevalence of up to 1.3 % in the general population [7]. In a recent study by Ahuja et al, the prevalence of VWD, platelet function defects and clotting factor deficiencies in adolescent girls with menorrhagia, ranged between 5–36, 2–44 and 8–9 %, respectively [8]. However, in nearly 50 % of all cases, a definitive etiology for abnormal uterine bleeding cannot be reached [9].

The aim of this study was to investigate the incidence and characteristics of bleeding disorders associated with menorrhagia in adolescent girls referred to our pediatric hematology center.

Methods

This study is a retrospective chart review of adolescent girls between the ages of 12–17 with a diagnosis of heavy menstrual bleeding or menorrhagia. Between January 2010 and December 2014 they were evaluated by a gynecologist and referred to a pediatric hematologist in the Yuzuncu Yil University Teaching Hospital, one of Eastern Turkey's leading hospitals. The university ethics committee approved the study. The medical records were reviewed for

a diagnosis of menorrhagia or heavy menstrual bleeding. The diagnosis of menorrhagia was based and relied on the patients own history, including menses described as heavy or irregular, and supporting features such as the passage of clots, soaking a pad or tampon in less than 1 h and the duration of menses for more than 7 days. Patients with known organic pelvic pathologies, systemic diseases, oral contraceptive users and use of medications that inhibit platelet aggregation, like nonsteroidal anti-inflammatory drugs, or selective serotonin reuptake inhibitors users, were excluded from the study.

The adolescent girls included in the study were diagnosed by the gynecology department with menorrhagia or DUB and referred to our hematology clinic for evaluation of their bleeding disorders. Their charts were reviewed for demographic data, their history and physical examination findings, menarche age, family or a previous bleeding history, including gingival bleeds, easy bruising, heavy bleeding during dental work and during prior surgery. Laboratory findings were evaluated, including: the whole blood count, peripheral blood smear, blood group, ferritin, liver transaminases, urea, creatinine assays, platelet function analyzer 100 (PFA-100), prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen, von Willebrand factor antigen (VWF:Ag), VWF ristocetin cofactor (VWF:RCo), factor VIII (FVIII) and if necessary other factors. The platelet function test was applied by aggregation in response to agonists' ristocetin, adenosine diphosphate, collagen and epinephrine using whole blood lumiaggregometry analysis, which is considered to be the gold standard method for the detection of PFDs. It is a policy of our clinic that the VWF:Ag and VWF:RCo levels were analyzed after the patients had rested for 15 min, due to the fact that the VWF report is effected by stress factors like anxiety or fatigue.

The following criteria were used for the diagnosis of bleeding disorders: The criteria for a laboratory diagnosis of VWD were assessed by assays of VWF:Ag, VWF:RCo, and FVIII coagulant; diagnosis of VWD based on avVWF:Ag and or VWF:RCo level of less than 45 IU/dL for individuals with blood type O and <50 IU/dL for those with non-O blood types, according to our laboratory's reference values; criteria for the diagnosis of Glanzmann thrombasthenia (GT) were normal PT, aPTT, platelet count, and morphology, no curve with ADP, epinephrine, collagen; and normal curve with ristocetin in platelet aggregation by lumiaggregometry; criteria for a diagnosis of Bernard-Soulier syndrome (BSS) were low platelet count, large platelets and normal aggregation with ADP, epinephrine and collagen, and no curve with ristocetin; immune thrombocytopenic purpura (ITP) was diagnosed based on a platelet count of $<100,000/\text{mm}^3$ and a normal or increased number of megakaryocytes and/or megakaryoblasts on a bone marrow

smear [19]. A diagnosis of factor X deficiency was reached when the level of factor X was lower than 50 %; the results of coagulation studies and diagnoses were extracted from the relevant medical record charts. Patients with no diagnosis of bleeding disorders were reevaluated by a gynecologist before finally being diagnosed with DUB. Both pediatric hematologists and gynecologists managed the treatments for all patients with menorrhagia, which is not aimed under the scope of this study.

Statistical analysis was performed using a software package SPSS 13 version. Data was reported as mean $\pm$ SD and descriptive statistics were used for continuous variables. The Kruskal-Wallis test was used when making comparisons between the groups. $P < 0.05$ was considered statistically significant.

Results

During the study period, 52 patients presented with menorrhagia and referred to our pediatric hematology clinic but 50 adolescents with a completed coagulation assays were identified. 2 of these 52 patients did not accept the advised coagulation test and so did not included in the study. The mean age of patients was 14.8 ± 1.42 years, ranged from 12 to 17 years. None of the patients were sexually active. The mean menarche age for study population was 12.47 ± 0.55 years. Overall, the mean hemoglobin concentration and MCV were 11.6 ± 3.47 mg/dl and 80.62 fl. Overall; the iron deficiency anemia was seen in 22 patients (42 %). Mild anemia (hemoglobin concentration between 10 and 12 g/dL), moderate anemia (hemoglobin concentration between 8 and 9.9 g/dL) and severe anemia (hemoglobin concentration <8 g/dL) were found in 8, 5, and 9 patients, respectively. The lowest hemoglobin level was 4.2 g/dl in a 14 year-old patient with 1 months of continued menorrhagia without any bleeding disorders that was a neglected case. Bleeding disorders were detected in 22 % of patients (n:11).

The most common bleeding disorder was VWD (5/11 patients: 45.4 %), followed by platelet function disorders (PFD) (2/11, 18.1 %) and ITP (2/11, 18.1 %). Eight of 22 anemic patients had bleeding disorders (36.3 %). One patient with GT and one patient with BSS were seen as PFD. Overall, the bleeding sites other than menorrhagia like epistaxis, gingival bleeding or ecchymosis with little trauma was seen in six patients (12 %), four in patients with bleeding disorders and two in patients without bleeding disorders. The six out of the 50 patients who had bleeding sites other than menorrhagia were: four epistaxis, one ecchymosis and one gingival bleeding. The other bleeding sites in menorrhagic adolescents were seen

statistically with more frequency in patients with other bleeding disorders than those without ($p < 0.05$).

All patients in study group underwent pelvic ultrasound examinations before being referred to the pediatric hematology clinic and none of them had organic pelvic pathologies. When patients were analyzed according to blood group, 14 patients had O-blood group and the others were non-O blood group. Table 1 shows the demographic and laboratory characteristics of 50 enrolled adolescents with menorrhagia. The mean time passed from menarche to first admission for menorrhagia was 2.1 years in menorrhagic girls with any of bleeding disorders and 2.6 years in menorrhagic patients without bleeding disorders which is statistically not different ($p = 0.224$).

When we analyzed the patients with bleeding disorders and without bleeding disorders, we have found that history for other bleeding sites, low platelet count and prolonged activated partial thromboplastin time and anemia were significantly more frequent in patients with bleeding disorders ($p < 0.05$). However, there was no statistically significant difference between patients with and without bleeding disorders with regards to mean hemoglobin level, severe anemia, low ferritin level, blood transfusions and family history for bleeding disorders. Table 2 shows clinical and laboratory comparisons of patients' characteristics with and without bleeding disorders.

Discussion

In our study, we aimed to evaluate and determine the frequency and types of bleeding disorders in adolescent girls with menorrhagia. Menorrhagia is an important health problem in adolescent girls for several reasons: it is one of the main causes of anemia in adolescents; it has considerable implications on life quality, education levels and performance of adolescent students. It is reported that menorrhagia affects approximately 20 % of menstruating woman [10] but is reported more frequent in adolescent girls. In one study, up to 37 % of adolescent females was affected by menorrhagia [4]. Menorrhagia in adolescents is predominantly caused by the immaturity of the hypothalamic-pituitary-ovarian axis, which leads to anovulatory DUB but other bleeding disorders must be excluded [11]. The guidelines recommended by American College of Obstetricians and Gynecologists (ACOG) stated that health care providers should screen all adolescents with abnormal uterine bleeding for bleeding disorders [12]. This study confirms that a proportion of bleeding disorders as high as 22 % was seen in adolescent girls with menorrhagia. Among these disorders, VWD and platelet dysfunction were the most common.

Table 1 Demographic and laboratory characteristics of adolescent girls with menorrhagia (n:50)

Variable	Value
Age at the time of admission (mean, SD)	14.8 ± 1.42 (12–17)
Age at menarche (mean, SD)	12.47 ± 0.55
Sexually active patients (n, %)	0
Patients with bleeding sites other than menorrhagia (n, %)	6 (12 %)
Mean hemoglobin (g/dl)	11.6 ± 3.4
Mean platelet count ($\times 10^3$ /ml)	282.6
Mean prothrombin time (s)	13.3
Mean activated partial thromboplastin time (s)	30.08
Mean fibrinogen (mg/dl)	295.5
Mean PFA-100 collagen epinephrine (s)	76.14
Mean PFA-100 collagen ADP (s)	69.82
Mean VWF:Ag (IU/dL)	73.14
Mean VWF:RCo (IU/dL)	77.8
Mean FVIII (%)	68.96
Blood transfusions (n, %)	16 (32 %)
Patients with anemia (n, %)	21 (42 %)
Blood group types	
Group O (n, %)	14 (28 %)
Non-group O (n, %)	36 (72 %)
Menorrhagia	
With bleeding disorders (n, %)	11 (22 %)
Without bleeding disorders (n, %)	39 (78 %)
Bleeding disorders (n, %)	
VWD (n, %)	5 (45.4 %)
ITP (n, %)	2 (18.1 %)
BSS (n, %)	1 (9.09 %)
GT (n, %)	1 (9.09 %)
Factor X deficiency (n, %)	1 (9.09 %)
Aplastic anemia (n, %)	1 (9.09 %)

SD standard deviation, PFA platelet function analyzer, VWF von Willebrand factor, ITP immune thrombocytopenic purpura, GT Glanzmann thrombocytopenia, BSS Bernard-Soulier syndrome

VWD is the most commonly seen bleeding disorder in adolescent girls with menorrhagia, affecting 1 % of general population [13]. The diagnosis of VWD varies according to the study population and several factors have some affect on plasma levels in VWF, such as age, ethnicity, blood groups, inflammatory mediators, endocrine hormones and stress factors [13]. Miller et al reported that VWF levels vary according to phases of the menstrual cycle with the lowest level occurring during menses and peak levels during the late follicular phase [14]. When test results are low to normal, or minimally decreased, the tests should be repeated if bleeding symptoms and family history suggests VWD [15].

It is reported that the prevalence of menorrhagia in adolescents with VWD is 5–36 % [11]. In our study, VWD was observed in 45.4 % of patients, which is consistent with data from literature.

Platelet function disorders are a heterogeneous group of disorders with no clear distinctions, and in a recent study by Philipp CS, it was stated that PFD is observed more commonly than VWD in woman with menorrhagia. Our findings were not in agreement with that [16]. The PFD was seen 18.1 % of adolescents with menorrhagia in our case cohort, while VWD was seen in 45.4 %. Amongst PFDs, both BSS and GT are considered major hereditary PFDs that can cause significant menorrhagia.

Studies have reported that 51 % of women with BSS and 13–98 % of women with GT have menorrhagia [17, 18].

Immune thrombocytopenic purpura is an acquired-autoimmune disease that leads to an increased rate of platelet destruction and bleeding diathesis. There are two types of ITP: the acute form, which is mostly seen in children and a self limiting, the benign form of the disease and the chronic

Table 2 Comparison of variables between menorrhagic adolescents with and without bleeding disorders

Variables	Px with bleeding disorders	Px without bleeding disorders	P value
Age (mean, SD)	14.91 ± 1.38	14.77 ± 1.46	0.778
Time of diagnosis after after menarche, year (mean, SD)	2.11 ± 1.25	2.63 ± .22	0.224
Other bleeding sites (n, %)	4 (36.3 %)	2 (5.1 %)	0.04*
Mean Hb (mean, SD)	10.24 ± 2.71	12.05 ± 3.59	0.128
Mean MCV (mean, SD)	77.97 ± 9.49	81.36 ± 6.36	0.170
Low ferritin (n, %)	6 (54.5 %)	15 (38.4 %)	0.374
Anemia (n, %)	8 (72.7 %)	9 (23.07 %)	0.01*
Severe anemia (Hb < 7 g/dl) (n, %)	1 (9.09 %)	6 (15.3 %)	0.12
Familial bleeding history (n, %)	1 (9.09 %)	6 (15.3 %)	0.12
Need for transfusions (n, %)	4 (36.3 %)	12 (30.7 %)	0.226
Prothrombin time (mean, SD)	14.26 ± 4.06	13.06 ± 0.88	0.084
aPTT, (mean, SD)	34.91 ± 17.94	28.72 ± 2.82	0.039*
Fibrinogen, (mean, SD)	300.18 ± 87.85	294.23 ± 81.03	0.834
VWF:Ag, (mean, SD)	57.82 ± 31.59	77.46 ± 27.48	0.048*
VWF:RCO, (mean, SD)	61.18 ± 30.65	82.59 ± 15.34	0.002*
PFA-100 collagen ADP, (mean, SD)	41.18 ± 23.11	77.90 ± 17.85	0.001*
PFA-100 collagen epinephrine, (mean, SD)	40.91 ± 25.19	86.08 ± 35.72	0.001*
Factor VIII, (mean, SD)	53.67 ± 27.32	73.28 ± 15.20	0.003*

*Indicates statistically significant difference

aPTT activated partial thromboplastin time, VWF:Ag: von Willebrand factor antigen, PFA: platelet function analyzer

form. The prevalence of ITP in children is estimated to be about 1.9 to 6.4 cases per 100,000 per year and 3.3 cases per 100,000 per year in adults [19]. Bevan et al studied 71 adolescent girls admitted for menorrhagia and found five of them to have ITP (7.04 %), in our study we found two patients with ITP with acute onset (18.1 %) and both of them had a history of recent viral infections [20]. One of these two patients in our study presented with epistaxis and menorrhagia and was diagnosed with ITP. In a study from our center by Akbayram et al that reviewed 260 pediatric ITP patients between 1995 and 2009 years, they found four ITP patients with menorrhagia (2 %). In that study, 20 % of the girls with acute ITP were above 10 years, the others were under the age of 10 and had not had their menarche; this finding explains the low number of ITP patients with menorrhagia in that particular study [22]. However, our study population was adolescent girls who have menses so the data of 18.1 % of our patients (n:2) with menorrhagia were rational and reasonable in that respect.

Clotting factor deficiencies are the least common bleeding disorder, as a cause of menorrhagia. It is reported that the most common clotting deficiency is factor XI and it occurs in 1.0–11.9 % of women with menorrhagia [21]. In our study, one case of a 12 year-old adolescent girl with moderate factor X deficiency (plasma factor 2 %) was referred to our clinic with a complaint of severe

menorrhagia starting from just after menarche and when her detailed history was taken it was learnt that she had had severe gingival bleeding following a dental procedure. In a recent study, Gursel T et al studied 376 university students and 82 of them showed menorrhagia with a quantitative assessment of bleeding with PBAC and they found two patients with clotting factor deficiency: one of them with mild factor XI deficiency and the other with mild factor VII deficiency [21]. We think that our finding was different because the factor X deficiency is seen at a relatively higher frequency in our region than other parts of Turkey due to the high rates of parental consanguinity in the eastern part of Turkey.

Our study has some limitations. First, due to its retrospective nature, and the data reviewed from medical records possibly missing some information. Another, and important limitation, is the issue of menorrhagia assessment itself. As far as we are aware from literature, the pictorial blood assessment chart (PBAC) is an objective, quantitative and easy method that has high sensitivity and specificity for the detection of menorrhagia. Although we had the detailed anamnesis of the patients for a diagnosis of menorrhagia we were unable to use the PBAC because our study was retrospective. However, we think that it could be an important approach for physicians diagnosing adolescents with menorrhagia.

In conclusion, bleeding disorders are commonly found in adolescents with menorrhagia and our study shows that bleeding disorders form a high proportion of the cases of menorrhagia in adolescent girls. An adolescent with heavy menstrual bleeding and history of nose or gingival bleeding should be evaluated for congenital bleeding disorders. Even if there is a suspicion a bleeding disorder in an adolescent girl with menorrhagia a diagnosis is important, so this will lead to early detection and improve her future health. In order to treat these patients correctly, the evaluation and differential diagnosis of menorrhagia in adolescents should be undertaken using a multidisciplinary approach, including both pediatric hematologists and gynecologists.

Compliance with Ethical Standards

Conflict of interest Kamuran Karaman, Nesrin Ceylan, Erbil Karaman, Sinan Akbayram, Hatice Tuba Akbayram, Sultan Kaba, Mesut Garipardıç, Ahmet Fayik Öner declare that they have no conflict of interest.

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