Case Report

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Afibrinogenemia: A rare cause of refractory puberty menorrhagia

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Abstract:

Excessive menstruation after attaining menarche during adolescent age group is known as puberty menorrhagia (PM). The most common presentation includes anemia due to excessive blood loss. We are reporting a rare case of PM secondary to a congenital bleeding disorder.

Keywords:

Afibrinogenemia, menorrhagia, puberty

Introduction

Normal menstrual cycle is a coordinated sequence of events involving the hypothalamus, pituitary, ovary and uterus. The onset of puberty is often associated with irregular and heavy uterine bleeding, known as puberty menorrhagia (PM) occurring due to immature hypothalamo-pituitary axis, anovulatory cycles, unopposed estrogen levels and breaking down of unstable endometrial lining.[1] PM can also occur in other conditions like dysfunctional uterine bleeding, idiopathic thrombocytopenic purpura, genital tuberculosis, polycystic ovarian disease, hypothyroidism, acute leukemia, and coagulation disorders.[1] We are reporting one such case of PM due to underlying congenital bleeding disorder.

Case Report

A 13-year-old developmentally normal adolescent girl presented with complaints of heavy menstrual bleeding since she attained menarche five months back. During the first cycle, she had normal flow lasting for 5 days but in her second cycle, she had heavy bleeding for a period of 11 days. She was admitted and transfused with 4 units of fresh frozen plasma (FFP), 2 units of cryoprecipitate, and 2 units of whole blood. Her post-transfusion hemoglobin increased to 8.9 g/dl. Again in the subsequent cycle, she continued to have heavy menstrual bleed, and she was started on oral medications Norethisterone 5mg and tranexamic acid 500mg. Despite treatment, she continued to have prolonged bleeding, and the patient was brought to our hospital for further management.

The child was born to 3rd degree consanguineous parents. She has an elder brother who is completely normal. Both the parents are asymptomatic and never had any bleeding manifestations. However, this girl had a history of developing subcutaneous hematoma over the forehead following a fall and another hematoma over the maxillary region following another fall in childhood. There was a positive history of 4–5 episodes of prolonged bleeding following trivial injury in the past. No history of epistaxis, gastrointestinal bleeds, hematuria, oral bleeds, and hemarthrosis in the past.

After going through her past medical history and performing a thorough physical examination and the necessary radiological imaging, a bleeding disorder was strongly suspected. Her coagulation profile showed prothrombin time (PT) >2 min, activated

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partial thromboplastin time (APTT) >3 min, thrombin time >2 min, international normalized ratio >10 and fibrinogen antigen - 0%, undetectable levels of fibrinogen activity. Bleeding time (BT) and clotting time (CT) were >15 min, and clot retraction test revealed no clot. Platelet count and morphology were within normal limits.

Based on the clinical presentation and laboratory results, a diagnosis of congenital hypofibrinogenemia was made.

All the options of exogenous replacement such as human fibrinogen concentrate, cryoprecipitate, and FFP were discussed with parents. The child was started on low dose combined oral contraceptive pills and was advised to review after 3 months. In her subsequent visit, her menstrual flow had considerably decreased and was symptomatically feeling better. The girl is currently on follow-up and is doing well.

Discussion

There are numerous causes for puberty menorrhagia (PM) which includes dysfunctional uterine bleeding, idiopathic thrombocytopenic purpura, genital tuberculosis, polycystic ovarian disease, hypothyroidism, acute leukemia, and coagulation disorders.[1]

Congenital afibrinogenemia is an autosomal recessive condition caused by mutations of the genes located on chromosome 4 (q26–q28) and can be either homozygous or heterozygous.[2] Homozygous state results in afibrinogenemia, and heterozygous state results in hypofibrinogenemia or normal fibrinogen levels. Inherited fibrinogen disorders can manifest as quantitative defects (afibrinogenemia and hypofibrinogenemia) or qualitative defects (dysfibrinogenemia).

Quantitative fibrinogen deficiencies may result from mutations affecting fibrinogen synthesis or processing, while qualitative defects are caused by mutations causing abnormal polymerization, defective cross-linking, or defective assembly of the fibrinolytic system.

Symptoms in the neonatal period include umbilical cord hemorrhage, bleeding from an umbilical stump, intracranial hemorrhage, bleeding from heel prick site, and mucosal bleeding. Older children may present with muscle hematomas, bruising following trivial injuries, epistaxis, hemarthrosis, gastrointestinal bleeding, bleeding into the central nervous system, etc. Severe bleeding manifestations occur usually following surgeries and trauma. Females tend to present with a spectrum of symptoms in view of the various physiological changes occurring at different phases in a woman's life, such as PM, infertility, spontaneous recurrent abortions, antepartum, and postpartum hemorrhage. Young girls usually present with menorrhagia at the onset of menarche, which may be the only symptom. Rare incidences of intraperitoneal hemorrhage following ruptured corpus luteal cyst have also been documented in the literature. Women in the reproductive age group are more vulnerable particularly during the childbearing period.

Diagnosis is established by demonstrating decreased activity and/or decreased levels of plasma fibrinogen. Results of all the screening coagulation tests usually reveal prolonged BT, CT, PT, and APTT.

The mainstay treatment for acute bleeding episodes is plasma fibrinogen concentrate, FFP, or cryoprecipitate.[3] Each cryoprecipitate bag contains 225–250 mg of fibrinogen, and therapy with 100 mg/kg of fibrinogen provides a hemostatic plasma level.[4] The half-life of fibrinogen is 3–5 days, and frequent infusions are not necessary. Due to the rarity of spontaneous bleeds and the risk of acquiring hepatitis and HIV with multiple transfusions, prophylactic fibrinogen therapy is usually not advocated. Rare incidences of anti-fibrinogen antibodies, and thromboembolic complications have been documented in literature.[5]

Prolonged low-dose oral contraceptive pills could be given prophylactically to prevent ovulation associated bleeding in young ladies with menorrhagia.

Considering the increased maternal and fetal morbidity and mortality in patients with congenital afibrinogenemia, it has been advocated to maintain plasma fibrinogen levels between 500 and 1000 mg/dl throughout the pregnancy by means of regular fibrinogen concentrate infusions or cryoprecipitate transfusions.[6]

Conclusion

Bleeding and clotting disorders should be considered in the differential diagnosis of refractory PM. Clinicians should have a good knowledge and high index of suspicion to diagnose and treat underlying causes of PM early.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the parents have given their consent for images and other clinical information to be reported in the journal. The parents understand that name and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

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Conflicts of interest
There are no conflicts of interest.

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