

Congenital Prothrombin Deficiency: A Rare Cause of Puberty Menorrhagia

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Abstract

During the transitioning through puberty, adolescents present with varied gynaecological issues, among which puberty menorrhagia is a significant complaint. The most common underlying cause of puberty menorrhagia is anovulation, other causes being endocrine dysfunction, PCOS and bleeding disorders. Congenital prothrombin deficiency is an extremely rare inherited coagulopathy, affecting one in two million of general population. Depending on the severity of deficiency they present with myriad bleeding tendencies, including epistaxis, soft tissue bleeds, GI hemorrhage, intracranial hemorrhage, menorrhagia, excessive post traumatic and post-surgical bleeding. Here, we present a very rare case of congenital prothrombin deficiency presenting primarily with puberty menorrhagia.

Keywords: Puberty menorrhagia; Congenital prothrombin deficiency; Factor II deficiency; Inherited coagulopathy

Introduction

Puberty signifies a complex interplay between the endocrine milieu, reproductive organ systems and haematological functioning. Smooth transitioning through puberty which is characterised by menarche is an important physiological milestone, heralding the onset of a girl's reproductive life. About half of adolescent menstrual complaints are constituted by abnormalities in cycle pattern, quantum of bleeding, ranging from scanty to profuse [1]. Puberty menorrhagia has most commonly been attributed to anovulation. Blood dyscrasias, though less common, are a significant cause of menorrhagia. Congenital prothrombin deficiency is an extremely rare inherited coagulopathy which manifests with a myriad of excessive bleeding tendencies. Congenital prothrombin deficiency primarily presenting as puberty menorrhagia is amongst the rarest of clinical scenarios, which to the best of our literature review, is being reported for the first time.

Case Presentation

A 15 year old girl presented to our emergency wing with complaints of severe menorrhagia, breathlessness, palpitations and easy fatigability for four days. The adolescent girl had attained menarche 4 months prior and had presented to us during her third menstrual cycle. During the first two cycles, she experienced heavy menstrual bleeding, for which she had consulted local physicians elsewhere. On both occasions she was managed with a total of eleven blood transfusions for anemia on inpatient basis. She received oral progestogens during the course of her hospital stay and was subsequently advised regular intake of hematinics and oral contraceptive pills. No further assessment was performed.

After an interval of amenorrhea for 2 months, she had discontinued her medications and presented to us with the third episode of menorrhagia. She gave no significant history of easy bruisability or increased bleeding tendencies. Parental marital history revealed second

degree consanguinity and her brother had a history of excessive bruising and bleeding following trivial trauma since childhood.

On examination, she was severely pale, with a pulse rate of 120 beats per minute. Her cardiovascular and respiratory system revealed no abnormalities. Her abdomen was soft, with no organomegaly. She was investigated further to assess the severity and underlying cause of menorrhagia. Hemogram revealed haemoglobin concentration of 4.7 g/dL, WBC count of 5000 /mm³ and platelet count of 2,80,000 /mm³. Peripheral smear showed microcytic hypochromic cells with anisopoikilocytosis, suggestive of iron deficiency anemia. Liver function and thyroid function tests were within the normal range. Bleeding and clotting time at 2 minutes 15 seconds and 3 minutes 30 seconds respectively reflected normal values. Coagulation profile showed prolonged prothrombin time (test - 15.3s control - 38.3), prolonged activated partial thromboplastin time (test - 34.4s control - 52.0s) and normal prothrombin time and was suggestive of a common pathway defect. Following relevant mixing assays, she was found to have Factor II deficiency with an activity of 2%. The other clotting factors revealed no abnormalities in the assays. A transabdominal ultrasound showed normal morphology of uterus, ovaries and other intrabdominal organs.

On account of symptomatic severe anemia, patient was transfused two packed cells and was started on oral tranexamic acid and progestogens for the active bleeding. As menorrhagia subsided with medical management, further transfusion of fresh frozen plasma was withheld.

Further coagulation profile of the sibling revealed prothrombin deficiency with 3% activity. The patient was then discharged on hematinics and cyclical oral contraceptive pills.

Discussion

Adolescent health issues have significant implications on psychosocial and physical well being of the individual. In India, owing to poverty and socio-cultural inhibitions health care seeking behaviour by women for reproductive centric issues is low, thus, timely diagnosis and treatment still remains a challenge.

Anovulation constitutes around 80% of the cases associated with puberty menorrhagia. Anovulation in the initial years following menarche occurs due to the immaturity of the hypothalamic-pituitary-ovarian axis. Other conditions associated with puberty menorrhagia include thyroid disorders, PCOS and haematological disorders. An estimated 10-20% of women with menorrhagia have an underlying coagulopathy [2,3]. Isolated menorrhagia with the onset of puberty may be the first manifestation of an underlying bleeding disorder. To the best of our literature search, this is the first case report of congenital prothrombin deficiency presenting primarily as puberty menorrhagia.

In a study evaluating menorrhagia in Indian women, platelet dysfunction was the most common cause of inherited bleeding disorders accounting for about 84% of these women. These qualitative platelet defects include Bernard Soulier syndrome and Glanzmann's thrombasthenia. Amongst inherited coagulopathies, Von Willebrand's disease was most frequently encountered, involving about 12% of these women. Deficiency of Factors XIII, XII, VII, IX were other rare causes that were detected [4]. In many studies evaluating causes of puberty menorrhagia in various population sub groups, Von Willebrand's disease and platelet dysfunction were the commonly noted inherited defects [5,6].

Congenital Prothrombin deficiency is an extremely rare coagulation disorder, with an estimated prevalence of about 1 in two million of general population [7]. The mode of inheritance is autosomal recessive, affecting males and females equally. It is characterised by either homozygous or compound heterozygous mutations of the F2 prothrombin gene [8]. Following vascular injury, prothrombin yields thrombin under the influence of Factor X. The thrombin thus formed triggers fibrin generation and clot formation, leading to hemostatic plug formation along with platelets.

Two types of prothrombin deficiency have been described. Type 1 deficiency is true hypoprothrombinemia evidenced by low levels and low activity of plasma prothrombin. Type 2 deficiency is a dysprothrombinemia associated with near normal or normal levels of prothrombin, but reduced activity owing to synthesis of a dysfunctional protein.

Prothrombin deficiency manifests with a prolongation of prothrombin time, activated partial thromboplastin time and decreased activity on factor assays. Immunoassay of plasma FII antigen helps in differentiating hypoprothrombinemia from dysprothrombinemia [9].

The severity of the condition depends on the extent of compromise in the activity of the deficient factor. Around 20-40% of prothrombin level is essential for hemostasis and activity of less than 5% is associated with severe symptoms [10]. The more severe forms manifest early as umbilical cord bleeding or intracranial hemorrhage. Other common presentations include epistaxis, easy bruisability, mucosal and soft tissue bleeding, prolonged bleeding post trauma and heavy menstrual bleeding. Adverse obstetric outcomes of miscarriage, antepartum hemorrhage and recurrent postpartum hemorrhage have also been reported [11-13]. Life threatening menorrhagia in a parous woman has also been reported [13]. In rural India, girls are seldom involved in sports or other physical activities, which might explain the absence of significant bruising or excessive bleeding following trauma in our patient despite only a 2% activity of prothrombin. With the onset of menarche, she probably faced the first challenge to her

coagulation system and subsequently presented with near life threatening menorrhagia.

Management of bleeding in prothrombin deficiency may require replenishment of the deficient factor using Prothrombin complex concentrate, which contains equal amounts of Factor II and Factor IX. Fresh Frozen Plasma maybe used to restore Factor II activity if PCCs are unavailable [9].

Conclusion

Excessive menstrual bleeding is a reliable predictor of possible underlying coagulopathy, many of which are first diagnosed following evaluation for menorrhagia [14]. A high index of suspicion, coupled with systematic evaluation for menorrhagia is essential for the diagnosis of coagulopathies in affected women. Prompt diagnosis of underlying pathology goes a long way in establishing quality of life and decreasing the burden of further medical catastrophes. Institution of appropriate treatment, multidisciplinary approach and follow-up, with required lifestyle modifications form the cornerstone of management.

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