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A RARE CASE OF VON WILLEBRAND DISEASE AS A CAUSE OF MENORRHAGIA SINCE MENARCHE: A CASE REPORT FROM WESTERN INDIA WITH BRIEF REVIEW

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Abstract- Puberty menorrhagia is a common symptom to present but if not investigated as per protocol, a rare cause of it, like von Willebrand disease can be missed for years and anemia as a result, might make the patient handicapped in her developing age. A 23 year old woman from Western India presented with menorrhagia since menarche. Investigations revealed borderline low levels of vWF antigen diagnosed as von Willebrand's disease Type I. Treated initially by antifibrinolytics without much response. Further investigations showed hypothyroidism and finally diagnosed as Acquired vWD. Thyroxine administration corrected the bleeding disorder.
Keywords- Menorrhagia, von Willebrand Disease, Hypothyroidism, India
Key Message-In the absence of defined guidelines, testing of vW factor should be considered, especially in females with history of unexplained menorrhagia since menarche.

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Introduction

Von Willebrand disease (vWD) is most common amongst inherited bleeding disorders with a prevalence of approximately 1% in general population [1]. It is under diagnosed in India showing 11% prevalence due to limited Studies. Hereditary platelet function defects are a major cause of menorrhagia in Indian women [2]. Amongst the coagulation defects, vWD is the commonest as reported from the Caucasian population. It is an autosomally inherited congenital bleeding disorder involving a qualitative or quantitative deficiency of von Willebrand factor (vWF). Dominant and recessive patterns of transmission also exist. Von Willebrand factor is a large multimeric glycoprotein present in blood plasma produced constitutively in endothelium (Weibel-Palde bodies), megakaryocytes (α-granules of platelates), and subendothelial connective tissue that is necessary for proper platelet adhesion, it protects coagulant factor VIII against degradation [3,4]. There are three main types of von Willebrand disease: Type 1 (quantitative deficiency of vWF), the most common. Type 2 (qualitatively abnormal vWF) is less common. Type 3 (complete absence of vWF), and pseudo von Willebrand, a rarer form. The presenting signs and symptoms are variable [5]. Acquired Von Willebrand disease is a rare entity that is primarily associated with lympho- and myeloproliferative disorders. Recent reports are showing association between vWD and hypothyroidism, complete correction of the clotting abnormality after thyroxine supplementation has been cited. Deficient protein synthesis seen in hypothyroidism with reduction in clotting factor levels is the suggested patho-physiological mechanism [6]. In females, prolonged menorrhagia could be a symptom of vWD which is misinterpreted as gynecological than hematological entity. The diagnosis of vWD factor is complex and difficult for milder forms of the disease. Common tests required are Factor VIII levels, vWF Ag and Ristocetin assay. Testing for vWD should be considered in adolescents without pelvic pathology.

Case Report

The patient was a 23 year old female with menorrhagia since menarche, attained at 13th year of age. Chief complains were irregular and prolonged menstrual cycles with 30-35 days of heavy bleeding at every menstruation, which would used to stop only after estrogen and progesterone administration.

In her past history, to control menorrhagia, oral contraceptive pills (OCP) were continued for eight years. To prevent side effects of OCPs, she took ayurvedic treatment without any relief. On ultrasonography ovaries were polycystic for which 2mg Ciproteron Aacetate and 0.035mg Ethinyl Estradiol combination for three cycles were given. However menstrual irregularities and menorrhagia continued. She required high dose of estrogen- progesterone to stop bleeding, with recurrence of bleeding on reducing the dose. Hematologist was consulted for further investigations. On evaluation by hematologist, she denied any history of easy bruising, epistaxis etc. No family history of a bleeding disorder or thyroid disorder. On general examination, she was anemic with puffiness of face and generalized edema. Height was 145 cm and weight was 61 kg, without any clinical features of hypothyroidism, lymphade-

nopathy or spleenomegaly. Her cardio-respiratory, gastrointestinal system was normal, Gynecological examination was normal.

Investigations Revealed the Following
Hemoglobin-6.4gm%;
Total leukocyte count of 8.5×10^3/L;
Platelet count of 4.24×10^5/l;
Peripheral blood film showed microcytes 2+ with pencil cells 2
Bleeding Time: 2 minutes 1second;
Clotting Time: 6 minutes 4seconds.
Blood group of patient was AB Rh Positive.
Factor XIII screening test was Negative
Von Willebrand Antigen (*vWF Ag*): 41.11% (reference range for O Blood Group: 52-154% and for Non-O blood group: 60-200%).
Diagnosed: Low Borderline Type I von Willebrand disease.
Prothrombin Time: 14 seconds with control of 12 seconds and INR - 1.16.
APTT- 38 seconds with control being 31 seconds.
Renal and liver function tests were normal.
Thyroid Stimulating Hormone- 8.06 uIU/ml (normal range: 0.25-5 uIU/ml).
Microsomal Antibody Titer (TPO): 76.14 U/mL: Positive (negative< 5.61U/mL).
Diagnosed: hypothyroidism.
Final Diagnosed: Acquired von Willebrand Disease secondary to hypothyroidism.

Therapy
- Initially correction of anemia was done with blood transfusion and intravenous iron therapy along with protein supplementation, further maintained by oral iron.
- For menorrhagia, intravenous followed by oral Tranaximic acid in the dose of 1000 mg eight hourly was tried without much help.
- For PCOD- 2mg Ciproteron Aacetate and 0.035mg Ethinyl Estradiol combination cyclically for three cycles. Despite this, menorrhagia continued.
- After diagnosed as hypothyroid: Oral Thyroxin, started initially as 100µg daily and gradually increased to 125µg daily.
- After six months she is euthyroid with regular menstruation without menorrhagia.
- Hematologist advised Low Purity Factor VIII if vWF Ag doesnot return to normal, which was not required. Haemostatic function and hemoglobin is stable at present.
- vWF Ag returned to normal: 88.42%, with the reference range of 60-200% for Non-O group.

Discussion
This patient was diagnosed initially as Type I von Willebrand's disease. Hypothyroidism was diagnosed later, finally given the diagnosis of acquired vWD secondary to hypothyrodisam. On correction of the hypothyroid state, the menstrual irregularities were corrected suggesting that, thyroid hormones played a role in reducing the levels of vWF. Factor VIII, which on multimeric analysis was normal, i.e. there was a quantitative defect of vWF leading to factor VIII deficiency causing acquired von Willebrand's disease. vWF antibody acts as a inhibitor for synthesis of the vWF reducing functional factor VIII molecules as large molecules of vWF are essential for stabilizing factor VIII. Low vWF levels cause degradation of factor VIII very fast leading to apparent low factor VIII levels [6], resulting in bleeding disorders. Other underlying disorders such as systemic lupus erythematosus[7] non-Hodgkin's lymphoma [8] and myeloma [9] show similar pathogenesis. Hypothyroidism may cause a decrease in the circulating factor VIII level without the presence of an inhibitor [10] because at a cellular level triiodothyronine acts on nuclear receptors to cause an increase in m-RNA sequences for synthesis of various factors [11].

Conclusion
Testing for vW factor should be considered in young patients with menorrhagia even though they do not show any bleeding episodes from other sites. In our case, in the situation of hypothyroidism detected first and started with thyroxine, it was quite possible that diagnosis of acquired vWD would have been missed. Failure to diagnose an underlying inherited bleeding disorder may have an important and dire, implication for health of women.

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