



Case Report

Hemophilia A and C in a female: The first case report in literature

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ABSTRACT

Introduction: One of the relatively rare hemostatic disorders is coagulation factors' deficiency, where a single factor or multiple factors can be deficient. All hereditary coagulation factors' deficiencies are autosomal recessive, so they can manifest in both genders, but Hemophilia A and B are X-linked disorders. Therefore, females can rarely be affected. This paper reports the first case of simultaneous coagulation factors' deficiencies of FVIII and FXI in a female.

Case presentation: A 17-year-old female came to the office due to prolonged epistaxis, with a history of severe menstrual bleeding and frequent episodes of epistaxis. In her familial history, a brother complained of epistaxis episodes. Bleeding time and prothrombin time were normal but activated partial thromboplastin time was increased. Von Willebrand disease was excluded, and she was diagnosed with hemophilia A and C.

Discussion: Females can be affected with X-linked disorders such as hemophilia A and B in some rare cases: a carrier mother and affected father, skewed X chromosome inactivation, Turner syndrome, inhibiting antibodies (acquired hemophilia), or a sporadic mutation on the most activated X chromosome. On the other hand, Hemophilia C is an autosomal recessive disease. Treatment of such cases is a challenge, and the recombinant coagulation factors are the treat-of-choice.

Conclusion: Although Von Willebrand disease is the most common hereditary bleeding disorder in females, other rare diseases could be suspected such as Hemophilia. X-linked Hemophilia should be kept in mind as a differential diagnosis in any female patient suffering from hemorrhage.

1. Introduction

Coagulation factors' deficiencies are relatively rare disorders in general, and deficiencies of factors VII (FVII) and XI (FXI) are the most common with 39% and 26% of the affected population respectively [1]. While the prevalence of Hemophilia A (FVIII deficiency) is 1 in 5000 males [2] but it is much rarer than in females.

Hemophilia A and Hemophilia B (FIX deficiency) are both recessive X-linked disorders [3], so females are hardly affected. In contrast, all other coagulation factors' deficiencies are autosomal recessive [4–6]. The most famous one is Hemophilia C (FXI deficiency), which is – unlike other types of hemophilia – usually asymptomatic except for menorrhagia, or leads to mild bleeding after traumas [4].

More than one coagulation factor deficiencies, which are called

Familial Multiple Coagulation Factor Deficiencies (FMCFDs), are yet much rarer and represent challenges in diagnosis and treatment. They are classified into three groups: the first one is the inheritance of two independent coagulation factors' deficiencies, the second is a defect in one gene, and the third is caused by cytogenetic abnormalities [7]. These disorders are clinically presented with a wide range of hemorrhagic signs and symptoms. This paper reports the first case of simultaneous coagulation factors' deficiencies of FVIII and FXI in a female.

2. Case presentation

A 17-year-old female presented to Ibn Rushd Hospital due to prolonged epistaxis and severe menstrual bleeding. Medical history was unremarkable except for recurrent episodes of epistaxis in childhood. In

Abbreviations: FVIII, factor VIII; FXI, factor XI; FVII, factor VII; FMCFDs, familial multiple coagulation factor deficiencies; ECG, electrocardiogram; WBC, white blood cell count; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ESR, Erythrocyte sedimentation rate; PT, prothrombin time; aPTT, activated partial thromboplastin time; IU, international unit.

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her familial history: a brother also complained of recurrent epistaxis. Physical examination showed mild ecchymosis without any muscular or soft tissue hematomas or hemarthrosis, and there was no jaundice. Vital signs were measured; blood pressure was 90/50 mm Hg, pulse rate was 110 beats/min, Electrocardiogram (ECG) revealed normal sinus rhythm.

Initial laboratory tests showed: Blood type A+, Platelets' count: 190,000/mm³, Hemoglobin 4 g/dl (low)- white blood cell count (WBC): 6900/mm³, Glucose blood level: 90 mg/dl, Alanine aminotransferase (ALT): 35 U/L, Aspartate aminotransferase (AST): 32 U/L, Erythrocyte sedimentation rate (ESR) in the first hour was 11 mm/hour, C- reactive protein was 2 mg/L (normal), lactate dehydrogenase: 340 U/L, Prothrombin activity: 97%, Prothrombin time (PT) and bleeding time were normal, and due to marked prolongation of activated partial thromboplastin time (aPTT) which was 95s, screening for Von Willebrand disease was performed through antigen test and it was negative. Therefore, other disorders such as hereditary coagulation factors deficiencies were suggested. Coagulation factors tests revealed very low activity of factors VIII (41%) and XI (48%) and normal activity of factor IX (63%). Consequently, Hemophilia A and C were diagnosed. The investigations of the inner-coagulation-path factors of her family revealed that her father and one of her brothers had coagulation factor XI deficiency. We performed an abdominal ultrasound and it showed normal uterine and ovaries, and we did a Karyotype that revealed a normal genotype of 46XX so, we excluded Turner Syndrome. Depending on the previous findings our patient was diagnosed with Hemophilia A and C, without performing a genetic analysis because it is unavailable in Syria.

The patient was hospitalized and treated with recombinant factor VIII 1000 IU/day until recovery. Due to the poor general situation in Syria, we couldn't follow up by frequent examining of factor VIII level or even continuing the treatment with recombinant factor VIII. Instead, we followed up the patient by aPTT measurements. Moreover, as an alternative treatment; frozen plasma or cryoprecipitate are given, and the aPTT level was recovering (29s) so we excluded acquired Hemophilia. To manage the massive acute epistaxis episodes, we transfused packed red blood cells, and we performed anterior nasal packing. The patient was also treated with 5 mg of Norethisterone daily to make pharmaceutical menopause.

The patient's follow-up revealed a significant state improvement and lack of epistaxis occurrence.

3. Discussion

Coagulation factors' deficiencies are rare disorders where single or multiple factors can be insufficient. Our case reported a female with FVIII and FXI deficiency. It is a rare combination that was only described in ten male cases [8,9], and this is the first case in literature that mentions a female with both Hemophilia A and Hemophilia C.

The most common single factor deficiencies are FVII, Hemophilia A, B, C or the deficiencies of FVIII; FIX; FXI respectively, and factor XII or Hageman factor deficiency. More than one factor deficiencies are called (FMCFDs) which consist of three types as previously mentioned. Our patient is an example of the first type of FMCFDs, which is two isolated coagulation factors' deficiencies in FVIII and FXI. The most common example of the second type of FMCFDs; a defect in one gene that causes two coagulation factors deficiencies, is the combination of FV and FVIII deficiencies [7].

Genetically, Hemophilia A and B are X-linked disorders, so that they manifest mainly in males, but females can also be affected in some rare cases such as: a girl to a carrier mother and affected father, skewed X chromosome inactivation, Turner syndrome, inhibiting antibodies (acquired Hemophilia), or the rarest reason: a sporadic mutation on her most activated X chromosome [2,10].

The patient presented with frequent bleeding episodes and was finally diagnosed with Hemophilia A and C.

The most common symptom of coagulation factors' deficiencies is bleeding. It depends on the level of the factor deficiency and is classified

into three types; mild, moderate and severe [11]. Our patient had a severe form of bleeding and complained of epistaxis and severe menstrual bleeding. Patients who have only FXI deficiency usually suffer from mild oral bleeding and post-operative bleeding [4]. Whereas Hemophilia C is an autosomal recessive disease and our patient has a positive familial history in her father and brother. Consequently, her mother must be a carrier.

As for Hemophilia A, we excluded Turner syndrome by her normal (46: XX) karyotype and disclaimed the inhibiting antibodies' theory by a successful plasma transfusion therapy. The remaining possible explanations are a carrier mother or a sporadic mutation, with skewed X chromosome inactivation in the patient. The definite explanation needs genetic analysis which is not available in Syria.

Even a negative genetic analysis of the mother does not exclude that she is a carrier. She may have a mix of affected and normal X chromosomes due to her mosaicism [2].

The treatment of two Hemophilia is very challenging in light of the safety, the financial limitations and the availability of the efficient treatment. The treat-of-choice is to give the patient a regular supply of recombinant factors but, because they are expensive, other treatments can be used such as plasma-derived factors, which we used to treat our patient [11].

4. Conclusion

Although Von Willebrand's disease is the most common hereditary bleeding disorder in females, other rare diseases could be suspected such as Hemophilia. X-linked Hemophilia should be kept in mind as a differential diagnosis in any female patient suffering from hemorrhage.

Conflicts of Interest

The authors declare that they have no competing interests.

Provenance and peer review

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Declaration of competing interest

The authors declare that they have no competing interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.amsu.2021.102561>.

Ethical approval

Not required for case reports at our hospital. Single case reports are exempt from ethical approval in our institution.

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Author contribution

MSA, RB and HS: analyzed and interpreted the patient data, wrote the manuscript and revision. JA: data collection and wrote the manuscript. MNS: designed the manuscript and corresponding author. RA: managed the patient, edited and supervised the manuscript. All authors

read and approved the final manuscript.

Registration of research studies

1. Name of the registry: not applicable.
2. Unique Identifying number or registration ID: not applicable.
3. Hyperlink to your specific registration (must be publicly accessible and will be checked): not applicable.

Guarantor

Mohammad Nour Shashaa.

Consent

Written informed consent was obtained from the patient's legal guardian for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

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