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CASE REPORT.

Recurrent epistaxis in a woman who was a carrier of hemophilia: A case report.

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ABSTRACT

Carriers of hemophilia may have variable baseline levels of Factor VIII and an association of an increased hemorrhagic tendency. This clinical case reports a case whereby a 22-year-old woman was diagnosed as a carrier of hemophilia with a Factor VIII level of 11% when the patient presented with recurrent epistaxis. The report discusses the diagnosis and management of the patient as well as the consensus guidelines of the International Society of Thrombosis and Hemostasis.

Keywords: hemophilia; women; guidelines, management.

Introduction:

Hemophilia A is an infrequent X-linked hemorrhagic disease that typically causes hemorrhages in men, the severity of which depends on the levels of Factor VIII. Based on the levels of Factor VIII the disease is classified as mild, moderate or severe, with the hemorrhagic complications being in relation with the Factor VIII levels. Women are usually asymptomatic carriers of hemophilia, but it has been reported the levels of Factor VIII are very variable and as a result of inactivation of the normal X-chromosome the patients may have low levels of Factor VIII and therefore at risk of bleeding [1, 2]. In addition, deleterious mutations in the normal X-chromosome have reported to cause a hemophilic phenotype [3]. As such, the possible diagnosis of a congenital bleeding disorder may not be considered in the differential diagnosis. This is especially true if there is no family history of a bleeding disorder or the patient has not undergone previous surgeries or dental extractions, simple first line blood tests, the Prothrombin time, the Activated Partial Thromboplastin Time and a Bleeding Time may suggest the need for further investigation.

This paper reports the case of a 22-year-old woman with menorrhagia y recurrent epistaxis and no family history of a bleeding disorder. The patient was found to be carrier of hemophilia with a serum FVIII level of 11%: the management of these patients according to latest guidelines, especially during pregnancy is reviewed. The need for a multi-disciplinary approach and combined management between differing medical teams cannot be more highlighted.

Clinical Case:

A 22-year-old woman presented with recurrent epistaxis to the local Emergency Service. She was treated using cauterization to the bleeding points on three occasions, however the epistaxis recurred. There was no family history of bleeding disorders nor had the patient undergone dental extractions or previous surgeries. Apart from an abundant menstruation there had been no history of other hemorrhages. The patient was prescribed an oral anticontraceptive which although decreased the abundant menstruation it continued to be abundant. Urine analysis did not demonstrate microscopic hematuria and tranexamic acid was added to the treatment.

An initial evaluation showed a normal platelet count of 372,000 platelets/mm^3. A normal prothrombin time of 78%, a bleeding time of 3 minutes and a partial activated thromboplastin time (APTT) of 48 seconds (normal < 38 seconds). Using mixtures with normal plasma of 1:1 and 1:4 the APTT corrected to the normal value indicating a deficiency of a factor of the intrinsic system of coagulation. Subsequent evaluation of the intrinsic system showed a deficiency of FVIII of 11%. The patients' blood group was O Rhesus positive, a contributing factor to the level of Factor VIII. Levels of Factor IX, XI, von Willebrand Antigen, Ristocetin Co-factor, union to collagen were all normal. Factor VIII levels were repeated two weeks later which demonstrated a FVIII level of 13% and there was no clinical signs of inflammation and the C-reactive protein and ESR were in the normal range.

Examination of the nasal fossa revealed multiple polyps, and a decision to surgically remove them was made. The patient was treated with Factor VIII replacement to reach levels of 50% and underwent surgical resection. There were no further hemorrhages and the post-operative period was un-eventful.

Discussion:

Hemophilia A is a recessive X-linked congenital hemorrhagic disorder. It is caused by several mutations in the Factor VIII gene which results in a decreased production of Factor VIII [1, 2]. The inactivation of the X chromosome is epigenetic in nature, occurring at the blastocyst stage of embryonic development. Its inactivation occurs with the formation of heterochromatin and hypermethylation of CpG. The ratio of this inactivation of X-linked genes in normal females can range from 50:50 whereby each X chromosome is active in an equal number of cells or a skewed inactivation with a ratio of 0:100 in which the activity of genes results from only one chromosome [1-3]. This skewed inactivation due to Lyonization of the non- hemophilic X chromosome is associated with low Factor VIII levels. However, it has been reported that this skewed X chromosome inactivation may be caused by the presence of a deleterious mutation on the non-hemophilic X chromosome. Such mutations have been described in three patients, affecting the PGK1, SYTL4 and NKAP genes. The authors concluded that the inactivation of the non-hemophilic X chromosome resulted in the selection of the hemophilic X chromosome and thus causing a skewed distribution and therefore a hemophilic phenotype [4].

In this case report the serumFactor VIII level was 11% and was associated with heavy menstrual bleeding and recurrent severe epistaxis. Phenotypically normal females with the O blood group have up to a 25% reduction in Factor VIII levels, the O blood group affecting the von Willebrand factor antigen [5]. Notwithstanding, it has been reported that there was no correlation between Factor VIII levels and blood group O patients and non-O group patients [6]. Although the hemorrhagic complications of Factor VIII deficiency are well documented in male patients, there is little information of hemorrhagic complications in female carriers. Although carriers may have Factor VIII levels in the normal range, they may still have an increased hemorrhagic tendency especially after dental extractions, post-partum hemorrhages and minor surgery [7, 8]. In a cohort study reported by Garagiola et al [9], there was an association between the Bleeding Assessment Tool and Factor VIII levels, being higher in those with a Factor VIII of less than 20%, 86% versus 41% of women with a Factor VIII level of more than 20%. The 2018 Scientific and Standardization Committee of the International Society on Thrombosis and Hemostasis (SCC-ISTH) defined mild hemophilia if patients had; an isolated FVIII level of < 40%; a mutation of the DNA in the F8 gene or a family member with the same characteristics; all tests should be repeated to confirm FVIII levels; female carriers with a FVIII <40% are considered as positive for hemophilia and finally, that it is important to identify these hemophilic carriers in the management of these patients in order to prevent or treat hemorrhages [10].

These guidelines were updated in 2021 to provide a consensus guideline to define hemophilia in women. The consensus opinion classified patients based on their clinical history of previous hemorrhage and the levels of Factor VIII. The patients were classified into five groups; firstly, patients with a Factor VIII level of ≥ 40% and no history of hemorrhage; secondly patients with a Factor VIII level of ≥ 40% and a clinical history of bleeding; thirdly those with a Factor VIII of between 5% and 40% (mild hemophilia); fourthly those with a Factor VIII level of between 1% and 5% (moderate hemophilia) and finally those patients with a Factor VIII of < 1% (severe hemophilia). These consensus guidelines were intended to improve the criteria of making a diagnosis of hemophilia in women, its management and to uniform the definitions of hemophilia used in clinical research [11]. In this case report it was not possible to analysis mutations in the X-non hemophilic gene using next generation sequencies as in other countries and as such it was not possible if these mutations were present of not [4].

This patient could be in the future become pregnant which requires a multidisciplinary approach to prevent hemorrhages both with a normal birth or if there is need of a Caesarian Section.

If the deficiency of FVIII is known before pregnancy occurs, it is recommended that genetic counselling should be carried out so as to point out the risks of a males having hemophilia or females being carriers [12, 13]. The sex of the fetus should be determined using ultrasound [13] or testing for fetal DNA in the maternal circulation [14]. If the fetus is feminine no further measures as far as delivery is concerned, however if the fetus is masculine the management is different.

Management of hemophilia carriers is essentially the same as in male hemophiliacs. If the menstruation is abundant the use of an oral contraceptive may decrease the hemorrhage. If this is not sufficient tranexamic acid can be used during the menstruation in order to prevent fibrinolysis and thus decrease the bleeding [10, 11]. If it is necessary to increase the levels of FVIII such as before surgery, desmopression (DDAVP) is the recommended first line treatment [10]. It has been recommended that all hemophilia carriers should undergo a trial of DDAVP to determine the response, with FVIII levels been measured one and four hours after DDAVP infusion [11]. If the patients are unresponsive to DDAVP whereby the FVIII levels do not increase sufficiently or there are contraindications for the use of DDAVP these patients should be treated with FVIII concentrates [11]. The development of inhibitors to FVIII concentrates is rare in female carriers [14, 15]. Part of this is due to the use of DDAVP rather than FVIII concentrates [11].

Except during pregnancy, the management of carriers is the same as for male hemophiliacs. During pregnancy the following recommendations have been made: Firstly, FVIII levels should be measured previous to the pregnancy and repeated during the third trimester (32-34 weeks) to determine whether or not treatment is required. In carriers with a deficiency classified as moderate or severe hemophilia the FVIII levels remain low [16, 17]. The recommendations in many guidelines uses a Factor VIII level of 50% as a cutoff point, in those patients with a Factor VIII level < 50% treatment when replacement therapy is indicated [12, 18, 19]. However, recent Dutch guidelines recommend a cutoff point of 80% to indicate replacement therapy [20]. If the sex of the fetus is feminine normal obstetric indications are followed with a control at one year of life [13]. If the fetus is masculine, it is necessary to discuss the different methods of delivery and pain control. The avoidance of atraumatic management is necessary, avoiding instrumental deliveries, fetal scalp electrodes, fetal blood sampling and intramuscular injections

[13]. An unassisted vaginal delivery is recommended unless there is prolongation of the second stage of labor or fetal distress [13]. DDAVP can be safely administered in the first and second trimester if invasive procedures are necessary, however in the third trimester and at the time of delivery its safety has not been proven [21]. Although it has been reported that its use of the first two trimesters DDAVP should be used with caution due to the fact that it may cause insufficiency of the placenta due to vasoconstriction, the risk of spontaneous abortion due to placental insufficiency and hyponatremia in the mother and fetus. With regards to the method of delivery, the consensus view is that vaginal delivery is recommended as that a Caesarian section does not eliminate the risk of fetal intracranial hemorrhage and increases the need for replacement therapy and risk of hemorrhage in the mother and in fact may increase the risk of fetal intracranial hemorrhage [16, 17]. The use of vacuum extraction of the fetus is contraindicated as is the use of forceps and allowing a long second stage of labor [16, 17]. As such it is suggested that the method of delivery should be based on obstetrical grounds.

Post-partum the levels of FVIII should be maintained > 50% for three days after a vaginal delivery and five days after a Caesarian section, in addition tranexamic acid 1gm 3-4 times a day should be given for 7 days [13]. However, the optimum management of these patients to prevent post-partum hemorrhage has not been determined. The reported literature in terms of patient outcomes is hampered in their ability to distinguish between obstetric causes and that resulting from the bleeding disorders [22]. Furthermore, it has been reported that the use of prophylactic treatment in patients with a Factor VIII < 50% did not decrease the incidence of primary postpartum hemorrhage. Whereas the use of tranexamic acid decreased the risk of secondary postpartum hemorrhage [23]. Management strategies for the prevention of primary postpartum hemorrhage have included the use of blood transfusions, FVIII, cryoprecipitate, prostaglandins and tranexamic acid, the use of DDAVP was not mentioned [24-26]. In lactating women DDAVP has been detected in breast milk and as such its use is not recommended [27]. In breastfeeding in women, the use of tranexamic acid is safe and thus can be used [28]. More recently the bivalent monoclonal antibody emicizumab has been used in hemophiliac patients with or without inhibitors [29-31]. A pregnant woman with severe hemophilia A was treated with recombinant FV II activated and tranexamic acid together with emicizumab whereby the antibody was detected in cord blood [32]. Although not approved by the

FDA for use in pregnant women, it has a possible role in the management of these patients.

Conclusions: Women with mild hemophilia may experience hemorrhagic complications even with levels of FVIII associated with mild hemophilia and without a family history of hemophilia. The combination of the clinical bleeding history and Factor VIII levels is a possible key to bleeding risk in women who are hemophilia carriers. This requires a multi-disciplinary approach to the patients management.

Ethical Committee:

The case report was approved by the local ethics committee.

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Conflict of Interest:

The author has no conflict of interest.

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