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A Clinical Case Study on Hemophilia A in a Child from Esmeraldas Province, Ecuador

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Abstract

Hemophilia A is a coagulation disorder where the main clinical manifestation is the presence of hemorrhage. The aim of the study was to characterize hemophilia A through the results obtained in a case study of a child from Ecuador. The epidemiological study, at a descriptive level, was a clinical case that consisted of a 3-year-old Ecuadorian male patient, who at 3 months of age presented spontaneous hematomas in the lower limbs and back area. At 5 months of age, he was diagnosed with acute bronchitis with a clinical picture accompanied by nausea, vomiting and greenish liquid stools with mucus. Physical examination showed the presence of hydrocele in the first 2 months of birth. Laboratory data indicated that the patient had decreased coagulation factor VIII (less than 0.3), classifying the disease as mild. The patient's family tree indicated that the maternal uncle had hemophilia A, so there was a 50% probability that the patient presented the pathology. The present study reported the case of a 3-year-old male patient with hemophilia A, concluding that it is of utmost importance for the physician to thoroughly investigate the patient's family history and make an early diagnosis by taking an umbilical cord blood sample to determine the levels of coagulation factors.

Keywords: *Hemophilia A, Factor VIII, TPT, Hemorrhage, Hematoma*

1. Introduction

Hemophilia is described since ancient times, the Talmud shows how some men after being circumcised have acute hemorrhages that led to death. The Hebrew physician Moses Maimonides in the twelfth century discovers that if children had hemophilia it was the mothers who transmitted it, which proves to be an early recognition of the hereditary nature of the disorder. It is known as a "royal disease"

because it is suffered by various members of the European nobility (Bolton-Maggs & Pasi, 2003). It was first described by that name in 1828 by Dr. Friedrich Hopff. The prevalence of hemophilia A is estimated at 1 in 6,000 males, mainly affecting males, but a symptomatic form of hemophilia A has been described in female carriers, usually with a mild clinical picture (Orphanet, 2023). In India there is a higher incidence of patients with this disease.

Hemophilia A is an entity of low prevalence, which is part of the group of Hereditary Alterations of Hemostasis. It is characterized by a severe, hereditary, recessive, X-linked bleeding disorder caused by the absence or decrease of factor VIII (Martínez-Rider et al., 2017). Hemostasis is a defense mechanism, when the vascular endothelium suffers an injury, the hemostatic process initiates the coagulation cascade to restore vascular integrity and prevent further bleeding. Platelet activation occurs at the site of vascular rupture, initiating the enactment of clotting factors and the formation of fibrin, resulting in a plug of platelets and fibrin to inhibit further bleeding.

Factor VIII, whose deficiency causes Hemophilia A, provides an essential improvement of thrombin generation and the enactment of fibrin formation to inhibit further bleeding. Factor VIII binds to von Willebrand factor to protect it from proteolytic degradation. Bleeding in hemophilia is the result of defective stabilization of fibrin secondary to inadequate fibrin generation, resulting in secondary hemostasis failure (Salen & Babiker, 2017).

The disorder results from a mutation in the factor VIII gene (F8; MIM # 300841), is located on chromosome X (Soucie et al., 1998). When males possess only one X chromosome it is enough for them to develop the disease. In females who have two X chromosomes, the mutation must occur on both chromosomes for the disease to occur. Hemophilia A is characterized clinically by a hemorrhagic tendency proportional to the degree of hemostatic factor deficiency, classified into (Argentine Society of Hematology, 2017); (1) Severe hemophilia: < 1% of factor; bleeding may be spontaneous; very recent bleeding episodes; involvement with several joints; (2) Moderate hemophilia: between 1 and 5% of the factor; may bleed from negligible trauma; infrequent bleeding; and may have joint involvement; (3) Mild hemophilia: > 5% of the factor; may bleed from severe trauma; very infrequent hemorrhages and joint involvement is rare.

Severe cases of hemophilia A usually develop during childhood. As babies grow, spontaneous bleeding episodes occur in deep muscles or joints, causing pain, acute swelling, and early restricted movement of the joint. In children under 2 years of age, major complications, such as bleeding and inhibitor formation, occur in response to treatment, which has an impact throughout life. Patients may experience spontaneous bleeding in any organ system, including the kidneys, gastrointestinal tract, and brain. Genitourinary and gastrointestinal bleeding causes hematuria, melena, or hematochezia.

Without prophylactic treatment, these people suffer from two to five episodes of spontaneous bleeding per month (National Organization For Rare Disorders, 2021). Unfortunately, many patients who do not have an early diagnosis of Hemophilia A, go on to present symptoms in adulthood usually after a tooth extraction. Doctors are not able to diagnose this pathology immediately after birth, due to the lack of knowledge of the disease on the part of the parents and the lack of attention to the presence of bruises after placing vitamin K. Children can be exposed to hemorrhages, with brain haemorrhage being the most serious complication and the leading cause of death (Stanford Children's Health, 2021).

Treatment for people diagnosed with Hemophilia A should be comprehensive, seeking to promote physical and psychosocial health, improving their quality of life and reducing morbidity and mortality (Srivastava et al., 2013). Its main objective is to prevent and treat bleeding with deficient clotting factor (Ministry of Health and Social Protection, 2015).

According to the report of the World Federation of Hemophilia with cut in 2017, in Ecuador there are 854 cases that are reported, 755 belong to Hemophilia A. The provinces of Guayas and Pichincha are the ones with the highest incidence of this pathology. In the province of Esmeraldas, 3 cases of Hemophilia A are reported, 2 in the Basic Hospital of Esmeraldas and this case is registered in the

Delfina Torres de Concha Hospital in 2018, the year in which the patient shows hematomas and hemarthrosis. Treatment is prophylactic based on factor VIII and with the use of general measures by parents.

In general, this pathology is detected late and if it affects a vital organ it has serious consequences of morbidity and mortality and mental disability. The scientific dissemination of clinical cases such as this is justified, since it emphasizes the importance of early diagnosis through family history, which can lead to the taking of a correct treatment and thus avoid lethal outcomes, harmful to their health. The objective of the study is to characterize Hemophilia A through the results obtained in a case study of a child from Ecuador.

2. Methods

The epidemiological study, of descriptive level, was a clinical case that lay in a 3-year-old Ecuadorian male patient, who product of eutocic delivery, which at 3 months of age presented bruises spontaneously in lower limbs and back area. At 5 months he was diagnosed with acute bronchitis with a clinical picture accompanied by nausea, vomiting and greenish liquid stools with the presence of mucus. Physical examination revealed the presence of hydrocele in the first 2 months of birth. In the coagulation and hemostasis report, tests revealed deficiency in coagulation factor VIII (0.3%), prolonged range of prolonged thromboplastin time (PTT). This study was supported by a review of the advanced literature on Hemophilia A.

This case study was observational, retrospective and cross-sectional, using the updated literature review on the subject, as well as the patient's clinical history. In addition, an open interview was conducted with a hematology specialist and the patient's parents, with the informed consent of the guardian responsible for the minor. Bibliographic reviews of Hemophilia A were carried out in scientific articles published in databases and metasearch engines, from which valid and reliable information was extracted from journals indexed to Scopus. Publications in English and Spanish, published in any country between 2015 and 2021, were considered. The keywords used were: "Hemophilia A"; "factor VIII"; "TPT"; "TP"; "hemorrhage"; and "hematoma".

The study was carried out guaranteeing the privacy of the data related to the case studied, avoiding any disclosure of these and complying with the ethical criteria established by the Helsinki Conference. This ethical document, which was adopted in 1964 by the World Medical Association and has been updated several times since, sets out the principles for conducting research involving human subjects. The last update was carried out in 2013.

3. Results And Discussion

Case Presentation

Newborn male of 3 years, son of parents from Esmeraldas, Ecuador, product of fourth gestation, mother of 28 years, father of 32 years, with history of consanguinity. Within the personal pathological history, his maternal uncle suffers from Hemophilia A. The mother goes in the company of her son to the General Hospital of Esmeraldas, on February 10, 2022, refers that the child has bruises in the area of buttocks and thighs, manifesting falling only with the simple fact of being on his knees or sitting for a short time. He mentions that about a year ago he had a ruptured frenulum, and seeing that the bleeding did not stop he took him to the emergency room.

The doctor, based on the history of the mother, decided to perform a laboratory study on the patient to rule out a possible case of hemophilia. Figure 1 shows the laboratory report of coagulation and hemostasis

INFORME DE LABORATORIO DE COAGULACION Y HEMOSTASIA

EXAMEN: **FACTOR VIII DE LA COAGULACIÓN**
RESULTADO: Inferior a 0,3 %
MÉTODO: Coagulometría
INTERVALO DE REFERENCIA:
50 a 150 %

EXAMEN: **FACTOR VON WILLEBRAND**
MUESTRA: PLASMA CITRATADO
RESULTADO: 88,97 %
MÉTODO: ELFA (Ensayo de fluorescencia ligado a enzimas)
INTERVALO DE REFERENCIA:
52 a 154 %

EXAMEN: **FACTOR IX DE LA COAGULACIÓN**
RESULTADO: 66,20 %
MÉTODO: Coagulometría
INTERVALO DE REFERENCIA:
50 a 150 %

Figure 1. Laboratory report of coagulation and hemostasis.

Laboratory data indicated that the patient had decreased coagulation factor VIII (less than 0.3), classifying the disease as mild. Figure 2 shows the patient's family tree. The patient's family tree indicated that the maternal uncle suffered from Hemophilia A, so there was a 50% probability that the mother is a carrier, 50% probability that the patient presented the pathology and 50% probability that his sister is also a carrier.

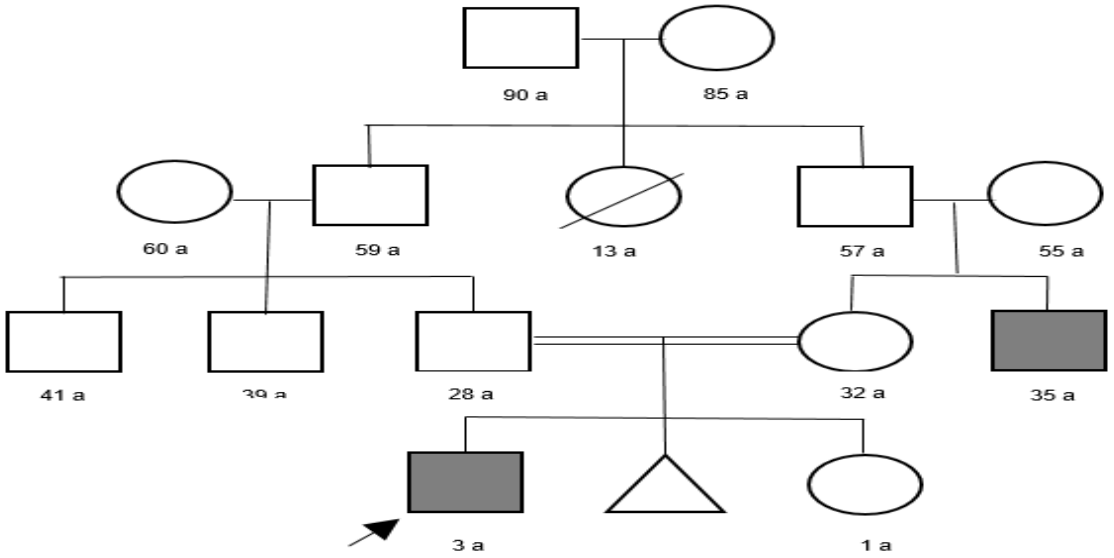

Figure 2. Family tree of the patient.

Background
Gynecological-obstetric history of the mother: pregnancy 3, delivery 3, abortion 0. None of the patient's sisters presented symptoms of hemorrhage.

Prenatal history: 7 controls and 4 ultrasounds without apparent pathology, complete vaccination schedule, alcohol consumption during the first month of pregnancy, hospitalization for dehydration.

Postnatal history: birth at the Las Palmas-Esmeraldas Type C Health Center, at term 38 weeks, due to cephalovaginal delivery, spontaneous crying, adequate tone and coloration before the first minute of life.

Physical examination: weight: 4,000 g, height: 51.4 cm, APGAR: 9, head circumference; 34 cm, FR: 40 resp/min, HR: 135 beats/min, T: 36 C°, oxygen saturation: 92%, complete presence of primitive reflexes, normocephalic head, normotensive fontanelle, spontaneous ocular opening, permeable nostrils, moist mouth and palate, normally implanted ear pavilions, normal neck, expandable chest, ventilated lungs, rhythmic heart without murmurs, soft abdomen, depressible with hydro-aerial noises, male genitalia, enlarged testes of size compatible with hydrocele, patent anus, symmetrical limbs.

Among the more than 6,000 human diseases caused by single-gene defects (Jackson et al., 2018), plasma deficiencies of coagulation proteins are of great importance to the hematologist, as they lead to a lifelong hemorrhagic tendency with significant morbidity and mortality if not properly managed (Khosla & Valdez, 2018). Hemophilia A is the second genetic disorder associated with severe bleeding and the most common of the inherited entities linked to the X chromosome (Mannucci, 2002). It is inherited in an autosomal recessive manner.

That is, if the mother is a carrier and the father does not have the disease, there is a 50% probability that each son will suffer from it (as in the present case) and a 50% probability that each daughter will be a carrier. On the other hand, if the father has hemophilia and the mother is not a carrier of the gene, all daughters will be carriers and none of the sons will present the disease (CDC's, 2020).

Newborns suffering from this pathology are not usually detected early due to the ignorance of relatives, the bruises that occur after the first vaccines are usually unnoticed. It is not until the presence of excessive, unexplained bleeding, large, deep bruising and joint pain, that make the disease evident.

In the present clinical case, the most up-to-date and used treatments for Hemophilia A are counteracted, as well as its correct diagnosis. A randomized clinical trial by Manco-Johnson et al. demonstrates that primary prophylaxis of bleeding episodes is the standard of care, whose preventive regimen is superior to episodic treatment of bleeding, as it reduces the rate of its occurrence, occurrence and joint damage. Gringeri et al. confirm and strengthen this evidence (Manco-Johnson et al., 2007). However, the degree of adherence is optimal in children and adolescents, due to the burden created by the need for 2-3 or more weekly intravenous injections (Rahav et al., 2006; Saxena, 2013).

Two recombinant coagulation factors with a long half-life (LH) are authorised in 2014: FIX fused with Fc eftrenonacog alfa and FVIII fused with Fc efmoroctocog alfa (Powell et al., 2012; Shapiro et al., 2012). Pivotal clinical studies in adults and children demonstrate that these products are effective in stopping or preventing bleeding as part of prophylactic and episodic treatment regimens that could also be used to safely manage surgery (Mahlangu et al., 2014; Santagostino et al., 2012).

In practice, FVIII LH products can be effectively administered twice instead of three times per week, but most patients are not satisfactorily protected against bleeding with weekly dosing regimens (Aledort et al., 2019)). Despite advances in the availability of LHS factors, unmet needs remain (Aledort et al., 2019; Mancuso & Santagostino, 2017). HA patients with FVIII inhibitors remain poor candidates for prophylaxis that can only be provided by avoiding products such as CCPA and rFVIIa, which are very expensive and difficult to administer on a regular preventive basis (Gringeri etal., 2003). Taking into account these drawbacks, therapeutic approaches are developed that are not based on the replacement of the deficient factor. This takes place in two main ways: (i) for HA, mimicking the coagulant activity of FVIII; and (ii) for both HA and HB, increasing defective thrombin formation through inhibition of natural anticoagulants (antithrombin, tissue factor pathway inhibitor, and activated protein C) (Mannucci, 2020).

Haemophiliac patients are stratified according to bleeding risk; (1) Severe: < 1% factor (< 0.01 IU/mL): Spontaneous bleeding in joints and muscle; (2) Moderate: 1 to 5% (0.01-0.05 IU/mL) Occasional spontaneous bleeding; (3) Mild: 5 to 40% (0.05-0.4 IU/mL). Severe bleeding from major trauma or surgery.

In this clinical case the patient is diagnosed with mild AH, the treatment of choice is concentrated FVIII (Srivastava et al., 2013) FVIII dose = weight in kg x desired increase in factor level (IU/dl) x 0.5. Patient weighing 15 kg, who is expected to raise factor VIII to 30 IU/dl 15 kg x 30 (desired increase in IU/dl level) x 0.5 = 225 FVIII units 2 times a week and is called after one month to assess response to treatment. To date it does not develop inhibitors, which indicates a favorable response.

4. Conclusion

In this clinical case the patient is diagnosed with mild AH. Hemophilia A is a disease with autosomal recessive inheritance, of low incidence worldwide, so it is recommended to have correct genetic counseling and counseling to parents inquiring about the main family pathological history. The clinical picture is varied so it is important to make an early diagnosis to avoid complications in the quality of life of the patient and provide a correct treatment based on the degree of the disease, and the needs of the patient. Research related to the development of new treatments should be encouraged.

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