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CASE REPORT

When to consider hemophilia in the neonatal period? a case report

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Abstract

Objective: To report the case of a newborn admitted to a university hospital for blood dyscrasia, describing the clinical, laboratory and final diagnosis of hemophilia. **Case study:** Male newborn, term infant, without perinatal intercurrents, diagnosed with congenital syphilis, showing ecchymoses at sites of venous puncture, cephalohematoma, right ankle hemarthrosis, right upper limb induration and dyscrasia during hospital stay. After dosing of coagulation factors, he was diagnosed with factor IX deficiency: moderate hemophilia B or Christmas disease. He was discharged after clinical improvement for hematology outpatient follow-up. **Discussion:** The presence of abnormal bleeding in newborns should always raise the suspicion of the diagnosis of hemophilia, since the early diagnosis of the disease is of paramount importance in the prevention of hemorrhagic events.

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INTRODUCTION

Hemophilia is a recessive hereditary disease linked to the X chromosome that affects male individuals but can also occur through random mutation and affect girls. It is a hemorrhagic disorder associated with low coagulation factor activity, affecting the hemostatic system. Hemophilia A occurs because of factor VIII deficiency and hemophilia B because of factor IX deficiency. Newborns are not commonly diagnosed with this disease, and thorough investigation should be performed if there is abnormal bleeding; intracranial hemorrhage is the most frequent clinical manifestation in newborns with hemophilia.¹ Diagnosis is most common between the age of 1 and 2 years when the infant starts moving about, which causes articular lesions that are typical of the disease (hemarthrosis). In Brazil, there are approximately 16,000 patients with hemophilia, 52% with type A and 10% with type B.² The incidence of hemophilia B is 1 in approximately 30,000–40,000 male births.³

Disease severity is based on the degree of coagulation factor deficiency. Levels of factor VIII and IX lower than 1% of the normal level (50–100 U/dL) indicate severe hemophilia. The disease is classified as moderate when levels are 1%–5% and mild if they are 5%–30% of the normal level. Absent or reduced activity of factors VIII and IX affects thrombin formation and consequently the conversion of fibrinogen into fibrin, i.e., clots do not form, which leads to bleeding.^{4,5,6}

The objective of this work was to report the case of a newborn admitted to a university hospital for blood dyscrasia investigation and to describe the clinical and laboratory findings that led to the final diagnosis of hemophilia.

The present study was approved by the institutional review board (Federal Fluminense University CAAE:79103717.5.0000.5243). The authors declare no conflicts of interest related to this study.

CASE DESCRIPTION

We report the case of a newborn male, born through vaginal delivery at term, with Apgar scores at 1 and 5 min of 7 and 8, respectively, weighing 3590 g, which is appropriate for the gestational age, and without perinatal complications. During pregnancy, the mother was adequately treated for syphilis, and VDRL titer at admission was 1/64. The newborn's VDRL titer was 1/4 in the peripheral blood and negative in the cerebrospinal fluid. During hospitalization to treat congenital syphilis, the patient developed pallor in the skin and mucosae, ecchymosis at venipuncture locations, a tumor in the right parietal lobe suggestive of cephalohematoma, edema in the right ankle joint (hemarthrosis), and induration in the right arm. Except for the bruises, the other lesions were not related to the puncture sites. Neonatal hearing screening, pulse oximetry, and red reflex test were performed, with normal results. Laboratory test results revealed blood dyscrasia: hemoglobin 11.8, hematocrit 34.9%, platelets 410,000, leukocytes 18,820, (0/3/0/0/1/57/35/4), TAP 66.1%, partial thromboplastin time

(PTT) 129 s, ratio 5.64, INR 1.33. At 15 days old, the patient was transferred from the maternity ward, where he was born, to the Antonio Pedro University Hospital for diagnostic investigation. Examinations at admission found hemoglobin 13.1, hematocrit 40.8%, platelets 413,000, leukocytes 19,800 (0/10/0/0/3/36/38/13), INR 1.0, PTT not detectable, and TAP 102%. Imaging examinations (radiography of the skull, long bones, and feet and abdominal ultrasound) showed no alterations, except for the cerebral ultrasound and cranial computed tomography, which showed right posterior parietal subgaleal hematoma and cephalohematoma, respectively. The patient showed good progress, with no new bleeding; he was discharged for outpatient monitoring at the hematology department, where the diagnosis of factor IX deficiency was confirmed: moderate hemophilia B after coagulation factor testing (factor IX 2.3% and factor VIII 213.9%). There were no similar cases in the family history.

DISCUSSION

This patient had no family history of the disease, similar to nearly all patients with hemophilia, as approximately 30% of hemophilia cases result from random mutation and a positive family history is not necessary. In cases of hereditary transmission of the disease, women tend to be only carriers, whereas men develop the pathology.^{4,7}

The disease is often diagnosed in infants when they begin to move about, due to the subsequent traumas, considering the low rate of suspicion during the neonatal period. Abnormal bleeding (spontaneous or iatrogenic) in newborns suggests the possibility of hemorrhagic disorders and should be promptly investigated to ensure that patients who have the disease begin treatment as soon as possible. In this report, the neonate presented with subgaleal bleeding (cephalohematoma), typically found in neonates with hemophilia. Cephalohematomas can lead to death from hypovolemic shock if they continue to bleed.^{1,5,8} The patient also presented with other types of bleeding, which are frequently reported and helped assist in diagnosis, such as muscle hematoma, hemarthrosis, ecchymosis, and bruising in venipuncture sites.⁵

Laboratory assessment of the coagulation system is also important in the investigation of hemophilia. Prothrombin time (PT) evaluates the extrinsic pathway of the coagulation cascade and PTT evaluates the intrinsic pathway. In patients who present with bleeding with normal platelet levels, normal PT, and increased PTT, factor VIII, IX, or XI deficiency or the presence of the intrinsic pathway inhibitor should be suspected. The reference values are known to vary between laboratories.^{3,9} In this case, factor IX deficiency confirmed the diagnosis of hemophilia B.^{2,10}

After diagnosis, treatment on demand or prophylaxis should be initiated. Prophylaxis is meant to prevent new articular lesions; it consists of regular administration of coagulation factors and may be continuous (at least 45 weeks of treatment)

or intermittent (<45 weeks of treatment). It is associated with better outcomes compared with treatment on demand when hemorrhage is occurring or to prevent an event, as in the case of pre-operative administration. Preventive treatment reduces the number of hemorrhagic events and improves patient quality of life, especially when started early. Replacing the coagulation factors, in terms of dose interval and quantity, varies according to the type and severity of hemophilia and lifestyle of each individual. CF replacement is based on the patient's weight, activity of the coagulation factor, and clinical situation. Furthermore, CFs can also be administered at home via infusion in patients meeting the criteria.³ Treatment is currently based on the replacement of the absent CFs from purified human plasma. Reposition of factor IX in hemophilia B is 20–40 IU/kg/day, and its half-life is 18–24 h; it is therefore administered two to three times per week, also according to the severity of the disorder and the lifestyle of each patient.^{1,11}

The large load of transfusions in hemophilic patients with subsequent production of IgG alloantibodies (inhibitors) that neutralize the effect of the replaced coagulation factors increases the risk of treatment failure.¹¹ The development of products with a prolonged half-life has reduced the demand for treatment in many patients. In patients with hemophilia B, therapeutic levels can be obtained with replacement every 2 weeks. However, the high cost of prophylactic therapy and the risk of bleeding due to low coagulation factors have encouraged research in the area of gene therapy.¹²

Better-quality recombinant concentrates with increased kinetics are currently gaining popularity, and in the future, gene therapy is expected to allow patients to produce the deficient CF. In this way, techniques using viral vectors for the gene have been used with good therapeutic results, low toxicity, and initially without inhibitor emergence and are a promising breakthrough for a cure for the disease. However, they are costly and the variability among individuals is still high, and further studies are therefore needed to establish a new therapy. This is also the case in research on therapies based on hematopoietic stem cells or on lentiviral vectors, which are even more promising.¹²

Thus, early diagnosis allows anti-bleeding prophylaxis to be initiated through regular replacement of coagulation factors, thereby reducing potential complications and providing a better quality of life for the patient. Neonatologists' role in recognizing signs suggesting abnormal bleeding in neonates is critical, especially in those with increased PTT only, and they should always bear in mind that a positive family history of hemophilia is not always necessary and that in more severe cases, massive intracranial hemorrhages may develop, which can lead to death in newborns.

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