Hemophilia in the newborn without family history – pattern of clinical presentation of three patients

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Abstract

Introduction. Hemophilia is the most frequently diagnosed inborn clotting factor deficiency in the newborn. In about half of the cases diagnosis is made during neonatal period. However, due to different clinical presentation comparing to older children, hemophilia in the newborn could be misdiagnosed, especially in the setting of negative family history. Case report. Clinical features of three newborns with negative family history for hemophilia are described. All three newborns were the first born children with uneventful perinatal history, and they were referred for investigation of convulsions, soft tissue tumorous mass and sepsis, respectively. Prompt diagnosis of underlying bleeding disorder and adequate substitution therapy lead to the good outcome in all three boys. Conclusion. Symptoms and signs of hemophilia in the newborn could be at time misleading and contribute to delayed treatment. High index of suspicion on inherited bleeding disorder is warranted in every neonate with intracranial bleeding.

Key words:
hemophilia A; neonatology; diagnosis, differential; factor VIII.

Introduction

Hemophilia is the most frequent inherited bleeding disorder diagnosed in the newborn. Clinical presentation in newborns is different compared to toddlers and older children, and in the absence of positive family history could result in delayed diagnosis and treatment 1.

The aim of this paper is to present clinical findings of three newborns with hemophilia A referred to a tertiary pediatric centre for evaluation of pathological conditions other than bleeding disorders, and to discuss possible pitfalls of unrecognized hemophilia.

Case reports

First case described a nine days old boy who was referred for surgical management of a tumor in the left gluteal area. He was the first child of healthy unrelated parents and uneventful pregnancy. In the 3rd and 4th day of life he was treated with phototherapy for physiological jaundice in the

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Regional hospital. Physical examination was normal except for the finding of a tumor in the left gluteal area. While obtaining blood samples for bilirubin levels, prolonged bleeding was observed at the venepuncture site, but hemostasis was not evaluated. On admission to our ward he was in a good general condition, with a palpable tumor in the left gluteus. Ultrasound revealed a mass with irregular borders, measuring 4 × 4 cm. This finding was also confirmed on computerized tomography (CT). He had hemoglobin of 143 g/L, red blood cell count (RBC) 3.98 × 10^9/L, and hemostatic test showed an prolonged activated partial thromboplastin time (aPTT) of 76.1 seconds (reference range 25–35 seconds). Coagulation factors assay revealed severe deficiency of FVIII (0.96 IU/mL). With regular substitution therapy the large gluteal tumor started to decrease. Due to a fast resolution on substitution treatment we concluded that it was a large intramuscular hematoma.

Second case described a three-week-old boy admitted to the intensive care unit because of seizures. On the day of admission his parents noticed on two occasions involuntary movements of the right hand and right facial muscles. He was the firstborn child of healthy unrelated parents with a negative family history for inherited diseases. Labor was uneventful and after birth he received intramuscular vitamin K, and was immunized against hepatitis B and tuberculosis, without complications. Also, after birth, hematoma on the upper right eyelid was noticed (Figure 1). At home, for the next three weeks, there were no concerns. He gained the expected weight and his behavior was normal. The hematoma on eyelid remained static.

Seizures were treated with phenobarbital. Blood counts showed normochromic anemia of hemoglobin level 93 g/L and RBC 3.1 × 10^9/L. Cranial ultrasound revealed large intracerebral hematoma in the right occipital lobe, and the CT confirmed the diagnosis, and revealed extension of the hemorrhage in the ventricles (Figure 2). Coagulation studies revealed normal prothrombin time (PT), with prolonged aPTT of 79.1 seconds (reference range 25–35 seconds). Assay of coagulation factors showed marked deficiency of FVIII (1 IU/mL). On immediate substitution of FVIII hematoma did not enlarge, but his level of consciousness was severely depressed. FVIII was given to achieve levels of 100% and after three days of conservative management evacuation of hematoma was performed under FVIII cover; the postoperative course was uneventful and 100% level of FVIII was maintained for fourteen days. He was discharged with phenobarbital and has received secondary prophylaxis with 50 μ/kg of FVIII weekly.

Third case described a two days old newborn who was referred for investigation of disturbed general condition and suspected sepsis. He was the first child with negative family history for bleeding disorders and other inherited diseases and uneventful labor. He had hematoma on the right heel due to blood sampling for Guthrie test, multiple large hematomas at the sites of venepuncture (Figure 3) and large cephalhematomas. On admission he had severe anemia with a hemoglobin level of 82 g/L and RBC 2.2 × 10^9/L. Hemostatic tests revealed a normal PT with prolonged aPTT of 82.4 seconds (reference range 25–35 seconds). Severe anemia and poor general condition with widespread hematomas initially raised suspicion on disseminated intravascular coagulation (DIC). However, platelet count and fibrinogen level were in the normal range. Level of FVIII was 0.8 IU/mL and the diagnosis of hemophilia was established.
Discussion

Hemophilia has a worldwide distribution and occurs either in the form of familial disease or as a sporadic disease, due to de novo mutations. Well established recommendations are already in place for management of pregnancy and newborns with positive family history for hemophilia. Sporadic cases of hemophilia can result in severe bleeding with lifelong morbidity if not promptly diagnosed and treated. Physiological alterations of the hemostatic system of newborns and at times nonspecific clinical presentation in the setting of a negative family history for haemophilia still represents a diagnostic challenge for neonatologists and hematologists for diagnosing sporadic cases of hemophilia.

Patients in our group were referred for evaluation of congenital tumor, convulsions, and systemic infection. In the first patient, although prolonged bleeding was noticed at the site of venepuncture, an inherited bleeding disorder was not entertained as a possibility, and the tumor-like formation in the right gluteus was the reason for referral. It is unusual that despite large hematoma patient was not anemic. An event that could result in hematoma formation was not identified; no intramuscular injections were given at this site. Vitamin K was applied to the anterior part of thigh and was not the cause of hematoma.

The second patient suffered unusual late occurrence of an intracerebral haemorrhage. According to data from previous reports, the median time for diagnosis of intracranial hemorrhage is 4.5 days. The hematoma on the upper eyelid, unusual for uncomplicated and noninstrumental delivery, was not a warning sign neither for neonatologist in the nursery nor for the pediatrician in the primary care. After substitution treatment and neurosurgical intervention, this child has been completely well and with normal developmental milestones at the eleven months of age. Due to possibility of rebleeding, he has been put on secondary prophylaxis with 50 U of FVIII weekly.

The third patient was referred for treatment of sepsis. Prolonged bleeding in the setting of serious diseases in the newborn could be attributed to acquired disorders of hemostasis, most frequently DIC. Although this patient had no evidence of DIC, coexistence of inherited and acquired bleeding disorders in the newborn are described, and are a particularly challenging diagnostic problem. Large cephalohematomas and severe anemia after noninstrumental and uncomplicated delivery did not raise a suspicion that bleeding disorder was the main cause of his disturbed general condition.

While historical reports suggest that a diagnosis of hemophilia during the neonatal period is infrequent (in about 10% of hemophilia cases), contemporary reports indicate that about 50% of patients with hemophilia are diagnosed during the neonatal period. Iatrogenic causes of bleeding, at the site of venepuncture or intramuscular injections are the commonest signs of hemophilia in the newborn. Prompt recognition of the newborn with hemophilia is of paramount importance since potentially lifelong consequences of unrecognized bleeding, like those in children with ICH, could be avoided. Incidence of sporadic cases of hemophilia is traditionally estimated to be around 30%, but it could be more frequent. This implies that diagnosis of sporadic cases of hemophilia in the newborns is underestimated, especially in children with moderate and mild forms of FVIII or FIX deficiency.

Conclusion

Lack of recognition among health caregivers as to when to investigate for a coagulation disorder in the neonate, especially in preterm infants, could contribute to delayed diagnosis and inappropriate treatment. Bearing in mind these facts, assays for FVIII and FIX should be a part of evaluation of neonates with bleeding, especially in those with intracranial hemorrhage.

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References


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