An Infant With Prolonged Circumcision Bleeding and Unexplained Coagulopathy

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Abstract Tyrosinemia type I is a rare autosomal recessive disorder. Fulminant onset of liver failure can occur in the first few months of life. Because all of the clotting factors are produced exclusively in the liver except factor VIII, coagulation abnormalities are very common in patients with severe liver disease. Rarely a significant coagulopathy in the absence of overt signs of liver disease may be seen in hereditary tyrosinemia. We present a 4 weeks-old tyrosinemic infant who presented with severe bleeding after circumcision and no other signs of liver failure. The diagnosis of tyrosinemia should be kept in mind in differential diagnosis of bleeding disorders especially a severe coagulopathy unresponsive to vitamin K, and fresh frozen plasma, even when other signs of liver failure are absent.

Keywords Tyrosinemia · Bleeding · Liver failure

Introduction

Tyrosinemia is a rare paediatric metabolic liver disorder. Hereditary infantile tyrosinemia, or tyrosinemia I is an autosomal recessive disorder (OMIM #27670) due to the absence of fumarylacetoacetate hydrolase (FAH), a required enzyme of tyrosine metabolism [1]. Hereditary tyrosinemia may present in infancy as a severe hepatorenal disorder, with gross abdominal distension, ascites, and hepatosplenomegaly. These features are well recognized. A further major problem may be a profound hemorrhagic disorder [2]. Because all of the clotting factors are produced exclusively in the liver except factor VIII, coagulation abnormalities are very common in patients with severe liver disease. Rarely a significant coagulopathy in the absence of overt signs of liver disease may be seen in hereditary tyrosinemia [3]. We present a 4 weeks-old tyrosinemic infant who presented with severe bleeding after circumcision and no other signs of liver failure.

Case Report

A 4 weeks-old male patient was presented with prolonged bleeding after circumcision. He was born as the fourth child of a consanguineous family via caesarian section after an uneventful pregnancy. The parents were both healthy, but it is learned that his two female siblings were death when they were 2 and 5-months-old because of an unknown disease. Our patient's physical examination revealed 1 cm hepatomegaly. There was no splenomegaly or ascites. Laboratory analyses showed anemia with a hemoglobin (Hb) level of 9.5 g/dl, mean corpuscular volume (MCV) 89 fl, white blood cell count (WBC) 10,200/mm³, and platelets 124,000/mm³. The reticulocyte count

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Table 1 Results of laboratory tests

Test/Time	4 Weeks old	8 Weeks old	16 Weeks old
Hemoglobin (gr/dl) (<i>n</i> : 12–15)	9.5	10.1	9
Thrombocyte (/mm ³) (<i>n</i> : 150,000–400,000)	124 000	114 000	78 000
WBC (/mm ³) (<i>n</i> : 4500–13500)	10,200	9.2	5.4
AST (IU/l) (<i>n</i> : 5–34)	36	40	104
ALT (IU/l) (<i>n</i> : 3–55)	18	32	44
Albumin (gr/dl) (<i>n</i> : 3.5–5.0)	3.5	3.4	2.5
GGT (IU/l) (<i>n</i> : 5–55)	NA	NA	84
Alkaline phosphatase (IU/l) (<i>n</i> : 40–150)	NA	NA	1890
Glucose (mg/dl) (70–110)	74	80	70
Total bilirubin (mg/dl) (0.2–1.2)	0.8	1.2	2.4
PT (sec) (<i>n</i> : 12.2–14.4)	39	42	46
INR	4.1	3.8	4.2
PTT (sec) (<i>n</i> : 26–37.2)	92	83	94
Fibrinogen (mg/dl) (<i>n</i> : 150–350)	154	104	74

NA not administered

was 1%. The peripheral blood smear revealed normocytic cells with no hemolytic findings. Serum glucose, creatinine, urea, electrolytes, albumin and transaminases were found to be in normal ranges. Coagulation studies revealed prothrombin time (PT) 39 s, international normalized ratio (INR) 4.1, partial thromboplastin time (PTT) 92 s, and serum fibrinogen 154 mg/dl (Table 1). Viral serology including hepatitis and TORCH was negative.

Because of the bleeding tendency after circumcision and elevated prothrombin time (PT)—partial thromboplastin time (APTT) levels, a late vitamin K deficiency was thought to be a reason, and intravenous vitamin K was administered. However, this treatment caused no improvement in the coagulopathy. Fresh frozen plasma was given five times, and led to only transient improvement in his coagulopathy. Blood sample for coagulation factor levels had been taken before fresh frozen plasma administration. Factors VII, II, and X levels were found to be 2, 19, and 54%, respectively. According to these results the patient had been diagnosed as possible coagulation factor deficiency (Factor VII?). The patient discharged from the hospital and followed up at outpatient clinic.

One month later (at the age of 8 weeks) the patient still had prolonged PT and PTT levels with normal liver function tests. Blood sample for coagulation factor levels had been taken again and very low Factor VII level (5%) was found. We observed hepatomegaly (3 cm below right costal margin), splenomegaly (3 cm below left costal margin), anemia, thrombocytopenia and worsening liver function tests at the age of 16 weeks. Therefore, it was possible to be an inherited metabolic disease which

accompanied to hepatic dysfunction. The history of intermarriage and infant sibling deaths was supporting this theory. In fact, blood and urine amino acid analyses revealed elevated levels of serum tyrosine (173 mg/Lt, normal level is <17 mg/Lt) and urine tyrosine (959 mg/g creatinin, normal level is <165 mg/g creatinin) as suspected. The level of succinylacetone in urine was three times higher than normal as a result of urine organic acid analyses. Alfa fetoprotein level was 39,000 ng/ml.

The patient was diagnosed as tyrosinemia type I. Diet of the patient was regulated with tyrosine-restricted formula and we began to give nitrofloromethylbenzoylcyclohexandione (NTBC) to our patient. Finally, during his last follow up visit, he was 6 months old. He was using NTBC and tyrosine-restricted diet. Final coagulation factor levels were as follows: AFP: 349 s, PT: 27 s, INR: 2.1 and APTT: 60 s. Complete blood count and electrolytes were normal and liver and spleen were nonpalpable.

Discussion

Hypertyrosinemia is observed with deficiencies of tyrosine aminotransferase, 4-hydroxy phenylpyruvate dioxygenase (4-HPPD) or FAH. Tyrosinemia type I is a rare autosomal recessive disorder with clinical and pathological manifestations involving mainly the liver, kidney and peripheral nerves [1]. Fulminant onset of liver failure can occur in the first few months of life. Rarely, the infant with tyrosinemia type I become symptomatic before 2 weeks of age, the usual presentation is between 2 and 6 months of age [4].

Circumcision is a religious tradition in Muslim society. As an Islamic country, in Turkey all Muslim boys are circumcised between the ages 1 month–14 years. Bleeding remains the commonest complication encountered during and after circumcision. Excessive bleeding may be due to anomalous vessels or to the presence of a bleeding disorder [5]. The differential diagnosis in a neonate with bleeding presenting after circumcision would include inherited deficiency of clotting factors, hemorrhagic disease of newborn due to vitamin K deficiency and inherited metabolic disease presenting as hepatocellular dysfunction in the newborn period. The coagulation factors are synthesized in the liver, with exception of Factor VIII which is produced by endothelium. In the presence of severe liver disease, there is a failure to synthesize the clotting factors, leading to progressive failure of coagulation, with low concentrations of all the clotting factors except factor VIII [2].

Our patient applied to our department with the complaint of bleeding after circumcision. Primarily, this patient was suspected to have a bleeding disorder like late vitamin K deficiency. When the patient did not respond the vitamin

K, we investigated the common pathway of coagulation factors levels. The patient did not have sign of liver disease except both PT and PTT elevation. During the follow up, anemia, thrombocytopenia hepatomegaly, and the other findings of hepatocellular injury were developed. Because intermarriage and two siblings were died due to an unknown disease, an inherited metabolic disease was a possible diagnose, and tyrosinemia was proven in this case with metabolic tests.

In the review of the literature we found only one case report of tyrosinemia who presented with coagulation disorders without signs of liver failure [3]. The diagnosis of tyrosinemia should be kept in mind in differential diagnosis of bleeding disorders especially a severe coagulopathy unresponsive to vitamin K, and fresh frozen plasma, even when other signs of liver failure are absent.

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