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Case Report Open Access

A Newborn with a Blueberry Muffin Rash, Hepatosplenomegaly, Thrombocytopenia and Severe Cholestatic Jaundice at Birth

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Abstract

Neonatal cholestasis is characterized by an elevation of conjugated bilirubin. It occurs in approximately 1 in 2500 term infants. Gaucher Disease (GD) is an exceptionally rare cause of neonatal cholestasis. We report a male term newborn with a blueberry muffin rash, hepatomegaly and massive splenomegaly at birth. His total serum bilirubin (TSB)/direct was 13.5/11.9 mg/dL, and platelet count 20,000 bil/L. A leukocyte beta-glucosidase level was 0 and full sequencing of the *GBA* gene showed that he was homozygous for the pathogenic complex allele p.D409H and a second variant p.H255Q, consistent with the diagnosis of the severe phenotype GD type 2.

Keywords: Neonatal; Cholestatic jaundice; Thrombocytopenia

Introduction

Neonatal cholestasis, a manifestation of hepatobiliary dysfunction, is characterized by an elevation of conjugated or direct reacting bilirubin. The most common identified causes in the first months include biliary atresia, idiopathic neonatal hepatitis, infection, and a multiplicity of other causes [1-3] including some 20 lysosomal storage disorders [4,5] one of which is GD.

Case Presentation

This 38 3/7week gestation, 3010g male was born by cesarean section to a 22-year-old primigravida, blood group O, Rh D positive mother, following an uncomplicated pregnancy. The parents are non-consanguineous Albanians and all prenatal and perinatal tests were negative. There was no history of any metabolic or liver disease in the family and the mother was rubella immune. The Apgar scores were 6 and 9 at 1 and 5 minutes and the physical examination revealed a blueberry muffin rash over his back and lower extremities, hepatomegaly 3-4 cm below the costal margin and a spleen enlarged down to the pelvis. The neurologic examination was normal and there were no dysmorphic features.

His blood group was O positive with a negative direct antiglobulin test. At age 1 hour the TSB/direct was 13.5/11.9 mg/dL, AST 1194 (47-150 U/L), ALT 308 (6-50 U/L) alkaline phosphatase 202 (150-420 U/L),albumin 3.5 (3.5-3.9 g/dL), ferritin 1152 (25-200 ng/ml). Complete blood count revealed a hemoglobin 15.7 g/dL, hematocrit 48.3%. and was remarkable for a platelet count of 20,000 bil/L, white blood count (wbc) 26.1 bil/L and nucleated red blood cells 46.5/100 wbc. The peripheral smear revealed myelocytes, reactive lymphocytes, smudge cells, echinocytes and polychromasia.

A platelet transfusion increased his platelet count to 39,000 bil/L and he received intensive phototherapy. Blood glucose was <10 mg/dL and he required 13.5 mg/kg/min glucose IV to maintain euglycemia. By age 14 hours his TSB/ direct had increased to 17.0/10.3 mg/dL and a double volume exchange transfusion was performed which lowered the TSB to 9.4/6.2 mg/dL.

His hospital course was characterized by persistent severe total and direct hyperbilirubinemia, thrombocytopenia requiring several platelet transfusions, hepatomegaly and massive splenomegaly. In spite of intensive phototherapy, the TSB ranged between 16.3/12.3-21.1/14.3 mg/dL. Ursodeoxycholic acid produced no decrease in the direct bilirubin level and attempts to decrease the intensity of the phototherapy consistently resulted in an increase in the total and direct bilirubin levels. Nucleated red blood cell counts remained elevated throughout the first month and, on hospital day 7, his end-tidal carbon monoxide level, corrected for ambient carbon monoxide, was significantly elevated at 4.6 ppm, confirming the presence of ongoing significant hemolysis [6]. Breast milk was introduced on day 7 and he was on full feeding from day 9. On day 13 the TSB was 19.9/15.1 mg/dL and phototherapy was discontinued.

Cultures of blood, urine and cerebrospinal fluid were negative as were TORCH titers and repeated urine cytomegalovirus cultures and cytomegalovirus PCR. The VDRL was non-reactive and Ebstein-Barr and echo-virus (molecular detection) were negative. Ophthalmic examination was normal as was a cranial ultrasound. He initially received ampicillin, cefotaxime and acyclovir and subsequently ganciclovir but all were discontinued following the negative culture results.

An abdominal ultrasound demonstrated hepatomegaly with heterogeneous liver echotexture with no focal masses or cysts, marked splenomegaly with spleen extending from the diaphragm to the left lower quadrant without portal hypertension. Cranial and cardiac ultrasound exams were negative. Abdominal MRI on day 10 showed normal iron quantification and a massively enlarged spleen with a dilated, tortuous splenic vein.

Urine bile acid excretion was increased ruling out a hepatic synthesis defect and gamma glutamyl transpeptidase was normal. His triglycerides were 222 mg/dL and maximum ferritin was 2004 ng/mL.

Newborn metabolic screen, soluble IL-2 receptor, alpha-1 antitrypsin level and alpha-1 antitrypsin phenotype were all normal. Urine organic acids showed marked elevation of 4 hydroxyphenyl lactic acid and 4 hydroxyphenyl pyruvic acid with normal plasma amino acids, inconclusive for any disease.

At age 18 days a leukocyte beta-glucosidase level was 0, compatible with Gaucher disease (GD). Full sequencing of *GBA* showed that he was homozygous for the pathogenic complex allele p.D409H and a second variant p.H255Q, consistent with the diagnosis of the severe phenotype GD type 2 [7]. He required 9 platelet transfusions and, at discharge on day 19, his platelet count was 40,000 bil/L and TSB was 22.3/16.2 mg/dL

Final Diagnosis

Neonatal Gaucher disease type 2.

Follow-up

As an outpatient, his severe direct hyperbilirubinemia and thrombocytopenia persisted. At age 5 weeks the TSB was 20.7/19.5 mg/dL and platelet count 43 bil/L. Palliative care was provided and he died at home at age 4 months. An autopsy was not obtained.

Discussion

The most likely causes of direct hyperbilirubinemia in a newborn with hepatosplenomegaly, a blueberry muffin rash and thrombocytopenia are the TORCH group of infections and other congenital viral infections, but testing for these conditions was negative. Imaging, including MRI was noncontributory as were tests for inborn errors of metabolism. The complete absence of leukocyte beta-glucosidase suggested a diagnosis of GD which was subsequently confirmed with genetic testing.

GD is an exceptionally rare cause of neonatal cholestasis. In a review of 17 studies encompassing 1692 infants with conjugated hyperbilirubinemia in infancy, only one case of GD was identified [2]. GD is the most prevalent of the inherited sphingolipidoses and is the most common genetic disorder in Ashkenazi Jews. Our patient, however, was born to Albanian parents, as was one of the previously reported cases [8] (see below). Direct hyperbilirubinemia is not a common feature of GD although it was present in each of the neonatal case reports we identified [8-11]. In one case the direct bilirubin was dramatically elevated to 32.0 mg/dL, (with a TSB of 49.5 mg/dL) [10] on day 2 and in our infant it was 16.1 mg/dL (TSB 20.3 mg/dL) on day 5, levels rarely seen in the newborn.

Lysosomal storage disorders (LSDs) are rare inborn errors of metabolism with an incidence of 1 in 1500-7000 live births [4]. As one of only 20 neonatal LSDs, [4] type 2 GD in the newborn is extremely rare and, with an estimated incidence of about 1/100,000 live births, it is not surprising that its recognition in the neonate is a challenge [4].

GD, an autosomal recessive disorder, is mainly due to mutations in the glucocerebrosidase gene encoding the lysosomal enzyme acid β-glucosidase [4], inducing enzyme deficiency and lysosomal accumulation of specific substrates that accumulate and cause deterioration of cerebellar and tissue function [5]. Three clinical forms of Gaucher disease have been described: type 1, or non-neuronopathic; type 2, or acute neuronopathic; and type 3, or subacute neuronopathic [12].

Perinatal type 2 GD is a severe and uncommon variant [4,12] characterized by hepatosplenomegaly, thrombocytopenia, secondary to hypersplenism [4] and bone marrow infiltration, and anemia. In its most severe and lethal form, it can present in utero as non-immune hydrops fetalis and congenital icthyosis in the newborn [12].

GD leads to anemia and low platelets, bone marrow infiltration, bone damage and hepatosplenomegaly [4]. The marked elevation of the end-tidal carbon monoxide level in our patient on day 7 (in spite of a double volume exchange transfusion on day 1) and the persistent elevation in the nucleated red blood cell count, documented significant ongoing hemolysis, a finding not recorded previously in GD. An increase in red cell destruction and bilirubin production has been reported in adult rats following short-term biliary obstruction [13]. Bile salts have been shown to have membrane-damaging properties [14] and elevated bilirubin levels together with bile salts might also damage red blood cell membranes [13].

The natural history and clinical presentation of perinatal-lethal GD, a severe and rare variant of acute type 2, is quite different from classic type 2 GD. Only 20% of the patients with the type 2 variant have isolated visceral involvement at presentation, with neurological symptoms appearing later [9]. The features of perinatal-lethal GD include hepatomegaly [4], and purpura associated with thrombocytopenia due in part to the splenomegaly that develops. Anemia is associated with hydrops, but is neither profound nor frequent enough to explain it. Fetal cases are reported with skin abnormalities and a peculiar facial appearance with low-set ears, small nose with flat bridge and anteverted nares and, less frequently, hypertelorism, microstomia, eversed lips, microretrognathia and microcephaly [12]. Our case did not present with neurological signs until age 3 months when he was irritable and had difficulty swallowing.

The gold standard for diagnosis is determination of glucocerebrosidase (beta-glucosidase) activity in a blood sample. If this is normal, GD is very unlikely. In most perinatal-lethal GD, glucocerebrosidase activity is absent or severely deficient [12]. Usually, serum angiotensin converting enzyme, ferritin and alkaline phosphatase are highly elevated [15]. In our infant, the ferritin was consistently elevated (lowest value > 600 ng/ml), although the alkaline phosphatase was normal. .

Santamaria et al reported 3 unrelated patients with the same genetic mutations as our patient [p.D409H;p.H255Q] strongly suggesting that this double mutant allele has a single origin in a region around Albania, comprising the Balkans and the Adriatic area of Italy [7]. In vitro expression studies and the concomitant presence of p.H255Q and p.D409H mutations practically eliminate enzyme activity, demonstrating a cumulative effect and a worsening of the associated phenotype [7].

In 1991, GD became the first lysosomal storage disorder to be treated successfully with enzyme replacement therapy [16]. The major limitations are the inability of large molecules such as enzymes to cross the blood–brain barrier. Our patient received genetic counselling and the parents decided to provide palliative care only, with no specific treatment.

Conclusion

Gaucher disease must be considered in a newborn infant with hepatosplenomegaly, thrombocytopenia and direct hyperbilirubinemia with no evidence of infection or biliary obstruction. An early diagnosis

of perinatal-lethal type 2 Gaucher disease will help in the management and counselling for this rare condition.

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Conflict of Interest

The authors declared no potential conflict of interest with respect to the research, authorship and/or publication of this article.

Declaration

The authors received no financial support for the research, authorship and/or publication of this article. MRL wrote the initial draft of this manuscript and contributed to all of the subsequent drafts. She reviewed and approved of the final draft. MRL, CP and MJM provided clinical care for this infant, reviewed all of the drafts of this manuscript and approved of the final draft. MJM reviewed and contributed to all drafts of this manuscript and was responsible for writing the final draft.

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