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BMH Med. J. 2022;9(3):73-76. **Case Report**

Decoding the Mystery of Sky High Bililurbin Levels in a Child with Hereditary Spherocytosis- The Co-existence of Crigler Najjar Syndrome Type 2

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Abstract

Hereditary Spherocytosis (HS) is the most prevalent cause of hemolytic anemia in children due to red cell membrane defect. Crigler-Najjar syndrome type II, is an inherited disorder of bilirubin metabolism due to defect in UDP-glucuronosyltransferase (UGT1A1) gene. Cases with co-existence of HS and UGT1A1 deficiency are rarely reported in literature. Here, we report a child with HS who presented with cholelithiasis at an early age and developed extremely high levels of bilirubin without any significant hemolysis or biliary tract obstruction. He was worked up and genetic sequencing (whole exome analysis) confirmed the co-existence of type II Crigler-Najjar syndrome along with Hereditary Spherocytosis. Child underwent cholecystectomy and splenectomy. Establishing the complete diagnosis helped in pre-operative stabilization and uneventful post-operative period.

Keywords: Hereditary Spherocytosis, Crigler Najjar Syndrome Type 2, children, co-existence

Introduction

Hereditary Spherocytosis (HS) is the most prevalent cause of hemolytic anemia in children due to red cell membrane defect. Most of the patients have well-compensated hemolysis. The clinical features may vary according to the severity of the disease and include icterus, splenomegaly and cholelithiasis due to chronic hemolysis [1].

Crigler-Najjar syndrome type II, is an inherited disorder of bilirubin metabolism due to defect in UDP-glucuronosyltransferase (UGT1A1) gene [2]. Cases with co-existence of HS and UGT1A1 deficiency are rarely reported in literature. Here, we report a child with HS who presented with cholelithiasis at an early age and developed extremely high levels of bilirubin without any significant hemolysis or biliary tract obstruction. He was worked up and genetic sequencing (whole exome analysis) suggested the co-existence of type II Crigler-Najjar syndrome along with Hereditary Spherocytosis.

Case Description

A young boy, known case of Hereditary Spherocytosis, was hospitalized with history of fall followed by multiple episodes of vomiting. He was treated conservatively as a case of mild traumatic brain injury in pediatric ICU. Physical examination showed icterus and hepatosplenomegaly. Family history revealed that his elder sibling, father, grandfather, aunt, cousins had HS and had undergone splenectomy and cholecystectomy at various ages. The Pedigree chart depicting his family tree is shown in **Figure 1**.

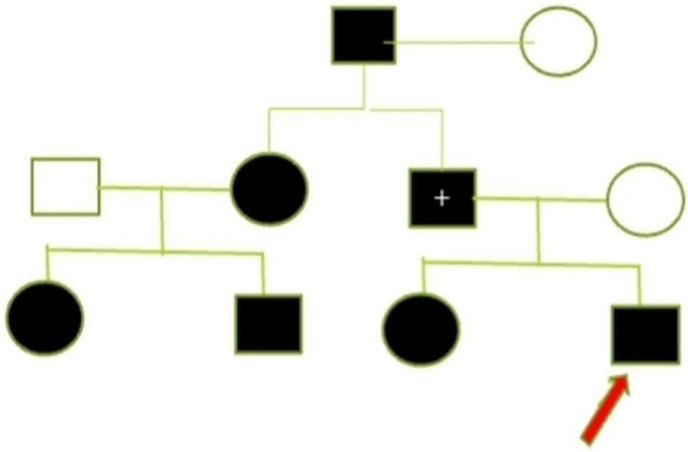

Figure 1: Pedigree chart of the child showing multiple affected members in the three generations

On preliminary investigations, his hemoglobin was 12.9 gm/dL, reticulocyte count was elevated (7.5%) and other cell lines were normal. Serum bilirubin was elevated (total:28 mg/dl, direct:14 mg/dl), with normal liver enzymes. Peripheral smear was consistent with spherocytic hemolytic anemia and osmotic fragility test was positive. Although the general condition of the child improved, there was progressive increase in icterus and serum bilirubin levels. On day 5 of hospital stay, bilirubin levels increased to total of 61 mg/dl and direct fraction of 17 mg/dl. Serial complete blood count didn't show any fall in Hb levels and liver enzymes including GGT continued to be normal (**Table 1**).

Table 1: Serial values of complete blood count and liver function tests

	Day 1	Day 5	Day 10 (5 days after starting phenobarbitone)	Before Splenectomy	On 2 weeks follow up post-surgery
Hb (g/dl)	12.9	11.9	10.2	9.8	12.9
TLC (/mm^3)	9300	6700	13500	20200	13900
Platelet count (/µL)	3.18 lakhs	3.33 lakhs	4.46 lakhs	4.28 lakhs	7 lakhs
Total bilirubin(mg/dl)	28	61	12.26	5.75	1.05
Direct bilirubin(mg/dl)	14	17	3.94	2.27	0.22
SGOT (U/L)	41	66	66	85	
SGPT (U/L)	34	31	36	53	
Alkaline phosphatase (U/L)	287	192	287	234	
GGT (IU/L)		23	25		

On further investigation, USG abdomen showed multiple cholelithiasis, but had no features of biliary tract obstruction. Magnetic Resonance Cholangiopancreatography (MRCP) done also ruled out any biliary tract obstruction. Very high bilirubin levels in the absence of significant hemolysis or liver

dysfunction, and without any biliary tract obstruction were the unusual features in the child. A further review of the family history revealed that his sister who had undergone splenectomy and cholecystectomy and had an unexplained rapid rise in the serum bilirubin levels (45 mg/dl) postoperatively. Considering all these, a coexistent disorder of bilirubin metabolism was suspected and whole exome sequencing was done. He was given a trial of oral phenobarbitone following which serial bilirubin levels showed decreasing trend. Pneumococcal vaccination was given as per the protocol. He was discharged and planned for elective surgery later. By the time, his clinical exome was available which revealed two mutations - Ankyrin (ANK 1) mutation, consistent with hereditary spherocytosis and another homozygous mutation in UGT1A1 gene, suggestive of Crigler-Najjar syndrome type 2. Final diagnosis was Hereditary Spherocytosis with coexistent Crigler-Najjar syndrome type II. Child had normal bilirubin levels on oral phenobarbitone maintenance and underwent elective laparoscopic splenectomy and cholecystectomy. His postoperative period was uneventful and was discharged after 2 days. He was continued on low dose oral phenobarbitone and his bilirubin levels remains normal on follow up.

Discussion

Hereditary spherocytosis is an autosomal dominant genetic disorder with intrinsic defects in RBC membrane that render red cells spheroid, less deformable and vulnerable to splenic sequestration and destruction. Disease occurs due to mutations in spectrin, ankyrin and band 3 genes [3]. Significant hemolysis results in anemia, jaundice, splenomegaly and often gall stones. Peripheral smear shows spherocytosis and osmotic fragility test is commonly used as a screening test. Among the described screening tests, the eosin-5'-maleimide (EMA) binding assay is most specific. The treatment includes folate supplementation, blood transfusion if needed, splenectomy and cholecystectomy if indicated [4].

Crigler-Najjar syndrome is a rare inherited genetic disorder affecting bilirubin metabolism, which results in high levels of unconjugated bilirubin. Type I Crigler-Najjar syndrome is an autosomal recessive severe disease due to complete absence of UDP glucuronosyl transferase activity. Affected children develops severe unconjugated hyperbilirubinemia leading to kernicterus and usually don't survive beyond 2 years without treatment. Treatment options include phototherapy, plasmapheresis and exchange transfusion. The curative treatment available is liver transplantation. Type II Crigler-Najjar syndrome is a relatively milder disease with marked reduction in UDP glucuronosyl transferase activity, resulting in less severe jaundice [5]. However, the bilurubin levels can increase during stress as in the child described in the report. Bilurubin levels and jaundice in Type 2 Crigler Najjar Syndrome improves on treatment with phenobarbitone.

Unusual clinical features like early development of gall stones and the very high bilirubin levels in the absence of significant hemolysis, liver dysfunction or biliary tract obstruction made the authors think beyond HS in the index child. The coexistence of Type II Crigler-Najjar syndrome with Hereditary Spherocytosis is extremely rare and there are hardly few published case reports [6]. It is also notable that Genetic testing is handy and indispensable to make diagnosis of rare inherited disorders like Crigler-Najjar Syndrome. Establishing the complete diagnosis helped to stabilize the patient before surgery and for an uneventful post-operative period. In hemolytic anemias like HS, disproportionately elevated bilirubin levels compared with the degree of hemolysis, warrants detailed evaluation.

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