SCIENCEFORECAST
A digital science library

Case Report
Published: 11 Oct, 2018

Journal of Clinical Case Reports

Crigler Najjar Syndrome Type I, A Rare but Severe Cause of Unconjugated Hyperbilirubinemia in Children

Habtamu A*

Department of Pediatrics and Child Health Consultant Pediatrics Gastroenterologist/Hepatologist, Addis Ababa University, Addis Ababa, Ethiopia

Abstract

A rare and severe autosomal recessive disorder of bilirubin metabolism. It has been associated with consanguinity in some patients. Infants without any evidence of hemolysis, can develop severe, permanent, unconjugated hyperbilirubinemia within the first few days of life resulting in chronic kernicterus.

Keywords: Crigler Najjar Syndrome, Unconjugated; Bilirubin metabolism

Introduction

A rare and severe autosomal recessive disorder of bilirubin metabolism [1]. The incidence of Crigler Najjar syndrome is 0.6–1.0 per million live births. Occurs in all races and has been associated with consanguinity in some patients [2]. It is characterized by non-hemolytic unconjugated hyperbilirubinemia. According to serum total bilirubin concentration (STBC), CNS (Crigler Najjar Syndromes) are classified into two types: type I (CNS-I), in which the STBC is more than 25 times that of the normal level ranging from 342 to 684 μmol/L, and type II (CNS-II), in which it is 6-25 times with a range of STBC within 103-342 μmol/L [3,4].

In 2002, Al Shurafa et al. analyzed the outcome of six children with Crigler-Najjar syndrome type I & reported that the first three living after liver transplants for this syndrome in Saudi Arabia and the Middle East. Two developed acute hepatocellular rejection, (treated with methylprednisolone pulse treatment) & one had a biliary leak (surgically repaired). Post-op bilirubin levels returned to normal in all three and no further phototherapy was required [5].

Few hundred cases reported since the first report in 1952 by Crigler and Najjar in six infants in three families. All six infants developed severe, permanent, unconjugated hyperbilirubinemia within the first few days of life, without any evidence of hemolysis. Five of the six infants died of kernicterus by the age of 15 months [2].

The sixth infant was free of neurologic disease until 15 years of age, when kernicterus suddenly developed in adolescent and died six months later [2].

Case Presentation

A 2-years and 4 months old female presented with Jaundice noticed since 10th day of life. She was investigated for the cause of jaundice and all were unremarkable (TORCH screening, sepsis work-up, hypothyroidism screening and chromosomal analysis were negative). She was on pediatrics gastroenterology/hepatology clinic for follow-up and periodic phototherapy. While on follow-up, she developed altered mentation and abnormal body movement since 1yr and 8 months of age. At which time, investigations for enzyme deficiencies were considered and investigated.

Physical examinations

No dysmorphic features

Deep icteric sclera and skin, hepatomegally of 4cms BRSCM with TVLS 10cms, modified GCM= 3/5, otherwise, no clonus, rigidity and was normotonic.

Investigations

Total serum Bilirubin 34, direct 22 (almost all the time) T3, T4, TSH- Normal, VDRL, Nonreactive, DNA PCR for HIV was negative, CMV, Toxoplamosis all were nonrevealing, Liver enzymes and liver function tests were normal, hepatitis viral markers (HBSAg, anti HCV antibody and HAV antibody) were negative. U/S- Normal, no evidences of Biliary atresia, and choledochal

OPEN ACCESS

*Correspondence:
Abebe Habtamu, Department of Pediatrics and Child Health Consultant Pediatrics Gastroenterologist/ Hepatologist, Addis Ababa University, Addis Ababa, Ethiopia.
E-mail: Abebe2018@gmail.com

Received Date: 30 May 2018
Accepted Date: 09 Oct 2018
Published Date: 11 Oct 2018

Citation: Habtamu A. Crigler Najjar Syndrome Type I, A Rare but Severe Cause of Unconjugated Hyperbilirubinemia in Children. J Clin Case Rep. 2018; 1(2): 1013.

ISSN 2643-8194

cyst. This time, Patient was sent abroad (America) for genetical analysis.

Genetical analysis was reported as follows.

UGT1A1 mutations deserted in association with CN I have included nonsense, frame shift and missence mutations. Patients with type II CN, typically have 2 missence mutations, but may also be compound heterozygous for one missence and one nonsense frame shift mutation.

The frame shift mutation we identified on your patient has been described in one patient, who was compound heterozygous for this frame shift mutation, and CN type 2. We suspect your patient is homozygous for the frame shift mutation (unless the patient also carries a deletion of the UGT1A1 gene, which is making the mutation appear homozygous), and so based on homozygosity for frame shift mutation, I would predict that this fits best for CN (Crigler Najjar type I) type I mutation, although clinical findings should always be taken into account.

Discussion

CNS I (Crigler Najjar syndrome type I) should always be suspected in infants who developed persistent jaundice due to unconjugated bilirubin within the first few days after birth. These children have, normal LFT, may have neurologic symptoms due to kernicterus. Occasionally, late onset kernicterus in adolescence may be possible.

Classic clinical presentation

The hallmark of CNS I is pure unconjugated hyperbilirubinemia, ≈20 to 25 mg/dl but can be as high as 50mg/dL. Stool color is normal, but fecal urobilinogen excretion is diminished due to the marked reduction in the conjugation of bilirubin and rate of Bilirubin production, Bone marrow morphology, and RBC morphology and survival are normal

Prenatal diagnosis and genetic counseling are recommended because of the high frequency of consanguinity.

Inhibitors of hemeoxygenase, such as tin-protoporphyrin or tin-mesoporphyrin, results in marked inhibition of the enzyme activity in various organs. A single dose of tin-mesoporphyrin administered in neonates, shortly after birth, resulted in an average of 76% reduction of bilirubin and abolished the need for phototherapy [6].

Histopathologic findings are nonspecific on light and electron microscopy. Exclusion of other persistent unconjugated hyperbilirubinemia conditions in infancy is necessary. In our case, 2 years and 4 months old female child who had no response for phototherapy and early phenobarbitone, genetical analysis revealed Crigler Najjar syndrome type I.

A liver transplant is the only definitive treatment for Crigler-Najjar syndrome type I. It rapidly normalizes bilirubin levels. Despite its risks, some advocate prophylactic liver transplantation to avoid the risk of kernicterus which may not be fully reversible once it is established. Hepatocyte transplantation is a promising alternative [7].

Conclusion

Definitive diagnosis can be made by in vitro expression of mutant DNA from patients but this method is too elaborative and expensive for routine use. UGT1A1 mutations deserted in association with CNS I has included nonsense, frame shift and missence mutations. Patients with type II CN, typically have 2 missence mutations, but may also be compound heterozygous for one missence and one nonsense frame shift mutation.

Taking the poor response for medical treatment (medical history) and genetical analysis, this patient is a real case of Crigler Najjar syndrome type I.

References

1. Nelsone 19th edition.
2. Hong YS, Jin JY, Lee WR. A Case of Gilbert's Syndrome with Severe Neonatal Hyperbilirubinemia. J Korean Soc Neonatol. 2010;17: 266-269.
3. Canu G, Minucci A, Zuppi C, Capoluongo E. Gilbert and Crigler Najjar syndromes: an update of the UDP-glucuronosyltransferase 1A1 (UGT1A1) gene mutation database. Blood Cells Mol Dis. 2013; 50: 273-280.
4. Strassburg CP. Hyperbilirubinemia syndromes (Gilbert-Meulengracht, Crigler-Najjar, Dubin-Johnson, and Rotor syndrome). Best Pract Res Clin Gastroenterol. 2010; 24: 555-571.
5. Center for Arab Genomic Studies A division of Sheikh Hamadan Award for Medical Sciences. The catalogue for Transmission Genetics in Arabs CTGA Database.
6. Aloulou H, et al. Type I Crigler Najjar syndrome – 30 cases. Tunis Med. 2010; 88: 707-709.
7. Richard A. Galbraith, George s, Drummond and Attallah Kappas. Suppression of bilirubin production in the Crigler Najjar Type I Syndrome: Studies with the Hemi Oxygenase inhabitor Tin-Mesoporphyrin. Pediatrics. 1992; 89:175.