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Short Report

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Crigler-Najjar syndrome type II: A rare case report of a young adult

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Abstract

Crigler-Najjar syndrome is a rare autosomal recessive disorder caused by mutations in the coding region of UGT1A1 gene resulting in grossly reduced hepatic activity of glucuronyl transferase. Absence or decrease activity of this enzyme leads to accumulation of unconjugated bilirubin in the body causes unconjugated hyperbilirubinemia. Here, we report a 25 years old female patient presented to us with the complaints of jaundice since birth which occasionally aggravates on sleep disturbance, fasting state or any stressful condition and usually improves on phenobarbital therapy. This report is about an extremely rare case of Crigler-Najjar syndrome type 2.

Keywords: Crigler-Najjar syndrome; UGT1A1; Phenobarbital; UDP-glucuronyltransferase; Hyperbilirubinemia;

Introduction

Bilirubin metabolism comprises uptake of bilirubin from blood, intracellular storage, become conjugated by UDP glucuronyltransferase and then excreted into bile. Any abnormalities in these processes lead to hyperbilirubinemia. Isolated unconjugated hyperbilirubinemia usually results from increased bilirubin production as with hemolysis or ineffective erythropoiesis, decreased bilirubin uptake or impaired bilirubin conjugation. Regarding unconjugated hyperbilirubinemia, neonatal jaundice and Gilbert syndrome are common causes. Whereas Crigler–Najjar Syndrome (CNS) is an extremely rare autosomal recessive disorder caused by specific variants in the UDP-Glucuronosyltransferase 1A1 (UGT1A1) gene. These genetic mutations result in either a complete or partial loss of function of the enzyme it encodes [1]. CNS is believed to affect individuals of all racial backgrounds and occurs equally in both males and females [2]. Crigler-Najjar syndrome is classified into two types based on clinical criteria, including molecular and functional characteristics, the severity of symptoms, and response to phenobarbital. Type I is the more severe form, with nearly no UDP-glucuronosyltransferase enzyme activity, while Type II is milder, showing reduced enzyme activity. Central nervous system complications, particularly kernicterus, primarily affect individuals with Crigler-Najjar Type I [3]. This disorder occurs in fewer than one in every 1,000,000 births [2].

Case report

The patient, 25 years old unmarried female with no known comorboditis, from Chattogram, Bangladesh presented to outpatient department in Gastroenterology ward, CMCH with complaints of yellow discoloration of sclera, skin and urine. On query, she is persistently jaundiced since birth which occasionally aggravates on sleep disturbance, stressful condition & flu like illness and usually improves after oral phenobarbital therapy for short duration. She gives no history of recurrent fever, abdominal pain, generalised itching, spontaneous bleeding, haematemesis, malaena, repeated blood transfusion during her course of illness. According to her parents statement, she had no history of umbilical infection in childhood and no history of hospitalization for any significant illness. She sometime takes Phenobarbital as oral form for a short duration when jaundice is increased. She has no significant drug history other than Phenobarbital. Her menstruation is normal.

Her parents are alive, has consanguinal marriage. Both are diabetic. She has one sister who is apparently healthy & well. There has no other significant medical illness in her family members. On clinical examination, She is moderately icteric with normal vitals. Abdomen is soft, non tender & no organomegaly. Other systemic examination reveals no abnormality.

Investigation profile

Name of investigation	Patient's value	Normal value
1. CBC Haemoglobin ESR MCV MCH MCHC	 12.4 g/dl 17mm 89.1 fl 27.1 pg 30.5 g/dl	 12-15 g/dl 0-20 mm in 1st hr 76-96 fl 27-32 pg 31.5-34.5 g/dl
2. PBF	Suggestive of neutrophilia	
3. HB Electrophoresis	Normal study HbA: 97.5% HbA2: 2.5 %	
4. Serum Bilirubin	Total = 12.78 mg/dl Conjugated: 0.20 mg/dl Unconjugated: 12.58	Adult: 0.3-1.1 mg/dl
5. Serum ALT	22 U/L	5-50 U/L
6. Serum ALP	58 U/L	Adult: 39-117 U/L
7. Serum Album	4.5 g/dl	3.4-4.8 g/dl
8. RBS	113 mg/dl	<140 mg/dl
9. Reticulocyte	1.0 %	Adult : <2%
10. LDH	127 U/L	<234 U/L
11. HbsAg	Negative	
12. Anti HCV	Negative	
13. Serum ANA	Negative (32.88 IU/ml)	<40 IU/ml
14. USG of Whole Abdomen	Cholelithiasis	

Genetic analysis was not possible due to limited resources. After investigation report review, differnetial diagnoses were Crigler-Najjar syndrome type-II and Gilbert syndrome. The former one was considered more likely because serum bilirubin was >6 mg/dl.

Discussion

Hereditary unconjugated hyperbilirubinemia has been classified into two major groups, Gilbert syndrome & Crigler Najjar syndrome. Crigler-Najjar syndrom is of two types; CNS type-1 & type-2. CNS type-1 was first described by Crigler Najjar in 1952 [4], which is due to complete absence of bilirubin UDGT activity [2].

CNS type-2 was first described in 1962 by Arias, which is also called Arias syndrome [5]. There is partial deficiency of enzyme activity. Hence jaundice is less severe in CNS type-2 than that of CNS type-1 [2].

All these types of hereditary unconjugated hyperbilirubinemia can be distinguished on the basis of serum bilirubin level, presence of karnicterus & response to phenobarbitone drug therapy [7]. In Gilbert syndrome, serum bilirubin level is usually ranging from 1 mg/dl to 6 mg/dl. In CNS TYPE-1, it is ranging between 20 mg/dl to 45 mg/dl and in CNS TYPE-2, it is usually between 6 mg/dl to 20 mg/dl [7]. In this case, when she presented to us, total serum bilirubin level was 12.78 mg/dl with jaundice and liver function tests were normal with no neurological impairment.

Response to phenobarbitone is most useful difference between CNS TYPE-1 & TYPE-2 [2]. In CNS TYPE-2, hyperbilirubinemia can be reduced by more than 25% during treatment with phenobarbitone (60-120 mg/day for 2 weeks), which presumably works induction of residual bilirubin UDGT activity. But a response to phenobarbitone is not found in CNS type-1 patient [8,9]. Our patient showed about 28% reduction of total serum bilirubin level after 2 weeks phenobarbitone therapy at a dose of 60 mg/day (After treatment total serum bilirubin level was 9.23 mg/dl).

Mutation analysis of UGT1A1 was not possible due to limited resource. The diagnosis was confirmed on the basis of clinical presentation of the patient, serum unconjugated bilirubin level criteria, response to phenobarbitone therapy and absence of neurological impairment.

Conclusion

CNS type II is a rare condition. Careful history taking and proper workup can make the diagnosis early. Lifelong treatment with phenobarbital may slow down the possible complications, such as permanent risk of developing neurotoxicity, acute cholangitis etc. Proper counselling regarding consanguineous marriage, hydration, dietary and life style modification should be done to minimise the progression to complications.

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