CASE REPORT

An Unusual Case of Type I Crigler–Najjar Disease in a Young Adult: A Case Report

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Abstract

Crigler-Najjar syndrome (CNS) is a genetic disorder. It has a mostly autosomal recessive pattern of inheritance. Unconjugated to conjugated bilirubin conversion in the liver requires the enzyme Uridine 5′-diphosphate-glucuronosyltransferase (UDP-glucuronosyltransferase), which is absent or exhibits low activity in CNS. It is a significant contributor to congenital nonhemolytic jaundice. Following an aberrant gene mutation causes an increase in the bilirubin burden in the blood and is inherited within families. We present a case of a 22-year-old man who has had type I CNS since birth. There is minimal neurological damage, but there is a considerable increase in unconjugated bilirubin. Phenobarbital therapy had no impact on the reduction of bilirubin load. The primary goal is to reduce unconjugated bilirubin, although liver transplantation is the only curative treatment option for type I CNS.

Keywords: Crigler–Najjar syndrome, Hyperbilirubinemia in young adult, Unconjugated hyperbilirubin.

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Introduction

The estimated incidence of autosomal recessive CNS is less than one patient per million.[1] The activity of the hepatic UDP-glucuronosyl-transferase enzyme (HUDP-GTase) is affected. Since the HUDP-GTas activity is completely absent in CNS type I individuals, unconjugated bilirubin accumulates severely in the base of the forebrain, midbrain (basal ganglia), and cerebellum. Bilirubin-induced neurological damage is being reported especially during the first years of life after birth due to the accumulation of unconjugated bilirubin.[1] Hemolysis, impaired absorption, poor metabolism, and liver bilirubin release are all possible causes of elevated blood bilirubin levels. These patients need the utmost care and appropriate workup in the intensive care unit (ICU) setting with monitoring.

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Patient consent statement: The author(s) have obtained written informed consent from the patient for publication of the case report details and related images.

Case Description

We present a case of a 22-year-old male who presented to the emergency department with yellowish discoloration of sclera, abdominal pain which was on and off for the last 15 days, and undiagnosed liver disease. He gave a history of consumption of alcohol occasionally and there were no signs of pedal edema, spider nevi, asterixis, melena, hematemesis, or any focal neurological deficit. He also gave no history of any recent drug consumption or addiction. According to his father, he was jaundiced since birth. He had normal developmental milestones in his childhood. His family members had no history of blood transfusion therapy.

During admission, he was afebrile and icteric with the following vitals—heart rate—100 beats per minute, blood pressure—90/50 mm Hg and peripheral oxygen saturation was 95% on room air, respiratory rate was 18/minute, and Glasgow Coma Scale—15/15.

The patient's hematological laboratory testing was within normal range. Ultrasonography of the whole abdomen showed no organomegaly.

Total bilirubin was 34.8 mg/dL (conjugated bilirubin 2.9 mg/dL and unconjugated bilirubin 31.9 mg/dL), with normal values of serum glutamic oxaloacetic transaminase, serum glutamic pyruvic transaminase, aspartate aminotransferase, γ-glutamyl transpeptidase, and alkaline phosphatase. The level of serum copper was 110 µg/mL (normal 70–130 µg/mL) and the serum ceruloplasmin level was 31.0 mg/dL (normal 15.0–60.0 mg/dL). Figure 1 shows the yellowish discoloration of the sclera. Viral serology was found to be negative. No schistocytes were found in the peripheral blood smear and the test for malaria was found to be negative. Initially measured serum ammonia was 54 (normal 15–45 µg/dL) but later on, it raised to 229. Urine analysis for bilirubin traces was absent. Autoimmune causes were also excluded as antinuclear antibodies, antismooth muscle antibodies, and anti-liver-kidney microsomal antibodies were negative. Treatment with phenobarbital did not affect bilirubin level. Ultrasonography demonstrated a normal hepatic span and all liver functions test were within normal limits except very high unconjugated serum bilirubin 31.9 mg/dL, thus the differential diagnosis of benign unconjugated hyperbilirubinemia was made, which includes Crigler–Najjar disease (CND) and Gilbert syndrome. However, in this instance, the diagnosis of type I CNS was further made based on a markedly elevated level of unconjugated bilirubin, a positive history of kernicterus in childhood, and no

Table 1: Different characteristics of benign isolated unconjugated hyperbilirubinemia

Characteristics	*Type I CND*	*Type II CND*	*Gilbert syndrome*	*Current case*
Inheritance	Autosomal recessive	Autosomal recessive	Autosomal recessive	Not evaluated
Total bilirubin (mg/dL)	18–50	6–25	<6	34.8
Unconjugated bilirubin (mg/dL)	++++	+++	+	31.9
Kernicterus	Very high	High	Maybe absent	Absent
UGT enzyme activity	Absent	10%	30%	cannot be assessed
Treatment	Phototherapy plasmapheresis	Phenobarbital	Not required	No effect from phenobarbital treatment

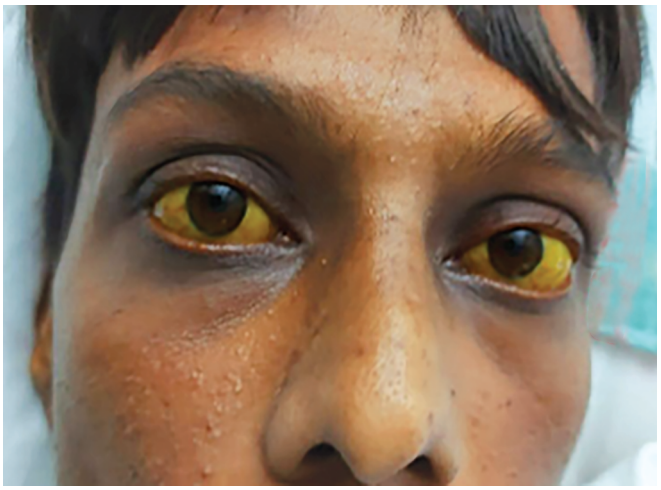

Fig. 1: Photographic image of the face showing yellowish discoloration (reproduced after patient information and consent)

response to phenobarbital treatment. Written informed consent was taken for this case report. The patient was shifted to the gastro medicine ward after 6 days of ICU admission.

Discussion

Bilirubin is mainly formed by the breakdown of hemoglobin as a byproduct. Then it binds with albumin and is transported to hepatocytes in the liver. Bilirubin undergoes glucuronidation within the hepatocytes by conjugation with glucuronic acid and this step is catalyzed by the enzyme HUDP-GTase. Conjugated (direct) bilirubin is secreted into bile which is water soluble. The end product of heme metabolism is bilirubin of which 80% is derived from the breakdown of hemoglobin from erythrocytes, and 20% from nonhemoglobin proteins. Acute liver dysfunction may be fatal. Most of the congenital and possible acquired causes of liver dysfunction have been excluded. Our region had more reported cases of alcohol-induced liver dysfunction. If these cases are not promptly assessed and managed early then the patient may have rapid deterioration in their health which may lead to hepatic necrosis, sepsis, multiple organ failure, and death. The congenital diseases if diagnosed in manhood are mainly benign in nature and they required no specific treatment.[1] For making a diagnosis, the genetic cause should be ruled out.[2] In our case, even the other causes of hyperbilirubinemia were excluded, but the cause of persistent hyperbilirubinemia is still unexplained. The differential diagnosis of CNS is always thought of if the child presents with severe jaundice at the time of birth. Clinical evaluation, family history, and genetic, and laboratory testing may help to further confirm the diagnosis. Liver function tests will detect an increased level of unconjugated bilirubin in the blood or bile doesn't have conjugated bilirubin. The molecular gene targeted evaluation is needed to detect *uridine diphosphate glucuronosyltransferase (UGT) 1A1* gene mutations. However, in our case, genetic testing was not done due to the unavailability of genotyping kit at our center. Type I CNS is an autosomal recessive disease characterized by a complete absence of HUDP-GTase activity. Because the coding area of the UGT gene is mutated (missense mutation), the enzyme produced is structurally abnormal, with no bilirubin-conjugating capacity. Some patients who do not show any signs of hepatic encephalopathy with type I CNS in adulthood may survive but few patients after attaining the age of 16–18 years may not survive due to the development of bilirubin-induced neurological dysfunction (kernicterus).[3,4] Similar to the previous case report, our patient was a 25-year-old male with normal physical status and health at the time of initial laboratory evaluation apart from raised unconjugated serum bilirubin. There are few reported cases of type II CNS disease that may be presented with kernicterus. It is important to distinguish between the causes of isolated unconjugated hyperbilirubinemia that is, both types of CNS and Gilbert's disease has different treatments and prognoses (Table 1). Gilbert syndrome manifests in adulthood but as per the report, the total bilirubin is found to be <6 mg/dL. Although the diagnosis can be confirmed by viewing multiple parameters which include clinical evaluation, positive phenobarbital treatment response (decrease in serum bilirubin concentration by 20–25% in type II CNS), analysis of bile, liver tissue biopsy (HUDP–GTase assay) and molecular genetic assessment.[5] Due to thick skin, increased skin pigmentation, less body surface area to body mass, and phototherapy are less effective in these adults. Plasmapheresis is the alternative technique for the removal of raised bilirubin (unconjugated) in case of severe hyperbilirubinemia. However, in our case, no feature of bilirubin-induced neurological dysfunction was seen. The definitive and therapeutic treatment for CNS I is liver transplantation. An interprofessional team and an evidence-based approach for early diagnosis and management with close follow-up are mostly required in the management of CNS patients.

Conclusion

Diagnosis of CNS is always challenging for treating physicians. It needs multidisciplinary teamwork and a systematic approach to diagnosing and managing the patient. However, for a definitive diagnosis thorough history, specific physical findings, laboratory workup, and molecular genetic testing are necessary.

Informed Consent

We obtained consent to reproduce the photograph of the patient's face in the publication.

Authors Contribution

We verify and confirm that each author contributed to every stage of this manuscript equally.

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