Crigler-Najjar Syndrome Type II Diagnosed in a Patient with Jaundice Since Birth

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ABSTRACT

Crigler-Najjar syndrome type II is caused by mutations in the UGT1A1 gene resulting in severely reduced hepatic activity of UDP-glucoronyltransferase – an enzyme required to convert bilirubin into a more soluble form that can then be removed from the body. Absence or severe deficiency of this enzyme can lead to bilirubin accumulation in the body resulting in yellow skin and eyes (jaundice). The earliest signs of this disease can be apparent in the neonatal period. Patients with Crigglar-Najjar syndrome type II respond to phenobarbital therapy which decreases their chances of getting bilirubinemia by 60-70% in 3 weeks. A 17 years old boy presented with the complaint of gastroenteritis. On examination, he was jaundiced and his parents reported that it has been present since birth. He was admitted in the hospital with the differential diagnosis of Gilbert syndrome, but later it was found that the unconjugated bilirubin levels were higher than those required for Gilbert's criteria. We report, herein, an extremely rare case of Crigler-Najjar syndrome type II and how the patient responded to phenobarbital therapy. Periods of fasting, stress and any kind of illness can worsen unconjugated hyperbilirubinemia leading to complications like kernicterus, so higher levels of unconjugated bilirubin should be addressed immediately and the patient along with his/her family should be educated about this disease.

Key Words: *Crigler-Najjar syndrome, Type II, Autosomal recessive, Phenobarbital.*

INTRODUCTION

Crigler-Najjar syndrome Type II is a rare genetic disease characterised by a persistent unconjugated hyper-bilirubinemia. Bilirubin is water insoluble and is conjugated with glucuronic acid to make it water soluble to be excreted in the bile. UDP-glucuronosyltransferase 1A1 (UGT1A1) enzyme, found in the liver, helps in this process.[1] In Crigler-Najjar patients, this enzyme is either inactive (type I) or severely reduced (type II).[1,2] Therefore, bilirubin cannot be excreted into the bile and remains in the blood causing a high plasma level of unconjugated bilirubin, which then leads to jaundice and may lead to kernicterus (bilirubin encephalopathy) due to bilirubin toxicity. The disease is inherited as an autosomal recessive trait. Several gene alterations have been discovered in Crigler-Najjar syndrome patients, leading to reduced or absent UGT1A1 activity. Full-length cDNA for human UGT1A1 has been cloned and sequenced successfully.[3] The incidence of this disease is not exactly known; but according to the cases described in literature, it is thought that only a few hundred cases have been reported and the incidence is even less than one in one million live births.[4]

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CASE REPORT

A 17 years old unmarried Pakistani male student, presented with the complaint of gastroenteritis. On examination, the patient was diagnosed with jaundiced and on further questioning, the patient's father explained that his son was jaundiced since birth and one of his paternal cousins (who is 13 years old now) has the same condition. It was also found that the parents and grandparents of both the affected individuals had consanguineous marriages. However, they both had normal developmental milestones and were good students at school. After admission, his clinical examination was performed.

There was no visceromegaly. His CNS was intact with normal superficial and deep tendon reflexes. His respiratory and cardiovascular systems were normal. Investigations revealed total serum bilirubin of 18.6 mg/dL (conjugated fraction 0.5 mg/dL and unconjugated fraction: 18.1 mg/dL), aspartate aminotransferase 35 U/L (normal <40 U/L), alanine aminotransferase 28 U/L (normal <56 U/L), alkaline phosphatase 125 U/L (normal <390 U/L), γ-glutamyl transpeptidase 28 U/L (normal <49 U/L), and prothrombin time 13.9 s (control 13.2 s). There was no evidence of intravascular hemolysis, and serum lactate dehydrogenase levels were 200U/L (normal 140U/L to 280U/L). Reticulocyte count 0.7% (normal: 0.5% to 2.5%), serum haptoglobin, 150 mg/dl (normal: 30 mg/dl to 200 mg/dl), and serological markers (HBsAg, anti-HCV, anti-nuclear antibody, smooth muscle antibody,

Figure 1: Icterus in the patient of Crigler-Najjar Syndrome Type 2.

liver-kidney microsomal antibody) were negative. Serum ceruloplasmin level was 26.0 mg/dl (normal 15.0 to 60.0). Ultrasound abdomen showed a normal liver and with no evidence of biliary obstruction. In view of the raised indirect bilirubin with normal liver function tests and no hemolysis, clinical differential diagnoses of Crigler-Najjar syndrome type II and Gilbert syndrome were suspected. The Crigler-Najjar syndrome type II was considered more likely because serum bilirubin was >6 mg/dL.[5] He was first treated for his complaints of vomiting and diarrhoea.

On the basis of his history, clinical examination, and laboratory results, he was diagnosed with Crigler-Najjar syndrome type II. We demanded his paternal cousin's reports and it also showed similar results with higher levels of unconjugated bilirubin of 9.8 mg/dl and similar complaints of icterus. After his diagnosis was made, the next challenge was to lower his unconjugated bilirubin levels. A 90 mg dose of phenobarbital was started, spreading over three doses. Oral hydration was encouraged. His liver function tests (LFTs) were repeated every day; and the unconjugated bilirubin started to drop from 18.6 mg/dl to 11.5 mg/dl in two weeks period. The patient was kept under observation for further one week to evaluate the treatment with phenobarbital; and it was observed that the unconjugated bilirubin could not be lowered more than 11.5 mg/dl.

The patient was discharged with proper dietary, lifestyle, and genetic counselling; and was advised for follow up with the same treatment. His follow-up investigation after one month of discharge from the hospital, revealed unconjugated bilirubin level maintained at 12.0 mg/dl.

DISCUSSION

Crigler-Najjar (CN) syndrome, type II, unlike type I, is a potentially benign disease and jaundice may occur in a newborn during infancy or later in childhood in contrast to CN type I, where patients present with persistent, marked jaundice at or soon after birth; and if untreated, leads to death due to the kernicterus by the age of 2 years. Patients with CN type II usually have serum bilirubin levels ranging between 10 and 20 mg/dL (175 and 350 μmol/l) and seldom develop kernicterus, although neurological dysfunction may occur, if hyperbilirubinemia is exacerbated by fasting, drugs or infectious diseases.[6]

Differentiation between Gilbert syndrome and CN type I and II is important since treatment and prognosis are different between these entities. Although the diagnosis is usually made on clinical grounds, response to phenobarbital (decrease by at least 25 % in CN type II), bile analysis, measurement of UDP-GT on liver tissue, and genetic testing can be used to confirm the diagnosis.[7] Although generally unnecessary treatment options for patients with CN type II include phenobarbital, it can be used if there is persistently high bilirubinaemia. During crises of hyperbilirubinaemia, whole-body blue-light phototherapy or plasma exchange transfusion may be utilised to lower bilirubin levels to prevent encephalopathy. However, using drugs that displace unconjugated bilirubin from plasma-protein binding sites, for example, sulfonamides, salicylates and penicillin should be avoided.

All three types of hereditary unconjugated hyperbilirubinemia are distinguished on the basis of serum bilirubin level, response to phenobarbitone, and the presence of kernicterus. Total serum bilirubin level ranging between 1 mg/dL and 6 mg/dL is found in Gilbert syndrome, between 20 mg/dL and 45 mg/dL in CN type I, between 6 mg/dL, and 20 mg/dL in CN type II.[8] One way of clinically differentiating CN I from CN II is through the response of phenobarbitol. CN II has a better response showing up to 30% reduction in the levels of unconjugated bilirubin levels, while CN I typically displays no response. The reason for such response lays in the fact that in CN II patients, there is residual activity of UGT, while in CN I, UGT activity is absent.

The genetic analysis of this patient was not carried out because of limited resources; and the diagnosis was confirmed on the basis of unconjugated bilirubin levels criteria, described previously, and the clinical presentation of the patient.

A handful of cases of CN type II from Pakistan have been reported but this is the first of its kind as two patients from the same family have been diagnosed despite the fact that this syndrome is rare and the two couples they were born to were first cousins.

CN type II is rare and challenging for the physicians to diagnose it early; but with proper work up and careful history taking, it can be diagnosed; and its progression to complications which include permanent risk of developing neurotoxicity and acute cholangitis,[9] which are both potentially fatal later in life, can be slowed down by lifelong treatment with phenobarbital,[10] proper hydration, dietary and life-style modifications such as avoiding periods of stress and patient's counselling on consanguineous marriage. Research work is required to study the molecular genetics and various kinds of mutations encountered in this syndrome, so that its treatment modalities can be modified.

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