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Case Report

Gilbert syndrome with elevated liver enzymes!

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ABSTRACT

Gilbert syndrome is a benign autosomal recessive condition of defective bilirubin metabolism in the liver. This syndrome may manifest with recurrent episodes of jaundice due to reduced glucuronidation of bilirubin resulting in raised unconjugated bilirubin levels but normal levels of transaminases. It results from polymorphisms in the UGT1A1 gene responsible for the conjugation of bilirubin. Even though it is a benign condition, it is of clinical importance because the hyperbilirubinemia can be precipitated by certain conditions like puberty, stress, infections, and menses. The present case report involves a case of Gilbert syndrome that is unveiled by drug-induced hepatitis.

1. Introduction

Jaundice is a major clinical symptom usually associated with liver diseases and hemolytic disorders. However, there are other well-documented inherited causes of hyperbilirubinemia with varied clinical manifestations. Among these, Gilbert syndrome is a hereditary benign condition causing unconjugated hyperbilirubinemia with otherwise normal transaminases and liver function tests.[1] GS was first described by Gilbert and Lereboulette in 1901 as a chronic, yet benign, condition of jaundice, the cause of which was unrelated to hemolytic disease.[2] It usually presents as recurrent episodes of hyperbilirubinemia usually in the pubertal period with a slight male preponderance.[3] Even though the serum bilirubin levels are elevated, there is no treatment required for the condition as it has an excellent prognosis.

2. Case History

A 14year old boy from rural Telangana was admitted to the pediatric ward with a history of yellowish discoloration of eyes and skin and passing dark-colored urine for one-week duration. There was no history of pale-colored stools, fever, vomiting, or loss of appetite. The child used unknown herbal medication for two days after the onset of jaundice following which there was further deepening of jaundice. He had a history of similar illness two months prior to this episode which was preceded by a two-day history of fever and vomiting. He took herbal medication at that time for three days following which jaundice subsided within one week. On physical examination, icterus was present in the eyes and all over the body with no pallor and no focal neurological deficit. Per abdomen, examination showed tender mild hepatomegaly. Slit-lamp examination of the eye showed no evidence of a Kayser-Fleischer ring.

3. Investigations

Complete hemogram, CRP, and ESR were within normal limits. Liver function test results from the day of admission

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Table 1: Showing liver function test results:

Parameters	9/12/2022 (Day 1 of admission)	12/12/2022 (Day 4 of admission)	15/12/2022 (Day 7 of admission)	19/12/2022(Day 9 after admission-after 72 hours of trial of phenobarbitone)	11/1/2023 (during recent visit)
TSB*(mg/dl)	25.3	24	20.4	14.6	3.3
DB^{Ď} (mg/dl)	12.2	11	10.1	7.7	2
ALT^{ĎĎ} (U/L)	1772	1260	751	581	254
AST(U/L)	1889	1227	780	667	282

TSB: Total Serum Bilirubin, DB: Direct Bilirubin, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase.

to the follow-up visit were described in table 1. There was no hemolysis noted on the peripheral blood smear. Viral markers for Hepatitis B & C viruses were negative and Hepatitis A IgG antibody was positive. Urine for bile salts and bile pigments was positive. LDH and serum ferritin were elevated. The coagulation profile was within normal limits. Serum Ammonia levels(392mcg/dl) were elevated (Normal=17-90). Antinuclear antibodies, Liver kidney microsomal antibodies, and smooth muscle antibody titers were within normal limits. 24 hours urine copper and ceruloplasmin levels were within normal limits. USG abdomen showed mild hepatomegaly and normal liver architecture.

As common causes for hepatitis like viral hepatitis, autoimmune hepatitis and Wilson's disease were ruled out and as there was a history of intake of herbal medication, drug-induced hepatitis was considered. Toxicity caused due to herbal medication intake causes hepatocyte injury which can led to hepatomegaly and rise in hepatic transaminases.[4] Due to persistently high serum bilirubin levels, a trial of phenobarbitone was started following which there was an improvement in serum bilirubin levels as shown in Table 1. So, the possibility of enzymatic defects opened up. Keeping the possibility of Gilbert syndrome, Polymerase chain reaction followed by bi-directional Sanger Sequencing was performed to identify the variants in the UGT1A1 gene which showed that the subject was homozygous for 7 TA repeats in the UGT1A1 promoter and hence at risk for Gilbert syndrome.

Following admission, supportive care was given and the child was monitored for signs of hepatic encephalopathy. After ten days of hospital stay child was discharged on oral phenobarbitone and advised to follow up for every week. During the latest visit after 25days of using phenobarbitone, LFT was done which showed total serum bilirubin of 3.3 mg/dl and direct bilirubin of 2mg/dl. AST and ALT levels were 282 and 254U/L respectively.

4. Discussion

Gilbert syndrome is the most common benign hereditary hyperbilirubinemia syndrome without any other comorbidities. Although the prevalence of Gilbert's syndrome is 5-10% in the white population (5), according to a study by Kulkarni et al., the prevalence in India is 0.71% (3) It is a disorder of ineffective conjugation of glucuronic acid to bilirubin leading to an increase in unconjugated bilirubin levels in the blood. It is due to common polymorphisms resulting in TA insertion in the promoter region of UGT1A1 leading to decreased binding of the TATA-binding protein and decreased normal gene activity by approximately 30% .[5]

Clinical manifestations are characteristically present during early adolescence and are more frequently found in males.[1,3] Most cases are diagnosed around puberty due to higher hemoglobin turnover and endogenous steroid hormone-induced inhibition of bilirubin glucuronidation. The syndrome is usually asymptomatic and is usually seen as jaundice during periods of stress such as fasting, dehydration, fatigue, and menstruation.[6]

Diagnosis of Gilbert syndrome is made by unconjugated hyperbilirubinemia usually aggravated by acute stress, with no evidence of hemolysis and hepatocyte damage and absence of other disease processes.[7] In this, the bilirubin levels are typically below 4mg/dl.[1] but it can fluctuate depending on exacerbating factors. In the present case also, bilirubin levels were decreased to 3.3mg/dl following treatment with phenobarbitone.

The differential diagnosis also includes Crigler Najjar syndrome type 1 and 2, but due to its rare presentation and as there is no history of neonatal jaundice, it was ruled out.[8] Unlike the previously published case reports, the present case report includes higher serum bilirubin levels at the time of presentation that resolved gradually which is similar to case reports by Harharpreet et al and Floris et al.[9,10] It also had raised transaminases which is attributed to the hepatocyte injury caused by suspected herbal medication intake that is aggravated by chronic liver disorder (Gilbert syndrome) as mentioned by David Recardo et al.[4]

5. Conclusion

As Gilbert syndrome is the most common benign hereditary hyperbilirubinemia syndrome, it should be considered in the differential diagnosis in cases that present with recurrent episodes of unconjugated hyperbilirubinemia. But

depending on the associated pathology, the presentation and LFT picture may vary considering the current case.

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None.

7. Conflict of Interest

None.

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