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Case Report

Isolated Unconjugated Hyperbilirubinemia in Adults: The Gilbert's Versus Criggler Najar Syndrome Type 2 Conundrum.

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ABSTRACT

Gilbert's syndrome is a genetic disorder characterised by non-hemolytic unconjugated hyperbilirubinemia. It is caused by mutations in the UGT1A1 gene which codes for the enzyme uridine diphosphate glucoronosyl transferase-1, which conjugates bilirubin for excretion. Affected individuals are usually asymptomatic apart from a mild jaundice and investigations reveal a mild isolated indirect hyperbilirubinemia. This may be exacerbated in the face of environmental and physical stressors. It is very similar in presentation to Criggler-Najjar syndrome (CNS) type 2. There is a small risk of kernicterus in patients with CNS type 2 needing daily phenobarbitone therapy. This risk is miniscule in Gilbert's syndrome. Genetic testing for polymorphisms of the UGT1A1 gene is the diagnostic clincher for Gilbert's syndrome, but it can also be picked up by evaluating the response to phenobarbitone and fasting, particularly in resource poor settings. Due to limited availability, case reports documenting the genetic mutational analysis are sparse. We reported one such rare case with an unusually high indirect hyperbilirubinemia in Gilbert's syndrome confirmed by both phenobarbitone response and genetic analysis.

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Introduction

Unconjugated hyperbilirubinemia is a cause for evaluation in adults. In the absence of hemolysis and liver disease, genetic disorders should be sought. Our case report shows that rarely, Gilbert's may present with a very high unconjugated hyperbilirubinemia in adults. Although genetic analysis clinches the diagnosis, in resource poor settings, the phenobarbitone test becomes particularly useful to differentiate it from Criggler-Najjar syndrome (CNS) type 2.

In CNS type 2 also there is unconjugated hyperbilirubinemia. However, unlike Gilbert's, the hyperbilirubinemia is much more marked and jaundice persists as serum bilirubin never touches normal. Intercurrent illnesses, fasting and stressors can raise bilirubin enough to even cause kernicterus in CNS type 2. Therefore a daily single bedtime dose of phenobarbitone is recommended in CNS type 2 whereas Gilbert's needs no specific therapy in daily life. Hence, a good clinical suspicion can distinguish the two and the right advice and diagnosis can help abate or manage further episodes of jaundice in patients of Gilbert's syndrome.

Case Report

A 40-year-old labourer presented to the emergency with complaints of yellowish discolouration of skin and eyes and passage of highly coloured urine for seven days. This was not associated with any pain abdomen, nausea, vomiting, the passage of clay-coloured stools or any pruritus. There was a history of heat exhaustion, loose stools and fever lasting 2-3 days, about a week back, after which the patient noticed deepening jaundice. On probing further, the patient gave a history of recurrent jaundice at least three to four times over the past five years. It was insidious and resolved on its own over a month each time. There was no history of addictions, blood transfusions, chronic ailments, weight loss, or intemperate habits. He was the fourth sibling out of six, born from a non-consanguineous marriage and father of four children. There was no history of similar complaints in the family. On general physical examination, he was icteric but with no other signs of liver cell failure. He was hemodynamically stable, and systemic examination was also unremarkable.

Investigations showed haemoglobin of 13.1 g/dL, a total leukocyte count of 10,000/mm^3 and a platelet count of 1.6 lac/mm^3. A liver function test (LFT) showed total bilirubin of 12.9 mg/dL, of which the indirect component was 10.1 mg/dL and the direct fraction was 2.8 mg/dL. Liver enzymes were normal, and there was no coagulopathy. The renal function test (RFT) had urea of 97 mg/dL and a creatinine of 2.8 mg/dL. Serum electrolytes and serum protein were within normal limits. Blood tests for hepatitis B, C and HIV were negative. No evidence of ongoing hemolysis, as confirmed by normal serum lactate dehydrogenase (LDH) and no hemoglobinuria. Direct and indirect Coomb's tests were both negative. Leptospira IgM and IgG were also both Negative. Ultrasonography of the abdomen was normal.

The patient seemed dehydrated, and the RFT also responded to hydration, bringing the creatinine to 1.2 mg/dL within two days, with adequate urine output. Since there was a history of recurrent jaundice and an isolated unconjugated hyperbilirubinemia, we suspected a genetic disorder of conjugation, our differentials being CNS Type 2 and Gilbert's syndrome. As the immediate genetic analysis was unavailable, oral phenobarbitone was empirically started in a dose of 60mg thrice a day. The patient was discharged with advice to follow up with serial LFTs. The fall in bilirubin was quite dramatic (as seen in *Figure 1*). As the patient had developed slight transaminitis, the dose of phenobarbitone was reduced to twice daily, yet the bilirubin continued to fall and turned normally. This proved the diagnosis of Gilbert's syndrome, with jaundice possibly ensuing the dehydration episode. Further, we withheld the phenobarbitone, and the patient's bilirubin remained normal.

The genetic analysis done in follow-up showed heterozygosity for UGT1A1*6 G71R and, mainly, a homozygous polymorphism for UGT1A1*28/28 genotype, A(TA)7TAA. This results in two extra (TA) bases in the promoter region of UGT1A1, which was suggestive of minimal enzyme activity and, thus, Gilbert's syndrome.

Discussion

The Gilbert syndrome, also known as Gilbert-Meulengracht syndrome after its discoverers in France and Germany, is a hereditary condition heralded by intermittent isolated unconjugated hyperbilirubinemia in the absence of any other cause, such as hepatocellular disease or hemolysis.[1] It is the most common congenital hyperbilirubinemia syndrome, occurring in 3-13% of the population and varying with ethnicity.[2,3] There is at least a 50% decrease in the hepatic bilirubin UGT activity.[4]

The patients are mostly unaware of their diagnosis as they have characteristic asymptomatic jaundice, usually noticed by the onlookers.[5] The degree of hyperbilirubinemia is typically less than 5 mg/dL, and conjugated bilirubin is less than 20% of the total bilirubin fraction.6 Our case is perhaps the only case of Gilbert's syndrome documented in the literature, with a high degree of hyperbilirubinemia.[7]

What is also noteworthy in Gilbert's syndrome is the response to phenobarbitone. This becomes particularly useful to differentiate it from its close friend, another cause of unconjugated hyperbilirubinemia in adults, CNS type 2. CNS type 2 is also a hereditary disorder of bilirubin metabolism characterized by marked unconjugated hyperbilirubinemia due to a much reduced (<10%) activity of hepatic bilirubin glucuronosyltransferase coded by UGT1A1. There is persistent jaundice as the bilirubin levels never reach normal and intercurrent illnesses, fasting, and other stressors may elevate bilirubin enough to cause kernicterus. Hence a single bedtime dose of phenobarbitone is recommended. CNS Type 2 is less severe than CNS type 1 where this hepatic enzyme is absent, and kernicterus, progressive bilirubin encephalopathy, ensues, causing mortality in most cases. The chances of kernicterus are very minimal in Gilbert's syndrome.

The phenobarbitone test is a simple test in which the fall in bilirubin levels in response to phenobarbitone administration has to be evaluated. In Gilbert's syndrome, following phenobarbitone administration, the bilirubin levels normalise entirely. In CNS type 2, the fall in bilirubin levels is usually more than 30 percent, but the levels never normalise. The dose of phenobarbitone used is 1-5 mg/kg/day, titrated to 60-180 mg/ day in single or divided doses.[8] Other tests that can be used as alternatives include the caloric deprivation test, in which an increase in jaundice can be seen after 48 hours of a 300 kcal/ day caloric deprivation. Patients with Gilbert's syndrome had a 3 to 5-fold exaggeration of the baseline bilirubin level.[9] Alternatively, phenytoin and phenazone have also been used in diagnosis. In genetic analysis, we found a homozygous polymorphism for UGT1A1*28/28 genotype, A(TA)7TAA, which is a commonly reported variant in the Indian ethnic group.[10]

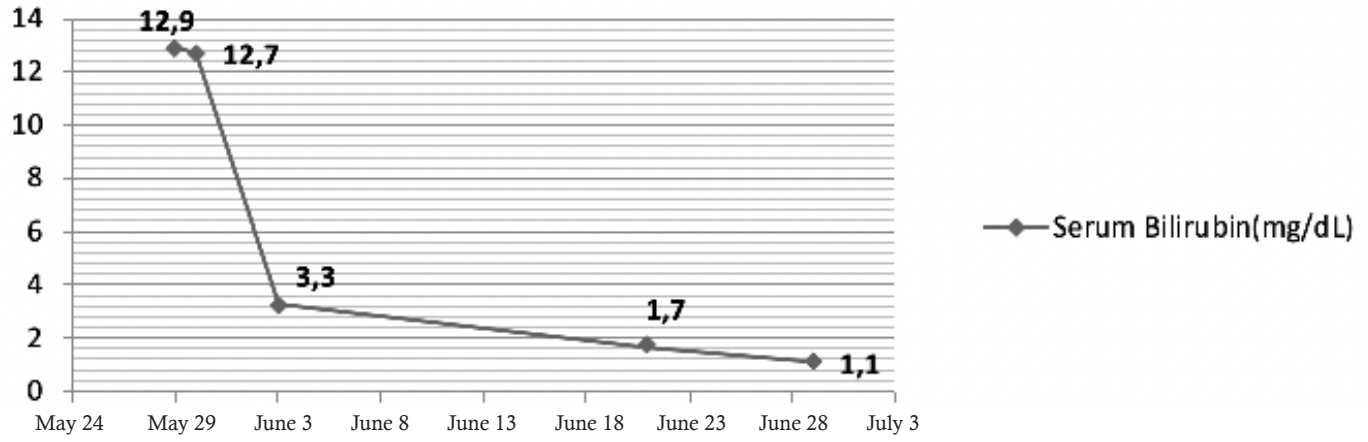

Figure 1. Showing fall of serum bilirubin after adding phenobarbitone on June 3.

In resource-poor settings where genetic confirmation is unavailable or delayed, the response to phenobarbitone can conveniently differentiate between CNS type 2 and Gilbert's syndrome. While CNS type 2 therapy is lifelong, Gilbert's syndrome may need only awareness and no continuous treatment. Patients must be sounded about triggers such as dehydration, intercurrent illnesses, exhaustive exercise, menstruation and hepatotoxic drugs, which can precipitate disproportionate jaundice.[5]

Concluisons

When evaluating a case of chronic megaloblastic anaemia, we should not forget this rare association with G-NETs. They can perpetuate the anaemia through ulceration and bleeding. There is also the risk, even in sporadic cases, for them to evolve into a malignant lesion, thus changing the patient's prognosis. The most commonly known is the association of gastric neuroendocrine tumour type I with macrocytic anaemia due to vitamin B12 deficiency. To our knowledge, there are no reports in the literature about an association of this type of tumour with folate deficiency-induced anaemia. Therefore we consider the publication of this case to help our colleagues.

Conflict of Interests

The authors declare that they have no conflict of interest.

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Informed Consent

Written consent was obtained from the patient.

Authors' Contribution

Literature Review, Critical Review, Manuscript preparing held by all authors.

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