CASE REPORT

GILBERT SYNDROME: A CASE SERIES

Sushant Mane, Ashwini Ronghe

Abstract

Gilbert Syndrome (GS) 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 a deficiency or decreased activity of uridine diphosphate-glucuronyl transferase 1A1 (UGT1A1). It normally presents in adolescent age group especially in females because it is thought to be triggered due to increase in bilirubin production under the effect of steroid hormones released in that age. We present a case series where Gilbert Syndrome was clinically diagnosed in three male patients, all below ten years of age with unconjugated hyperbilirubinemia. All three children had gallstones.

Key words: Unconjugated Benign Bilirubinemia, Arias Type Hyperbilirubinemia, Meulengracht Syndrome, Familial Non-hemolytic Jaundice

Introduction

Gilbert syndrome (GS) is the most common hereditary bilirubin mechanism disorder due to decreased activity of uridine diphosphate-glucuronyl transferase 1A1 (UGT1A1) and is associated with unconjugated hyperbilirubinemia in the absence of liver disease or haemolysis. (1) It has a prevalence of 3- 7% in the general public (2,3) with preponderance in female population. (4) It is diagnosed around puberty due to an increase in bilirubin production under the influence of steroid hormones. (1) We present a case series of 3 pre-adolescent males who were all clinically diagnosed as Gilbert syndrome.

Case 1: A 6 years old male child presented with yellowish discoloration of eyes since 1 ½ years of age and intermittent abdominal pain in right hypochondrium for five months. This yellowish discoloration wasn't evaluated till the present age as the child was asymptomatic. On examination no signs of liver cell failure were seen and he had a just palpable liver and spleen. Other systemic examination was normal. Investigations are depicted in Table 1.

Case 2: An 8 ½ years old male child presented with yellowish discoloration of eyes for two years and epigastric abdominal pain for two weeks. Systemic examination was normal. Investigations are depicted in Table 1.

Case 3: An 8 years old male child was referred to our hospital for further management. A physician had noticed jaundice in the child during a health camp conducted in the patient's school. The child was absolutely asymptomatic and systemic examination was normal. Investigations are depicted in Table 1.

Table 1: Investigations of all patients

vestigations	Case 1	Case 2	Case 3
Hemoglobin (gm/dl)	10.8	12.2	12.5
Red Blood Cell (cells /cumm)	400,000	345,000	411,000
White Blood Cell (cells/cumm)	8300	7600	5600
Platelets (cells/cumm)	520,000	328,000	268,000
Packed Cell Volume (%)	30.2	35.5	34.2
Reticulocyte count (%)	0.5	1	0.8
Aspartate Aminotransferase (IU/L)	32	24	32
Alanine Aminotransferase(IU/L)	16	36	38
Alkaline Phosphatase (IU/L)	183	136	176
Albumin (g/dl)	4.2	3.8	4.5
Globulin (g/dl)	2.4	2.6	3
Total Bilirubin (mg/dl)	11.3	9.2	10
Direct Bilirubin (mg/dl)	2	2.1	1.5
Indirect Bilirubin (mg/dl)	9.3	7.1	8.5
Prothrombin time (secs)	12	11	14
Gamma Glutamyl Transpeptidase (IU/L)	20	42	15
Haptoglobulin (g/dl)	59.8	66	88
Lactic Acid Dehydrogenase (IU/L)	100	94	114
Hepatitis B Surface Antigen (HbsAg) & Hepatitis C Virus antibody (HCV)	negative	negative	negative
Hemoglobin electrophoresis	Hemoglobin S absent	Hemoglobin S absent	Hemoglobin S absent
Sickling test	Negative	Negative	Negative
Osmotic fragility	Normal	Normal	Normal
USG abdomen	Multiple small gall stones. Liver normal	Multiple small gall stones. Liver normal	Normal

In all 3 patients, presence of jaundice with multiple gall stones and no anemia prompted the diagnosis of Gilbert Syndrome. Crigler-Najjar type II was ruled out clinically on the basis of rarity of the disease, no neonatal jaundice and a mild disease as patients only had yellow skin. Enzyme testing and gene testing could not be done due to financial constraints. Two children with cholelithiasis were started on ursodeoxycholic acid and all patients were treated with phenobarbitone 5mg/kg to decrease the jaundice.

Discussion

There are very few studies establishing the prevalence of Gilbert syndrome in India. (5,6) A study conducted in healthy blood donors estimates the prevalence to be as high as 6%. (5) The syndrome is usually asymptomatic and is only seen as jaundice during periods of stress such as fasting, dehydration, fatigue, menstruation etc. (1,3) This is the reason for its presentation in adolescent age group. (1) Another reason postulated is s due to the production of steroid hormones at puberty which affect bilirubin metabolism. (4) Our cases were clinically diagnosed with Gilbert syndrome in pre-pubertal age group. There have been two other reports where Gilbert Syndrome presented in prepubertal age. (7,8) One was in 4 prepubertal children who were orthotropic liver transplant recipients, which as per the authors could be due to GS transferred from donor liver after ruling out rejection, cholestasis, cholangitis, viral infection, or haemolysis. It was found that in these patients the donor livers belonged to adult males. (7) In another case, a 6 years 10 month old boy was admitted for recurrent abdominal pain and vomiting and was diagnosed to be having GS on rifampin test which was considered to be diagnostic back then. Rifampin being a cytochrome P-450 isoenzyme inducer competes for the excretory pathways in the liver and in patients of Gilbert syndrome, who have reduced levels of UGT, causes an exaggerated elevation in unconjugated total serum bilirubin levels. (8)

The differential diagnosis of GS include Crigler-Najjar type 1, Crigler-Najjar type 2, Dubin-Johnson Syndrome and Rotor Syndrome. Of these Dubin-Johnson Syndrome and Rotor Syndrome show conjugated hyperbilirubinemia and can be easily differentiated. (9) Crigler-Najjar type 1 is rare and presents in neonatal period as unconjugated hyperbilirubinemia which doesn't respond to phenobarbitone and requires phototherapy and liver transplant. (9) It was thus eliminated, as our patients gave no such history. In order to differentiate Crigler-Najjar type 2 from Gilbert syndrome which show similar features the definitive test would be UGT1A1 activity. (9) However, this test was not done in our patients due to cost issues. We ruled out Crigler-Najjar type II on the basis of the following three features: rarity of the disease with prevalence of 1 case per 1 million births (10), no mention of neonatal jaundice on birth history and clinical severity as the patients had no other complaints other than yellow skin which favoured the diagnosis as Gilbert syndrome.

Thus we conclude that Gilbert syndrome is a benign clinical condition with no consequence rather than yellow skin and does not merit any treatment. The patient must be reassured of its benign nature, as it has excellent prognosis and normal life expectancy. (11) Pediatricians must hence keep in mind the possibility of GS in children that present with unconjugated hyperbilirubinemia.

Funding : None

Conflict of Interest : None

References :

1. Fretzayas A, Moustaki M, Liapi O, Karpathios T. Gilbert syndrome. Eur J Pediatr. 2012;171:11–15
2. Kim YH, Yeon JE, Jung GM, Kim HJ, Kim JS, Byun KS, et al. A study of polymorphism in UDP-glucuronosyl transferase 1 (UGT-1A1) promoter gene in Korean patients with Gilbert's syndrome. Taehan Kan Hakhoe Chi. 2002;8:132–138.
3. Lee JH, Moon KR. Coexistence of gilbert syndrome and hereditary spherocytosis in a child presenting with extreme jaundice. Pediatr Gastroenterol Hepatol Nutr. 2014 Dec;17(4):266-9.
4. Muraca M, Fevery J. Influence of sex and sex steroids on bilirubin uridine diphosphate-glucuronosyltransferase activity of rat liver. Gastroenterol. 1984; 87:308–13.
5. Kulkarni RG, Lakshmidevi KB, Ronghe V, Dinesh US. Gilbert's syndrome in healthy blood donors what next? Asian J Transfus Sci. 2016 Jan-Jun;10(1):63-6.
6. Farheen S, Sengupta S, Santra A, Pal S, Dhali GK, Chakravorty M, et al. Gilbert's syndrome: High frequency of the (TA)7 TAA allele in India and its interaction with a novel CAT insertion in promoter of the gene for bilirubin UDP-glucuronosyltransferase 1 gene. World J Gastroenterol. 2006 Apr14;12(14):2269-75.
7. Vajro P, DeVincenzo A, Lucariello S, Migliaro F, Sokal E, Bernard O, Vilei T, Muraca M. Unusual early presentation of Gilbert syndrome in pediatric recipients of liver transplantation. J Pediatr Gastroenterol Nutr. 2000 Sep;31(3):238-43.
8. Keren G, Mazilis A. Gilbert syndrome presenting in a young boy, confirmed by the rifampin test. Isr Med Assoc J. 2007 Aug;9(8):626-7.
9. Maheshwari A, Carlo WA. Blood disorders. In: Kliegman RM, Stanton BF, St. Geme lll JW, Schor NF, Behrman RE, editors. Nelson textbook of pediatrics. 19th edn. Philadelphia, USA. Elsevier Saunders. 2011
10. Shakuntala PN, Poornima M, Padmalatha VV, Rao SR. Successful Pregnancy Outcome In Maternal Crigler Najjar Syndrome Type II. Online J Health Allied Scs. 2012;11(3):12
11. Mohan M, P LS, Reddy PV. Pregnancy with gilbert syndrome - a case report. J Clin Diagn Res. 2014 Jun;8(6):OD01-2.

From: Department of Paediatrics, Grant Government Medical College, Sir J.J. Group of Hospitals, Mumbai, India.

Address for Correspondence: Dr Ashwini Ronghe, 10, Shanti Dham, Pestom Sagar, Road no-1, Chembur, Mumbai-400089, India.

Email : ashuronghe@gmail.com

DOI : 10.7199/ped.oncall.2017.18