ORIGINAL RESEARCH PAPER
Volume - 10 | Issue - 05 | May - 2021 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

GILBERT SYNDROME-ASYMPTOMATIC UNCONJUGATED HYPERBILIRUBINEMIA: A CASE SERIES

General Surgery

Dr Maulik Sharma PG Resident, Department Of General Surgery, Mahatma Gandhi Medical College And Hospital, jaipur.

Dr Rajkamal Kanojiya Professor And Unit Head,department Of General Surgery, Mahatma Gandhi Medical College And Hospital, jaipur.

Dr Rajat Goyal* PG Resident, Department Of General Surgery, Mahatma Gandhi Medical College And Hospital, jaipur. *Corresponding Author

ABSTRACT

Gallstones are the commonest cause affecting the hepato-biliary system. Jaundice associated with gallstones are generally direct, commonly due to obstructive cause. Unconjugated hyperbilirubinemia with cholelithiasis is commonly present in hemolytic disease. In the absence of hemolytic cause or systemic causes, congenital cause of which is Gilbert' Syndrome. This study aims clinical approach to the patient of gallstones with Gilbert's syndrome. This is a study of 24 patients with gallstone associated with increased indirect bilirubin, who underwent surgery. Patients underwent blood investigations and ultrasound to confirm the diagnosis. Obstructive cause was ruled out . All patients underwent laparoscopic cholecystectomy as routine. 20 patients were having Gilbert's syndrome after ruling out other systemic causes. Gilbert's syndrome can be identified in individuals presenting with gallstone disease.

KEYWORDS

cholelithiasis, indirect, congenital hyperbilirubinemia, cholecystectomy, jaundice

INTRODUCTION

In 1900 Gilbert et al. published an account of a heterogeneous group of patients characterized by the intermittent presence of elevated levels of indirect (unconjugated) bilirubin in their blood. Later these authors classified such patients into three categories: 'cholemie physiologique', 'cholemie simple familiale', and 'icte're chronique simple'. Gilbert's syndrome refers to those patients falling into the second category, while patients in the last category should be regarded as cases of haemolytic anaemia(1,2)

The criteria to diagnose Gilbert's syndrome has been summarised by Powell et al(3)

I) Elevated levels of unconjugated bilirubin in plasma on three occasions.
2) No past history of viral hepatitis.
3) No abnormal physical findings apart from icterus.
4) All routine tests of liver function normal.
5) Haematological investigations, including haemoglobin, peripheral film, reticulocyte count, and erythrocyte fragility, show no evidence of haemolysis.

From time to time in this condition there is a mild elevation of the plasma unconjugated bilirubin concentration.

Powell et al.(3) reported the range of total plasma bilirubin to be o.I-6.2 mg/ I00 ml in patients, on which more pateints had maximum level of less than 4.0 mg/ 100 ml. Coexistence of gall stone disease with gilberts syndrome is often reported.

METHODS AND MATERIAL:-

24 patients admitted to the Mahatma Gandhi Medical College and Hospital for elective cholecystectomy for gallbladder stones during the 3 year period were included. Among 24 individuals of cholelithiasis with unconjugated hyperbilirubinemia on initial presentation, 4 patients were excluded as they had normal LFT on repeat investigations. After ruling out other causes of unconjugated hyperbilirubinemia, 20 individuals suspected of Gilbert's syndrome.

20 of these patients, 18 males & 2 females . Mean age of presentation was 30.58±4.7years and 32.5±5.2 years for males and females respectively. The 4 patients were further evaluated and kept on regular follow up in gastroenterology department.

All patients underwent laparoscopic cholecystectomy. Prior to surgery, patients were counselled regarding jaundice; chances of recurrent or persistent jaundice post- surgery, due to Gilbert's syndrome. Intra- operative findings of all patients were unremarkable; no events noted. 7 patients had thick walled gallbladder (wall thickness >4 mm), which appeared inflammatory. On final histopathology, gallbladder specimen in all patients were unremarkable.

The immediate post-operative course was unremarkable in most patients. 9 patients had recurrent jaundice on first post-operative day, which was unconjugated in nature. All patients discharged home by second post-operative day, and followed up after 10 days. On follow-up, none of the patients were symptomatic, and showed excellent post-operative recovery. They were all back to their daily activities without much hindrance.

CASE	AGE/ SEX	RETICULOCYTE COUNT	PRE-OP LFT				POST- OP LFT				NO.OF STONES	GALL BLADDER HISTOLOGY
			S.BIL (T/D/I)	SGOT	SGPT	ALK PO4	S.BIL (T/D/I)	SGOT	SGPT	ALK PO4		
Case 1	36/M	0.8	2.0/0.2/1.8	32.2	37.4	52.4	2.6/0.3/2.3	35.2	33.7	47.3	MULTIPLE	CHRONIC CHOLECYSTITIS WITH CHOLELITHIASIS
Case 2	42/M	0.7	2.1/0.1/2.0	16.1	26.2	42.3	2.8/0.1/2.7	19.1	45.1	56.4	SINGLE	CHOLELITHIASIS
Case 3	38/F	1.0	2.7/0.3/2.4	23.2	28.9	65.4	1.0/0.2/0.8	21.2	52.2	46.5	SINGLE	CHRONIC CHOLECYSTITIS WITH CHOLELITHIASIS
Case 4	40/M	0.6	0.8/0.4/0.4	40.5	58.9	78.5	0.4/0.1/0.3	32.5	21.9	50.3	MULTIPLE	CHOLELITHIASIS
Case 5	46/M	0.5	1.7/0.1/1.6	38.6	42.8	54.3	0.5/0.1/0.4	33.6	43.8	41.2	MULTIPLE	CHOLELITHIASIS
Case 6	33/F	1.2	3.3/0.3/3.0	12.9	20.9	40.2	0.4/0.2/0.2	15.9	25.9	65.1	SINGLE	CHOLELITHIASIS
Case 7	32/M	0.9	0.4/0.1/0.3	33.7	40.4	67.1	0.8/0.4/0.4	35.3	38.4	52.0	SINGLE	CHOLELITHIASIS
Case 8	39/M	0.7	3.4/0.2/3.2	37.2	49.0	54.0	1.2/0.3/0.9	34.2	59.0	41.5	SINGLE	CHRONIC CHOLECYSTITIS WITH CHOLELITHIASIS

Case 9	26/M	0.5	1.7/0.1/1.6	26.1	33.7	48.5	1.7/0.1/1.6	28.9	48.4	63.0	MULTIPLE	CHOLELITHIASIS
Case 10	32/F	0.7	1.6/0.2/1.4	32.6	45.1	76.0	3.3/0.3/3.0	34.7	39.3	67.4	SINGLE	CHOLELITHIASIS
Case 11	40/M	0.9	0.9/0.2/0.7	40.0	52.2	88.4	1.1/0.3/0.8	35.7	45.2	40.5	SINGLE	CHOLELITHIASIS
Case 12	44/M	1.0	2.8/0.3/2.5	38.7	21.9	40.5	.4/0.1/0.3	39.9	29.9	41.3	SINGLE	CHOLELITHIASIS
Case 13	58/M	1.5	2.5/0.3/2.2	45.3	60.0	67.1	0.8/0.4/0.4	40.7	49.0	43.0	MULTIPLE	CHRONIC CHOLECYSTITIS WITH CHOLELITHIASIS
Case 14	49/M	1.3	2.2/0.3/1.9	32.2	46.8	41.3	0.5/0.1/0.4	33.7	53.8	41.3	MULTIPLE	CHOLELITHIASIS
Case 15	25/M	0.7	2.2/0.2/2.0	31.6	58.0	43.0	2.0/0.2/1.8	37.2	49.0	53.0	MULTIPLE	CHRONIC CHOLECYSTITIS WITH CHOLELITHIASIS
Case 16	29/F	1.3	2.9/0.1/2.8	27.0	23.1	43.5	2.1/0.1/2.0	30.0	29.5	45.1	MULTIPLE	CHOLELITHIASIS
Case 17	46/M	0.6	2.8/0.2/2.6	36.1	43.8	53.0	2.7/0.3/2.4	26.1	46.8	56.7	SINGLE	CHOLELITHIASIS
Case 18	35/M	0.8	1.1/0.3/0.8	35.3	33.3	42.5	0.9/0.2/0.7	29.7	39.3	60.0	SINGLE	CHOLELITHIASIS
Case 19	39/M	1.4	3.2/0.2/3.0	37.2	49.8	59.4	0.9/0.2/0.7	32.6	34.8	40.6	MULTIPLE	CHRONIC CHOLECYSTITIS WITH CHOLELITHIASIS
Case 20	41/M	0.7	2.8/0.1/2.7	42.4	50.4	57.8	3.2/0.2/3.0	40.0	37.4	46.5	MULTIPLE	CHOLELITHIASIS
Case 21	52/M	0.9	2.6/0.3/2.3	16.8	32.2	41.3	3.3/0.2/3.1	20.8	38.2	70.0	MULTIPLE	CHOLELITHIASIS
Case 22	29/M	1.1	2.8/0.1/2.7	30.0	42.1	43.0	1.1/0.3/0.8	32.4	32.4	88.4	SINGLE	CHOLELITHIASIS
Case 23	37/M	1.0	3.2/0.2/3.0	18.8	20.0	38.2	0.5/0.1/0.4	28.9	30.9	43.5	MULTIPLE	CHRONIC CHOLECYSTITIS WITH CHOLELITHIASIS
Case 24	42/M	0.6	3.3/0.2/3.1	37.9	40.9	60.1	1.0/0.2/0.8	40.9	38.2	62.1	MULTIPLE	CHOLELITHIASIS

DISCUSSIONS

Gilbert syndrome is described as chronic, hereditary, nonhemolytic, mildly unconjugated hyperbilirubinemia associated with the impaired hepatic clearance of bilirubin but otherwise normal hepatic structure and function.. It is not an uncommon condition with a worldwide prevalence rate between 4% and 16% [4]; with about 7.4% prevalence in northern India [5]. In a recent report, the incidence of cholelithiasis in Gilbert Syndrome was 8.9%, with a slight male preponderance .

The genetic basis for pathogenesis of Gilbert Syndrome is based on mutation in the promoter region of UGT1A1 gene, resulting in increased bilirubin monoglucuronide excretion in bile [6,7-11]. Two polymorphisms in UGT1A1; namely G71 Rexon and A(TA)7TAA in the TATA box of promoter region are most common , and responsible for development of Gilbert Syndrome [7-9]. The length of repeats of TA in the promoter region is a modulator of enzyme activity; the higher the serum bilirubin levels , greater is the number of repeats, greater is the association with cholelithiasis [10,11]. Studies show increased risk for development of cholelithiasis in patients with Gilbert Syndrome . Persistently elevated bilirubin levels is risk factor for black pigment stone formation . The increased biliary output ,along with reduced enterohepatic circulation of bile salts is additional risk factor for cholelithiasis [12]. It is rare for Gilbert syndrome to be diagnose before puberty and the diagnosis is discovered most often following illness, fasting for surgery or after any stress and it usually occurs in the middle age .

Symptomatic gallstone disease is a common occurrence among adult obese women, especially in northern India . This is in accordance with literature, which supports Gilbert Syndrome as predominantly affecting middle aged males . When GSD is associated with hyperbilirubinemia, they are further evaluated with MRCP or EUS to rule out choledocholithiasis, malignancy or underlying liver disease. Unconjugated hyperbilirubinemia in an otherwise normal individual is itself a challenge in evaluation and management.

According to the Genetic Testing Registry data provided to the National Centre for Biotechnology Information (NCBI), the genetic testing of GS by PCR with the UGT1A1 gene has 99-100% sensitivity and 100% accuracy and precision. However, the limited availability and high cost of this investigation limits its use in routine cases. Moreover, the diagnosis of GS would be of academic interest and would not alter the management protocol in the patient who presented for symptomatic gallstone disease.

Hence, it is important to be aware of Gilbert Syndrome in patients presenting as gallstones with unconjugated hyperbilirubinemia. A prudent approach can avoid unnecessary and repeated investigations. Additionally, an informed consent should be obtained for persistent and fluctuating jaundice despite uneventful surgery owing to Gilbert Syndrome, as it can avoid future confusion. This will not only improve the quality of practice and patient care, but reduce health care costs by avoiding unnecessary and invasive investigations.

Gilberts' patients usually present with jaundice exacerbation following periods of stress or starvation. Hence, it is expected to witness some jaundice in the post-operative period after major abdominal operations under general anesthesia [13]. In our case series, 9 patients developed recurrent jaundice immediately post- surgery; which resolved spontaneously within a week. The pre-operative counselling helped allaying any fears in the mind of patients, with regards to unsuccessful surgery.

Also, we were unable to comment on any long-term follow-up; since once fully recovered, these patients hardly ever returned to the surgical team. Patient presenting with raised unconjugated fraction there was an overlap with biliary obstructive lesions. This may be explained by the effect of prolonged cholestasis on hepatocyte function. Gilbert's syndrome should be considered as a cause of recurrent and persistent unconjugated hyperbilirubinemia in the middle-aged male patient presenting with cholelithiasis.

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