

## A case of Inherited Unconjugated Hyperbilirubinemia foran incidental surgery: Anesthetic management and Review

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**Abstract:** Congenital indirect hyperbilirubinemia occurs due to the relative deficiency or absence of the primary conjugating enzyme uridine diphosphate-glucuronyltransferase. The enzyme UDP glucuronyltransferase is responsible for the conjugation of bilirubin in liver. The enzyme is also essential for transport of many other substrates including drugs, hormones, toxins and neurotransmitters. Thus, anaesthetic management of such a case is quite challenging. Avoiding drugs which use this enzyme for its metabolism or excretion during the perioperative period allows safe conduct of anaesthesia for these patients. We report a case of inherited unconjugated hyperbilirubinemia for an incidental surgery and review the different types of congenital indirect hyperbilirubinemias.

**Keywords:** Anaesthesia, bilirubin, inherited unconjugated hyperbilirubinemia, Crigler-Najjar syndrome, Gilbert syndrome

### I. Introduction

Inherited unconjugated hyperbilirubinemias are rare hereditary disorders of bilirubin conjugation usually diagnosed by exclusion, in the absence of overt hemolysis or liver disease. Bilirubin is conjugated into a more soluble form by the enzyme UDP-glucuronyltransferase [1]. Many anaesthetic drugs are metabolized in the liver via conjugation by the same enzyme. Hereditary deficits in this enzyme system can potentially affect the metabolism of these drugs leading to adverse outcomes. Despite this significance, reports on anaesthetic management of patients with inherited unconjugated hyperbilirubinemia syndrome are few.

### II. Case History

A 25 year old, 50 kg male patient, presented with abdominal pain and vomiting for one week. Patient had similar complaints ten months back for which he was evaluated and found to have a colonic mass. He had undergone limited resection anastomosis in some other hospital. Biopsy proved to be adenocarcinoma and patient underwent six cycles of chemotherapy. Post-operative period was uneventful. Patient had history of yellowish discoloration of eyes since childhood and yellowish discoloration of urine on and off. Patient was evaluated during childhood for jaundice but he did not follow up and so no other details were available regarding the work up.

The present investigations revealed normal complete blood count and renal function test. LFT showed total bilirubin 18.7 mg/dl, Direct bilirubin 1.8 mg/dl, Indirect bilirubin 16.9 mg/dl, AST 42 IU/L, ALT 60 IU/L, ALP 102 IU/L, GGT 7 IU/L, Total protein 7.1 g/dl, albumin 4.5 g/dl, globulin 2.6 g/dl, PT 16 sec, INR 1.9 and aPTT 26 sec. Viral markers were negative. USG Abdomen showed no significant abnormality. Colonoscopy showed post limited resection end to end anastomosis transverse colon status and otherwise normal study

Peripheral smear showed normocytic normochromic RBCs and a reticulocyte count of 1%. Hematologist opinion was obtained which suggested an inherited unconjugated hyperbilirubinemia and advised to rule out hemolysis and Wilson's disease correlating with a CECT abdomen. Medical gastro enterologist opined on an inherited unconjugated hyperbilirubinemia most probably Gilbert syndrome or Crigler – Najjar syndrome. Other differential diagnoses were immune hemolytic anemia and Wilson's disease. Serum ceruloplasmin, serum copper and LDH values were within normal limits.

Subacute intestinal obstruction due to adhesions was the provisional diagnosis. Laparoscopic adhesiolysis was planned.

Patient was assessed under ASA PS II and was accepted for anaesthesia with added risk. Four units of fresh frozen plasma were transfused and three doses of Inj. vitamin K given preoperatively. The repeated INR was 1.5. Preoperative vitals were within normal limits. Premedication was with Inj. Glycopyrrolate 0.2mg, Inj. Midazolam 1 mg and Inj. Fentanyl 100ug. The patient was preoxygenated with 100 % O<sub>2</sub> for 3 minutes and induced with Inj. Propofol 100mg and Atracurium 30mg. Airway was secured with a size 8 cuffed endotracheal tube. Patient was connected to circle system and maintained with N<sub>2</sub>O: O<sub>2</sub> – 2: 1 and Isoflurane – 0.2% – 1%. Intra operative period was uneventful. Post operatively after spontaneous respiratory attempts, patient was

reversed with inj. Neostigmine 2.5 mg and inj. Glycopyrrolate 0.5 mg. Patient was extubated after thorough suctioning.

Immediate post-operative period was uneventful. Post-operative liver function tests were similar to the pre-operative with no significant deterioration of liver function. Patient was observed for five days for untoward events and discharged with advice to follow up in surgery, medical gastroenterology and hematology department.

### III. Discussion

Three familial disorders have been recognized reflecting differing degrees of deficiency in the ability to conjugate bilirubin namely, Gilbert syndrome, Crigler-Najjar syndrome type I and Crigler-Najjar syndrome type II [1].

Augustine Gilbert and Pierre Lereboullet first described the **Gilbert syndrome** [2], the most common inherited cause of unconjugated hyperbilirubinemia, in 1901. This autosomal-recessive condition is characterized by intermittent jaundice due to under activity (10-30% of normal) of Uridine Diphosphate Glucuronyl Transferase [1]. At least 30% of the patients are asymptomatic, although nonspecific symptoms, such as abdominal cramps, fatigue and malaise, are common. Jaundice is mild (less than 4mg/dl) and the most commonly performed laboratory studies like peripheral blood smear and lactate dehydrogenase (to rule out hemolysis) and liver function tests (with the exception of unconjugated hyperbilirubinemia), are normal. Usually, the diagnosis of Gilbert's syndrome is that of exclusion. Diagnosis may be confirmed by giving phenobarbital which relieves the jaundice and IV nicotinic acid which aggravates it [3]. Any stress can aggravate the symptoms of Gilbert's syndrome e.g., fasting, surgery, infection, exercise, fatigue, alcohol intake and menstruation [4].

Congenital familial nonhemolytic jaundice with kernicterus was first reported by Crigler and Najjar in 1952 [5]. Later, Crigler-Najjar syndrome of two distinct types was described.

**Crigler-Najjar syndrome Type I** is the more severe disease form in which there is a complete absence of enzyme activity. The total serum bilirubin range is typically 20–45 mg/dL. Kernicterus is a distinct risk of type I disease and often occurs before the age of 20. Phototherapy is the mainstay treatment for patients with type I disease. Phototherapy reduces the levels of unconjugated bilirubin via photochemical reactions converting them into more polar photo isomers, which can be excreted directly without conjugation. Plasmapheresis and plasma exchange [6, 7] are used temporarily during acute exacerbations associated with trauma or other superimposed stresses. Liver transplantation is the only permanent therapy available and should be done before significant neurologic damage ensues.

**Crigler-Najjar syndrome Type II**, also known as Arias' syndrome [8], is autosomal recessive with variable penetrance characterized by a partial enzyme deficiency (10% of UDPGT activity) where jaundice typically becomes apparent by one year of age. The total serum bilirubin range is typically 6-25 mg/dL. The mainstay of treatment for these patients is oral administration of drugs known to induce the UDPGT enzyme, thereby increasing bilirubin conjugation and conversion to the water-soluble, easily excreted form. Drugs that induce glucuronyltransferase activity include phenobarbital, phenytoin, dexamethasone, hydrocortisone, para-aminosalicylic acid, omeprazole, clotrimazole, and rifampicin [9-11]. Of these, rifampicin and phenobarbital are used most commonly.

Different authors use different values for predicting significant jaundice because different techniques are used for bilirubin estimation in different laboratories. Hence, the local laboratory should define the cut off value for significant jaundice [12]. Anaesthesiologists should be aware of the conditions leading to decreased glucuronyltransferase activity and metabolic alterations in patients submitted to anaesthesia, to prevent intraoperative toxicity of anaesthetic drugs.

Perioperative goals in Gilbert's syndrome are to (a) minimize fasting and perform the surgery in the morning session, preferably as the first case (b) minimize stress by providing adequate analgesia during the intraoperative as well as during the postoperative periods (c) avoid hepatotoxic drugs and drugs that are exclusively metabolized by the liver (d) maintain hepatic blood flow by keeping the mean arterial pressure >60 mmHg and (e) avoid polypharmacy.

The anaesthetic goal in caring for patients with Crigler-Najjar disease is prevention of increased free bilirubin in the serum. Highly protein-bound drugs may displace bilirubin from albumin. The ability of drugs used in anaesthesia to displace bilirubin from albumin should necessitate a meticulous choice and administration of anaesthetic agents in appropriate dosage.

General anaesthesia was chosen in our patient primarily because laparoscopic adhesiolysis required a paralysed and anesthetised patient. To avoid prolonged fasting, we kept this patient first on the list. Five percent dextrose was started early on the morning of surgery to avoid dehydration and hypoglycemia induced stress.

Propofol was chosen, over thiopentone or ketamine, as it is metabolized by both liver and kidney providing a safety margin. Besides, thiopentone and ketamine alter liver functions in a dose-dependent fashion [13,14]. Displacement of bilirubin from albumin induced by the fatty acid components of propofol is known to occur, resulting in increased free bilirubin but is less compared to thiopentone and etomidate. Fentanyl was considered safe as its effect, after a single bolus dose, is terminated by redistribution to muscle and fat. Subsequent metabolism is primarily by N-dealkylation to norfentanyl and its hydroxylation along with norfentanyl [15]. Remifentanyl is a safer alternative due to its ultra-short duration of action and its metabolism by blood and tissue esterase. Atracurium was preferred due to its Hofmann degradation, ester hydrolysis and minimal effect on plasma bilirubin levels. Cisatracurium could have been the other safer alternative due to its similar metabolic pathway independent of liver [16].

Among inhalational agents, halothane should be avoided during anaesthesia because of its high liver metabolism (20%) and its potential to cause postoperative jaundice. Sevoflurane undergoes 2% and Isoflurane has 0.2% liver metabolism. All volatile agents decrease total liver blood flow, and hepatic arterial buffer response. This decrease is maximum with halothane and minimum with Isoflurane. Inhaled anaesthetics do not have a direct effect on the protein binding of bilirubin, although mild postoperative increases in serum bilirubin have been reported in surgical patients receiving sevoflurane and isoflurane [17], but without evidence of hepatotoxicity. For the above-mentioned reasons, Isoflurane was the preferred volatile anaesthetic [17]. Diclofenac sodium and pentazocine were used for postoperative analgesia. Paracetamol and morphine were specifically avoided as they are metabolized by conjugation in the liver utilizing the enzyme deficient in these cases [18], besides being high protein bound there by increasing the free fraction of bilirubin. During laparoscopic procedures, the increased intra-abdominal pressure caused by pneumo-peritoneum may decrease the hepatic blood flow which has to be considered.

Studies have shown that controlled ventilation, inhalational anaesthetics and surgical stress can decrease liver blood flow. Regional anaesthesia probably preserves liver blood flow as long as normotension is maintained. Epidural anaesthesia might be superior to general anaesthesia as the stress associated with general anaesthesia can lead to release of catecholamines, which can decrease liver blood flow. The rare but potential hepatotoxicity associated with the inhalational anaesthetics also makes regional anaesthesia more attractive. Amide local anaesthetics, which are the most commonly used, are metabolized primarily by microsomal P-450 enzymes in the liver (N-dealkylation and hydroxylation). The rate of liver metabolism among amides varies as follows: Prilocaine > Lignocaine > Mepivacaine > Ropivacaine > Bupivacaine. Local anaesthetics bind to two major proteins, alpha-1-acid glycoprotein and albumin. Although local anaesthetics can bind albumin and can displace other molecules, the affinity of local anaesthetics for albumin is 5–10,000 times lower than the affinity for alpha-1-acid glycoprotein. Lignocaine is 55%–65% protein bound in adults, whereas mepivacaine, ropivacaine, and bupivacaine are 75%–80%, 94%, and 85%–95% protein bound, respectively. Hence, Bupivacaine is the preferred agent for epidural anaesthesia.

#### IV. Conclusion

Although, inherited unconjugated hyperbilirubinemias are rare benign conditions with an indolent course, they pose a clinical challenge for anaesthesiologists. The under activity of bilirubin-UGT can lead to toxicity of most anaesthetic agents, and this fact is of utmost importance to the anaesthesiologists while choosing the type of anaesthesia. It is prudent to use regional anaesthesia whenever possible and, if general anaesthesia is required, it is better to use short-acting agents or those with extra hepatic metabolism.

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