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JAUNDICE: A BASIC REVIEW

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ABSTRACT

Jaundice is a complex disease. Jaundice is actually the high bilirubin level in the body. Yellowing of skin, mucous membranes and skin are common presentations of jaundice. Jaundice has various variants including pre-hepatic jaundice (due to hemolysis of red blood cells), hepatic jaundice (due to defect in capture, conjugation and excretion of bilirubin by liver) and post hepatic jaundice (due to the obstruction of extra hepatobiliary system).

The causes of various variants of Jaundice are either acquired or congenital. High plasma bilirubin level can cause various manifestations involving satiety, gastrointestinal bleeding, diarrhea, anemia, edema, weight-loss and can be fatal because it can cause psychosis, lethargy, seizures, coma or even death. High bilirubin level can help in the diagnosisof Jaundice. Differential diagnosis of various variants of Jaundice can be carried out on the basis of bilirubin level (conjugated and unconjugated), ultrasonography and other radiological techniques. The proper management of Jaundice is high water intake and low fat diet. The primary effective treatment for pre-hepatic jaundice and neonatal physiological jaundice is phototherapy. Infusion of immunoglobulins is also used for treatment of pre-hepatic jaundice. Proper nutrition, steroids and immunosuppressant are used for treatment of hepatic jaundice. The treatment for post hepatic jaundice is decompression and surgery.

1. INTRODUCTION

Jaundice is defined as a yellowing of skin, mucous membranes and sclera due to the deposition of yellow- orange bile pigment i.e. bilirubin.[1] The bilirubin is an endogenously synthesized pigment that can be toxic specially in newborn children.[2] The bilirubin in unconjugated form has a typical spectrographical peak at 450 nm.[3] The word Jaundice is actually a derivative of French word 'Jaune' which means 'yellow'.[1] Jaundice indicates the hyper bilirubinemia and that excessive level of bilirubin may be in conjugated or unconjugated form. The clinical presentations of jaundice appear when bilirubin level exceeds 34.2 µmol/L or 2 mg/dL.[4]

The substrate for the production of bilirubin is heme group. The heme is catabolized at alpha carbon bridge by an enzyme heme oxygenase and results in the liberation of iron, carbon monoxide and biliverdin. The biliverdin is further acted upon by biliverdin reductase to form bilirubin.[5] 80 % of bilirubin is derived from the heme group of haemoglobin. This haemoglobin comes from thedestruction of red blood cells in the reticuloendothelium of liver, spleen and bone marrow. The remaining 20% of bilirubin comes from multiple sources like myoglobin, cytochromes etc.[6,7] 3.8 mg/kg or approximately 250-300 mg bilirubin is produced daily in normal adults. The amount of bilirubin production in neonates is much higher than adults.[8]

The bilirubin produced is then transported to the liver in the bound form with plasma albumin. The dissociation constant for first albumin binding site is Kd=7 X 107M-

1.[9] Conjugation of bilirubin takes place in the liver by UDP-glucronyltransferase and this conjugation is essential for water solubility and elimination.[6,7] The activity of UDP-glucronyltransferase is influenced by age, gender, thyroid hormones and microsomal enzyme inducing agents, such as phenobarbital, rifampicin etc.[10-14] Conjugated bilirubin is excreted into the bile. The bile is then passed to the duodenum via biliary system. Inside the intestine some bilirubin is metabolized by the intestinal flora into urobilinogens and then reabsorbed. These urinobilinogensare then removed by the kidney and excreted via urinary system.[6,7] The production and metabolism of bilirubin is shown in ***Figure I***.[15]

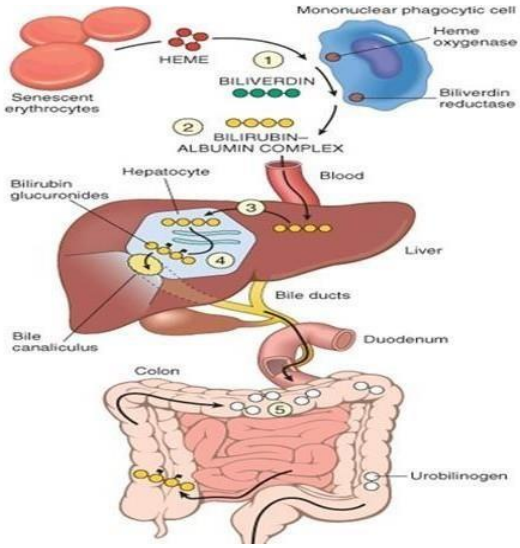

Figure I: Production and metabolism of bilirubin.

Types:

On the basis of causes Jaundice can be classified into three types.4

- Pre-hepatic Jaundice
- Hepatic Jaundice
- Post hepatic Jaundice
- Pre-hepatic Jaundice

Pre hepatic jaundice is such type of jaundice which is caused due to hemolysis therefore it is also known as hemolytic jaundice. The major cause of enhanced hemolysis is defective plasma membrane of red blood cells. This vulnerable cell membrane cannot bear theshear stress and hence ruptures resulting in hemolysis thus causing the increased serum bilirubin level.[16,17] Overview of pre-hepatic jaundice is given in Figure 1(b).[18]

Etiology:

The pre hepatic jaundice is mainly caused due to hemolysis. The causes of pre-hepatic/hemolytic jaundice are classified into two groups:

Congenital Causes:

Congenital causes of hepatic jaundice involve following:[19,20]

- Spherocytosis
- Elliptocytosis
- Congenital LCAT deficiency
- Thalassemia
- Sickle cell anemia
- Stomatocytosis
- Acanthocytosis
- Echinocytes
- GSH synthase deficiency
- Pyruvate kinase deficiency
- G6PD deficiency
- Erythroblastosis fetalis

Acquired causes:

Acquired causes of pre-hepatic jaundice involvefollowing:[19,20]

- Resorption of extensive hematomas
- Auto immune hemolysis
- Transfusion reactions
- Trauma
- Microangiopathy
- Hemolytic uremic syndrome
- Long distance runners
- Disseminated intravascular clot
- Infections e.g. malaria, etc.
- Toxins e.g. snake venoms, etc.
- Chemicals e.g. nitrites, aniline dyes,etc.
- Paroxysmal nightly hemoglobinuria
- Thrombotic thrombocytopenic purpura
- Hypophosphatemia
- Vitamin B12 deficiency
- Folic acid deficiency

Clinical presentations:

Patients with hemolytic jaundice are presented with Anemia, Yellowing of sclera, dark yellow-brown colored urine, yellowish skin and high bilirubin levels.[21]

Hepatic jaundice:

Hepatic jaundice is a type of jaundice in which the basic defect lies within the liver mainly in the hepatocytes.

The liver captures bilirubin from plasma proteins mainly albumin, then after conjugation excretes in the bile via biliary system. Any pathology of the liver leading to defect in capture, conjugation and excretion can cause hepatic jaundice. Main enzyme of conjugation is UDP- Glucronyltransferase. This is commonly immature at birth and its under-activity can cause so called Neonatal Physiological Jaundice. Further this enzyme can be defective due to the genetic mutation of the UTG1A gene on chromosome 2. This gene encodes for UDP- Glucronyltransferase and thus the defective conjugating enzyme leads to the hepatic jaundice.[22-24] Any defect in the hepatic excretory mechanism of bilirubin can also cause hepatic jaundice. The excretory mechanisms involve hepatocytic bile acid-independent secretion, hepatocytic bile acid-dependent secretion and bile ductular secretion. Any defect in the above mentioned excretory mechanisms can lead to the accumulation of bilirubin in blood causing hepatic jaundice.[25-34] Overview of hepatic jaundice is given in Figure 1b.[18]

Etiology:

Hepatic jaundice is caused due to the defect in capture, conjugation and excretion of bilirubin by liver.[35-38] Hepatic causes of the jaundice can be classified in to two types:

Congenital causes:

Congenital causes of hepatic jaundice are following:[38,39]

- Wilson's Disease
- Rotor's Syndrome
- Haemochromatosis
- CriglerNajar syndrome
- Gilbert's syndrome
- Dubin-Johnson's syndrome

Acquired causes:

Acquired causes of hepatic jaundice are following:[38,39]

- Viral Hepatitis
- Alcoholic Hepatitis
- Auto immune Hepatitis
- Drug related Hepatitis (e.g. NSAIDs)
- Sepsis
- Pregnancy
- Systemic Diseases (e.g. celiac disease)
- Malnutrition
- Physical Trauma
- Hepatic Adenoma

Clinical presentations:

The clinical presentations of hepatic jaundice include abdominal pain, fever, vomiting and nausea along with the complications involving satiety, gastrointestinal bleeding, diarrhea, anemia, edema, weight-loss and associated weakness, if unchecked leading to mental disturbances like kernicterus, coma or even death.[40]

Post hepatic jaundice:

Post hepatic jaundice is such type of a jaundice in which the cause lies in the biliary portion of hepatobiliary system. The major cause of post hepatic jaundice is extra-hepatic biliary obstruction. Therefore it is also known as obstructive jaundice.[41] Overview of post hepatic jaundice is given in Figure 1b.[18]

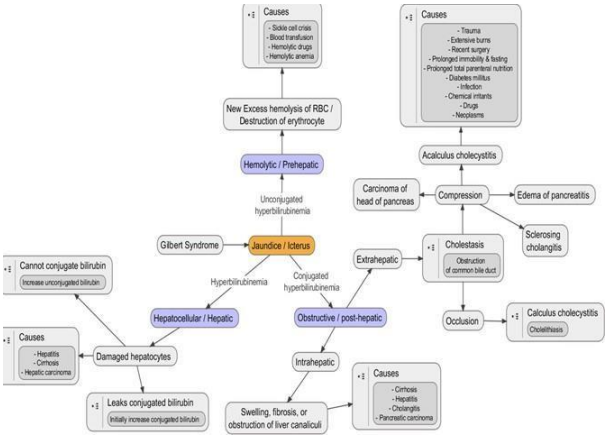

Figure II: Overview of types and causes of jaundice. Etiology

The major cause of post hepatic jaundice is extra-hepatic biliary obstruction.[41] The causes of obstruction may be classified into two types:

Congenital causes:

The congenital obstruction involves following:[41,42]

- Biliary Atresia
- Cystic Fibrosis
- Idiopathic dilation of common bile duct
- Pancreatic biliary malfunction
- Choledochal Cyst

Acquired Causes:

The acquired obstruction involves following:[42-49]

- Portal biliopathy

- Cholecystitis
- Trauma
- Pancreatitis
- Strictures
- Choledocholithiasis
- AIDS
- Intra-Abdominal Tuberculosis
- Tumors
- Common bile duct Obstruction

The classification of obstruction on the basis ofanatomical location is give in Table 2a.[45]

Clinical presentation:

The clinical manifestations of obstructive jaundice aredark urine, pale stools and generalized pruritus. History of fever biliary colic, weight loss, abdominal pain and abdominal mass are also the representatives of obstructive jaundice.[42] Obstructive Jaundice may lead to various complications including cholangitis, pancreatitis, renal and hepatic failure.

Table III: Classification of obstruction on the basis ofanatomical location.

CLASSIFICATION OF OBSTRUCTIONON THE BASIS OFANATOMICAL LOCATION		
Top third obstruction	**Middle third obstruction**	**Bottom third obstruction**
Polycystic Liver Disease	Mirizzi Syndrome	Pancreatic Tumors
Oriental Choangiohepatit	Cystic Fibrosis Intrabiliary	Ampullary Tumors
Sclerosing Cholangitis	Parasites Choledochal	Duodenal Diverticula
Iatrogenic injuryto the Bile Duct	Cysts	Penetrating Duodenal Ulcer

DIFFERENTIAL DIAGNOSIS:

The pre-hepatic jaundice can be differentiated from hepatic and post hepatic jaundice exclusively on the basis of elevated serum levels of unconjugated bilirubin and urobilinogen, which are raised in case of pre-hepatic jaundice. The serum levels on conjugated bilirubin, alkaline phosphatase, Alanine transferase and Aspartate transferase are seen normal in the case of pre-hepaticjaundice. The urinary excretion of conjugated bilirubin is also not present in pre-hepatic jaundice.[50]

The hepatic jaundice can be differentiated from post hepatic and pre hepatic jaundice on the basis of five timeshigh bilirubin levels. In hepatic jaundice due to hepatitis the bilirubin levels may be ten times higher than their maximum values.[38,51] Hepatic jaundice can be differentially diagnosed from post hepatic jaundice on thebasis of abdominal ultrasonography and other radiological technique.[38] However the hepatic jaundice can be differentiated from pre-hepatic jaundice on the basis of diagnostic markers, like alpha-1 Antitrypsin, Ceruloplasmin,Immunoglobulins,etc.[35,38,39,51] Elevated serum bilirubin level along with the conjugation is a key diagnosis of post hepatic jaundice. Serum bilirubin is usually less than 20 mg/dL. In pancreatic cancer the serum bilirubin may rise up to 40 mg/dL. Serum gamaglutamyltranspeptidase (Serum GGT), alkalinephosphatase and transaminases may be elevated.

Tumour markers like CA-125, CA19-9 and CEA are usually elevated in cancerous obstruction.[42] The diagnosisof obstructive jaundice can further be confirmed by ultrasonography, plain abdominal x-ray, computedtomography, contrast-enhanced multi sliced computed tomography, endoscopic retrograde cholangiopancreatography (ERCP), Percutaneous trans- hepatic cholangiography (PTC), Endoscopic Ultrasound, Magnetic Resonance cholangiopancreatography (MRCP), Cholescintigraphy, Radionuclide scanning angiography and Staging Laparoscopy.[4,43,44]

THERAPEUTIC APPROACHES AND MANAGEMENTS:

Pre-hepatic jaundice:

Infusion of immunoglobulins is used as primary treatment for pre-hepatic jaundice.[52] Phototherapy is considered as an effective treatment of high levels ofbilirubin in pre-hepatic jaundice.[53,54] Bilirubin rapidly decreases within two hours of onset of phototherapy.[55] However the duration of therapy and the strength of light treatment depend upon the severity of hyperbilirubinemia.[54-56] Metaloporphyrins are alsoconsidered as a treatment possibility of pre-hepatic jaundice, because these metaloporphyrins target thehemeoxygenase enzyme to limit the production of bilirubin.[57]

Hepatic jaundice:

Treatment and Management of hepatic jaundiceinvolves[58]

Phenobarbital can be used for treatment of neonatal physiological jaundice however it is not frequently used due to certain drawbacks involving somnolence and febrile seizures.

- Supportive therapy - fluids, rest, pain relief - for Hepatitis A.
- Abstinence from alcohol and cessation of medications contributing to liver dysfunction.
- Steroids - for autoimmune hepatitis.
- Immunosuppressant - for autoimmune hepatitis.
- Interferon - for chronic hepatitis B and C.
- Liver transplantation for fulminant hepatitis and end stage liver failure.

Post hepatic jaundice:

Low fat diet should be given to patient suffering from post-hepatic jaundice to minimize the discomfort due to fat ingestion and diarrhea.[35,59] The treatment of the post hepatic obstructive jaundice is mechanical decompression however the complications and other symptoms are also necessarily treated. Decompression can be done by surgical bypass, percutaneous insertion of stents, removal of lesions and endoscopic insertion of stents.[45] Dexchlorophenramine, Hydroxyzine, Cholestyramine, Ursodeoxycholic acid and Naltrexone are used as a therapeutic approach in treatment and management of post hepatic jaundice.[35,59]

2. CONCLUSION

Jaundice is very common disease. Yellowing of skin, sclera and mucous membranes are common manifestations of jaundice due to defect in production, metabolism and excretion of bilirubin. The causes of jaundice are either congenital or acquired. Serum bilirubin level and ultrasonography are used for differential diagnosis. High water intake and low fat diet are best proper managements of jaundice. The treatment of jaundice varies with the type of jaundice.

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