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Review paper on pathology of Jaundice

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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 haemolysis of red blood cells).[1]Jaundice is a common clinical finding in clinical practice of hepatologists and general practitioners. Clinical presentation of jaundice manifests through yellow skin and sclera coloration. Evaluation of every patient includes detailed medical history and examination. [2]
Jaundice is a common symptom of inherited or acquired liver diseases or a manifestation of diseases involving red blood cell metabolism. Recent progress has elucidated the molecular mechanisms of bile metabolism, hepatocellular transport, bile ductular development, intestinal bile salt reabsorption, and the regulation of bile acids homeostasis.[3]
Key word:-Jaundice, pathophysiology of jaundice, bilirubin metabolism.

I. INTRODUCTION:-

Jaundice (from the French jaune meaning yellow), refers to the yellowish discolouration of the skin, sclera and mucousmembranes that accompanies deposition of bilirubin in tissues. It develops when serum bilirubin levels are elevated above 34 mmol/L (2 mg/dL), with yellow discolouration of the sclera being the site where jaundice is detected earliest due to high elastin content of sclera and its strong binding affinity for bilirubin.[4]
Patency of the biliary tree and free drainage of bile into the intestine are important for normal hepatic function. Substances normally excreted into the bile will accumulate in the vascular system owing to obstruction of the biliary tree and the inability to excrete bile into the intestine. These substances, including bile salts, have systemic toxic effects.[1] Patients with obstructive jaundice are inclined to develop nutritional deficits, infectious complications, acute renal failure, and impairment of cardiovascular function.[5]

Jaundice is yellowish skin, White's of eyes, and body fluid. It is caused by increase amount of bilirubin in blood. Bilirubin is yellowish pigment that is produced from the breakdown of heme, primarily from haemoglobin, red blood cells (RBC)[6]. Jaundice is when clinically there is an increase in the amount of bilirubin in the serum rising above 85mmol/l (5mg/dl). When in utero, unconjugated bilirubin is cleared in the placenta to produce cord serum bilirubin of approximately 35mmol/L (2mg/dl). After birth, jaundice is a reflection of the bilirubin present in the liver, the rate of hepatic excretion and the ability to bind to serum proteins to retain the bilirubin present in the plasma. Many variations in individual responses to bilirubin load prevent specific levels of psychological jaundice. [7]

New born jaundice occurs in up to 85% of all live births.In the absence of haemolysis, sepsis, birth trauma or prematurity, it usually resolves within 3–5 days without significant complications However, epidemiological evidence suggests that severe neonatal jaundice (SNJ) results in substantial morbidity and mortality.SNJ has been recognised as a significant cause of long-term neurocognitive and other sequelae, cerebral palsy, non-syndromic auditory neuropathy, deafness and learning difficulties. The burden is unacc income countries (LMICs) and has prompted calls for intense scrutiny and attention. Under the millennium development goals, the potential impact of adverse perinatal conditions such as preterm birth complications and birth asphyxia on thriving and well-being beyond survival rarely received attention.[8]

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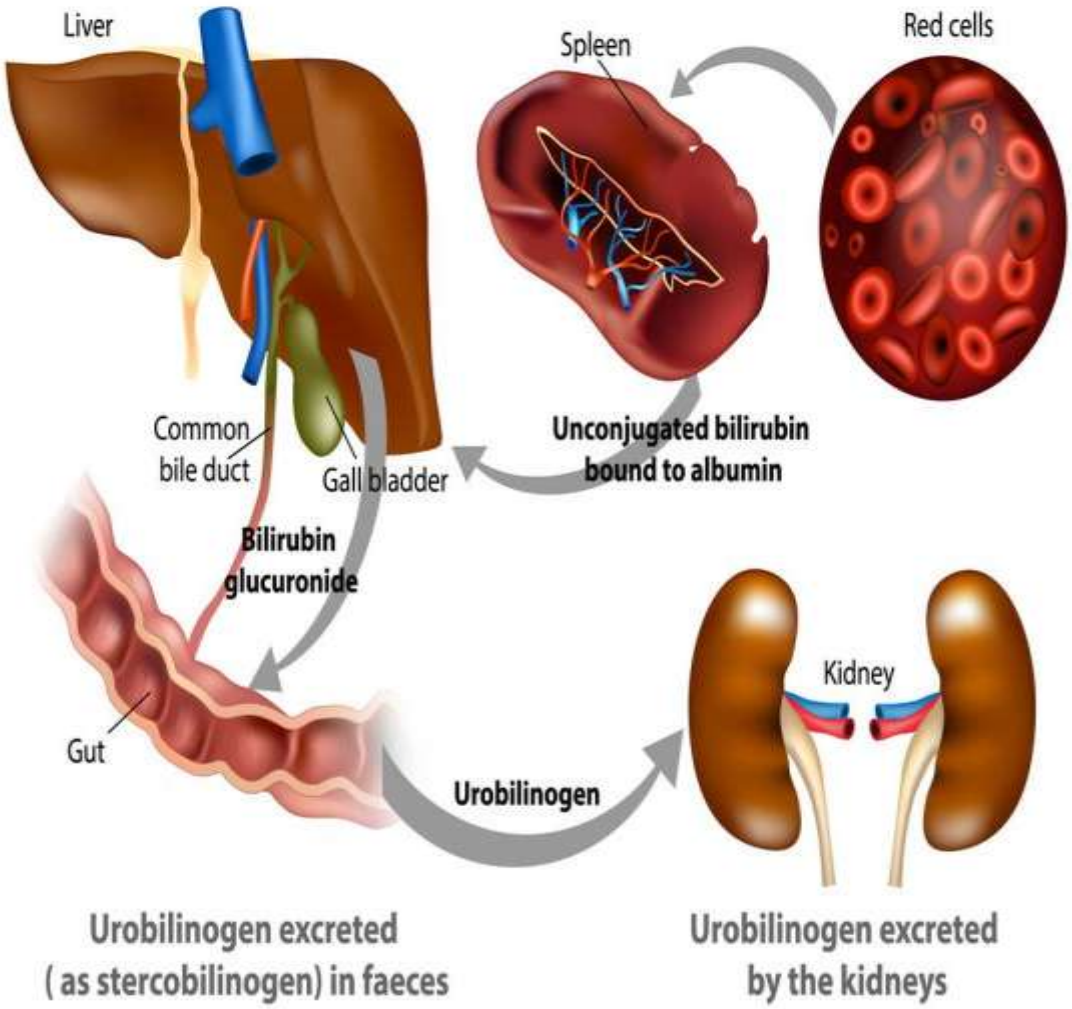

Fig- production and metabolism of bilirubin.

PHYSIOLOGY OF ITCH

Itch begins with stimulation of skin receptors and nerve endings by pruritogens. This results in activation of polymodal and mechanically insensitive C-fibres. These synapse with secondary neurons in the distal horn which then travel in the contralateral spinothalamic tract and synapse with third order neurones in the thalamus. From the thalamus neurons project to a number of cortical and subcortical areas.

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Thalamic nuclei activated in itch	
Histamine	Cowhage
Ventral posterior lateral	Ventral posterior lateral
Ventral posterior inferior	Posterior
Posterior	Supragenículate
	Medical geniculate
	Pulvinar

Cortical and subcortical structures activated in itch	
Histamine	Cowhage
Primary and secondary somatosensory cortex	Primary and secondary somatosensory cortex
Posterior parietal cortex	Posterior parietal cortex
Superior middle temporal cortex	Superior middle temporal cortex
Posterior cingulate cortex	Posterior cingulate cortex
Anterior cingulate cortex	Anterior cingulate cortex
Precuneus	Precuneus
Cuneus	Cuneus
	Insulator cortex
	Claustrum
	Basal ganglia
	Putamen

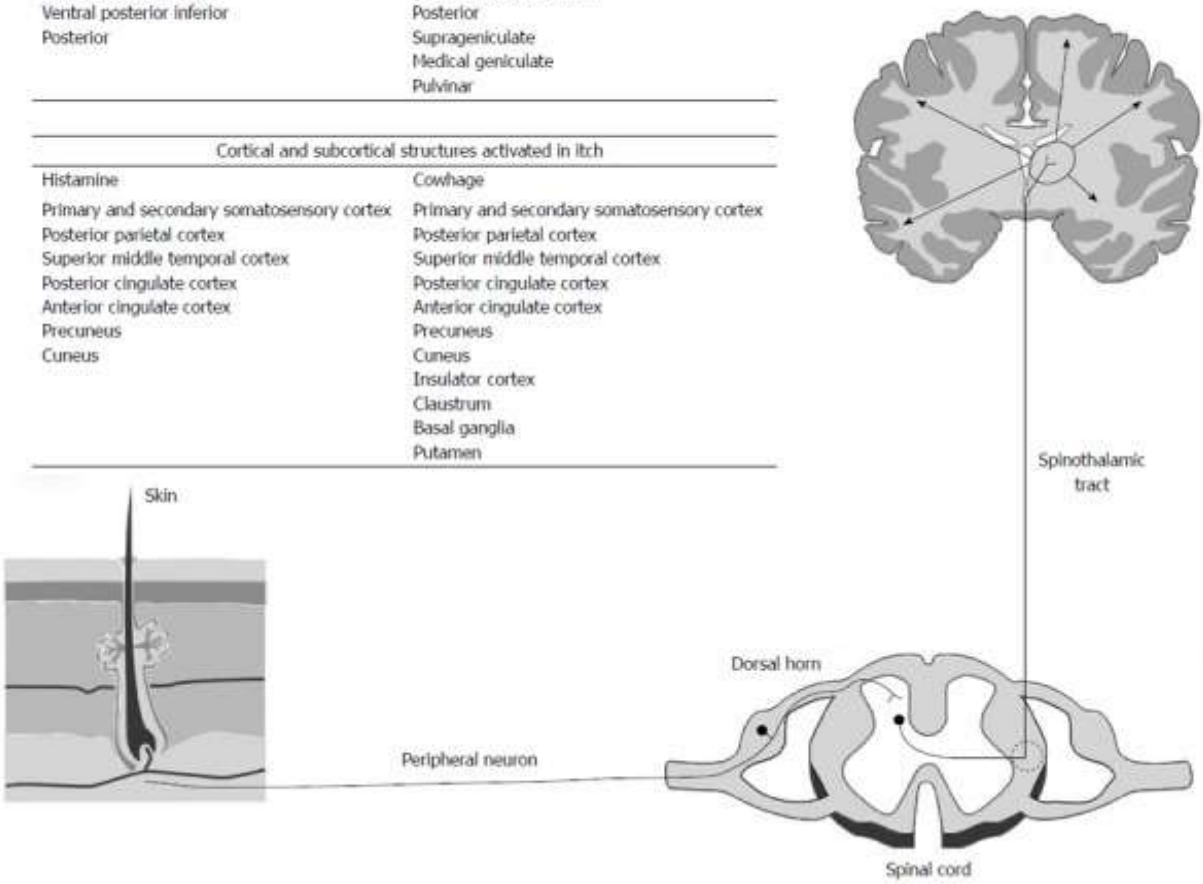

Figure 1 Summary of the peripheral and central neuroanatomy of the itch pathway (adapted from Dhand and Aminoff.

PATHOPHYSIOLOGY OF ITCH IN JAUNDICE

Several mechanisms have been proposed to explain the itch that accompanies jaundice. Early theories concentrated on defining a pruritogen released by the liver whose accumulation in skin accounts leads to itch while later theories have concentrated on defining neural circuits involved in the mediation of itch.

Bile salts

Aretaeus, who first recognized the association of jaundice and itch, maintained that itchy skin was due to the presence of "prickly bilious particles" within the skin.This theory remains popular since biliary drainage is usually associated with improvement in itch. However, there is often an immediate effect before a fall in plasma bilirubin.

Histamine

Histamine is the principle mediator of allergic reactions and is released by mast cells and circulating basophils. Bile salts, particularly chenodeoxycholate and deoxycholate, stimulate the release of histamine from mast cells and plasma histamine concentrations are increased in pruritic patients .However, pharmacological doses of bile salts are required to stimulate histamine release from mast cellsand histamine antagonists have not been successful in treating pruritic patients.

Serotonin

Intradermal injection of serotonin causes itch in healthy volunteers and treatment of pruritic

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patients with selective serotonin reuptake inhibitors sertraline and paroxetine has been useful in treating pruritis. However, using the 5-HT_3-receptor antagonist ondansetron has not been consistently effective in improving itch.

Steroids

Steroid hormones may be mediators of pruritis based on the observation that female cholestatic patients often report more intense and prolonged pruritis in comparison with male patients and the itch present in intrahepatic cholestasis of pregnancy typically is most intense in the third trimester when the highest concentrations of steroids and their metabolites are observed. The itch rapidly subsides after delivery and parallels the fall in urinary steroid levels.

Opioids

Endogenous opioids are involved in the mediation of pruritis. Epidurally administered opiates are associated with itching and increased levels of circulating endogenous opioids are seen in animal models of cholestasis and in jaundiced patients .Increased expression of preproenkephalin and met-enkephalin are seen in cholestatic livers suggesting that endogenous production is increased.

Lysophosphatidic acid

Elevated levels of lysophosphatidic acid (LPA) have been found in the plasma of pruritic patients, and intradermal injection is associated with itching. LPA is formed from lysophosphatidylcholine by the enzyme autotaxin and is a signalling molecule that acts on a number of specific G-protein coupled receptors present on neuronal cell membranes.[9]

Bilirubin Metabolism and Pathophysiology of Jaundice

Degradation of heme is responsible for bilirubin formation. The majority of hem derives from haemoglobin of erythrocytes, whereas small parts originate from ineffective erythropoiesis and degradation of other hem-containing proteins such as myoglobin, catalases, and cytochrome P450 isoenzymes .Bilirubin formation is a 2-phase process, where in the first phase, heme transforms to biliverdin, and in the second phase through reductase, biliverdin is transformed to unconjugated bilirubin . Unconjugated bilirubin is water insoluble and as such is transported with albumin to the liver, where conjugation occurs. The process of conjugation in the liver is intermediated by uridine diphosphate (UDP)-glucuronyltransferases. Conjugated bilirubin from liver cells is transferred to the biliary system and through bile it enters the intestines. [10]

Treatment / Management

Treatment of choice for jaundice is the correction of the underlying hepatobiliary or haematological disease, when possible.

Pruritis associated with cholestasis can be managed based on the severity. For mild pruritis, warm baths or oatmeal baths can be relieving. Antihistamines can also help with pruritis. Patients with moderate to severe pruritis respond to bile acid sequestrates such as cholestyramine or colestipol. Other less effective therapies include rifampin, naltrexone, sertraline, or phenobarbital. If medical treatments fail, liver transplantation may be the only effective therapy for pruritis.[11]

What are the different types of jaundice:-

Pre-hepatic jaundice: Health conditions that affect the blood's rate of breaking down blood cells cause bilirubin to overflow into bodily tissues. It occurs before the blood reaches the liver.

- **Hepatic jaundice:** Hepatic jaundice happens when your liver tissue becomes less effective at filtering out bilirubin from your blood.
- **Post-hepatic jaundice:** This type of jaundice happens when bilirubin filtered from the blood can't drain properly into the bile ducts or digestive tract to be passed out of the body. It occurs after bilirubin is filtered out in the liver and occurs because of a blockage.[12]

Conditions that can cause jaundice include:-

- Infections of the liver from a virus (hepatitis A, hepatitis B, hepatitis C, hepatitis D, and hepatitis E) or a parasite
- Use of certain drugs (such as an overdose of acetaminophen) or reactions to other medicines or or exposure to poisons (for example, poisonous mushrooms)
- Birth defects or disorders present since birth that makes it hard for the body to breakdown bilirubin (such as Gilbert syndrome, Dubin-Johnson syndrome, Rotor syndrome, or Crigler-Najjar syndrome)
- Chronic liver disease
- Gallstones or gallbladder disorders causing blockage of the bile duct
- Blood disorders
- Cancer of the pancreas

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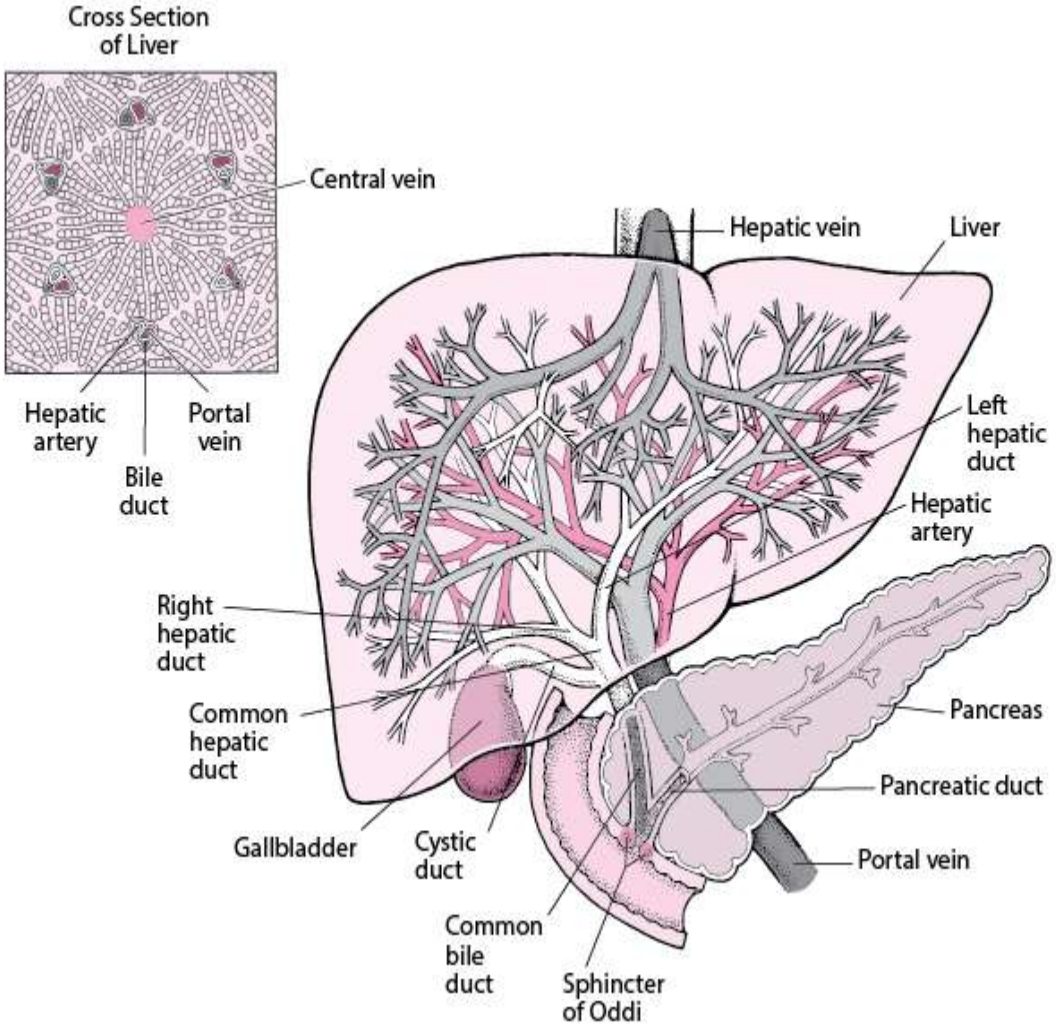
- Bile build-up in the gallbladder because of pressure in the belly area during pregnancy (jaundice of pregnancy).[13]

1. in Adults

By **Danielle Tholey** , MD, Sidney Kimmel Medical College at View of the Liver and



The **most common causes** of jaundice are

- Hepatitis
- Alcohol-related liver disease
- A blockage of a bile duct by a gallstone (usually) or tumor
- A toxic reaction to a drug or medicinal herb.

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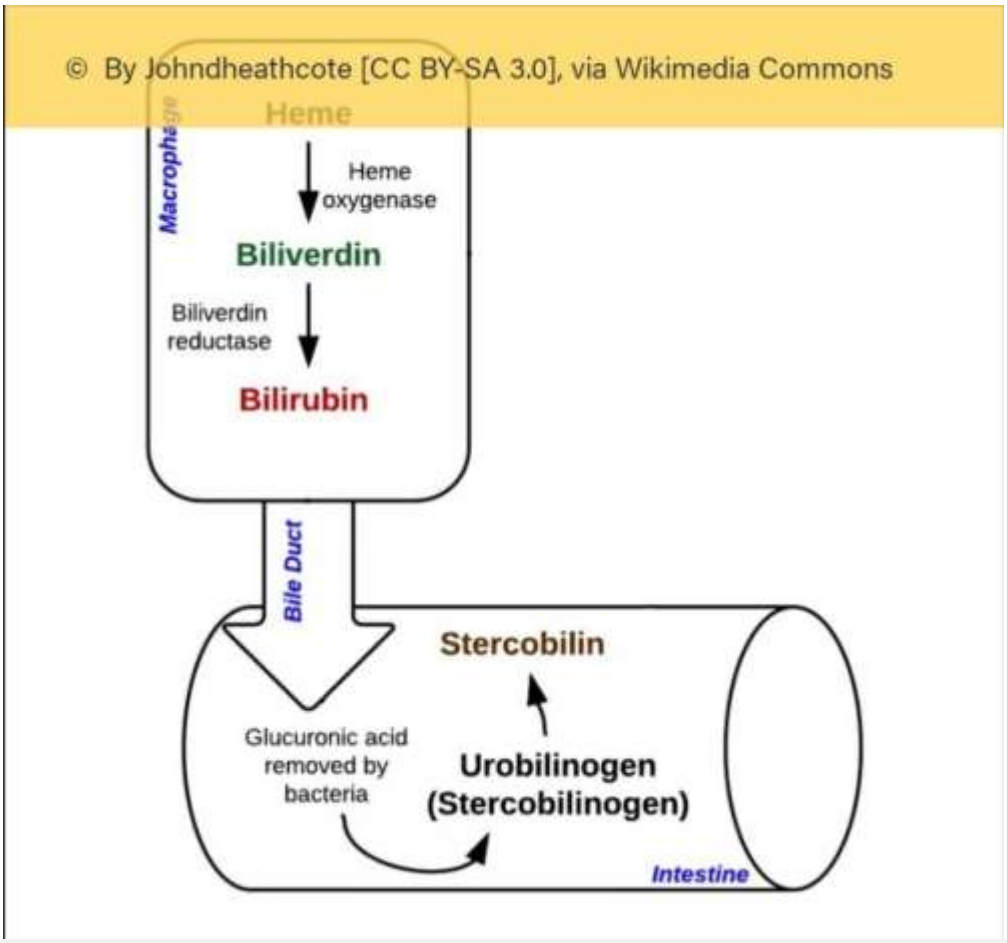
Physical Examination:-



Physical examination of the patient with jaundice reveals yellow coloration of the skin and sclera and other tissues. If the patient is conscious, well oriented, and without any neurological disturbances, it may be assumed that cause of jaundice is probably not hepatocellular injury, and additional investigationmay be oriented to obstruction. Further examination of the skin may show hematomas, which could solely be the underlying cause of jaundice or point to defects in the coagulation cascade. If the cause of the jaundice is chronic liver disorder, physical examination may be useful in detecting spider naevi, palmar erythema, Dupuytren contractures, hepatomegaly, splenomegaly, or ascites. Spider naevi areusually seen on the upper parts of the body, thorax, neck, arms, and face.[14]

Pathophysiology:-

Jaundice results from **high levels of bilirubin** in the blood. Bilirubin is the normal breakdown product from the **catabolism of haem**, and thus is formed from the destruction of red blood cells.Under normal circumstances, bilirubin undergoes **conjugation within the liver**, making it water-soluble. It is then **excreted via the bile** into the GI tract, the majority of which is egested in the faeces as urobilinogen and stercobilin (the metabolic breakdown product of urobilingoen). Around 10% of urobilinogen is reabsorbed into the bloodstream and excreted through the kidneys. **Jaundice** occurs when this **pathway is disrupted**.[15]

Imaging:-

The imaging used will depend on the presumed aetiology. An **ultrasound abdomen** is usually first line, identifying any obstructive pathology present or gross liver pathology (albeit often user dependent).

Magnetic Resonance Cholangiopancreatography (MRCP) is used to

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visual the biliary tree, typically performed if the **jaundice is obstructive**, but US abdomen was inconclusive or limited, or as further work-up for surgical intervention.

A **liver biopsy** can be performed when the diagnosis has not been made despite the above investigations[16]

Laboratory Evaluation:-

Laboratory tests usually serve to confirm the pathophysiology of jaundice. Sometimes they may demonstrate a specific etiology as well (Chopra and Griffin, 1985).

The complete blood count may provide evidence for haemolysis by demonstrating anemia in a patient without blood loss or a blood smear with spherocytes or other oddly shaped erythrocytes. Haemolysis may be proven via a reticulocyte count, Coomb's test, or other specific tests of erythrocyte enzymes. Leucocytosis and neutrophilic are unusual in viral hepatitis, although common in cholangitis and alcoholic hepatitis. Eosinophilia plus jaundice is suspicious for toxic hepatitis on a basis of hypersensitivity.

A jaundiced patient without urinary bilirubin has either haemolysis or a hepatic defect in bilirubin uptake or conjugation. Marked persistent proteinuria in a jaundiced patient is suspicious for amyloid.

Liver function tests are nonspecific indicators of liver disease. None of them alone provides a sensitive evaluation of liver function. Many of the enzymes tested have potential sources other than the liver. Their interpretation is possible only in the light of a thorough history and meticulous physical examination. Even then, their value is often realized only alter serial determinations have been obtained.[17]

II. CONCLUSION:-

Jaundice is one of the most visual clinical signs that both patients and physicians can easily recognize. It warrants further investigation regarding the cause of jaundice. Especially for obstructive jaundice, there are common medical conditions that are responsible for it. It would be crucial for physicians to diagnose and treat them as early as possible. By being aware of this simple yet important clinical sign, a numerous hepatobiliary and pancreatic diseases can be diagnosed early for benefiting patients through appropriateandprompt treatment.[18]

Hyperbilirubinemia is more severe in new-borns. Therefore precautionary measure should be adopted by both parents, and clinicians to diagnose and treat the disease properly. Government and public health organizations should arrange seminars, workshops and trainings for mothers regarding neonatal jaundice. Medical scientists should search for new treatments and preventive measures having no side effects and capable of recovering babies more speedily. Partners should screen their ABO blood groups as well as Rh factor before marriage. Consanguineous marriages should be avoided.[19]

The high incidence of neonatal jaundice combined with theshortening of post natal stay at hospital make the earlyscreening and surveillance for neonatal hyperbilirubinemia essential to ensure that these infants are not missed, as it isstill not known at what level bilirubin can cause a significant risk of brain damage. [20] The understanding of “bile biology” not only provides insights into the mechanisms of liver pathophysiology but also facilitates the diagnosis of genetic liver diseases and the development of novel treatments[21]

Jaundiceis a common but potentially life-threatening condition. Referral to a specialist is necessary if jaundice persists beyond the neonatal

period. The differentiation between medical and surgical causes should be made early on by measuring

the blood level of conjugated and unconjugated bilirubin[22].

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