CME MODULE

ON APPROACH TO A CASE OF

JAUNDICE

STATE INSTITUTE OF HEALTH AND FAMILY WELFARE
UTTAR PRADESH

AKNOWLEDGEMENTS

GUIDENCE

Shri. Partha Sarthi Sen Sharma, *IAS,*
Principal Secretary,
Department of Medical Health and Family Welfare,
Government of Uttar Pradesh

DIRECTION AND LEADERSHIP

Dr. Rajaganapathy R., *IAS,*
Director, SIHFW, Uttar Pradesh &
Director (Administration)
Medical and Health Services, Uttar Pradesh

Course Director

Virendra Atam
Professorand Head,
Department of Medicine,
King George's Medical University, Lucknow

Lead Author

Ajay Kumar Patwa
Additional Professor
Department of Medicine,
King George's Mecical University, Lucknow

Co - AUTHOR (S): Department of Medicine, K.G.M.U., Lucknow

Amit Kumar
Assistant Professor
Department of Medicine,
King George's Mecical university,
Lucknow

Satish Kumar
Assistant Professor
Department of Medicine,
King George's Mecical university,
Lucknow

Mahak Lamba
Assistant Professor
Department of Medicine,
King George's Mecical university,
Lucknow

Deepak Bhagchandani
Assistant Professor
Department of Medicine,
King George's Mecical university,
Lucknow

Anil Gangwar
Assistant Professor
Department of Medical Gastroenterology,
King George's Mecical university,
Lucknow

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Dr. Diwakar Yadav
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Dr. Neelam
Research Assistant


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MESSAGE

Shri Brajesh Pathak
Hon'ble Deputy Chief Minister
Minister of Medical Health and Family Welfare
Department Government of Uttar Pradesh

Unlike other low- and middle-income countries, infectious diseases are still predominant, and non-communicable diseases (NCDs) are emerging without replacing the burden of infectious diseases in India, where it is imposing a double burden of diseases on households in the country. Certain studies in their findings revealed that more than 33% of the individuals are still suffering from infectious diseases out of the total ailing population in India.

Under National Health Policy 2017, many initiatives, such as "Ayushman Bharat," PM-JAY, and National Digital Health Mission (NDHM) in 2021, have been launched by the government of India in the recent years to address the health needs with a holistic approach to ensuring better health facilities.

However, merely improving health infrastructure will not cover all the needs but skill up-gradation and knowledge enhancement of Medical Officers in Provincial Health & Medical Services in Uttar Pradesh is equally important.

Continuing Medical Education (CME) allows Medical Professionals to update their knowledge base and opportunity for knowledge creators to share their learning with breadth of the medical community. CMEs provide an opportunity for all medical professionals to come together and get to know each other, thereby leading to excellent networking opportunities.

PHCs/CHCs serve as a first port of call to a qualified doctor in the public health sector and though these CME programmes recent knowledge and skills will be imparted to Medical Officers in systematic manner to update the existing proficiency of Medical Officers. This will definitely improve the patient care, patient confidence and patient satisfaction.

In this direction the State Institute of Health & Family Welfare, Uttar Pradesh (SIHFW),with the help of Subject Matter Experts has started developing Modules for CME which are need of the hour required for our health personnel. I hope that this module on Continuing Medical Education (CME) on Approach to a Case of Jaundice for Medical Officers in Provincial Health & Medical Services in Uttar Pradesh, will help our Medical Officers in knowledge upgradation on concurrent intervention practices.

I wish the team SIHFW that they should continue developing such module on CME for the benefit of Medical Officers in Provincial Health & Medical Services in Uttar Pradesh that will ultimately benefit their patients too.

(Brajesh Pathak)


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MESSAGE

Shri Mayankeshwar Sharan Singh

Hon'ble State Minister
Medical Health and Family Welfare
Department Government of Uttar Pradesh

The narratives of public health are facing a significant challenge in demographic and epidemiological transitions, particularly in low- and middle-income countries (LMICs). This transition has changed the pattern and distribution of morbidity and mortality among inhabitants and exaggerated the burden on these countries' pre-existing inadequate public health systems.

Although several life-threatening diseases have been cured through various preventive, curative, and policy measures, infectious diseases are still one of the leading causes of death in LMICs. Jaundice is one such condition, which if left untreated or treatment is delayed can lead to loss of life.

I am proud of the fact that the State Institute of Health & Family Welfare, Uttar Pradesh (SIHFW) through this module on Continuing Medical Education (CME) on Approach to a Case of Jaundice for Medical Officers in Provincial Health & Medical Services in Uttar Pradesh, is addressing the need of knowledge up-gradation in clinical management of cases of jaundice.

Pre-hepatic jaundice, Hepatocellular jaundice and Post-hepatic jaundice or obstructive jaundice and other such emergencies warrant quick and effective actions. This module on Approach to a Case of Jaundice will help MOs managing such cases at their level and if the situation demands then refer the patient to higher level at the earliest

It is important to note that to achieve the desired goals and objectives of the Department of Health and Family Welfare, we must enhance the skills of our Medical Officers in order to cater to the demands of public health services with best of their capabilities. This CME module on Approach to a Case of Jaundice will definitely serve as a tool to achieve above mentioned goal.

I wish team at SIHFW success in their endeavors of aiding an improved health service delivery system through such CME on Trauma Care and Emergency Management.

(Mayankeshwar Sharan Singh)


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FOREWARD

Shri Partha Sarthi Sen Sharma

Principal Secretary
Department of Medical, Health and Family Welfare
Government of Uttar Pradesh

Jaundice or Hyperbilirubinemia is a very common condition that affects newborns in their first few weeks of life. The main cause of jaundice is the high level of the bilirubin substance in the blood. As bilirubin is toxic to brain cells, acute bilirubin encephalopathy can occur in cases of extreme jaundice. This condition can result in brain trauma and lead to kernicterus, which causes repetitive and uncontrolled movements, a permanent upward look, and hearing loss. Thus, a timely diagnosis and treatment can help in preventing long-term damage.

Continuing Medical Education (CME) on Approach to a Case of Jaundice for Medical Officers in Provincial Health & Medical Services in Uttar Pradesh, has been developed with the intent to impart latest knowledge so that the Medical Officers in Provincial Health & Medical Services in Uttar Pradesh might stay abreast of the rapidly evolving practices in medical and medicine and provide timely intervention to the patients of jaundice.

The module is a composite interpretation of recent development in screening, prevention and primary management of cases of jaundice with inputs required for Medical Officers to enhance their skills and knowledge, ultimately leading to improved health care services to the masses.

I would like to take this opportunity to congratulate State Institute of Health & Family Welfare (SIHFW), Uttar Pradesh and other subject matters experts in developing such a comprehensive module. I hope this CME module will provide scope to revisit on clinical management of cases of Jaundice.

(Partha Sarthi Sen Sharma)


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MESSAGE

Dr. Renu Srivastava Varma

Director General Medical & Health Services
Uttar Pradesh

Jaundice is a clinical manifestation of elevated serum bilirubin. Jaundice affects approximately 6 out of 10 otherwise healthy newborns, mainly due to immature hepatic conjugation and uptake. Jaundice due to alcoholic liver disease, as well as nonalcoholic liver disease, is more common in men, while primary biliary cholangitis as an underlying cause of jaundice is dominantly seen in women.

From general practitioners point of view, timely and adequate assessment of the patient with jaundice is of great importance. Epidemiology data suggest that incidence of jaundice varies depending on the underlying cause, and it is more common in certain age groups.

Appropriate clinical management of cases of jaundice is very important in saving lives of the affected person. Through this module on Continuing Medical Education (CME) on Approach to a Case of Jaundice for Medical Officers in Provincial Health & Medical Services in Uttar Pradesh, State Institute of Health & Family Welfare (SIHFW), Uttar Pradesh has developed a comprehensive CMEs detailing out steps to deal with the patient with jaundice including detailed medical history, careful clinical examination, and appropriate laboratory and imaging techniques.

This module on Continuing Medical Education (CME) on Approach to a Case of Jaundice will prove to be of great importance at the primary care level, which will help in early screening, detection, referrals and treatment of patients. I hope that after this CME, Medical Officers in Uttar Pradesh will be able to scale up the services delivery in provide screening, management, referral and treatment in their health facilities, thus benefitting communities.

In addition to improving clinical and technical area of expertise, this CME will lead to providing improved access to health services and enhancing patient satisfaction and population health.

With the development of this module SIHFW has established genuine links between the theory and practice of healthcare management. I wish team SIHFW the best and hope that many such customized CME modules will be published in the near future.

(Dr. Renu Srivastava Varma)


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MESSAGE

Dr. Anita Joshi

Director General Family Welfare,
Directorate of Family Welfare
Uttar Pradesh

Jaundice is a common clinical finding in clinical practice of hepatologists and general practitioners. It is important for a Medical Practitioner to understand pathophysiological mechanism of jaundice, clinical approach to the patient with jaundice, and laboratory and imaging techniques. This module on Continuing Medical Education (CME) on Approach to a Case of Jaundice for Medical Officers in Provincial Health & Medical Services in Uttar Pradesh is intended to reinforce established practices along with contemporary best case study scenarios.

This module will enhance skills of Medical Officers who are posted at CHCs/PHCs in managing emergencies at the primary level and refer the cases to a higher level timely.

By collating the relevant information in the field of clinical management of Jaundice covering all domains, the module seeks to be a working document which can also be reviewed and updated periodically based on the experience of the implementation of the public health services.

I am especially pleased to note that although CMEs in Uttar Pradesh healthcare ecosystem are still in its nascent stage but such developments will lead the way forward in creating tailored CMEs for diagnosis, referral services, patient safety, quality care management and authentic knowledge delivery.

It is vital to introduce CMEs combining video and live demonstrations along with simulation-based skill modules and rigorous assessments led by experts in order to measure further impact.

I congratulate the faculties at State Institute of Health & Family Welfare, Uttar Pradesh in developing this convergent module along with experts from the field. This module addresses the need to have a holistic view on public health by also discussing other relevant guidelines and policies that seek to public health service delivery system.

(Dr. Anita Joshi)


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MESSAGE

Dr. Deepa Tyagi

Director General (Training)
Medical and Health Services
Uttar Pradesh

Jaundice, also known as hyperbilirubinemia, is a yellow discoloration of the body tissue resulting from the accumulation of an excess of bilirubin. Deposition of bilirubin happens only when there is an excess of bilirubin, a sign of increased production or impaired excretion. Jaundice is a difficult condition for the affected person, hence while approaching the patient with jaundice, due diligence like detailed medical history, careful clinical examination, and appropriate laboratory and imaging techniques etc is needed. Association with other symptoms can be extremely helpful in establishing the differential diagnosis of jaundice.

Through this module on Continuing Medical Education (CME) on Approach to a Case of Jaundice for Medical Officers in Provincial Health & Medical Services in Uttar Pradesh, State Institute of Health & Family Welfare, Uttar Pradesh with the help of Subject Matter Experts has provided a comprehensive, coherent and research-based insight to clinical management of jaundice.

This module has been designed and written for Medical Officers and healthcare professionals and takes government perspective in consideration, drawing upon and comparing ideas and developments from national and international health care practices.

The faculties at State Institute of Health & Family Welfare, Uttar Pradesh and the team of experts of the field has done a commendable job by publishing this module on CME on Approach to a Case of Jaundice for Medical Officers in Provincial Health & Medical Services in Uttar Pradesh. I hope the participants coming to attend their upcoming CME will take advantage of this initiative and make the most in their field with this handy module.

(Dr. Deepa Tyagi)


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ACKNOWLEDGEMENT

Dr. Rajaganapathy R.

Director
State Institute of Health and Family Welfare
Uttar Pradesh

The purpose of Continuing Medical Education (CME) is to facilitate life-long learning among Medical Officers so that their practices may reflect the best medical care for their patients. The goal of CME is to help Medical officers enhance their performance in practice, in turn enhancing patient care and satisfaction.

Taking this into consideration, State Institute of Health & Family welfare (SIHFW), Uttar Pradesh with the help of Subject Matter Experts, has developed a customized Continuing Medical Education (CME) on Approach to a Case of Jaundice for Medical Officers in Provincial Health & Medical Services in Uttar Pradesh, to provide exposure to Medical Officers in in Provincial Health & Medical Services in Uttar Pradesh in recent development in the field of clinical management of cases of jaundice.

Development of this module was a monumental task. I would take this opportunity to acknowledge the efforts of faculties of State Institute of Health and Family Welfare (SIHFW), Uttar Pradesh and of Additional Prof. Dr. Ajay Kumar Patwa, Gastroenterology & Hepatology Unit, Department of Medicine, King George Medical University (KGMU), Lucknow, Uttar Pradesh and his team.

I congratulate the faculties at SIHFW & KGMU for coming up with the CME module. I am looking forward to a wider dissemination of this module and feedback on its efficacy in the coming months.

(Dr. Rajaganapathy R.)


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INDEX

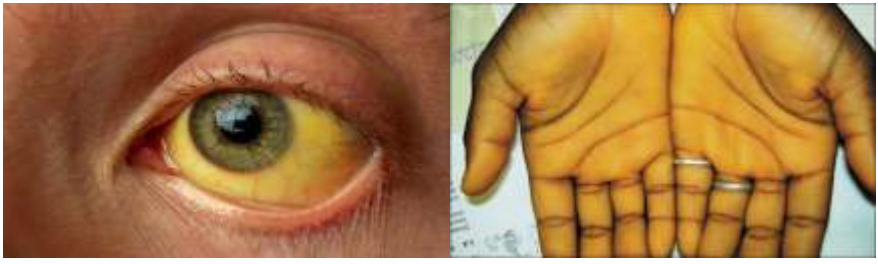
CHAPTER 1

INTRODUCTION: CLINICAL EPIDEMIOLOGY, DEFINITION, ANATOMY, PHYSIOLOGY, BIOCHEMISTRY OF JAUNDICE

AUTHORS: ANIL GANGWAR, DEEPAK BHAGCHANDANI

INTRODUCTION

Jaundice, also known as hyperbilirubinemia, is defined as a yellow discoloration of the body tissue resulting from the accumulation of excess bilirubin. Deposition of bilirubin happens only when there is an excess of bilirubin, and this indicates increased production or impaired excretion. The degree of serum bilirubin elevation can be estimated by physical examination. Slight increases in serum bilirubin level are best detected by examining the sclerae for icterus. Sclerae have a particular affinity for bilirubin due to their high elastin content, and the presence of scleral icterus indicates a serum bilirubin level of at least 51 µmol/L (3 mg/dL) (Figure 1).



jaundice eye jaundice Palm

Figure 1.1. Examination of sclerae and palms for icterus

If the examiner suspects scleral icterus, a second site to examine is underneath the tongue. As serum bilirubin levels rise, the skin will eventually become yellow in light-skinned patients and even green if the process is long-standing; the green colour is produced by oxidation of bilirubin to biliverdin.

The differential diagnosis for yellowing of the skin is limited. In addition to jaundice, it includes carotenoderma, the use of the drug quinacrine, and excessive exposure to phenols.

Carotenoderma is the yellow colour imparted to the skin of healthy individuals who ingest excessive amounts of vegetables and fruits that contain carotene, such as carrots, leafy vegetables, squash, peaches, and oranges. In jaundice the yellow coloration of the skin is uniformly distributed over the body, whereas in carotenoderma the pigment is concentrated on the palms, soles, forehead, and nasolabial folds. Carotenoderma can be distinguished from jaundice by the sparing of the sclerae.

Another sensitive indicator of increased serum bilirubin is darkening of the urine, which is due to the renal excretion of conjugated bilirubin. Patients often describe their urine as tea- or cola-coloured. Bilirubinuria indicates an elevation of the direct serum bilirubin.

Clinical Epidemiology of Jaundice

The prevalence of jaundice differs among patient populations; newborns and elderly more commonly present with the disease.

The causes of jaundice also vary with age, as mentioned above. Around 20 percent of term babies are found with jaundice in the first week of life, primarily due to immature hepatic conjugation process. Congenital disorders, overproduction from hemolysis, defective bilirubin uptake, and defects in conjugation are also responsible for jaundice in infancy or childhood. Hepatitis A was found to be the most afflicting cause of jaundice among children. Bile duct stones, drug-induced liver disease, and malignant biliary obstruction occur in the elderly population. Men have an increased prevalence of alcoholic and non-alcoholic cirrhosis, chronic hepatitis B, malignancy of pancreas, or sclerosing cholangitis. In contrast, women demonstrate higher rates of gallbladder stones, primary biliary cirrhosis, and gallbladder cancer.

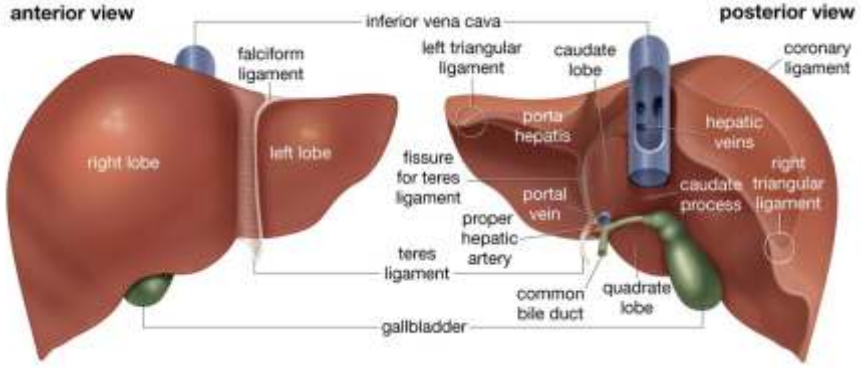
Kernicterus or Bilirubin-induced neurologic dysfunction (BIND), a complication of severe jaundice is a very rare cause of death in neonates with a death rate of 0.28 deaths per one million live births.

Anatomy of the Liver

Gross Anatomy of Liver

Parietal peritoneum covers the liver except for the bare area, where the liver comes in direct contact with the diaphragm and is suspended by fibrous tissue and the hepatic veins.

The peritoneal reflections that surround the bare area comprise the superior and inferior coronary ligaments and the right and left triangular ligaments, which attach the liver to the diaphragm; these avascular attachments are not true ligaments but are in continuity with Glisson capsule

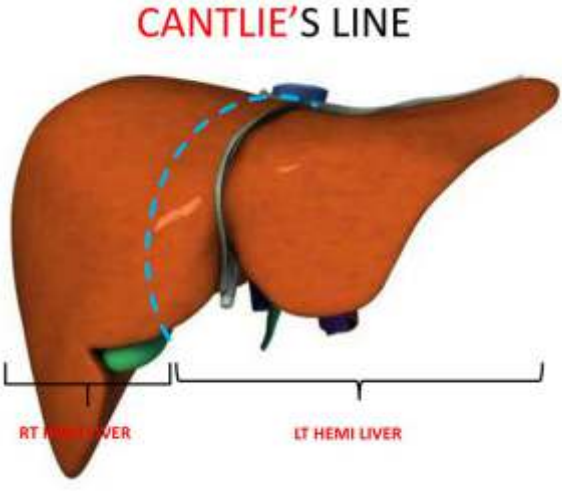


Gross liver anatomy

Figure 1.2. Gross anatomy of liver

Traditionally, 4 lobes are distinguished in the liver based on its external appearance: right, left, caudate, and quadrate. On the anterior surface, the falciform ligament divides the liver into the right and left anatomic lobes. On the inferior surface, the quadrate lobe is defined by the gallbladder fossa, porta hepatis, and ligamentum teres hepatis. The caudate lobe is delineated by the inferior vena cava groove, porta hepatis, and ligamentum venosum fissure. Although these lobes are convenient and well known, they are not true functional lobes.

The true right and left lobes of the liver are of roughly equal size and are divided not by the falciform ligament, but by a plane passing through the bed of the gallbladder and the notch of the inferior vena cava. This plane, which has no external indications, is called the *Cantlie line*.



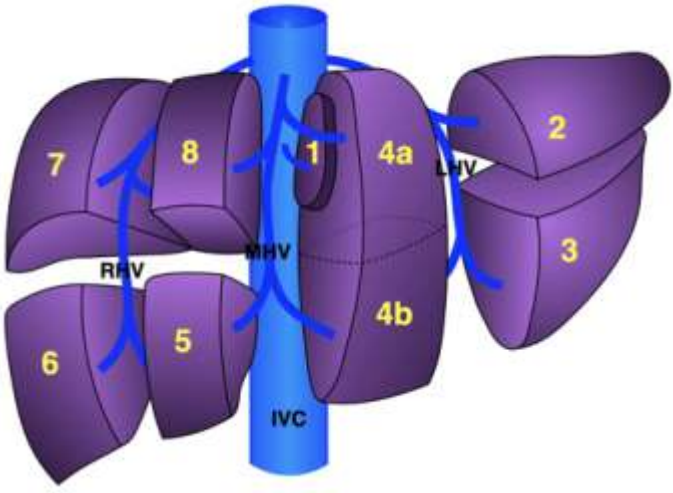
Cantle line

Figure 1.3. Cantle's line dividing right and left lobe of the liver

Segments of Liver

Based on arterial blood supply, portal venous blood supply, biliary drainage, and hepatic venous drainage, the liver is divided into right and left functional lobes, each of which is divided into 2 segments, and these are further subdivided into 2 subsegments.

As per the Couinaud systems, the subsegments are numbered from 1 to 8, with the caudate lobe being subsegment 1 and the others following in a clockwise pattern.



Couinaud segmental anatomy liver

Figure 1.4. Couinaud system showing the subsegments of liver

The liver receives approximately 70% of its blood supply and 40% of its oxygen from the portal vein and 30% of its blood supply and 60% of its oxygen from the hepatic artery.The portal vein is formed from the confluence of the superior mesenteric vein and the splenic vein. The hepatic artery commonly arises from the celiac trunk, although occasionally it arises from the superior mesenteric artery. Three major hepatic veins drain into the inferior vena cava, although in 60% to 85% of persons, the left and middle veins unite to enter the inferior vena cava as a single vein .

The classic lobule of the liver was described in 1833 by Kiernan as a hexagon with a central vein at its center and portal tracts at 3 corners. Because many glands have a duct as the center of their functional unit, Mall envisioned the basic unit of the liver to be the portal unit, defined at its center by a portal tract and at its periphery by central veins.The liver acinus was defined in 1954 by Rappaport as the parenchyma around terminal afferent portal and arterial vessels

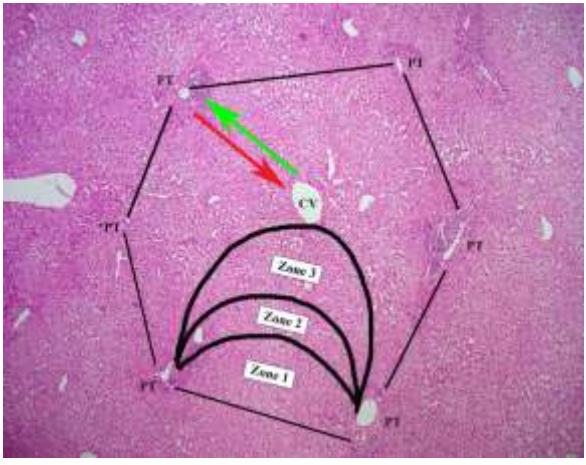
that supply this group of hepatocytes with blood. At the periphery of the acinus lies the terminal hepatic venule (the “central vein”) which drains several acini.In this model, the following 3 zones exist:

(1) The periportal zone (zone 1), which is supplied by blood with high oxygen content;

(2) The intermediate zone (zone 2); and

(3) The perivenular zone (zone 3), which receives blood that is relatively low in oxygen content.

The acinus represents a functional and structural unit that facilitates the description of lesions such as bridging necrosis and fibrosis Gluconeogenesis occurs largely in the periportal region (zone 1), whereas glycolysis occurs predominantly in the centrilobular region (zone 3)



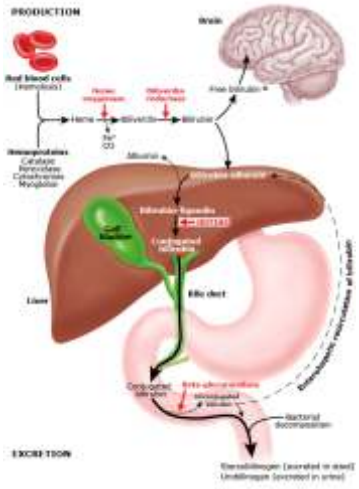
hepatic lobule anatomy

Figure 1.5. Microscopic anatomy of hepatic lobule

Bilirubin Metabolism

Bilirubin is a breakdown product of heme (ferroprotoporphyrin IX). About 4 mg/kg body weight of bilirubin is produced each day, nearly 80% from the breakdown of hemoglobin in senescent red blood cells

and prematurely destroyed erythroid cells in the bone marrow and the remainder from the turnover of hemoproteins such as myoglobin and cytochromes distributed throughout the body.The initial steps of bilirubin metabolism occur in reticuloendothelial cells, predominantly in the spleen. Heme is converted to biliverdin by the microsomal enzyme heme oxygenase. Biliverdin is then converted to bilirubin by the cytosolic enzyme biliverdin reductase.

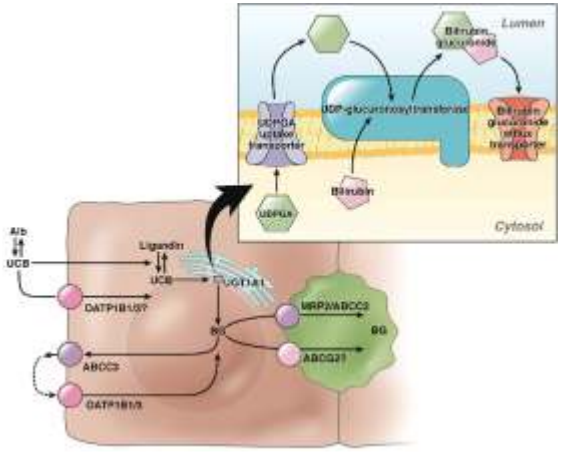


bilirubin metabolism

Figure 1.6. Production, transport, conjugation, excretion and enterohepatic circulation of bilirubin

Bilirubin formed in reticuloendothelial cells is lipid soluble and virtually insoluble in water. In order to be transported in blood, unconjugated bilirubin must be solubilized. The process is initiated by reversible, noncovalent binding to albumin, which has both high-affinity and lower-affinity binding sites for unconjugated bilirubin. The unconjugated bilirubin-albumin complex passes readily through the fenestrations in the endothelium lining the hepatic sinusoids into the space of Disse, where the bilirubin dissociates from albumin and

is taken up by hepatocytes via a protein-mediated, facilitated process, possibly mediated by a liver-specific organic anion transport protein. After entering the hepatocyte, unconjugated bilirubin is bound in the cytosol to a number of proteins, including proteins in the glutathione *S*-transferase superfamily.These proteins serve to reduce efflux of bilirubin back into the serum and present the bilirubin for conjugation. The enzyme bilirubin uridine diphosphate glucuronyl transferase (B-UGT) found in the endoplasmic reticulum solubilizes bilirubin by conjugating it to glucuronic acid to produce bilirubin monoglucuronide and diglucuronide.The now hydrophilic bilirubin diffuses to the canalicular membrane for excretion into the bile canaliculi.



bilirubin transport and conjugation

Figure 1.7. Schematic diagram showing molecular mechanism of conjugation and transmembrane transport of bilirubin

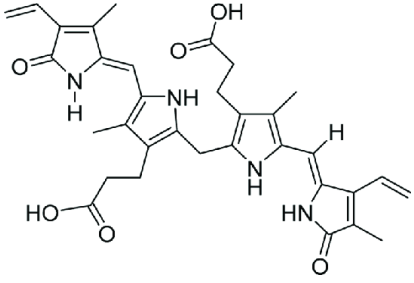
Conjugated bilirubin is transported across the canalicular membrane by the multidrug resistance–associated protein 2 (MRP2) via an ATP-dependent process.This is the only energy- dependent step in bilirubin metabolism and explains why even patients with ALF have a

predominantly conjugated hyper- bilirubinemia. Once in the bile, conjugated bilirubin passes undisturbed until it reaches the distal ileum and colon, where bacteria containing β-glucuronidases hydrolyze conjugated bilirubin to unconjugated bilirubin, which is further reduced by bacteria to colourlessurobilinogen.The urobilinogen is either excreted unchanged, oxidized and excreted as urobilin (which has an orange colour), or absorbed passively by the intestine into the portal venous system. The majority of the absorbed urobilinogen is re-excreted by the liver. A small percentage filters across the renal glomerulus and is excreted in urine. Unconjugated bilirubin is never found in urine because in the serum it is bound to albumin and not filtered by the glomerulus. The presence of bilirubin in urine indicates conjugated hyperbilirubinemia and hepatobiliary disease.

Biochemistry of Jaundice

Structure Of Bilirubin

Two dipyrroles joined by a central methene bridge

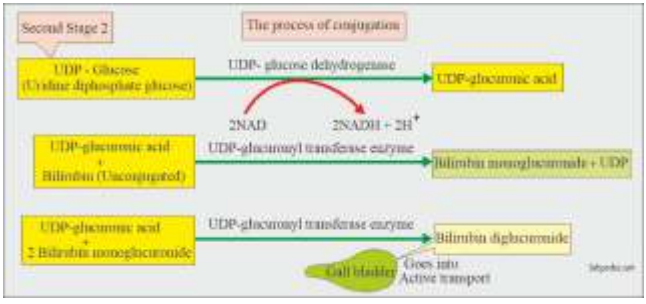


Chemical-structure-of-bilirubin

Figure 1.8. Molecular structure of bilirubin

The terms *direct* and *indirect bilirubin*, which correspond roughly to conjugated and unconjugated bilirubin, respectively, derive from the original van den Bergh reaction.

Conjugation of Bilirubin



bilirubin conjugation stages

Figure 1.9. Stages in conjugation of bilirubin

Using the diazo method, normal values of total serum bilirubin are between 0.3 and 1.0 mg/dL. Normal values for the indirect component are between 0.2 and 0.8 mg/dL.

Type of bilirubin	Normal range
Total bilirubin	0.3 to 1.0 mg/dL
Conjugated (direct) bilirubin	<0.3 mg/dL
Unconjugated (indirect) bilirubin	0.2 to 0.8 mg/dL

Normal_ranges_for_bilirubin_levels

Figure 1.10. Normal ranges of different types of bilirubin

In general, if the direct acting fraction is less than 15% of the total, the bilirubin can be considered to be entirely indirect. The most frequently reported upper limit of normal for conjugated bilirubin is 0.3 mg/dL. The presence of even a mild increase in conjugated bilirubin in the serum should raise the possibility of liver injury. The measurement and fractionation of serum bilirubin in patients with jaundice allows differentiation between parenchymal (hepatocellular) and obstructive (cholestatic) jaundice.

Delta bilirubin is found in cases of prolonged and severe elevation of serum conjugated bilirubin levels, and because of the strength of the covalent binding, the half-life of delta bilirubin is that of albumin, 14 to 21 days, which far exceeds the usual serum half-life of bilirubin of 4 hours. The identification of delta bilirubin explains why the decline in serum bilirubin in some patients with prolonged jaundice seems to lag behind clinical recovery and why some patients with conjugated hyperbilirubinemia do not have bilirubinuria.

CHAPTER 2

INTRODUCTION: ALGORITHMIC APPROACH TO A CASE OF JAUNDICE

AUTHOR : VIRENDRA ATAM

Introduction

Evaluation of a case of jaundice needs a systematic work up. Figure 1 explains the algorithmic approach to a case of jaundice. The initial step, while evaluation of jaundice, is to perform appropriate laboratory tests in order to determine:

- Whether the patient has isolated elevation of serum bilirubin?
- If so, bilirubin elevation due to an increased unconjugated or conjugated fraction?
- If the hyperbilirubinemia is accompanied by other liver test abnormalities, is the disorder hepatocellular or cholestatic?
- If cholestatic, is it intrahepatic or extrahepatic cholestasis?

Isolated elevation of bilrirubin

1) Unconjugated hyperbilirubinemia

When directcomponent of bilirubin is <15%, it is considered as unconjugated hyperbilirubinemia. Itresults from either overproduction of bilirubin (hemolytic disorders and ineffective erythropoiesis) or from impaired hepatic uptake/conjugation of bilirubin.

Hemolytic disorders can be inherited or acquired. Inherited disorders include spherocytosis, sickle cell anemia, thalassemia, and deficiency of red cell enzymes like pyruvate kinase and glucose-6 phosphate dehydrogenase.

Acquired hemolytic disorders include microangiopathic hemolytic anemia, paroxysmal nocturnal hemoglobinuria, autoimmune hemolysis, and parasitic infections (e.g., malaria, babesiosis).

Impaired bilirubin conjugation occurs in three genetic conditions: Criggler-najjar syndrome Type I and type II and Gilbert's syndrome.

Criggler-Najjar type 1 syndrome is an exceptionally rare condition found in neonates, characterized by severe jaundice (serum bilirubin levels of >25mg/dl), and neurologic impairment due to kernicterus. These patients have complete absence of bilirubin UDPGT activity.

Criggler-Najjar Syndrome Type II is more common with serum bilirubin levels of 6-25 mg/dl. Mutation in bilirubin UDPGT gene causes the reduction (typically <10%) of the enzyme's activity.

Gilbert's syndrome is also characterized by impaired conjugation of bilirubin- typically 10-35% of normal. They have mild jaundice (serum bilirubin levels of < 6mg/dl).

2) Conjugated hyperbilirubinemia

When direct bilirubin is >15% of total bilirubin, hyperbilirubinemia si conjugated. It is found in two rare inherited conditions: Dubin-Johnson syndrome and Rotor syndrome and conditions causing obstructive jaundice.

Dubin Johnson syndrome: It occurs due to mutation in gene for MRP2. These patients have altered excretion of bilirubin into the bile ducts.

Rotor syndrome: It occurs due to deficiency of major hepatic drug reuptake transporters OATP1B1 and OATP1B3.

Elevation of serum bilirubin with other liver test

These groups of patients can be divided into those with primary hepatocellular process and those with cholestasis (intrahepatic or extrahepatic).

Enzyme tests [ALT (Alanine aminotransferase), AST (Aspartate aminotransferase) and ALP (Alkaline phosphatase)] are helpful in differentiating between a hepatocellular process and cholestatic

process. Patients with hepatocellular process generally have a rise in aminotransferases that is disproportionate to that in alkaline phosphatase, whereas patients with cholestatic pattern have a rise in alkaline phosphatase that is disproportionate to rise in aminotransferases.

In addition to enzymes test, all jaundiced patients should be tested for serum albumin and prothrombin time- to assess liver function. A low albumin level suggests a chronic process such as cirrhosis or cancer. An elevated prothrombin time suggests significant hepatocellular dysfunction.

1) Hepatocellular conditions

Hepatocellular jaundice is characterized by predominant elevation of transaminases. The common conditions causing hepatocellular jaundice are viral hepatitis, alcoholic hepatitis, Drug toxicity-e.g., acetaminophen, isoniazid, Wilson's disease, autoimmune hepatitis.

2) Cholestatic conditions

When pattern of liver suggests a cholestatic disorder, the next step is to determine whether it is intrahepatic or extrahepatic cholestasis. Next appropriate test is to confirm obstructive cause by getting levels of GGT (Gamma Glutamyl Transferase) and getting an ultrasound done. The absence of biliary dilation suggests intrahepatic cholestasis.

A. Intrahepatic cholestasis

A number of conditions which causes hepatocellular type of injury can also present as cholestatic variant. Both hepatitis B and C virus can cause cholestatic hepatitis (fibrosing cholestatic hepatitis).

Drugs most commonly associated with cholestasis are anabolic steroids, contraceptive steroids, chlorpromazine, tolbutamide, erythromycin, trimethoprim; sulfamethoxazole; and ampicillin, clavulanic acid.

Primary biliary cholangitis (PBC) (autoimmune) and primary sclerosing cholangitis (PSC) are also the causes of intrahepatic cholestasis.

Other causes of intrahepatic cholestasis are cholestasis of pregnancy, total parenteral nutrition, sepsis, veno occlusive disease, and graft versus host disease.

B. Extrahepatic cholestasis

Causes of extrahepatic cholestasis can be benign or malignant. Among malignant causes are cholangiocarcinoma, pancreatic, gall bladder and ampullary carcinomas.

Benign causes are choledocholithiasis (most common), post operative biliary strictures, AIDS cholangiopathy, Mirizzi's syndrome, parasitic disease, and chronic pancreatitis.

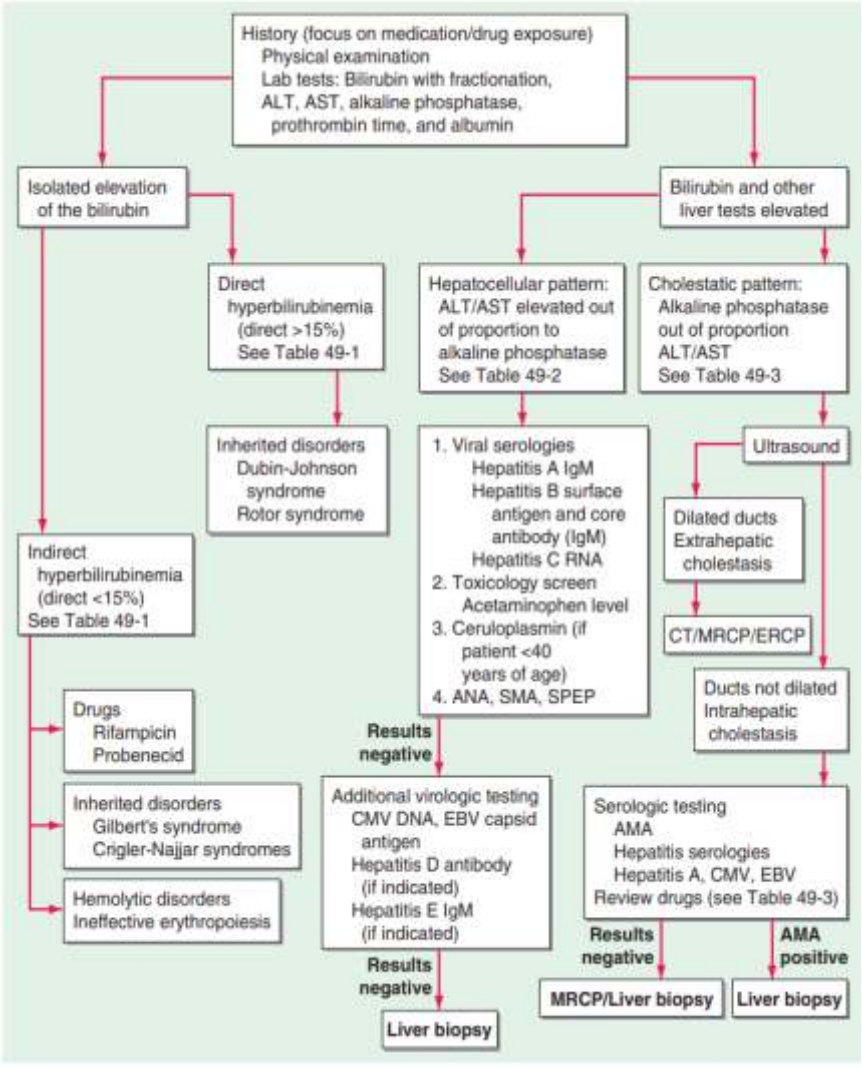


Figure 2.1. Algorithm for approach to a case of jaundice

Real life case scenarios (Case 1):

A 25-year-old male complains of yellowish discoloration of eyes and skin for 1 month. He presented to a district hospital. On examination, icterus was present, no organomegaly was felt. Blood investigations were ordered which shows Hb-12mg%, TLC- 8000/mm3, Platelet count- 1.6 lac/mm3, Bilirubin (T)- 5.8 mg/dl, Direct bilirubin-0.8 mg/dl, SGOT-37 U/L, SGPT-42U/L, ALP-210 U/L. GBP shows no features of hemolysis and LDH and uric acid levels are within normal range.

What is the most likely diagnosis?

a) Criggler-Najjar syndrome Type II

b) Gilbert's syndrome

c) Hemolytic anemia

d) Choldocholithiasis

Discussion

- The patient has isolated increase in only the unconjugated portion of bilirubin.
- As there is indirect hyperbilirubinemia present, among above mentioned options, choledocholithiasis can not be the answer as it causes mainly direct hyperbilirubinemia.
- As there is no feature of hemolysis, we are left with either Criggler-Najjar syndrome or Gilbert's syndrome.
- To differentiate between these 2 syndromes, further genetic studies or enzymes studies are required, which are available only at special centers.
- Since Gilbert syndrome is more commonly prevalent than Criggler-Najjar syndrome Type II, Gilbert syndrome is a better option in this case.

- As the patient is a young male, chances of having a fatal type of genetic disorder is less, we should also counsel for the disease most probably being a benign one and refer the patient to a tertiary care or a specialty center.
- Further plan should be to determine the cause of isolated indirect hyperbilirubinemia by genetic and enzyme based studies.

Case 2:

A 57-year-old female presented with complaints of fatigue and yellowish discoloration of eyes for 1 month. She has a history of cholecystectomy in view of cholelithiasis 2 years ago and history of multiple PRBC transfusions in the past. On general examination, pallor and icterus is present. On abdominal examination, moderate splenomegaly is present. Blood investigations show Hb-6.5 mg/dl, TLC-8800/mm3, PC-1.2 lac/mm3, Total bilirubin- 5.9 mg/dl, Direct bilirubin-0.7 mg/dl, SGOT-30 U/L, SGPT-20 U/L, ALP- 208 U/L, Reticulocyte count -15%. LDH and Uric acid levels were raised. Urine R/M shows urobilinogen- positive. Direct Coomb's test was positive.

What is the most likely diagnosis?

a) Autoimmune hemolytic anemia

b) Thalassemia

c) Sickle cell anemia

d) G6PD deficiency

Discussion

- Firstly, the patient is suffering from indirect hyper bilirubinemia.
- As the patient is having splennomegaly and Reticulocyte counts are high too, chances of the patient having a hemolytic condition is high.

- Raised levels of LDH and anemia also suggest the same.
- As the patient is an elderly woman, and there are no mentions of the patient suffering from a similar episode in the past, chances of the patient having an inherited disease in the structure of RBCs are less.
- Autoimmune hemolytic anemia (AIHA) occurs when your immune system makes RBC as unwanted substances. As a result, your body produces antibodies that destroy red blood cells as unwanted substances. As a result, your body produces antibodies that destroy RBC, which can lead to anemia and jaundice.
- AIHA is highly manageable but is fatal if left untreated.
- A peripheral smear should be sent for evaluation and to look for spherocytes.
- Causes of AIHA should be sought and further tests to diagnose the patient's condition should be sent.

Case 3:

A 45-year-old female presented with, colicky pain in right hypochondrium for 45 days, yellowish discoloration of eyes and urine for 1 month, itching all over the body for 1 month. Blood investigations were ordered which shows Hb-12mg%, TLC-8000/mm3, platelet count-1.6 lac/mm3, Total bilirubin- 6.8 mg/dl, Direct bilirubin-5.8 mg/dl, SGOT-37 U/L, SGPT-42U/L, ALP-1000U/L. USG W/A shows dilated common bile duct and intrahepatic biliary radicals.

What is the most likely diagnosis?

A) Choledocholithiasis
B) Primary Biliary Cirrhosis
C) Primary Sclerosing Cholangitis
D) Viral Hepatitis

Discussion

- In the above mentioned case, direct hyperbilirubinemia is present as can be discerned by raised levels of direct bilirubin and ALP.
- USG shows dilated common bile duct which is suggestive of extra-hepatic cholestasis.
- Choledocholithiasis is one of the most common cause of extra-hepatic cholestasis. To confirm the diagnosis, next line of investigation is either MRCP (diagnostic) or ERCP (diagnostic plus therapeutic).

Case 4:

A 28-year-old male present with complains of fever for 15 days, episodes of loose stools 15 days back and yellowish discoloration of eyes and skin for 7 days. On examination, hepatomegaly is present with tenderness in the right hypochondrium. Blood investigations were ordered which show Hb-12 gm%, TLC-18000/mm3, Platelet Count-1.6 lac/mm3, Total bilirubin -6.8 mg/dl, Direct bilirubin-3.8 mg/dl, SGOT-2000 U/L, SGPT-3600 IU/L, ALP-300 IU/L. USG of abdomen shows coarse echotexture of liver with normal intrahepatic biliary radicles.

What is the most likely diagnosis?

a) Acute Viral Hepatitis

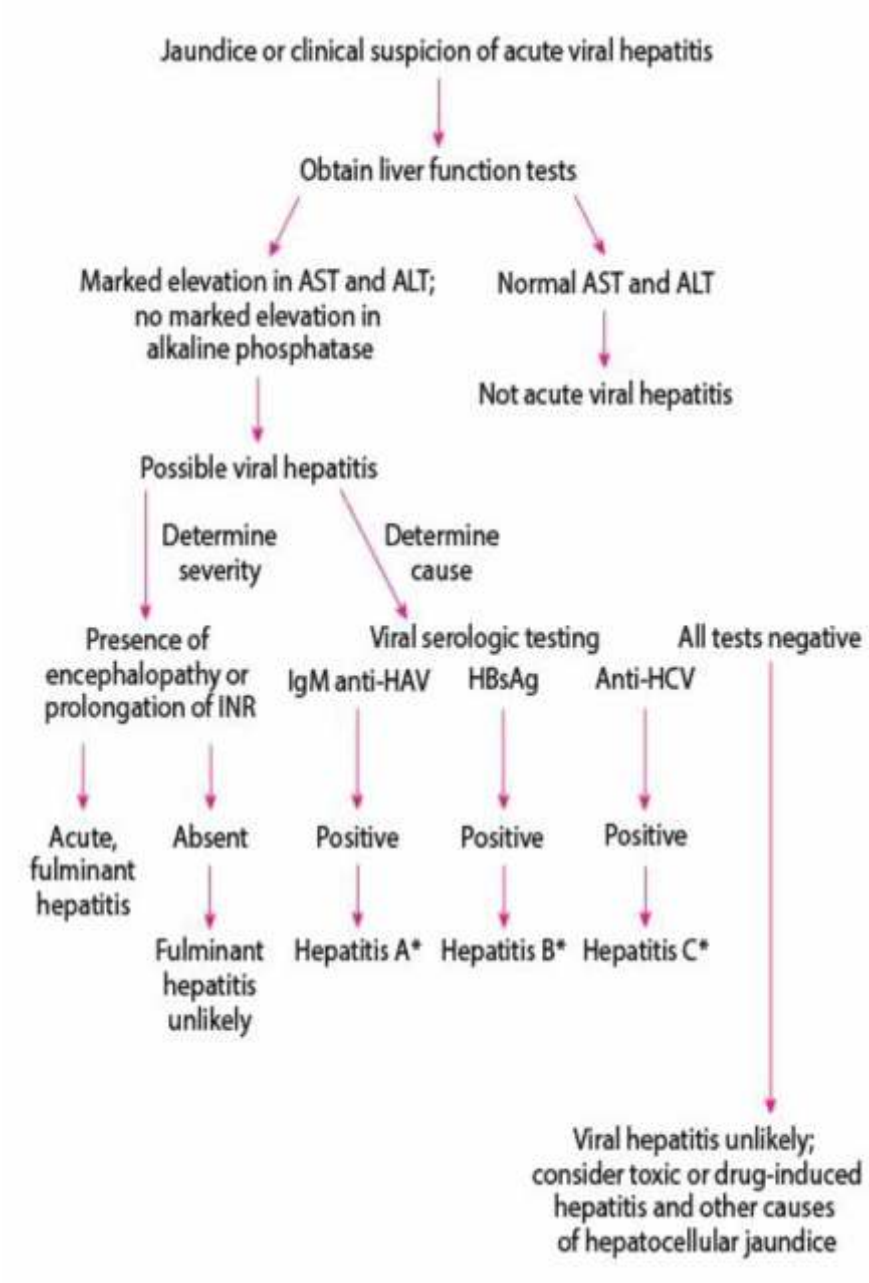
b) Choledochal Cyst

c) Hemolytic Anemia

d) Drug toxicity

Discussion

- Firstly, the patient has mixed hyperbilirubinemia with elevated levels of both direct and indirect bilirubin.
- At the same time the patient also has raised levels of liver enzymes.
- This suggests that the patient might be having a cause of hepatocellular jaundice.
- Most common causes of hepatocellular jaundice are acute viral hepatitis.
- Hepatitis A and E are the most common infectious causes of acute hepatitis and usually have a self-limited clinical course, resolving in 2 to 4 weeks with supportive treatment that includes IV fluids, anti emetics, and symptomatic treatment.
- Further plan should be to send investigations for viruses causing acute hepatitis- Hepatitis A, Hepatitis B, Hepatitis C and Hepatitis E.
- Below described algorithm gives an idea about how to proceed a case of acute viral hepatitis.


Jaundice or clinical suspicion of acute viral hepatitis
Obtain liver function tests
Marked elevation in AST and ALT; no marked elevation in alkaline phosphatase
Normal AST and ALT
Not acute viral hepatitis
Possible viral hepatitis
Determine severity
Determine cause
Presence of encephalopathy or prolongation of INR
Viral serologic testing
All tests negative
IgM anti-HAV
HBsAg
Anti-HCV
Acute, fulminant hepatitis
Absent
Positive
Positive
Positive
Fulminant hepatitis unlikely
Hepatitis A*
Hepatitis B*
Hepatitis C*
Viral hepatitis unlikely; consider toxic or drug-induced hepatitis and other causes of hepatocellular jaundice

Case 5:

A 32-year-old male presents with complains of breathlessness on exertion for 8 years, palpitations for 1-year, yellowish discoloration of eyes and urine for 10 days. On examination, neck veins are engorged, icterus present, pedal edema present, liver is palpable below subcostal space which is tender on palpation. Free fluid is present in abdomen. On auscultation, pansystolic murmur is heard over tricuspid area, low pitch mid-diastolic murmur is heard over mitral area, which is not radiating to anywhere.

Blood investigations were ordered which show Hb-12 mg%, TLC-7000/mm^3, Platelet Count-1.3 lac/mm^3, Total bilirubin-6.8 mg/dl, direct bilirubin- 3.4 mg/dl, SGOT-2400 U/L, SGPT-3000U/L, ALP-350U/L. USG of abdomen shows mildly coarse echotexture of liver with mild ascites.

Quiz 7.1: What is the most likely diagnosis?

a) Acute viral hepatitis

b) Congestive hepatitis

c) Drug toxicity

d) Malaria

Discussion

- Firstly the patient is having increase in both direct and indirect fractions and also increased levels of liver enzymes.
- USG is suggestive of mildly coarse echotexture of liver with ascites, which suggests that the patient might be having some intrinsic pathology of liver, likely a hepatocellular condition, which is subacute to chronic in duration.
- The clinical features of the above-mentioned patient are suggestive of the patient having features of right heart failure (increased JVP, palpitations and pedal edema).

Quiz 7. 2: What is the next line investigation will you advise for?

Ans- 2-D ECHO

2-D ECHO was done which shows Severe Mitral Stenosis, Severe Tricuspid Regurgitation, Severe Pulmonary Artery Hypertension, Dilated inferior vena cava, With dilated LA, RA, RV with good LV systolic function.

Case 6:

A 10-year-old boy received a sulfonamide antibiotic as prophylaxis for recurrent urinary tract infections. Although he was previously healthy and well nourished, he became progressively ill and presented with generalized weakness, easy fatiguability and yellowish discoloration of eyes. Blood investigation were ordered which shows Hb-6.5 mg/dl, TLC-8800/mm3, PC-1.2 lac/mm3, bilirubin-5.9 mg/dl, direct bilirubin-0.7 mg/dl, SGOT-30 U/L, SGPT-20 U/L, ALP-102 U/L, reticulocyte count -12%. LDH and Uric acid levels were raised. Urine examination shows raised urobilinogen.

What is the next line investigation to confirm the diagnosis?

a) HPLC
b) G6PD enzyme levels
c) Thick and thin smear
d) Viral Markers

Discussion

- Firstly the patient is suffering from indirect hyper bilirubinemia.
- The patient also has anemia and raised levels of LDH and Uric acid and urine examinationshowed raised urobinogen, which is suggestive of the patient having hemolysis.
- Since the onset of the hemolytic episode was after the intake of a sulfonamide drug, the patient might be having an episode of drug induced hemolytic anemia, which is likely in inherited diseases of enzyme deficiencies.

- Identification and discontinuation of precipitating agent is critical in cases of G6PD deficiency. Affected individuals are treated with bed rest and O2 support. If anemia is severe, blood transfusion is indicated.

Case 7:

A 45-year-old female, known case of hypothyroidism, presents with complains of pruritus for 2 months, yellowish discoloration of eyes and urine for 15 days and generalized weakness for 15 days. On examination, icterus present, pigmented xanthelasma on eyelids were seen. On abdominal examination, hepatomegaly is present. Blood investigations were ordered which show Hb-11mg%, TLC-7500/mm3, platelet count-1.3lac/mm^3, bilirubin-7.8 mg/dl, direct bilirubin-5.8 mg/dl, SGOT-20 IU/L, SGPT-22 IU/L, ALP-850U/L. USG of abdomen shows coarse echotexture of liver.

What is the next line investigation?

a) Anti mitochondrial antibodies

b) 24-hour urinary copper

c) Iron binding capacity

s) p-ANCA

Discussion

- Firstly the patient has direct hyperbilirubinemia with raised ALP levels.
- USG is suggestive of coarse echotexture of liver, which suggests that the patient is having intrahepatic cholestasis.
- Mitochondrial antibodies are measured routinely by ELISA (in titres >1:160)- are present in over 95% of patients with primary biliary cholangitis.
- Viral markers and anti mitochondrial antibodies should be assessed.

- Liver biopsy shows characteristic histological features of portal tract infiltrates, mainly of lymphocytes and plasma cells. Approximately 40% have granulomas. Most of the early changes are in zone 1. Later, there is damage to bile ducts with ductular proliferation.
- Lack of medical therapy has made PBC a major indication of liver transplantation.

Case 8:

A 27-year-old male was admitted in the emergency department with a history of progressive yellowish discoloration of skin and eyes, nausea, and fatigue for the last 7 days. It was associated with generalized pruritus. He denied abdominal pain, fever, chills, diarrhea, abdominal distention, melena, hematemesis, myalgia, joint pain, and other symptoms at the time of presentation. The patient recollected a similar episode of yellowish discoloration about a year ago, but it resolved without medical attention. He was not taking any medications. He denied a family history of jaundice and liver disorders on his mother's side. The patient lived with his mother and worked at a veterinary hospital as an animal handler. He had a history of alcohol consumption since the age of 14 and mentioned that until last year he was consuming half litre of Vodka daily, reporting multiple failed attempts at quitting. He denied intravenous drug use, blood transfusion and multiple sexual partners. Physical examination was notable for icteric sclera and jaundice of his whole body including the palms and soles. Abdominal examination revealed marked hepatomegaly with liver edge palpable up to 5 cm below the right costal margin.

Initial laboratory studies were significant for elevated liver enzymes (AST 170 IU/L, ALT 64 IU/L, ALP 649 IU/L, GGT- 3,792 U/L), elevated total bilirubin of 15.7 mg/dL with direct bilirubin of 11.75 mg/dL, albumin 2.2 mg/dL.

What' is the most likely diagnosis?

A) Alcoholic hepatitis

B) Choledocholithiasis

C) NASH

D) Autoimmune hepatitis

Discussion

- Alcoholic liver disease (ALD) is clinically silent with little or no symptoms, especially in the patients with early ALD and compensated cirrhosis.
- On top of that, most patients are reluctant to openly admit their drinking behaviour, so diagnosis depends highly on clinical suspicion, various laboratory tests, and sometimes even invasive tests.
- In most cases, ALD can be diagnosed easily with reliable history, hepatic function panel, and imaging to support the diagnosis.
- Patients with ALD typically have elevated red blood cell MCV, moderate elevations of AST and ALT (typically less than 400 IU/L with AST/ALT ratio of >2), elevated serum bilirubin, GGT, and INR, and low albumin and platelet count.
- Acute-phase reactants such as serum ceruloplasmin, ferritin, and alpha-1 antitrypsin may be elevated in patients with severe alcoholic hepatitis.
- Generally, clinical and laboratory features are often adequate to establish the diagnosis of ALD in a patient with long-standing history of heavy alcohol use.
- Further plan should be a complete workup for the complications of alcoholic liver disease including fibroscan and upper GI endoscopy.

- A detailed plan and psychiatric evaluation should be sought for evaluation for alcohol use disorder and a detoxification programme should be made.

CHAPTER 3

COMMON CAUSES OF ISOLATED HYPERBILIRUBINEMIA AND THEIR MANAGEMENT (REAL LIFE CASE-BASED APPROACH)

AUTHOR : MAHAK LAMBA

INTRODUCTION

Isolated hyperbilirubinemia is defined as increase in serum bilirubin without any abnormality in other function tests. It may be isolated direct (conjugated) or isolated indirect (unconjugated) hyperbilirubinemia. Both have different causes (Table 1).

Table 1. **Causes of Isolated Hyperbilirubinemia**

I. Indirect hyperbilirubinemia
A. Hemolytic disorders
B. Ineffective erythropoiesis
C. Increased bilirubin production
1. Massive blood transfusion
2. Resorption of hematoma
D. Drugs
1. Rifampin
2. Probenecid
3. Antibiotics—cephalosporins and penicilllins
E. Inherited conditions
1. Crigler-Najjar types I and II
2. Gilbert's syndrome
II. Direct hyperbilirubinemia (inherited conditions)
A. Dubin-Johnson syndrome
B. Rotor syndrome

Disorders of bilirubin metabolism leading to unconjugated hyperbilirubinemia

Increased Bilirubin Production

Hemolysis

Increased destruction of erythrocytes leads to increased bilirubin turnover and unconjugated hyperbilirubinemia. Hemolysis alone cannot result in a sustained hyperbilirubinemia of more than 68 µmol/L (4 mg/dL). Higher values imply concomitant hepatic dysfunction. When hemolysis is the only abnormality, the result is a purely unconjugated hyperbilirubinemia, with the direct fraction

being ≤15% of the total serum bilirubin. In the presence of hepatic dysfunction, hemolysis may produce a component of conjugated hyperbilirubinemia in addition to an elevated unconjugated bilirubin concentration. Prolonged hemolysis may lead to the precipitation of bilirubin salts within the gallbladder or biliary tree, resulting in gallstones in which bilirubin is the major component.

Ineffective Erythropoiesis

During erythroid maturation, small amounts of hemoglobin may be lost, and a fraction of erythroid cells is destroyed within the marrow. These processes account for a small proportion of bilirubin. In various disorders, including thalassemia major, megaloblastic anemias due to folate or vitamin B12 deficiency, congenital erythropoietic porphyria, lead poisoning, and various congenital and acquired dyserythropoietic anemias, the bilirubin derived from ineffective erythropoiesis is increased, reaching as much as 70% of the total.

Miscellaneous

Degradation of hemoglobin of extravascular collections of erythrocytes, such as those seen in massive tissue infarctions or large hematomas, may lead transiently to unconjugated hyperbilirubinemia.

Decreased hepatic biliary clearance

Decreased Hepatic Uptake

Decreased hepatic bilirubin uptake is believed to contribute to unconjugated hyperbilirubinemia of Gilbert's syndrome (GS). Several drugs, including flavaspidic acid novobiocin, and rifampin, as well as various cholecystographic contrast agents, have been reported to inhibit bilirubin uptake.

Impaired Conjugation

Physiologic Neonatal Jaundice

Many hepatic physiologic processes are incompletely developed at birth. Levels of UGT1A1 are low, and alternative excretory pathways allow passageof unconjugated bilirubin into the gut. Since the intestinal flora that convert bilirubin to urobilinogen are also undeveloped, an enterohepatic circulation of unconjugated bilirubin ensues. As a consequence, most neonates develop mild unconjugated hyperbilirubinemia between days 2 and 5 after birth. Peak levels are typically <85–170 µmol/L (5–10 mg/dL) and decline to normal adult concentrations within 2 weeks. Prematurity, often associated with more profound immaturity of hepatic function and hemolysis, can result in higher levels of unconjugated hyperbilirubinemia. A rapidly rising unconjugatedbilirubin concentration, or absolute levels >340 µmol/L (20 mg/dL), puts the infant at risk for bilirubin encephalopathy, or kernicterus. Treatment options include phototherapy, which converts bilirubin into water-soluble photoisomers that are excreted directly into bile, and exchange transfusion.

Acquired Conjugation Defects

A modest reduction in conjugating capacity may be observed in advanced hepatitis or cirrhosis. Various drugs, including pregnanediol, novobiocin, chloramphenicol, gentamicin, and atazanavir, may produce unconjugated hyperbilirubinemia by inhibiting UGT1A1 activity. Bilirubin conjugation may be inhibited by certain fatty acids that are present in breast milk, of mothers whose infants have excessive neonatal hyperbilirubinemia (*breast milk jaundice*). In transient familial neonatal hyperbilirubinemia (Lucey-Driscoll syndrome), there may be a UGT1A1 inhibitor in maternal serum.

Hereditary defects in bilirubin conjugation

Three familial disorders characterized by differing degrees of unconjugated hyperbilirubinemia have long been recognized.

Crigler-Najjar Syndrome, Type I

CN-I is characterized by striking unconjugated hyper bilirubinemia of 340–765 µmol/L (20–45 mg/dL) that appears in the neonatal period and persists for life. Other hepatic biochemical tests such as serum aminotransferases and alkaline phosphatase are normal, and there is no evidence of hemolysis. Hepatic histology is also essentially normal except for the occasional presence of bile plugs within canaliculi. Bilirubin glucuronides are virtually absent from the bile, and there is no detectable constitutive expression of UGT1A1 activity in hepatic tissue. Neither UGT1A1 activity nor the serum bilirubin responds to administration of phenobarbital or other enzyme inducers. Unconjugated bilirubin accumulates in plasma, from which it is eliminated very slowly by alternative pathways that include direct passage into the bile and small intestine, possibly via bilirubin photoisomers. This accounts for the small amount of urobilinogen found in feces. No bilirubin is found in the urine. First described in 1952, the disorder is rare (estimated prevalence, 0.6–1.0 per million). Pedigree analyses show an autosomal recessive pattern of inheritance. The majority of patients (type IA) exhibit defects in the glucuronide conjugation of a spectrum of substrates in addition to bilirubin, including various drugs and other xenobiotics. These individuals have mutations in one of the common exons (2–5) of the *UGT1* gene. In a smaller subset (type IB), the defect is limited largely to bilirubin conjugation, and the causative mutation is in the bilirubin-specific exon A1. More than 30 different genetic lesions of *UGT1A1* responsible for CN-I have been identified, including deletions, insertions, alterations in intron splice donor and acceptor sites, exon skipping, and point mutations that introduce premature stop codons or alter critical amino acids.

Crigler-Najjar Syndrome, Type II (CN-II)

This condition was recognized in 1962 and is characterized by marked unconjugated hyperbilirubinemia in the absence of abnormalities of other conventional hepatic biochemical tests, hepatic histology, or hemolysis.

It differs from CN-I in several specific ways: (1) average bilirubin concentrations are lower in CN-II; (2) only infrequently associated with kernicterus; (3) bile is deeply colored,and bilirubin glucuronides are present, with a striking, characteristic increase in the proportion of monoglucuronides; (4) UGT1A1 in liveris usually present at reduced levels (typically ≤10% of normal); and (5)while typically detected in infancy, hyperbilirubinemia was not recognized in some cases until later in life. Reduction of serumbilirubin concentrations by >25% in response to enzyme inducerssuch as phenobarbital distinguishes CN-II from CN-I. Bilirubin concentrationsduring phenobarbital administration do not return to normal but are typically in the range of 51–86 µmol/L (3–5 mg/dL). Although the incidence of kernicterus in CN-II is low, instances have occurred, not only in infants but also in adolescents and adults, often in the setting of an intercurrent illness, fasting, or another factor that raises the serum bilirubin and reduces serum albumin levels. For this reason, phenobarbital therapy is widely recommended, a single bedtime dose often sufficing to maintain clinically safe serum bilirubin concentrations.

Over 100 different mutations in the *UGT1* gene have been identified as causing CN-I or CN-II. Missense mutations are more common in CN-II patients.

Gilbert Syndrome

This syndrome is characterized by mild unconjugated hyperbilirubinemia, normal values for hepatic biochemical tests, and normal hepatic histology. Serum bilirubin concentrations are most often <51 µmol/L (<3 mg/dL), although both higher and lower values are frequent. The clinical spectrum of hyperbilirubinemia fades into that of CN-II at serum bilirubin concentrations of 86–136 µmol/L (5–8 mg/dL). Bilirubin concentrations may fluctuate substantially in any given individual. More elevated values are associated with stress, fatigue, alcohol use, reduced caloric intake,and intercurrent illness, while increased caloric intake or administrationof enzyme-inducing agents produces lower bilirubin levels.GS is most often diagnosed at or shortly after puberty or in adult lifeduring routine examinations. UGT1A1 activity is typically reduced to 10–35% of normal,and bile pigments exhibit a characteristic increase in bilirubin monoglucuronides.Hepaticbilirubin clearance is reduced to an average of one-third of normal.Administration of phenobarbital normalizes both the serum bilirubinconcentration and hepatic bilirubin clearance. Themagnitude of changes in the serum bilirubin concentration inducedby provocation tests such as 48 h of fasting or the IV administrationof nicotinic acid has been reported to be of help in separating GSpatients from normal individuals.

GS is common, with many series placing its prevalence as high as 8%. Males predominate over females by reported ratios ranging from 1.5:1 to >7:1. The disposition of most xenobiotics metabolized by glucuronidation appears to be normal in GS. The principal exception is the metabolism of the antitumor agent irinotecan (CPT-11), whose active metabolite (SN-38) is glucuronidated specifically by bilirubin-UDP-glucuronosyltransferase. Administration of CPT-11 to patients with GS has resulted in several toxicities, including intractable diarrhea and myelosuppression. HIV protease inhibitors indinavir and atazanavircan inhibit UGT1A1, resulting in hyperbilirubinemia that is most pronounced in patients with preexisting GS.

Most older pedigree studies of GS were consistent with autosomal dominant inheritance with variable expressivity. Studies in Europe and the United States found that nearly all patients had normal coding regions for UGT1A1 but were homozygous for the insertion of an extra TA (i.e., A[TA]7TAA rather than A[TA]6TAA) in the promoter region of the first exon.

Phenotypic expression of GS due solely to the A[TA]7TAA promoter abnormality is inherited as an autosomal recessive trait. Seven different missense mutations in the *UGT1* gene that reportedly cause GS with dominant inheritance have been found in Japanese individuals. Another Japanese patient with mild unconjugated hyperbilirubinemia was homozygous for a missense mutation in exon 5. GS in her family appeared to be recessive.

Table 2. Differential Characteristics of Gilbert and Crigler-Najjar Syndromes

Feature	Crigler-Najjar Syndrome		Gilbert Syndrome
	Type I	Type II	
Total serum bilirubin, µmol/L (mg/dL)	310-755 (usually >345) (18-45 [usually >20])	100-430 (usually≤345 (6-25 [usually ≤20])	Typically≤70 µmol/L(≤4mg/dL) in absence of fasting or hemolysis
Routine liver tests **Response to phenobarbital** **Kernicterus** **Hepatic histology**	Normal None Usual Normal	Normal Decreases bilirubin by >25% Rare Normal	Normal Decreases bilirubin to normal No Usually normal; increased lipofuscin pigment in some
Bile characteristics **Color** **Bilirubin fractions**	Pale or colorless >90% unconjugated	Pigmented Largest fraction (mean:57%) monoconjugates	Normal dark color Mainly deconjugates but monoconjugates increased (mean:23%)
Bilirubin UDP-glucuronosyltransferase activity	Typically absent; traces in some patients	Markedly reduced: 0-10% of normal	Reduced: typically 10-33% of normal
Inheritance (all autosomal)	Recessive	Predominantly recessive	Promotor mutation: recessive Missense mutation: 7 of 8 dominant; 1 reportedly recessive

Disorders of bilirubin metabolism leading to mixed or predominantly conjugated hyperbilirubinemia

In hyperbilirubinemia due to acquired liver disease (e.g., acute hepatitis, common bile duct stone), there are usually elevations in the serum concentrations of both conjugated and unconjugated bilirubin. Although biliary tract obstruction or hepatocellular cholestatic injury

may present on occasion with a predominantly conjugated hyperbilirubinemia, it is generally not possible to differentiate intrahepatic from extrahepatic causes of jaundice based on the serum levels or relative proportions of unconjugated and conjugated bilirubin.

Familial defects in hepatic excretory function

Dubin-Johnson Syndrome (DJS)

This benign, relatively rare disorder is characterized by low-grade, predominantly conjugated hyperbilirubinemia. Total bilirubin concentrations are typically between 34 and 85 µmol/L (2 and 5 mg/dL) but on occasion can be in the normal range or as high as 340–430 µmol/L (20–25 mg/dL) and can fluctuate widely in any given patient. The degree of hyperbilirubinemia may be increased by intercurrent illness, oral contraceptive use, and pregnancy. Because the hyperbilirubinemia is due to a predominant rise in conjugated bilirubin, bilirubinuria is characteristically present. Aside from elevated serum bilirubin levels, other routine laboratory tests are normal. Physical examination is usually normal except for jaundice, although an occasional patient may have hepatosplenomegaly. Patients with DJS are usually asymptomatic. In women, the condition may be subclinical until the patient becomes pregnant or receives oral contraceptives, at which time chemical hyperbilirubinemia becomes frank jaundice. Even in these situations, other routine liver function tests, including serum alkaline phosphatase and transaminases, are normal.

A cardinal feature of DJS is the accumulation of dark, coarsely granular pigment in the lysosomes of centrilobular hepatocytes. As a result, the liver may be grossly black in appearance.

Biliary excretion of a number of anionic compounds is compromised in DJS. These include various cholecystographic agents, as well as sulfobromophthalein (Bromsulphalein [BSP]), a synthetic

dye formerly used in a test of liver function. In this test, the rate of disappearance of BSP from plasma was determined following bolus IV administration. BSP is conjugated with glutathione in the hepatocyte; the resulting conjugate is normally excreted rapidly into the bile canaliculus. Patients with DJS exhibit characteristic rises in plasma concentrations at 90 min after injection, due to reflux of conjugated BSP into the circulation from the hepatocyte. Bile acid disposition, including hepatocellular uptake and biliary excretion, is normal in DJS. These patients have normal serum and biliary bile acid concentrations and do not have pruritus. By analogy with findings in several mutant rat strains, the selective defect in biliary excretion of bilirubin conjugates was found to reflect defective expression of MRP2 (ABCC2), an ATP-dependent canalicular membrane transporter. Several different mutations in the *ABCC2* gene produce the Dubin Johnson phenotype, which has an autosomal recessive pattern of inheritance. Patients with DJS also have a diagnostic abnormality in urinary coproporphyrin excretion. There are two naturally occurring coproporphyrin isomers, I and III. Normally, 75% of the coproporphyrin in urine is isomer III. In urine from DJS patients, total coproporphyrin content is normal, but >80% is isomer I.

Rotor Syndrome (RS)

This benign, autosomal recessive disorder is clinically similar to DJS, although it is seen even less frequently. The liver in patients with RS has no increased pigmentation and appears totally normal. The only abnormality in routine laboratory tests is an elevation of total serum bilirubin, due to a predominant rise in conjugated bilirubin. This is accompanied by bilirubinuria. In RS, the gallbladder is usually visualized on oral cholecystography, in contrast to the nonvisualization that is typical of DJS. Total urinary coproporphyrin excretion is increased in RS, in contrast to the normal levels seen in DJS. Although the fraction of coproporphyrin I in urine is elevated, it is usually <70% of the total, compared with ≥80% in DJS. Although clearance of BSP from plasma is delayed in RS, there is no reflux of conjugated BSP back into the circulation as seen in DJS. Recent studies indicate that the molecular basis of RS results from simultaneous deficiency of the hepatocyte plasma membrane transporters OATP1B1 (SLCO1B1) and OATP1B3 (SLCO1B3). This results in reduced reuptake by these transporters of conjugated bilirubin that has been pumped out of the hepatocyte into the portal circulation by MRP3 (ABCC3).

Benign Recurrent Intrahepatic Cholestasis (BRIC)

This rare disorder is characterized by recurrent attacks of pruritus and jaundice. The typical episode begins with mild malaise and elevations in serum aminotransferase levels, followed rapidly by rises in alkaline phosphatase and conjugated bilirubin and onset of jaundice and itching. The cholestatic episodes, which may begin in childhood or adulthood, can vary in duration from several weeks to months, followed by a complete clinical and biochemical resolution. Between episodes, physical examination is normal, as are serum levels of bile acids, bilirubin, transaminases, and alkaline phosphatase.

The disorder has an autosomal recessive pattern of inheritance. BRIC is considered a benign disorder in that it does not lead to cirrhosis or end-stage liver disease. However, the episodes of jaundice and pruritus can be prolonged and debilitating, and some patients have undergone liver transplantation to relieve the intractable and disabling symptoms. Treatment during the cholestatic episodes is symptomatic. A gene termed *FIC1* was recently identified and found to be mutated in patients with BRIC. The protein encoded by *FIC1* has been shown to play a role in bile canalicular excretion of various compounds. A second phenotypically identical form of BRIC, termed BRIC type 2, has been described resulting from mutations in the bile salt excretory protein (BSEP), the protein that is defective in progressive familial intrahepatic cholestasis (PFIC) type 2.

Progressive Familial Intrahepatic Cholestasis

This name is applied to three phenotypically related syndromes. PFIC type 1 (Byler's disease) presents in early infancy as cholestasis that may be initially episodic. However, in contrast to BRIC, Byler's disease progresses to malnutrition, growth retardation, and end-stage liver disease during childhood. This disorder is also a consequence of an *FIC1* mutation. PFIC type 2 is associated with a mutation in the protein originally named *sister of P-glycoprotein*, now known as *bile salt excretory protein* (BSEP, ABCB11), which is the major bile canalicular exporter of bile acids. PFIC type 3 has been associated with a mutation of MDR3 (ABCB4), a protein that is essential for normal hepatocellular excretion of phospholipids across the bile canaliculus. Although all three types of PFIC have similar clinical phenotypes, only type 3 is associated with high serum levels of γ-glutamyl transferase (GGT) activity. In contrast, activity of this enzyme is normal or only mildly elevated in symptomatic BRIC and PFIC types 1 and 2.

Table 3. Principal Differential Characteristics of Inheritable Disorders of Bile Canalicular Function

	DJS	ROTOR	PFIC1	BRIC1	PFIC2	BRIC2	PFIC3
Gene **Protein** **Cholestasis**	*ABCCA* MRP2 No	*SLCO1B1/SLCO1B3* OATP1B1/1B3 No	*ATP8B1* FIC1 Yes	*ATP8B1* FIC1 Episodic	*ABCB11* BSEP Yes	*ABCB11* BSEP Episodic	*ABCB4* MDR3 Yes
Serum GGT **Serum bile Acids**	Normal Normal	Normal Normal	Normal ↑↑	Normal ↑↑ during Episodes	Normal ↑↑	Normal ↑↑ during episodes	↑↑ ↑↑
Clinical Features	Mild conjugated hyperbilirubinemia; otherwise, normal liver function; dark pigment in liver; characteristic pattern of urinary coproporphyrins	Mild conjugated hyperbilirubinemia; otherwise, normal liver function; liver without abnormal pigmentation	Severe cholestasis beginning in childhood	Recurrent episodes of cholestasis beginning at any age	Severe cholestasis beginning in childhood	Recurrent episodes of cholestasis beginning at any age	Severe cholestasis beginning in childhood; decreased phospholipids in bile

Abbreviations: BRIC, benign recurrent intrahepatic cholestasis; BSEP, bile salt excretory protein; DJS, Dubin-Johnson syndrome; GGT, γ-glutamyl transferase; MRP2, multidrug resistance–associated protein 2; OATP1A/1B, organic anion transport proteins 1B1 and 1B3; PFIC, progressive familial intrahepatic cholestasis; ↑↑, increased.

Case 1.

A 16-year-old boy came to hospital for yellowish discolouration of skin, vomiting and frequent tonsillitis. His mother told that the boy was jaundiced since birth. On further inquiry, his paternal cousin (18 years old) and grandparents of both affected individuals have the same condition. In addition, the parents of the patient were first cousins.

Total serum bilirubin was 18.2 mg/dL (unconjugated bilirubin 17.7 mg/dL), SGOT 22 U/L (normal <38 U/L), SGPT 24 U/L (normal <40 U/L), GGT 17 U/L (normal 49 U/L), ALP 21.2 U/L (normal <500 U/L). The HBsAg and anti-hepatitis C virus HCV antibody were negative. The ultrasonography indicated normal liver with no biliary obstruction.

Q 1.1. What is the most likely diagnosis?

A. Crigler-Najjar Syndrome-I

B. Crigler-Najjar Syndrome-II

C. Gilbert syndrome

D. Rotor syndrome

Answer. B. Crigler-Najjar Syndrome-II

Discussion

This patient has history of jaundice since birth with family history suggestive of hereditary hyperbilirubinemia. He has unconjugated hyperbilirubinemia. Among the above listed options Rotor syndrome can not be the answer as it causes conjugated hyperbilirubinemia. On the basis of clinical history, examination and laboratory findings, CN-II and Gilbert syndrome is suspected.

Q 1.2. What further investigations are required to confirm diagnosis?

A. Genetic and enzyme studies

B. CT abdomen

C. Fibroscan

D. Coombs test

To confirm diagnosis UGT1 gene analysis and UGT1A1 enzyme activity test is required.

Management

For the treatment of Crigler-Najjar Syndrome-II Phenobarbital is given. In this patient phenobarbital 30 mg BD was given. His LFTs were repeated after regular intervals and the unconjugated bilirubin level reduced to 10.2 mg/dL within one month. The patient was advised to follow up after four weeks and was discharged after proper genetic and lifestyle counselling.

Case 2.

A 23-year-old male presented to medicine OPD with jaundice. The jaundice was preceded by a period of stress related to an exam he had 4 days earlier. He did not have vomiting, abdominal pain, diarrhoea, or alteration of mental status.

On further enquiry it was revealed that he had repeated episodes of jaundice over the last five years. On average, he had 5 episodes of jaundice in a year and episodes were associated with a period of stress or intercurrent illnesses. The last three episodes of jaundice were triggered by an upper respiratory tract infection. He had normal abdominal examination.

His CBC showed a hemoglobin of 14 gm/dl with an MCV of 82 fl. WBC count was normal and the platelet count was 211,000. There was no feature of hemolysis, and the LDH was 132 IU/l (normal range up to 248 IU/l). The Alanine Transaminase (ALT) was 20 IU/l and the Aspartate transaminase (AST) was 23 IU/L (normal up to 30 IU/l) and the alkaline phosphatase was 78 IU/l (normal up to 150 mg/dl). Both Hepatitis B surface antigen and Anti Hepatitis C antibody were negative. The total bilirubin was 3.8 mg/dl (Normal < 1.0 mg/dl), and from this, the conjugated (Direct) bilirubin fraction was only 0.2 mg/dl.

Q 2.1. What is the most likely diagnosis?

A. Crigler-Najjar Syndrome
B. Gilbert's syndrome
C. Hepatitis
D. Hemolysis

Answer. B. Gilbert's syndrome

Discussion

This patient has history of recurrent episodes of jaundice precipitated by some illness or stress. There is unconjugated hyperbilirubinemia. This patient's liver enzymes i.e. SGOT and SGPT are within normal range so hepatitis is ruled out. There is no evidence of hemolysis and LDH is in normal range so hemolysis cannot be the answer. Crigler-Najjar Syndromeusually have total bilirubin >20 mg/dl and this patient's total bilirubin is 3.8 mg/dl, so the possible diagnosis in this case is Gilbert's syndrome.

Q 2.2. What further investigations are required to confirm diagnosis?

Genetic and enzyme studies are required to confirm the diagnosis

Management

Symptomatic treatment is given for Gilbert's syndrome. Genetic and lifestyle counselling is needed for further management of Gilbert's syndrome. This patient was advised to avoid stressful conditions and prolonged fasting.

Case 3.

A 14-year-old girl presented with yellowish discolouration of eyes and palms and loss of appetite associated with weight loss for the past 6 months. She also reported easy fatiguability for the past 2 weeks. She had no history of abdominal pain, pale stools or bone pain. She had no history of substance abuse, blood transfusions or drug intake. She attained menarche 3 years back and had no menstrual complaints. Parents reported that she has been on a vegetarian diet. Her birth history, developmental history and family history were unremarkable. She had a body mass index (BMI) of 14.6 kg/m^2, and physical examination showed icterus, mild pallor, normal liver span and no splenomegaly. Respiratory, cardiovascular and central nervous system examination was normal. The ophthalmic evaluation did not reveal Kayser-Fleischer rings.

Q 3.1. What is the most likely diagnosis?

A. Crigler-Najjar Syndrome

B. Gilbert's syndrome

C. Hepatitis

D. Hemolytic jaundice

Answer. D. Hemolytic jaundice

Discussion

This patient has anaemia with jaundice. Among the above available options hemolytic jaundice is the only condition in which anaemia with jaundice is seen.

Q 3.2. What further investigations are required to confirm diagnosis?

In this case to find out the cause of anaemia with jaundice; CBC, Peripheral smear, LFT, LDH, iron profile, B12 levels, Folate levels, HBsAg and HCV are required.

This patient had anaemia (haemoglobin: 9.1 g/dL; haematocrit: 27.8%), decreased red blood cell (RBC) count (2.15×10^{12}/ L), increased red cell volume (mean corpuscular volume 117.4 fL), elevated red cell distribution width (17.2%), reticulocytosis (2.43 %), elevated lactate dehydrogenase (LDH; 764 IU/L), elevated unconjugated bilirubin (total bilirubin: 6.5 mg/dL, direct bilirubin: 0.5 mg/dL) and normal liver enzymes.

There is unconjugated hyperbilirubinemia and MCV & RDW is elevated. Peripheral smear showed macrocytosis, occasional spherocytes, predominant neutrophil count (78%) with hyper-segmented forms and other cell lines in normal limits. Folate levels, iron studies,HBsAg and HCV were normal. Serum vitamin B_{12} assay showed very low levels (25 pg/mL), confirming the diagnosis of Macrocytic anaemia caused by vitamin B12 deficiency.

Management

In patients who are deficient due to a strict vegan diet, an oral supplement of B12 is adequate for repletion. In this patient Repeat investigations, after 6 months of oral therapy with vitamin B_{12} (1500 µg/day) persisted to show macrocytosis, hyper-segmented neutrophils unconjugated bilirubinaemia, normal haemoglobin and improving vitamin B_{12} levels (75.2 pg/mL).

Investigations done 10 months after initial presentation showed haemoglobin, reticulocyte count, bilirubin, LDH and serum vitamin B_{12} within normal limits. Peripheral smear showed a normal morphology of neutrophils and RBCs.

With cobalamin therapy and dietary changes, she reported improvement in activity and appetite and a weight gain of 8 kg. Her BMI increased from 14.6 to 17.2 kg/m^2. Her jaundice resolved and she is under regular follow-up.

People who are strict vegetarians and, most particularly, people who do not consume eggs, milk, or meat can develop cobalamin deficiency. Counsel these people to either change their dietary habits or remain on supplementary vitamin B-12 therapy for their lifetime. An oral tablet of 100-200 µg taken weekly should provide adequate therapy.

CHAPTER
4

COMMON CAUSES OF HEPATOCELLULAR JAUNDICE AND THEIR MANAGEMENT (REAL LIFE CASE BASED APPROACH)

AUTHOR : SATISH KUMAR

INTRODUCTION

In hepatocellular (or intrahepatic) jaundice, there is dysfunction of the hepatic cells. The liver looses the ability to conjugate bilirubin, but in cases where it also may become cirrhotic, it compresses the intrahepatic portions of the billiary tree to cause a degree of destruction. This leads to both unconjugated and conjugated bilirubin in the blood, termed as mixed picture.[1]

Diagnostic Evaluation of Hepatocellular Jaundice

Hepatocellular diseases that can cause jaundice include viral hepatitis, drug or environmental toxicity, alcohol, and end-stage cirrhosis from any cause (Table 1).

Wilson's disease occurs primarily in young adults. Autoimmune hepatitis is typically seen in young to middle-aged women but may affect men and women of any age. Alcoholic hepatitis can be differentiated from viral and toxin-related hepatitis by the pattern of the aminotransferases: patients with alcoholic hepatitis typically have an AST-to-ALT ratio of at least 2:1, and the AST level rarely exceeds 300 U/L. Acute viral hepatitis and toxin-related injury patients have severe enough to produce jaundice typically have aminotransferase levels >500 U/L, with the ALT greater than or equal to the AST. While ALT and AST values <8 times of normal may be seen in either hepatocellular or cholestatic liver disease, values 25 times normal or higher are seen in primarily in acute hepatocellular diseases.

Cirrhotic patients with jaundice can have normal or only slightly elevated aminotransferases levels.

When the clinician determines that a patient has a hepatocellular disease, appropriate testing for acute viral hepatitis includes a hepatitis A IgM antibody assay, a hepatitis B surface antigen and core IgM antibody assay, a hepatitis C viral RNA test, and, depending on circumstances, a hepatitis E IgM antibody assay. Because it can take many weeks for hepatitis C antibody to become detectable, its assay is an unreliable test if acute hepatitis C is suspected.Studies for hepatitis D and E viruses, Epstein Barr Virus(EBV), and cytomegalovirus (CMV) may also be indicated.

Ceruloplasmin is the initial screening test for the Wilson disease. Testing for autoimmune hepatitis usually includes an antinuclear antibody assay (ANA)and measurement of specific immunoglobulins.

Drug induced hepatocellular injury can be classified as either predictable or unpredictable. Predictable drug reactions are dose dependent and affects all patients who ingest a toxic dose of the drug in question. The classic example is acetaminophen hepatotoxicity. Unpredictable or idiosyncratic drug reactions are not dose dependent and occur in minority of patients. A great number of drugs can cause idiosyncratic hepatic injury.

Environmental toxins are also important cause of hepatocellular injury. Example includes industrial chemicals as vinyl chloride, herbal preparations containing pyrrolizidine alkaloids (Jamaica bush tea) or Kava, and the mushrooms Amanita phalloides and A. Verna, which contain highly hepatotoxic amatoxins.

Laboratory tests-

A battery of tests are helpful in the initial evaluation of a patient with unexplained jaundice. These include total and direct serum bilirubin measurement with fractionation; determination of serum aminotransferase, alkaline phosphatase, and albumin concentrations; and prothrombin time tests. Enzyme tests (alanine

aminotransferase [ALT], aspartate aminotransferase [AST], and alkaline phosphatase [ALP]) are helpful in differentiating between a hepatocellular process and a cholestatic process. Patients with a hepatocellular process generally have a rise in the aminotransferases that is disproportionate to that in ALP, whereas patients with a cholestatic process have a rise in ALP that is disproportionate to that of the aminotransferases. The serum bilirubin can be prominently elevated in both hepatocellular and cholestatic conditions and therefore is not necessarily helpful in differentiating between the two. In addition to enzyme tests, all jaundiced patients should have additional blood tests—specifically, an albumin level and a prothrombin time—to assess liver function. A low albumin level suggests a chronic process such as cirrhosis or cancer. A normal albumin level is suggestive of a more acute process such as viral hepatitis or choledocholithiasis. An elevated prothrombin time indicates either vitamin K deficiency due to prolonged jaundice and malabsorption of vitamin K or significant hepatocellular dysfunction. The failure of the prothrombin time to correct with parenteral administration of vitamin K indicates severe hepatocellular injury. The results of the bilirubin, enzyme, albumin, and prothrombin time tests will usually indicate whether a jaundiced patient has a hepatocellular or a cholestatic disease and offer some indication of the duration and severity of the disease. The causes and evaluations of hepatocellular and cholestatic diseases are quite different.

Treatment of Hepatocellular Jaundice-

It depends on individual aetiology. Glimpses of specific treatment are given in table 1.

SN	Common causes of hepatocellular Jaundice	Diagnostic investigations	Specific treatment
1	Viral hepatitisHepatitis A, B, C, D, and E	Hepatitis A and E IgM antibodies, HBsAg, HBV DNA for HBV, Anti HCV antibody, HCV RNA for HCV	Antiviral drugs for hepatitis B (Tenofovir, entecavir, interferon,), and C (Sofosbuvir, Velpatasvir, Daclatasvir). Hepatitis A and E are self resolving and needs symptomatic treatment.
2	Epstein-Barr virus, Cytomegalovirus,Herpes simplex virus, Varicella zoster virus	RT-PCR for detection viral RNA	
3	Alcoholic hepatitis	Clinical SGOT>SGPT	Abstinence from alcohol, liver supportives (nutrition and steroids), liver transplantation
4	Chronic liver disease and cirrhosis	USG abdomen, fibroscan, UGI endoscopy etc.	Treatment as per aetiology, Liver transplantation
5	Drug toxicity	Clinical	Drug withdrwal
5a	Predictable, dose-dependent (e.g., acetaminophen)	Clinical	Dose reduction or withdrawl
5b	Unpredictable, idiosyncratic (e.g., isoniazid)	Clinical	Dose reduction or withdrawl
6	Environmental toxins Vinyl chloride Jamaica bush tea—pyrrolizidine alkaloids Kava Kava Wild mushrooms—*Amanita phalloides, A. Verna, Giloy*	Clinical	Agent withdrwal
7	Wilson's disease	KF Ring, S. ceruloplasmin, 24 hr urinary copper, liver biopsy	Chelating agents like Penicillamine, Zinc (Cuprimine, Depen)
8	Autoimmune hepatitis	Smooth muscle antibodies (SMA), antinuclear antibodies (ANA), and antibodies to liver kidney microsome type 1 (anti-LKM1)	Immunosuppresants like steroids (prednisone), azathioprine (steroid-sparing agent) , Mycophenolate mofetil, liver transplantation

Real life scenarios

CASE SCENARIO 1-

A male in his early 30s, presented to the Emergency Department with the chief complaint of yellowing of his skin and typically white sclera of his eyes. This was preceded by five days of progressive fatigue and flu-like symptoms. He admit to current HIV prophylaxis medication for the reason of "being smart (multiple sex partners)." He did admit to previous intravenous drug use with last administration three years prior. He also has produced several tan-colored bowel movements, dark urine, subjective fevers, and nausea.

Negative history-He denied any abdominal pain, vomiting, diarrhea, hematuria, or rashes.

He also denied having completed any recent travel, insect or chemical exposures, or any known sick contacts and any previous surgery.

Physical examination revealed a well-nourished, diffusely jaundiced male in no acute distress. The patient was alert and oriented and answering all questions appropriately, albeit with short answers.

Laboratory evaluation- showed thrombocytopenia (88,000), hyperbilirubinemia (9.2 mg/dL, direct 6.4 mg/dl), transaminasemia (2238 U/L and 3806 U/L), and elevated PT-INR (i.e., prothrombin time-international normalized ratio) of 15.9 sec/1.54.

Radiological investigations- CT of the abdomen showed gall bladder contraction with wall edema and mucosal hyper-enhancement. No gallstones were identified and the liver, common bile duct and pancreas were all within normal limits.

QUIZ-

Q 1. What is your probable diagnosis?

A. Acute Viral Hepatitis

B. Alcoholic hepatitis

C. Bacterial septic hepatitis

D. Choledocholithiasis

Answer-

D/D-The differential diagnosis includes bacterial, viral, fungal, parasitic, and alcoholic hepatitis.Also included are causes of extra-hepatic obstruction such as cholelithiasis, cholecystitis, choledocholithiasis, and malignancy of the biliary and pancreatic tissue.

Diagnosis- Acute Viral Hepatitis

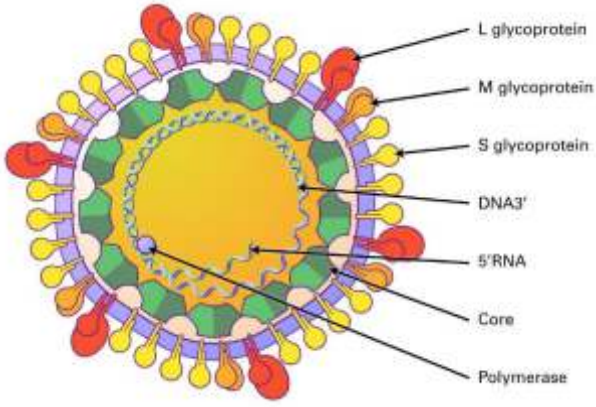


Figure 1. Schematic structure of Hepatitis A virus

Acute viral hepatitis is inflammation of the liver, generally meaning inflammation caused by infection with one of the five hepatitis viruses (A,B,C,D,E). In most people, the inflammation begins suddenly and lasts only a few weeks. The hepatitis A virus is the most common cause of acute hepatitis in adults, followed by the hepatitis B virus.

Engaging in certain activities, such as getting a tattoo or body piercing, sharing needles to inject drugs, or having multiple sex partners, increases the risk of developing hepatitis.

All forms of viral hepatitis present with similar symptoms, (jaundice, fever, abdominal pain, nausea, and fatigue) they are also different in many ways.

Definitive studies for acute HAV (as well as HBV and HCV) can be obtained through a viral hepatitis panel. Acute HAV is indicated by positive Anti-HAV IgM whereas IgG indicates past exposure

Q 2.How will you manage this case??

Management-

Management of acute HAV includes IV fluids and electrolyte correction, anti-emetics, and avoidance of hepatotoxic medications (e.g., acetaminophen and ciprofloxacin) and alcohol intake. Antiviral and antibiotic medications are not indicated in uncomplicated acute HAV.

As hepatitis A and hepatitis E viruses (HAV and HEV) are both transmitted by enteric, that is digestive or by fecal, routes (fecal-oral route), patients should be instructed on strict hand hygiene and those working in the food industry should delay return to work until their jaundice has resolved. The HAV vaccine should be given.

Hepatitis B

Inflammation of the liver where transmission is most commonly spread through sexual contact, injection drug use, or any exposure to infected blood or body fluids.

Acute HBV infection typically resolves, but in around 2% of cases, infection progresses to fulminant hepatitis, which has a case fatality rate of 63% to 93%. [2]

People with a compromised immune system are at elevated risk of developing chronic infection.However, the transmission and development of hepatitis B can be prevented through vaccine.

Management-

Acute infection— meaning it is short lived and will go away on its own — you may not need treatment. Instead, your provider might recommend rest, proper nutrition, plenty of fluids and close monitoring while your body fights the infection. In severe cases, antiviral drugs or a hospital stay is needed to prevent complications.

Chronic infection-Antiviral drug (entecavir (Baraclude), tenofovir (Viread), lamivudine (Epivir), adefovir (Hepsera) and telbivudine), Interferon alfa-2b (Intron A), liver transplantation and other supportive management.

Hepatitis C:

Inflammation of the liver where transmission is primarily through injection drug use, while sexual transmission is rare but the likelihood increases with the number of sexual partners and co-infections with HIV.

The disease progresses from an acute stage to a chronic stage around 70% of the time. But hepatitis C rarely causes acute hepatitis.

Management- After getting viral load and genotype of the HCV, antiviral drugs (Sofosubuvir 400, Daclatasvir 60, Velpatasvir 100 etc) are given for three to six month.

Hepatitis D-

Hepatitis D virus (HDV) is a virus that requires hepatitis B virus (HBV) for its replication.

Hepatitis D virus (HDV) affects globally nearly 5% of people who have a chronic infection with hepatitis B virus (HBV).Broken skin (via injection, tattooing etc.) or through contact with infected blood or blood products infection spreads.

The combination of HDV and HBV infection is considered the most severe form.

Hepatitis D infection can be prevented by hepatitis B immunization, but treatment success rates are low.

HEPATITIS E-Fecal-oral route transmission, principally via contaminated water.

A vaccine to prevent hepatitis E virus infection has been developed and is licensed in China, but is not yet available elsewhere.

· There is no specific treatment capable of altering the course of acute hepatitis E. As the disease is usually self-limiting, hospitalization is generally not required. Hospitalization is required for people with fulminant hepatitis and should also be considered for symptomatic pregnant women.

CASE SCENARIO 2-

A 50-year-old man presented at a local hospital with a fever, loss of appetite, and watery diarrhoea (more than 10 times per day) in August 2022. He had been a heavy drinker for about 10 years, and he consumed approximately 250 g of alcohol per day in the previous 6 mo. On admission, laboratory data showed a significant increase in the WBC count [WBC, 17280/μL (neutrophils 82.4%)], C-reactive protein level (CRP, 3.97 mg/dL), total bilirubin level (T.bil, 8.0 mg/dL), SGOT 3000 U/L, SGPT 1500 U/L, SALP 1000 U/L and PT (55%).Enhanced computed tomography (CT) image showed marked hepatomegaly with severe steatosis, splenomegaly, and a diffuse, edematous colon.

QUIZ-

Q. 1-What is your probable diagnosis?

A. Alcoholic hepatitis

B. Viral hepatitis

C. Chronic alcoholic liver disease

D. Autoimmune hepatitis

Reply-Alcoholic hepatitis- is a clinical syndrome characterized by a fever, jaundice, and liver failure after chronic alcohol consumption.[3,4]. A significant increase in the WBC count and serum levels of endotoxin and pro-inflammatory cytokines (*e.g.*, IL-6, IL-8, and TNF-α) is common in cases of severe alcoholic hepatitis. SGOT to SGPT ratio is 2:1. SGOT rarely exceeds 300 U/L.

Q 2.How will you manage this case??

Management

Abstinence from alcohol, nutrition therapy, liver supportives, antibiotics *etc*., are initial treatments for severe AH. However, severe AH still has a high mortality, because no effective treatment has been established.

Rifaximine a product of rifampicin (1st line ATT), L-Orginine L-Arthinine (LOLA), lactulose, probiotics, high bowel wash, faecal transplantationetc. are used for hepatic encephalopathy.

Maddrey Modified Discriminant factor -(MDF) score > 32 (DF= (4.6 × PT prolongation) + total serum billirubin in mg/dL.) and/or encephalopathy indicates a very poor prognosis, and the reported 28-d mortality rate ranges from 34%-40%.

Prednisolone 32mg p.o. daily for 4 weeks, then taper for 4 weeks or pentoxiphylline 400 mg p.o. TID for 4 weeks is used. The complications of acute renal failure and sepsis are significant poor prognostic factors.

Hepatorenal syndrome can be managed by albumin, terlipressin or by haemodialysis. Various complications of AH are managed by different ways. But liver transplantation is whole and sole treatment. In our case, the patient presented with a significantly increased WBC count, jaundice, marked hepatomegaly, and ascites, and liver failure progressed to acute renal failure and infectious enteritis (ACLF with complications).

Considering his MDF score, we predicted that his prognosis would be very poor and needs liver transplantation.

CONCLUSION- Upto 40% patients with severe alcoholic hepatitis die within 6 months of onset of clinical syndromes. Alcoholic liver disease and alcoholic hepatitis is increasing in India. Early diagnosis and treatment can prevent development of cirrhosis and decompensation. Abstinence is the key factor in the mangement of alcoholic hepatitis.

CASE SCENARIO 3-

A 31-year-old female patient came with arthralgia and skin lesion, provisional diagnosis of systemic lupus erythematosus was made. She developed seizures and was hospitalized. She had hydrocephalus on computed tomography scan and pulmonary infiltrates were seen on chest X-ray and was started on ATT empirically in view of tuberculous meningitis (TBM). After 3 weeks, patient developed yellowish discolouration of eyes and urine with deranged liver profile SGOT-320 U/L, SGPT 137 U/L, and total bilirubin/direct bilirubin 3.3/3.1 mg/dl. Viral markers were negative.

QUIZ-

Q.1-What is your probable diagnosis?

A. Drug induced hepatitis/drug toxicity

B. Autoimmune hepatitis

C. Acute viral hepatitis

D. Environmental toxins

R**eply-Drug induced acute hepatitis (ATT induced)**

This is suspected case of central nervous system (CNS) TB with ATT induced hepatitis (SGOT increased to 5 times upper normal limits and increased bilirubin).

Antituberculosis drug (ATT)-inducible cytochrome P-4502E1 (CYP2E1) is constitutively expressed in the liver. Recent studies show that polymorphism of the N-acetyltransferase 2 (NAT2) genes and glutathione-S-transferase (GST) are the major susceptibility risk factors for ATT-induced hepatitis.

Drug-induced liver injury (DILI) is one of the most important reasons for discontinuation of drugs and treatment failures.

Drug-induced liver injury (DILI) secondary to antituberculous treatment (ATT) is reported in 2–28% of patients varying with the definition, study population and treatment regimen.

Risk factors associated with this potentially fatal complication include co-infection with HIV, hepatitis B or C, pre-existing chronic liver disease, high alcohol intake, malnutrition, advanced age, female sex and slow acetylators.

Q.2.-How will you manage this case??

Management

According to British Thoracic Society guidelines for CNS TB 2009, in such cases, pyrazinamide may be withdrawn, but in this case as bilirubin is elevated, rifampicin also may be stopped. The patient should be started on isoniazid, ethambutol, and amikacin. Liver function tests should be monitored daily and rechallenge be started with rifampicin, once SGOT is normalised.

CHAPTER
5

CHOLESTATIC JAUNDICE

AUTHOR : AMIT KUMAR

Introduction

Cholestatic jaundice is defined as predominant increase in alkaline phosphate and gmma glutamyl transpetidasse (GGT) in out proportion to transaminases alongwith rise in serum bilirubin. This may be caused by either extrahepatic biliary tree obstruction or intrahepatic obtruction of biliary canaliculi or failure to secrete conjugated bilirubin in biliary canaliculi from hepatocytes.

Diagnostic evaluation of cholestatic jaundice

When the pattern of the liver tests suggests a cholestatic disorder, the first step is to determine whether it is intra- or extrahepatic cholestasis (Table - 1). Distinguishing intrahepatic from extrahepatic cholestasis may be difficult. History, physical examination, and laboratory tests often are not helpful. The next appropriate test is an ultrasound. The ultrasound is inexpensive, does not expose the patient to ionizing radiation, and can detect dilation of the intra- and extrahepatic biliary tree with a high degree of sensitivity and specificity. The absence of biliary dilation suggests intrahepatic cholestasis, while its presence indicates extrahepatic cholestasis. False-negative results occur in patients withpartial obstruction of the common bile duct or in patients with cirrhosis or primary sclerosing cholangitis (PSC), in which scarring prevents the intrahepatic ducts from dilating.

Although ultrasonography may indicate extrahepatic cholestasis, it rarely identifies the site or cause of obstruction. The distal common bile duct is a particularly difficult area to visualize by ultrasound because of overlying bowel gas.

Appropriate next tests include computed tomography (CT), magnetic resonance cholangiopancreatography (MRCP), endoscopic retrograde cholangiopancreatography (ERCP), percutaneous transhepatic cholangiography (PTC), and endoscopic ultrasound (EUS). CT and MRCP are better than ultrasonography for assessing the head of the pancreas and for identifying choledocholithiasis in the distal common bile duct, particularly when the ducts are not dilated. ERCP is the "gold standard" for identifying choledocholithiasis. Beyond its diagnostic capabilities, ERCP allows therapeutic interventions, including the removal of common bile duct stones and the placement of stents. PTC can provide the same information as ERCP and it also allows for intervention in patients in whom ERCP is unsuccessful due to proximal biliary obstruction or altered gastrointestinal anatomy. MRCP has replaced ERCP as the initial diagnostic test in most cases. EUS displays sensitivity and specificity comparable to that of MRCP in the detection of bile duct obstruction and allows biopsy of suspected malignant lesions.

In patients with apparent *intrahepatic cholestasis*, the diagnosis is often made by serologic testing in combination with a liver biopsy. The list of possible causes of intrahepatic cholestasis is long and varied (Table – 1). A number of conditions that typically cause a hepatocellular pattern of injury can also present as a cholestatic variant. Both hepatitis B and C viruses can cause cholestatic hepatitis (fibrosing cholestatic hepatitis). This disease variant has been reported in patients who have undergone solid organ transplantation. Hepatitis A and E, alcoholic hepatitis, and EBV or CMV infections may also present as cholestatic liver disease.

Drugs may cause intrahepatic cholestasis that is usually reversible after discontinuation of the offending agent, although it may take many months for cholestasis to resolve. Drugs most commonly associated with cholestasis are the anabolic and contraceptive steroids.

Cholestatic hepatitis has been reported with chlorpromazine, imipramine, tolbutamide, sulindac, cimetidine, and erythromycin estolate. It also occurs in patients taking trimethoprim; sulfamethoxazole; and penicillin-based antibiotics such as ampicillin, dicloxacillin, and clavulanic acid. Rarely, cholestasis may be chronic and associated with progressive fibrosis despite early discontinuation of the offending drug. Chronic cholestasis has been associated with chlorpromazine and prochlorperazine.

Primary biliary cholangitis is an autoimmune disease predominantly affecting women and characterized by progressive destruction of interlobular bile ducts. The diagnosis is made by the detection of antimitochondrial antibody, which is found in 95% of patients. *Primary sclerosing cholangitis* is characterized by the destruction and fibrosis of larger bile ducts. The diagnosis of PSC is made with cholangiography (either MRCP or ERCP), which demonstrates the pathognomonic segmental strictures. Approximately 75% of patients with PSC also have inflammatory bowel disease.

The *vanishing bile duct syndrome* and *adult bile ductopenia* are rare conditions in which a decreased number of bile ducts are seen in liver biopsy specimens. This histologic picture is also seen in patients who develop chronic rejection after liver transplantation and in those who develop graft-versus-host disease after bone marrow transplantation. Vanishing bile duct syndrome also occurs in rare cases of sarcoidosis, in patients taking certain drugs (including chlorpromazine), and idiopathically.

There are also familial forms of intrahepatic cholestasis. The familial intrahepatic cholestatic syndromes include *progressive familial intrahepatic cholestasis* (PFIC) *types 1–3* and *benign recurrent intrahepatic cholestasis* (BRIC) *types 1 and 2*. BRIC is characterizedby episodic attacks of pruritus, cholestasis, and jaundice beginning at any age, which can be debilitating but does not lead to chronic liver disease.

Serum bile acids are elevated during episodes, but serum γ-glutamyltransferase (γ-GT) activity is normal. PFIC disorders begin at childhood and are progressive in nature. All three types of PFIC are associated with progressive cholestasis, elevated levels of serum bile acids, and similar phenotypes but different genetic mutations. Only type 3 PFIC is associated with high levels of γ-GT. *Cholestasis of pregnancy* occurs in the second and third trimesters and resolves after delivery. Its cause is unknown, but the condition is probably inherited, and cholestasis can be triggered by estrogen administration.

Other causes of intrahepatic cholestasis include total parenteral nutrition (TPN); nonhepatobiliary sepsis; benign postoperative cholestasis; and a paraneoplastic syndrome associated with a number of different malignancies, including Hodgkin's disease, medullary thyroid cancer, renal cell cancer, renal sarcoma, T-cell lymphoma, prostate cancer, and several gastrointestinal malignancies. The term *Stauffer's syndrome* has been used for intrahepatic cholestasis specifically associated with renal cell cancer. In patients developing cholestasis in the intensive care unit, the major considerations should be sepsis, ischemic hepatitis (“shock liver”), and TPN-related jaundice. Jaundice occurring after bone marrow transplantation is most likely due to veno-occlusive disease or graftversus-host disease. In addition to hemolysis, sickle cell disease may cause intrahepatic and extrahepatic cholestasis. Jaundice is a late finding in heart failure caused by hepatic congestion and hepatocellular hypoxia. Ischemic hepatitis is a distinct entity of acute hypoperfusion characterized by an acute and dramatic elevation in the serum aminotransferases followed by a gradual peak in serum bilirubin.

Jaundice with associated liver dysfunction can be seen in severe cases of *Plasmodium falciparum* malaria. The jaundice in these cases

is due to a combination of indirect hyperbilirubinemia from hemolysis and both cholestatic and hepatocellular jaundice. Weil's disease, a severe presentation of leptospirosis, is marked by jaundice with renal failure, fever, headache, and muscle pain.

Causes of *extrahepatic cholestasis* can be split into malignant and benign (Table - 1). Malignant causes include pancreatic, gallbladder, and ampullary cancers as well as cholangiocarcinoma. This last malignancy is most commonly associated with PSC and is exceptionally difficult to diagnose because its appearance is often identical to that of PSC. Pancreatic and gallbladder tumors as well as cholangiocarcinoma are rarely resectable and have poor prognoses. Ampullary carcinoma has the highest surgical cure rate of all the tumors that present as painless jaundice. Hilar lymphadenopathy due to metastases from other cancers may cause obstruction of the extrahepatic biliary tree.

Choledocholithiasis is the most common cause of extrahepatic cholestasis. The clinical presentation can range from mild rightupper-quadrant discomfort with only minimal elevations of enzyme test values to ascending cholangitis with jaundice, sepsis, and circulatory collapse. PSC may occur with clinically important strictures limited to the extrahepatic biliary tree. IgG4-associated cholangitis is marked by stricturing of the biliary tree. It is critical that the clinician differentiate this condition from PSC as it is responsive to glucocorticoid therapy. In rare instances, chronic pancreatitis causes strictures of the distal common bile duct, where it passes through the head of the pancreas. AIDS cholangiopathy is a condition that is usually due to infection of the bile duct epithelium with CMV or cryptosporidia and has a cholangiographic appearance similar to that of PSC. The affected patients usually present with greatly elevated serum alkaline phosphatase levels (mean, 800 IU/L), but the bilirubin level is often near normal. These patients do not typically present with jaundice.condition is probably inherited, and cholestasis can be triggered by estrogen administration.

GLOBAL CONSIDERATIONS

While extrahepatic biliary obstruction and drugs are common causes of new-onset jaundice in developed countries, infections remain the leading cause in developing countries. Liver involvement and jaundice are observed with numerous infections, particularly malaria, babesiosis, severe leptospirosis, infections due to *Mycobacterium tuberculosis* and the *Mycobacterium avium* complex, typhoid fever, infection with hepatitis viruses A–E, EBV, CMV, viral hemorrhagic fevers including Ebola virus, late phases of yellow fever, dengue fever, schistosomiasis, fascioliasis, clonorchiasis, opisthorchiasis, ascariasis, echinococcosis, hepatosplenic candidiasis, disseminated histoplasmosis, cryptococcosis, coccidioimycosis, ehrlichiosis, chronic Q fever, yersiniosis,brucellosis, syphilis, and leprosy. Bacterial infections that do not necessarily involve the liver and bile ducts may also lead to jaundice, as in cholestasis of sepsis. The presence of fever or abdominal pain suggests concurrent infection, sepsis, or complications from gallstones. The development of encephalopathy and coagulopathy in a jaundiced patient with no preexisting liver disease signifies acute liver failure, which warrants urgent liver transplant evaluation.

Treatment of cholestatic jaundice

Specific treatment

It depends on individual etiology. Glimpses of specific treatment are given in table 2.

Symptomatic treatment

Cholestatic jaundice patient may have intense pruritus. They need antistaminics (hydroxyzine, cetrizine, fexofenadine etc.), ursodeoxycholic caid, cholestyramine or cholestipol for control of jaundice.

Table 1. **Diagnostic investigations and specific treatment for common causes of cholestatic jaundice**

Common causes of cholestatic jaundice	**Diagnostic investigations**	**Specific treatment**
I. **Intrahepatic**		
A. **Viral hepatitis**		
1. Fibrosing cholestatic hepatitis— Hepatitis A, hepatitis B and C	IgM antibody for HAV, HBsAg, HBV DNA for HBV, anti-HCV antibody, HCV RNA for HCV	Antiviral drugs (e.g. Tenofovir entecavir for HBV and Sofosbuvir, Velpatasvir, Daclatasvir for HCV)
2. Epstein-Barr virus infection, cytomegalovirus infection	RT-PCR for detection viral RNA	Ganciclovir or Valganciclovir
B. **Alcoholic hepatitis**	Clinical SGOT> SGPT	Abstinence from alcohol , liver supportives (nutrition and steroids) Liver transplantation
C. **Drug toxicity**	Clinical	Drug withdrawal
1. Pure cholestasis—anabolic and contraceptive steroids	Clinical	Dose reduction or withdrawal
2. Cholestatic hepatitis—	Clinical	Dose reduction or

chlorpromazine, erythromycin estolate		withdrawal
3. Chronic cholestasis—chlorpromazine and prochlorperazine	Clinical	Dose reduction or withdrawal
D. **Primary biliary cholangitis**	Clinical AMA ,ANA	UDCA and liver transplantation
E. **Primary sclerosing cholangitis**	Clinical ERCP/MRCP	Liver transplantation
F. **Vanishing bile duct syndrome**	Clinical, Liver biopsy	Liver transplantation
1. Chronic rejection of liver transplants		Liver transplantation
2. Sarcoidosis	Clinical, S.ACE,	Steroids, Liver transplantation
3. Drugs	Clinical	Dose reduction and withdrawal
G. **Congestive hepatopathy and ischemic hepatitis**	Clinical ,ECG, 2 D ECHO, NT -Pro BNP ,SGOT> SGPT	Diuretics, treat underlying heart disease
H. **Inherited conditions**		
1. Progressive familial intrahepatic cholestasis	Clinical	Liver transplantation
2. Benign recurrent intrahepatic cholestasis	Clinical	Symptomatic
I. **Cholestasis of pregnancy**	Clinical	Early termination of pregnancy, Liver transplantation
J. **Total parenteral nutrition**	Clinical	Balanced nutrition
K. **Nonhepatobiliary sepsis**	Clinical	Antibiotics

L. **Benign postoperative cholestasis**	Clinical	Wait and watch
M.**Paraneoplastic syndrome**	Clinical, PET Scan	Individulaised according to secretary product
N. **Veno-occlusive disease**	Clinical	Liver transplant
O. **Graft-versus-host disease**	Clinical	Immunosuppresion, Liver transplant
P. **Infiltrative disease**		
1. Tuberculosis	Clinical, ZN stain for AFB, CBNNAT, Chest x ray, CT abdomen	ATT
2. Lymphoma	Clinical, Bone marrow, Immunophenotyping	Chemotherapy
3. Amyloidosis	Clinical, Liver biopsy	Steroids Liver transplant
Q. **Infections**	Clinical	
1. Malaria	Clinical, MP Blood thick smear	Chloroquin, Artimisinin, Artemether
2. Leptospirosis	Clinical, IgM leptospira	Doxycyclin, Azithromycin and Ceftriaxone
II. **Extrahepatic**		
A. Malignant		
1. Cholangiocarcinoma	CT, MRI/MRCP, PET scan, FNAC/Biopsy, CA 19-9	Surgery ERCP Chemoradiotherapy
2. Pancreatic cancer	CT, MRI/MRCP, PET Scan, Ca 19-9	
3. Gallbladder cancer	UGS, CT, MRI/MRCP , PET	Surgery ERCP

	Scan	Chemoradiotherapy
4. Ampullary cancer	USG, MRI/MRCP, PET Scan	Surgery ERCP
5. Malignant involvement of the porta hepatis lymph nodes	Clinical, CT, MRI, PET Scan	Surgery ERCP
B. **Benign**		
1. Choledocholithiasis	USG, CT, ERCP, MRI/MRCP	Surgery ERCP
2. Postoperative biliary strictures	USG, CT, ERCP/MRCP	Surgery ERCP
3. Primary sclerosing cholangitis	Clinical, ERCP/MRCP	Liver transplantation
4. Chronic pancreatitis	Clinical, S.Amylase , S.Lipase MRCP	Pancreatic enzyme
5. AIDS cholangiopathy	Clinical	ART
6. Mirizzi's syndrome	Clinical	Surgery
7. Parasitic disease (ascariasis)		Antihelminthics

Real life case based scenaios

Case - 1

A 60-year-old man presents with jaundice, 5 kg weight loss, intermittent nausea, and decreased appetite over the last month. He has a history of hypertension, hyperlipidemia, and diabetes. There is no past surgical history. He takes hydrochlorothiazide, simvastatin, and metformin. His BP, cholesterol, and diabetes are under good control. He has drinks three beers each day and smoked half a pack of cigarettes per day for the last 40 years. He has no abdominal pain, but he has noticed that his stools have become lighter in color and his urine has become tea-colored. He presents in the outpatient office accompanied by his wife and three of his children, who have urged him to seek medical attention.

Quiz 1.1. What should be the best differential diagnosis?

1. Obstructive jaundice

2. Gall bladder cancer with extrahepaic cholestatic jaundice

3. Viral hepatitis

4. Periampullary cancer with extrahepaic cholestatic jaundice

Differential Diagnosis

Hepatocellular Causes	**Extrahepatic/Obstructive Causes**
Viral hepatitis	Choledocholithiasis
Alcoholic hepatitis	Cholangitis
Drug-induced hepatitis	Benign stricture
Cirrhosis	Pancreatic adenocarcinoma

Speaking Intelligently

When asked to see an older patient with jaundice, we worry about cancer. A helpful start in patients with this clinical presentation is to decide whether the cause is hepatocellular or obstructive. These two categories serve as a useful framework to think about elevated serum bilirubin levels. Treatment of hepatocellular causes is generally supportive, while treatment of obstructive causes is with endoscopy or surgery. History taking allows to create a diagnostic hypothesis. Laboratory values and imaging help to corroborate this hypothesis. Liver function tests (LFTs) are crucial. Ultrasonography evaluates the hepatic parenchyma and biliary ducts.

Clinical Thinking

Use the framework mentioned above to focus history taking and to come up with a working differential diagnosis.

Use LFTs and imaging (ultrasound, CT, MRI) to help corroborate your hypothesis.

Pattern recognition of LFTs aids in diagnosis. *Please see the algorithm*.

History

History of associated pain or lack of pain is important.

If an elderly patient presents with painless jaundice, think malignancy. This presentation will be associated with weight loss, fatigue, and poor appetite.

If abdominal pain is present, the differential diagnosis is broad. Choledocholithiasis causes intermittent RUQ abdominal pain followed by more constant pain. Acute hepatitis can cause distension of the liver capsule and subsequent vague RUQ pain. Chronic abdominal pain that is dull in nature can be related to invasion of pancreatic cancer into adjacent tissues.

Past medical history is important: History of gallstones (choledocholithiasis), colon cancer (liver metastases), or chronic pancreatitis (bile duct strictures).

Take a good social history, including the following: travel, food ingestions, multiple sexual partners, alcohol use, cigarette use, injection drug use, tattoos, herbal medications, and new medications.

Family history: Between 5% and 10% of patients with pancreatic cancer have a family history of pancreatic cancer.

Physical Examination

Jaundice appears as yellowing of the skin, yellowing under the tongue, or scleral icterus (yellowing of the sclerae). This usually occurs with total serum bilirubin levels greater than 3.5 mg/dL.

Fractionate the bilirubin: If indirect bilirubin is predominant, hemolysis and *Gilbert syndrome* (hereditary condition caused by the decreased ability of glucuronyltransferase to conjugate bilirubin) are the top two diagnoses. If direct bilirubin is predominant, the differential includes intrahepatic dysfunction vs. biliary duct obstruction.

In the presence of fever, think cholangitis.

Asterixis (flapping of hands with arms extended; “stopping traffic”) and encephalopathy are signs of hepatocellular dysfunction.

Signs of chronic liver disease: spider angiomas, palmar erythema, caput medusae, and gynecomastia and testicular atrophy in men.

Abdominal exam: Inspect the abdomen for ascites (think malignancy or cirrhosis); listen for bowel sounds; assess hepatic size and palpate for hepatosplenomegaly and tenderness in RUQ (choledocholithiasis or acute hepatitis).

Tests for Consideration

Albumin and PT/INR are markers of liver function (prothrombin and albumin are synthesized in the liver).

Interpretation of LFTs

A hepatocellular pattern of injury is indicated by transaminases that are elevated out of proportion to the bilirubin and alkaline phosphatase. This is seen commonly in intrinsic liver disease, such as viral hepatitis.

A cholestatic pattern of injury is indicated by bilirubin and alkaline phosphatase levels that are elevated out of proportion to transaminase levels. A typical example of this pattern would be choledocholithiasis. In patients with an isolated elevation of alkaline phosphatase, a γ-glutamyl transpeptidase level should be obtained; levels are elevated in patients with hepatobiliary disease but not if the elevated alkaline phosphatase is the result of a bone disorder.

The ratio of AST to ALT can point toward the etiology of liver disease. Amylase/lipase: Can help to assess involvement of the pancreas. PT/INR: These values evaluate the liver's synthetic function. An elevated PT/INR can also occur if the patient is malnourished secondary to vitamin K deficiency.

Chem 7: Electrolyte derangements occur secondary to underlying pathology. With decreased oral intake, many of these patients can be quite volume depleted, so the serum creatinine is important to know. Severe liver dysfunction can cause chronic hypoglycemia. CBC: Reduced platelet counts and anemia are common in cirrhotic patients. Leukocytosis is nonspecific, but a marked elevation may suggest cholangitis.

CA 19-9: Marker for pancreatic cancer.

α-fetoprotein: Marker for hepatocellular carcinoma.

IMAGING CONSIDERATIONS→ Abdominal ultrasound: Least expensive and least invasive; ultrasound should be the first test done for those with jaundice; it visualizes the bile ducts, echotexture of the liver, gallbladder, and pancreas; normal CBD diameter is 4 mm; when ultrasound is performed with Doppler, direction of portal blood flow and presence of thrombi in the portal system can be determined. → CT Abdomen and pelvis: Noninvasive; good view of the entire abdominal cavity; requires oral and intravenous contrast for best visualization; patient could have allergy to IV dye or have elevated creatinine that would not allow IV dye to be used, thereby hindering the benefits of the study.

→MRI/MRCP (MRI/magnetic resonance cholangiopancreatography) : Similar utility and drawback as CT but better visualisation of biliary tree.

Case - 2

56 years male hypertensive patient presented with yellowish discolouration of eyes and urine for last 6 months, mass in right upper abdomen for last 5 months and low grade fever for last 1 month. Yellowish discolouration of urine and eyes is gradually onset, progressive, without any prodromal symptom at onset, and is associated with pruritus, clay colour stool but no abdominal pain although there is a mass in right upper abdomen. There is also history of passage of black tarry stool 2 months back, which lasted for about 7 days. No history of vomiting or hematemesis, or alteration of bowel habit. He also having low grade fever without chill and rigor. Fever occurs both day and night without any pattern and is associated with weight loss, anorexia, easy fatigability. No urinary complaint. Patient has no other systemic symptoms.

· On general examination, nutrition poor, pallor moderate and deeply jaundiced. No cervical lymphadenopathy. Abdominal examination-shape and contour of abdomen normal. Umbilicus

normal. Liver and spleen not palpable. A lump palpable in the right hypochondriac region extending to the epigastric and right lumbar region. The lower, medial and the lateral margins are palpable and the upper margin passes deep to the right costal margin. The palpable swelling appears to be the palpable gall bladder. There is no free fluid in the abdomen. Bowel sounds are audible. Per rectal examination not done.

· Provisional Diagnosis Obstructive jaundice probably due to periampullary carcinoma in a hypertensive patient posted for exploratory laparotomy followed by Whipple's pancreatico-duodenectomy if operable. Why Obstructive Jaundice? Patient complains of- 1. Gradually progressive increase in yellowish discoloration of eyes and urine. 2. Patient is having itching all over the body and 3. He is passing clay coloured stool since the onset of jaundice. Why periampullary carcinoma ? 1. Patient is elderly. 2. History of painless progressive jaundice for last 6 months. 3. Patient had melena 2 months back. 4. Anorexia and weight loss for last 6 months. 5. Lump in his right side of upper abdomen for last 3 months. 6. No history of biliary colic 7. Gallbladder is palpable, which is tense cystic in feel and is non tender.

· Differential Diagnosis 1.Cholangio-carcinoma 2.Carcinoma of gallbladder 3.Choledocho-lithiasis 4.Lymph node mass in the porta causing biliary obstruction (Metastatic, lymphoma, tuberculosis) 5.Bile duct stricture 6.Sclerosing cholangitis 7. Chronic pancreatitis

· Management Plan Kausch – Whipple's Procedure

CHAPTER 6

REFERRAL AND CONSULATAION IN JAUNDICE: A MULTIMODALITY APPROACH

AUTHOR : AJAY KUMAR PATWA

Introduction: What is referral?

In simple terms, referral is sending a patient to another healthcare system for better management. It is a set of activities undertaken by a health care provider or facility in response to its inability to provide the quality or type of intervention suitable to the need of the patient. To be more precise, it is not an act of passing the ball from one hand to another just because of overburdened number of patients but it is fine balance between primary, secondary and tertiary care level healthcare systems. A high proportion of patients seen at the outpatient clinics at secondary or tertiary facilities could be appropriately looked after at primary health care centers at lower overall cost to the patient and the health system.

Why to refer

Rationalizing the usefulness is the most critical component of the referral process. A good referral can help to ensure that the patients receive cheap and optimal care at the appropriate level, hospital facilities are used optimally and cost-effectively, patients who need specialist services, can access them in a timely way and primary health services are well utilized and their reputation is enhanced. Referral of patient may be for either ambulatory care such as OPD consultation, diagnostics, and ambulatory procedures (e.g. endoscopy etc.) or for admissions. Referral conditions will be used in consonance with facilities available, skills sets available at the facility and prevailing standard treatment guidelines available in the State. Few general conditions for referral are:

Case scenarios

1. When a patient needs a specific diagnostic tool that is not available at the health centre/primary facility level (example: pathological tests and ultrasound)

A 21 years old male presented to primary health centre with complaint of low grade fever, malaise and bodyache with for 5 days. Examination showed mild icterus and mild right upper quadrant tenderness in abdomen without any organomegaly.

Opinion quiz 1.1: What should be the best differential diagnosis?

1. Jaundice with fever

2. Acute hepatitis

3. Acute viral hepatitis

4. Hepatitis

Answer: The treating physician made diagnosis of fever with jaundice.

Opinion quiz 1.2: What should be the initial management?

1. Adequate hydration and paracetamol

2. Empirical antibiotic

3. Calcium and multivitamin

4. Refer to higher centre

Answer: The treating physician started adequate hydration and paracetamol and referred to higher centre for LFT and ultrasound.

Blood tests showed bilirubin: total 4.5 mg/dl, direct 3.2 mg/dl, ALT 768 IU/ml, AST 338 IU/ml and ALP 360 IU/ml. Abdominal ultrasound which showed mild hepatomegaly. Other organs were normal.

Opinion quiz 1.3: What should be the differential diagnosis?

1. Jaundice with fever
2. Acute hepatitis
3. Acute viral hepatitis
4. Hepatitis

Answer: Acute hepatitis was diagnosed.

Same treatment was advised by medical officer there. He was referred to medical college for further up of etiology of acute hepatitis. Here HBsAg, HCV, HAV, HEV was and IgM anti-HAV was found to be positive. No further testing or treatment was advised. Patient improved within next two weeks and was referred back to PHC for further follow up.

2. When a patient requires a technical intervention that is not within the capacity of the health centre; Example: surgery

A 38 years old lady presented to PHC with complain of right upper qudrant pain and jaundice (yellow eyes and urine) for 15 days. Examination showed deep icterus with palpable gall bladder lump.

Opinion quiz 2.1: What should be the best differential diagnosis?

1. Painful jaundice with gall bladder lump
2. Gall bladder cancer with obstructive jaundice
3. Mirrizi syndrome
4. Periampullary cancer with obstructive jaundice

Answer: The treating physician made diagnosis painful jaundice with gall bladder lump and referred to higher centre for further management.

At tertiary care level, blood tests showed bilirubin: total 14.5 mg/dl, direct 12.2 mg/dl, ALT 68 IU/ml, AST 38 IU/ml and ALP 560 IU/ml. Abdominal ultrasound showed cholelihiasis with cystic duct stone obstructing the CBD with upstream dilatation with IHBRD. Other organs were normal.

Opinion quiz 2.2: What should be the best differential diagnosis?

1. Painful jaundice with gall bladder lump

2. Gall bladder cancer with extrahepaic cholestatic jaundice

3. Mirrizi syndrome

4. Periampullary cancer with extrahepaic cholestatic jaundice

Answer: The treating clinician diagnosed Mirrizi syndrome.

Opinion quiz 2.3: What should be the best management?

1. Open cholecystectomy

2. ERCP followed by laparoscopic cholecystectomy

3. Calcium and multivitamin

4. PTBD

Answer: Surgical opinion was taken. ERCP followed by laparoscopic cholecystectomy.

Patient recovered well after surgery. She was discharged after 7 days and referred back to PHC for further follow up.

3. When the patient needs expert advice whether to undergo medical or surgical treatment. (e.g. Gall bladder cancer)

A 40 years old lady presented to PHC with complain of right upper quadrant pain and jaundice for 40 days. Examination showed deep icterus with palpable gall bladder lump.

Opinion quiz 3.1: What should be the best differential diagnosis?

1. Painful jaundice with gall bladder lump

2. Gall bladder cancer with extrahepaic cholestatic jaundice

3. Mirrizi syndrome

4. Periampullary cancer with extrahepaic cholestatic jaundice

Answer: The medical officer diagnosed painfull jaundice with gallbladder lump and referred the patient to higher centre.

At tertiary health centre, blood tests showed bilirubin: total 14.5 mg/dl, direct 12.2 mg/dl, ALT 68 IU/ml, AST 38 IU/ml and ALP 560 IU/ml. Abdominal ultrasound showed cholelihiasis with gall bladder neck mass obstructing the CBD with upstream dilatation with IHBRD. Other organs were normal.

Opinion quiz 3.2: What should be the best differential diagnosis?

1. Painful jaundice with gall bladder lump

2. Gall bladder cancer with extrahepaic cholestatic jaundice

3. Mirrizi syndrome

4. Periampullary cancer with extrahepaic cholestatic jaundice

Answer: Gall bladder cancer with extrahepaic cholestatic jaundice was diagnosed.

Surgical opinion was taken. CECT abdomen showed gall bladder neck mass obstructing the CBD with upstream dilatation with IHBRD without any regional lymph nodal involvement.

Opinion quiz 2.3: What should be the best management?

1. Open radical cholecystectomy with hepaticojejunostomy

2. ERCP followed by laparoscopic radical cholecystectomy

3. Calcium and multivitamin and counselling

4. PTBD followed by laparoscopic radical cholecystectomy

Answer: Surgical opinion planned ERCP followed by laparoscopic radical cholecystectomy. Patient recovered well after surgery and was refrred back to PHC for further follow up.

4. When a patient needs in-patient care (e.g. Cerebral Malaria)

A 21 years young man presented to PHC with high grade fever for 6 days with jaundice for 3 days with vomiting and altered sensorium for 1 day. Examination showed deep coma, dehydration with icterus.

Opinion quiz 4.1: What should be the best differential diagnosis?

1. Acute viral hepatitis
2. Cerebral Malaria
3. Acute febrile icteric encephalopathy
4. Weil syndrome

Answer: The treating physician diagnosed acute febrile icteric encephalopathy. Hemogram was normal and smear for malaria was negative.

Opinion quiz 4.2: What should be the initial management?

1. Intravenous fluid and injection ceftriaxone
2. Intravenous fluid and injection artesunate
3. Intravenous fluid and injection meropenem plus tigecycline
4. Immediately refer to higher centre

Answer: The treating physician staeted intravenous fluid and injection ceftriaxone and referred to higher centre.

He was admitted in emergency. Blood tests showed plasmodium falciparum in smear as well in serology.

Opinion quiz 4.3: What should be the most appropriate management?

1. Intravenous fluid and injection ceftriaxone
2. Intravenous fluid and injection artesunate
3. Intravenous fluid and injection meropenem plus tigecycline
4. Mechanical ventillation

Intravenous artesunate, fluids and antipyretics were started. Patient recovered after 2 days and was referred back.

5. For co-management or further management of the illness e.g. complications in pregnancy

A 24 years old lady with 32 weeks pregnancy presented at PHC with jaundice, right upper quadrant pain for last one week and mild drowsiness for 2 days. Examination showed mild drowsiness with mild icterus with mild tender hepatomegaly.

Opinion quiz 5.1: What should be the best differential diagnosis?

1. Third trimester pregnancy with jaundice and encephalopathy

2. HELLP syndrome

3. Acute viral hepatitis

4. Acute fatty liver of pregnancy

Answer: The treating physician made a diagnosis of third trimester pregnancy with jaundice and encephalopathy and referred to higher centre for further evaluation and management. She was admitted in obstetrics and gynecology department of district hospital. Blood tests showed bilirubin: Hb 6.9 g/dl, TLC 12000/cmm, PLT 74000/cmm, total 3.5 mg/dl, direct 2.2 mg/dl, ALT 118 IU/ml, AST 148 IU/ml and ALP 560 IU/ml and LDH 599 IU/ml. Abdominal ultrasound which showed 32 weeks pregancy with IUGR with mild hepatomegaly with grade I fatty liver. Other organs were normal.

Opinion quiz 5.2: What should be the best differential diagnosis?

1. Third trimester pregnancy with jaundice and encephalopathy

2. HELLP syndrome

3. Acute viral hepatitis

4. Acute fatty liver of pregnancy

Answer: HELLP syndrome was diagnosed.

After initial treatment she was refrerred to obstetrics and gynecology department of KGMU. Her drowsiness worsened. Ultrasound here showed IUD. Acute liver failure cause HELLP syndrome with IUD was diagnosed.

Opinion quiz 5.3: What should be the most appropriate management?

1. Intravenous fluids and and antibiotics
2. Early termination of pregnancy
3. Therapeutic plasma exchange
4. All the three

Early termination of pregnancy was done. She was transferred to Medicine departement for further management. Therapeutic plasma exchange was started. Patient recovered and was referred back to PHC for further follow up.

6. For a second opinion (e.g. Gilbert syndrome)

A 22 years young man presented to PHC with LFT report. His bilirubin was 2.5 mg/dl, direct 0.4 mg/dl, indirect 2.1 mg/dl, AST 32 IU/ML, ALT 40 IU/ML and ALP 123 IU/ml.

Opinion quiz 6.1: What should be the best differential diagnosis?

1. Hemolytic jaundice
2. Gilbert syndrome
3. Criggler Najjar Syndrome
4. Isolated indirect type hyperbilirubinemia

Answer: The medical ofiicer diagnosed isolated indirect type hyperbilirubinemia and referred the patient to CHC for second opinion. His Hb was 12.8 g/dl, TLC 4200/cmm, PLT 197000/ cmm, MCV 81 fl, MCHC 30 g/dl, LDH 132 IU/ml.

Opinion quiz 6.2: What should be the best differential diagnosis?

1. Hemolytic jaundice

2. Gilbert syndrome

3. Criggler Najjar Syndrome

4. Isolated indirect type hyperbilirubinemia

Answer: The treating physician diagnosed Gilbert syndrome and referred to Medicine department of KGMU for confirmation and further advice.

Opinion quiz 6.3: What should be the next line of investigation?

1. Ultrasound

2. CT scan

3. MRI

4. UGT1A1 gene analysis

Answer: His UGT1A1 gene analysis showed >80% activity with homozygous for TT suggestive of Gilbert syndrome.

Opinion quiz 6.4: What should be the most appropriate management?

1. Counselling about the disease

2. To avoid dehydration, stress, pathological use of recreational substances

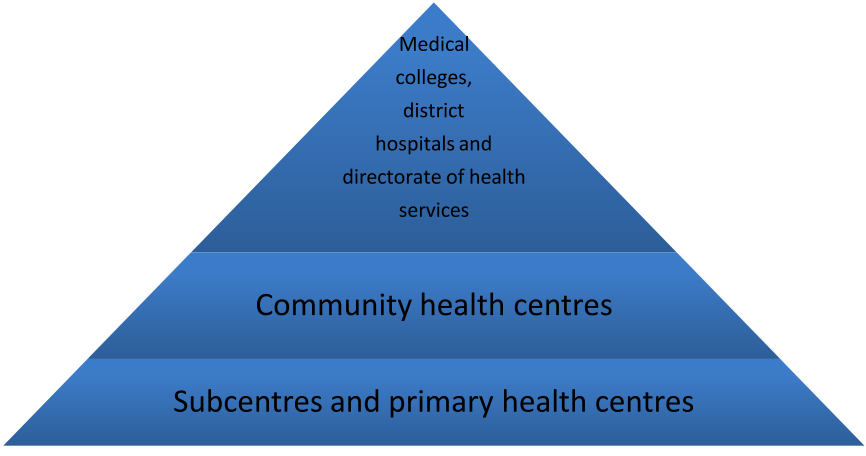
3. Live 52

4. All the three

He was counselled about the disease and not to be concerned about the genetic variant and benign nature of disease and to avoid dehydration, stress, pathological use of recreational substances.

Where to refer

Figure 1 represents the levels of care and usual referral apettern in our country and table 1 shows the common indications for referral. However, it is consulting physician who uses his/her commonsense whwere to refer a patient for best of care.



When to refer

Table 2 gives an idea about categorisation of a referral according to timing, expected location and common examples in each category. Once again the decision of treating physician should be more practical based on commonsense rather theoratical.

Table 2. NCEPOD classification of interventions based on timing

SN	Common referrals	Indications
1.	Radiology	1. Diagnostic: Ultrasound/CT/MRI/MRCP for anatomy/patho-anatomy of hepatobiliary and other systems 2. Therapeutic interventionas: PTBD in hilar biliary obstruction
2.	Pathology	Examination of blood, body fluids, tissue biopsy specimens
3.	Microbiology	Serological tests, eg. Viral and autoimmune markers, bactrial and fungal cultures
4.	Transfusion	Blood and components transfusion

	Medicine	
5.	Medical Gastroenterology and hepatology	Endoscopy ERCP
6.	Medical oncology/ Radiation oncology	Chemoradiotherapy
7.	Surgery/ Surgical gastroenterology/ Surgical oncology	Surgical procedures
8.	ICU and CCM	For critical care support
9.	Obstetrics and gynecology	1. Termination of pregnancy in AFLP 2. Fetal well-being in other causes
10.	Forensic medicine and toxicology	Toxicological screen

When to refer

Table 2 gives an idea about categorisation of a referral according to timing, expected location and common examples in each category. Once again the decision of treating physician should be more practical based on commonsense rather theoratical.

Table 2. NCEPOD classification of interventions based on timing

Code	Category	Description	Target time to referral centre	Expected location	Example Scenarios	Typical procedures
1	Immediate	Immediate (A) lifesaving or (B) organ-saving intervention. Resuscitation simultaneous with surgical treatment.	Within minutes of decision to intervene	Within the same premises (ICU, HDU, OT)	1. Acute cholangitis with shock 2. Acute heart failure with ischemic hepatopathy 3. AVH with ALF with extrahepatic organ failure 4. Acute on chronic liver failure with extrahepatic organ failure	1. Fluid resuscitaion, vasopressors, antiobiotics Diuretics for HF 2. Therapeutic plasma exchange 3. Liver transplant
2	Urgent	Acute onset or	Within hours	Within the	1. Acute common	a) ERCP

Code	Category	Description	Target time to referral centre	Expected location	Example Scenarios	Typical procedures
		deterioration of conditions that threaten life, or organ survival; relief of distressing symptoms.	of decision to intervene and normally once resuscitation completed	same suburban area/city/ town	bile duct obstruction 2. Acute Budd Chiari Syndrome 3. AVH with ALF without extrahepatic organ failure 4. Acute on chronic liver failure without extrahepatic organ failure	b) Surgical CBD exploration c) Radiological HV/ IVC stenting d) Therapeutic plasma exchange e) Liver transplant
3	Expedited	Stable patient requiring early intervention for a condition that is not an immediate threat to life, or organ survival	Within days of decision to intervene	Across/ within city/town	1. Obstructive jaundice without other complications 2. Acute viral hepatitis with prolonged cholestasis 3. Cholestasis of pregnancy	1. ERCP 2. Surgical resecetion/ anstomosis (Whipple's procedure) 3. Therapeutic plasma exchange
4	Elective	Interventions planned or booked in advance of routine admission to hospital	Planned	Across/ within city/town	Obstructive jaundice without other complications	1. ERCP 2. Surgical resecetion/ anstomosis (e.g. Whipple's procedure)

Summary

Referral and second consultation are important parts of patient management. Decision on timing, place and reason for referral are critical in optimal patient care.

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