

Jaundice In Elderly

N.S Neki

Introduction

Jaundice, or icterus, is a yellowish discoloration of tissue resulting from the deposition of bilirubin. The presence of scleral icterus indicates a serum bilirubin of at least $51\mu\text{mol/L}$ (3 mg/dL). About 70-80% of the 250-300 mg of bilirubin produced each day is derived from the breakdown of hemoglobin in senescent red blood cells. The remainder comes from prematurely destroyed erythroid cells in bone marrow and from the turnover of hemoproteins such as myoglobin and cytochromes found in tissues throughout the body. The bilirubin present in serum represents a balance between input from production of bilirubin and hepatic/biliary removal of the pigment. Hyperbilirubinemia may result from (a) overproduction of bilirubin; (b) impaired uptake, conjugation, or excretion of bilirubin; or (c) regurgitation of unconjugated or conjugated bilirubin from damaged hepatocytes or bile ducts. Conventionally it is described as pre hepatic, hepatic and post hepatic causes of jaundice respectively (1). There are major changes in liver size (reduced by 20%), blood flow (reduced by 30%) and activity of liver enzymes (cytochrome p450 & SOD, So reduced hepatic drug clearance), (2) occurring with age and so the profile and presentation of jaundice in an elderly patient >65 years old is also different. The presence of an advanced liver disease or cirrhosis is more frequent in old patients as the first clinical presentation. A cautious individual evaluation is therefore required in aged patients. No significant differences in diagnostic investigations or treatment options occur between the elderly and the young (3).

Pathophysiology

Specially in elderly patient RBC half life shortened so turnover may increase, liver shows above mentioned changes in structure and functions, so hepatic causes may behave as severe cases of jaundice, and chances of malignancy increases at this age can cause mechanical obstruction to bile flow if involve outflow tract of bile, can result in obstructive jaundice.

Different causes of jaundice in elderly patients

Malignancy, bile duct stones and alcohol were the three most commonly occurring causes in most of the studies undertaken & literatures (2,4,5,6,7).

Hepatic Causes

Alcoholic liver disease (ALDs): It is one of the

commonest causes of jaundice in elderly (2,4,5) & it is dubbed as 'invisible epidemic' of elderly ALD. As there has been increase in alcoholism over 65 years and increase in the life expectancy (2) or a loss of life partners and, thus, loneliness and depression. 28% of cases of ALD are over the age of 65 years. It is more common in men than in women but the gap is narrowing. Most have prolonged course of 20-30 years leading to cirrhosis and additional 5 years of severe symptoms prior to death. Jaundice and ascities are late symptoms. Once they start developing, most patients die within one year (2).

Elderly person's liver is more susceptible to the toxic effect of ethanol (8). Recent studies have shown that there are important pharmacokinetic differences in ethanol metabolism between older and younger subjects. Among men, the area under the curve was significantly greater in older subjects in both the intravenous fed and oral fasted states, but interestingly not in the oral fed state. In women there was a highly significant difference in the oral fasted state only. These age related differences seen most clearly in the fasted state imply decline in one or more mechanisms responsible for rapid ethanol metabolism within the first hour after ingestion (9). Signs and symptoms were more severe at presentation in the 70+-year-old age group than in the young patients though the elderly more often presented with symptoms not directly related to liver disease. Prognosis was age-related, 1 year mortality was 50% among cirrhotics over the age of 60 versus 7% under 60 years. Alcohol consumption at presentation was similar in all age groups with no evidence of a significant reduction in the elderly. The care of older patients with ALD will become an increasing problem in developed countries where alcohol consumption has continued to rise (10).

Hepatocellular carcinoma (HCC): It is one of the commonest cause of elderly patients presenting with jaundice (2,4,5,6). HCC usually presents in old age. Risk factors for HCC include chronic HCV infection, chronic HBV infection, cirrhosis of liver and hemochromatosis. Patient usually presents late with abdominal pain, weight loss, anorexia, hepatomegaly and jaundice. Metastasis from GI malignancy is also an additional risk factor for development of liver carcinoma. Dohmen *et al* (11) analyzed 36 patients aged > 80 years and concluded that

From the Department of G. Medicine, Govt Medical College and Guru Nanak Dev Hospital, Amritsar. 143001, India.

Correspondence to : Dr N.S Neki Professor Medicine, Govt Medical College and Guru Nanak Dev Hospital, Amritsar. 143001, India.

the survival rates are not significantly different from the non-elderly group, and that the advanced stage of HCC, not an advanced age, has the greatest influence on the survival rate in extremely elderly patients (11-13). Hoshida *et al* (14) evaluated 135 patients with chronic liver disease aged > 80 years and found that most patients (63.5%) would die of diseases other than liver diseases, such as pneumonia, especially in the non-cirrhosis group. It is reasonable that the extremely elderly patients without HCC die of diseases other than liver diseases. However, in their study, 18 patients with HCC at the start of observations had a poor prognosis. There is no statistical difference in the overall survival rate between the extremely elderly and non-elderly groups after the diagnosis of HCC (15).

Viral hepatitis: There are important differences in the epidemiology, clinical presentation, and management of viral hepatitis in the elderly compared with younger individuals. Acute hepatitis A is more clinically severe in older individuals and, although acute hepatitis B and C are most commonly recognized in young adults with high-risk behaviors, acute infection can also occur in the elderly (16). In one of the study, it was found that the most common etiology of acute viral hepatitis in the elderly is acute non-A, non-B hepatitis, followed by acute hepatitis in HBsAg carrier and acute type B hepatitis. Acute hepatitis in HBsAg carrier is the most common etiology in the young and middle-aged patients (17). Several physiological changes associated with aging, greater prevalence of co-morbid conditions, and cumulative exposure to hepatotropic viruses and environmental hepatotoxins may contribute to worse outcomes of viral hepatitis in the elderly. Although pharmacotherapy for hepatitis B and C continues to evolve, the efficacy, tolerability, and side effects of these agents have not been studied extensively in elderly adults (16). Amongst all types of hepatitis, people older than 65 years of age tend to develop more severe disease than those who are younger. Several physiological changes associated with aging, greater prevalence of co-morbid conditions, and cumulative exposure to hepatotropic viruses and environmental hepatotoxins may contribute to worse outcomes of viral hepatitis in the elderly. Although pharmacotherapy for hepatitis B and C continues to evolve, the efficacy, tolerability, and side effects of these agents have not been studied extensively in elderly adults (16). There is no drug treatment for hepatitis A. The Food and Drug Administration has approved several medications for hepatitis B, although comorbidities in the elderly may preclude their use. Hepatitis C is generally treated with interferon alpha and ribavirin in patients who can tolerate these agents (18).

Autoimmune hepatitis: Autoimmune hepatitis (AIH) is widely believed to be a disease of young women and menopause. Little is known about the frequency and

clinical characteristics in patients aged >65 yr. In one of the study it was found that, presentation with acute icteric hepatitis is similar to that of younger patients, supporting the assumption that beneficial effects of hormonal changes associated with menopause are not as pronounced in AIH as in other autoimmune diseases. Human leukocyte antigen type seems to have an influence on the age of onset of AIH. Prognosis is excellent, and AIH should be considered in the older patient to avoid delayed initiation of immunosuppressive therapy (19, 20). In other study there were no significant differences between the groups with respect to mode of onset (acute, insidious, asymptomatic), other clinical signs at presentation, biochemical parameters, types or titres of autoantibodies, incidence of histological cirrhosis, response to therapy or related side effects. There were also no significant differences in liver-related deaths or transplantation, or the frequencies of HLA DR3 or DR4 (21).

Obstructive variety of jaundice: Common causes of obstructive jaundice in elderly are found to be malignancy, bile duct calculi and drug induced amongst elderly people (22, 23). Obstructive jaundice is among the most frequent indications for abdominal operation upon the elderly. (23) Biliary tract tumors are not that common but these are serious causes of obstructive jaundice.

Biliary system cancer: Gall bladder cancer classically presents with the triad of jaundice, hepatomegaly, and a mass in the right upper quadrant (Courvoisier's sign). Another biliary system cancer i.e. cholangiocarcinoma, typically manifests as jaundice, pruritus, weight loss, and abdominal pain. Presentation in elderly population was not compared with young individuals in prior studies in case of carcinoma as they are rarely found outside the age group of elderly (24). Amongst elderly, cholelithiasis i.e. the presence of gallstones in the gallbladder, is found to be the commonest risk factor for cholangiocarcinoma. It may be associated with symptoms of obstruction. (25)

Acute cholangitis: Obstruction within the biliary duct system may lead to inflammation of the gallbladder ie cholecystitis or it may manifest as cholangitis or infection. Cholangitis is diagnosed clinically by the classic symptoms of fever, pain, and jaundice, known as Charcot's triad. Cholangitis most commonly occurs because of an impacted gallstone. Amongst elderly incidence of suppurative cholangitis is relatively high because of immunocompromised state and negligence. This can result in death (26).

Ca pancreas: Pancreatic cancer is the fourth leading cause of cancer deaths among men and women, being responsible for 6% of all cancer-related deaths. In the absence of predisposing conditions, such as familial pancreatic cancer and chronic pancreatitis, pancreatic cancer is unusual in persons younger than 45 years. After age 50 years, the frequency of pancreatic cancer increases linearly. The median age at diagnosis is 69 years

in whites and 65 years in blacks; some single-institution data reported from large cancer centers suggest that the median age at diagnosis in both sexes has fallen to 63 years of age. Approximately 75% of all pancreatic carcinomas occur within the head or neck of the pancreas, 15-20% occur in the body of the pancreas, and 5-10% occur in the tail. The initial symptoms of pancreatic cancer are often quite nonspecific and subtle in onset. Patients typically report the gradual onset of nonspecific symptoms such as anorexia, malaise, nausea, fatigue, and midepigastic or back pain. Development of advanced intra-abdominal disease is characterised by Presence of ascites, a palpable abdominal mass, hepatomegaly from liver metastases, or splenomegaly from portal vein obstruction. Jaundice is due to compression of ampulla of Vater occurs only with carcinoma involving head of pancreas. (26)

Pre-hepatic causes: These are extremely rare in elderly patients as a cause of jaundice and can be divided as causes with increase RBC turnover- like myeloproliferative disorders (MPDs), megaloblastic anemia and hemolysis- autoimmune haemolytic anemias are common in this category. (27)

Investigations

Jaundice will be evident if the total bilirubin is >35 micro mol/L. In jaundice, the essential and rapid differentiation of the main causes (hepatitis, biliary stasis, hemolysis, resolution of haematoma or congenital causes) can often be achieved by assessing urinary bilirubin and urobilinogen. Urinary bilirubin is normally absent but is conjugated when present (dark urine). Raised urinary bilirubin with absent or reduced urobilinogen is suggestive of obstructive jaundice. Normal or raised urinary bilirubin with elevated urobilinogen suggests hepatocellular or increased red cell breakdown (eg haemolytic jaundice). Urine dipstick assay should be tested fresh using reagent dipsticks

LFTs : Alkaline phosphatase is considerably increased with either extrahepatic or intrahepatic biliary disease. The most common diseases in geriatric patients include gallstones, pancreatic carcinoma, drugs & alcohol. Serum transaminases are usually very high in hepatocellular disease (like viral hepatitis). Aspartate aminotransferase (AST) is raised more than alanine aminotransferase (ALT) in cirrhosis, intrahepatic neoplasia, haemolytic jaundice and alcoholic hepatitis. ALT is raised more than AST in acute hepatitis and in extrahepatic obstruction. ALT levels of less than 100 IU/L with jaundice suggest obstructive jaundice. ALT over 400 IU/L suggests diffuse acute hepatocellular damage (for example, in viral hepatitis). ALT between 150-400 IU/L suggests chronic active hepatitis, viral or drug-induced hepatitis. Alcoholism is one of the leading cause of hepatic injury in case of elderly patients so is true for jaundice in them. Gamma-glutamyltransferase (GGT) is sensitive but not specific

for excess alcohol intake. In elderly patients raised MCV with raised GGT is suggestive of alcohol abuse and if accompanied by raised ALT, suggests liver cell damage approximate values of each of these investigations are in similar reference range as compared to young adults and there is no significant variation described in literature. (28)

Other investigations: Complete blood count including a reticulocyte count and peripheral blood smear to detect haemolysis. ESR may be elevated for example in primary biliary cirrhosis (PBC) which is commoner in the age group of 40-60 years of age. Lactate dehydrogenase is raised in haemolysis. Hepatitis serology should be done in all elderly patients with cholestasis, as differentiating hepatitis from extrahepatic obstructive causes may be very difficult. Prothrombin time may be prolonged because of vitamin K malabsorption. This can manifest as malena or hematemesis in an elderly patient. (28)

Imaging: Plain radiographs are of little value, as few biliary tract calculi are radiopaque. USG can detect liver abnormalities, hepatosplenomegaly and gallstones. It is useful to identify the extrahepatic causes of biliary obstruction but is also good at identifying intrahepatic disease (for example, malignant disease).

MRI scanning and magnetic resonance cholangiopancreatography (MRCP): MRCP has been recommended with a predictive scoring system to reduce the number of patients undergoing unnecessary endoscopic retrograde cholangiopancreatography (ERCP). It may become the test of choice in obstructive jaundice. Percutaneous transhepatic cholangiography is used much less often. (29)

Liver biopsy: A liver biopsy is needed to look for the architecture of the liver and is used mostly for determining prognosis. It also may be necessary for diagnosis if serum and imaging studies do not lead to a firm diagnosis. Liver biopsy can be particularly helpful in diagnosing autoimmune hepatitis or biliary tract disorders (e.g., primary biliary cirrhosis, primary sclerosing cholangitis). Patients with primary biliary cirrhosis are positive for antimitochondrial antibody, and the majority of those affected by primary sclerosing cholangitis have antineutrophil cytoplasmic antibodies. (30)

Treatment

This is dependant upon underlying pathology responsible for jaundice. This can be divided according to etiology.

Prehepatic jaundice: In treating pre-hepatic jaundice, the main strategy is to prevent the breakdown of red blood cells ie causing the level of bilirubin to build up in the blood. In cases of infections, such as malaria, the use of medication to treat the underlying infection is usually recommended.

Intra-hepatic jaundice: In cases of intra-hepatic jaundice, there's little that can be done to repair any liver damage, although the liver can often repair itself over

time. Therefore, the aim of treatment is to prevent any further liver damage occurring. For liver damage that's caused by infection, such as viral hepatitis or glandular fever, anti-viral medications may be used to help prevent further damage. If the damage is due to exposure to harmful substances, such as alcohol or chemicals, avoiding any further exposure to the substance is recommended. In severe cases of liver disease, a liver transplant is ultimate option. However, only a small number of people are suitable candidates for a transplant and the availability of donated livers is limited. In an elderly patients, hepatic causes are usually severe and they present late, so emergency management and supportive care is life saving in them and carries much more significance (27-30).

Post-hepatic jaundice: This is one of the leading cause of jaundice in elderly. In most cases of post-hepatic jaundice, surgery is recommended to unblock the bile duct system. Impacted gallstones typically require cholecystectomy or endoscopic removal, depending on the stone location. Biliary strictures and infection should be considered in elderly patients with postoperative jaundice (31). Many patients usually are not offered surgery because of associated co-morbidities if offered, during surgery, it may also be necessary to remove the gallbladder, a section of the bile duct system, a section of the pancreas to prevent further blockages occurring (32).

Conclusion

Jaundice in elderly usually present into later stages with more severe disease with poor prognosis as benign causes of jaundice are less common as compared to serious and mostly malignant. A comprehensive approach coupled with proper laboratory tests is required to find out correct aetiology of jaundice in elderly. Treatment depends upon the etiology. Mostly treated medically due to other co morbidities. In few settings surgery is required.

References

- Pratt DS, Kaplan MM. Jaundice In: Harrison's Principles Of Internal Medicine. 18th (Ed) Chap. 42, Vol 1. 324-28, USA, Mac-Graw hill, 2012.
- Lecture Notes: Elderly Care Medicine By Claire G. Nicholl, K. Jane Wilson. Wiley Blackwell 2012.
- Premoli A, Paschetta E, Hvalryg M, et al. Characteristics of liver diseases in the elderly: a review. *Minerva Gastroenterologica e Dietologica* 2009;55(1):71-8.
- Lubczyska-Kowalska W, Matysiak T, Sapian B, et al. Causes of jaundice in elderly patients. *Mater Med Pol* 1991;23(1):25-8.
- Anna T, Sally S, William H. Jaundice in primary care: a cohort study of adults aged >45 years using electronic medical records. *Family Practice* 2011; 0:1-5.
- Peter LMJ. Liver disease in the elderly. *Best Practice & Research Clinical Gastroenterology* 2002;16(1):149-58.
- Pashankar D, Schreiber RA. Jaundice in older children and adolescents. *Pediatr Rev* 2001;22:219-26.
- Helmut KS, Felix S. Alcoholic Liver Disease in the elderly: *Clinics in Geriatric Medicine* 2007;23(4):905-21.
- Beresford TP, Lucey MR. Ethanol metabolism and intoxication in the elderly. In: Beresford TP, Ganberg E, eds. Alcohol and aging. New York: Oxford University Press, 1995:117-27.
- Potter JF, James OFW. Clinical Features and Prognosis of Alcoholic Liver Disease in Respect of Advancing Age. *Gerontology* 1987;33:380-87.
- Dohmen K, Shirahama M, Shigematsu H, Irie K, Ishibashi H.: Optimal treatment strategy for elderly patients with hepatocellular carcinoma. *J Gastroenterol Hepatol*; 2004; 19:859-65.
- Dohmen K, Shigematsu H, Irie K, Ishibashi H. Trends in clinical characteristics, treatment and prognosis of hepatocellular carcinoma. *Hepatogastroenterology* 2003; 50: 1872-77.
- Arbaje YM, Carbone PP. Hepatocellular carcinoma in the very elderly: to treat or not to treat? *Med Pediatr Oncol* 1994; 22:84-87.
- Hoshida Y, Ikeda K, Kobayashi M et al. Chronic liver disease in the extremely elderly of 80 years or more: clinical characteristics, prognosis and patient survival analysis. *J Hepatol* 1999; 31: 860-66.
- Health and Welfare Statistics Association. Life expectancy. *J Health Welfare Stat* 2004; 51: 67-68.
- Andres F Carrion, Paul Martin. Viral Hepatitis in the elderly. *Am J Gastroenterology* 2012;107(5):691-97.
- Lin SM. Acute viral hepatitis in the elderly. *Chang gung Medical J* 1993;16(1):14-8.
- Jeannette YW. Hepatitis in the elderly: Still a Scourge. *Am Society of Consultant Pharmacists* 2012;7: 472-81.
- Christoph S, Stephan K. Autoimmune hepatitis in the elderly. *Am J Gastroenterology* 2001; 96:1587-91.
- Parker DR, Kingham JGC. Autoimmune hepatitis in the elderly. *Gut* 1998 42: 448.
- Thawab AC, Sylvia B, Bernard CP, et al. Autoimmune hepatitis (AIH) in the elderly: A systematic retrospective analysis of a large group of consecutive patients with definite AIH followed at a tertiary referral centre. *J Hepatology* 2006; 45: 4:575-83.
- Huete-Armijo A, Exton-Smith AN. Causes and diagnosis of jaundice in the Elderly. *Br Med J* 1962; 1(5285): 1113-14.
- Morse ST, Ralph A. Obstructive jaundice in the elderly patient. *Am J Surgery* 1962;104(4):587.
- Custis K. Common biliary tract disorders. *Clin Fam Pract* 2000; 2: 141-54.
- Kaloo AN, Kantsevov SV. Gallstones and biliary disease. *Prim Care* 2001;28:591-606
- Available at : emedicine.medscape.com/article/280605-overview, Feb 20, 2013. Accessed on: June 2013
- Michel HB, Kathleen S, Teresa SK. Anemia in Older Persons. *AAFP* 2010;82(5):480-487
- Available at : <http://www.patient.co.uk/doctor/Abnormal-Liver-Function-Tests.htm> Accessed on: June 2013
- O'Regan D, Tait P. Imaging of the jaundiced patient. *Hosp Med* 2005;66(1):17-2.
- Pasha TM, Lindor KD. Diagnosis and therapy of cholestatic liver disease. *Med Clin North Am* 2006;80:995-1019
- Molina EG, Reddy KR. Postoperative jaundice. *Clin Liver Dis* 1999;3:477-88.
- Custis K. Common biliary tract disorders. *Clin Fam Pract* 2000; 2:141-54.