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Review Article

Obstructive Jaundice

Fekaj E[1]*, Jankulovski N[2] and Matveeva N[3]

[1]Department of Abdominal Surgery, University Clinical Centre of Kosovo, Pristina, Republic of Kosovo

[2]University Clinic for Digestive Surgery, Faculty of Medicine, Ss. Cyril and Methodius University, Skopje, FYROM

[3]Institute of Anatomy, Faculty of Medicine, Ss. Cyril and Methodius University, Skopje, FYROM

***Corresponding author:** Fekaj Enver, Department of Abdominal Surgery, University Clinical Centre of Kosovo, Pristina, Republic of Kosovo

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Abstract

The most common causes of obstructive jaundice are choledocholithiasis, structures of the biliary tract, cholangiocarcinoma, carcinoma of pancreas, pancreatitis, parasites and primary sclerosing cholangitis. Diagnosis of this syndrome is based on clinical examination, laboratory findings, imaging and endoscopic examination. Regardless of the cause, the physical obstruction causes a predominantly conjugated hyperbilirubinemia. Obstructive jaundice can be complicated with renal dysfunction, hemostasis impairment, hepatic dysfunction, increased intestinal permeability, and other complications. When mechanical biliary obstruction is diagnosed, surgical, endoscopic or radiologic intervention is usually recommended. Endoscopic Retrograde Cholangiopancreatography is an established diagnostic and therapeutic tool for pancreaticobiliary diseases including choledocholithiasis. However, Magnetic Resonance Cholangiopancreatography has gradually become an alternative diagnostic tool and is considered to be a noninvasive diagnostic technique in biliary diseases. In patients, in which gallbladder stones are associated with common bile duct stones, there is no consensus whether laparoscopic or endoscopic approach should be the first treatment. In spite of the advances made in diagnostic procedures over the past several decades, only about 20% of pancreatic cancers are found to be resectable at the time of presentation. Various palliative therapeutic strategies have been described. Today, the most common treatments are endoscopic biliary stenting and surgical biliary bypass surgery. The recommendation is that endoscopic stenting should be performed in patients with a poor prognosis (i.e., a life expectancy less than six months), and that patients with a life expectancy of greater than six months should be treated with biliary bypass because of the better long-term results associated with surgery.

Keywords: Obstructive jaundice; Jaundice; Conjugated bilirubinemia

Abbreviations

ALT: Alanine Transaminase; AST: Aspartate Transaminase; GGT: Gama- Glutamiltranspeptidase; ALP: Alkaline Phosphatase; ERCP: Endoscopic Retrograde Cholangiopancreatography; PT: Prothrombin Time; CBD: Common Bile Duct; CT: Computed Tomography; MRCP: Magnetic Resonance Cholangiopancreatography; MRI Magnetic Resonance Imaging; PTC: Percutaneous Transhepatic Cholangiopancreatography; CD4+: Cluster of Differentiation 4; CD8+: Cluster of Differentiation 8

Introduction

Obstructive jaundice results from biliary obstruction, which is blockage of any duct that carries bile from liver to gallbladder and then to small intestine [1]. The most common causes of obstructive jaundice are choledocholithiasis, structures of the biliary tract, cholangiocarcinoma, carcinoma of pancreas, pancreatitis, parasites and primary sclerosing cholangitis [2].

Stones in the common bile duct occur in 10-15% of patients with gallstones. These stones account for more than 80% of common bile duct stones; they migrate from the gallbladder and are similar appearance and chemical composition to the stones found elsewhere in the biliary tree. Primary bile duct stones may develop infrequently within the common bile duct many years after a cholecystectomy [3].

The prevalence of gallbladder and bile duct stones rises with age [4]. Up to 90% of patients with pancreatic head carcinoma exhibit the signs and symptoms of obstructive jaundice at the time of presentation [5].

This article highlights the diagnosis, complications and treatment modalities of obstructive jaundice. The aim of this review is to improve the understanding and management of this syndrome.

The Diagnosis of Obstructive Jaundice

The clinical presentation

The clinical manifestations are dependent on the main etiologies of the disease, and they include the increasing jaundice and abdominal pain for several days, followed by waxing and waning of the pain and jaundice at a background level as the stone disimpacts and reimpacts in the common bile duct, and jaundice with unremitting symptoms, darkening of urine, anorexia, weight loss, and malaise related to malignancies [6].

Regardless of the cause, the physical obstruction causes a predominantly conjugated hyperbilirubinemia. Conjunctival icterus is generally a more sensitive sign of hyperbilirubinemia than generalized jaundice [7]. The lack of bilirubin in the intestinal tract is responsible for the pale stools typically associated with biliary obstruction. The cause of itching (pruritus) associated with

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biliary obstruction is not clear. Some believe it may be related to the accumulation of bile acids in the skin. Others suggest it may be related to the release of endogenous opioids [8].

Laboratory findings

Regardless of the cause of cholestasis, serum bilirubin values (especially direct) are usually elevated. In the early phases of obstruction and with incomplete or intermittent obstruction, serum bilirubin levels may only be mildly elevated.

Alkaline Phosphatase (ALP): A membrane-bound enzyme localized to the bile canalicular pole of hepatocytes, ALP is markedly elevated in patients with biliary obstruction. ALP levels are elevated in nearly 100% of patients, except in some cases of incomplete or intermittent obstruction. Values are usually greater than three times the upper limit of the reference range. An elevation less than three times the upper limit is evidence against complete extrahepatic obstruction.

Gama-Glutamiltranspeptidase (GGT): These levels are elevated in patients with diseases of the liver, biliary tract, and pancreas when the biliary tract is obstructed. Levels parallel the levels of ALP in conditions associated with cholestasis.

Serum Transaminases: (ALT, AST): Levels of these are usually only moderately elevated in patients with cholestasis but occasionally may be markedly increased, especially if cholangitis is present.

Prothrombin Time (PT): This may be prolonged because of malabsorption of vitamin K. Correction of the PT by parenteral administration of vitamin K may help distinguish hepatocellular failure from cholestasis. Little or no improvement occurs in patients with parenchymal liver disease [9].

Imaging Examination

Transabdominal sonography

Ultrasound is the preliminary investigation of choice for the diagnosis of the presence of obstruction and to some extent the level of obstruction. Ultrasonography could pick up the presence of biliary obstruction in 78-98% of cases [10]. Accurate detection of the level of obstruction is possible in 27-95% of cases, and to a much lesser extent the cause of obstruction, about 23-88% of cases. Poor test performance at detecting common bile duct stones with sensitivities 25-58% and specificities 68-91%. Its accuracy ranging is about 47-90% for distinguishing benign from malignant causes. Sensitivities for pancreaticobiliary malignancies range from 5% for ampullary to 67-81% for pancreaticobiliary malignancies [10,11].

Endoscopic sonography

Endoscopic ultrasonography overcomes the limitation of evaluation of distal Common Bile Duct (CBD) by transabdominal sonography. It is very accurate in diagnosing CBD calculi with an overall accuracy of 96% as compared with 63% sensitivity of transabdominal sonography especially with small calculi with non- dilated biliary system [12]. It also picks up small resectablepancreatobiliary mass with high sensitivity, 93-100% [13].

Computed Tomography

Traditional Computed Tomography (CT) scan is usually considered more accurate than ultrasonography for helping determine the specific cause and level of obstruction. The accuracy of conventional CT in determining the presence and level of obstruction has been 81-94% and 88-92% respectively [14]. CT scan has limited value in helping diagnose common bile duct stones because many of them are radiolucent and CT scan can only image calcified stones. CT cholangiography by the spiral CT technique is used most often to image the biliary system and makes possible visualization of radiolucent stones and other biliary pathology [15].

Magnetic Resonance Cholangiopancreatography (MRCP) and MRI

MRCP is a non-radiating, non-invasive and yet a highly sensitive method of investigating obstructive lesions of the biliary tract [17]. It has a sensitivity of 95% and specificity of 95% for demonstrating the level and presence of biliary obstruction [16]. MRCP can be considered as the new gold standard for the investigation of biliary obstruction and permits reservation of ERCP to patients with a high probability of therapeutic intervention [17].

Endoscopic Retrograde Cholangiopancreatography (ERCP)

ERCP is an outpatient procedure that combines endoscopic and radiologic modalities to visualize both the biliary and pancreatic duct systems. Besides being a diagnostic modality, ERCP has a therapeutic application because obstructions can potentially be relieved by the removal of stones, sphincterotomy, and the placement of stents and drains. The sensitivity and specificity of ERCP are 90% and 98% respectively. Complications of this technique include pancreatitis, perforation, hemorrhage, sepsis, and adverse effects from the drugs used to relax the duodenum. ERCP is still considered the criterion standard for imaging the biliary system, particularly if therapeutic intervention is planned [17].

Percutaneous Transhepatic Cholangiopancreatography (PTC)

It is especially useful for lesions proximal to the common hepatic duct. The accuracy of PTC in elucidating the cause and site of obstructive jaundice is 90-100% for causes within the biliary tract [17].

Obstructive Jaundice-Related Complications

Intestinal permeability in obstructive jaundice

Gastrointestinal tract is not only a passive organ of nutrient absorption, but it additionally displays important endocrine, immunologic, metabolic, and barrier functions. The presence of bile and bile acids in the intestinal lumen is associated with a number of positive effects, contributing to a normal gut barrier function. Bile acids have positive effects in immune, biological, and mechanical barrier. Experimental studies has shown that bile and bile acids affects homing and distribution of T- lymphocytes in the gut-associated lymphatic tissue, and its absence results in decreased numbers of CD4+ and CD8+ T-lymphocytes [18]. Bile acids have been reported to inhibit the growth of certain bacteria such as Bacteroides, Clostridia, Lactobacillus and Streptococci. Absence of bile salts results in a disturbed intestinal bacterial balance with overgrowth of gram negative bacteria [19]. In addition, bile exerts trophic effects on the intestinal mucosa, increasing villous density and inducing hypertrophy of the intestinal wall components [20].

All the components of gut barrier integrity can be affected by biliary obstruction and the absence of bile within the intestinal lumen [18].

Altered intestinal tight junction expression and increased intestinal apoptosis are accompanied by significant alterations of the intestinal oxidative state, which represent an additional important factor in promoting intestinal injury in obstructive jaundice [21,22]. Increased intestinal permeability has been postulated to be a key factor contributing to bacterial and endotoxin translocation and the pathogenesis of septic and renal complications in patients with extrahepatic biliary obstruction [23].

A suppressed clearance capacity of Kupffer cells, the main hepatic macrophage population, attributed to accumulation of bile acids into liver, permits "spillover" of endotoxin from portal into systemic circulation, with consecutive release of proinflammatory cytokines, potentially leading to the development of the so called "gut derived sepsis" [18].

Hemostasis impairment in patient with obstructive jaundice

As part of the multifactorial role of liver in protein synthesis, many coagulation factors (fibrinogen, prothrombin, V, VII, VIII, IX, X, XI, XII, XIII, prekalikrein), natural anticoagulants (antithrombin-III, heparin cofactor-II, Protein C, Protein S), and compounds of the fibrinolytic system (plasminogen, a2 – antiplasmin) are produced in the liver. A prolonged liver disease, either biliary obstruction or parenchymal liver disease, is consecutively accompanied by abnormal clotting. Bacterial translocation plays a key role in the pathophysiology of hemostasis impairment in patients with obstructive jaundice. The hemostatic derangement in a patient with obstructive jaundice is multifactorial and difficult to assess. An uncomplicated but prolonged benign cholestasis will drive to hemorrhagic diathesis. If septic complications and/or pancreatic involvement are superimposed, the net effect on hemostasis might be a prothrombotic state. When malignancy has been documented, the situation is more complicated. Mucous adenocarcinomas of the pancreas and hepatocellular carcinomas can induce activation of hemostasis. Thromboembolic events, especially in the former, are common and serious complicating events resulting in poor prognosis. Unresolved cholestasis may progressively lead to liver dysfunction and evolution of cirrhosis. In these cases, more generalized hemostatic disorders affecting practically all pathways are observed: thrombocytopenia, decreased synthesis and clearance of coagulation factors and inhibitors, dysfibrinogenemia, hyperfibrinolysis and overt disseminated intravascular coagulation along with portal vein stasis and thrombosis may converge to a single patient [24].

Obstructive jaundice and renal dysfunction

The current evidence, mainly derived from experimental models, indicates that jaundice alone (independent of liver parenchymal disease) affects the integrity of the cardiovascular function. These effects are: 1) Reduction in peripheral vascular resistance, which results in systemic hypotension, 2) Depression of myocardial performance, and 3) Initial and profound natriuresis and diuresis that may lead to volume depletion.

Furthermore, most of the experimental data suggest that neither bilirubin nor bile acids have a direct nephrotoxic effect, and therefore, renal complications in experimental obstructive jaundice are mainly due to prerenal factors. In addition to the deleterious effects of bile acids on the kidney and the circulation, it is clear that factors related to the liver parenchymal damage associated with obstructive jaundice may have an independent contribution to the pathogenesis of "arterial underfilling" which will further predispose these patients to prerenal failure and eventually to acute tubular necrosis.

Clearly, the peripheral and renal hemodynamic effects of "surgical" jaundice are much more marked than that of "medical" jaundice associated with cirrhosis. This difference can be attributed to a higher prevalence and severity of endotoxemia in obstructive jaundice and the deleterious effects of endotoxin on both the peripheral and the renal microcirculation. In addition, the elevated levels of circulating bile acids in obstructive jaundice contribute to a more severe hemodynamic perturbation by a direct effect on the systemic circulation, by a cardiodepressor effect, and probably by a hypovolemic effect [25].

Obstructive jaundice and hepatic dysfunction

Obstructive jaundice can lead to pathophysiologic disorders including functional lesions of the liver and kidney, functional disturbance of blood coagulation, gastric mucous membrane injury, reduced immune function and dysfunction of liver regeneration [26].

Current pathophysiological studies on obstructive jaundice have shown that the damage to the liver, kidney, and immune system of the patients are closely related to endotoxemia [27].

High-grade biliary obstruction begins to cause cell damage, and if it unrelieved may lead to secondary biliary cirrhosis [28,29]. In patients with obstructive jaundice bile acids can induce liver cells apoptosis [30]. Although apoptosis is a highly regulated mechanism, aberrant levels of apoptosis can occur at any time from embryogenesis to adulthood, resulting in a variety of pathological conditions [31,32]. The mechanisms by which bile acids induce apoptosis in hepatocytes are still not entirely known [33]. Indeed, pathophysiological concentrations of bile acids induce apoptosis both by directly activating death receptors [34], and inducing oxidative damage and mitochondrial dysfunction, a combination that strongly sensitizes to apoptosis [35,36].

Treatment Modalities

When mechanical biliary obstruction is diagnosed, surgical, endoscopic or radiologic intervention is usually recommended [19]. The obstructive jaundice syndrome is very common and frequently requires surgical treatment. Its prevalence has increased more than twice since 1980s [37]. Despite advances in preoperative evaluation and postoperative care, intervention, especially surgery, for relief of obstructive jaundice still carries high morbidity and mortality rates, mainly due to sepsis and renal dysfunction [19].

Endoscopic Retrograde Cholangiopancreatography (ERCP)

In the pre-endoscopy and pre-laparoscopic era, the standard treatment for patients suffering from gallstones accompanied with common bile duct stones was open cholecystectomy and common bile duct exploration. With the advent of laparoscopic and endoscopic techniques, several alternative treatments, such

as laparoscopic cholecystectomy, preoperative or postoperative endoscopic retrograde cholangiopancreatography and endoscopic sphincterotomy and laparoscopic common bile duct exploration, have been developed to treat choledocholithiasis. In the past two decades, laparoscopic cholecystectomy has become gradually accepted as the first choice for the treatment of cholecystolithiasis. Consequently, confirmed or suspected cases of common bile duct stones have been routinely removed *via* a two-stage management using endoscopic retrograde cholangiopancreatography/ endoscopic sphincterotomy following by laparoscopic cholecystectomy [38].

In up to 20% of cases, gallbladder stones are associated with common bile duct stones. Despite the wide variety of examinations and techniques available nowadays, two main open issues remain without a clear answer: how to cost-effectively diagnose common bile duct stones and, when they are finally found, how to deal with them. Two main "philosophical approaches" face each other for patients with an "intermediate to high risk" of carrying common bile duct stones; on one hand, the "laparoscopic-first" approach, which mainly relies on intraoperative cholangiography for diagnosis and laparoscopic common bile duct exploration for treatment, and, on the other hand, the "endoscopic-first" attitude, variously referring to magnetic resonance cholangiography, endoscopic ultrasonography and/or endoscopic retrograde cholangiography for diagnosis and endoscopic sphincterotomy for management. Concerning common bile duct stones diagnosis, intraoperative cholangiography, endoscopic ultrasonography and magnetic resonance cholangiography are reported to have similar results. The recent literature, regarding management, seems to show better short and long-term outcome of surgery in terms of retained stones and need for further procedures. Thus, although no consensus has been achieved and common bile duct stones management seems more conditioned by the availability of instrumentation, personnel and skills, endoscopic treatment is largely preferred worldwide [39].

ERCP is an established diagnostic and therapeutic tool for pancreaticobiliary diseases including choledocholithiasis. However, the diagnostic value of ERCP in biliary diseases, especially benign diseases, has decreased markedly due to inherent invasion. Magnetic Resonance Cholangiopancreatography (MRCP) has gradually become an alternative and is considered to be a noninvasive diagnostic technique in biliary diseases [40].

Surgical treatment

In spite of the advances made in diagnostic procedures over the past several decades, only about 20% of pancreatic cancers are found to be resectable at the time of presentation [41,42]. In the palliative setting, differentiation between carcinomas of the pancreatic head and the distal biliary tree is often impossible. However, both of these malignancies are usually adenocarcinomas and have the same symptoms when they reach advanced stages. Up to 90% of these patients exhibit the signs and symptoms of obstructive jaundice at the time of presentation [43].

Various palliative therapeutic strategies have been described. Today, the most common treatments are endoscopic biliary stenting and surgical biliary bypass surgery with or without concomitant gastrojejunostomy. In addition, radiologically-guided percutaneous transhepatic biliary drainage or transhepatic stent placement is typically reserved for patients with unresectable disease, and who are unable to undergo endoscopic drainage. The main goal of palliative therapy in patients with unresectable carcinoma of the pancreatic head or distal biliary tree is to resolve the biliary obstruction. There is still disagreement as to whether endoscopic or surgical palliation is associated with a better outcome, and there have been a number of retrospective studies which have shown the superiority of one treatment or the other. The studies have shown that endoscopic stenting has lower morbidity during the initial post-procedural period. However, as the length of follow-up increased in these studies, 20-50% of patients developed complications, such as cholangitis or recurrent jaundice. However, while studies of patients who underwent hepaticojejunostomy found that these patients had higher morbidity rates during the initial postoperative period as well as longer post-procedural hospital stays, the occurrence of long-term sequel such as recurrent jaundice was unusual (0-7%).

Several authors have stated that patient prognosis should guide the decision as to whether surgery or stent placement is more clinically appropriate. They recommended that endoscopic stenting should be performed in patients with a poor prognosis (i.e., a life expectancy less than six months), and that patients with a life expectancy of greater than six months should be treated with biliary bypass because of the better long-term results associated with surgery [44].

Conclusion

When mechanical biliary obstruction is diagnosed, surgical, endoscopic or radiologic intervention is usually recommended. Endoscopic Retrograde Cholangiopancreatography is an established diagnostic and therapeutic tool for pancreaticobiliary diseases including choledocholithiasis. However, Magnetic Resonance Cholangiopancreatography has gradually become an alternative diagnostic tool and is considered to be a noninvasive diagnostic technique in biliary diseases. In patients, in which gallbladder stones are associated with common bile duct stones, there is no consensus whether laparoscopic or endoscopic approach should be the first treatment. Only about 20% of pancreatic cancers are found to be resectable at the time of presentation. Today, the most common treatments are endoscopic biliary stenting and surgical biliary bypass surgery. The recommendation is that endoscopic stenting should be performed in patients with a poor prognosis (i.e., a life expectancy less than six months), and that patients with a life expectancy of greater than six months should be treated with biliary bypass because of the better long-term results associated with surgery.

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