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Hepatolithiasis: A Dangerous Spectral End Point of Stone Disease

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***Abstract*—*Hepatolithiasis is one of the most complex stone disease of the hepatobiliary system. The disease causes significant damage to the liver including the chance of developing a cholangiocarcinoma. Though the disease is rampant in East Asian countries isolated cases are seen even on the Indian subcontinent. Since experience is lacking in our country to treat this uncommon condition awareness of this condition will enable the surgeon diagnose and develop a proper surgical treatment plan which best suits the patient depending upon the severity of the disease process. A brief review of the etiopathogenesis, diagnosis and management is presented in this paper*.

***Keywords*—** *Hepatic Lithiasis Diagnosis Management*.

I. INTRODUCTION

Hepatic lithiasis is defined as the presence of gall stones in the bile duct proximal to the confluence of the right and left hepatic ducts, irrespective of the coexistence of gall stones in the common bile duct or the gall bladder. [1] The disease is endemic in the Asia-Pacific region with a prevalence rate of 30-50%. [2] Population mobility has led to an increase in the incidence of this disease in other regions.

II. ETIOPATHOGENESIS

Epidemiology

The disease is more common in the fifth and sixth decades of life. There is no gender preference. Concomitant intrahepatic and extra hepatic stones are commonly encountered in older age groups especially in the seventh and eighth decades which constitute 70% of all hepatolithiasis cases.[1,2] Malnutrition and low socio-economic states are usually associated with higher incidence of stone disease.

Etiology

Intrahepatic stone formation is associated with variety of conditions. Post op strictures, sclerosing cholangitis, Caroli's disease and neoplasms resulting in biliary stenosis and stasis. [1] Effectively any condition which leads to chronic stasis predisposes to intrahepatic stone formation. Parasitic biliary tract infections with C. Sinesis and A. lumbricoides are commonly associated with hepatolithiasis. [2, 3] Various orther hypothesis have been proposed to explain the pathogenesis of hepatic lithiasis. Leptin is a product of OB gene. It has a role in modulating lipid metabolism which may be involved in the increased biliary cholesterol secretion and gall stone formation. In various studies however it was found that leptin, CCK, lipids and lipoproteins in patients with hepatolithiasis were the same when compared with those in cholelithiasis.[4] Hence leptins and its alternation of lipid metabolism may obviously not be responsible for hepatolithiasis. [4]

CFTR (cystic fibrosis transmembrane receptor) is expressed on biliary canalicular cells and is vital in alkalization and solubilisation of bile. Strictures from cystic fibrosis disease combined with over expression of CFTR may be responsible for initiating intrahepatic stone formation. [5] Biliary strictures from parenchymal ischemic changes may cause varices within the bile ducts. Cavernous transformation of the portal vein in antiphospholipid syndrome may cause mechanical obstruction of bile ducts with resultant formation of hepatic lithiasis. Hemolytic anemias with biliary over production may lead to increased production of pigment stones. [6] Retrograde migration of these stones may also lead to hepatolithiasis.

Types of Stones in Hepatolithiasis

There are two types of stones commonly encountered in hepatolithiasis - 1) calcium bilirubinate stones (brown pigmented stones) and 2) Cholesterol stones. Majority of the stones are calcium bilirubinate stones. (Figure 1) These are due to a variety of factors – precipitation of calcium bilirubinate, alteration in cholesterol metabolism and biliary strictures with super imposed infection with beta-glucouronidase producing bacteria.[7] These are typically seen with primary hepatic calculi whereas secondary hepatic stones are usually seen in the western hemisphere and have more cholesterol with little association with biliary strictures, stasis and infection.

There are *various classifications of hepatolithiasis* based on the severity of the disease process as well as the severity of symptomatology.[1,8,9,10]

1) Tsunoda classification – severity based grading based intrahepatic anatomical findings in the disease. (Table 1)
2) Symptom based severity grading proposed by the hepatolithiasis research group of Japan which is also based on severity of the disease. (Table 2)

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3) Dong's classification which proposes treatments for various classes of hepatolithiasis. (Table 3) Type I and type IIb hepatolithiasis are best treated by partial hepatectomy. Type IIc patients are best suited for transplantation. Whereas hepaticojejunostomy is best for Eb and Ec type of hepatolithiasis.

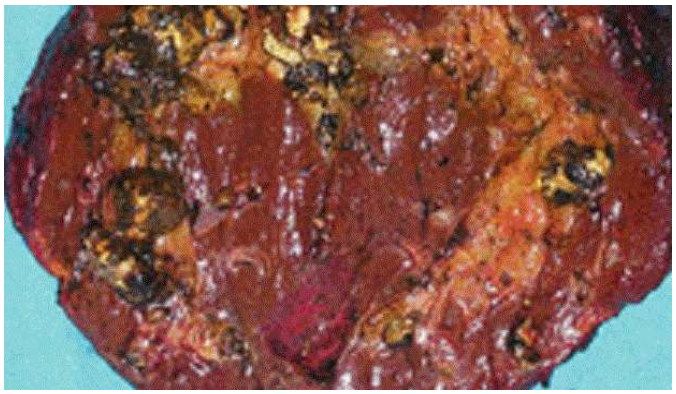

Fig. 1. Sectioned resected liver lobe showing hepatolithiasis

TABLE 1. Tsunoda classification.

Tsunoda Class	Findings
I	No dilatation or stricture of intrahepatic ducts
II	Diffuse dilatation of intrahepatic ducts without strictures
III	Unilateral disease with solitary or multiple cystic dilatation of intrahepatic ducts with strictures
IV	Unilateral disease with solitary or multiple cystic dilatation of intrahepatic ducts with strictures

TABLE 2. Grading of severity of hepatolithiasis described by the Hepatolithiasis Research Group, Japan.

Grade	Symptoms
I	No symptoms
II	Abdominal pain
III	Transient jaundice or cholangitis
IV	Continuous jaundice, sepsis or cholangiocarcinoma

TABLE 3. Dong's Classification of hepatolithiasis.

Type	Definition
I	Localized stone disease either unilobar or bilobar
II	Diffusely distributed stones
IIa	Without hepatic atrophy; no strictures of the intrahepatric bile ducts
IIb	Atrophy limited to a segment/ Stricture of the intrahepatic bile ducts
IIc	With biliary cirrhosis and portal hypertension

Additional Type E	Extrahepatic stones
Ea	Normal sphincter of Oddi
Eb	Relaxation of the sphincter of Oddi
Ec	Stricture of the sphincter of Oddi

III. CLINICAL DIAGNOSIS

In a few asymptomatic patients, the disease may be diagnosed incidentally on abdominal USG. [11] Majority of patients are asymptomatic. Typical symptoms are epigastric or right upper quadrant pain, jaundice and fever. These features typically define Charcot's triad of cholangitis. If the patient presents at a later stage they may have features of cholangitis leading to hepatic abscess and pyogenic biliary sepsis.[12, 13] A select few patients may even develop thrombocytopenia and enhanced platelet activation resulting in coagulopathies.[6] Bacterial cholangitis leads to secondary sclerosing cholangitis, biliary strictures, parenchymal atrophy and liver abscesses terminating into systemic sepsis. In patients with heavy stone load, the chances of gall stone pancreatitis are very high. The occurrence of a concomitant cholangiocarcinoma especially in patients with calcium bilirubinate stones is very high. Chronic bacterial infection superimposed on biliary stasis leading to persistent irritation causes mucosal adenomatous hyperplasia eventually leading to cholangiocarcinoma. [13] Hence the presence of a concomitant cholangiocarcinoma has to be kept in mind while dealing with patients with long standing hepatolithiasis.

IV. DIAGNOSIS

Various aspects of the stone disease need to be studied before deciding the best therapeutic option for the disease. [12,13] Hence the main aims in diagnosis are:

1) Accurate localization of the stones
2) Biliary strictures
3) Identifying involved lobes of the liver
4) Excluding concomitant cholangiocarcinomas

Ultrasonography (USG)

Ultrasonography findings in hepatolithiasis are variable but quite diagnostic [13]

1) Intra hepatic stones are picked up as echogenic spots with post acoustic shadowing. (Figure 2)
2) Bile duct dilatation is also diagnosed
3) High echogenicity rim on the anterior surface of stones is strongly indicative of calcium content
4) Calcium bilirubinate stones have marked biliary dilation peripheral to stones, whereas ductal dilation in cholesterol stones is usually restricted to the site of the stone.

Since ultrasonography is performer dependent, it may at times fail to differentiate between intrahepatic stones from pneumobilia.

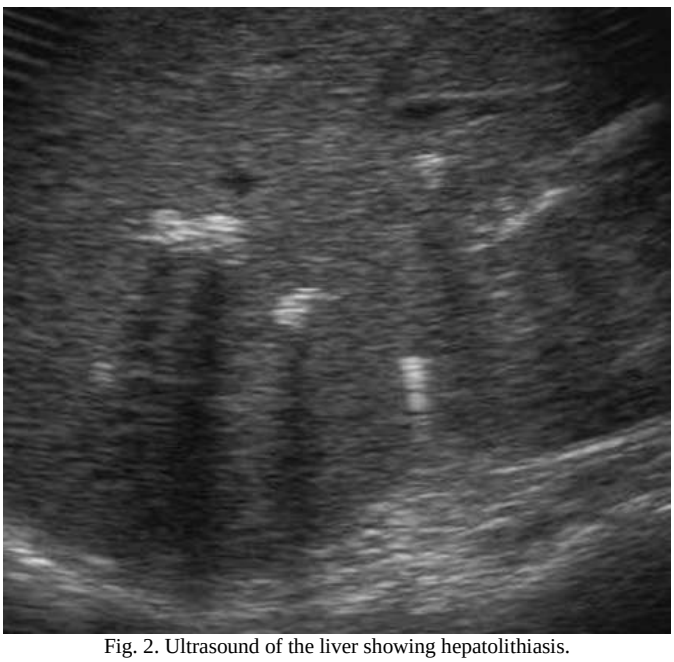

Fig. 2. Ultrasound of the liver showing hepatolithiasis.

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Contrast enhanced computed tomography (CECT)

Triple phase CECT is the investigation of choice. (Figure 3) It will typically show

1) Define ductal anatomy with respect to ductal dilation and biliary strictures.
2) Assess the stone load.

It is also helpful in diagnosing cholangiocarcinomas. [13,14]

Cholangiocarcinomas will typically exhibit

1) Periductal soft tissue density
2) Ductal wall thickening or enhancement
3) Portal vein involvement or obstruction
4) Lymph node involvement

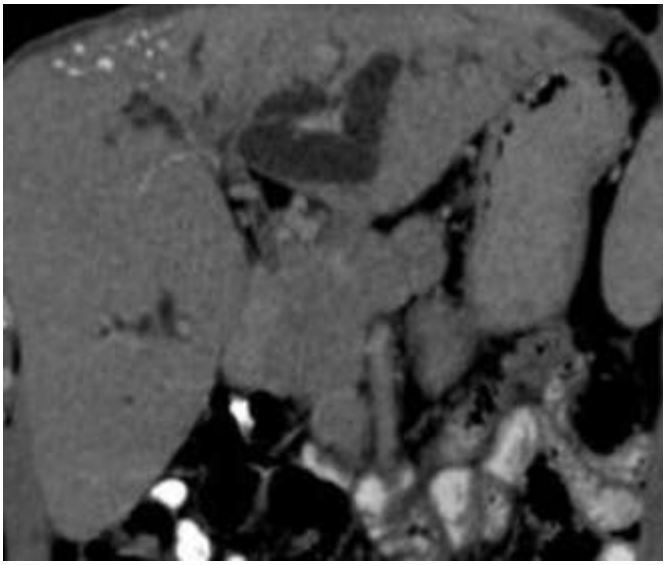

Fig. 3. CECT showing hepatolithiasis

Magnetic Resonance Imaging (MRI)

MRI is another investigation which may also help especially in cases of obstructive jaundice. [12, 13] It helps in determining the level and the cause of obstruction. Diagnosis of cholangiocarcinoma is the biggest challenge despite the availability of CT and MRI. Even intraoperatively it may be very difficult to pick up cholangiocarcinoma as the affected segment is significantly fibrosed thereby obscuring the malignancy. Estimation of CEA levels may help in providing evidence of cholangiocarcinoma in patients with hepatolithiasis.

ERCP

ERCP is an extremely important diagnostic tool in hepatolithiasis. [13] It may be considered the gold standard in diagnosis. It has the added advantage of stone extraction and biopsy of intraductal lesions followed by insertion of stents in order to relieve obstruction in cases of cholangitis.

V. MANAGEMENT

Aims of treatment in hepatolithiasis are

1) Resolving on going infection
2) Prevent recurrent cholangitis and subsequent fibrosis of liver
3) Decreasing the need for recurrent instrumentation
4) Prevent progression to cholangiocarcinoma and in rare cases even removal of known intraductal tumors.

Surgical options

Partial hepatectomy remains the treatment of choice especially for lesions which are associated with significant liver fibrosis. [14-16]

Indications for left hepatectomny are

1) Unilobular hepatolithiasis particularly left sided.
2) Atrophy fibrosis with multiple abscesses secondary to hepatolithiasis
3) Concomitant intrahepatic cholangiocarcinoma.
4) Multiple intrahepatic stones with biliary strictures that cannot be treated percutaneously or endoscopically.

Indications for right hepatectomy

Predominantly right sided disease (but associated with very high morbidity). In cases where CBD strictures are accompanied with a combination of intra and extra hepatic stones, resection of atrophic hepatic segments with hepaticojejeunostomy may be required. [16] If expertise is available then a laparoscopic approach can also be attempted. [17] In many cases hepatectomy with CBD exploration and T-tube insertion may be required. [18,19] Newer innovative methods such as creation of subcutaneous tunneled hepatocholangioplasty with utilization of gall bladder in cases with localized hepatolithiasis with no distal CBD strictures with normal gall bladder. [13] In recent times laparoscopic hepatectomies have also been described. [17] If the liver parenchyma is diffusely affected by this disease leading to cirrhosis and portal hypertension culminating into hepatic failure then liver transplantation remains the only option. [20]

Few centers have described alternatives to surgery. This includes endoscopic resection of peripheral biliary stenosis to aid evacuation of intrahepatic stones followed by chemical bile duct embolization using ethanol and N-butyl cyanoacrylate.

VI. COMPLICATIONS OF SURGERY

The morbidity associated with hepatic resection is quite high. The complications of surgical intervention are

1) Recurrent biliary sepsis
2) Hepatic fibrosis
3) Cirrhosis
4) Wound infection
5) Bile leakage – biliary leakage is best approached by USG guided percutaneous drainage or naso-biliary drainage. Left sided leaks are more common. These may require revisional surgery in the form of left lateral segmentectomy or even hepatectomy.[18]

Recurrence

Factors which influence the recurrence of the disease are variable. [15]

These include

1) Non-surgical modalities of treatment
2) Biliary cirrhosis
3) Residual stones

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4) Strictures

In patients who have undergone surgical treatment, bilateral hepatic stone disease and limited resection of liver are important risk factors for the disease. [15]

VII. Conclusion

Hepatolithiasis is one of the most complex stone disease of the biliary passages. Identification of ductal anatomy, stone load and its impact on surrounding liver parenchyma is essential to decide the most optimum treatment plan for the patient.

Evaluation of extent of the disease is important in determining the extent and nature of the resection. Optimizing the patient prior to surgery is therefore necessary to reduce the morbidity and mortality associated with surgical treatment of this complex disease.

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