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Review Article

Gall stones: a fundamental clinical review

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ABSTRACT

Formation of stones in the gall bladder is known as cholelithiasis. About 10% to 20% of Western population are suffering from gall stones and this percentage is increasing day by day. Biochemically gall stones are classified into black pigment stones, brown pigment stones and cholesterol stones. Gall stones can be anatomically located at two possible sites; in the gall bladder known as cholelithiasis and in the common bile duct known as choledocholithiasis. Gall stones may present with symptoms known as symptomatic gallstones or without symptoms known as asymptomatic gallstones. The major causes of gallstones are high cholesterol diet, low bile salt levels, decreased gall bladder motility etc. Obesity, female gender, family history, rapid weight loss and vitamin B12 or folic acid deficiency are considered as important risk factors in the development of gall stones. The clinical presentations include acute cholecystitis and febrile illness with pain and tenderness in the right upper quadrant (Murphy sign). Generalized body weakness and weight loss are considered as generalized symptoms of gallstones. The complications include cholangitis, empyema of gall bladder, pancreatitis, abscess formation, porcelain gall bladder and gall bladder perforation. The differential diagnosis of gall stones is carried out based on endoscopy, ALT and AST serum levels. Non-surgical treatment for gall stones is oral dissolution therapy. The standard surgical treatment for gall stones is cholecystectomy.

Keywords: Bile, Cholesterol, Gall bladder, Jaundice, Leukocytosis

INTRODUCTION

Formation of stones in gall bladder is known as Cholelithiasis (gall stones).[1] They mostly occur in adults as compared to children population.[2]

The frequency of gall stones among children population is 1.9%.[3] 10% to 20% adult population of Western countries suffer from gall stones and its prevalence in India 3% to 6%.[4,5] Among various variants of gall stones about 70 % patients have cholesterol stones, and 30% have pigmented gall bladder stones. The prevalence of brown pigment stones is highest in East Asia.[6,7] About 80% of patients having cholelithiasis remain unaware of their disease and about 1% to 2% patients per year develop complications due to unawareness and need surgery as treatment.[8] In USA the diagnosis of cholelithiasis is most impatient among various

gastrointestinal and hepatic disorders. The common surgical operation performed in America and Europe is Cholesystectomy.[9]

Biochemical classification of gall stones

Gallstones are classified into following:

- Black pigment stones
- Brown pigment stones
- Cholesterol stones.[10]

Black pigment stones

A black pigmented stone contains predominately bile. Super saturation of bile along with calcium bilirubinate lead to formation of black pigment stones. Black pigment stones are composed of less than 30% cholesterol.[11] These are present in patients associated with Hemolytic Jaundice, Sickle Cell Disease, Cystic Fibrosis, Hereditary Spherocytosis, Gilbert Syndrome and in Illeal Crohn's Disease. Increased entero-hepatic circulation of bilirubin also contributes to the formation of black pigment stones. In West 30% of gall stones comprise of black pigment stones.[12] Patients having black pigment stones commonly do not have bacterial infection and mostly these stones are present in gall bladder.[11]

Black pigment stones commonly show amorphous appearance. In sickle cell anemia risk of black pigment stones increases due to increase in unconjugated bilirubin which leads to precipitation of calcium bilirubinate. This type of precipitation of calcium bilirubinate leads to formation of black pigment stones.[12]

Brown pigment stones

Brown pigment stones are also known as bile pigment stones, bilirubin stones, earthy stones or muddy stones. On average 43 % of cholesterol content is found in brown pigment stones.[13] In addition brown pigment stones also have amorphous material and mucous glycoprotein. These stones are primarily present in bile ducts and are associated with bacterial infection or parasitic infection and bile stasis.[11]

In brown pigment stones, intrahepatic and extra hepatic gallstones are different in composition from each other. Their surface has various shapes from round to faceted and exhibit various colors like yellowish brown, greenish brown and black brown. Brown stones are frequently found in Asian population.[14]

Cholesterol stones

These are most commonly found gall stones which contain up to 70% of cholesterol content. In addition, they also contain bile pigment, glycoprotein and calcium salts. Patients with cholesterol gall stones have decreased bile salt synthesis and increased biliary secretion of cholesterol due to increase cholesterol intake. Patients with cholesterol gall stones also have impaired gall bladder emptying in postprandial state.[15] Their color varies from light yellow to dark green. They are usually oval in shape and each often have a dark central spot of about 2-3 cm long.

In Pediatrics Population cholesterol stones are less common. In Diabetic patients there is a risk of impaired gall bladder motility that leads to cholesterol gall stones. Inflammation in gall bladder wall may also be a risk factor for gall stones formation. Bacterial DNA is commonly not found in gall stones having a cholesterol content greater than 90%.[16] Cholesterol stones are frequently found in Western community. The pathogenesis of cholesterol gall stones is shown in (Figure 1).[17]

The comparison between black pigment stones, brown pigment stones and cholesterol stones is given in (Table 1).

Anatomical classification of gall stones

There are two types of stones depending upon their anatomical variations in location:

- Cholelithiasis
- Choledocholithiasis

Cholelithiasis

Formation of stones within in the gall bladder is known as cholelithiasis. 88-94% patients suffering from gall stones have stone in gall bladder. Stones may be black pigment stones, brown pigment stones or cholesterol stones.[10]

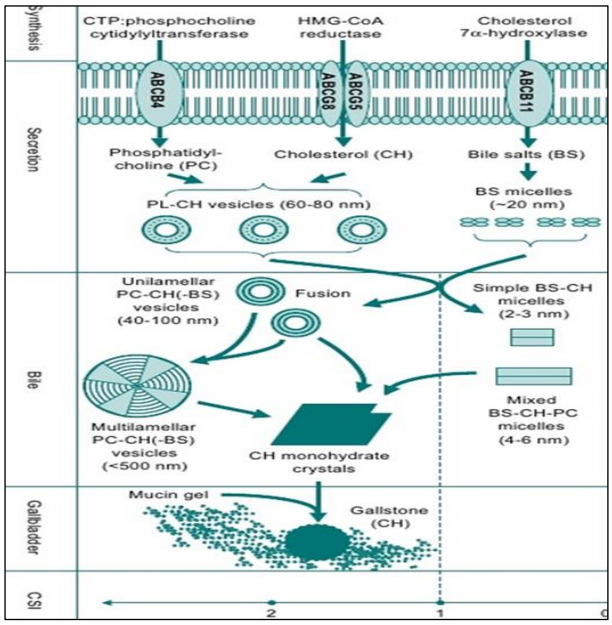

Figure 1: Pathogenesis of cholesterol gallstones.

Table 1: Comparison between various types of gall stones.

Type of stone	Black pigment stones	Brown pigment stones	Cholesterol stones
Color	Black	Brown	Yellow to dark green
Shape	Various Shapes	Various shapes rounded to faceted	Oval in shape with dark central spot
Cholesterol content	30%	43%	70%
Associated diseases	Gilbert syndrome, sickle cell disease, cystic fibrosis	Bacterial infection, Parasitic infection	Diabetes mellitus
Epidemiology	Western population	Asian Population	Western population
Bacterial or parasitic infection	Absent	Present	Present

Choledocholithiasis

In this type, the stones are located in the common bile duct. 6-12% patients suffering from gall stones have stone in common bile duct (CBD) and their presence in CBD increases with age.

Clinical classification of gall stones

Clinically gall stones are classified into two types:

- Asymptomatic gall stones
- Symptomatic gall stones

Asymptomatic Gall Stones

The percentage of asymptomatic gall stones among the patients suffering from cholelithiasis is about 70 % and the patients with the progression of asymptomatic to symptomatic are about 10 to 20%. However, the majority of patients show symptoms before going towards the complexity of disease.[18]

The candidates susceptible for laparoscopy are those patients who are suffering from sickle cell anemia, diabetes mellitus, gall bladder carcinoma, the patient with porcelain gall bladder and female less than 60 years waiting for transplant.

There is no evidence available that shows that lifestyle modification for example decrease fatty food intake and increase in exercise have influence on prevention and decrement of incidence of symptoms in people suffering from asymptomatic gallstones.[19]

Symptomatic Gall Stones

The symptomatic gallstones present with symptoms of recurrent attacks of pain, nausea and vomiting. The pain in epigastric region or in right upper quadrant may radiate backward towards shoulder. The character of recurrent pain plays an important role in diagnosis of symptomatic gallstones.[20]

Etiology

High cholesterol diet plays an important role in the development of gallstones. The main cause of development of gallstones is the alteration of balance between pro-nucleating and anti-nucleating factors. Low bile salt levels and decreased gall bladder motility play an important role in the development of gall stones.[20] Gall bladder mucin is an important factor in the formation of gall stones. Delayed large bowel transit times favor the formation of gall stones. Cholesterol supersaturation increased de-conjugation of bilirubin glucuronides and increased biliary bilirubin load are telltale to the formation of gall stones.[21] The causes of gall stones have been summarized in (Table 2).

Table 2: Causes of gall stones.

Causes of gall stones
High cholesterol diet
Altered balance between pro-nucleating and anti-nucleating factors
Low bile salts level
Decreased gall bladder motility
Gall bladder mucin
Delayed large bowel transit time
Cholesterol supersaturation
Increased de-conjugation of bilirubin glucuronides
Increased biliary bilirubin load

Risk factors

Female gender, family history, fecundity, obesity, type 2 diabetes (DM) and hyperinsulinemia are an important risk factors for development of gallstones.[21] The dietary factors which increase the risk of formation of gall stones are high carbohydrate diet and high fatty acid diet. In contrast to this unsaturated fats, coffee, alcohol and

physical activity reduce the risk of development of gall stones.[22,23] Biliary strictures, rapid weight loss and vitamin B12 or folic acid deficiency also promote the formation of gall stones. Drugs like oral contraceptives (OCPs) also favor the formation of gall stones.[24] The incidence of development of gallstones also increases during pregnancy.[25]

Clinical presentations

The clinical presentations of gall stones include acute cholecystitis and febrile illness with pain and tenderness in the right upper quadrant (Murphy Sign). Persistent pain, fever and jaundice may also be present and are collectively known as Charcot's triad and if this triad is associated with septic shock and altered level of consciousness then it is collectively known as Raynaud's pentad. The clinical manifestations of gall stones also include biliary colic, jaundice and acute pancreatitis.[26] Leukocytosis, sepsis, transient alcoholic or clay-colored stools, fatty food intolerance, chills, nausea and vomiting are also included in clinical presentations of gall stones. General weakness and loss of weight can also be considered as generalized symptoms of gall bladder stones.[27]

Mild rise in alkaline phosphatase level (ALP) may be the indicative of severe form of gall stone disease. The clinical presentations of gall stones have been summarized in (Table 3).

Table 3: Clinical presentations of gall stones.

Signs and Symptoms
Febrile illness
Pain and tenderness in right upper quadrant
Jaundice
Fever
Biliary colic
Nausea
Vomiting
Clay colored stools
Fatty food intolerance
Sepsis
Chills
Weight loss

Complications

The complications of gall stones include following:

- Empyema of gall bladder
- Gangrenous gall bladder
- Abscess formation
- Mucocele of the gall bladder
- Gall bladder perforation
- Biliary peritonitis
- Bile duct obstruction
- Cholangitis
- Pancreatitis
- Cholecysto-colic fistula
- Cholecysto-duodenal fistula
- Gallstone ileus
- Porcelain gall bladder
- Gall bladder cancer
- Cholangiocarcinoma.[28,29]

Differential diagnosis

Gall stones are diagnosed based on abdominal symptoms including pain in the right upper quadrant. However, pain in this area is not specific for gall stones. The pain in the right upper quadrant can occur due to dyspepsia, duodenal ulcer, hepatic ulcer and acute myocardial infarction. The differential diagnosis of gall stones can be carried on the basis of endoscopy and ALT/AST serum levels.[30]

Multiple radiological techniques including ultrasonography (USG), Hepatobiliary Imino-diacetic Acid scan (HIDA-scan), Magnetic Resonance Cholangiopancreatography (MRCP), Computed Tomography (CT), Endoscopic Retrograde Cholangiopancreatography (ERCP), Percutaneous Trans-hepatic Cholangiopancreatography (PTC) and plain abdominal radiography (X-ray) help in diagnosis of gall stones and complications of gall stones. Moreover, these techniques are also useful in excluding other causes of acute abdominal pain e.g. intestinal obstruction, renal stones, and chronic pancreatitis.[31,32]

Management

Gall stone disease is managed on the basis presence or absence of symptoms, complications, function of gall bladder and on the basis of composition and size of gall stones.[33]

Non-surgical treatment of gall stones disease

It involves the use of bile acids as an oral dissolution therapy for dissolving the gall stones. The available bile acid therapy, which is used probably, includes deoxycholic acid and chenodeoxycholic acid, is effective and tolerated. The symptoms related to biliary colic are treated with pethidine which is given with an antispasmodic agent like atropine or glycopyrronium.[34] The acute biliary colic pain treated with NSAIDs (non-steroidal anti-inflammatory drugs) and anti-spasmodic drugs like scopolamine. Drugs inhibiting cholesterol formation like statins influence the cholesterol gall stones and dissolution. The disadvantage is the recurrence of gall stones in 25 % of patients within five years after treatment. External shock wave lithotripsy (ESWL) can be used in treatment of gall stones.[35]

Surgical treatment of gall stones disease

The surgical treatment is the standard treatment for gall stone disease. Primary procedure for the symptomatic gallstone disease is cholecystectomy which involves low risk for its recurrence and provides relief in biliary pain in 92% of patients. Laparoscopic cholecystectomy is much better than open cholecystectomy due to low mortality rate, less pain and shorter hospital stay. Prophylactic treatment along with laparoscopic cholecystectomy is recommended for patients suffering from the complications of gall stones.[36]

DISCUSSION

Among the three types of classification of gall stones, the biochemical classification is the most important one. All the types of gall stones contain cholesterol in varying amounts; however, the black pigment stones are mostly associated with increased enterohepatic circulation of bilirubin as a result of various hemolytic diseases.[12] So, it can easily be concluded that these kind of gall stones are more difficult to be prevented. On the other hand, brown pigment and cholesterol stones are directly related to high cholesterol levels. Moreover, both these types of stones are associated with bacterial or parasitic infections and bile stasis such as in diabetics.[11] Hence, the above mentioned discussion leads to conclusion that these stones can be prevented by avoiding high carbohydrate and fatty diet.[22,23] Management of gall stones depends upon presenting symptoms.

Patients presenting with acute pain are managed with NSAIDs and anti-spasmodic drugs. Ursodeoxycholic acid is considered to be very effective in preventing gall stones. A prospective study conducted on randomized patients revealed that frequency of gall stones formation significantly reduced with the using of ursodeoxycholic acid. While, in Asia cholecystectomy is standard surgical treatment for gall stones, as it involves low risk of recurrence.[36]

A cochrane review trial was conducted to compare the various parameters of open and laparoscopic cholecystectomy like mortality, complications and morbidity. This trial concluded that there is no such acceptable difference between open and laparoscopic cholecystectomy.

A new modern technique is developing for better and complete treatment of gastrointestinal problems. A new recently advanced technique is being developed to perform surgery without any kind of skin incisions. This advanced technique allows access to intraabdominal cavity via natural human body orifices like mouth, vagina and anus. This experimental technique involves the usage of highly flexible endoscopes and is known as natural orifice transluminal endoscopic surgery.[37]

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