CHAPTER 83
Cholelithiasis (Gallstones)

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Introduction

Cholelithiasis (gallstones) in children is being diagnosed with increasing frequency in developed countries. This is related to an increase in recognition due to the widespread use of ultrasound (US) scans for abdominal complaints and an increase in the frequency of the disease secondary to some predisposing factors. These factors include an increase in childhood obesity, common use of total parenteral nutrition in fasting premature infants, an increase in the incidence of necrotising enterocolitis requiring ileal resection, more frequent use of lithogenic medications (e.g., ceftriaxone), improved medical treatment, longer survival of patients with haemolytic disease, and an increase in adolescent pregnancy. In Africa, children with sickle cell disease are more affected by cholelithiasis, and the incidence increases with age.

Demographics

The incidence of cholelithiasis in children is reported to be 0.15–0.22%, whereas the incidence in adults is approximately 10%.[1] The incidence of cholelithiasis in patients with sickle cell disease has been reported to be 10–70% in the United States.[1] In Nigeria, the prevalence of gallstones diagnosed in a predominantly teenage population of children with SS haemoglobin was found to be 9%, but there was a higher prevalence of 24.1% in older sickle cell patients.[2] A prevalence of 4% was found in Ghanaian children with sickle cell disease[3] and 9.4% in Senegalian sickle cell children.[4]

Embryology of the Bile Ducts

The liver develops from an endodermal bud in the ventral floor of the foregut at about 22 days gestation. The cells of the cranial portion give rise to the mature hepatocytes, intrahepatic bile ducts, proximal extrahepatic bile ducts, and gallbladder. The distal extrahepatic bile ducts are derived from cells in the caudal portion.

Physiologic Maturation of the Biliary System

Hepatocytes perform a wide variety of essential physiologic tasks, including production of plasma proteins, gluconeogenesis, glycogenolysis, biotransformation of toxins and chemicals, bile acid metabolism, cholesterol regulation, and bilirubin excretion. During gestation, many of these functions are performed for the foetus through placental transport and maternal hepatic function. Many of the excretory functions of the foetal liver mature only after birth. The physiologic immaturity of the premature liver plays a role in the pathophysiology of a variety of neonatal diseases characterised by abnormal bile composition or flow.

Maturation of Bile Acid Metabolism and the Enterohepatic Circulation

Bile acids are amphipathic sterols formed in the liver by stereospecific additions and modifications of cholesterol. Bile acid metabolism is a critical determinant of cholesterol regulation. The interaction of bile acids, phospholipids, and cholesterol leads to mixed micelle formation, allowing biliary excretion of these lipids and other compounds, and facilitating intestinal absorption of dietary fat.

The enterohepatic circulation maintains the bile acid pool by recycling 90% of the excreted bile acid. This occurs through a sodium-bile acid transport system, present on the ileal brush border that absorbs bile acid against a concentration gradient. The bile acids return to the liver through the portal circulation, where they are actively secreted by a second sodium-bile acid cotransporter across the hepatocyte canalicular basolateral membrane. Bacteria present in the jejunum and ileum metabolise a portion of the primary bile acids to secondary bile acids, which are passively absorbed in the colon and re-enter the hepatic circulation. Maturation of hepatic and ileal bile acid transport does not begin until around the time of birth.

Foetuses and newborns have qualitative differences from adults in bile acid composition. Foetal bile contains an increased chenodeoxycholic/cholic acid ratio, a predominance of taurine conjugates, and the presence of unusual bile acids with specific hydroxylations seen in adults with cholestasis. Therefore, the preterm or term infant has several predispositions to cholestasis. The diminished bile acid pool and decreased intraluminal concentration of bile acid result in decreased bile acid flow, which favours the development of sludge or cholelithiasis.

Maturation of Bile Pigment Excretion

Most bilirubin is the end product of the degradation of haem derived from erythrocytes normally removed from the circulation and destroyed in the reticuloendothelial system.

Erythrocyte half-life is shorter in the foetus and neonate, and therefore production of unconjugated bilirubin is greater than in an adult. Bilirubin UDP-glucuonyl tranferase activity, which conjugates bilirubin, is first detected at about 20 weeks gestation and remains low until after birth. The reabsorption of unconjugated bilurubin from the intestine may also contribute to the increased bilirubin load after birth. Conjugated bilirubin gradually accumulates in meconium during foetal life. Bacterial flora responsible for the conversion of conjugated bilirubin to urobilin are absent or reduced in the gut of the newborn infant, which allows the enzyme B glucuronidase to deconjugate the accumulated bilirubin. This process results in the absorption of a significant load of unconjugated bilirubin from the newborn intestine.

Pathogenesis

The pathogenesis of cholelithiasis in children is multifactorial and differs according to age at presentation. In infants, the normal immaturity of the hepatic excretory function and the enterohepatic circulation lower the threshold for stone formation when combined with lithogenic factors (parenteral alimentation, fasting, dehydration, furosemide treatment, ileal resection related to necrotising enterocolitis or volvulus, biliary tract anomalies, and polycythaemia). In this age group, cholestasis can manifest as liver functional abnormality, as biliary sludge, or as true cholelithiasis directly related to the duration of fasting.

In the prepubertal child, stones are more likely to be idiopathic or related to chronic haemolysis, cystic fibrosis, ileal resection, or ceftriaxone therapy. In this age group, stone composition is predominantly calcium bilirubinate or calcium carbonate, and the gender incidence is equal.

After puberty and in the adult population, stones are more likely to be predominantly cholesterol. The solubility of cholesterol depends on the concentration of lecithin, bile salts, and cholesterol within bile. Any

disturbance in the concentration of these three substances may leave the bile lithogenic and predisposed to formation of cholesterol stones. These stones result when the bile cannot solubilise all the cholesterol. In this age group, there is an increased female-to-male ratio. Racial and genetic influences, obesity, oral contraceptives, and pregnancy are also predisposing factors.

Haemolytic Disease

Pigmented stones can be black or earthy brown (calcium bilirubinate). Black-pigmented stones usually are associated with a haemolytic process such as sickle cell disease, thalassaemia major, hereditary spherocytosis, pyruvate kinase deficiency, autoimmune haemolytic anaemia, or other haemolytic processes. Calcium bilirubinate stones are found in patients with infected bile or biliary structures. Although the exact cause of the development of pigmented stones is unclear, the bile in these patients contains an excess amount of unconjugated bilirubin and beta-glucuronidase, an enzyme produced by bacteria that may hydrolyze soluble bilirubin glucuronide to insoluble unconjugated bilirubin and glucuronic acid. Unconjugated bilirubin may form calcium bilirubinate. Stasis and nucleating factors also may play roles in the development of these stones. Jaundice also may occur intermittently because of haemolysis; therefore, jaundice does not necessarily mean that common duct calculi are present.

Sickle Cell Anaemia

The incidence of gallstones increases with age in children with sickle cell anaemia: 12% are affected in the 2–4 year age group and 42% in the 15–18 year group.[2] It can be difficult to differentiate symptoms of biliary colic from an abdominal crisis in the sickle cell patient. Utrasound should be performed in all children with sickle cell disease and abdominal pain, as there is an increased risk of complications related to cholelithiasis in patients with sickle cell disease. Careful preoperative preparation of a child with sickle cell anaemia is essential to avoid perioperative sickling of the abnormal red blood cells. This sickling may be precipitated by hypoxia, hypovolaemia, acidosis, hypothermia, and a high level of haemoglobin S. Cholecystectomy is currently not recommended for children with sickle cell disease unless symptomatic. Cholecystectomy should be performed electively rather than as an emergency procedure during a haemolytic crisis. Partial exchange transfusion is necessary before operation to reduce the haemoglobin S level to less than 40%.

Thalassaemia Major

The incidence of gallstones varies from 2.3% to 23% and increases with age.[1] The risk of cholelithiasis in the patient population with thalassaemia major is decreasing because of hypertransfusion therapy that blocks the bone marrow so that the fragile cells of thalassaemia major are no longer produced. For all symptomatic patients and for patients undergoing splenectomy in whom preoperative ultrasound shows the presence of gallstones, cholecystectomy is recommended.

Hereditary Spherocytosis

Hereditary spherocytosis is rare in the Africa population.[5] The incidence of cholelithiasis in this disease is 43–63% and is slightly more common in girls than boys. Abdominal ultrasound should be performed before elective splenectomy to detect the presence of gallstones. Demonstration of stones dictates that a simultaneous cholecystectomy should be performed.

Congenital Deformities of the Gallbladder

Agenesis, duplication, bilobation, floating gallbladder, diverticula, and ectopia are usually of no real clinical relevance unless they impair gallbladder emptying; calculi are frequent in such cases.

Clinical Presentation

Clinical presentation depends on age. Gallstones are frequently asymptomatic in all age groups and detected on evaluation for other problems. Diagnosis in infancy requires clinical suspicion because the presentation is nonspecific. Persistent direct hyperbilirubinaemia should lead to an evaluation of the biliary tract, including evaluation for cholelithiasis. Jaundice and fever in an infant with any predisposing factors should lead to prompt evaluation for stones.

In older children, the presenting complaint is almost always abdominal pain. Younger children may not be able to localise abdominal pain, whereas older children have more typical right upper quadrant or subscapular pain. Diagnosis is often delayed due to a lack of suspicion in children and an absence of predisposing conditions. Evaluation of children with recurrent unexplained abdominal pain should include an evaluation for biliary disease. Abdominal pain in patients with chronic haemolysis or other predisposing factors should prompt immediate biliary evaluation.

Presentation in the postpubertal population is similar to that in adults. Pain is usually dull and subcostal in location and may radiate to the subscapular region. Fatty food intolerance with associated nausea and vomiting may be present.

In children with chronic cholecystitis and cholelithiasis, the physical examination is often normal. Patients with acute cholecystitis may show elevated temperature, signs of dehydration, nausea, and right upper abdominal tenderness and muscle guarding. Some patients may have a tender, palpable mass (Murphy's sign). Laboratory findings include leukocytosis and elevated serum direct bilirubin, alkaline phosphatase, and glutamyl transferase levels. Because pancreatitis can occur in 10% of such patients, serum amylase and lipase level should be monitored as well.

Diagnosis

Most gallstones in children are radiolucent, and US is the diagnostic modality of choice. Ultrasound diagnosis (Figure 83.1) of stones requires the presence of moveable, echogenic structures within the gallbladder, with associated shadowing. Sludge is a fluid substance that on US examination can be seen layering out in the dependent portion of the gallbladder. An US finding of an impacted stone at the ampulla, associated gallbladder wall thickening, or localised pericholecystic fluid support the clinical diagnosis of acute cholecystitis.

Common bile duct dilatation suggests choledocholithiasis, and confirmatory endoscopic retrograde cholangiopancreatography (ERCP) or operative or transhepatic cholangiography may be required.

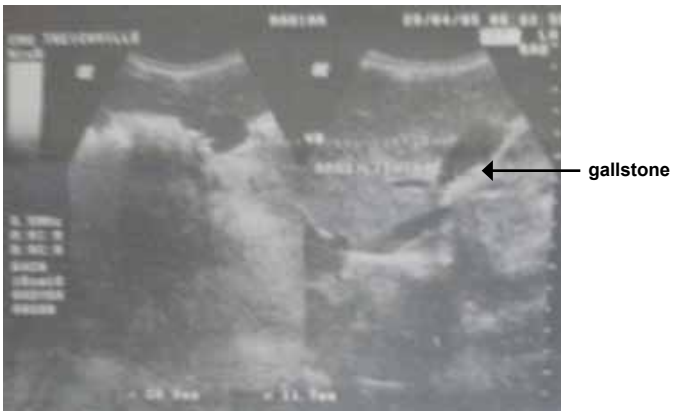

Figure 83.1: Ultrasound of an 8-year-old sickle cell disease girl with gallstone.

Differential Diagnosis

Hydrops of the Gallbladder

Acute distention of the gallbladder with oedema of the gallbladder wall has been reported in association with septic or shocklike states, severe diarrhoea with dehydration, hepatitis, scarlet fever, Kawasaki disease, leptospiroses, and mesenteric adenitis. Hydrops is suspected if a palpable mass of the gallbladder is confirmed by US. Generally, hydrops resolves spontaneously. If symptoms intensify, cholecystectomy may be necessary.

Acalculous Cholecystitis

Acalculous cholecystitis may occur as a complication during treatment of various disease states. This condition may occur in newborns, but it is more common in older children. Patients are often severely ill and sometimes intubated in an intensive care unit, so early manifestations of the disease are not evident. The most common presentation is deterioration and signs of sepsis in a previously stable patient. The diagnosis is confirmed by US, which demonstrates gallbladder distention and intraluminal echogenic debris. Treatment in mild cases can be conservative with antibiotics, but if the patient's condition deteriorates, cholecystectomy should be performed. If the patient is very ill, percutaneous or open cholecystostomy may be useful as a temporary measure.

Biliary Dyskinesia

Biliary dyskinesia is a distinct clinical entity that occurs primarily in older children and adults. It is characterised by poor gallbladder contractility and the presence of cholesterol crystals in the gallbladder bile. There is often a delay in diagnosis in patients with this condition because US does not show cholelithiasis. Biliary dyskinesia is diagnosed with a cholecystokinin-stimulated hepato-iminodiacetic acid (HIDA) scan that shows poor biliary excretion.

Other differential diagnoses of right upper quadrant pain are acute appendicitis, peptic ulcer disease, inflammatory bowel disease, hepatitis, pancreatitis, intussusception, acute sequestration crisis, and malaria fever.

Treatment

Numerous nonoperative therapies were introduced for the management of gallstones, including dissolution of cholesterol gallstones with oral administration of chenodeoxycholic acid, the use of extracorporeal shock-wave lithotripsy, and percutaneous endoscopic cholecystolithotomy. These therapies have been all but abandoned. In developed countries and in some developing countries, laparoscopic cholecystectomy has become the preferred standard for the management of symptomatic children with cholelithiasis.[1,4,6,7]

Preoperative ultrasound is performed on each patient to confirm the diagnosis of cholelithiasis and to evaluate the presence or absence of common duct involvement. In developed countries, if choledocholithiasis is suspected on initial evaluation, ERCP and sphincterotomy are recommended before laparoscopic cholecystectomy. The expertise to remove the stones endoscopically is not available in all children's hospitals, however. If choledocholithiasis is documented and the stones cannot be removed endoscopically, the surgeon must decide whether to proceed with laparoscopic cholecystectomy and laparoscopic choledochal exploration or to perform an open operation.

Laparoscopic Cholecystectomy

Laparoscopic cholecystectomy is now the standard method for cholecystectomy for children in more developed locations. Since the technique is so technologically dependent, however, it is not appropriate for resource-poor locations that do not have a dependable supply of electricity or the money to purchase enough equipment to have reserve supplies whenever there is a malfunction of the primary equipment (a frequent occurrence, even in developed locations). There is a very steep learning curve for this procedure, and the complications of injury or ligation of the common bile duct are often catastrophic. Therefore laparoscopic cholecystectomy is recommended only for the most advanced African hospitals with excellent equipment and supplies. It is quite important that all surgeons undertaking laparoscopic cholecystectomy know how to expertly perform open cholecystectomies and common bile duct explorations.

Procedure

General endotracheal anaesthesia is administered with a muscle relaxant to assist with the pneumoperitoneum. The abdomen is prepared and draped in a sterile fashion.

1. A 10-mm incision is made in a vertical direction through the umbilical skin and carried down through the umbilical fascia with a cautery.

2. A 10-mm port is introduced directly into the abdominal cavity.

3. A pneumoperitoneum is created with insufflation of CO_2 up to a maximum pressure of 15 mm Hg.

4. The other ports are introduced under telescopic vision after creation of the pneumoperitoneum. The position of the other incisions and ports varies according to the patient's size. It is important to place these ports widely in the younger patient because the intraabdominal working space is reduced. Two 3- or 5-mm ports are placed on the right side of the abdomen, one below the right costal margin and one in the right mid to lower abdomen.

5. The fourth incision is 5 mm (or 10 mm if a 10-mm endoscopic clip applier is required), and it is situated in the epigastric region in the older child or to the left of the midline in the younger child.

6. The fundus of the gallbladder is grasped with a grasping forceps that has been introduced through the lower, lateral cannula, and the gallbladder is retracted superiorly and ventrally over the liver.

7. The infundibulum is retracted to the patient's right using the right upper port for access. This allows the cystic duct to enter the common duct as close to a 90° angle as possible. If the infundibulum is retracted cephalad instead, the cystic duct approaches the common duct, and injury or ligation of the common duct is more likely to occur.

8. The cystic duct is skeletonised. Cholangiography often is not necessary, but if it is, it can be performed at this point by making an incision in the cystic duct and introducing a cholangiogram catheter.

9. If a cholangiogram is not performed, or after it is performed, the cystic duct is triply clipped and divided between the proximal clips and the distal third clip, leaving two clips on the cystic duct stump and one clip on the duct next to the gallbladder so that bile will not be leaking during the rest of the case.

10. The cystic artery is triply clipped and divided in a similar fashion in Calot's triangle.

11. The gallbladder is dissected from its liver bed in a retrograde fashion with a hook or spatula cautery. Before complete detachment of the gallbladder from the liver, the area of the dissection is inspected carefully and haemostasis is achieved. The gallbladder is detached completely from its liver bed.

12. The telescope is moved from the umbilical port to the cannula of the epigastric port.

13. The gallbladder is removed through the umbilical cannula or through the fascial defect if it is necessary to remove the cannula.

14. The dissected area is inspected again and haemostasis assured. Ports and instruments are removed, and the incisions are closed.

Advantages

The advantages of the laparoscopic approach include less operative discomfort, reduced hospitalisation, and early return to full activity.[7,8] Laparoscopic cholecystectomy decreases the chance for wound infection, a common complication following open cholecystectomy in developing countries. Even sickle cell disease children can benefit from laparoscopic cholecystectomy if the following rules of general anesthesia are respected: preoperative transfusion or blood exchange and the prevention of pain, hypovolaemia, hypothermia, and acidosis during the perioperative period.

Open Surgery

Using a right subcostal incision, the same steps as for the laparoscopic cholecystectomy can be performed. In cases of acute cholecystitis, the cystic duct may be difficult to visualise. In these instances, the gallbladder can be taken down in a prograde direction (from fundus to ampulla)

before ligating the cystic duct and artery. This more safely identifies the junction of the gallbladder and cystic duct and minimises the chance of damage to the common bile duct.

Complications

Significant complications have been reported in laparoscopic cholecystectomies. There is a definitive learning curve with a significant decrease in complications with increased operator experience. Bile duct injuries have been reported in 0.1–2.3% of patients, and bile leak in 1.5–2.0% of patients.[1]

In sickle cell disease children, postoperative complications include acute chest syndrome, haemolysis, and vaso-occlusive crisis.[6]

Key Summary Points

1. Jaundice may occur intermittently in haemolytic cholelithiasis (sickle cell disease) children because of haemolysis; therefore, common bile duct calculi are not necessarily present.
2. Jaundice and fever in infants with any other disposing factor (ileal resection, fasting, dehydration, parenteral nutrition, necrotising enterocolitis, biliary tract anomalies, polycythaemia) should prompt evaluation for stones.
3. It is important before surgery to rule out choledocholithiasis by ultrasound.
4. In sickle cell disease, cholecystectomy is currently not recommended unless symptomatic, and cholecystectomy should be performed electively rather than as an emergency procedure during a haemolytic crisis.
5. Partial exchange transfusion is necessary before operation to reduce the haemoglobin S level in sickle cell disease children.
6. In patients with spherocytosis, ultrasound is recommended before splenectomy; demonstration of a stone dictates that a simultaneous cholecystectomy should be performed.
7. African paediatric surgeons must have training in laparoscopic surgery and be able to do laparoscopic cholecystectomy safely because the advantages are important in developing countries.
8. During laparoscopic cholecystectomy, it is important to retract the infundibulum laterally, which orients the cystic duct at a right angle to the common bile duct.

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