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Chapter

Clinical Conditions, Complications of Cholelithiasis, and Symptom Scoring Suggestion

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Abstract

Gallstones in the gallbladder are asymptomatic in many patients but can cause serious morbid and mortal problems in a significant number of patients. In addition to simple symptoms such as nausea, vomiting, and abdominal pain, gallstones can cause serious complications such as cholecystitis, cholangitis, bile duct obstruction, pancreatitis, biliary perforation, biliary fistula, and biliary neoplasty. It is important that the problems that may arise due to gallstones are adequately known by physicians and even by patients and their relatives. Being unaware of the possible effects of gallstones can lead to under-treatment and serious complications. Assigning a score to the symptoms and clinical conditions associated with gallstones in proportion to their severity and making accurate comparisons with these scores in clinical trials is important for the use of common language and convenience in studies.

Keywords: bile, cholecystitis, complication, gallstone, symptom score

1. Introduction

Although gallstones are common in adults, they are less common in children. The prevalence of gallstones in children is between 0.13 and 1.9% [1, 2]. In recent years, gallstones have become an important health problem in children. The prevalence of gallbladder diseases in children and adults has increased markedly in recent years in direct proportion to the widespread use of radiologic methods such as ultrasonography (US) or the increase in risk factors such as obesity. Risk factors for gallstone formation include female gender, genetics, hemolytic diseases, hepatobiliary diseases, cystic fibrosis, total parenteral nutrition (TPN), ileal disease or ileal resection, infections, hypothyroidism, hyperlipidemia, diabetes, use of certain drugs including cephalosporin's, age, and obesity [1, 3]. Gallstones may occur due to a predisposing risk factor or may be idiopathic [4–6]. In a multicenter study conducted in Italy, the presence of risk factors was reported in 47.5% of patients with gallstones [7].

Patients with gallstones may present to hospitals with a wide range of symptoms of varying severity. Cholelithiasis can lead to a variety of complications ranging from tolerable abdominal pain and nausea to severe morbid and fatal complications such as biliary obstruction, pancreatitis, etc. Less than 50% of those with gallstones actually

develop symptoms and fewer (10%) develop potentially life-threatening complications [8]. Many gallstones are asymptomatic and are detected incidentally. Cholecystectomy is considered the gold standard in symptomatic gallbladder stones [9, 10].

Although there are sufficient studies in the literature on gallstones in adults, studies evaluating the pediatric age group are limited. The management of gallstones in children is mostly done according to the guidelines for adults.

It is obvious that a good knowledge and a good definition of the clinical problems that may be caused by gallstones is an important factor in planning the follow-up and treatment process. Therefore, we can recommend a symptom-scoring system based on the severity of the symptoms associated with gallstones as a good tool for the literature to use a common language and to facilitate clinical trials.

2. Clinical conditions and complications associated with cholelithiasis

2.1 Asymptomatic

Many gallstones are asymptomatic and are detected incidentally. It has been shown that 17–50% of childhood gallbladder stones are asymptomatic [1, 11, 12]. Unlike children, the rate of asymptomatic patients is higher in adults (80%) [13, 14]. In addition, risk factors such as hemolytic anemia have been reported at a higher rate (67.7–80%) in asymptomatic patients compared to symptomatic patients [4, 15]. It has also been reported that the mean age is lower in asymptomatic patients [14]. Asymptomatic patients may be diagnosed at a younger age because they are under closer clinical follow-up due to the risk factors they carry. When gallstones are detected by the US in adults, most cases (70–80%) have no symptoms [14, 16]. On the contrary, it has been shown that only 40% of children and infants in whom gallstones are detected do not have biliary symptoms [1]. Although the general approach in asymptomatic gallstones is non-surgical follow-up, some publications recommend cholecystectomy in appropriate patients.

2.2 Abdominal pain and biliary colic

The pain from gallstone disease is characteristically severe. It can be felt in the epigastrium, right upper quadrant, or both. Onset is relatively sudden and often awakens the patient. The intensity of the pain is constant, may radiate to the upper back, may be associated with nausea, and may last for hours or sometimes up to a day. This visceral pain, which is both diffuse and poorly localized, is caused by the activation of sensory afferents that innervate internal organs [17]. Postprandial epigastric or right upper quadrant pain and right shoulder pain sometimes radiating to the back or upwards can last from a few minutes to several hours. Intense pain is often accompanied by nausea and vomiting. Pain due to gallstones of this character is called biliary colic. The gallbladder is mainly stimulated to contract by cholecystokinin released from the small intestinal mucosa. Biliary colic pain is caused by contractions of the gallbladder that do not result in emptying due to blockage of the bile duct by stones. This pain goes away after the gallbladder stops contracting or when the cystic duct becomes patent again. Biliary colic usually starts gradually after heavy meals and lasts for several hours with the same intensity, felt in the right upper quadrant. This pain is different from renal colic or intestinal colic. In renal colic, there is pain in the lumbar region and the pain associated with ureteral peristalsis lasts for a few minutes and

then passes. Periods of pain and relaxation follow each other. There is costovertebral angle tenderness. In intestinal colic, the pain is like a stabbing pain, lasts for seconds, and then subsides. The pain is in the central part of the abdomen and is wandering. Patients notice pain when the abdomen is resting and bowel sounds increase. Other diseases that may be confused with biliary colic include peptic ulcer disease, irritable bowel disease, inflammatory bowel disease, gastroesophageal reflux disease, and pulmonary embolism [18]. In an Austrian study, it was shown that gallstones were the cause of 6% of abdominal pain cases presenting to emergency departments [19]. Dyspeptic symptoms such as indigestion, belching, bloating, abdominal discomfort, heartburn, and certain food intolerances are common in people with gallstones, but these are probably not related to the stones themselves, as they often persist after cholecystectomy. Young children may be unable to express themselves and describe abdominal pain. This may be one reason why the frequency of colicky pain is different in young children and older children and adults. Corte et al. [7] examined the distribution of clinical presentation in different age groups and found that the rate of colicky pain was higher in older children. When infectious conditions such as cholecystitis or cholangitis develop due to the stone, abdominal pain is more often accompanied by vomiting and even fever.

2.3 Acute cholecystitis

Typically, calculus cholecystitis develops when gallstones (and less often bile sludge) block the outflow of bile from the gallbladder, usually in the cystic duct. Acute cholecystitis is more likely to occur in patients with large solitary stones and biliary pancreatitis is more likely to occur in patients with multiple small stones [20]. Acute cholecystitis may be the first presenting symptom of symptomatic gallstones in 15–20% of cases [21]. Patients with acute cholecystitis experience severe pain that lasts for a long time, and in acute cholecystitis the obstruction is persistent. In acute cholecystitis, pain is usually present for more than 24 hours. The corrosive chemicals in the bile cause inflammation and edema in the wall of the sac. Nausea and vomiting are common. On physical examination, there is marked tenderness in the right upper quadrant, often with a specific mass or a feeling of fullness. Local peritoneal signs and fever are common. Murphy's sign is present. Acalculous cholecystitis can also be seen in 5–10% of patients presenting with cholecystitis and typically these patients are critically ill [22]. There are other causes of acute cholecystitis, such as ischemia; chemicals entering the bile secretions; motility disorders associated with drugs; infections with microorganisms, protozoa, and parasites; collagen disease, and allergic reactions.

Complications of acute cholecystitis:

1. Gallbladder empyema is the filling of the gallbladder with pus.

2. Gallbladder gangrene

3. Pericholecystic abscess is the most common complication (50%),

4. Free perforation,

5. Cholecystoenteric fistula (15%, it is the most common cholecystoduodenal fistula).

6. Acute emphysematous cholecystitis constitutes 1% of acute cholecystitis cases. Gas is detected in the gallbladder wall and lumen. This picture can be seen on standing direct abdominal radiographs. A total of 75% of the cases are male and 40% are diabetic. It is usually seen over 60 years of age. A total of 30% of cases do not have stones. The causative bacteria are *Clostridium perfringes*, *E. Coli*, and *Klebsiella*.

2.4 Chronic cholecystitis

Chronic cholecystitis is actually highly prevalent in gallstones. However, since it is not presented to the clinic, the diagnosis of chronic cholecystitis can be made as a pathologic diagnosis after cholecystectomy. In children and adults with cholecystectomy, chronic cholecystitis has been reported with a rate of 85–90% on pathologic examination of calculus gallbladders [7]. Long-term trauma to the gallbladder wall caused by gallstones, high or abnormal bile acid exposure, and associated long-term inflammation leading to DNA damage may be closely related to the development of hepatobiliary cancers, including gallbladder cancer [23].

2.5 Cholangitis

Acute cholangitis and cholecystitis are mostly caused by stones in the bile ducts and gall bladder. The causes of acute cholangitis include cholelithiasis, benign biliary stricture, congenital factors, postoperative factors (bile duct injury, *etc.*), inflammatory factors, malignancy, duodenal tumor, pancreatitis, parasitic infestation, external compression, blood clot, bilio-enteric anastomosis, *endoscopic retrograde cholangiopancreatography (ERCP), biliary prosthesis, and iatrogenic* factors. Acute cholangitis is a morbid condition characterized by acute inflammation and infection of the bile duct. The onset of acute cholangitis involves two factors. These are increased bacteria in the bile duct and increased intraductal pressure in the bile duct allowing translocation of bacteria or endotoxins into the vascular system (cholangio-venous reflux). In acute cholangitis, with increased intraductal bile pressure, bile ducts tend to be more permeable to the translocation of bacteria and toxins. This process leads to serious infections such as liver abscesses and sepsis, which can be fatal.

"Liver fever" was a term first used by Charcot in his report published in 1877 [24]. Intermittent fever accompanied by chills, right upper quadrant pain, and jaundice became known as the Charcot triad. The Charcot triad is widely used as one of the most important diagnostic criteria. In fact, only 22% of patients with cholangitis present with all three of these symptoms [25]. The most common symptoms are fever and abdominal pain (in up to 80% of patients), but abdominal pain is absent in half of the elderly and 60–70% of patients have jaundice [26]. Charcot triad has high specificity but low sensitivity. In the Tokyo criteria, which were last set in 2018, a scoring system was determined for the diagnostic criteria and severity assessment criteria of cholangitis [27]. Diagnostic Criteria for Acute Cholangitis are criteria used to make the diagnosis in the presence of cholestasis and inflammation based on clinical signs or blood tests in addition to imaging-based biliary findings. Patients with acute cholangitis can present with any severity, ranging from self-limiting to severe and/or potentially life-threatening illness. If appropriate medical care is not provided immediately, patients with acute cholangitis are at risk of developing serious and potentially fatal infections such as sepsis. For severe cases, decompression of the biliary tract (biliary drainage) is necessary as a therapeutic procedure or to prevent increasing severity. Recent advances in endoscopic biliary drainage, together with the

administration of antimicrobial agents, have contributed to a reduction in the number of deaths due to acute cholangitis. However, if the time window for biliary drainage is missed, it remains a life-threatening disease. Most cases respond to initial medical treatment consisting of general supportive care and intravenous antimicrobial therapy. Some cases do not respond to medical treatment and clinical findings and laboratory data do not improve. Such cases can progress to sepsis with or without organ dysfunction and require appropriate management including intensive care, organ supportive care, and emergency bile drainage in addition to medical treatment. In patients with suspected acute cholangitis, early bile drainage or infection source control can be provided without waiting for a definitive diagnosis [28]. Despite the emergence of responses to antimicrobial therapy and biliary drainage, there is a mortality rate of approximately 10% due to acute cholangitis [29].

Reynolds syndrome or "acute obstructive cholangitis" was defined by Reynolds and Dargan [30] in 1959 as a syndrome consisting of fever, jaundice, and abdominal pain as well as lethargy or mental confusion and shock caused by biliary obstruction. They noted that emergency surgical bile decompression is the only effective procedure to treat the disease. These five symptoms were later called the Reynolds pentad.

2.6 Choledocholithiasis

Gallstones can cross the cystic duct and pass into the choledochal and common bile ducts. Sometimes gallstones can form directly in the common bile ducts. The symptoms of choledocholithiasis vary greatly. Patients often present with conditions ranging from obstructive jaundice to life-threatening conditions such as ascending cholangitis and pancreatitis. It has been reported that 10% of patients with choledocholithiasis may also develop pancreaticobiliary malignancies [31]. Scoring systems for the prediction of choledocholithiasis have been reported in the literature [32–35]. Currently, the first choice for choledochal stones is usually endoscopic methods such as ERCP, sphincterotomy, and papilla dilatation. There are some authors who argue that laparoscopic choledochotomy should be the first choice for choledochal stones because of the risk of enterobiliary reflux and associated cholangitis and malignancy that may be caused by chronic biliary inflammation after these endoscopic interventions [36–39].

2.7 Pancreatitis

Mill metric gallstones are known to block the bile and pancreatic duct, increasing the risk of pancreatitis, choledocholithiasis, and cholangitis. The rate of millimetric stones has been reported as 8% in the literature [40]. In 10–15% of patients with symptomatic cholelithiasis, the initial presentation is a complication such as gallstone pancreatitis or common bile duct obstruction [41]. Pancreatitis has been reported with a rate of 8–12% in adult gallstones and gallstones have been shown to be the most common cause of acute pancreatitis [42, 43]. Studies in children have shown that 6.9% and 17.6% of pancreatitis is caused by gallstones. Biliary pancreatitis is more common in women [44, 45]. In most patients with biliary pancreatitis, pancreatitis has a mild episode [46]. Epigastric or upper quadrant pain can last for several hours and may be associated with nausea and vomiting. Physical examination usually reveals epigastric fullness and tenderness, but peritoneal findings are usually absent. For most patients, symptoms improve significantly in 3–4 days. Treatment is primarily hydration and antibiotherapy in the presence of signs of infection. Endoscopic interventions to relieve the obstruction of the biliary and pancreatic duct remain the preferred choice.

2.8 Mirizzi syndrome

Mirizzi syndrome is a rare condition caused by obstruction of the common bile duct or the main hepatic duct by external compression of multiple embedded gallstones or a single large embedded gallstone in Hartman's pouch. Mirizzi syndrome may also result from an inflammatory process secondary to erosion caused by an embedded gallstone in the gallbladder infundibulum or in Hartmann's pouch and cystic duct [47]. Imaging modalities such as US, computed tomography, ERCP, and magnetic resonance cholangiopancreatography (MRCP) are useful in making the preoperative diagnosis in patients with clinical findings of obstructive jaundice [48]. Symptoms are similar to those of cholecystitis but can be confused with other obstructive conditions such as cholangitis caused by the presence of choledochal stones and jaundice. Mirizzi syndrome is a rare complication of symptomatic cholelithiasis, most commonly found in women aged 50–70 years [49]. Although more rarely, Mirrizzi syndrome has also been reported in children [50, 51]. Over time, stone compression and inflammation together may lead to erosion of the common bile duct, forming a cholecystobiliary fistula. Different classifications of Mirizzi syndrome have been made over the years [52, 53]. The treatment for Mirizzi syndrome is cholecystectomy. Five types of Mirizzi syndrome are accepted.

Mirizzi syndrome classification (Csendes classification): [54].

Type 1 (11%): There is the extrinsic compression of the common bile duct by an impacted gallstone.

Type 2 (41%): Consists of a cholecystobiliary fistula involving one-third of the circumference of the bile duct.

Type 3 (44%); the cholecystobiliary fistula compromises up to two-thirds of the circumference of the bile duct.

Type 4 (4%); the cholecystobiliary fistula has destroyed the bile duct wall, and comprises the whole circumference of the bile duct.

Type 5; corresponds to any type of Mirizzi associated with a bilioenteric fistula with or without gallstone ileus.

2.9 Biliary fistula

In the later stages of inflammation caused by prolonged pressure on the wall of the sac, gallstones can lead to erosion of the sac wall and wall of the adjacent luminal organ and finally to fistula formation.

2.9.1 Cholecystocholedochal fistula

Stones sitting in the neck of the sac erode the cystic duct over time, the neck of the sac merges with the choledochal and the cystic duct disappears. These stones, partly occupying the sac (neck) and partly occupying the choledochal duct, cause jaundice. If the diagnosis is not made before cholecystectomy, a large defect in the choledochal duct is seen when the sac is removed and the operation becomes more complex. If a preoperative diagnosis is made, the stones are removed by opening the sac at the appropriate site and a cholecytoduodenal or jejunal anastomosis is performed.

2.9.2 Cholecystoduodenal

A large stone, usually sitting in Hartman's pouch, may penetrate the duodenum in the chronic process.

2.9.3 Cholecystoenteric

Fistula may also occur in segments of the small intestine or colon other than the duodenum.

2.10 Gallstone ileus

Gallstone ileus is a rare complication seen in 0.3–0.5% of patients with cholelithiasis [55]. It usually occurs in the elderly (late 70–80s), is more common in women than men, and is the underlying etiology in 1–4% of patients with intestinal obstruction. It most commonly results in small bowel obstruction. The average size of obstructed gallstones is 4 cm [56, 57]. Bouveret syndrome is a rare (1–4%) form of gallstone ileus in which the embedded stone causes gastric outlet obstruction [58]. The stone enters the stomach through a cholecystogastric or cholecystoduodenal fistula before passing into the duodenum and can cause gastric outlet obstruction. Gallstones may rarely cause obstruction in the colon (8%) [59, 60]. These usually occur secondary to pathologic narrowing at that level with diverticular disease [61, 62]. Gallstone ileus can usually be diagnosed intraoperatively.

2.11 Neoplasia

Although gallbladder metaplasia has been reported in 75% of adult cholecystectomies in histopathologic examinations of calculus gallbladders [63], there are no studies reporting metaplasia in children. Although metaplasia or dysplasia has been reported quite frequently in calculus sacs, its potential to develop into neoplasia is not clearly known. The risk of gallbladder cancer appears to be increased in patients with large stones [20]. In 95% of patients with gallbladder cancer, there are also stones in the gallbladder, but this may not be evidence that gallstones increase the incidence of cancer; it may simply be a coincidence (coexistence of two diseases). There are also studies reporting a 2–24-fold relative risk of gallbladder cancer development for patients with cholelithiasis compared to those without gallstones [64]. The dominant mechanism proposed for this relationship between gallstones and cancer is the transformation of the gallbladder wall from metaplasia to dysplasia and malignancy during the chronic inflammatory process [65].

3. Symptom scoring

Scales for symptom scoring have been described as diagnostic tools for choledocholithiasis, acute cholangitis, or acute cholecystitis [66, 67]. These scores are based on detailed questioning of patients' symptoms or examinations. Since the clinical picture of gallstones ranges from asymptomatic to severe morbid symptoms, and the symptoms that may be seen are diverse, it may be useful for clinicians and researchers to classify cases according to the severity of the clinical picture in order to more rationally describe the clinical picture and to facilitate further research. In our clinical study published in 2016 [15], we applied such a symptom scoring. The aim was to prevent confusion in clinical trials by using symptom scoring indicating the severity of the clinical picture for each patient instead of specifying the symptoms individually. Symptom scoring was performed by adapting the symptom severity classification according to the study of Ana Cristina et al. [3] in 2012 (**Table 1**).

Symptoms	Score
Asymptomatic	0
Mild symptoms, dyspeptic complaints (nausea and vomiting, abdominal pain)	1
Acute cholecystitis (fever, leukocytosis, severe abdominal pain)	2
Biliary obstruction (severe symptoms such as jaundice, biliary dilatation, pancreatitis, cholangitis, biliary fistula, sepsis)	3

Table 1.
Symptom scoring system.

We think that the use of symptom scoring will provide technical convenience by eliminating the confusion and disorganization that may arise in studies, especially in multicenter meta-analyses, and will be useful in order to make a more rational comparison and to create a common language.

In our study using this symptom-scoring system, we found that the symptom score was generally higher in adolescence than in early childhood. This may be related to the inability of younger children to describe their complaints clearly and to overlook mild complaints. The mean symptom score was found to be significantly higher in females, older age, and idiopathic patients and lower in neurologic patients and patients receiving TPN. Although the symptom score was also higher in patients with multiple and mill metric stones, the difference was not statistically significant. Based on this symptom scoring, it is possible to say that the symptoms associated with gallstones are more severe in girls, and idiopathic patients, and severity increases with increasing age.

4. Conclusion

Cholelithiasis remains a major health problem for adults and children. Cholecystectomy is one of the most common surgical procedures in the world. Cholelithiasis may be asymptomatic or may present with serious, morbid, and fatal clinical pictures. It is important that the clinical conditions that may occur due to cholelithiasis are well-known and defined by the physicians involved. Cholelithiasis is a disease that requires a careful diagnostic process followed by a careful treatment process.

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