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Biliary Dyspepsia: Functional Gallbladder and Sphincter of Oddi Disorders

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1. Introduction

Biliary-type abdominal pain is common and often presents a clinical challenge for physicians. True biliary colic consists of episodes of steady pain across the right upper quadrant and epigastric regions, lasting from 30 minutes to 6 hours [1]. Such abdominal pain, when it lasts longer than 6 hours, is likely due to complications of gallstone disease such as acute cholecystitis or acute pancreatitis, or represents a non-biliary source of pain [1].

1.1. Cholelithiasis, biliary pain and atypical dyspepsia

Classical biliary pain that occurs in the setting of gallstones represents symptomatic cholelithiasis. The symptoms associated with gallstones however are frequently confusing. In fact, only 13% of people with gallstones ever develop biliary pain when followed for 15–20 years [2], meaning that most (70-90%) patients with gallstones never experience biliary symptoms. Vague dyspeptic complaints like belching, bloating, flatulence, heartburn and nausea are not characteristic for biliary disease [3, 4]. Therefore, it is not surprising that cholecystectomy often fails to relieve such ambiguous symptoms in those with documented gallstones. In fact, cholecystectomy fails to relieve symptoms in 10-33% of patients with documented gallstones [5]. If the abdominal pain is misdiagnosed and instead due to functional gut disorders like irritable bowel syndrome, cholecystectomy would not provide a favorable outcome [4, 5, 6].

1.2. Functional gallbladder disease

Biliary-type abdominal pain (also termed biliary colic) in the context of a structurally normal gallbladder has been referred to as "biliary dyspepsia". True biliary pain manifests as steady,

severe epigastric or right upper quadrant pain that might radiate through to the back and right infrascapular regions, lasting for at least thirty minutes but less than 6 hours. It can be associated with symptoms of nausea and vomiting, and may awaken the patient from sleep [8]. Episodes are recurrent but usually in a sporadic and quite erratic frequency. Its functional nature should be supported by an absence of markers of organic disease: normal liver and pancreatic biochemistries, and negative diagnostic imaging. No structural basis should be evident to explain the pain.

Functional biliary pain has also been termed: *gallbladder dyskinesia*, *chronic acalculous gallbladder dysfunction*, *acalculous biliary disease* and *chronic acalculous cholecystitis [9]*. "Biliary dyskinesia" implies a motility disorder resulting from abnormal motor function of the gallbladder (manifest as impaired emptying) and/or sphincter of Oddi (increased tone)[10].

1.3. Functional disorders of the biliary tract (Sphincter of Oddi dysfunction)

Following removal of the gallbladder, biliary pain has been attributed to sphincter of Oddi dysfunction (SOD). SOD represents intermittent obstruction to the flow of biliopancreatic secretions through the sphincter of Oddi in the absence of biliary stones or a ductal stricture [11]. The Rome III Consensus has developed criteria for functional biliary-type pain (Table 1) [8].

2. Epidemiology

Dyspepsia overall is a common symptom in the general population with reported prevalence rates ranging between 10-45% [12]. Such estimates are confounded by the use of differing criteria for defining dyspepsia as well as a recurrent failure to exclude patients who primarily report heartburn symptoms[12]. Nevertheless, dyspepsia remains a common issue with annual incidence rates estimated between 1-6%[13]. In the United States, there were 4,007,198 outpatient visits for gastroenteritis or dyspepsia and 130,744 hospital admissions for functional or motility disorders in 2009 [14]. This represents a 26% increase from the year 2000, which suggests an upsurge in the overall incidence of dyspepsia[14].

Epidemiology of functional gallbladder disease (i.e.; Frequency of biliary pain with a normal appearing gallbladder e.g. without gallstones)

The true prevalence of biliary dyspepsia is unknown. Estimates are generally based on the presence of non-specific clinical features and a lack of structural findings on ultrasonographic investigation of the biliary system. In large Italian population-based studies, 7.6% of men and 20.7% of women experienced biliary pain yet lacked gallstones on abdominal ultrasonography [15, 16].

With the advent of minimally invasive surgery, biliary dyskinesia has become a new indication for laparoscopic cholecystectomy increasing 348% in adults [17] and escalating 700% in pediatric patients over approximately a decade [18]. Large scale case series now list biliary

dyskinesia as the primary indication for cholecystectomy in 10-20% of adults [17, 19-22] and 10-50% of pediatric patients [23-26].

Epidemiology of functional sphincter of Oddi disorders (i.e.; Frequency of biliary pain after the gallbladder has been removed – postcholecystectomy).

In the US householder survey of presumably healthy adults, 69% expressed symptoms indicating a functional gastrointestinal syndrome within the previous three months and 1.5% had biliary dyspepsia following cholecystectomy [27]. Women were more commonly afflicted at 2.3% than men at 0.6% [27]. Nevertheless, sphincter of Oddi dysfunction (SOD) is uncommon in this population. SOD, when documented by ERCP manometry, occurs in less than 1% of the patients who have had their gallbladders removed and accounts for the abdominal pain in 14% of the patients with postcholecystectomy pain [28].

3. Pathophysiology

3.1. Acute biliary pain

The biliary tract normally is a low-pressure conduit though which bile secreted from the liver reaches the duodenum. The gallbladder acts as a reservoir for decompression while storing bile in the interdigestive periods overnight and throughout the day [29]. Even in the digestive phase, gallbladder contraction does not elicit marked pressure spikes within the biliary tree because the sphincter of Oddi effectively relaxes. The hormone cholecystokinin (CCK) is primarily responsible for this reciprocity.

In the setting of cholelithiasis, biliary pain is assumed to originate from either an obstructive event (the gallbladder contracting on a closed cystic duct which is blocked by a gallstone) that increases intrabiliary pressure and/or inflammation (cholecystitis)[10]. Such obstruction also appears to stimulate the gallbladder mucosa to produce a phospholipase, which then hydrolyses fatty acids off lecithin to yield lysolecithin in bile. Lysolecithin, acting as a biological detergent, might then initiate an inflammatory reaction (cholecystitis). Subsequently, inflammatory mediators could trigger painful stimuli, while mechanoreceptor afferent fibers in the gallbladder and biliary tree conduct visceral pain information to the spinal cord and the brain. Thus, motor contraction, sensory afferents producing painful sensations and obstruction/inflammation may all play a role in the perception of acute biliary-type pain.

3.2. Chronic functional biliary pain

The basis for chronic functional biliary pain appears to reside in visceral hypersensitivity, altered central processing, and/or abnormal gastrointestinal motility. Prolonged or intense noxious stimuli, particularly when repeated, lead to sensitization of visceral nociceptors. These peripheral sensory neurons respond to potentially damaging stimuli by sending nerve signals to the spinal cord (dorsal horn) and then projecting centrally to the brain – the thalamus and cortex, the site of pain perception. Chronic irritation might then influence afferent input and the release of neuroactive chemicals in the dorsal horn of the spinal cord. Even when the

peripheral irritation ceases, synaptic changes in the spinal cord can persist, causing "pain memory". Thus, irritation to the biliary tract can potentially sensitize the nervous system. In some, the central nervous system becomes so sensitive that *hyperalgesia* results: severe pain evoked by only mildly painful stimuli. Persistent central excitability might subsequently result in *allodynia*: innocuous stimuli produce pain [30, 31]. Thus, the basis for abnormally heightened biliary sensations can reside at any level: either altered receptor sensitivity of the viscus, increased excitability of the neurons in the spinal cord dorsal horn, and/or altered central modulation of sensation, including psychological influences that affect the interpretation of these sensations. Further, central hyperexcitability can effect changes in the dorsal horn.

Acalculous biliary pain may represent a generalised motor disorder of the duct: the irritable gallbladder/sphincter of Oddi[10]. The abnormalities identified by impaired gallbladder emptying or increased tone in the sphincter of Oddi, for example, may reflect a more generalised motility disorder of the gut [32]. Moreover, biliary-type pain could originate from a neighbouring structure: for example, abnormal small intestinal motility. Gut smooth muscle in functional gut disorders exhibits altered sensitivity to regulatory peptides such as CCK, precipitating abdominal pain in some patients and confounding the interpretation of intestinal versus biliary pain.

Functional biliary disorders have been most prominently linked to abnormal motility of the gallbladder and/or sphincter of Oddi, in part because techniques exist to detect them in clinical practice. Biliary pain is construed to result in most instances from increased gallbladder pressure from either abnormal gallbladder contraction ("dyskinesia") and/or structural or functional outlet obstruction either at the exit from the gallbladder (e.g.; abnormal cystic duct) or at the sphincter of Oddi ("the fighting gallbladder"). Reduced emptying and pain however may also reflect diminished gallbladder contractility ("hypokinesia"). Decreased gallbladder emptying has been attributed to abnormal CCK release, decreased gallbladder CCK receptor sensitivity or density, or increased cystic duct receptor sensitivity to CCK with impaired smooth-muscle contractility producing outlet obstruction [33].

Impaired gallbladder emptying, however, is also an important pathogenetic component in cholesterol gallstones. Cholesterol gallstone formation begins when the liver produces bile supersaturated with cholesterol, in excess of the solubilizing agents, bile salts and lecithin. In this first stage, the liver secretes excess cholesterol into bile canaliculi that is accompanied by lecithin as small, unilamellar vesicles. These fuse in this supersaturated bile to become cholesterol-rich, multilamellar vesicles (liquid crystals). Aided by nucleating factors (biliary proteins), cholesterol microcrystals precipitate out of solution. Mucin, a glycoprotein, secreted by the gallbladder mucosa, then acts as a matrix scaffold to retain these cholesterol microcrystals. Diminished gallbladder contractility facilitates retention, providing the residence time that is necessary for these microcrystals to agglomerate and grow into overt gallstones. Cholesterol constitutes the vast majority (>85%) of gallstones. A minority of gallstones are black pigment stones. These are composed of calcium bilirubinate polymers that result from abnormal bilirubin metabolism. Such black pigment stones tend to develop in advanced age, Crohn's disease, extensive ileal resection, cirrhosis, cystic fibrosis, and chronic hemolytic states [34].

Hence, a smooth muscle defect producing gallbladder hypomotility is intrinsic to cholesterol gallstone formation and disease [35, 36] and also occurs in chronic acalculous disease [37]. Both conditions yield biliary pain, creating a potentially confusing scenario. Evidence of microlithiasis in the gallbladder bile in some patients with biliary dyskinesia [38] may merely indicate that excessive cholesterol, likely a stage of stone formation in which macroscopic gallstones were not evident, compromised signal transduction in the gallbladder and was the mechanism for reduced emptying. Certainly any bile crystals or sludge may eventually result in calculous disease, causing obstruction of the gallbladder and symptoms of biliary pain, but this must be distinguished from functional gallbladder disease. The mechanism for chronic cholecystitis is unclear [39], while cholesterolosis with its accumulation of lipid products (triglycerides and cholesterol precursors and esters) is likely too common to have any clinical importance as a cause of biliary pain [38].

Gallbladder dysmotility is also associated with other conditions including functional gastrointestinal disorders, pregnancy, diabetes mellitus, obesity, cirrhosis [40], and the use of various medications (including atropine, morphine, octreotide, nifedipine, and progesterone) [41]. Interestingly, gut smooth muscle in the irritable bowel syndrome (IBS) also exhibits altered sensitivity to regulatory peptides such as CCK [42]. It is, therefore, not surprising that the gallbladder empties abnormally in some patients with IBS [43-45].

Although in sphincter of Oddi dysfunction, pain has classically been attributed to abnormal smooth muscle motility, there may also be a component of visceral hypersensitivity. Here, the hypersensitivity might arise in a structure adjacent to the sphincter, the duodenum [46, 47].

3.3. Biliary dyspepsia and fatty food intolerance

Despite biliary dyspepsia suggesting impaired digestion, there is no consistent relationship to eating. Historically, the abdominal discomfort and bloating that follow a heavy, fatty meal has been termed "fatty food" intolerance, connoting an association between fat content in the diet and biliary dyspepsia [48, 49, 59]. Patients with biliary dyspepsia may eat fewer meals, perhaps because their symptoms onset after eating [51]. In some, the sensation of fullness experienced relates to the amount of fat consumed. The presumed basis is fat releasing CCK and peptide YY, which are gut hormones important in regulating hunger and satiety. Patients with biliary dyspepsia, particularly those experiencing higher scores for nausea and pain, have higher concentrations of fasting and postprandial CCK compared to healthy individuals[50]. However, just as dyspepsia is not a particular manifestation of gallstone disease, fatty foods do not necessarily precipitate attacks of biliary colic [3, 52].

4. Differential diagnoses

Structural causes affecting the gastrointestinal tract should be considered in any patient presenting with dyspepsia (Table 2) [12]. Gallstones, biliary sludge and microlithiasis must be eliminated [12]. As decreased gallbladder emptying is a key investigation leading to the

diagnosis of a functional gallbladder disorder, other causes of impaired gallbladder emptying should be identified to obviate confounders (Table 3) [53].

Must include episodes of pain located in the epigastrium and/or right upper quadrant and all of the following:
1. Episodes lasting 30 minutes or longer
2. Recurrent symptoms occurring at different intervals (not daily)
3. The pain builds up to a steady level
4. The pain is moderate to severe enough to interrupt the patient's daily activities or lead to an emergency department visit
5. The pain is not relieved by bowel movements
6. The pain is not relieved by postural change
7. The pain is not relieved by antacids
8. Exclusion of other structural disease that would explain the symptoms
Supportive criteria:
The pain may present with 1 or more of the following:
1. Pain is associated with nausea and vomiting
2. Pain radiates to the back and/or right infrasubscapular region
3. Pain awakens from sleep in the middle of the night

Table 1. Rome III Diagnostic Criteria for Functional Gallbladder and Sphincter of Oddi Disorders [8]

Gastrointestinal Disorders
Gastroesophageal reflux disease
Gastric or esophageal cancer
Gastric infections
Gastroparesis
Inflammatory bowel disease
Irritable bowel syndrome
Peptic ulcer disease
Food intolerances
Drug intolerances
Pancreaticobiliary Disorders
Cholelithiasis, choledocholithiasis
Pancreatitis
Pancreatic neoplasms
Systemic Disorders
Adrenal insufficiency
Diabetes mellitus
Hyperparathyroidism
Renal insufficiency
Thyroid disease

Table 2. Organic Causes for Dyspepsia [12]

Primary gallbladder disease
Cholesterol gallstones
Prior to stone formation as evidenced by microcrystals of cholesterol and following medical dissolution
Pigment stones
Hemoglobinopathies
Cholecystitis
Acute or chronic, with or without stones
Metabolic disorders
Obesity, diabetes, pregnancy, VIPoma, sickle hemoglobinopathy
Neuromuscular defects
Myotonia dystrophic Denervation (spinal cord injury, vagotomy)
Functional gastrointestinal diseases: functional dyspepsia, functional abdominal pain
Irritable bowel syndrome
Deficiency of cholecystokinin
Celiac disease, fasting/TPN
Drugs
Anticholinergic agents, calcium channel blockers, opioids, ursodeoxycholic acid, octreotide, cholecystokinin-A receptor antagonist, nitric oxide donors, female sex hormones (progestins)

Table 3. Causes of Impaired Gallbladder Emptying [52]

5. Diagnosis

The diagnosis of functional disorders of the gallbladder and sphincter of Oddi should be based on the Rome III criteria for functional gallbladder and sphincter of Oddi disorders (Table 1).

5.1. Functional gallbladder disease

1. Preliminary investigations to rule out structural disease that might be the origin of the pain must include liver and pancreatic biochemistries and esophagogastroduodenoscopy. All should be normal in functional gallbladder disorder. The search for gallstones must be scrupulous. Transabdominal ultrasound is critical in being capable of detecting stones down to 3-5 mm in size. Endoscopic ultrasound (EUS) is more refined for microlithiasis: tiny stones < 3mm and biliary sludge [10]. Microscopic examination of gallbladder bile collected from the duodenum following IV CCK stimulation can detect deposits, either cholesterol as birefringent crystals (Figure 1) or pigment in the form of dark red-brown

calcium bilirubinate. Both techniques are fairly specific (in the order of 90%). Detection of microlithiasis by EUS however is more sensitive (96% versus 67%) than microscopic bile examination [54, 55], and also more available in most centres. Regardless, the use of these investigations in biliary dyskinesia is limited by their invasive nature.

Figure 1. Cholesterol microcrystals in aspirated duodenal bile following CCK stimulation. The collected golden brown duodenal bile is first centrifuged and then examined under polarizing microscopy. As seen here, cholesterol is evident as birefringent, rhomboid-shaped crystals, characteristically with a notch in one corner.

2. Assessment of gallbladder emptying by cholecystokinin-cholescintigraphy is currently the key to diagnosing functional gallbladder disorder. The gallbladder ejection fraction (GBEF) is best measured via a nuclear medicine hepatobiliary scan. The radiopharmaceutical, technetium 99m-labelled iminodiacetic acid (HIDA), when infused intravenously, is readily taken up by hepatocytes, excreted into the bile, and accumulates in the gallbladder [37, 56, 57]. Infusion of the CCK analogue, Sincalide™ (the 8-amino acid C-terminal fragment of cholecystokinin, CCK-8), then initiates gallbladder evacuation (Figure 2). There has been a wide variation in methodology, leading to a consensus recommendation: Sincalide™ should be infused at 0.02μg/kg over 60 minutes. Normal gallbladder ejection fraction should be ≥ 38%, according to a recent consensus conference [58]. In selected cases of recurrent biliary pain in which no structural cause is evident, no stone disease is apparent and there exists no other associated cause for impaired gallbladder emptying, cholecystectomy is a reasonable consideration when the gallbladder ejection fraction is reduced at less than 35-40% [59].
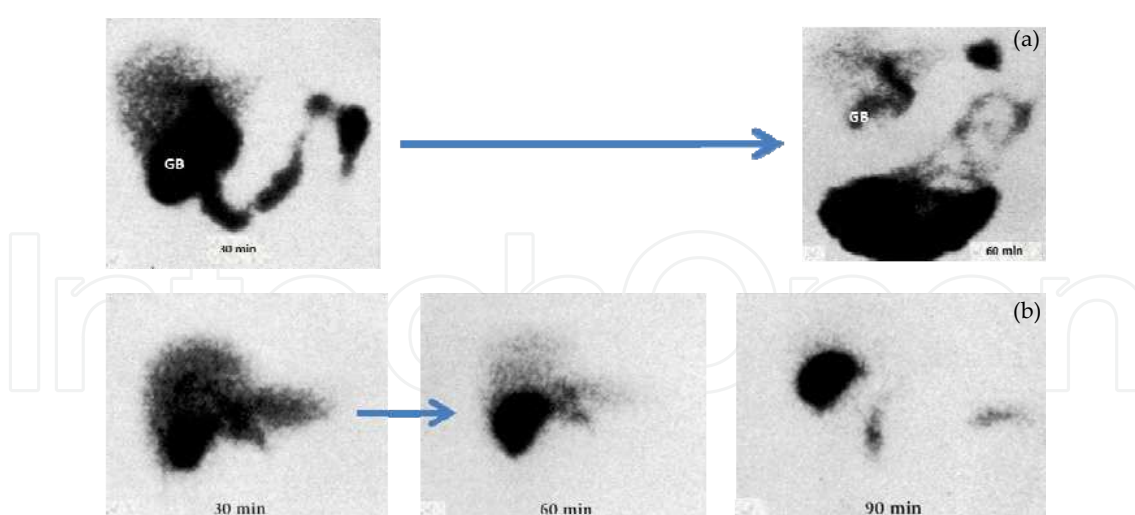
Figure 2. A. Normal gallbladder emptying on CCK-cholescintigraphy. The gallbladder is visualized 30 minutes after the injection of the 99m-labelled technetium iminodiacetic acid radiopharmaceutical (HIDA scan). Cholecystokinin is then infused (shown as arrow). Prompt gallbladder emptying (70% here) then ensues with the radiolabel ejected into the small intestine. The gallbladder is depicted as GB, before and after the CCK infusion. [52], B. Abnormal gallbladder emptying. Although the gallbladder fills, becoming well visualized at 30 minutes, the CCK infusion (arrow) has little effect thirty minutes later at 60 minutes into the study or even with an additional thirty minutes at 90 minutes. The liver washes out during this period of time. [52]

There is as yet no predictive value for CCK-cholescintigraphy in those with established yet uncomplicated ('silent") gallstones. The influence of gallbladder evacuation on the develop‐ ment of biliary symptoms and on the severity of disease remains unclear [56]. The sluggish gallbladder does not protect an individual with stones from developing pain.

The use of a fatty meal to stimulate gallbladder contraction may be more physiological and cheaper than CCK but does not enjoy an established protocol with normal values. Another limitation is that endogenous CCK release depends upon gastric emptying of the meal; gastroparesis often accompanies functional gastrointestinal disorders [58].

Real-time ultrasound has also been used to measure volume changes as the gallbladder empties. Its advantage over a nuclear medicine scan obviates exposing the patient to ionizing radiation. Quantitative ultrasonography, based on geometric assumptions, however is operator-dependent, limiting its accuracy. Although 3-dimensional and 4-dimensional ultrasounds appear to correlate reasonably well with HIDA scans in identifying reduced gallbladder ejection fractions [60], CCK-cholescintigraphy is more precise and remains the standard [56, 58, 60].

The CCK-provocation test aimed to reproduce the biliary pain following an infusion of CCK, implicating the gallbladder as the culprit. This test has fallen out of favor due to lack of objectivity and specificity for biliary dyskinesia [42, 61]. Rapid infusion of CCK can elicit abdominal pain even in normal individuals [10].

The algorithm for diagnosing and managing functional gallbladder disorder is outlined in Figure 3 [8].
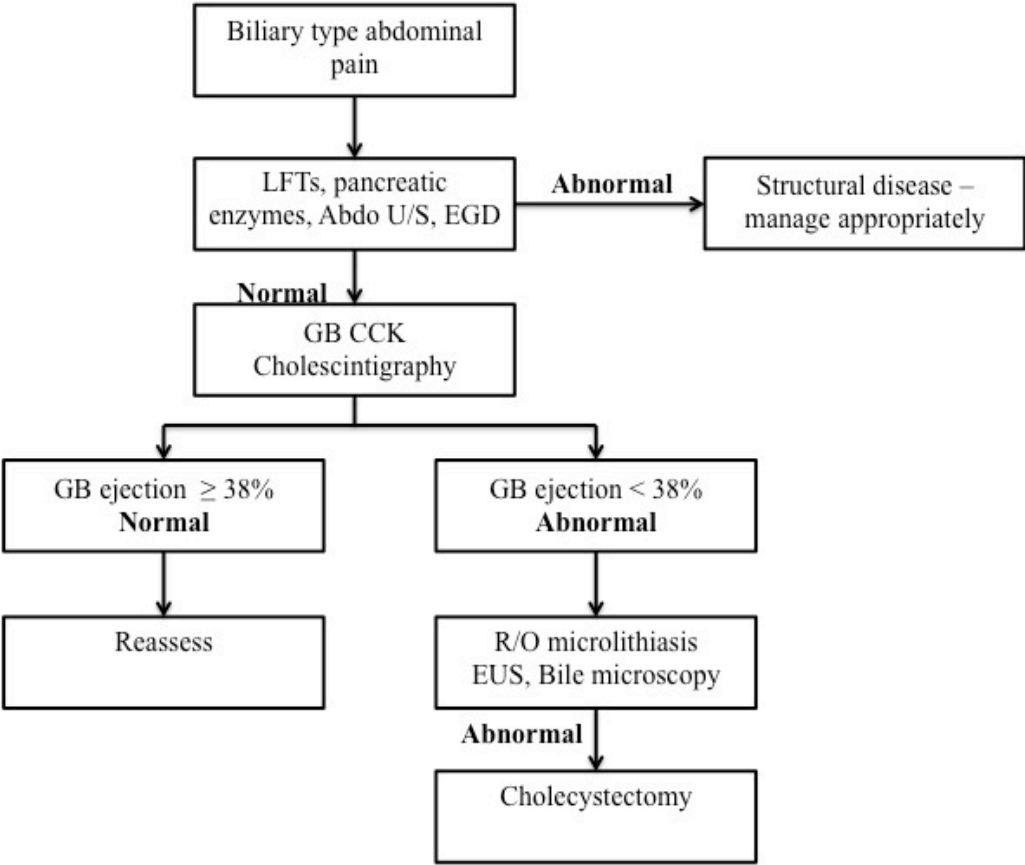
Figure 3. Algorithm for the diagnostic workup and management for biliary dyspepsia due to functional gallbladder disorder [8]. Patients with biliary type abdominal pain should initially undergo non-invasive investigations including relevant laboratory work and an abdominal ultrasound. An endogastroduodenoscopy (EGD) should then be performed and if any structural abnormalities, should be treated by medical, endoscopic or surgical management. A gallbladder cholecystokinin (GB CCK) cholescintigraphy can be subsequently performed. If there is abnormal ejection, EUS (endoscopic ultrasound) or bile microscopy can be used to further investigate for microlithiasis. Even in the absence of microlithiasis, if the ejection fraction is abnormal on GB CCK cholescintigraphy and no obvious confounding factor identified, consider referring the patient for a cholecystectomy.

5.2. Functional Sphincter of Oddi Disorder (SOD)

Sphincter of Oddi dysfunction implies that the basis is a motility disorder of the sphincter that intermittently results in pain, elevated liver and/or pancreatic enzymes, a dilated common duct and potentially pancreatitis. The Milwaukee classification originally categorizes SOD into three types, separating functional biliary and pancreatic sphincter of Oddi disorders on the basis of symptoms, laboratory tests and radiological imaging [8, 62-65] (Table 4). As these require an invasive procedure, endoscopic cholangiopancreatography (ERCP), to measure common duct size and biliary drainage, the criteria have been revised to use non-invasive imaging for estimating duct size of on an abdominal ultrasound [64].

Biliary type
Type I:
Typical biliary type pain Liver enzymes (AST, ALT or ALP) > 2 times normal limit documented on at least 2 occasions during episodes of pain Dilated CBD > 8 mm in diameter Positive manometry for biliary SOD (seen in 65-95% of patients)
Type II:
Biliary type pain and one of the above criteria (laboratory or imaging)
Type III:
Biliary type pain only
Pancreatic type SOD
Type I:
Pancreatic type pain Amylase and/or lipase > 2 times upper normal limit on at least 2 occasions during episodes of pain Dilated pancreatic duct (head > 6 mm, body > 5 mm)
Type II:
Pancreatic type pain, and one of the above criteria (laboratory or imaging)
Type III:
Pancreatic type pain only

Table 4. Modified Milwaukee Classification of Sphincter of Oddi dysfunction [8, 61, 62, 64-66].

As in biliary dyspepsia due to gallbladder dysfunction, patients with suspected SOD should undergo evaluation with serum liver and pancreas biochemical tests, abdominal ultrasound, and esophagogastroduodenoscopy to rule out underlying structural disease as a cause for their abdominal symptoms. Consideration should also be given to magnetic resonance cholangio-pancreatography (MRCP) to eliminate structural lesions such as stones, strictures and tumors. Dysfunction potentially might affect either or both segments of the sphincter of Oddi: biliary versus pancreatic sphincters or both (e.g.; occurring simultaneously).

a.   Functional Biliary Sphincter of Oddi Disorder

Type I manifest biliary pain; abnormal liver biochemistries (elevated aminotransferases, alkaline phosphatase and/or bilirubin) >2 times normal on two or more occasions; plus a dilated common bile duct > 8mm on abdominal ultrasound. Most will exhibit biliary SO dysfunction on formal manometry. They are considered to have stenosis of the sphincter causing structural outflow obstruction.

Type II patients with biliary sphincter dysfunction experience the biliary-type pain plus exhibit one of either the laboratory or the imaging abnormalities.

Type III patients only complain of the pain. There are no laboratory or imaging abnormalities

b.   Functional Pancreatic Sphincter of Oddi Disorder [65, 66]

Pancreatic-type SOD encompasses patients with pancreatic-type pain, elevated serum amylase or lipase plus pancreatic duct dilation.

Type I has pain, lipase elevation and pancreatic duct dilation

Type II has pain plus either lipase elevation or pancreatic duct dilation.

Type III has only pancreatic-type pain.

Investigations

1.   ERCP Manometry.

The "gold" standard to diagnose SOD is sphincter of Oddi manometry. This entails endoscopic retrograde cholangiopancreatography (ERCP) allowing passage of a manometric catheter through the duct and measurement of basal sphincter pressures on slow withdrawal of the catheter. A basal sphincter pressure of greater than or equal to 40 mmHg is used to diagnose SOD [67]. Manometry is abnormal in 65-100% with type I, 50-65% with type II, and falls to 12-60% of biliary type III SOD patients [65, 67, 68]. Positive manometric findings, based on type, are similar in both types of sphincter dysfunction. The distinction between types I, II, and III SOD, however, is important as it may predict a favorable response to endoscopic sphincterotomy and thus, guide further management. The algorithm for diagnosing and treating functional biliary sphincter of Oddi dysfunction is outlined in Figure 4.

2.   Non-invasive Methods

Additional non-invasive methods for diagnosing SOD have been studied, given the inherent risk of complications in sphincter of Oddi manometry, particularly precipitating pancreatitis, and the generally poor outcomes especially in patients with biliary type III SOD [69].

a.   Ultrasonographic measurement of duct diameter

The common bile duct normally has a diameter of 6mm or less in healthy individuals whose gallbladders are intact. Above 8mm indicates biliary obstruction. This value becomes somewhat obscure following cholecystectomy, a situation in which dilation occurs to 10mm even in those without symptoms [70]. Adding a fatty meal to release CCK seeks to show duct dilation to indicate SO dysfunction but its diagnostic usefulness is limited.

b.   Magnetic resonance pancreatography (MRCP)

Administration of the hormone secretin increases pancreatic exocrine secretion [71]. In suspected SOD involving the pancreas, secretin improves MRCP visualization of the pancreatic ducts to eliminate structural disease and elicits duct dilation [72]. Overall, secretin-stimulated magnetic resonance cholangiopancreatography (ss-MRCP) is not sensitive in predicting abnormal manometry results in patients with suspected SOD type III, though somewhat accurate in predicting results in patients with SOD type II (73%) [73].
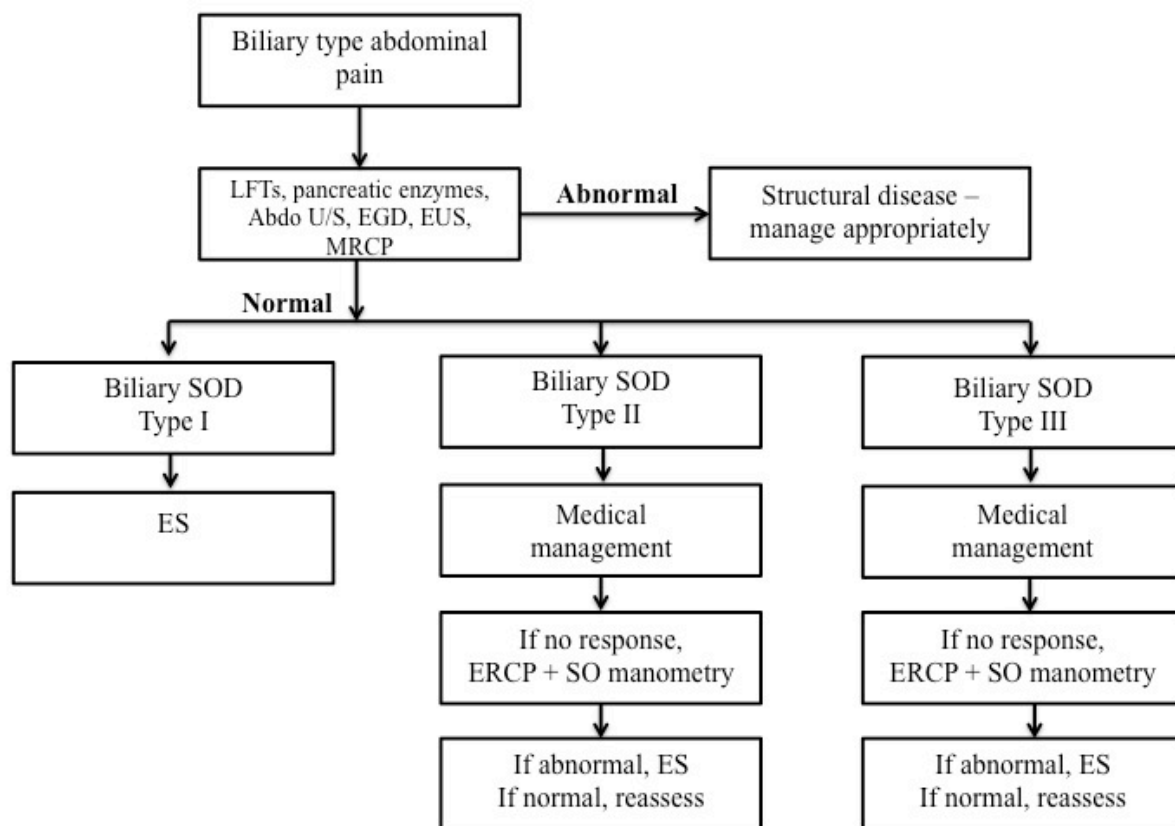
Figure 4. Algorithm for the diagnostic workup and management of sphincter of Oddi disorder (SOD) [8] Patients with biliary type pain should initially undergo non-invasive investigations including relevant laboratory work and an abdominal ultrasound. An endogastroduodenoscopy (EGD), endoscopic ultrasound (EUS) and a magnetic resonance cholangiopancreatography (MRCP) should then be performed. Any structural abnormalities detected should be treated by medical, endoscopic or surgical management. SOD should be classified as Type I, Type II and Type III according to the Milwaukee classification described in the text,. Patients with Type I disease will benefit from an endoscopic sphincterotomy (ES). Otherwise first line management should be medical. If there is no response, an ERCP with sphincter of Oddi manometry (SO manometry) can be performed. If manometry is abnormal, ES is indicated. If normal, alternative medical therapies can be attempted.

c.   Endosonography

Endoscopic ultrasound (EUS) generally has a low yield in diagnosing abnormalities in the context of a normal upper endoscopy and imaging studies in patients with SOD Type III [72, 74]. Only 8% of patients with suspected SOD Type III (normal endoscopy and standard imaging studies) have any pathology at EUS [74].

d.   Hepatobiliary scintigraphy [10]

Nuclear medicine scanning of the biliary tract (choledochoscintigraphy) uses 99mTc HIDA as the radiopharmaceutical to measure biliary emptying: the transit time from the liver to the duodenum. Prolonged duodenal arrival reflects SO dysfunction [75]. Specificity approaches 90% but reported sensitivities are variable [76]. Although lacking controlled studies, choledo-

choscintigraphy is a reasonable non-invasive test before embarking on an intrusive approach with ERCP-manometry.

e.   Morphine-prostigmine provocation (Nardi) test

The Nardi test assesses the response to an injection of morphine and prostigmine to provoke biliary sphincter spasm and stimulate pancreatic enzyme secretion. A positive test should elicit typical symptoms and/or increase in serum activities of pancreatic and/or liver enzymes. This provocative test is not specific or sensitive: 60% of normal individuals and others with IBS have a positive test [77]. Sphincterotomy decreases the pain and enzymatic response (amylase and lipase) to such provocation in only about 50% of individuals [78].

6. Management

a.   Functional Gallbladder Disorder

Medical

The medical options for management of functional biliary disorders are quite limited. The spice turmeric (Curcuma longa) modulates multiple cell signalling pathways and is a putative therapy for inflammatory bowel disease [79]. In patients with biliary dyspepsia, the extracts of Curcuma seem to reduce abdominal pain at least during the first week of treatment [80]. Oddly, curcumin increases gallbladder contraction. Tenoten, an anxiolytic, appeared to decrease the pain syndrome, burning and belching, and increase gallbladder contraction in a small Russian study assessing patients with biliary dyskinesia and personality disorders [81]. Such reports have marked limitations including small patient numbers and unclear diagnostic criteria for biliary dyspepsia. As such, further studies are needed to clarify any role for medical therapy in biliary dyskinesia, including use of agents like tricyclic antidepressants that help visceral hypersensitivity.

Surgical

Although there may be a rising tide of cholecystectomies being performed for biliary dyskinesia, most reports touting efficacy are retrospective reviews with small sample sizes and lack appropriate non-operative controls. One meta-analysis supported the notion of surgery in adults that provided 98% symptomatic relief compared to 32% with non-operative management [59]. Although the success rate in pediatric patients may reach 80% in some reports, a retrospective assessment of outcomes indicated no difference over a 2 year follow up: three-quarters of both the surgical and non-surgical groups improved [82]. Further, gallbladder emptying assessed by CCK-cholescintigraphy may not be a sensitive test that predicts a benefit from cholecystectomy [83]. Certainly cholecystectomy for dyspeptic complaints of gassiness, bloating, indigestion and fatty food intolerance is disappointing [84]. Despite the Rome III consensus [8], the literature does not yet support cholecystectomy being done routinely for biliary dyspepsia.

b. Functional Sphincter of Oddi Disorder

The aim in patients with SOD is to reduce the resistance caused by the sphincter of Oddi to the flow of bile and/or pancreatic juice [3]. This can be achieved by medical, endoscopic or surgical methods.

Medical

Medical management of sphincter of Oddi dysfunction is also unclear. Therapy has been primarily focused on the use of smooth muscle relaxants. Nifedipine, a calcium channel antagonist, has previously been studied with conflicting results in the treatment of sphincter of Oddi dysfunction. Nifedipine 20mg can significantly decrease the basal pressure in the sphincter of Oddi and also reduce the amplitude, duration and frequency of phasic contractions [85]. This effect is not seen at lower doses of nifedipine; unfortunately, hypotension is a common side effect at the higher dose. Nevertheless, nifedipine use over 3 months decreases pain, especially in patients with predominant antegrade propagation of phasic contractions [86]. Once treatment ceases, the effect becomes lost in a week [86]. Nicardipine also appears to have a similar effect on the sphincter of Oddi with a decrease in basal and phasic pressures following a single infusion [87].

Trimebutine (a spasmolytic), sublingual nitrates or a combination of both agents provides complete or partial relief of pain in most cases (64-71%) [88, 89]. All such studies however are limited by small patient numbers.

Several other medications such as anticholinergics (e.g.; hyoscine butylbromide), antispasmodics (e.g.; tiropramide), opioid antagonists (e.g.; naloxone), alpha-2 adrenergic agonists (e.g.; clonidine), and even corticosteroids may have a potential benefit in managing sphincter of Oddi dysfunction or functional gallbladder disorder [90]. Nevertheless, reports are limited in quality; well-done clinical trials are warranted.

Endoscopic Therapy

The goal of endoscopic therapy is to disable the dysfunctional sphincter through various methods. Botulinum toxin, a neurotoxin, when injected directly into the ampulla of Vater at endoscopy, improves symptoms in 44% of SOD patients for 6 to 12 weeks after the treatment [91]. Unfortunately, repeated injections of botulinum toxin may be associated with antibody formation and a subsequent reduced efficacy [90]. Hence, rather than being used to treat sphincter of Oddi dysfunction, botulinum toxin injections appear more helpful in directing further therapy, predicting the success of endoscopic sphincterotomy for pain relief [90, 91].

Endoscopic sphincterotomy (ES) is the current treatment for SOD Type I. At ERCP, deep cannulation of the bile (or pancreatic) duct allows electrocautery to sever the biliary or the pancreatic segment of the sphincter of Oddi. Pain relief after an ES is 90-95% in Type I patients, 85% in Type II patients with an abnormal sphincter of Oddi manometry and 55-60% in Type III patients with an abnormal manometry [92, 93]. Conversely, in patients with a normal manometry, the relief rates are much reduced: 35% for Type II and <20% in Type III patients, respectively [92, 93]. Complications from this procedure are mostly due to pancreatitis, which can be seen in up to 20% of patients [94]. ES as an indication of SOD results in a 2-5 fold increase

in complications compared to the risk when performing this procedure for ductal stones [95, 96]. Placing a temporary stent in the pancreatic duct helps lessen such complications.

Surgical

Surgical options include transduodenal biliary sphincteroplasty with a transampullary septoplasty [97]. Due to the advances in endoscopic techniques, surgery is generally reserved for patients who experience restenosis or when endoscopy is not available [97]. Endoscopy is preferred with lower cost, morbidity and mortality compared to surgical procedures.

7. Summary

Functional gallbladder disease and sphincter of Oddi disorders can be quite frustrating for the patient as well as the physician, in terms of arriving at a diagnosis and effective therapeutic options. Initially, non-invasive investigations should be performed. Further, sphincter of Oddi manometry requires specialized endoscopic equipment as well as physician expertise. Unfortunately, this is not readily available in many centers. Perhaps with the procurement of these resources in the future, physicians may be able to predict which patients with SOD will benefit from endoscopic or surgical therapy. In terms of management, medical therapies should be tried as first line. Further, surgical and endoscopic management in type II and type III SOD should be initiated with caution. The suggested algorithm should assist the investigation and management of these patients (Figure 3 and 4).

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