Biliary Dyskinesia in Pediatrics

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Abstract

Biliary dyskinesia (BD) is a diagnosis that is being made increasingly in children. It is defined by abdominal pain thought to be biliary in nature based on location and character; a completely normal gallbladder on imaging tests, typically ultrasound; and decreased gallbladder contraction in response to a pharmacological stimulus. Unlike other functional gastrointestinal disorders (FGIDs) that are treated with medications, behavioral therapy, and/or dietary modification, current clinical practice has accepted cholecystectomy as the treatment of choice for BD, which now accounts for up to 50% of cholecystectomies in children. Although well-designed trials are missing, accumulating evidence argues against such an approach. First, BD is by definition a benign disorder without risk of truly relevant complications. Second, despite reportedly high rates of satisfaction with postoperative outcomes, most children continue to experience symptoms. Lastly, limited long-term studies have demonstrated comparable benefit of operative and conservative therapy. To summarize, BD should be seen as a more localized manifestation of functional abdominal pain, which may improve over time independent of the type of therapy chosen. Despite the widespread adoption of minimally invasive surgery in pediatrics, a different risk-benefit ratio favors conservative treatment for this benign disorder.
Biliary dyskinesia (BD) falls into the spectrum of functional gastrointestinal disorders (FGIDs), which are defined by symptom patterns, chronic course, a negative impact on quality of life, and the absence of structural abnormalities. Although consensus criteria for pediatric patients are missing, expert panels provided a diagnostic framework for adults that may provide some guidance (Table 1).

The criteria emphasize impaired gallbladder function as a defining biomarker and include a supporting factor as further evidence, namely the lasting benefit after cholecystectomy. Although certainly not the primary criterion, this indirect support implicitly accepts an empiric surgical treatment trial, which positions BD uniquely among the diverse functional disorders affecting the gastrointestinal tract.

**IMPORTANCE**

Recurrent abdominal pain is common in children and adolescents, with prevalence estimates between 0.5% and 19%. Children with abdominal pain are likely to seek and receive medical care, with chronic abdominal pain accounting for up to 15% of visits with general pediatricians and more than half of pediatric gastroenterology consultations. Although pain often triggers diagnostic testing even in the absence of alarm symptoms (such as weight loss, fevers, vomiting, and anemia), underlying organic disorders are rare. Thus, FGIDs are the primary cause of chronic discomfort in children and adolescents. About 10% of children with functional abdominal pain will present with discomfort primarily localized in the right upper abdomen, raising concerns about dysfunction within the biliary system. Despite the rise in obesity, gallstone disease remains very uncommon in children, hence subsequent speculations about dysfunction of the gallbladder. With the advent of functional gallbladder imaging and minimally invasive surgery, BD has become a common indication for cholecystectomy in adults. Reports of cholecystectomies for BD in children started surfacing only about 15 years ago but now account for up to 50% of the gallbladder surgeries in pediatric series. Although the overall volume of operations remains relatively small compared to cholecystectomies performed in adults, the more than seven-fold increase of operations performed annually in children for BD during the past decade shows a widespread acceptance and increasing burden. This rise not only stands in stark contrast with the lack of accepted criteria for this diagnosis in children, but it also positions BD uniquely among FGIDs since the diagnosis of this benign disorder without known complications is routinely considered as indication for surgery.

**PATHOPHYSIOLOGY**

The gallbladder and biliary tract control transport of bile to the duodenum. In the fasting state, bile is stored and concentrated in the gallbladder and the sphincter of Oddi limits bile flow into the duodenum. Post-prandially, cholecystokinin (CCK) is released from enteroendocrine cells in the duodenum, binds to receptors on gallbladder muscle cells and the sphincter of Oddi, resulting in gallbladder contraction and sphincter of Oddi relaxation to allow bile to enter the duodenum. Although not proven experimentally or supported by systematic clinical studies, abdominal pain in BD is thought to be related to increased pressure within the gallbladder lumen caused by uncoordinated gallbladder contractions in the setting of either structural or functional outflow obstruction or partial cystic duct obstruction from either inflammatory stenosis or spasm occurring during gallbladder contraction.

**DIAGNOSIS**

The diagnostic criteria for BD as defined for adults is largely based on symptoms thought to arise from a diseased gallbladder in the absence of documented abnormalities on imaging studies — typically an abdominal ultrasound examination, and normal laboratory test-

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**TABLE 1.**

Diagnostic Criteria for Functional Gallbladder Disorder

1. Episodes of right upper-quadrant or epigastric pain and all of the following:
   - Pain lasting 30 minutes or longer.
   - Recurrent symptoms occurring at different intervals (not daily).
   - The pain builds up to a steady level.
   - The pain is moderate to severe enough to interrupt the patient’s daily activities or lead to an emergency department visit.
   - The pain is not relieved by bowel movements, postural change, or antacids.
   - Other structural disease that would explain the symptoms is excluded.

2. Supportive criteria:
   - Pain with one or more of the following: nausea and vomiting, radiation to the back or right subcostal area, awakening from sleep related to pain.

3. Gallbladder present.


5. Normal liver enzymes, conjugated bilirubin, and amylase/lipase.

6. Abnormal gallbladder ejection fraction (< 40%) after a continuous infusion of a CCK analog over a 30-minute period.

7. A positive therapeutic response with absence of recurrent pain for longer than 12 months after cholecystectomy.

Data from Behar et al.1
ing combined with impaired gallbladder function (Table 1). In their description of disease characteristics, the expert panel emphasized the intermittent nature and chronicity of pain, as constant discomfort is unusual for hollow-organ pain and because most acute illnesses resolve with little or no intervention. These diagnostic guidelines center on abnormal gallbladder function, which does not only give the disorder its name, but presumably differentiates it from other disorders with similar symptoms, such as functional dyspepsia, peptic ulcer disease, or gastroparesis. Again focusing on adults, an expert panel recommended scintigraphic assessment with the hepatobiliary iminodiacetic acid scan to visualize the biliary tree and gallbladder, followed by a slow infusion of the CCK analog sincalide, which triggers gallbladder contraction and allows to calculate the gallbladder ejection fraction (GBEF). Based on data obtained in healthy volunteers, ejection fractions of less than 40% are considered abnormal. Although never validated in children, these criteria have largely been adopted in pediatric clinical practice; however, some investigators have raised questions about their utility, since abnormal test results did not predict response to treatment. These findings mirror more extensive studies in adults that did not support the use of functional gallbladder imaging as a diagnostic or prognostic tool.

**TREATMENT**

As gallbladder disease falls into the domain of surgical treatment, cholecystectomy is generally accepted as the treatment of choice in BD. Since its first description in the pediatric literature, several case series have described positive outcomes in the majority of cases operated. Considering the often shifting phenotype of functional illnesses and the generally good prognosis of FGIDs in the majority of the affected children, it is important to compare these data to alternative treatments. Unfortunately, well-designed trials are missing. In adults, only one small, randomized trial without active intervention in the control group showed a benefit of surgery. Focusing on case series describ-
ing the impact of cholecystectomy in children, the reported response rates generally confirmed a likely benefit in the majority of patients. However, chances of improvement tend to drop with larger sample sizes and longer follow-up time (Table 2, Figure 1). More importantly, a retrospective analysis comparing the outcomes of conservative and operative therapy in children with BD showed identical results 2 years after the initial diagnosis. More detailed assessments of postoperative outcomes should also make clinicians more hesitant, once it comes to moving toward surgery in BD. Although the majority of operated children tend to be satisfied with the results, even responders continue to report a lower quality of life than their peers. A complementary approach that looked at symptom resolution in details may explain this finding, since nearly 90% of the patients studied continued to experience symptoms after cholecystectomy; however, these patients still responded that they were satisfied with the results of surgery. These data fit into the larger context of our understanding of functional pain syndromes in children and

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Data not available where blank.

CCY = cholecystectomy; F/U = follow-up; GB-EF = gallbladder ejection fraction.
Biliary dyskinesia should be seen as a manifestation of functional abdominal pain.

Table 3

<table>
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<th>What Do We Know About Biliary Dyskinesia in Children?</th>
<th>What Should We Do for Children with Biliary Dyskinesia?</th>
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<td>Rates of diagnosis or surgery are on the rise.</td>
<td>Biliary dyskinesia should be seen as a manifestation of functional abdominal pain.</td>
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<td>Validated diagnostic criteria and prognostic indicators are missing.</td>
<td>Remind patients and parents that the disorder is benign and has no known complications.</td>
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<td>Surgical outcomes do not seem to be superior to conservative therapy when assessed after 2 years.</td>
<td>Surgery may not be as helpful as initially thought and should thus be deferred.</td>
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<td>Medical treatment seems to be equally effective and may thus be preferable due to its lower risk.</td>
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likely are more realistic. They may, in part, reflect a more skewed cohort of patients with lasting and more severe symptoms that prompt repeated clinical encounters, testing, and eventual operative treatments. Consistent with such an interpretation, children with more significant functional abdominal or other pain syndromes face a long-term outlook with a nearly 50% likelihood of ongoing or recurrent functional pain problems during adolescent and/or adult life.28,29

With a rising number of operations despite an apparently declining or unclear benefit, can we select candidates who are more likely to gain from surgery based on test results? The lack of well-designed trials obviously does not allow an answer. Investigators have tried but have been unable to identify independent predictors of lasting benefit.30 Similarly, the typical definition of an abnormally low GBEF did not correlate with outcomes in yet another study.31 Using the above mentioned symptomatic response to the CCK agonist infusion also does not function as a prognostic tool in children.27,32

CONCLUSION

The currently available data on BD in pediatric patients show a widening gap between clinical practice and supportive evidence (Table 3). Although BD accounts for a relatively small fraction of children with abdominal pain, it is being increasingly diagnosed in pediatrics even though no formal definition exists for this age group. The diagnosis relies on the combination of symptoms and a defining biomarker, the documented impairment of gallbladder function. Yet, this disease-defining biomarker has never been critically examined in children and does not does predict response to treatment. The treatment, in turn, places BD into a unique situation as it falls into the hand of surgeons, although the admittedly small risk of surgery cannot be justified by any known long-term complication or risk of the illness itself. Perhaps even more importantly, limited evidence suggests that the outcomes of operative and active conservative management are equivalent. Thus, to avoid surgical removal of a potentially normal organ (the gallbladder), clinicians should consider BD as a variant of abdominal pain-related FGIDs, and use the less aggressive medical, dietary, and/or psychological approaches that are available.33

REFERENCES