



## Biliary hyperkinesia: A potentially surgically correctable disorder in adolescents



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### ABSTRACT

Biliary colic, which is characterized by intermittent, usually postprandial, right upper quadrant pain, is a common complaint in the pediatric population and usually prompts further evaluation with an abdominal ultrasound. Those patients without evidence of cholelithiasis are sometimes referred for a hepatobiliary iminodiacetic acid scan with cholecystokinin stimulation (CCK-HIDA) to assess gallbladder function. When the gallbladder empties poorly, the diagnosis of biliary dyskinesia, defined as a gallbladder ejection fraction less than 35%, is made, and cholecystectomy can be considered. There is a subset of symptomatic patients, however, who have an abnormally high ejection fraction, defined as greater than 65%. The approach to the treatment of these patients with biliary hyperkinesia is still undetermined, as there is little in the literature regarding this entity. With IRB approval (protocol #1307002185), we report our series of three adolescent females found to have biliary hyperkinesia whose symptoms immediately resolved following laparoscopic cholecystectomy.

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Biliary hyperkinesia is a previously described but poorly understood cause of biliary symptoms in the adult population but has not been described in children. It is diagnosed with a CCK-HIDA cholescintigraphy scan to measure gallbladder ejection fraction. Successful resolution of symptoms has been achieved with laparoscopic cholecystectomy in adults.

### 1. Case report

#### 1.1. Patient 1

A 16-year-old girl presented with a three-week history of sharp, postprandial right upper quadrant pain necessitating multiple visits to the emergency department. Both a right upper quadrant ultrasound and an abdominal CT scan performed at presentation revealed no obvious source of her pain. She subsequently underwent a CCK-HIDA scan, which demonstrated a gallbladder ejection fraction of 81%. Repeat cholescintigraphy

after referral to our institution showed an ejection fraction of 71%. Of note is that the patient's mother reported a remote history of similar symptoms and was also found to have no evidence of cholelithiasis; after a cholecystectomy, the mother's symptoms resolved and she has not experienced any issues since then.

#### 1.2. Patient 2

An 18-year-old girl presented with several weeks of intermittent right upper quadrant pain and a 15-pound weight loss. Endoscopic examination of the esophagus, stomach and duodenum revealed no abnormalities and a CCK-HIDA scan demonstrated a gallbladder ejection fraction of 72% and also induced right upper quadrant pain upon administration of the synthetic cholecystokinin during the study.

#### 1.3. Patient 3

A 13-year-old girl presented with 6 months of nausea, vomiting and abdominal pain frequently associated with ingestion of food. An abdominal ultrasound was performed which suggested gallbladder cholesterol polyps. A gastric emptying scan was also performed and was normal. A subsequent CCK-HIDA scan showed a gallbladder ejection fraction of 77%.

Each of the three patients underwent an uneventful laparoscopic cholecystectomy with immediate resolution of their

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symptoms postoperatively. Pathologic examination of the specimens revealed no significant abnormality except for mild chronic inflammation in the first and third patients (there was no polyp in Patient 3). All patients remain pain-free post-operatively (mean follow up of 14 months).

## 2. Discussion

Physiologic biliary motility is determined by two factors: neurohormonal control and anatomic structure [1]. Both autonomic and hormonal mechanisms contribute to the regulation of gallbladder emptying. Mechanical obstruction (e.g. sphincter of Oddi dysfunction and cholelithiasis) can also impact flow through the biliary tree. Abnormal functioning of either of these two factors can produce symptoms of biliary colic, i.e. postprandial right upper quadrant pain, which in many cases can be relieved with laparoscopic cholecystectomy.

Vegunta et al. reported that in their experience in children, the most common indication for cholecystectomy is biliary dyskinesia, characterized by abnormal gallbladder motility with an ejection fraction of less than 35% indicating that this entity may be overlooked by others [2]. Decreased emptying of the gallbladder causes chronic stasis, which may induce chemical injury to the mucosa [1]. This disease process has been well studied, with up to 85% of patients reporting complete resolution of their symptoms post-operatively [2]. In the evaluation of biliary symptoms in children who have a non-diagnostic right upper quadrant ultrasound, the presence of a gallbladder ejection fraction less than 35% suggests a diagnosis of biliary dyskinesia and may guide further management. Those children with a gallbladder ejection fraction greater than 35%, however, have a less clear path to symptom relief.

In contrast, biliary hyperkinesia, which is characterized by a gallbladder ejection fraction greater than 65%, is a newly described entity with very little data to guide treatment. This condition was first reported in the literature in 1999 and since then only two reports have described the benefit of cholecystectomy in adults with biliary hyperkinesia [3,4]. In the first study, researchers found that 7/7 adult patients experienced symptom relief after undergoing cholecystectomy as compared to 0/7 patients who received no treatment; their mean gallbladder ejection fractions were 84.6% and 84.9% respectively [4]. Recently, DuCoin et al. identified nineteen patients with a mean gallbladder ejection fraction of  $75.1 \pm 19.4\%$  (with a minimum ejection fraction of 35%), who also presented with biliary pain and proposed a novel diagnosis of “normokinetic biliary dyskinesia” [5]. No such reports regarding biliary hyperkinesia exist in the pediatric literature.

In our series, two of the three patients with biliary hyperkinesia demonstrated histologic evidence of chronic cholecystitis, indicative of long-standing mucosal inflammation. DuCoin et al. similarly found chronic cholecystitis on histopathology in 18 of 19 patients [5]. In a normal gallbladder, cholecystokinin is released by the duodenal lumen in response to the ingestion of fats and amino acids thus inducing contraction and causing volume change within the gallbladder [1]. The state of *in vivo* cholecystokinin production and response, however, cannot easily be measured and the synthetic cholecystokinin stimulation provides only a snapshot of a patient's biliary physiology. Thus the mechanisms resulting in gallbladder inflammation in biliary hyperkinesia are unclear. It is known that the rate of gallbladder emptying decreases with age after childhood due to decreased sensitivity to cholecystokinin, perhaps indicating that increased sensitivity is responsible for increased ejection fraction in these adolescent patients [1]. It is also known that endogenous cholecystokinin levels are directly proportional to both the degree of gallbladder volume change and to the gallbladder intraluminal pressure

[1,6–8]. Cholecystokinin levels, however, have not been measured in patients with biliary hyperkinesia, though it is plausible that increased cholecystokinin secretion could lead to the increased gallbladder ejection fraction.

If increased cholecystokinin sensitivity or release is the etiology of the increased gallbladder ejection fraction in these patients, then the increased emptying could be accompanied by increased intraluminal pressure. This pressure may be the cause of mucosal injury, as evidenced by the chronic inflammation visible on histopathology, and possibly the source of the right upper quadrant. This is further supported by the fact that, interestingly, after removal of a normal gallbladder the release of cholecystokinin with meals is increased, yet our patients and those in other studies of gallbladder hypermotility report complete relief from symptoms [3–5,9]. Though cholecystokinin may cause relaxation of the lower esophageal sphincter leading to symptoms of gastroesophageal reflux, none of our patients reported any such symptoms [9]. Thus the effect of cholecystokinin on the gallbladder, and not the hormonal influences of cholecystokinin itself, appears to be the source of the pain and therefore the removal of its target organ should be sufficient to alleviate the symptoms.

Although biliary hyperkinesia is defined using a threshold value for gallbladder ejection fraction, with the CCK-HIDA scan as the gold standard for diagnosis, a recent study has shown that reproduction of symptoms following cholecystokinin injection is superior to measurement of ejection fraction in predicting improvement of symptoms following cholecystectomy in patients with biliary dyskinesia [10]. In our series, only Patient 2 had a specific mention of symptom reproduction in relation to CCK injection, yet this finding may represent the most important aspect of diagnostic testing to consider when planning treatment. In fact, DuCoin et al. employed reproducibility of symptoms upon infusion of CCK as a criterion in their diagnosis [5]. It is also important to consider the protocol for testing, as variability in CCK administration may preclude comparisons between institutions. In this series, both Patients 1 and 3 received 0.02  $\mu\text{g}/\text{kg}$  of Kinevac (synthetic cholecystokinin) during their CCK-HIDA scan which was performed in our institution; Patient 2 had a HIDA scan at an outside institution. Our protocol for cholecystokinin administration follows that recommended by Ziessman et al. for measurement of gallbladder ejection fraction in adults and uses the value obtained at 60 min as the reported ejection fraction [11]. Establishing a minimum value of gallbladder ejection fraction for biliary hyperkinesia would require greater standardization of the CCK-HIDA scan protocol.

Many questions remained unanswered in the pathophysiology and diagnosis of biliary hyperkinesia. A minimum ejection fraction beyond which the gallbladder is considered hypermotile has yet to be established. In this series, the gallbladder ejection fraction as measured on CCK-HIDA scan ranged from 72% to 81%. The symptoms of typical biliary colic were also included in the diagnostic criteria and there is evidence that reproduction of these symptoms after CCK administration may aid in diagnosis or help to predict postoperative outcome [10]. Perhaps most importantly, these prior studies reference the physiology of adults, which does not necessarily translate to that of children and adolescents.

Of the few studies published thus far examining patients with high gallbladder ejection fractions, all have noted success with resolution of symptoms following cholecystectomy. None of the studies have considered pediatric patients with biliary hyperkinesia. Based on its success in adults and the cases presented in this report, laparoscopic cholecystectomy appears to be an effective treatment for this condition in the pediatric population. Nevertheless, this remains a newly described and poorly studied entity and the disease course of biliary hyperkinesia is still unknown.

### 3. Conclusion

In this series, we report three adolescents with biliary hyperkinesia, defined as biliary colic symptoms with a gallbladder ejection fraction greater than 65%, each of whom had immediate resolution of symptoms following laparoscopic cholecystectomy. Three prior studies have examined gallbladder hypermotility in adults. However, the pathophysiology of this condition is not well understood. In children who present with symptoms of biliary colic but who have no findings on abdominal ultrasound suggesting cholelithiasis and who either have an abnormally high gallbladder ejection fraction or who have reproduction of symptoms upon CCK stimulation, the possibility of biliary hyperkinesia should be considered. We believe that biliary hyperkinesia should be regarded as a potentially surgically correctable condition in children and adolescents.

### Conflict of interest statement

No authors have any disclosures.

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