

# Normokinetic biliary dyskinesia: a novel diagnosis

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## Abstract

**Background** Biliary dyskinesia diagnosed with CCK-HIDA scan and ejection fraction less than 35 % has been successfully treated by laparoscopic cholecystectomy. However, a population of patients with symptomatic biliary pain and a normal CCK-HIDA scan never receive a diagnosis, and thus no definitive treatment. Some of these patients report a reproducible pain during their CCK-HIDA scan. It is hypothesized that these patients have a novel diagnosis, normokinetic biliary dyskinesia, and may have resolution of pain when treated with cholecystectomy.

**Methods** A retrospective chart review was completed looking for patients with biliary pain in accordance with the ROME III criteria. Additional inclusion criteria were (1) greater than age 18 years, (2) reproducible biliary symptoms during the CCK-HIDA scan, and (3) an ejection fraction greater than 35 %. Treatment modality was laparoscopic cholecystectomy. Descriptive statistics were performed, and data were reported as mean  $\pm$  standard deviation and range.

**Results** Nineteen patients met the inclusion criteria for this study from August 2008 to July 2011. There were 15 women and 4 men with a mean age of  $48.4 \pm 13.0$  years. The mean ejection fraction was  $75.1 \pm 19.4$  %. The average duration of preoperative symptoms was  $6.8 \pm 5.9$  months and postoperative follow-up was  $21.8 \pm 10.6$  months. Seventeen patients had complete resolution of symptoms, one had partial resolution, and one had no change. There was a complete resolution rate of 89.5 % and an improvement rate of 94.7 %.

**Conclusions** We suggest that patients who present with biliary pain, a normal CCK-HIDA scan with an ejection fraction greater than 35 %, and with reproducible symptoms on infusion of CCK could have a novel diagnosis: normokinetic biliary dyskinesia. Currently, these patients are excluded from the diagnosis of biliary dyskinesia and thus treatment. We hypothesize a potential new diagnosis, suggest cholecystectomy as treatment, and recommend a prospective study design for further evaluation.

**Keywords** Gallbladder · HIDA scan · Biliary dyskinesia · Cholecystectomy

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Biliary dyskinesia was originally defined as the presence of biliary colic without evidence of cholelithiasis on ultrasound of the gallbladder [1]. The diagnosis has evolved since this original description and was most recently updated by the ROME III criteria (Table 1) [2]. The criteria state that to confirm diagnosis there needs to be absence of sludge, stones, and microlithiasis, an abnormal ejection fraction less than 40 % with continuous infusion of cholecystokinin more than 30 min, and positive therapeutic response following cholecystectomy with absence of pain for 12 months [2].

The ability to measure ejection fraction and calculate gallbladder dysmotility was established with the advent of

**Table 1** Rome III criteria*Functional gallbladder and sphincter of Oddi disorders*

Diagnostic criteria must include episodes of pain located in the epigastrium and/or right upper quadrant and *all* of the following:

1. Episodes lasting 30 min or longer
2. Recurrent symptoms occurring at different intervals (not daily)
3. Pain builds up to a steady level
4. Pain is moderate to severe enough to interrupt the patient's daily activities or lead to an emergency department visit
5. Pain is not relieved by bowel movements
6. Pain is not relieved by postural change
7. Pain is not relieved by antacids
8. Exclusion of other structural disease that would explain the symptoms

ROME III committee also proposed three criteria after treatment to confirmed gallbladder dyskinesia in-long term follow up studies.

1. Absence of sludge, stones, or microlithiasis
2. Abnormal normal ejection fraction (<40 %) over continuous infusion of CCK over 30 min
3. Positive therapeutic response with absence of recurrent pain for more than 12 months

cholecystokinin <sup>99m</sup>technetium-labeled hepato-imino-diacetic acid (CCK-HIDA) scan. The accepted value for abnormal gallbladder ejection fraction has varied in the literature from <35 to <50 % [3–11]. However, most studies quote an abnormal ejection fraction as less than 35 %, as reported in the 2009 Cochrane review [6]. Currently, hypokinetic biliary dyskinesia is diagnosed by gallbladder ejection fraction less than 35 % on CCK-HIDA scan and has been successfully treated with laparoscopic cholecystectomy. Illustrating the efficacy of this treatment, resolution of symptoms reported in the literature has ranged from 94 to 100 % [3–5, 12].

However, in contrast to those patients with abnormal ejection fraction, there is a separate population of patients who have symptomatic biliary pain yet demonstrate normal ejection fraction upon CCK-HIDA scan. These patients never receive a diagnosis of biliary dyskinesia and, thus, no definitive treatment for their symptoms. For some of these patients, their symptomatic biliary pain is reproduced upon infusion of CCK during their HIDA scan. It is believed that these patients could have a novel diagnosis: normokinetic biliary dyskinesia. The purpose of this study was to provide a basis for this new diagnostic entity and to expand the treatment algorithm for patients with biliary dyskinesia.

## Materials and methods

After approval by the Institutional Review Board, a retrospective chart review of a single surgeon's practice was conducted

of all patients presenting with biliary pain in accordance with the ROME III. Criteria for inclusion in this study were (1) age older than 18 years, (2) documented reproducible biliary symptoms on administration of CCK during their HIDA scan, and (3) an ejection fraction greater than 35 %.

All patients had an ultrasound of the gallbladder, which showed no stones or visible sludge, as well as an upper endoscopy, which showed no pathology that could explain the biliary pain. Patients underwent a CCK-HIDA scan according to a protocol established in January 2008 by the Nuclear Medicine Department at Orlando Regional Medical Center. First, patients were administered 5.5 mCi of technetium <sup>99m</sup> intravenously. Next, the biliary system was imaged for 60 min. Finally, the gallbladder was stimulated with 0.02 µg/Kg of Sincalide (Kinevac, Bracco Diagnostics Inc., New Brunswick, NJ), the active synthetic portion of cholecystokinin. The infusion rate was over a 45-min period, and the biliary system was subsequently imaged for an additional 30 min. Before the scan, the patients were asked to report if they felt pain similar to their biliary colic at any point during the scan.

The ejection fraction was then calculated in each patient using the standard equation:

$$\text{GBEF} = (\text{Net pre-CCK GB} - \text{Net post-CCK GB at 30min}) / \text{Net pre-CCK GB}.$$

All patients were treated with laparoscopic cholecystectomy by the same surgeon. Clinical variables, including age, sex, duration of symptoms, biliary ejection fraction, duration of follow-up, resolution of symptoms, type of surgery, and final pathology, were recorded. All specimens were sent to pathology for histopathology review by a hepatobiliary pathologist. Pathologic criteria of chronic cholecystitis included hypertrophy of the gallbladder wall, diffuse hypertrophy of the muscularis propria, the presence of Aschoff-Rokitansky sinuses, and/or macrophages in the mucosal folds.

Patients were seen at a standard 1-week postoperative visit and were asked to complete a questionnaire describing their symptoms as complete resolution, partial resolution, or continuation of preoperative biliary pain. A follow-up scripted telephone interview was conducted by office staff. Patients were asked to provide feedback on their generalized hospital stay, pre- and postoperative care, and quality of the nursing staff. In addition, patients were asked whether they had complete resolution, partial resolution, or continuation of their biliary pain. Data were reported as descriptive statistics and calculated as mean ± standard deviation along with range.

## Results

Nineteen patients met the inclusion criteria for this study from August 2008 to July 2011. Of these patients, 15 were

women and 4 were men. The mean age at time of presentation was  $48.4 \pm 13.0$  years. All patients had an ejection fraction greater than 35 % with a mean of  $75.1 \pm 19.4$  % (range, 39–98 %) with reproducible biliary pain on administration of CCK during their HIDA scan. The average duration of preoperative symptoms was  $6.8 \pm 5.9$  months (range, 6 weeks to 24 months). The average postoperative follow-up was  $21.8 \pm 10.6$  months (range, 5–34 months).

All patients were treated with a laparoscopic cholecystectomy, which was scheduled as an elective outpatient procedure. The average operative time was 37 min. Sixteen of the 19 patients were discharged home the same day, whereas 3 patients required admission to the hospital for pain control. All were discharged in less than 48 h. There were no surgical complications.

Results of histopathology demonstrated chronic cholecystitis in 18 of 19 specimens. One specimen demonstrated chronic cholecystitis with cholesterosis.

Of the 19 patients included in this study, 17 had complete resolution of symptoms, 1 had partial resolution, and 1 had no change. There was a complete resolution rate of 89.5 % and an overall improvement rate of 94.7 %.

## Discussion

Evaluating gallbladder motility based on ejection fraction with the use of CCK-HIDA scan has refined the diagnosis of biliary dyskinesia [11, 13–15]. The gallbladder ejection fraction was originally reported by Krishnamurthy et al. in 1981 [16], who reported gallbladder contraction in response to CCK administration and quantified the contraction volume with a HIDA scan. At that time, the utility of the test was unknown, because the pathophysiology of biliary dyskinesia was still undergoing development.

An import factor that influences gallbladder ejection fraction is the rate at which cholecystokinin (CCK) is administered and, thus, the reproducibility of biliary pain [17–19]. The continuous slow infusion of CCK over 30–60 min is most physiologic, thus reflecting gallbladder kinetics more accurately [20–22]. In contrast, a rapid infusion rate can create abnormal gallbladder physiology and biliary kinetics, resulting in false-positive biliary pain during the CCK infusion. In most reports, rapid infusion of CCK over 2–3 min has been shown to yield highly variable results and unreliable findings [17–19]. It is this theory that supports previous work that CCK infusion associated with reproducible symptoms is not reliable [23–25]. For this reason, more recent studies [26, 27] have used infusion rates 30 min or greater. For example, the ROME III criteria recommends an infusion rate of 30 min [2], and a report by the General Clinical Nuclear Medicine Council (GCNMC)

recommends a rate of 60 min [28–30]. Our study employed both recommendations and used a CCK infusion rate of 45 min to reflect most accurately the physiologic gallbladder kinetics and reduce the likelihood of a false-positive biliary pain on CCK infusion.

In addition to variations in the rate at which CCK is administered, delineating normal from abnormal gallbladder ejection fraction also has varied throughout the literature. Some studies report abnormal ejection fraction as less than 35 %, whereas others report abnormal as less than 50 % [3–10, 31]. Fink-Bennett et al. subjectively defined biliary dyskinesia as an abnormal gallbladder ejection fraction less than 35 % [11]. Other studies, including the ROME III criteria, set the abnormal as less than 40 %. Still others have defined abnormal as less than 50 % based on two standard deviations below the known average gallbladder ejection fraction of 74 % [10, 12, 32]. This degree of variation seen in the definition of gallbladder ejection fraction has lead to inconclusive findings as to its significance in the diagnosis and management of biliary dyskinesia.

The diagnosis of hypokinetic biliary dyskinesia, patients with an ejection fraction less than 35 %, has been established. Expected resolution of symptoms after cholecystectomy within this subgroup of patients has been shown to be 94–100 % [3–5, 12]. Smaller retrospective studies support that the lower the ejection fraction, the more likely there is to be symptomatic relief after cholecystectomy [33–35]. However, many studies refute this, showing that ejection fraction is not a good predictor of outcome [36, 37, 40]. One study even examined subsets of patient with ejection fraction ranging from 0 to <50 % and found no correlation between relief of symptoms and degree of ejection fraction [5]. Furthermore, when using final histopathology as an outcome measure, there is no difference when comparing symptomatic patients with ejection fractions less than 35 % to those with ejection fractions greater than 35 %. This further confirms that biliary dyskinesia is not isolated to those patients with ejection fractions below 35 % [3, 4, 9, 27].

Recently, Rosenblatt et al. [26] evaluated biliary pain symptom provocation after CCK infusion regardless of gallbladder ejection fraction. His work illustrated that replication of symptoms after injection of CCK is superior to biliary ejection fraction in predicting symptomatic improvement after cholecystectomy. His point is radical in that it implies the HIDA scan may be irrelevant and that reproducible symptoms on CCK infusion are the only necessary diagnostic criteria. Many argue this point stating that CCK provocation test does not work alone and there is an array of organ stimuli to CCK [38, 39]. Whatever the case, in his study Rosenblatt did include 25 patients with ejection fractions greater than 35 %, but unfortunately he

did not report which specific patients had resolution of symptoms. In other words, we do not know what percentage of his patients with ejection fractions greater than 35 % had resolution of symptoms. Nevertheless, his study shows utility in treating patients with ejection fractions greater than 35 % with cholecystectomy.

A study by Adams et al. [40] further suggested that there is no value in evaluating biliary pain with either CCK-HIDA scans or calculated ejection fractions. They suggest omitting this portion of the workup and simply treat with cholecystectomy. Their study found a positive and negative likelihood ratio of 0.99 and 1.13 when comparing ejection fractions less than 35 % to those greater than 35 %, thus no utility of their study. Their evaluation of CCK-HIDA scans found that only 35 of 45 patients (78 %) with ejection fractions less than 35 % had resolution of biliary pain when treated with cholecystectomy, a number drastically different from what has been reported in the literature. Those with ejection fractions greater than 35 % had a resolution rate of 80 %, but this consisted of only five patients. A now known confounding factor of the study was the rapid 3- to 5-min infusion rate of

CCK. Adams concluded that biliary pain alone maybe sufficient grounds for cholecystectomy. This could hold true in some instances, but with this we lose the use of objective data, specifically ejection fractions via CCK-HIDA scans and with that a specific diagnosis. The study also examined those who continue with postcholecystectomy pain and implicates sphincter of Oddi dysfunction, finding that seven of eight unimproved patients had abnormal sphincter pressures. This hypothesis was further explored by Murray [43] who injected Botulinum toxin into the sphincter of Oddi of 25 patients reporting biliary pain in accordance with the ROME III criteria, again those with ejection fractions less than 40 %. Eleven of the 25 patients (44 %) reported relief of biliary pain and 10 of those were treated with sphincterotomy. All ten patients reported resolution of pain with a median follow-up period of 12 months. The prevalence of sphincter of Oddi dysfunction seen in the study was higher than expected, as the diagnosis is seen in approximately 10–15 % of postcholecystectomy patients with persistent systems [40–42]. Regardless, sphincter of Oddi dysfunction needs to be explored as a possible cause of postcholecystectomy pain.

**Fig. 1** Biliary Pain Algorithm



We agree that hypokinetic biliary dyskinesia is a recognized diagnosis, defined as those with a CCK-HIDA scan showing a biliary ejection fraction less than 35 %. We also agree that hypokinetic biliary dyskinesia has an established treatment of cholecystectomy. We hypothesize a new diagnosis, normokinetic biliary dyskinesia, defined as patients with biliary pain, who have a normal CCK-HIDA scan with an ejection fraction greater than 35 %, with reproducible symptoms on infusion of CCK. According to the standard algorithm, these patients are currently excluded from the diagnosis of biliary dyskinesia and thus do not receive definitive treatment. Currently, treatment recommendations for these patients are observation, reassessment, and symptomatic treatment [4, 7, 31]. We hypothesize that these patients who meet the diagnostic criteria of normokinetic biliary dyskinesia could benefit from cholecystectomy as treatment (Fig. 1). Although this study has a small sample size and requires further prospective investigation, it does demonstrate that a complete resolution rate of 89.5 % and an overall improvement rate of 94.7 % could be expected when treating this subset of patients with cholecystectomy. The goal is to further our understanding regarding the pathophysiology of biliary pain and hopefully to expand the treatment algorithm with further investigation.

## Conclusions

This study suggests a new diagnosis, normokinetic biliary dyskinesia, defined as a gallbladder ejection fraction greater than 35 % with reproducible biliary pain upon CCK infusion during HIDA scan. This small retrospective study demonstrated that when treated with cholecystectomy, a complete resolution rate of 89.5 % and an overall improvement rate of 94.7 % could be expected. These findings are significant and look promising but need to be confirmed with a larger prospective study due to the limited population size and retrospective nature of this study.

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