Published in final edited form as:

J Pediatr Gastroenterol Nutr. 2012 June ; 54(6): 776–779. doi:10.1097/MPG.0b013e3182455cf9.

Concomitant Gastroparesis Negatively Impacts Children with Functional Gallbladder Disease

Bruno P. Chumpitazi, MD, MPH^{1,2}, Stanton M. Malowitz, MD^{1,2}, Warren Moore, MD^{2,4}, G.S. Gopalakrishna, MD^{1,2}, and Robert J. Shulman, MD^{1,2,3}

¹Department of Pediatrics, Baylor College of Medicine, Houston, TX, USA

²Texas Children's Hospital, Houston, TX, USA

³Children's Nutrition Research Center, Houston, TX, USA

⁴Department of Radiology, Baylor College of Medicine, Houston, TX, USA

Abstract

Objectives—The aim of this study was to determine if concomitant gastroparesis and biliary dyskinesia occur in children, and if so, to determine if concomitant gastroparesis affects clinical outcome in children with biliary dyskinesia. **Methods:** We conducted a retrospective chart review of children with biliary dyskinesia (ejection fraction <35% on cholescintigraphy, with no other metabolic, or structural cause) who completed a solid-phase gastric emptying scintigraphy scan within 12 months of the abnormal cholescintigraphy. Children were classified into one of four clinical outcome groups (excellent, good, fair, poor).

Results—Thirty-five children with a mean follow-up time of 23.1 ± 17.3 (SD) months were included. 20 (57%) children were identified as having concomitant gastroparesis with biliary dyskinesia. Children with concomitant gastroparesis were more likely to have a poor clinical outcome compared to those with biliary dyskinesia alone ($P < 0.005$). In children undergoing cholecystectomy, those with concomitant gastroparesis were more likely to have a fair or poor clinical outcome compared to those with biliary dyskinesia alone ($P < 0.01$). Factors predicting a more favorable clinical outcome were having biliary dyskinesia alone, and not having limitations in activity (e.g. school absences) at time of presentation.

Conclusions—Concomitant gastroparesis may occur in children with functional gallbladder disorders. Concomitant gastroparesis may negatively impact clinical outcome in children with biliary dyskinesia.

Keywords

Biliary dyskinesia; Children; Gastroparesis; Outcome; Pediatric

INTRODUCTION

Functional gallbladder disease, commonly known as biliary dyskinesia, is a recognized cause of dyspeptic symptoms, including epigastric or right upper quadrant abdominal pain, nausea, and vomiting in adults (1). Though not formally recognized by the Rome III committee for functional gastrointestinal disorders in children (2), an increasing consensus

Corresponding Author/Reprint Requests: Bruno P. Chumpitazi, MD, MPH, Texas Children's Hospital, 6701 Fannin Street, CCC 1010.03, Houston, TX, USA 77030, Phone: 832-822-3602, Fax: 832-825-3633, chumpita@bcm.edu.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text, and links to the digital files are provided in the HTML text of this article on the journal's Web site (www.jpagn.org).

is forming that children, like adults, also have biliary dyskinesia (3). In fact, biliary dyskinesia is the most common indication for pediatric cholecystectomy at certain institutions (3). Biliary dyskinesia may result in significant morbidity given that up to 52% of children and 23% of adults with biliary dyskinesia may have no improvement or continue to have significant symptoms despite undergoing surgical cholecystectomy, the primary treatment (4). The reason for this remains unclear, leaving those affected and the clinicians caring for them to struggle with determining whether a cholecystectomy is helpful and the aftermath if a cholecystectomy is done without resolution of symptoms.

One potential aspect of the difficulty with the diagnosis and treatment of biliary dyskinesia may lie in its nonspecific presentation and the manner by which it is diagnosed. Evaluation is often done through cholecystokinin (CCK) stimulated cholescintigraphy with calculation of a gallbladder ejection fraction. A calculated gallbladder ejection fraction of 35% or less is considered to be abnormal in children (5, 6). However, a standardized protocol followed by all pediatric institutions has not been proposed to date. Moreover, dyspeptic symptoms are not specific to gallbladder disorders, and may occur in children with other entities, including gastroparesis (7).

To our knowledge, a potential overlap between gastroparesis and functional gallbladder disease has not been previously explored. We hypothesized that a subgroup of children with a diagnosis of biliary dyskinesia may have concomitant gastroparesis, and those with both motor disorders would be more likely to have an unfavorable clinical outcome. We therefore undertook a study to determine the prevalence of concomitant gastroparesis in children with biliary dyskinesia, and to determine if its presence affected long-term clinical outcome in children with biliary dyskinesia.

METHODS

A retrospective chart review of all children undergoing cholecystokinin stimulated cholescintigraphy at Texas Children's Hospital from 2002 to 2008 was completed. All children with a gallbladder ejection fraction of less than 35% who had completed a solid phase gastric emptying study within one year of the cholescintigraphy were identified. Of these children, those with documented cholelithiasis, microlithiasis, gallbladder wall thickening, peri-cholecystic fluid, or bile duct dilatation via ultrasonography or any other radiologic modality prior to or within 3 months after the cholescintigraphy were excluded. Children with an identified organic (e.g. peptic ulcer disease) etiology on endoscopic evaluation that could account for the dyspeptic symptoms as determined by the judgment of the primary gastroenterologist were excluded. Children who had laboratory elevations in aminotransferases, bilirubin, or gamma-glutamyl-transferase were also excluded. The study was approved by the Baylor College of Medicine Institutional Review Board.

CCK stimulated cholescintigraphy was performed in the same manner in all children. Children were nothing per os and were not allowed to be on narcotics of any form for at least 4 hours prior to tracer injection. Up to 5.0 mCi (adjusted based on Clark's formula for those less than 70 kg) of Technecium-99m methyltribromoisminodiacetic acid was injected (8). Nuclear images were obtained for 1 min per frame through 60 minutes, with extension up to 120 minutes if slow gallbladder filling occurred. After gallbladder filling, cholecystokinin (Sincalide, Bracco Diagnostics, Princeton, NJ, USA), was injected at a dose of $0.02 \mu\text{g kg}^{-1}$ (maximum $2 \mu\text{g}$) intravenously over 5 minutes. Images were obtained at 1 min/frame for 30 minutes after the start of the injection. Gallbladder ejection fraction was calculated as maximum emptying over the 30 minutes following injection with usage of the immediate pre-injection frame activity as the baseline (9, 10).

Solid-state gastric emptying scintigraphy was performed using a meal consisting of 120 mL of scrambled eggs, though one child with an egg allergy used oatmeal. The meal was radiolabeled with 0.5 millicuries of Technetium-99M sulfur colloid and orally fed to the patient. Images were obtained in the left anterior oblique projection while the patient was supine for 90 minutes. A half emptying time was calculated by using a linear fit method. A half emptying time greater than 90 minutes was considered delayed based on our institution's pre-determined standards.

Demographic data, height, weight, clinical symptoms, and interventions were captured. Proton-pump inhibitors or histamine receptor antagonists were classified as anti-secretory agents. Metoclopramide, domperidone, and erythromycin were classified as prokinetics. Tricyclic antidepressants, gabapentin, or selective serotonin receptor antagonists were classified as neuromodulators. Medications were included as an intervention if they were prescribed by the primary gastroenterologist for the dyspeptic symptoms at any point during the follow-up period whether or not they were still being used at the time of the last follow-up visit.

Baseline dyspeptic symptoms were obtained from the time of initial presentation. Dyspeptic symptoms that were evaluated included abdominal pain severity and frequency, nausea severity and frequency, and degree of food intolerance. Clinical outcome was determined by documented dyspeptic symptom characterization at the time of the last documented follow-up visit as compared to the baseline (first) visit in the electronic medical record. Food intolerance was defined as any exacerbation in a dyspeptic symptom associated with food intake. Activity limitation was defined as missing school days due to the symptoms or inability to complete desired extracurricular activities (e.g. sports) due to the symptoms. Weight loss was defined as a 10% decrease in baseline weight attributed to the dyspepsia.

Children were categorized into four clinical outcome groups based on physician documentation at the time of last-follow-up:

Poor: Any symptom worsening or no improvement in any symptom compared to baseline or activity limitation at the time of last follow-up as compared to baseline

Fair: Partial improvement in some but not all dyspeptic symptoms at the time of last follow-up as compared to baseline

Good: Improvement of all dyspeptic symptoms but not complete resolution of all symptoms at the time of last follow-up as compared to baseline

Excellent: Complete resolution of all symptoms

For analysis purposes, excellent and good outcomes were considered to be favorable and fair and poor outcomes were considered to be unfavorable.

Statistical Analysis

Data are reported as mean $\pm$ standard deviation. Comparisons between children with gastroparesis and biliary dyskinesia and those with biliary dyskinesia alone were done with χ^2 analysis when comparing proportions or independent Student t-tests. Comparisons between baseline and outcome were done with χ^2 analysis when comparing proportions or paired t-test analysis. Binary multivariate forward stepwise logistic regression was completed with favorable and unfavorable outcomes being the binary dependent variable. BMI % was categorized into two groups (BMI % > 85% and BMI% = or < 85%) for the logistic regression analysis. χ^2 analysis was used to compare proportions in all other testing done. A P value of <0.05 was considered as statistically significant. All statistical analyses were performed using SPSS (Somers, NY).

RESULTS

One hundred seventeen children were found to have an abnormal cholescintigraphy during the study interval, of whom 48 (41%) completed a gastric emptying scintigraphy study. Of these 48, thirty-five children met inclusion and exclusion criteria and were further studied. The mean follow-up time was 23.1 ± 17.3 (range: 1.7–55.0) months with a median follow-up time of 19 months. The mean length of time between gastric emptying scintigraphy and cholescintigraphy was 2.1 ± 2.8 (range: 0.1–11.0) months with a median time interval of 0.7 months. Twenty-three (67%) of children completed the gastric emptying scintigraphy prior to the cholescintigraphy study. Fifteen children (43%) were identified as having normal gastric emptying with biliary dyskinesia, and 20 children (57%) were identified as having concomitant gastroparesis and biliary dyskinesia. Children with biliary dyskinesia and concomitant gastroparesis did not differ from those with normal gastric emptying with respect to age, gender, race/ethnicity, private insurance, BMI%, ejection fraction on CCK stimulated cholescintigraphy evaluation, number of formally diagnosed psychiatric comorbidities, or activity limitation at baseline (online-only supplemental table, <http://links.lww.com/MPG/A86>)

Children with concomitant gastroparesis and biliary dyskinesia did not differ from those without gastroparesis with respect to presence of abdominal pain, exacerbation of pain with food intake, nausea, vomiting, or weight loss (supplemental Table). However, children with concomitant gastroparesis were more likely to have constipation, and there was a non-statistically significant trend for children without concomitant gastroparesis to have diarrhea (supplemental Table).

Other than the usage of prokinetics, children with biliary dyskinesia and concomitant gastroparesis did not differ from those with biliary dyskinesia alone with respect to frequency of cholecystectomy, use of neuromodulators, or use of anti-secretory therapy (supplemental Table).

Amongst the entire follow up population (Figure 1), children with concomitant gastroparesis (9/20) were more likely than those with biliary dyskinesia alone (0/15) to have a poor clinical outcome ($P < 0.005$). Those with concomitant gastroparesis (10/20) were less likely than those with biliary dyskinesia alone (13/15) to have a favorable outcome ($P < 0.05$). With the use of multivariate regression including demographic factors, symptoms, and gastric emptying scintigraphy results, only activity limitation (odds ratio: 42.8) at baseline ($P < 0.005$) and having an abnormal gastric scintigraphy (odds ratio: 19.3) evaluation ($P < 0.05$) predicted an unfavorable outcome ($r^2 = 0.61$).

When comparing children included in the study with a time interval of less than one month between cholescintigraphy and gastric emptying scintigraphy to those with an interval greater than one month between studies no difference was found with respect to demographics, symptoms, intervention or outcomes. Similarly, when comparing children with a follow-up of greater than 19 months with those less than 19 months, there was no difference in clinical outcome found between the groups. Therefore the time interval between scintigraphic studies, and the follow-up interval did not appear to have a measurable impact within the study.

When comparing the long term outcome among only those children who underwent a cholecystectomy, children with concomitant gastroparesis were still more likely to have an unfavorable outcome, ($P < 0.005$). Amongst all the children studied, no differences in outcome were found in those with constipation, usage of prokinetics, status postcholecystectomy, or having cholecystitis status post cholecystectomy,

DISCUSSION

We found that concomitant gastroparesis may occur in children with biliary dyskinesia, and that those with concomitant gastroparesis were more likely to have an unfavorable clinical outcome. In addition to concomitant gastroparesis, having activity limitation at baseline increased the likelihood of an unfavorable outcome.

More standardized methods are needed to help identify the primary cause of dyspeptic symptoms in children, particularly if a motor abnormality such as gastroparesis or biliary dyskinesia is suspected. Consensus recommendations to standardize solid-phase gastric emptying scintigraphy and cholescintigraphy in adults have recently been proposed (11, 12). Similar standardization of nuclear medicine techniques and normal values are lacking in children. The normal gastric emptying scintigraphy values in our study are used clinically on an every day basis within our institution based on internal standards. A value of a cholescintigraphy ejection fraction of 35% or less to identify children with biliary dyskinesia is the most common cutoff used in the literature (5, 6), and we followed this growing consensus.

The reason for a less favorable outcome in children with concomitant gastroparesis and biliary dyskinesia is unclear. One possibility may include misdirected therapies. Given that the symptoms of gastroparesis may overlap with those of biliary dyskinesia, identifying if one or the other is causing the majority of the symptoms is likely to be difficult. Therapies directed at only biliary dyskinesia (e.g. cholecystectomy) may not address the symptoms if there is gastroparesis present and vice versa. Having concomitant gastric and biliary motor abnormalities may suggest a more diffuse neuroenteric abnormality is occurring, and directed therapies may not be able to address this well. Diffuse motor abnormalities of numerous gastrointestinal organs, including the gallbladder and stomach, have been described in adults with chronic intestinal dysmotility (13).

Children with concomitant gastroparesis and biliary dyskinesia were more likely to have constipation in our study. In contrast, there was a trend toward diarrhea in children with biliary dyskinesia alone. These bowel habit findings may aide clinicians in identifying children in whom to consider further diagnostic testing for the etiology of dyspeptic symptoms, and may also support the possibility of a more diffuse process. Others have suggested a connection between bowel habits and dysmotility of other gastrointestinal organs. Altered gallbladder motility as measured via cross-sectional ultrasound in children with chronic constipation has been recently described (14). The authors found that children with constipation, whether impacted or not, were significantly more likely to have impaired gallbladder contractility as compared to controls (14). In a similar vein, another group recently identified dyspeptic symptoms and slowed gastric emptying in children with functional constipation (15). Both the dyspeptic symptoms and gastric emptying improved following osmotic laxative usage (15). Though having constipation did not predict an unfavorable outcome in a univariate or multivariate analysis in our study, given the potential relationship of constipation to both gastric emptying and gallbladder function, we suggest identifying the possible presence of constipation and if present, addressing constipation in every child with dyspeptic symptoms.

Multivariate analysis identified baseline activity limitation as a predictor of an unfavorable clinical outcome in our population. This may have been in part due to the usage of activity limitation within the clinical outcome measure in our study. Activity limitation (e.g. school absences) as an outcome has been used to measure success following cholecystectomy for childhood biliary dyskinesia (17) and is included in general pediatric quality of life measures (18) and those specific to childhood chronic abdominal pain (19). Given this, we felt it was

important to include this information in assessment of clinical outcome. Activity limitation due to symptoms may be a marker of severity, and this may account for more unfavorable outcomes at time of follow-up, though further evaluation of this is needed prospectively.

Other groups have identified factors such as gender (male), shorter duration of symptoms, type of symptoms (e.g. nausea), and ejection fraction on cholescintigraphy <15% as being predictive of successful resolution of symptoms following cholecystectomy in children with biliary dyskinesia (5, 20). However, different studies have not identified the same predictive factors. In a similar vein, baseline activity limitation and/or presence of gastroparesis as predictive factors have not been evaluated for by others. Part of the challenge may lie in the relatively small number of children described in the literature to date. Larger studies taking into account candidate predictive factors with more uniform outcome measures are needed for children with functional gallbladder disorders.

There are several limitations to this study. First, the study is retrospective, and therefore concomitant medications (e.g. antacids), probiotics, diet, follow-up intervals, and characterization of dyspeptic symptoms were not standardized. However, this may have been ameliorated in part by the fact that one gastroenterologist (G.G.) was involved in the care of the majority of the patients, helping to make management and outcome assessment more uniform. Second, generalizability may be limited as scintigraphic testing and protocols were institution standardized, and may not reflect the protocols used in other institutions. Third, selection bias may have occurred as not all children have routinely undergone both a gastric emptying scintigraphy and cholescintigraphy for dyspeptic symptoms at our institution. The included children may have had clinical factors that made clinicians suspect concomitant gastroparesis as being more likely.

To our knowledge, this study is the first to determine that children with biliary dyskinesia may have concomitant gastroparesis and the potential clinical impact of this association. Pending further studies investigating the relationship with biliary dyskinesia and gastroparesis, we suggest consideration for assessment for both motor disorders, particularly in a child with dyspepsia that has activity limitation at the time of presentation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank Cynthia Tsai for her assistance with obtaining portions of the data. Support was provided in part by the Texas Medical Center Digestive Disease Center (National Institutes of Health DK-58338) and the NASPGHAN Foundation/Nestle Nutrition Young Investigator Development Award (Dr. Chumpitazi).

References

1. Behar J, Corazziari E, Guelrud M, et al. Functional gallbladder and sphincter of oddi disorders. *Gastroenterology*. 2006; 130:1498–1509. [PubMed: 16678563]
2. Rasquin A, Di Lorenzo C, Forbes D, et al. Childhood functional gastrointestinal disorders: child/adolescent. *Gastroenterology*. 2006; 130:1527–1537. [PubMed: 16678566]
3. Vegunta RK, Raso M, Pollock J, et al. Biliary dyskinesia: the most common indication for cholecystectomy in children. *Surgery*. 2005; 138:726–731. discussion 731–723. [PubMed: 16269302]
4. Scott Nelson R, Kolts R, Park R, et al. A comparison of cholecystectomy and observation in children with biliary dyskinesia. *J Pediatr Surg*. 2006; 41:1894–1898. [PubMed: 17101366]

5. Constantinou C, Sucandy I, Ramenofsky M. Laparoscopic cholecystectomy for biliary dyskinesia in children: report of 100 cases from a single institution. *Am Surg.* 2008; 74:587–592. discussion 593. [PubMed: 18646475]
6. Michail S, Preud'Homme D, Christian J, et al. Laparoscopic cholecystectomy: effective treatment for chronic abdominal pain in children with acalculous biliary pain. *J Pediatr Surg.* 2001; 36:1394–1396. [PubMed: 11528613]
7. Chumpitazi B, Nurko S. Pediatric gastrointestinal motility disorders: challenges and a clinical update. *Gastroenterology and Hepatology.* 2008; 4:140–148. [PubMed: 21904491]
8. Veitch TA. Pediatric nuclear medicine, Part II: Common procedures and considerations. *J Nucl Med Technol.* 2000; 28:69–75. quiz 82. [PubMed: 10824616]
9. Adams DB, Tarnasky PR, Hawes RH, et al. Outcome after laparoscopic cholecystectomy for chronic acalculous cholecystitis. *Am Surg.* 1998; 64:1–5. discussion 5–6. [PubMed: 9457029]
10. Klieger PS, O'Mara RE. The clinical utility of quantitative cholescintigraphy: the significance of gallbladder dysfunction. *Clin Nucl Med.* 1998; 23:278–282. [PubMed: 9596151]
11. Abell TL, Camilleri M, Donohoe K, et al. Consensus recommendations for gastric emptying scintigraphy: a joint report of the American Neurogastroenterology and Motility Society and the Society of Nuclear Medicine. *Am J Gastroenterol.* 2008; 103:753–763. [PubMed: 18028513]
12. Ziessman HA, Tulchinsky M, Lavelly WC, et al. Sincalide-stimulated cholescintigraphy: a multicenter investigation to determine optimal infusion methodology and gallbladder ejection fraction normal values. *J Nucl Med.* 51:277–281. [PubMed: 20080900]
13. Rosa ESL, Gerson L, Davila M, et al. Clinical, radiologic, and manometric characteristics of chronic intestinal dysmotility: the Stanford experience. *Clin Gastroenterol Hepatol.* 2006; 4:866–873. [PubMed: 16797243]
14. Veras Neto MC, Yamada RM, da Costa Pinto EA. Gallbladder motility in children with chronic constipation. *J Pediatr Gastroenterol Nutr.* 2008; 46:414–418. [PubMed: 18367954]
15. Boccia G, Buonavolonta R, Coccorullo P, et al. Dyspeptic symptoms in children: the result of a constipation-induced cologastric brake? *Clin Gastroenterol Hepatol.* 2008; 6:556–560. [PubMed: 18378497]
16. Hiyama T, Yoshihara M, Matsuo K, et al. Meta-analysis of the effects of prokinetic agents in patients with functional dyspepsia. *J Gastroenterol Hepatol.* 2007; 22:304–310. [PubMed: 17295758]
17. Haricharan RN, Proklova LV, Aprahamian CJ, et al. Laparoscopic cholecystectomy for biliary dyskinesia in children provides durable symptom relief. *J Pediatr Surg.* 2008; 43:1060–1064. [PubMed: 18558183]
18. Varni JW, Seid M, Rode CA. The PedsQL: measurement model for the pediatric quality of life inventory. *Med Care.* 1999; 37:126–139. [PubMed: 10024117]
19. Malaty HM, Abudayyeh S, O'Malley KJ, et al. Development of a multidimensional measure for recurrent abdominal pain in children: population-based studies in three settings. *Pediatrics.* 2005; 115:e210–215. [PubMed: 15687428]
20. Carney DE, Kokoska ER, Grosfeld JL, et al. Predictors of successful outcome after cholecystectomy for biliary dyskinesia. *J Pediatr Surg.* 2004; 39:813–816. discussion 813–816. [PubMed: 15185202]

Figure 1.
Children with both biliary dyskinesia and gastroparesis were more likely to have a poor outcome
Ex= Excellent. BD= Biliary Dyskinesia. GP= Gastroparesis.