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Risk Factors Associated with Biliary Pancreatitis in Children

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Abstract

Little is known about risk factors for biliary pancreatitis in children.

Objectives—We characterized cases of pediatric biliary pancreatitis, compared biliary with non-biliary cases, examined differences in presentation between younger and older children, and studied features distinguishing gallstone- from sludge-induced pancreatitis.

Methods—We evaluated 76 episodes of biliary pancreatitis from 271 cases of acute pancreatitis in children admitted to a tertiary care hospital from 1994 to 2007.

Results—Of the 76 cases, 55% had gallstones, 21% had sludge, and 24% had structural defects. Hispanic children had a 2.85 ($p=0.01$) and 5.59 ($p=0.003$) higher probability for biliary pancreatitis than white and black children, respectively. Median serum amylase and lipase in children with biliary pancreatitis were 64% and 49% higher, respectively, compared to other etiologies ($p<0.05$). In multiple logistic regression, aspartate aminotransferase (AST) was an independent predictor of biliary pancreatitis ($OR=6.69$, $p=0.001$). When comparing gallstone- with sludge-induced etiologies, obesity was an independent predictor (38% more prevalent, $p<0.01$) of gallstone cases.

Conclusions—Hispanic ethnicity is a risk factor and AST is a biomarker for biliary pancreatitis over other etiologies. Furthermore, obesity can distinguish gallstone- from sludge-induced pancreatitis. These findings may spur prospective studies to determine the optimal evaluation and management of children with biliary pancreatitis.

Keywords

Acute pancreatitis; children; pediatric; biliary; gallstone; sludge; Hispanic ethnicity; obesity

Introduction

Acute pancreatitis is a severe inflammatory disease of the pancreas, which accounts for over 210,000 hospitalizations annually.[1] Biliary pancreatitis is a leading cause of acute pancreatitis in children, comprising 12 to 30% of all cases.[2] Although gallstones and other

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We have no conflicts of interest in submitting this work or having it published.

biliary diseases are common causes of acute pancreatitis in adults, very little is known about the presentation, risk factors, and outcomes of pediatric biliary pancreatitis or the features that distinguish it from other etiologies. Several studies have shown an increase in the incidence of acute pancreatitis in children during the past 20 years.[3–5] In a previously published report, we found a 53% increase in cases of acute pancreatitis between 1995 to 2000 and 2001 to 2006.[6] This finding was attributed to an increase in pediatric emergency department visits. As cases of biliary pancreatitis become more prevalent in children and because endoscopic or surgical intervention may be urgently needed, improved knowledge of factors that will assist in its timely diagnosis has become increasingly important.[7]

In children, biliary pancreatitis includes several etiologies such as obstruction of the common bile duct (CBD) by gallstones, biliary sludge or microlithiasis, choledochal cyst, and biliary tree anomalies.[6, 7] Predisposing factors for the development of gallstones include chronic hemolytic disease, obesity, cystic fibrosis, ileal resection, and chronic liver disease.[8] In contrast, biliary sludge often results from gallbladder stasis, such as with parenteral nutrition or during pregnancy.[9] Sludge may gradually develop into gallstones and obstruct the CBD, leading to pancreatitis.[10]

In this study we aimed to: (1) characterize the presentation of childhood biliary pancreatitis; (2) identify factors that distinguish children with biliary pancreatitis from those with other causes of pancreatitis; (3) compare biliary pancreatitis in younger and older children; and (4) examine differences between childhood gallstone- and sludge-induced pancreatitis.

Materials and Methods

Study Group and Inclusion Criteria

We evaluated 76 episodes of biliary pancreatitis occurring in 68 children from a database of 271 cases of acute pancreatitis in children of ages 0 to 20 years (224 children). These children were admitted to Yale-New Haven Children's Hospital in New Haven, Connecticut, between August 1994 and July 2007. We screened hospital admissions for cases of acute pancreatitis using ICD-9 codes. All personal identifiers were removed in the database for the study. The IRB of Yale School of Medicine approved the study protocol. Discussions of the overall cohort of patients, including etiologies, ethnic breakdown, referral trends for pancreatitis over time, and presentation and management trends, have been previously published by us.[6, 11]

Inclusion criteria for acute pancreatitis in this cohort are as previously described.[6] Briefly, inclusion in the study group required that pediatric patients possess any 1 of the following 3 characteristics relevant to acute pancreatitis: (1) serum amylase or lipase higher than 3 times the upper limit of normal; (2) radiographic evidence demonstrating acute pancreatitis (minimum of changes in pancreatic parenchyma or peripancreatic fluid) on computed tomography (CT) and ultrasound; (3) serum lipase increased more than 1.5 times the upper limit of normal (not a result of nonpancreatic causes of hyperlipasemia), along with the presence of 2 out of 3 clinical features—abdominal pain characteristic of acute pancreatitis, nausea or vomiting, or epigastric tenderness. As previously reported, the overwhelming majority of patients (90%) met inclusion criteria (1) or (2).[6]

Of the 594 records (282 patients) identified by ICD-9 codes for acute pancreatitis, 323 records were excluded because they failed to meet inclusion criteria, had an incomplete chart record (46) or were cases of chronic pancreatitis (18). The latter was evidenced by calcifications observed on CT or the presence of chronic pancreatic duct abnormalities by endoscopic retrograde cholangiopancreatography (ERCP).

Data Collection

Collected information included the etiology of pancreatitis, patient characteristics such as age, sex, ethnicity, and weight-for-age percentiles, biomarkers of pancreatitis (amylase, lipase, liver function tests), radiography, and hospital management. The etiology of pancreatitis assigned to each case was determined by the association reported in the chart record. Biliary pancreatitis was defined as gallstone pancreatitis, biliary sludge or microlithiasis, pancreatic divisum, sphincter of Oddi dysfunction, and other/structural. A diagnosis of sludge-induced pancreatitis required radiographic evidence of (1) sludge in the gallbladder or CBD; (2) CBD dilatation; and (3) the absence of gallstones. Sphincter of Oddi dysfunction was diagnosed using sphincter of Oddi manometry.[12] "Other/structural" biliary pancreatitis included cases in which an anatomic abnormality caused a disruption in normal pancreaticobiliary function. Non-biliary etiologies of pancreatitis included: medications, idiopathic, systemic illness, trauma, viral infection, a metabolic condition, ERCP, cystic fibrosis, and alcohol.

We stratified our cohort into three subsets. The first was a comparison between two groups within the entire cohort: non-biliary and biliary cases of pancreatitis. The second analysis evaluated differences between two age groups within the biliary subset: young children (0 to 10 years) and adolescents (11 to 20 years). The third was a comparison of two subsets of the biliary group: gallstone- and sludge-induced pancreatitis.

Statistical Analysis

Continuous variables were analyzed using the Student's t-test and the Wilcoxon rank sum test for normally and non-normally distributed data, respectively. Comparisons of discrete variables were performed by chi-square and Fisher exact test. A p-value of <0.05 in bivariate analyses was considered statistically significant. Associations with a p-value<0.10 from the bivariate analyses were included in multiple logistic regression models. Non-normally distributed data were log-transformed prior to conducting the adjusted analyses. Selection of important clinical predictors was performed using the backward step-wise approach. In the logistic regression models, variables with a p-value of <0.05 were considered significant independent predictors. Data were analyzed with SPSS 16 software (SPSS Inc., Chicago, IL). Age-adjusted percentiles for weight-for-age data were calculated using a program provided by the Centers for Disease Control (Atlanta, GA) and SAS (SAS Institute, Cary, NC).

Results

Etiologies of Biliary Pancreatitis

Biliary causes accounted for 28% of the 271 acute pancreatitis cases and represented the most common etiology in our study cohort. In 3% (2) of biliary cases, more than one other etiology was present. Gallstone- and sludge-induced pancreatitis accounted for most etiologies of biliary pancreatitis (55% and 21% of causes, respectively).

Other biliary etiologies included Sphincter of Oddi dysfunction (5%), pancreas divisum (5%), and other/structural causes (14%). The latter included pancreatic cyst or mass compressing the pancreatic duct, pancreatic duct stenosis, annular pancreas, and choledochal cyst. A direct comparison of these biliary etiologies was not conducted because the sample size was small.

Comparison of Biliary and Non-biliary Pancreatitis

There were 76 cases (68 children) of biliary and 195 cases (156 children) of non-biliary pancreatitis. In the biliary pancreatitis group, there were 17% fewer whites and a three-fold

increase in Hispanic children than in the non-biliary group (30.7% versus 10.9%, respectively; $p=0.001$) (Supplemental Digital Content Table 1). We found that twice as many overweight children were in the biliary group ($p=0.04$).

In the biliary group, the median amylase and lipase levels were 3.6 and 14.7 times greater than the upper limit of normal (ULN) (Supplemental Digital Content Table 1). Children with biliary pancreatitis had serum levels of amylase, lipase, and AST that were 64% ($p=0.05$), 49% ($p=0.04$), and 225% ($p<0.001$) greater, respectively, than in children with non-biliary pancreatitis. Though an 80% higher median total bilirubin was seen in children with biliary pancreatitis ($p<0.001$), the total bilirubin levels were within normal limits in both groups. Therefore, this difference did not appear to be clinically relevant.

The majority of children with pancreatitis (83%) had radiographic imaging performed (Supplemental Digital Content Table 1). In the biliary group, 13% more children had radiographic tests performed ($p=0.01$). Of patients who underwent radiography, an ultrasound was the most commonly performed test with greater than 80% frequency in both biliary and non-biliary cases. CT scans were performed in 51% more children with non-biliary pancreatitis than with biliary pancreatitis ($p=0.03$). Examination of hospital management trends included length of hospital stay, rate of gastroenterology consultation, and method of nutrition after a *non per os* (NPO) status (oral or parenteral). There were no significant differences between the two groups in any of these parameters.

In the adjusted analysis, Hispanic ethnicity ($p=0.01$) and AST ($p<0.001$) were significant independent predictors of biliary pancreatitis (Table 1A). Hispanic children had a 2.85 ($p=0.01$) and 5.59 ($p=0.003$) higher probability for biliary pancreatitis than white and black children, respectively. Although the unadjusted association of weight-for-age percentiles with the outcome was significant, it was not found to be an independent predictor in the final model. This was explained by the finding that Hispanic children were more likely to be overweight than other children ($p=0.03$).

Comparison of Younger and Older Children with Biliary pancreatitis

There were 15 cases (15 children) in the younger (0–10 year-olds) group and 61 cases (54 children) in the older (11–20 year-olds) group with biliary pancreatitis. The younger group constituted 20% of cases (Supplemental Digital Content Table 2). The most common etiologic category among younger cases was ‘other/structural,’ occurring with a 6-fold greater frequency than in older cases (43.7% versus 7.8%, respectively; $p=0.001$).

Comparison of Gallstone- and Sludge-induced Pancreatitis

There were 42 cases (40 children) of gallstone- and 16 cases (15 children) of sludge-induced pancreatitis. Cases of gallstone pancreatitis represented 72% of patients in this comparison group (Table 2). More than a third of children with gallstone pancreatitis were obese, while there were no such cases among those with sludge-induced pancreatitis ($p=0.01$). No significant differences in age, ethnicity, abdominal pain, and nausea or vomiting were observed.

Analysis of serum biomarkers also showed significant differences between both groups (Table 2). Median lipase in the gallstone group was 30.2 times the ULN and 2.3-fold higher than the sludge group ($p=0.02$). Similarly, median AST levels were nearly double the ULN and 84% higher than the sludge group ($p=0.03$). The median amylase level in the gallstone group was 4.80-fold higher than normal; and, although not statistically significant, there was a trend towards amylase levels being 90% greater than the sludge group ($p=0.07$).

Most children with gallstone and sludge-induced pancreatitis underwent radiographic imaging, with ultrasound as the most commonly performed test (Table 2). ERCP was only conducted in patients with gallstone pancreatitis (29% of gallstone cases, $p=0.02$). Hospital management trends differed significantly between the two groups. The median length of hospital stay in children with sludge-induced pancreatitis was 3 days longer than for children with gallstone pancreatitis ($p=0.003$). Conversely, the median time to starting oral or parenteral nutrition after acute NPO status in the sludge group was 2 days shorter than in the gallstone group ($p=0.002$). In addition, compared to children with gallstone pancreatitis, 53% more children with sludge-induced pancreatitis had pre-existing comorbidities (e.g. leukemia, insulin-dependent diabetes mellitus, seizure disorders, asthma, and inflammatory bowel disease).

In multiple logistic regression analysis, weight-for-age percentile was a significant independent predictor of gallstone pancreatitis in children ($p=0.02$) (Table 1B). Amylase, AST, or ethnicity were not found to be significant predictors of gallstone pancreatitis.

Discussion

This study uniquely characterizes the presentation of 76 cases of biliary pancreatitis in children from a total cohort of 271 cases of acute pancreatitis. The main findings were that among children with acute pancreatitis, Hispanic ethnicity is a risk factor and an elevated serum AST level is a biomarker for a biliary etiology. Additionally, in children with gallstone- or sludge-induced pancreatitis, obesity is a risk factor for gallstone pancreatitis.

Biliary tract disease represented the plurality (28%) of our pancreatitis cases, consistent with previous reports which have shown that biliary tract disease accounts for one of the top three causes of acute pancreatitis in children.[7, 13–17] Since endoscopic or surgical intervention may be urgently needed in the management of acute biliary pancreatitis, it is critically important to examine risk factors that distinguish biliary from non-biliary pancreatitis.[7] The finding that Hispanic ethnicity is a risk factor for a biliary etiology may be explained by higher rates of biliary tract disease in this population group, perhaps due to a genetic predisposition or obesity.[18–20] We also observed that Hispanic children were disproportionately overweight compared to white and black children. In logistic regression analysis, however, we found that Hispanic ethnicity was independently associated with biliary pancreatitis, whereas obesity was not. Thus, a biliary cause should be suspected in Hispanic children with acute pancreatitis.

Serum amylase and lipase measurements are commonly used in the diagnosis of acute pancreatitis.[2, 11, 15, 21] We found that the height of amylase, lipase, and AST levels was significantly higher in children with biliary pancreatitis than with non-biliary pancreatitis. A similar result was observed in adults.[22] In adjusted analysis, AST was found to be a significant biomarker for biliary pancreatitis. Although AST is a hepatic enzyme, obstruction of the common bile duct, which may occur in biliary pancreatitis, can lead to hepatic injury and thus an increase in AST and ALT levels.[23] Our results confirm that a biliary cause should be suspected in children with acute pancreatitis who present with high levels of amylase, lipase, or AST. However, further studies validating an appropriate cut-off level are necessary.

The present study shows that gallstone pancreatitis is common, representing just over half (55%) of our acute biliary pancreatitis cases. Sludge-induced pancreatitis (21%) comprised the second most common biliary cause. To our knowledge, this is the first study to compare the presentation and management of gallstone with sludge-induced pancreatitis. We report that obesity is a significant independent risk factor for the diagnosis of gallstone pancreatitis

in children with acute biliary pancreatitis. Although an odds ratio of 1.02 for weight-for-age percentiles appears low, the impact of this variable is sizeable. Our findings signify that for each unit increase in weight-for-age percentile, the probability of being diagnosed with gallstone pancreatitis over sludge increases by 2%. Therefore, compared to children of average weight-for-age (i.e. 50th percentile), overweight children (i.e. 85–95th percentile) have a 70–90% increased probability and obese children (i.e. 95–100th percentile) have a 90–100% increased probability of presenting with gallstone pancreatitis over sludge. Our findings are in some ways consistent with studies in adults, which demonstrate that obesity is a risk factor for the development of gallstones and for the severity of pancreatitis.[24–26] Thus, gallstone pancreatitis should be suspected in obese children with biliary pancreatitis.

In children with gallstone pancreatitis, the height of the lipase level was nearly double and AST was 86% higher than those with sludge-induced pancreatitis. A potential reason for this finding may be that, although biliary pancreatitis is associated with elevated hepatic enzyme levels, gallstones are more likely to cause a complete, albeit transient, obstruction of the CBD than sludge and thus lead to higher serum levels of AST. These biomarkers may be clinically useful in conjunction with radiographic imaging to differentiate gallstone- from sludge-induced pancreatitis.

A potential confounder in the interpretation of elevated transaminases as a biomarker of biliary pancreatitis is nonalcoholic steatohepatitis (NASH). In one study by Yener et al., 55% of adult patients with gallstones had associated NASH.[27] We know that obese patients are more likely to have NASH and more likely to have gallstone pancreatitis. However, at least by ultrasound, none of the children in our cohort had evidence of NASH or fatty liver.

Abdominal ultrasound was the most frequently used method of diagnostic imaging in all of our study groups, and it is one of the primary diagnostic studies used to evaluate gallstones and sludge.[28] However, due to constraints imposed by air and fluid-filled loops of bowel lying above the pancreas, the detection of gallstones in the CBD using abdominal ultrasound has a low sensitivity (50%) in patients with acute biliary pancreatitis.[29] Given the limitations of abdominal ultrasound, algorithms that incorporate risk factors, biomarkers, and diagnostic imaging may assist in the swift and accurate diagnosis of acute biliary pancreatitis. The increased use of CT scans in cases of non-biliary pancreatitis is likely due to the need for further investigation in order to ascertain the definitive cause of pancreatitis.

Though our findings require further validation in a multi-center, prospective study, taken together, they may be used in establishing a framework for diagnosing biliary pancreatitis in children. With earlier recognition of biliary pancreatitis and more accurate differentiation between gallstone- and sludge-induced pancreatitis, appropriate interventions including ERCP, ursodeoxycholic acid (in children with sludge), and/or cholecystectomy can be pursued more expeditiously, provide relief of symptoms, and reduce the recurrence of pancreatitis.[30] In addition to constraints inherent in a retrospective study, the limitations in our study are that all cases of pancreatitis were mild and based at a single center. Despite these limitations, to our knowledge, our study is the first to examine and distinguish the presentation and risk factors associated with gallstone versus sludge-induced pancreatitis in childhood. In summary, elevated AST, lipase, and amylase levels may distinguish biliary pancreatitis from other etiologies. Hispanic children are more likely to be diagnosed with biliary pancreatitis. Finally, obesity as well as elevated levels of AST and lipase in children with biliary pancreatitis may be useful in distinguishing gallstone pancreatitis from sludge-induced cases. We hope that our findings will assist in the development of algorithms to accurately diagnose biliary pancreatitis. Furthermore, these data may facilitate the design of

prospective studies to determine the optimal evaluation and management of children with biliary pancreatitis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Abbreviations

AST	Aspartate Aminotransferase
CT	Computed Tomography
CBD	Common Bile Duct
ERCP	Endoscopic Retrograde Cholangiopancreatography
MRCP	Magnetic Resonance Cholangiopancreatography
NPO	<i>Non Per Os</i>
NASH	Nonalcoholic Steatohepatitis
ULN	Upper Limit of Normal

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Table 1

Multiple Logistic Regression Analyses.

<i>A. Hispanic Ethnicity and AST: Risk Factors for Biliary Pancreatitis when Compared to Non-biliary Pancreatitis.</i>			
Model	Variable	Odds Ratio (95% CI)	p-value
Full Model	Ethnicity		
	Hispanic (reference)	-	0.02
	White	0.36 (0.16, 0.81)	0.01
	Black	0.18 (0.06, 0.57)	0.00
	Other	0.67 (0.13, 3.43)	0.63
	Weight-for-age percentile	1.00 (0.99, 1.01)	0.75
	Amylase (fold increase above ULN) *	1.84 (0.75, 4.53)	0.19
	Lipase (fold increase above ULN) *	0.96 (0.46, 2.01)	0.92
	AST (mg/dL) *	6.71 (2.75, 16.35)	0.00
Reduced Model	Hispanic (reference)	-	0.01
	White	0.35 (0.16, 0.79)	0.01
	Black	0.179 (0.058, 0.552)	0.003
	Other	0.68 (0.13, 3.46)	0.64
	Amylase (fold increase above ULN) *	1.80 (0.88, 3.67)	0.107
	AST (mg/dL) *	6.694 (2.793, 16.046)	<0.001
<i>B. Weight-for-age Percentile: Risk Factor for Gallstone Pancreatitis when Compared to Sludge-induced Pancreatitis.</i>			
Model	Variable	Odds Ratio (95% CI)	p-value
Full Model	Ethnicity		
	Hispanic (reference)	-	0.40
	White	0.44 (0.08, 2.29)	0.33
	Black	0.86 (0.61, 12.02)	0.91
	Other	0.08 (0.003, 1.96)	0.12
	Weight-for-age percentile	1.02 (1.00, 1.05)	0.05
	Amylase (fold increase above ULN) *	2.76 (0.45, 16.86)	0.27
	Lipase (fold increase above ULN) *	1.41 (0.39, 5.09)	0.60
Reduced Model	Weight-for-age percentile	1.02 (1.00, 1.04)	0.02
	Amylase (fold increase above ULN) *	3.25 (0.84, 12.7)	0.09

* Log-transformed

Table 2

Comparison of Cases of Gallstone- with Sludge-Induced Pancreatitis in Children

	Gallstone Cases=42	Sludge Cases=16	p-value
Characteristics			
Mean Age in Years (SD)	15.6 (3.6)	12.3 (6.0)	0.054
Female (% within group, n)	73.8 (31)	56.2 (9)	0.219
Ethnicity (% , n)			0.454
White	33.3 (14)	56.2 (9)	
Black	19.0 (8)	18.8 (3)	
Hispanic	45.2 (19)	18.8 (3)	
Other	2.4 (1)	6.2 (1)	
Median weight-for-age percentile (IQR) *	90.1 (46.6–98.4)	41.8 (16.3–90.8)	0.005 †
>95 percentile (% , n) *	37.5 (15)	0 (0)	0.006 ††
85–95 percentile (% , n) *	20.0 (8)	28.6 (4)	0.485
0–85 percentile (% , n) *	42.5 (17)	71.4 (10)	0.062
Signs & Symptoms (% within group, n)			
Abdominal Pain	100.0 (42)	86.7 (13)	0.111
Epigastric Tenderness	100.0 (41)	80.0 (12)	0.023 ††
Nausea/Vomiting	81.0 (34)	60.0 (9)	0.161
Chemistries: Median (IQR)			
Amylase (-fold increase above ULN)	4.80 (1.76–12.93)	2.52 (1.25–4.77)	0.070
Lipase (-fold increase above ULN)	30.20 (7.21–102.00)	13.13 (4.10–14.73)	0.022 †
AST (mg/dL)	90.00 (45.75–194.00)	49.00 (18.75–84.25)	0.034 †
Total Bilirubin (mg/dL)	0.99 (0.45–3.80)	0.57 (0.42–2.20)	0.186
Calcium (mg/dL) **	9.91 (5.43)	8.94 (0.56)	0.498
Glucose (mg/dL) **	113.20 (33.08)	126.31 (49.51)	0.313
Radiology Performed (% within group, n)	97.6 (41)	93.8 (15)	1.000
Modality (% of cases undergoing the following, n)			
US	87.8 (36)	100.0 (15)	0.374
CT scan	26.8 (11)	33.3 (5)	0.741
MRCP	12.2 (5)	13.3 (2)	1.000
ERCP	29.3 (12)	0 (0)	0.024 ††
Hospital Management Trends			
Median Length of Stay (n days, range)	5 (0–85)	8 (3–100)	0.003 †
GI Consult Ordered (% within group, n)	73.8 (31)	86.7 (13)	0.478
NPO at Admission, (% within group, n)	100 (42)	100 (14)	-
Median Time to Nutrition after NPO (n days, range)	3 (1–7)	1 (0–5)	0.002 †
Modality of Nutrition after NPO, (% within group, n)			
Oral (PO)	83.3 (35)	28.6 (4)	<0.001 ††

	Gallstone Cases=42	Sludge Cases=16	p-value
Parenteral	16.7 (7)	64.3 (9)	0.001 ^{††}
Enteral	0 (0)	7.1 (1)	0.560

^{*} Age-adjusted,

^{**} Calcium and Glucose was missing in 20.68% and 25.86% of cases, respectively.

[†] Wilcoxon rank sum test,

^{††} Fisher's exact test