Inflammatory Bowel Disease in Children with Elevated Serum Gamma Glutamyltransferase Levels

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Objective To assess the characteristics of inflammatory bowel disease and disease prognosis among children with elevated gamma glutamyltransferase (GGT) and primary sclerosing cholangitis (PSC)-ulcerative colitis (UC).

Study design Our longitudinal, population-based cohort comprised all children and young adults diagnosed with UC in the Canadian province of Manitoba between 2011 and 2018. Diagnosis of PSC was confirmed based on a combination of cholestatic biochemical markers and cholangiographic features. The Fisher exact test with Bonferroni correction was used to examine the relationship between categorical variables.

Results We enrolled 95 children with UC/Inflammatory bowel disease-unclassified with a median age at diagnosis of 14 years (IQR: 10.4-15.9 years) and 1399 person-years follow-up. Among them, 9 children developed PSC-UC, with an incidence rate of 6.43 new cases per 1000 person-years. In this cohort, 8 (72.7%) of 11 children with high baseline serum GGT levels developed PSC-UC in comparison with 1 (1.2%) of 84 children with normal serum GGT levels at baseline ($P < .001$). All children with high serum GGT levels at diagnosis had pancolitis in comparison with 63.9% of children with normal serum GGT levels ($P = .01$). Children with high serum GGT levels were more likely to be perinuclear neutrophil antibodies-positive than those with normal levels (90.9% vs 52.0%, $P = .01$).

Conclusions Our findings indicated that pediatric patients with UC and with even mild elevations of serum GGT levels, especially at baseline, might be predisposed to develop PSC. *(J Pediatr 2019;215:144-51)*.

Primary sclerosing cholangitis (PSC) and inflammatory bowel disease (IBD) share a complex and multifactorial genetic and environmental etiology, leading to immune dysregulation along the gut–liver axis.[1,2] A large, multicenter international cohort study estimated that 76% of children with PSC go on to develop IBD.[3] Among children with PSC-IBD, 83% had ulcerative colitis (UC), or inflammatory bowel disease–unclassified (IBD-U) phenotype, and the remaining 17% had Crohn's disease (CD).[3] Conversely, the number of patients with UC or IBD-U who develop PSC is relatively low, with estimates between 2.4% and 7.5%.[4] Patients with PSC-UC may have disease severity and phenotype that are distinct from IBD without PSC.[5-8] There have been very few studies that explored PSC-UC development in children, especially in Canada, which has one of the greatest incidence rates for childhood-onset IBD.[9,10] Gamma glutamyltransferase (GGT) is known to be a more consistent biochemical marker of PSC in children; evidence indicates that even mild serum GGT level elevation >50 U/L within the first few months since IBD diagnosis might be suggestive of underlying PSC.[11] Our longitudinal study aimed to investigate the difference in IBD phenotype, clinical characteristics, and disease prognosis among children with elevated serum GGT levels (>50 U/L) and PSC-UC in comparison with children with normal serum GGT levels and non-PSC UC, respectively.

Methods

Our longitudinal, population-based cohort comprised all children and young adults (≤17 years) diagnosed with IBD in the Canadian province of Manitoba

aHR	Adjusted hazard ratio
CD	Crohn's disease
GGT	Gamma glutamyltransferase
IBD	Inflammatory bowel disease
IBD-U	Inflammatory bowel disease-unclassified
pANCA	Perinuclear neutrophil antibodies
PSC	Primary sclerosing cholangitis
PUCAI	Pediatric Ulcerative Colitis Activity Index
UC	Ulcerative colitis

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between January 2011 and August 2018 and who consented to be enrolled in the **MA**nitoba **L**ongitudinal **P**ediatric **I**nflammatory Bowel **D**isease (MALPID) Registry.[12,13] The patients were recruited from the Winnipeg Children's Hospital, which is the only pediatric tertiary center in the province of Manitoba. The diagnosis of IBD was based on the clinical presentation, laboratory findings, radiographic imaging, and endoscopic and histopathologic evaluation. All patients had laboratory investigations in the form of complete blood count, differential leukocyte count, liver function tests, electrolyte panel, inflammatory markers, and serologic antibody markers obtained at diagnosis and every 3-6 months thereafter. The diagnosis of PSC was made on the discretion of the treating physician based on history, examination findings, and investigations that included complete liver function test profile with infection screen, auto-antibody and immunoglobulin profile, metabolic screen, drug metabolite assay, and liver imaging, including ultrasound scan and magnetic resonance examination and liver biopsy and histology. Unless lost to follow-up, all the children in our cohort were followed up to the age of 17 years, at which point they were transitioned into the adult IBD program.

Data Source and Definitions of Outcome Variables

Data extracted at baseline comprised age, sex, physician global assessment, Mayo endoscopy scores,[14] endoscopic IBD distribution including rectal sparing, isolated right-sided disease, patchy colitis, backwash ileitis, and laboratory markers including liver functions tests, serum albumin level, hemoglobin, perinuclear neutrophil antibodies (pANCA), and C-reactive protein. During follow-up, we abstracted details regarding IBD-related hospitalizations, IBD-related surgery, and response to overall therapy. Disease phenotype and behavior were categorized using Paris classification.[15] We defined clinical response to therapy as the reduction of disease activity index by ≥20 points compared with baseline or entering remission.[16] A Pediatric Crohn's Disease Activity Index/Pediatric Ulcerative Colitis Activity Index (PUCAI) score of ≥10 was considered as a clinical relapse only if it was a preceded by a phase of remission (Pediatric Crohn's Disease Activity Index/PUCAI <10) after initial presentation and initiation of therapy. Patients were categorized as corticosteroid-dependent if they needed an equivalent of >10 mg/d of prednisolone or equivalent within 3 months of initiation of corticosteroid therapy in the absence of recurrent disease or those who developed relapse within 3 months of corticosteroid withdrawal. Resistance to corticosteroid therapy was defined as lack of clinical response in patients who received dose equivalent to >0.75 mg/kg/day of prednisolone for more than 4 weeks.[17] Children diagnosed with IBD were divided into high serum GGT levels and normal serum GGTs level groups, by using 50 U/L as a cut-off value.[11] Also, patients were divided into 2 groups based on whether they had IBD alone or both IBD and PSC. Confirmation of PSC diagnosis was based on a combination of cholestatic biochemical markers along with the cholangiographic feature of multifocal structuring and biliary tree dilations or histopathology evidencing periductal, concentric fibrosis; fibro-obliterative cholangitis; or primary ductular involvement.[4]

Statistical Analyses

The incidence rate (represented as number of new cases per 1000 person-years) of PSC development in our IBD cohort was estimated by dividing the number of children who developed the condition divided by the sum of disease-free years for each child until PSC diagnosis was confirmed, date of loss to follow-up, transition to adult care, death, or date of end of study. The normality of numerical data was evaluated using the Shapiro–Wilk test. Continuous data were presented as mean ± SD or median and IQRs depending on data distribution. Categorical data were presented as frequency distribution tables with cross-tabulations. For all statistical tests, unequal variance was assumed. The Mann–Whitney *U* test was used to test the difference in median age between groups, and the Fisher exact test was used to test the relationship between categorical variables. For contingency table greater than 2 × 2, post-hoc analysis with Bonferroni correction was done to determine pair-wise significance. A Cox-regression model was used to calculate the hazards ratio with 95% CIs for the risk of relapse development during follow-up. The model was adjusted for sex, age at IBD diagnosis, and PUCAI at diagnosis to calculate the adjusted hazards ratio (aHR). The measure of linear correlation between PUCAI and serum GGT level was estimated using Pearson correlation and represented as correlation coefficients (r). The correlation between PUCAI and serum GGT level during longitudinal follow-up in patients with PSC-UC was estimated using multilevel linear regression. All tests were 2-tailed, and the level of significance was set at $P < .05$. Analyses were performed using SPSS (IBM Corp, Released 2013, IBM SPSS Statistics for Windows, Version 21.0; IBM Corp, Armonk, New York). Only descriptive data were provided for CD due to the small number of patients with CD-PSC. The study protocol was approved by the University of Manitoba Research Ethics Board.

Results

We enrolled 190 children with IBD with 2787 person-years follow-up, of whom 11 children developed PSC-IBD. Among them, 9 children developed PSC-UC, with an incidence rate of 6.43 new cases per 1000 person-years. The incidence rate of PSC-IBD was 3.95 per 1000 person-years. The crude point prevalence of PSC-IBD in the province of Manitoba estimated based on the 2016 Canadian census data[18] was 3.75 per 100 000 children. Of the 190 patients with IBD, 95 children had CD, 90 had UC, and 5 had IBD-U (**Figure 1**; available at www.jpeds.com). The cohort comprised 108 boys and 82 girls, with a median age of 13.71 years (IQR: 10.25-15.58).

Table I. Difference in disease characteristics between children who had high serum GGT levels at diagnosis and the children with normal serum GGT levels at diagnosis in the UC/IBD-U cohort

Characteristics	GGT >50 at diagnosis (n = 11)	GGT <50 (n = 84)	*P* value
Physician global assessment at diagnosis (%)			
Mild	4 (36.4)	23 (27.4)	.83
Moderate	5 (45.5)	46 (54.8)	
Severe	2 (18.2)	15 (17.9)	
IBD-related hospitalizations (any) (%)			
Yes	10 (90.9)	43 (51.8)	.02*
No	1 (9.1)	40 (48.2)	
IBD-related surgery (%)			
Yes	1 (9.1)	9 (10.7)	1.00
No	10 (90.9)	75 (89.3)	
Sex (%)			
Male	4 (44.4)	48 (57.1)	.22
Female	7 (55.6)	36 (42.9)	
Luminal disease distribution (Paris classification) (%)			
E1	0 (0.0)	7 (8.5)	1.00
E2	0 (0.0)	12 (14.6)	.35
E3	0 (0.0)	11 (13.4)	.36
E4	11 (100.0)	52 (63.4)	.01
pANCA status (%)			
Negative	1 (9.1)	36 (48.0)	.01*
Positive	10 (90.9)	39 (52.0)	
Mayo score (baseline endoscopy) (%)			
1 (Mild)	0 (0.0)	13 (15.7)	.44
2 (Moderate)	7 (63.6)	40 (48.2)	
3 (Severe)	4 (36.4)	30 (36.1)	
Family history (%)			
No	6 (54.5)	49 (62.8)	.74
Yes	5 (45.5)	29 (37.2)	
Rectal sparing (%)			
Yes	1 (9.1)	3 (3.6)	.40
No	10 (90.9)	80 (96.4)	
Isolated right-sided disease (%)			
Yes	0 (0.0)	1 (1.2)	1.00
No	11 (100.0)	81 (98.8)	
Patchy colitis (%)			
Yes	3 (27.3)	19 (22.9)	.72
No	8 (72.7)	64 (77.1)	
Backwash ileitis (%)			
Yes	2 (18.2)	12 (14.6)	.67
No	9 (81.8)	70 (85.4)	
Albumin level at diagnosis (%)			
Low	3 (27.3)	17 (23.3)	.72
Normal	8 (72.7)	56 (76.7)	
Hemoglobin level at diagnosis (%)			
Low	5 (50.0)	47 (62.7)	.50
Normal	5 (50.0)	28 (37.3)	
CRP level at diagnosis (%)			
High	5 (62.5)	32 (49.2)	.71
Normal	3 (37.5)	33 (50.8)	
Response to overall therapy (%)			
Responsive	9 (81.8)	69 (84.1)	1.00
Nonresponsive	2 (18.2)	13 (15.9)	
Response to infliximab (%)			
Responsive	4 (36.4)	19 (23.2)	.43
Nonresponsive	0 (0.0)	10 (12.2)	
Did not use	7 (63.6)	53 (64.6)	
Response to 5-ASA therapy (%)			
Responsive	5 (55.6)	50 (60.2)	1.00
Nonresponsive	4 (44.4)	32 (38.6)	
Did not use	0 (0.0)	1 (1.2)	
Resistant to steroids (%)			
Responsive	11 (100.0)	70 (84.3)	.73
Resistant	0 (0.0)	3 (3.6)	
Not used	0 (0.0)	10 (12.0)	
Steroid-dependence (%)			
Nondependent	4 (36.4)	55 (66.3)	.01*
Dependent	7 (63.6)	18 (21.7)	
Not used	0 (0.0)	10 (12.0)	

5-ASA, 5-aminosalicylic acid; *CRP*, C-reactive protein.
*Significant at .05 level, statistical test used: Fisher exact test.

PSC-UC

The UC cohort comprised 95 children with a median age at diagnosis of 14 years (IQR: 10.4-15.9 years). Among the 22 (23.2%) children who had serum GGT levels >50 U/L at any time point since diagnosis, 11 (50.0%) children had high serum GGT levels at the time of UC diagnosis.

High Serum GGT Levels at Baseline Presentation

Although not statistically significant, children who had high serum GGT levels at the time of UC diagnosis tended to be younger than those with normal serum GGT levels (10.18 ± 3.79 years vs 12.46 ± 4.01 years; $P = .09$). Baseline disease activity at diagnosis (both Physician Global Assessment and PUCAI) for those with high serum GGT levels (42.73 ± 14.73) vs normal serum GGT levels (43.72 ± 16.55) were similar ($P = .84$). However, the proportion of patients (Table I) who had IBD-related hospitalizations at any time during follow-up was significantly greater in the high serum GGT levels group ($P = .01$). All children with high serum GGT levels at diagnosis had pancolitis (Paris classification E4; $P = .01$). In our UC cohort, children with high serum GGT levels were more likely to be pANCA positive than those patients with normal serum GGT levels (90.90% vs 52.00%, $P = .01$). The proportion of children with corticosteroid dependence was significantly greater among those with high serum GGT levels at diagnosis in comparison with children who had normal serum GGT levels ($P = .03$). However, there was no significant difference in the development of resistance to corticosteroid therapy among the 2 groups.

Response to overall therapy as well as specific therapeutic options such as infliximab, 5-aminosalicylic acid, and corticosteroids was not significantly different between the high serum GGT levels group and normal serum GGT levels group. Serum GGT levels at diagnosis did not correlate with the PUCAI ($r = -0.03$; $P = .81$). There was no difference in relapse rates between patients with normal serum GGT levels and elevated serum GGT levels at diagnosis (aHR 1.67; 95% CI 0.80-3.47; Figure 2).

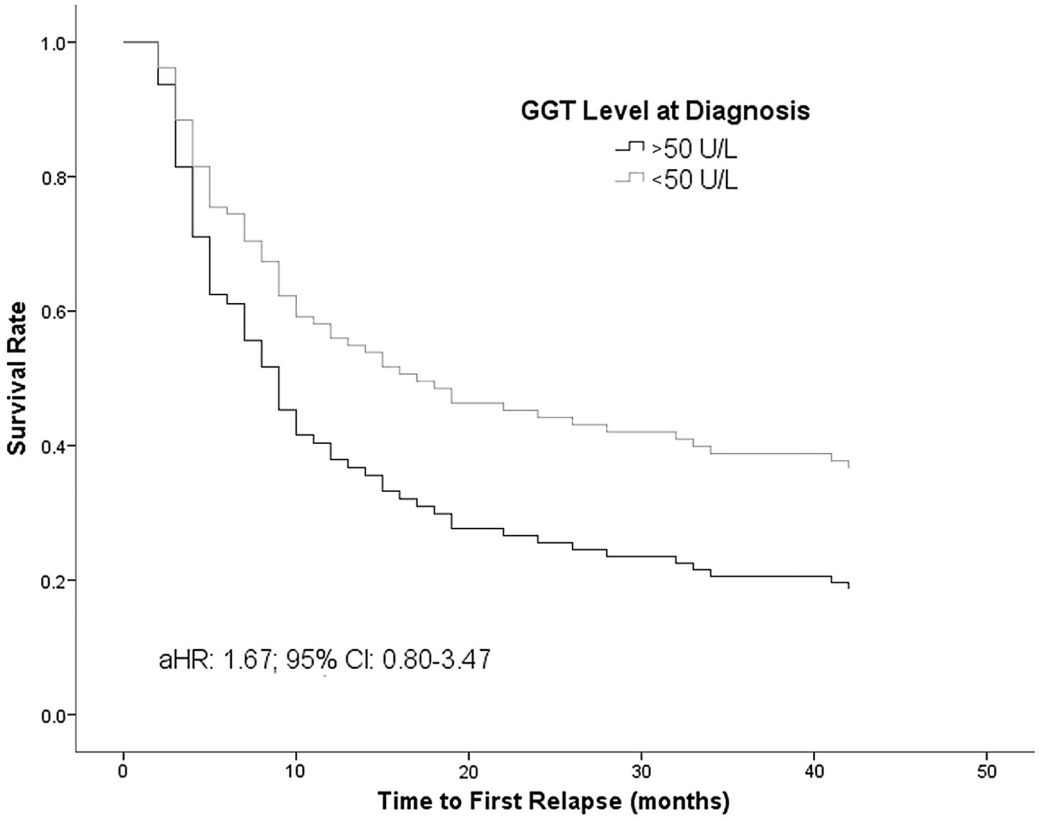

Figure 2. Survival plots for disease relapse during follow-up among patients with high serum GGT levels at baseline compared with patients having normal serum GGT levels. Adjusted for age at IBD diagnosis, sex, and PUCAI at initial diagnosis.

High Serum GGT Levels at Baseline Presentation or During Follow-Up

Although 18 (81.8%) patients with high serum GGT levels at any time during follow-up had pancolitis, the proportion was not significantly different from those with normal serum GGT levels. Among the 8 patients in the high serum GGT levels group who had suspected drug-induced hepatotoxicity (azathioprine-induced hepatotoxicity in 7 patients and mesalazine-induced hepatotoxicity in 1 patient), 1 patient was later diagnosed with PSC. In comparison with patients who had never developed high serum GGT levels during follow-up, the proportion of patients with positive pANCA was much greater in the high serum GGT levels group in comparison with the normal serum GGT levels group (85.0% vs 48.5%; $P = .003$). Moreover, a significantly greater proportion of patients in the high serum GGT levels group had IBD-related hospitalizations in comparison with patients who never developed high serum GGT levels (**Table II**).

PSC during Baseline or Follow-up

Among the patients with UC, there were 9 (8.9%) children who had a confirmed diagnosis of PSC with an incidence rate of 6.43 new cases per 1000 person-years. In comparison with the 8 patients who had elevated serum GGT levels at baseline (specificity: 98.80%; sensitivity: 72.73%), 1 patient did not have high serum GGT levels at diagnosis but had elevation at the sixth month of follow-up visit. Children with confirmed PSC-UC at the time of diagnosis (9.22 ± 3.11 years) were significantly younger compared with those with UC only (12.49 ± 4.03 years, $P = .01$). Similar to the high serum GGT levels group, despite having similar baseline clinical disease activity index, children with PSC had increased risk of at least 1 IBD-related hospitalization (**Table III**; available at www.jpeds.com) compared with children without PSC ($P = .04$). Similar to children with high serum GGT levels at diagnosis and follow-up, children with PSC were much more likely to have a positive pANCA titre as compared with children without PSC (88.9% vs 53.2%; $P = .04$). All 9 patients who were diagnosed with PSC had pancolitis ($P = .03$). There was no difference in the other endoscopic features, such as rectal sparing, right-sided disease, backwash ileitis, or patchy colitis, between the 2 groups. In contrast to the corticosteroid dependence evident in the high serum GGT levels group, there was no difference in corticosteroid dependence between the UC-PSC group and non-PSC group. There was no difference in the relapse rates (**Figure 3**) between patients who had PSC-UC and those who were UC, non-PSC (aHR 1.17; 95% CI 0.49-2.80). There was a good positive correlation (**Figure 4**; available at www.jpeds.com) between PUCAI

Table II. Difference in disease characteristics between children who had high serum GGT levels at any time point starting from baseline presentation and the children with normal serum GGT levels at in the UC cohort

Characteristics	GGT >50 (n = 22)	GGT <50 (n = 73)	*P* value
Physician global assessment at diagnosis (%)			
Mild	8 (36.4)	19 (26.0)	.57
Moderate	10 (45.5)	41 (56.2)	
Severe	4 (18.2)	13 (17.8)	
IBD-related hospitalizations (at least 1) (%)			
Yes	17 (77.3)	33 (45.8)	.01*
No	5 (22.7)	39 (54.2)	
IBD-related surgery (%)			
Yes	3 (13.6)	7 (9.6)	.69
No	19 (86.4)	66 (90.4)	
Sex			
Male	12 (54.5)	40 (54.8)	1.00
Female	10 (45.5)	33 (45.2)	
Luminal disease distribution (Paris classification) (%)			
E1	0 (0.0)	7 (9.9)	.19
E2	2 (9.1)	10 (14.1)	.73
E3	2 (9.1)	9 (12.7)	1.00
E4	18 (81.8)	45 (63.4)	.12
pANCA status (%)			
Negative	3 (13.6)	34 (51.5)	.003*
Positive	17 (85.0)	32 (48.5)	
Mayo score (baseline endoscopy) (%)			
1 (Mild)	3 (13.6)	10 (13.9)	.94
2 (Moderate)	12 (54.5)	35 (48.6)	
3 (Severe)	7 (31.8)	27 (37.5)	
Family history (%)			
No	11 (55.0)	44 (63.8)	.60
Yes	9 (45.0)	25 (36.2)	
Rectal sparing (%)			
Yes	2 (9.1)	2 (2.8)	.23
No	20 (90.9)	70 (97.2)	
Isolated right-sided disease (%)			
Yes	0 (0.0)	1 (1.4)	1.00
No	21 (100.0)	71 (98.6)	
Patchy colitis (%)			
Yes	6 (27.3)	16 (22.2)	.77
No	16 (72.7)	56 (77.8)	
Backwash ileitis (%)			
Yes	6 (28.6)	8 (11.1)	.08
No	15 (71.4)	64 (88.9)	
Albumin level at diagnosis (%)			
Low	5 (25.0)	15 (23.4)	1.00
Normal	15 (75.0)	49 (76.6)	
Hemoglobin level at diagnosis (%)			
Low	11 (57.9)	41 (62.1)	.79
Normal	8 (42.1)	25 (37.9)	
CRP level at diagnosis (%)			
High	9 (52.9)	28 (50.0)	1.00
Normal	8 (47.1)	28 (50.0)	
Response to overall therapy (%)			
Responsive	18 (81.8)	60 (84.5)	.75
Nonresponsive	4 (18.2)	11 (15.5)	
Response to infliximab (%)			
Responsive	7 (31.8)	16 (22.5)	.54
Nonresponsive	1 (4.5)	9 (12.7)	
Did not use	14 (63.6)	46 (64.8)	
Response to 5-ASA therapy (%)			
Responsive	12 (54.5)	45 (62.5)	.59
Nonresponsive	10 (45.5)	26 (36.1)	
Did not use	0 (0.0)	1 (1.4)	
Resistant to steroids (%)			
Responsive	20 (90.9)	61 (84.7)	.50
Resistant	1 (4.5)	2 (2.8)	
Not used	1 (4.5)	9 (12.5)	
Steroid dependence (%)			
Nondependent	11 (50.0)	48 (66.7)	.09
Dependent	10 (45.5)	15 (20.8)	
Not used	1 (4.5)	9 (12.5)	

*Significant at .05 level, statistical test used: Fisher exact test.

and GGT levels during longitudinal follow-up (r = 0.61, $P < .001$). Among the patients with PSC-UC, and except for 1 patient (11.1%) who had persistent elevation in GGT level, all patients had a decrease in GGT level during follow-up. The patient who had persistent GGT elevation went on to develop compensated liver cirrhosis and portal hypertension, unlike other patients with PSC-UC, who did not develop any major hepatic complications.

PSC-CD

Our CD cohort comprised 95 children, with a median age of 13.40 years (IQR: 10.30-15.30 years). In this cohort, there were only 5 children (5.3%) who had serum GGT levels value >50 U/L at diagnosis and 2 (2.1%) children with a confirmed diagnosis of PSC (**Table IV**; available at www.jpeds.com). The incidence rate of PSC in our CD cohort was 1.44 new cases per 1000 person-years. Both children with PSC-CD had ileocolonic (L3) disease and positive pANCA status.

Discussion

In this study, we compared the clinical IBD activity and phenotype among children who had serum GGT level elevation vs those with normal serum GGT levels in a population-based IBD cohort, and we identified 3 major findings. First, we found a high rate of PSC within children with IBD, especially UC. Second, we found that patients with even moderately high serum GGT levels at the time of UC diagnosis were more likely to develop PSC in comparison with patients who had elevation during follow-up. Also, we found that children with high serum GGT levels at baseline but not follow-up had pancolitis resembling typical children with PSC-UC.

We identified that 8.9% of patients with UC had PSC, which is greater than previously reported. A large multicenter study found that <2% of >1500 patients with pediatric IBD had PSC.[11] However, less than one-half of these patients ever had serum GGT levels assessed. Laboratory thresholds that initiated a workup for PSC, and the timing, type of imaging, and whether liver biopsies were performed were variable and center-specific. Our study was population-based, and all patients received a standard workup at even modest elevations of serum GGT levels. Our rate of 8.9% of PSC in UC is consistent with 8%-13% rates reported in other population-based studies[19] and in publications in which all patients with IBD underwent screening via magnetic resonance cholangiopancreatography[8,20] or liver biopsy.[21] A

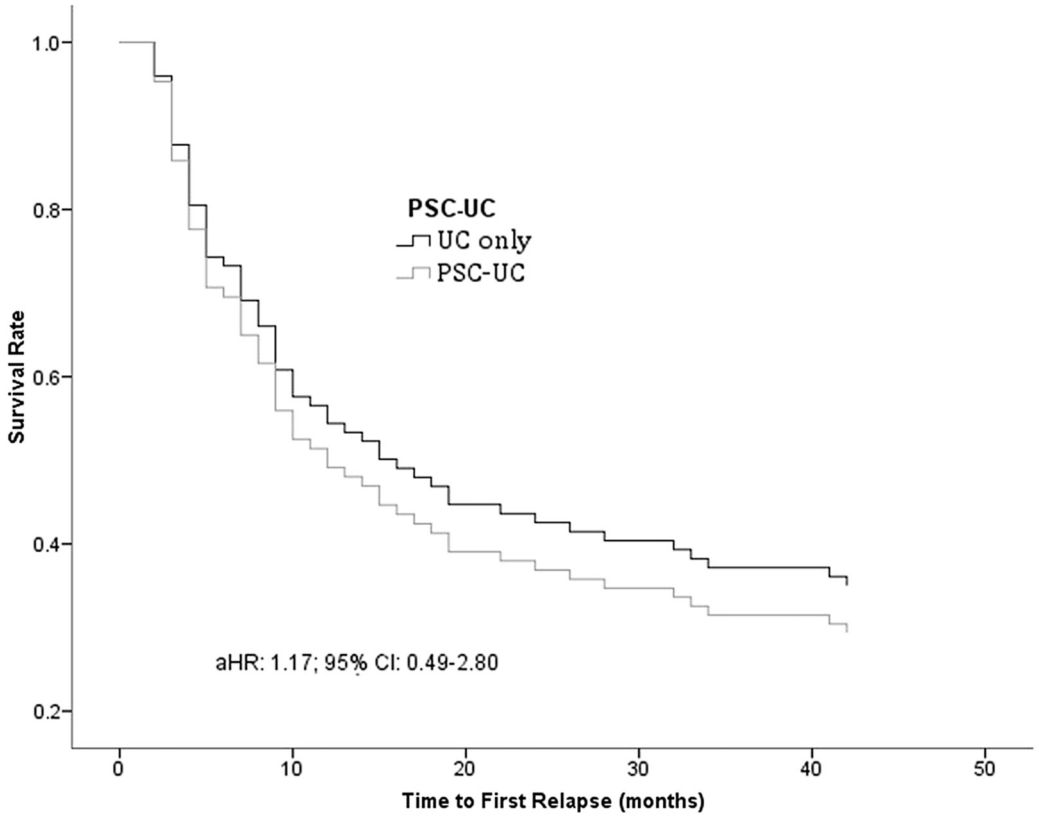

Figure 3. Survival plots for disease relapse during follow-up among patients with PSC-UC compared with patients with UC only. Adjusted for age at IBD diagnosis, sex, and PUCAI at initial diagnosis.

previous study recommended that serum GGT levels >252 U/L could be a potential marker for pediatric PSC-IBD diagnosis due to its high sensitivity and very good specificity.[22] Our finding indicates that all patients with pediatric IBDs who develop serum GGT level elevation, even if marginal, should be screened for underlying PSC.

Serum GGT level elevation at the time of IBD diagnosis could be a potential marker to facilitate early identification of PSC-UC. In a multicenter study, Deneau et al reported a median duration of 1 month between the diagnosis of IBD and hepatic pathology.[19] High serum GGT levels at diagnosis could be a reliable marker of asymptomatic PSC in children with UC. This is substantiated by the fact that all patients with PSC in our cohort were diagnosed within 6 months from UC diagnosis. The pediatric PSC consortium indicated that patients with greater serum GGT levels at the time of PSC diagnosis have worse outcome.[3]

Although all the patients with PSC-UC in our cohort had pancolitis, only 1 patient with UC was found to have rectal sparing, and the prevalence of backwash ileitis was not significantly different between the PSC group and PSC-free group. Most of the previously reported studies had found pancolitis with rectal sparing and backwash ileitis to be present in the patients with PSC-IBD.[5,23,24] The prevalence of pancolitis we reported in patients with PSC-UC is approximately close but greater than the rates reported by Lascurain et al (89.7%) and Shiau et al (96.7%).[25,26] However, a retrospective case series by Yoon et al reported 100% pancolitis in 13 children with IBD-PSC.[27] Moreover, the findings from our CD cohort regarding the pancolonic luminal disease distribution add further support to the prevalent concept that pancolitis being a characteristic feature of IBD-PSC irrespective of the IBD subtype. In our UC cohort, all patients with high serum GGT levels since baseline, irrespective of whether they progressed to develop PSC, had pancolonic disease distribution, which is indicative that patients with UC who have high serum GGT levels from the time of diagnosis, even in the absence of an established PSC diagnosis, have luminal disease similar to that of patients with PSC.

In our cohort, irrespective of whether the patients with UC had PSC, the majority of the patients with high serum GGT levels had positive pANCA. Studies in adults have indicated the presence of antibodies directed against the neutrophil components in patients with PSC, with the reported prevalence of pANCA subtype ranging from 26% to 94%.[28] Our finding of positive pANCA status in a majority of the patients with elevated serum GGT levels indicates the possibility that patients with positive pANCA are at a greater risk of bile duct injury, which may or may not progress to PSC depending on other (unknown) predispositions.

Patients with PSC-UC in our cohort had a greater risk of at least 1 IBD-related hospitalization in comparison with patients without PSC-UC. Immune mechanisms play an important role in the pathogenesis of both PSC and IBD.

Bacterial translocation or absorption of the bacterial endotoxins into the portal circulation through a chronically inflamed bowel has been proposed to play a role in the pathogenesis of PSC. Marelli et al suggested that because PSC and UC share the same pool of lymphocytes that cause organ damage, in the presence of cirrhosis, these lymphocytes are sequestered in the liver, resulting in less severe colon inflammation.[29] We speculate that when there is no cirrhosis but high serum GGT levels, as in almost all our subjects, there will be no lymphocytic sequestration eliciting more severe colonic inflammation that results in more hospitalization and steroid dependency.

Data were collected prospectively, within a population-based cohort, capturing all incident IBD cases in the province. However, a limitation is the relatively small number of patients. Magnetic resonance cholangiopancreatography and liver biopsies were not universally performed in all patients with IBD or all patients with serum GGT levels >50, and so additional cases of PSC may have been missed.

In conclusion, our findings indicated that pediatric patients with UC with even mild elevation of serum GGT levels, especially at baseline, have pancolitis, greater rates of hospitalization, and positive pANCA status, similar to that of children with PSC-UC. We suggest that patients with UC should undergo serum GGT levels assessment at the time of diagnosis and at each clinic visit during follow-up. Larger multicenter prospective studies are needed to confirm our results. ■

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50 Years Ago in *The Journal of Pediatrics*

The Hemolytic-Uremic Syndrome in Nonrelated Adopted Siblings

Chan J, Eleff MG, Campbell RA. J Pediatr 1969;75:1050-3

Chan et al described 2 adopted, biologically unrelated siblings who developed hemolytic-uremic syndrome (HUS) after a prodromal illness consisting of bloody diarrhea and vomiting. The children had been exposed to a third child who also had diarrhea and whose stool culture was positive for *Escherichia coli*. Earlier reports cited by Chan et al had suggested a familial or genetic predisposition to HUS; but, based on the unrelatedness of their cases and increasing hemagglutination inhibition assay titers against influenza in one of them, the authors speculated that HUS was caused by influenza.

The understanding of the etiologies and pathogenesis of HUS has evolved dramatically since Chan et al. It currently is understood that HUS represents multiple entities manifesting a common phenotype: intravascular hemolysis, thrombocytopenia, renal failure, and sometimes neurologic dysfunction, with pathologic specimens revealing microangiopathy and thrombosis. In children, the majority of HUS cases are caused by Shiga toxin-expressing *Escherichia coli* (STEC), which produces the angiopathy through direct effects of the toxin on the endothelium plus activation of the alternative complement pathway. Such cases are self-limited, and successful outcomes usually are achieved with meticulous supportive care. Most of the remaining pediatric HUS cases are linked to a variety of recessive genetic defects, collectively labeled atypical HUS (aHUS), which primarily result in activation of the alternative complement pathway. Cases of aHUS are characterized by recurrent illness and carry a poor prognosis, although trials currently underway are testing the benefit of eculizumab, a monoclonal anti-C5 antibody. Exacerbations of aHUS may be triggered by intercurrent infections, including influenza, but whether this virus can induce HUS independent of this genetic background is uncertain.

So, in retrospect, what did the children reported by Chan et al have? Based on what is known now, they probably suffered from HUS secondary to STEC, given the antecedent bloody diarrhea, with a coincident exposure to influenza. What did the siblings in the prior reports cited by Chan et al have? Perhaps aHUS? The investigators could not say 50 years ago, but were the same cases to present today, it is likely that the etiologies would be defined through the isolation of STEC or, in its absence, through a clinical, genetic, and immunologic evaluation for aHUS.

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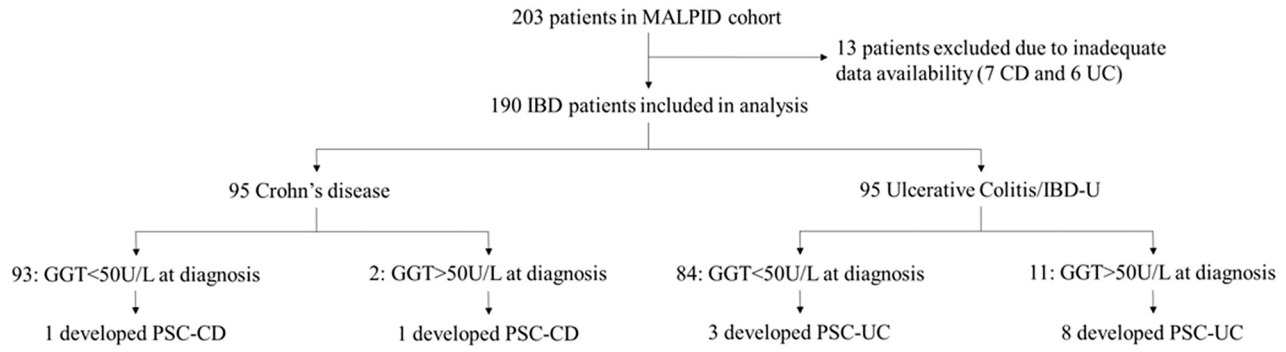

Figure 1. Representation of the overall study cohort and PSC development in each group. ***MALPID,*** **MA**nitoba **L**ongitudinal **P**ediatric **I**nflammatory Bowel **D**isease.

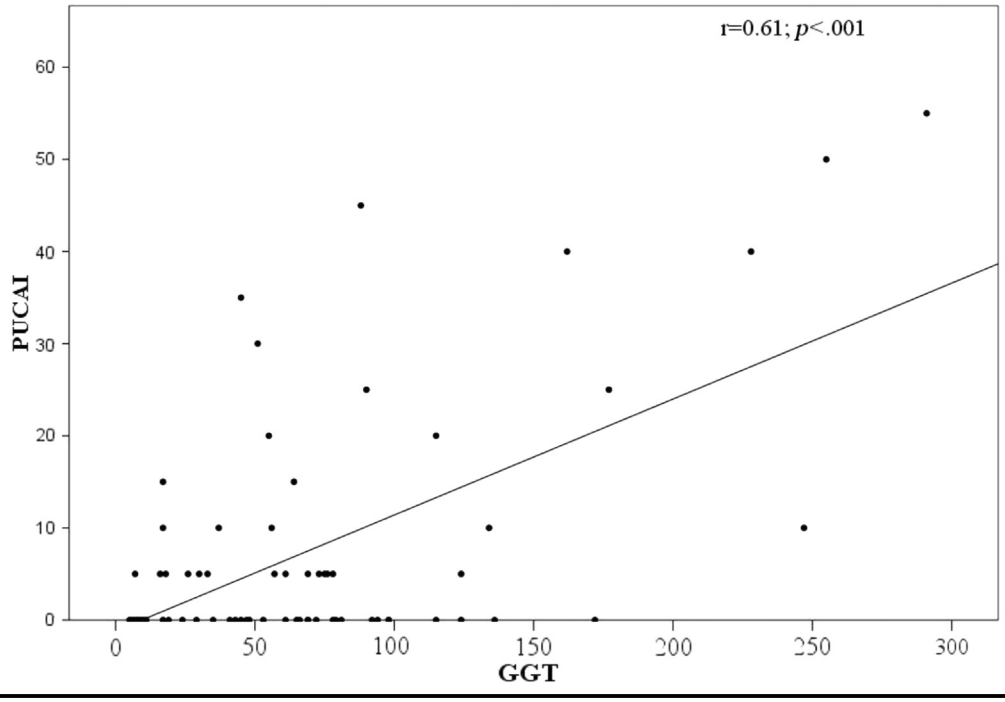

Figure 4. Scatterplot of correlation between PUCAI and GGT over the follow-up period.

Table III. Difference in disease characteristics between children who were tested positive for PSC and children without PSC in the UC/IBD-U cohort

Characteristics	PSC-UC (n = 9)	UC, no PSC (n = 86)	*P* value
GGT at diagnosis (%)			
High	8 (88.9)	3 (3.5)	<.001*
Normal	1 (3.3)	83 (96.5)	
Physician global assessment at diagnosis (%)			
Mild	3 (33.3)	24 (28.2)	.41
Moderate	6 (66.7)	44 (51.8)	
Severe	0 (0.0)	17 (20.0)	
IBD-related hospitalizations (any) (%)			
Yes	8 (88.9)	42 (50.0)	.03*
No	1 (11.1)	42 (50.0)	
IBD-related surgery (%)			
Yes	1 (11.1)	9 (10.6)	1.00
No	8 (88.9)	76 (89.4)	
Sex (%)			
Male	4 (44.4)	48 (56.5)	.51
Female	5 (55.6)	37 (43.5)	
Luminal disease distribution (Paris classification) (%)			
E1	0 (0.0)	7 (8.4)	1.00
E2	0 (0.0)	12 (14.5)	.60
E3	0 (0.0)	11 (13.3)	.59
E4	9 (100.0)	53 (63.9)	.03
pANCA status (%)			
Negative	1 (11.1)	36 (47.4)	.04*
Positive	8 (88.9)	41 (53.2)	
Mayo score (baseline endoscopy) (%)			
1 (Mild)	0 (0.0)	13 (15.5)	.64
2 (Moderate)	5 (55.6)	41 (48.8)	
3 (Severe)	4 (44.4)	30 (35.7)	
Family history (%)			
No	5 (55.6)	49 (62.0)	.73
Yes	4 (44.4)	30 (38.0)	
Rectal sparing (%)			
Yes	1 (11.1)	3 (3.65)	.34
No	8 (88.9)	81 (96.4)	
Isolated right-sided disease (%)			
Yes	0 (0.0)	1 (1.2)	1.00
No	9 (100.0)	82 (98.8)	
Patchy colitis (%)			
Yes	6 (66.7)	65 (77.4)	.44
No	3 (33.3)	19 (22.6)	
Backwash ileitis (%)			
Yes	3 (33.3)	11 (13.3)	.14
No	6 (66.7)	72 (86.7)	
Albumin level at diagnosis (%)			
Low	3 (33.3)	17 (23.0)	.68
Normal	6 (66.7)	57 (77.0)	
Hemoglobin level at diagnosis (%)			
Low	5 (62.5)	47 (61.8)	1.00
Normal	3 (37.5)	29 (38.2)	
CRP level at diagnosis (%)			
High	4 (57.1)	32 (49.2)	1.00
Normal	3 (42.9)	33 (50.8)	
Response to overall therapy (%)			
Responsive	7 (77.8)	70 (84.3)	.64
Nonresponsive	2 (22.2)	13 (15.7)	
Response to infliximab (%)			
Responsive	3 (33.3)	19 (22.9)	.57
Nonresponsive	0 (0.0)	10 (12.0)	
Did not use	6 (66.7)	54 (65.1)	
Response to 5-ASA therapy			
Responsive	6 (62.5)	51 (60.7)	1.0
Nonresponsive	3 (37.5)	32 (38.1)	
Did not use	0 (0.0)	1 (1.2)	
Resistant to steroids (%)			
Responsive	9 (100.0)	71 (84.5)	.70
Resistant	0 (0.0)	3 (3.6)	
Not used	0 (0.0)	10 (11.9)	
Steroid dependence (%)			
Nondependent	4 (44.4)	55 (65.5)	.17
Dependent	5 (55.6)	19 (22.6)	
Not used	0 (0.0)	10 (11.9)	

*Significant at .05 level; statistical test used: Fisher exact test.

Table IV. Characteristics of patients with CD and CD-PSC at diagnosis

Characteristics	CD, no PSC (n = 93)	CD-PSC (n = 2)
Luminal disease distribution (Paris classification) (%)		
L1	19 (10.6)	0 (0.0)
L2	9 (5.0)	0 (0.0)
L3	64 (35.6)	2 (100.0)
L4a	61 (33.9)	1 (50.0)
L4b	27 (15.0)	0 (0.0)
Physician global assessment at diagnosis (%)		
Mild	32 (34.4)	1 (50.0)
Moderate	39 (41.9)	1 (50.0)
Severe	22 (23.7)	0 (0.0)
Serum GGT level at diagnosis (%)		
High	4 (4.3)	1 (50.0)
Normal	89 (95.7)	1 (50.0)
Albumin level at diagnosis (%)		
Low	53 (57.0)	1 (50.0)
Normal	40 (43.0)	1 (50.0)
Hemoglobin level at diagnosis (%)		
Low	62 (66.7)	2 (100.0)
Normal	31 (33.3)	0 (0.0)
CRP level at diagnosis (%)		
High	63 (75.9)	1 (50.0)
Normal	20 (24.1)	1 (50.0)
IBD-related hospitalizations (at least 1) (%)		
Yes	39 (43.3)	1 (50.0)
No	51 (56.7)	1 (50.0)
Sex (%)		
Male	55 (59.1)	1 (50.0)
Female	38 (40.9)	1 (50.0)
Family history (%)		
No	33 (35.5)	1 (50.0)
Yes	60 (64.5)	1 (50.0)
pANCA status (%)		
Negative	83 (95.4)	0 (0.0)
Positive	4 (4.6)	2 (100.0)
Behavior (%)		
B1	76 (85.4)	2 (100.0)
B2	10 (11.2)	0 (0.0)
B3	1 (1.1)	0 (0.0)
B2B3	2 (2.2)	0 (0.0)
Perianal disease (%)		
Absent	69 (74.2)	2 (100.0)
Present	24 (25.8)	0 (0.0)
Response to overall therapy (%)		
Responsive	88 (94.6)	2 (100.0)
Non-responsive	5 (5.4)	0 (0.0)
Response to infliximab (%)		
Responsive	62 (66.7)	1 (50.0)
Non-responsive	3 (3.2)	0 (0.0)
Did not use	28 (30.1)	1 (50.0)
Steroid dependence (%)		
Nondependent	42 (45.2)	1 (50.0)
Dependent	12 (12.9)	0 (0.0)
Not used	39 (41.9)	1 (50.0)