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Distinct phenotypes of children with perianal perforating Crohn's disease[☆]

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Abstract

Purpose—Perianal perforating disease (PF) has been reported in approximately 15% of children with Crohn's disease (CD). It is unknown whether children who present with PF at the time of diagnosis have a different course than those that develop PF while on therapy.

Methods—From a prospective, single institution observational registry of children diagnosed with CD, we identified children with perianal perforating CD, defined as perianal abscesses and/or fistulae. Patients who presented with perianal perforating CD (PF-CD₀) were compared to those who developed perianal perforating CD (PF-CD₁) after initial diagnosis.

Results—Thirty-eight of 215 (18%) children with CD had PF-CD during a median follow up of 4.5 years. Patients with PF-CD₀ (n = 26) tended to be more likely male (81% vs. 50%, p = 0.07) and younger (9.3 yrs vs. 12.5 yrs, p = 0.02). PF-CD₁ (n = 12) patients were more likely to require diverting ileostomy (42% vs. 8%, p = 0.02) and colectomy (33% vs. 4%, p = 0.03). Multivariable analysis predicted increased rate of diverting ileostomy in the PF-CD₁ group (p = 0.007, OR 19.1, 95% CI 1.6–234.8).

Conclusion—Pediatric CD patients who develop PF while on therapy for CD have a more severe phenotype and are more likely to require diverting ileostomy or colectomy compared to those who present with PF-CD.

Keywords

Crohn's disease; Perianal Crohn's disease; Perforating; Inflammatory bowel disease; Seton

Crohn's disease (CD) in children is known for its variable presentation and difficulty in predicting disease course, including need for surgical intervention [1]. With the advent of

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observational registries over the last two decades, there has been great progress in understanding the natural history of inflammatory bowel disease in children. However, many questions remain unanswered and the disease, while increasing in incidence, remains relatively rare with an incidence of 25.4 per 100,000 children [2]. Perianal perforating Crohn's disease (PF-CD), defined as perianal disease with development of fistula and/or abscess is reported to complicate 9.4–21% of cases at ten years of follow-up [3,4]. Due to the relative rarity and variable presentation of CD in children, the pattern of progression and predictors of surgical intervention are not well understood in children with PF-CD [5,6]. While many studies have attempted to identify factors to predict risk of surgical intervention in children with CD, few have specifically evaluated PF-CD. Not surprisingly, it appears likely that development of PF-CD may confer increased need of surgical intervention owing to the development of abscesses or fistulae [7].

In this study, we queried a single institution prospective, observational registry of children with CD. We selected children with PF-CD and identified disease characteristics, medication requirements, rate of surgical intervention, as well as segregation of perianal procedures (such as, perianal abscess drainage and seton placement) from non-perianal bowel procedures (such as, colectomy and ileostomy) in children with PF-CD. We compared children who presented with perianal perforating CD (PF-CD₀) with those who developed perianal perforating CD (PF-CD₁) after initial diagnosis. Primary outcomes measures include need for surgical intervention, need for non-perianal bowel procedures (ileostomy or colectomy) and need for biologic therapy.

1. Patients and methods

1.1. Patient population

Data were obtained from an ongoing single institution observational registry of children diagnosed with inflammatory bowel disease (IBD) before age 21 that began accrual in 2002. We queried the database for all pediatric patients who presented with or developed PF-CD. Ethical approval was obtained from the local institutional review board prior to start of the study (IRB# 3766).

1.2. Inclusion criteria

As of March 1st, 2012, 215 children had been enrolled with a diagnosis of CD. Children enrolled in this study were required to participate in medical care at our institution for at least 6 months with a confirmed diagnosis of CD before the age of 21. A pediatric gastroenterologist evaluated all children and either established, or confirmed, a diagnosis of CD as previously defined by Bousvaros and the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHN) [8]. In addition, we only included patients with perianal perforating disease, defined as perianal disease with fistula or abscess.

1.3. Exclusion criteria

We excluded children with perianal disease limited to skin tags or fissures.

1.4. Description of variables

Multiple presenting factors included: age, gender, race, ethnicity, family history, body mass index, and disease location (e.g. upper tract, large bowel, small bowel, perianal etc.). Disease behavior (rates of internal penetrating, perianal penetrating and stricturing disease) were recorded. Stricturing was defined as occurrence of constant luminal narrowing demonstrated by radiologic, endoscopic or surgical examination combined with pre-stenotic dilatation and/or obstructive signs or symptoms. Internal penetrating disease was defined as evidence of entero-enteric or entero-vesicular fistulae, intra-abdominal abscesses or intestinal perforation. Perianal perforating disease was defined as perianal fistulas, perianal ulcers, and/or abscesses at any time in the course of disease.

Additional evaluation of medication requirements including use of corticosteroids, IBD directed antibiotics (e.g. metronidazole), immunomodulator use (e.g. azathioprine), and biological therapies (e.g. infliximab, adalimumab). All surgical interventions were recorded. Non-perianal bowel surgical procedures included small bowel resection with or without ileostomy; colon resection with or without colostomy, subtotal colectomy, total colectomy and stricturoplasty; perianal procedures included perianal abscess drainage, and seton placement or removal.

Outcomes measures include use of immunomodulatory or biologic agents, time to first surgical intervention, total number of surgical procedures, need for non-perianal bowel procedures, time to second surgical intervention and length of follow-up.

1.5. Statistical methods

All data were recorded into a standardized database program (Microsoft Excel, Seattle, WA). Wilcoxon test was performed on continuous variables and Fisher's exact test on categorical data. A p-value < 0.05 was considered significant and a p < 0.1 was considered a trend toward significance. Multivariable analysis was performed on variables with p < 0.2 from univariate analysis using multiple stepwise logistic regression modelling with the R software.

2. Results

2.1. Demographics

Of 215 CD patients in our database, we identified thirty-eight (18%) who presented with, or developed, PF-CD with a mean age of 10.3 ± 4.4 years. The cohort consisted of 27 boys and 11 girls with a median follow-up time of 4.5 years.

2.2. Perianal perforating disease at presentation (PF-CD₀)

Twenty-six (68%) patients presented with PF-CD₀ at a mean age of 9.3 ± 3.3 years and most were boys (81%)(Table 1). At time of presentation, most had evidence of small bowel (81%), and large bowel (73%) disease. A large percentage of children were of Jewish heritage (58%) and most were non-Hispanic Caucasian (77%). All children required medical therapy with most requiring immunomodulatory agents (77%) and/or biologic therapy (73%). Most children required a surgical procedure (69%) and the majority required incision

and drainage (62%) of a perianal abscess or Seton placement (27%)(Table 2). Only five (19.2%) children required a non-perianal bowel procedure with four (15%) requiring small bowel resection, two (8%) requiring diverting ileostomy, and one (4%) requiring colectomy. Overall, children in this cohort underwent a median of 1.5 surgical procedures during a median follow-up time of 4.5 years (0.4 to 16.1 years) following CD diagnosis.

2.3. Development of Perianal Disease while on Therapy (PF-CD₁)

Twelve patients (32%) of patients developed PF-CD₁ while on therapy (Table 1). This cohort had a mean age of 12.5 ± 4.4 years and were equally distributed 6 boys and 6 girls. They developed PF at a median time of 13.5 months after diagnosis of CD. Half (50%) were of Jewish heritage and the majority (92%) were non-Hispanic Caucasian. Eleven children were receiving immunomodulatory and/or biologic therapy prior to development of perianal disease with all receiving therapy following diagnosis. The majority of children in this group also required surgical intervention (67%) with most requiring abscess drainage (50%) and Seton placement (17%) (Table 2). Compared with the prior cohort, they had a different distribution and an increased number of non-perianal bowel procedures (50%): four (33%) required colectomy or colon resection, two (17%) required small bowel resection, and five (42%) required diverting ileostomy. Overall, children in this group underwent a median of 1.5 surgical procedures during a median follow-up time of 4.2 years (1.3–19.4 years) after initial CD diagnosis.

2.4. Univariate analysis

Univariate analysis of factors was performed and revealed that patients in the PF-CD₀ group were younger (9.3 yrs vs. 12.5 yrs, $p = 0.02$). They also had a trend towards increased prevalence of boys (81% vs. 50%, $p = 0.07$). There were no statistical differences in disease distribution or behavior at presentation, or during follow-up between the two groups. Use of immunomodulatory ($p = 0.67$) and biologic therapy ($p = 0.51$) was similar in both groups. Eleven children in the PF-CD₀ group required a 2nd procedure at a median time of 48 months while six children in the PF-CD₁ group underwent a 2nd procedure at a median time of 40.5 months ($p = 0.14$). The median number of total procedures performed was similar (1.5 vs. 1.5, $p = 0.59$). There was a trend toward an increased number of non-perianal bowel procedures in the PF-CD₁ group (50% vs. 19.2%, $p = 0.06$). However, the PF-CD₁ group was more likely than the PF-CD₀ patients to require diverting ileostomy (42% vs. 8%, $p = 0.02$) or colon resection (33% vs. 4%, $p = 0.03$). Rates of small bowel resection (15% vs. 17%, $p = 1.0$) and follow-up times were similar (4.5 vs. 4.2 years, $p = 0.34$). Tables 1 & 2.

2.5. Multivariable analysis

Multivariable exact logistic regression modeling of univariate factors with p values <0.2 identified older age ($p = 0.01$, OR 1.34 95% CI 1.1–1.7) and increased need for diverting ileostomy $p = 0.007$, OR 19.1, 95% CI 1.6–234.8) in the PF-CD₁ group compared with the PF-CD₀ group. Table 3.

3. Discussion

This is one of the largest studies with the long-term follow-up to prospectively evaluate the natural history of PF-CD in children. Further, it is the first to identify distinct disease phenotypes in those children who present with PF-CD compared with those who develop PF-CD while receiving similar therapy. The PF-CD₀ group is comprised mostly of younger boys with a disease course less complicated by the need for non-perianal bowel surgery. Conversely, the PF-CD₁ group was gender matched, older and had a much higher rate of non-perianal bowel procedures, most notably a 19-fold increased risk of diverting ileostomy.

Keljo and colleagues performed the first prospective study to better understand the natural history of perianal CD using an observational registry. They identified 28 of 276 CD patients with diagnosis of PF-CD within 30 days of CD diagnosis. They reported a 50% incidence of surgical intervention and a male predominance, but were unable to determine additional prognostic factors to predict course of perianal disease [9]. Their data was similar to our findings in the PF-CD₀ group, which demonstrated, male predominance and comprised about 10% of their cohort. By contrast, we included all patients with PF-CD at any time during their disease course, and identified an additional 33% of patients with PF-CD₁. This later group had different characteristics including mean older age, a larger percentage of girls, and more frequent diverting procedures.

Prior studies have shown the differences highlighted in the PF-CD₁ group predict more complicated disease course. Using a multicenter observational CD registry, Gupta and colleagues determined an adjusted hazard ratio of 1.12 for surgical intervention for each advancing year in age and a hazard ratio of 1.42 for female gender [10]. With respect to older age children, disease location may be age dependent with ileal disease presenting later in childhood and therefore potentially increasing the requirement for intestinal surgery [11]. Not surprisingly, since by definition PF-CD is associated with abscess or fistula, both of which have reported hazard ratios of 7.7 and 2.4 for surgical intervention, respectively [5,10].

Our data reveals markedly increased rates of diverting procedures (ileostomy or colectomy) in the PF-CD₁ group compared to the PF-CD₀ group, and the rate of bowel surgery is substantially higher in the PF-CD₁ compared to the published literature. Gupta and colleagues reported an overall incidence of intestinal resection in children with CD of 5.7%, 17%, and 28.4% at 1, 5, and 10 years respectively [10]. Among those with PF-CD₀, 19.2% had undergone surgical intervention at 4.5 year median follow-up, which is comparable to the data reported by Gupta. In contrast, those with PF-CD₁ had a 50% surgical intervention rate at 4.2-year median follow-up, which was more than double the rate reported by Gupta. The increased rate of surgical intervention in our patients may reflect our status as a tertiary referral center, which receives patients with increased disease complexity. Our findings distinguish the PF-CD₁ cohort and strongly supports our assertion that children in this group represent a distinctly more severe phenotype with similar intensity of immunomodulatory and biological therapy. Further, this group appears to be at high risk for surgical intervention and may warrant earlier introduction of biological therapy and incorporation into models such as those proposed by Siegel and colleagues [12].

While prospective in design, this study has several limitations including unknown bias from measuring multiple factors among multiple patients over a time course. It is well recognized that these time-varying variables can influence outcome and confound the data [13]. In addition, our center is a tertiary care center with many patients presenting with advanced disease and may not be representative of populations seen at other centers. Further, decisions regarding surgical therapy were gastroenterologist and surgeon dependent, hence the lack of a defined protocol may bias rates and types of surgical intervention. Despite being one of the largest studies evaluating perianal disease in children, our cohort is relatively small and therefore conclusions may be at risk of type II error.

4. Conclusion

Pediatric Crohn's disease patients who develop PF while on therapy following CD diagnosis have a more severe phenotype requiring significantly more frequent non-perianal surgical intervention including diverting ileostomy and colectomy, compared with those who present with PF at time of diagnosis of CD. Continued longitudinal study of this cohort may yield further insight in disease phenotype and hence have implications on management.

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Table 1Clinical characteristics of children. PF-CD₀ vs. PF-CD₁.

	PF-CD ₀ (N = 26)	PF-CD ₁ (N = 12)	P	OR	95% CI
Demographics					
Age in years (mean)(range)	9.3 (2–14)	12.5 (3–17)	0.02	-	-
Gender (% Male)	81	50	0.07	2.2	0.4–12.6
Ethnicity (% Jewish)	58	50	0.67	1.17	0.59–2.3
BMI (mean)	17.6	22.4	0.001	-	-
CD distribution/behavior at last follow-up (%)					
Upper tract	35	33	0.10	1.06	0.25–4.5
Small bowel	81	67	0.42	2.10	0.45–9.86
Large bowel	73	83	0.69	0.54	0.09–3.12
Stricture	19	25	0.69	0.71	0.14–3.65
Internal penetrating	4	8	0.54	0.44	0.03–7.69
Medication use (%)					
Aminosalicylates	46	33	0.5	1.71	0.41–7.14
Antibiotics	65	42	0.29	2.64	0.65–10.76
Corticosteroids	46	67	0.31	0.43	0.1–1.78
Immunomodulators	77	83	1.0	0.67	0.11–3.92
Biologics	73	83	0.69	0.54	0.09–3.12

Table 2Surgical therapy in children. PF-CD₀ vs. PF-CD₁.

	PF ₀ (N = 26)	PF ₁ (N = 12)	P	OR	95% CI
Any CD Surgery (%)	69	67	1.0	1.12	0.26–4.85
Non-perianal intestinal surgery (%)	19.2	50	0.06	0.24	0.05–1.06
Procedure type (%)					
Small bowel resection	15	17	1.0	0.91	0.14–5.81
Diverting ileostomy	8	42	0.02	0.12	0.02–0.74
Large bowel resection	4	33	0.03	0.08	0.01–0.82
I&D perianal abscess	62	50	0.73	1.6	0.4–6.36
Seton placement	27	17	0.69	1.84	0.32–10.84
Required 1st surgery (N)	85% (22)	67% (8)	0.39	0.36	0.07–1.8
Median months to procedure (range)	0 (0–45)	10.5 (1–168)	0.008	-	-
Required 2nd surgery (N)	42% (11)	50% (6)	0.41	3.0	0.49–18.2
Median months to procedure (range)	48 (1–79)	40.5 (7–195)	0.14	-	-
Median total procedures (range)	1.5 (0–3)	1.5 (0–5)	0.59	-	-
Median years follow-up (range)	4.5 (0.4–16.1)	4.3 (1.3–19.4)	0.34	-	-

Table 3

Multivariable analysis of factors associated with PF-CD₁.

	OR	Lower CI	Upper CI	P
Age	1.34	1.1	1.7	0.01
Diverting ileostomy	19.1	1.5	234.8	0.02