Increasing Rate of a Positive Family History of Inflammatory Bowel Disease (IBD) in Pediatric IBD Patients

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Abstract

The role of a positive family history in pediatric inflammatory bowel disease (IBD) in the era of biologic therapy has not been elucidated. We retrospectively reviewed the medical records of children with IBD and retrieved demographic and clinical characteristics, including the presence of a positive family history of IBD, IBD phenotype, disease course, and therapy. Overall, 325 children (age range at diagnosis 11-15 years) were included, of whom 82 (25.2%) had a positive family history. Children diagnosed during 2016-2020 had a higher frequency of positive family history compared to those diagnosed during 2010-2015 (31.8% versus 20.7%, respectively, $p = 0.024$). Children with a positive family history had a higher risk for a stricturing phenotype than those with a negative family history (11.3% versus 2.8%, respectively, $p = 0.052$). They more often received nutritional therapy (53.7% versus 36.6%, $p = 0.007$) and less often received corticosteroids (36.6% versus 52.7%, $p = 0.012$). More children with a negative family history needed intensification of biologic therapy ($p = 0.041$).

Conclusion*:* The rate of a positive family history of IBD in the pediatric IBD population is increasing. A positive family history may have some impact upon IBD phenotype but none on IBD outcome.

Summary

What is Known:

- Familial clustering of inflammatory bowel disease (IBD) has been reported in 5%-15% of IBD patients.
- The investigation of the impact of a positive family history upon IBD characteristics and severity revealed conflicting results.

What is New:

- In this cohort of 325 children with IBD, 25.2% had a positive family history.
- The rate of a positive family history of IBD in the pediatric IBD population is increasing.
- A positive family history may have some impact upon IBD phenotype but none on IBD outcome.

Introduction

Inflammatory bowel disease (IBD) is a chronic systemic inflammatory condition comprised of Crohn's disease (CD) and ulcerative colitis (UC). The disease is triggered and perpetuated by a complex interplay between genetic predisposition, dysregulated immune responses, and environmental factors [1, 2]. Familial clustering of IBD has been documented in numerous studies that reported a 5%-15% positive family history of IBD in both CD and UC [3–6]. A positive family history is considered a major risk factor for developing IBD [5, 7, 8]. Twin studies [9] have strengthened the significant role of genetic factors in the pathogenesis of IBD. A familial clustering of IBD not only reflects the genetic component of IBD, but it may also provide evidence of exposure to common environmental factors [10].

Several studies have investigated the impact of a positive family history upon IBD characteristics and severity, with conflicting results. A number of them have linked a positive family history to younger age at diagnosis of IBD [11–13]. Others have further suggested a positive relation between family history of IBD and a more aggressive disease [14–16], however, these results were challenged in other studies [17].

Recognizing the impact of family history on the natural history of IBD may have prognostic implications by improving risk stratification and prediction of disease-related complications. There are scarce data on the relation between family history and IBD outcome in the pediatric population during the last decade, characterized an era of biologic therapy and new therapeutic targets. The aim of this study was to evaluate the effect of a family history of IBD on the clinical phenotypes and the course of IBD in contemporary children.

Methods

Patient Population All children with a diagnosis of IBD who attended the Pediatric Gastroenterology Unit at Dana-Dwek Children's Hospital, Tel Aviv Sourasky Medical Center, between January 2010 and December 2020 and had a follow-up of at least 12 months were included. The unit is a tertiary referral center for pediatric IBD patients. The diagnosis of IBD was made according to the European Society for Pediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) revised Porto criteria for the diagnosis of IBD in children and adolescents [18].

Study Design We retrospectively reviewed the medical records of all the patients, including their demographic, clinical, laboratory, and endoscopic data. The data relevant to a family history of IBD (degree of relation, number of family members, their sex, and IBD type) were documented. Disease location, behavior, and extent were grouped according to the PARIS classification [19], as were induction and maintenance of medical therapy. The primary outcomes of the study were clinical remission at 12 and 36 months, need of biologic therapy, intensification of biologic therapy, disease exacerbations, need for hospitalizations, and any IBD-related surgery during the follow-up period. Clinical remission was defined according to the Pediatric Crohn's Disease Activity Index (PCDAI) [20] or the Pediatric Ulcerative Colitis Activity Index (PUCAI) [21]. Intensification of biologic therapy was defined as dose elevation and/or shortening of intervals between therapy administration. Disease exacerbation was defined as relapse of clinical symptoms after disease remission, accompanied with an elevation above 10 points in the PCDAI or the PUCAI. Hospitalizations were defined as all non-elective hospitalizations related to IBD.

Statistical Analyses Continuous variables were evaluated for normal distribution with histograms and Q–Q plots. Normally distributed continuous variables were expressed as mean and standard deviation (SD). Non-normally distributed continuous variables were expressed as median and interquartile range (IQR). Categorical variables were presented as frequency and percentage. Patients with IBD-undetermined (IBD-U) were included in the UC group for analysis. In addition, data on the closest degree family member were included for calculation of concordance of sex and disease type between that family member and the study patient. Categorical variables were compared between patients with and without a family history of

IBD by employing the chi-square test or Fisher's exact test, while continuous variables were compared by means of the independent samples t-test or the Mann-Whitney test. Univariate cox regression evaluated the association between a family history of IBD and the studied outcomes. The hazard ratio (HR) and 95% confidence interval (CI) were reported. All the statistical tests were 2-tailed. A p value < 0.05 was considered statistically significant. SPSS (IBM Corp. Released 2016. IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp.) was used for all statistical analysis.

Ethical Considerations The study was approved by the Institutional Review Board of the Tel Aviv Sourasky Medical Center (TLV-18-266). Informed consent was waived for this retrospective data analysis.

Results

Study population A total of 325 children with IBD were included in the study. There were 194 (59.7%) children with CD, 117 (36%) with UC, and 14 (4.3%) with IBD-U. Of them, 189 (58.2%) children were males and 136 (41.8%) were females, with a median (IQR) age of 13.9 (11–15) years at diagnosis. The demographic and clinical data of the patients are presented in Table 1.

Table 1
Demographic and clinical characteristics of the study cohort

	Total (*n* = 325)	**Positive family history of IBD** (*n* = 82, 25.2%)	**Negative family history of IBD** (*n* = 243, 74.8%)	*P*
IBD type				0.291
CD	194 (59.7%)	53 (64.6%)	141 (58%)	
UC	131 (40.3%)	29 (35.4%)	102 (42%)	
Age at diagnosis, years (range)	13.9 (11–15)	13.7 (12–15)	13.9 (11–15)	0.782
Time to diagnosis, months (range)	4 (2–6)	3 (2–6)	4 (2–6)	0.621
Males	189 (58.2%)	51 (62.2%)	138 (56.8%)	0.391
Ethnicity				0.644
Jewish	319 (98.2%)	80 (97.6%)	239 (98.4%)	
Arab	6 (1.8%)	2 (2.4%)	4 (1.6%)	
Upper GI involvement	155 (47.7%)	43 (52.4%)	112 (46.1%)	0.320
CD location				0.085
Ileocecal (L1)		21 (39.6%)	36 (25.5%)	
Colonic (L2)		4 (7.5%)	23 (16.3%)	
Ileocolonic (L3)		28 (52.8%)	82 (58.2%)	
CD behavior				0.052
Inflammatory (B1)		34 (64.2%)	104 (73.8%)	
Stricturing (B2)		6 (11.3%)	4 (2.8%)	
Penetrating (B3)		13 (24.5%)	33 (23.4%)	
Perianal involvement		9 (17%)	26 (18.4%)	0.814

IBD, inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitis; GI, gastro-intestinal; BMI, body mass index; ASCA, anti-Saccharomyces cerevisiae antibodies; ANCA, anti-neutrophil cytoplasmic antibodies; EEN, exclusive enteral nutrition; 5-ASA, 5-aminosalicylic acid.

	Total (n = 325)	Positive family history of IBD (n = 82, 25.2%)	Negative family history of IBD (n = 243, 74.8%)	*P*
UC extent				0.992
Proctitis (E1)		3 (10.3%)	10 (9.8%)	
Left-sided colitis (E2)		9 (31%)	29 (28.4%)	
Extensive colitis (E3)		5 (17.2%)	19 (18.6%)	
Pancolitis (E4)		12 (41.4%)	44 (43.1%)	
UC severity				0.829
Never severe (S0)		19 (65.5%)	69 (67.6%)	
Ever severe (S1)		10 (34.5%)	33 (32.4%)	
BMI Z-score at diagnosis	-0.50 ± 1.55	-0.32 ± 1.56	-0.56 ± 1.55	0.332
Extraintestinal manifestations	106 (32.6%)	26 (31.7%)	80 (32.9%)	0.839
ASCA positivity	74 (33.8%)	27 (41.5%)	47 (30.5%)	0.115
ANCA positivity	64 (29.5%)	20 (30.8%)	44 (28.9%)	0.787

IBD, inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitis; GI, gastro-intestinal; BMI, body mass index; ASCA, anti-Saccharomyces cerevisiae antibodies; ANCA, anti-neutrophil cytoplasmic antibodies; EEN, exclusive enteral nutrition; 5-ASA, 5-aminosalicylic acid.

	Total (n = 325)	Positive family history of IBD (n = 82, 25.2%)	Negative family history of IBD (n = 243, 74.8%)	*P*
IBD therapy				
EEN	133 (40.9%)	44 (53.7%)	89 (36.6%)	0.007
5-ASA	238 (73.2%)	57 (69.5%)	181 (74.5%)	0.379
Corticosteroids	158 (48.6%)	30 (36.6%)	128 (52.7%)	0.012
Immunomodulators:	166 (51.1%)	43 (52.4%)	123 (50.6%)	0.775
• Thiopurines	125 (75.3%)	30 (69.8%)	95 (77.2%)	
• Methotrexate	42 (25.3%)	13 (30.2%)	28 (22.8%)	
Biologic agents:	162 (49.8%)	44 (53.7%)	118 (48.6%)	0.425
• Infliximab	81 (50%)	15 (34.1%)	66 (55.9%)	
• Adalimumab	69 (42.6%)	23 (52.2%)	46 (39%)	
• Vedolizumab	10 (6.2%)	4 (9.1%)	6 (5.1%)	
• Ustekinumab	1 (0.6%)	1 (2.3%)	0	
• Golimumab	1 (0.6%)	1 (2.3%)	0	
Follow-up (months)	32 (16-57.5)	25.5 (12-52.5)	33 (17–60)	0.086

IBD, inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitis; GI, gastro-intestinal; BMI, body mass index; ASCA, anti-Saccharomyces cerevisiae antibodies; ANCA, anti-neutrophil cytoplasmic antibodies; EEN, exclusive enteral nutrition; 5-ASA, 5-aminosalicylic acid.

Family history of IBD Eighty-two (25.2%) children had a positive family history of IBD, including 53 (27.3%) with CD and 29 (22.1%) with UC (p = 0.291) (Table 2). Of them, 36 (43.9%) had a first-degree family member with IBD, and 46 (56.1%) had more than one family member with IBD. The type of IBD (CD or UC/IBD-U) was concordant with the family member's type of IBD in 58 (70.7%) patients: 42 (79.2%) CD and 16 (55.2%) UC (p = 0.022). The sex was concordant in 33 (40.2%) of the patients (21 pairs of males and 12 pairs of females) and discordant in 49 (59.8%) of the patients (30 pairs of male IBD patients with a female relative and 19 pairs of female IBD patients with a male relative). Forty (20.7%) of the 193 children that were diagnosed during 2010–2015 had a positive family history of IBD, while 42 of the 132 children that were diagnosed during 2016–2020 (31.8%) had a positive family history of IBD (p = 0.024).

Table 2
Characteristics of a family history of IBD among pediatric IBD patients

	All	CD	UC	*P*
Overall frequency of a positive family history of IBD	82 (25.2%)	53 (27.3%)	29 (22.1%)	0.291
Degree of relation(s) with IBD				0.166
1st	36 (43.9%)	26 (49.1%)	10 (34.5%)	
2nd	26 (31.7%)	13 (24.5%)	13 (44.8%)	
3rd and more	20 (24.4%)	14 (26.4%)	6 (20.7%)	
Number of relatives with IBD				0.834
1	59 (72%)	39 (73.6%)	20 (69%)	
2	16 (19.5%)	9 (17%)	7 (24.1%)	
3	6 (7.3%)	4 (7.5%)	2 (6.9%)	
4	1 (1.2%)	1 (1.9%)	0	
Concordance with IBD type	58 (70.7%)	42 (79.2%)	16 (55.2%)	0.022
Concordance with sex	33 (40.2%)	23 (43.4%)	10 (34.5%)	0.431

IBD, inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitis

Family history and IBD characteristics Children with CD that had a positive family history of IBD had a higher probability for the stricturing (B2) compared to the inflammatory (B1) phenotype ($p = 0.052$) (Table 1). In addition, children who had a positive family history of IBD were treated more frequently with nutritional therapy (exclusive enteral nutrition, EEN) and less with corticosteroids ($p = 0.007$ and $p = 0.012$, respectively). Specifically, more children with UC and a family history of IBD were treated with nutritional therapy compared to children without a family history (17.2% versus 3.9%, respectively, $p = 0.025$). A trend towards more frequent ileocecal disease compared to colonic disease was observed in children who had a positive family history of IBD ($p = 0.085$). There were no significant differences between familial and sporadic cases in terms of IBD type, age, sex, ethnicity, duration to diagnosis, disease extent, perianal involvement, extraintestinal manifestations, hemoglobin, serum inflammatory markers [C-reactive protein (CRP) and fecal calprotectin] at diagnosis and at follow-up, and therapy with 5-aminosalicylic acid (5-ASA), immunomodulators and biologic agents. A separate analysis of patients with CD and UC also revealed no significant differences.

Family history and IBD outcome Intensification of biologic therapy was significantly more frequent among pediatric IBD patients with a negative family history compared to those with a positive family history ($p = 0.041$) (Table 3). Intensification of biologic therapy in the CD patients was significantly more

frequent among those with a negative family history compared to a positive family history (32.6% versus 17.3%, respectively, $p = 0.008$). The HR (95% CI) for intensification of biologic therapy was 1.792 (1.005–3.195) for children with IBD who had a negative family history and 2.597 (1.224–5.525) for children with CD and a negative family history. No relation was found between family history and the risk for requiring biologic therapy, the number of biologic agents, IBD exacerbation, IBD-related hospitalization, or surgery. A further analysis failed to reveal any difference in IBD characteristics or outcome between patients with more than one family member, as well as between patients with first-degree relative compared to patients without any family history of IBD.

Table 3
Relation between family history of IBD and pediatric IBD outcome

	Total (*n* = 325)	**Positive family history of IBD** (*n* = 82)	**Negative family history of IBD** (*n* = 243)	*P*
Clinical remission at 12 months (*n* = 265)	183 (69.1%)	49 (74.2%)	134 (67.3%)	0.293
Clinical remission at 36 months (*n* = 177)	126 (71.2%)	32 (78%)	94 (69.1%)	0.268
Biologic therapy	162 (49.8%)	44 (53.7%)	118 (48.6%)	0.435
Intensification of biologic therapy	82 (50.6%)	15 (34.1%)	67 (56.8%)	0.041
IBD exacerbation	191 (58.8%)	40 (48.8%)	151 (62.1%)	0.187
IBD-related hospitalization	108 (33.2%)	31 (37.8%)	77 (31.7%)	0.194
IBD-related surgery	46 (14.2%)	12 (14.6%)	34 (14%)	0.835

IBD, inflammatory bowel disease

Discussion

This study was designed to determine the role of a positive family history in pediatric IBD in the era of biologic therapy. Taken as a whole, 25.2% of the children in our cohort had a positive family history of IBD, with a higher prevalence of a positive family history among the patients that were diagnosed during 2016–2020 compared to the prevalence between 2010–2015 ($p = 0.024$). While a positive family history of IBD had a mild impact on IBD phenotype, there was no significant impact on IBD outcome in the first years after diagnosis.

The frequency of a positive family history of IBD that was observed in our cohort, irrespective of IBD type was higher compared to the values published in older studies. This rate, however, was equivalent to other contemporary studies in western countries [16] that observed a high rate of familial clustering. The rate may be even higher in the Jewish population, that comprises the vast majority of our cohort [6]. In 2018, Schiff et al. [22] reported a 40% rate of familial cases of IBD in the Ashkenazi Jewish population in the UK. That high rate may reflect a greater genetic burden for IBD among that population compared to others. Furthermore, 28% of the patients with a positive family history in our cohort had more than one family member with IBD, and 8.5% had three family members or more. The high incidence of a family history of IBD in western countries compared to Asian countries [11, 14] might imply an environmental component in the pathogenesis of IBD.

The type of IBD was concordant with the family member's type in 70.7% of our population, and the concordance was significantly increased in CD compared to UC. Borren et al. [16] have also reported a similar rate of concordance for type of IBD. In their meta-analysis [17], Childers et al. reported a 9% prevalence of a family history of UC among UC patients, while the prevalence of a family history of CD among their UC patients was only 2%. Roma et al. [13] reported a concordance between the family member and the pediatric patient of 100% for UC and 58.3% for CD [9].

Several studies have suggested that a family history of IBD may be related to an IBD phenotype. In our cohort, children with CD who had a family history of IBD had a higher probability for a stricturing compared to an inflammatory phenotype ($p = 0.052$). In addition, there was a trend towards more frequent ileo-cecal involvement compared to colonic disease in children who had a positive family history of IBD ($p = 0.085$). Similarly to our results, Borren et al. [16] also observed an increased risk for complicated (stricturing or penetrating) CD in the presence of an affected first-degree family member, as did Andreu et al. [23] who reported a higher percentage of ileocolic location, penetrating behavior, and perianal disease in familial CD. Interestingly, another Israeli study by Ben-Horin et al. [24] observed no difference between sporadic and familial CD patients in terms of disease location, phenotype, complications, and medications. Other studies have also showed contrasting results [13, 14, 17, 25].

The children with a positive family history of IBD in our cohort, and specifically those with UC, were treated more frequently with nutritional therapy and less with corticosteroids. Nutritional therapy is a cornerstone of induction therapy for pediatric CD but not for UC. Nevertheless, the knowledge and experience of the families with its use may explain the more frequent utilization of nutritional therapy in familial cases. Roma et al. reported no difference in familial IBD with regard to other therapies, such as 5-ASA, immunomodulators, and biologic agents, as had been shown in other studies [13]. Contrary to our study, Hwang et al. [14] reported that anti-tumor necrosis factor alpha agents were more frequently used in familial cases of CD. Although familial cases have been associated with a younger age at diagnosis in many studies [11–13], no difference between age or duration to diagnosis was found in our current study or in others [14].

While the effect of family history on the IBD phenotype has been investigated in depth with conflicting results, that effect on IBD outcome is even more controversial. We found no correlation between the presence of family history of IBD and the major IBD outcomes, such as risk to biologic therapy, IBD exacerbation, IBD-related hospitalization, or surgery, in the first years after diagnosis of IBD. Nevertheless, we observed that intensification of biologic therapy was significantly less frequent in patients with a family history of IBD. This is opposed by several studies that reported an adverse effect of family history on IBD. Kuwahara et al. [11] reported a greater disease severity in familial cases. A high relapse rate in familial UC cases was also observed by Henriksen et al. [10], and a number of studies reported a higher risk for surgery in familial cases [14, 16, 26, 27]. However, our current results are in line with other studies that reported no relation between a family history of IBD and the risk of surgery [13, 17] or a more severe disease course (28). Importantly, the more severe phenotype that was observed in some of these studies does not necessarily imply a true more aggressive disease course, but may rather reflect a greater concern among patients, families, and physicians, that may be more likely to lead to the adoption of a more aggressive approach earlier in the disease course [14].

Our study is based upon a large database that contained extensive data on clinical disease characteristics, including phenotype, severity, therapy, and course. All of the patients in the study cohort had complete data at diagnosis and follow-up. To the best of our knowledge, this is the first study to describe the relation between a family history of IBD to disease outcome in the era of biologic therapy in a pediatric population. Furthermore, while most of the earlier studies had focused on first-degree relatives, we included patients with second- and third-degree relatives as well.

The study has several limitations that bear mention. Its retrospective design precludes any assessment of causality in the observed interaction between family history and IBD phenotype and outcomes. The chosen outcomes were clinical and did not include endoscopic assessment of mucosal healing due to a large diversity in the endoscopic follow-up descriptions. Finally, this is a single-center study. Importantly, while the presence of a family history of IBD supports but does not necessitate a certain genetic etiology, family members are likely to share environmental factors as well. The familial effect may also be mediated through differences in the microbiome [16]. Nevertheless, the recognition of a positive family history as a risk factor and as potential predictor of IBD phenotype and disease course is an important component of the care of the patients and their families, including improving risk stratification and prediction of disease-related complications.

To conclude, the prevalence of a positive family history of IBD is increasing. While familial cases have a more frequent stricturing phenotype, a positive family history has no significant impact on pediatric IBD outcome. Further studies that focus on the role of family history in the interrelationship between genetic and environmental factors in the pathogenesis of IBD and as a potential predictor of IBD prognosis are warranted.

Abbreviations

CD Crohn’s disease

EEN Exclusive enteral nutrition

ESPGHAN European Society for Pediatric Gastroenterology Hepatology and Nutrition

IBD Inflammatory bowel disease

IQR Interquartile range

PCDAI Pediatric Crohn’s Disease Activity Index

PUCAI Pediatric Ulcerative Colitis Activity Index

UC Ulcerative colitis

Declarations

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Code availability: N/A

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