Pediatric perianal Crohn's disease behavior in the era of biologic therapy

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ABSTRACT

Aim of the study. To describe perianal Crohn's disease behavior and the role of biological therapy in a sample of pediatric patients.

Methods. A retrospective study of pediatric patients with Crohn's disease (CD) treated in our institution from 2017 to 2021, with a minimum follow up period of 6 months, was conducted. Patients were divided whether they had perianal disease (PD) or not. Baseline characteristics, extension of disease, growth failure rate, aggressive pattern rate, use of biological therapy and need for surgery, among other variables, were compared between both groups. Clinical and/or radiological improvement in the last 6 months of follow up was considered good control of PD.

Results. Seventy eight pediatric patients with CD were included. Median age at diagnosis was 10.5 years, and median follow up time was 3.8 years. 64.1% patients were male. Of all, 15 (19.2%) had perianal disease, of which 10 had fistulizing findings and 5 had non fistulizing findings. PD was presented at diagnosis in 8 patients, and the rest developed it in a median time of 1 year from diagnosis. PD was associated with growth failure (p = 0.003), use of biological therapies (p = 0.005), and need for second line of biologics (p = 0.005). Most patients (12/15, 80%) had good control of PD with the treatment received.

Conclusions. CD patients with PD seem to need a more aggressive treatment, with biological therapies playing a key role for its handling nowadays. These patients require close nutritional evaluation that ensures proper development and growth.

KEY WORDS: Crohn's disease; Pediatric; Perianal disease; Biological therapy.

COMPORTAMIENTO DE LA AFECTACIÓN PERIANAL EN PACIENTES PEDIÁTRICOS CON ENFERMEDAD DE CROHN EN LA ERA DE LA TERAPIA BIOLÓGICA

RESUMEN

Objetivo del estudio. Describir el comportamiento de la enfermedad de Crohn perianal y el papel de la terapia biológica en una muestra de pacientes pediátricos.

Métodos. Estudio retrospectivo de pacientes pediátricos con enfermedad de Crohn (EC) tratados en nuestro centro entre 2017 y 2021, con un seguimiento mínimo de seis meses. Los pacientes se dividieron en función de si tenían enfermedad perianal (EP) o no. Se compararon entre ambos grupos las características iniciales, la extensión de la enfermedad, el índice de retraso en el crecimiento, el índice de patrón agresivo, el empleo de terapia biológica y la necesidad de cirugía, entre otras variables. Se consideró un buen control de la EP una mejoría clínica o radiológica en los 6 últimos meses de seguimiento.

Resultados. Se incluyeron 78 pacientes pediátricos con EC. La edad mediana en el momento del diagnóstico fue de 10,5 años, y el tiempo mediano de seguimiento fue de 3,8 años. El 64,1% de los pacientes eran varones. Del total, 15 (19,2%) tenían enfermedad perianal, de los cuales 10 presentaban hallazgos fistulizantes y 5 no fistulizantes. La EP estaba presente en el momento del diagnóstico en 8 pacientes, y el resto la desarrolló en una mediana de 1 año desde el diagnóstico. La EP se asoció con retraso en el crecimiento (p = 0,003), empleo de terapias biológicas (p = 0,005) y necesidad de una segunda línea de terapia biológica (p = 0,005). La mayoría de los pacientes (12/15, 80%) tuvieron un buen control de la EP con el tratamiento recibido.

Conclusiones. Los pacientes de EC con EP parecen necesitar un tratamiento más agresivo, en el que las terapias biológicas desempeñan hoy en día un papel fundamental. Estos pacientes precisan de una estrecha evaluación nutricional que garantice su correcto crecimiento y desarrollo.

PALABRAS CLAVE: Enfermedad de Crohn; Pediátrico; Enfermedad perianal; Terapia biológica.

INTRODUCTION

Crohn's disease (CD) is a chronic inflammatory condition that affects the gastrointestinal tract, estimated to

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present itself during childhood or adolescence in 20% to 25% of patients[1]. The annual incidence of CD is increasing worldwide and is currently estimated at 3-5/100,000 children. The disease burden remains high as prevalence surpasses 0.3%[2-4]. Patients with childhood-onset CD followed through adulthood have a 2-fold increased risk of death compared to the general population[5]. Perianal involvement is a highly prevalent complication in CD patients and is estimated to occur over the course of the disease in approximately 30% of cases[6,7]. In newly diagnosed child CD patients, the prevalence of these complications, which are also known as perianal disease (PD), varies from 8% to 26%[6]. The reported prevalence of PD varies across studies depending on the definition applied and the characteristics of the cohort studied. It has been estimated that in the pediatric CD population the probability of developing PD within 1 and 5 years from diagnosis is 9% and 26%, respectively[8].

Perianal manifestations of Crohn's disease are associated with significant morbidity[5,7]. The newly updated guidelines of the European Crohn's and Colitis Organization and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ECCO/ESPGHAN) for management of pediatric CD state that the presence of severe PD is a predictive factor for poor outcome, thus justifying a more aggressive treatment approach that may include up-front biological therapy[9,10].

In recent years, biological therapies have begun to be used in the pediatric population, and these approaches currently play a key role in the management of several diseases. The management of PD has improved since the introduction of these therapies, reducing the number of surgical procedures and improving the quality of life of patients[9-11].

The aim of our study was to describe the demographic and clinical features of a sample of pediatric patients with Crohn's disease and to study the role of biological therapies in the management of perianal involvement.

MATERIALS AND METHODS

Settings and design

Data were extracted retrospectively from the medical records of patients diagnosed with CD in our institution between 2017 and 2021. To be included, all patients were required to have a minimum 6-month period of follow-up. Diagnosis of CD was based on widely accepted clinical, endoscopic, and histological criteria[12]. Data were retrieved retrospectively from medical records containing care-related information on anthropometric measures and clinical features, changes in medication, and surgical procedures when needed.

Study variables

Data including sex, age at diagnosis, and follow-up time were recorded for each patient. Patients were divided into 2 groups according to the presence of PD. Diagnosis of PD was based on physical or radiological examinations, often accompanied with symptoms. In particular, pelvic magnetic resonance imaging (MRI) was an important tool for diagnosing asymptomatic patients. In addition, we described the type of PD, distinguishing between patients with fistulizing disease (fistulae evidenced on MRI scan or physical examination, abscesses) and non-fistulizing disease (skin tags or fissures). Effective management of PD as evidenced by clinical and/or radiologic improvement during follow-up was recorded.

Disease phenotype at the time of data collection was mainly categorized according to the Paris classification[13]. The sample was divided into 3 groups based on disease location, i.e., exclusively colonic, exclusively noncolonic, and both locations. The two former categories were considered to comprise less extensive disease and the latter represented greater extension. Disease behavior was used to classify patients into those with non-penetrating and non-stricturing pattern (B1), stricturing pattern (B2), and penetrating pattern (B3). Complicated disease was described as fistulizing or stricturing pattern at some time during follow-up (B2 or B3). Growth impairment (G1) was defined as significantly lower than expected z-score for height at any time.

Data analysis

Analysis of the two main groups (perianal and non-perianal) was performed at the end of follow-up and the variables studied were age at diagnosis, extension of disease, rate of complicated disease, growth impairment, need for surgery, and use of biological therapy. Data gathered on biological therapy included time of therapy initiation, changes in treatment, and the need for more than one biological drug. Need for surgery excluded drainage of abscess due to the lack of uniformity in data, as some cases were treated in other center before starting follow up at our hospital, and others drained spontaneously.

Categorical variables were reported as frequency and percentage values and were compared using the chi-square test or Fisher's exact test, as appropriate. Continuous variables were compared for asymmetric distribution using the Mann-Whitney test. Non-normally distributed continuous variables were reported as median and interquartile range (IQR). All statistical tests were 2-tailed and $p < 0.05$ was considered to indicate statistical significance. Statistical analysis was performed using the SPSS program, version 17. This study was approved by the ethics committee of our institution.

RESULTS

Seventy-eight pediatric patients were included in this study. Of them, 50 (64.1%) were males and 28 (35.9%) were females. Median age at diagnosis was 10.5 years (IQR, 7.4-13) and median of follow up was 3.8 years (IQR, 1.5-5.8).

Table 1. Characteristics of patients according to the presence of perianal disease.

	Patients without perianal disease n = 63 (81.1%)	*Patients with perianal disease n = 15 (19.2%)*	*p*
Sex (male), n (%)	39 (61.9)	11 (73.3)	0.41
Age at diagnosis, yr, median (IQR)	10.7 (8.5-13.2)	8.8 (6-11.3)	0.08
PARIS age, n (%)			0.302
• A1a: < 10 yr	24 (38.1)	8 (53.3)	
• A1b: 10-17 yr	38 (60.3)	7 (46.7)	
• A2: > 17 yr	1 (1.6)		
Location			
• Paris classification, n (%)			
- L1: 1/3 distal ileum +/- cecum	6 (9.5)	1 (6.7)	
- L2: colon	8 (12.7)	5 (33.3)	
- L2L4a: colon + proximal to Treitz	5 (7.9)	3 (20)	
- L3: ileocolon	23 (36.5)	2 (13.3)	
- L3L4a: ileocolon + proximal to Treitz	8 (12.7)	2 (13.3)	
- L3L4b: ileocolon + distal to Treitz and proximal to 1/3 distal ileum	5 (7.9)	2 (13.3)	
- L4a: proximal to Treitz	7 (11.1)		
- L4b: distal to Treitz and proximal to 1/3 distal ileum	1 (1.6)		
• Other classification, n (%)			
- Colonic only	8 (12.7)	5 (33.3)	
- Extracolonic only	14 (22.2)	1 (6.7)	
- Colonic + extracolonic	41 (65.1)	9 (60)	
• Extension, n (%)			0.712
- Lesser: colonic or extracolonic	22 (34.9)	6 (40)	
- Greater: colonic + extracolonic	41 (65.1)	9 (60)	
PARIS behavior, n (%)			
• B1: inflammatory	53 (84.1)	12 (80)	
• B2: stricturing	9 (14.3)	2 (13.3)	
• B3: penetrating	1 (1.6)	1 (6.7)	
Complicated disease, n (%)			0.707
• No (B1)	53 (84.1)	12 (80)	
• Yes (B2 and/or B3)	10 (15.9)	3 (20)	
PARIS growth, n (%)			0.003
• G0: no	59 (93.7)	9 (60)	
• G1: yes	4 (6.3)	6 (40)	
Follow up time, yr, median (IQR)	4 (1.4-5.5)	5.8 (2.7-7.6)	0.03

Perianal disease group

Fifteen out of 78 patients (19.2%) developed PD. Of these patients, 5 had non-fistulizing disease and 10 had fistulizing disease. Regarding the initial diagnosis of the latter group, 8 of 10 presented with perianal abscess and the remaining 2 patients were diagnosed due to incidental findings of intersphincteric fistulas on routine pelvic MRI scans. One of these initially asymptomatic patients presented an infected ulcer and rectal stenosis during follow-up. Eight patients presented PD at diagnosis and seven developed PD during follow-up within a median of 12 months from diagnosis (IQR, 7-24).

Most patients with PD (14/15, 93.3%) received biological therapy. Adalimumab was first-line therapy in 10 patients, and ustekinumab was the second choice when a change of biological treatment was necessary. Infliximab was used as first-line therapy in the rest of the patients, and adalimumab was the second drug in these cases.

As for the treatment of PD, 3 of 15 patients presented torpid evolution. Among these 3 patients, one needed multiple procedures including initial temporary fecal diversion to control her PD, which was presented as chronic destructive ulcer. Finally, total proctocolectomy with abdominoperineal resection and permanent ileostomy was performed in this case due to progression of both colon and perianal disease. Other patient with fistulizing PD needed seton placement for resolution of repeated abscesses, and periodically medical treatments for chronic perianal ulcer. The third patient with bad evolution had chronic perianal ulcers which required several changes in biological therapies to reach management.

Demographic and clinical characteristics of the perianal and non-PD groups are summarized in table 1. Regarding

Table 2. Medical treatment with Biological Therapies (BT) and need for surgery according to the presence of perianal disease.

	Patients without perianal disease n = 63 (81.1%)	*Patients with perianal disease n = 15 (19.2%)*	*p*
Need for BT, n (%)	34 (54)	14 (93.3)	0.005
Onset of BT from diagnosis, yr, median (IQR)	0.6 (0.24-1.7)	1.23 (0.3-3.2)	0.177
Number of BT used, n (%)			0.005
• One	29 (85.3)	6 (42.9)	
• More than one	5 (14.7)	8 (57.1)	
Need for surgery, n (%)	3 (4.8)	2 (13.3)	0.244

sex, 11 (73.3%) patients in the PD group were males and 39 of 63 (61.9 %) of patients without PD were males, with no statistically significant differences between both groups (p = 0.407). Median follow-up was significantly higher in the PD group (5.8 years, IQR 2.7-7.6 vs. 4 years, IQR 1.4-5.5; p = 0.03).

Of all, only one patient was older than 17 years-old (subgroup A2). We observed a trend toward earlier age at diagnosis in PD group, as median was 8.8 years (IQR, 6-11.3) compared to 10.7 years (IQR, 8.5-13.2) in non-PD group, although not reaching statistical significance (p = 0.081).

Regarding location of disease, no significant differences were found when patients were divided between less extensive disease (exclusively colonic and exclusively noncolonic) and more extensive disease (colonic and extracolonic involvement) (p = 0.71).

When studying disease behavior in all patients, we found that 65 (83.3%) were B1, 11 (14.1%) were B2, and 2 (2.6%) were B3. A comparison of behavior between PD and non-PD patients revealed no significant differences, as the rate of aggressive pattern was similar in both groups (B2 or B3 PD patients, 20% vs. B2 or B3 non-PD patients 15.9%; p = 0.707). PD group had significantly more growth impairment at diagnosis or during follow-up than non-PD group (40% vs. 6.3%, respectively, p = 0.003).

PD group received more biological therapy than non-PD group, as this treatment was necessary at some point in 93.3% and 54% of patients, respectively (p = 0.005) (Table 2). In addition, higher percentage of patients with PD required more than one biological drug compared to non-PD patients (57,1% vs. 14.7%, respectively, p = 0.005). Regarding time to initiation of biologics, no significant differences were observed between both groups (non-PD 0.6 vs. PD 1.23 years; p = 0.177).

Surgical treatment was necessary in 3 of 63 patients without PD (4.8%) and in 2 of 15 patients with PD (13.3%), though no significant differences were observed (p = 0.244) (Table 2). Surgical treatment in the non-PD group included terminal ileal resection in one patient and ileocaecal resection in another patient. Indication for surgery was intestinal obstruction due to luminal stenosis in both patients. In a third patient without PD, a terminal ileum resection was performed due to persistent inflammatory activity, which could not be manage with medical treatment.

Of all patients, 57 (73%) are in ongoing follow-up by our inflammatory bowel disease unit, 18 were discharged to an adult transition unit, and 3 did not complete follow-up for different reasons.

DISCUSSION

In this study, we evaluated phenotypic features, medium-term disease-specific outcomes, and the role of biological therapy in a medium-sized cohort of pediatric patients with CD according to the presence of perianal findings.

Interestingly, phenotype-related features such as sex or age at diagnosis did not differ significantly between groups, although patients with PD had a younger age at diagnosis, similar to the findings of Short et al.[14]. In contrast, another study showed that the group with the oldest age at diagnosis (17-21 years) had a higher rate of PD than younger children[8]. Previous pediatric studies have demonstrated an association between PD and sex, though this association has been found for female sex in some research[7] while other study has found a relationship with male sex[15].

Some phenotypic features have been related to PD, such as low body mass index or Black and South Asian ethnicity[14,16]. None of the studies reviewed that compared pediatric patients with and without PD reported an association between any other specific features and a more severe phenotype or luminal complications[7,14,15].

In contrast to previous studies performed in adults, we found no association between PD and a more complicated disease's course including internal fistulizing and/or structuring disease[17,18]. Attempts to determine whether PD in children predicts B2 and/or B3 disease have yielded contradictory findings[7,19,20]. Although the effect estimated was in the direction of an increased risk of B2/B3 disease in children with PD, this did not achieve statistical significance[16], as in our study.

In addition, no differences in disease location were shown between the two groups. A major percentage of isolated colonic location (L2) was obtained in PD group, though this failed to reach statistical significance. A similar finding was obtained by Keljo et al., although location categories were not specified[21]. We decided to unify categories regarding disease location as our sample was not as large as those reported in other studies. Using different categories from those commonly studied in the literature makes it difficult to compare our results to previous research. Overall, 3 pediatric studies examined whether disease location predicts the development of PD over time, and all concluded negatively[19,22,23].

As mentioned before, pediatric onset of CD is associated with more severe disease than adult-onset cases, and growth impairment due to CD starting in childhood may have a great impact on the patient´s further development[5,16,24]. In our study, we found that PD was associated with growth deficiencies during follow-up. Other pediatric studies conclude that PD does not predict linear growth impairment[20,25].

Prognostic factors for surgery have been studied in pediatric CD patients, including diagnosis during adolescence, growth impairment at diagnosis, NOD2/CARD15 polymorphisms, complicated disease behavior, and positive anti-Saccharomyces cerevisiae antibody status[16]. Perianal disease was not among the factors previously examined[19]. In our study we found no association between PD and an increased risk for surgery. This finding could be attributed to the higher use of biological treatment in the PD group, thus altering the natural history of the disease, but also to the fact that drainage of abscess was excluded. Moreover, the lack of association may be related to the low number of patients with PD included, which may have limited the power of prediction analyses.

Use of biological therapy

Anti-TNFα treatment is currently recommended as induction therapy for children with active perianal fistulizing disease; when necessary, anti-TNFα may be combined with surgery[11]. We observed an increased risk for biological therapy in children with perianal findings. In addition, refractoriness to treatment was higher in these patients since they required further modifications in biological treatment, which increased the complexity of management and disease burden. Combination therapy with an immunomodulator was not recorded, and this may have influenced our findings.

Adalimumab (ADA) was first-line biological treatment for most patients, followed by Infliximab (IFX). Change of biologic drug was indicated if blood therapeutic level was not achieved. There is a lack of studies comparing the efficacy of different anti-TNF in children, and there is also scarce evidence in adults. In a retrospective small-sized study, no differences were found in clinical efficacy when comparing IFX and ADA for the treatment of perianal fistulas[26].

As mentioned, the updated ECCO/ESPGHAN guidelines suggest early initiation of biological therapy when severe perianal disease is presented[10]. Several studies described an earlier initiation of biological treatment in PD patients[7,15,22]. In contrast, initiation of biological therapy was not significantly earlier among non-perianal disease patients in this study. One possible explanation may be that we chose not to distinguish between severe and mild PD, and the latter condition is not considered for this recommendation.

Limitations

This study has several limitations. Due to its retrospective nature, we collected no data on immunomodulator use, NOD2/CARD15 genetic factors, or disease-specific outcomes such as time to first hospitalization. Some perianal findings might have been missed even though perianal examination is a mandatory part of the physical examination in our center. Additionally, data on routine pelvic MRI scans were not recorded in all cases. Our findings should be interpreted with caution as they are based on a relatively small sample of patients and as a result few differences reached statistical significance; however, there are not many large series in children. This study was performed on a relatively homogeneous population of Spanish children who may have distinct phenotype features, which may have caused them to differ from other populations.

CONCLUSION

CD patients with PD seem to need more aggressive treatment, with biological therapy currently playing a key role in more complex patients. In our study, these patients did not start biological therapy sooner, but once the treatment began, they tended to require a change in strategy to control the disease. Patients with PD require increased nutritional support and intensified medical treatment with closer follow-up to reduce growth impairment.

Surgery could be necessary in a small proportion of pediatric patients with Crohn disease when acute intraluminal complications appear, and medical treatment fails.

Large-scale prospective studies are required to determine disease-specific features and ascertain whether this condition predisposes patients to higher rate of complications, earlier onset of biological treatment, and worse clinical outcomes overall.

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