Outcomes of Pediatric Fistulising Perianal Crohn's Disease

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ABSTRACT

Background: *Perianal disease is reported more widely in pediatric Crohn patients than in the past, and has been stated as an independent modifier of the disease behavior. In this study, we aimed to analyze the clinical characteristics and outcomes of fistulising perianal Crohn's disease (fpCD) in the pediatric age group.*

Methods: *A total number of 149 children with an established diagnosis of inflammatory bowel disease who have been diagnosed before 18 years of age and followed in our tertiary center were revised. Clinical, endoscopic, laboratory, and radiologic data of 50 patients with CD, who had at least 18 months follow-up data, were compiled.*

Results: *Of 50 patients, 26 (52%) were diagnosed as fpCD (38% at onset). More than half of the patients without any notable external orifices around the perianal area were diagnosed as fpCD by an magnetic resonance imaging (MRI). Pediatric fpCD patients had a higher disease activity score and platelet count, lower serum albumin level, and a higher rate of granuloma in the biopsy samples, compared with non-fistulising patients. A considerably high rate of surgical interventions (i.e., seton placement 46% and abscess drainage 15%) was performed in combination with infliximab.*

Conclusion: *Fistulising perianal Crohn's disease seems to be more common than previously reported in the pediatric age group. A severe course of the disease might serve as a warning for the development of fpCD. A careful physical examination and use of perianal MRI with a high index of suspicion may increase the likelihood of fistula detection, hence may change the treatment strategy.*

Keywords: *Pediatric, perianal fistulising Crohn's disease, seton*

INTRODUCTION

Pediatric Crohn's disease (CD) is associated with widespread involvement, severe and progressive course compared to the adults.[1-3] Presence of perianal lesions in Crohn's disease has been stated as an indicator of disease activity and a predictive factor for poor outcome.[4-6] Complaints related to perianal Crohn's disease such as pain or pruritus, purulent drainage, and bleeding also impair the quality of life.

Perianal disease is thought to be more common and more aggressive in patients with pediatric-onset CD, and the incidence ranges from 8% to 24% in pediatric patients.[6-9] This wide range of incidence of fistulising perianal CD (fpCD) can be attributed to the practical limitations as well as the limited experience in interpreting radiologic imaging, especially in childhood. The low index of suspicion and limited use of radiologic imaging of the pelvis and perianal area might underestimate the prevalence of fpCD. The prompt recognition of fpCD is very important not only for the treatment plan but also for relieving the symptoms and improving the quality of life. Though medical and surgical treatments are often partially effective, initiation of antibiotic treatment, surgical drainage, and seton placement when applicable, and avoiding steroid therapy are prerequisites for controlling the inflammation and improving the growth in children.[1,10,11]

Being a referral center for pediatric inflammatory bowel disease (IBD), the purpose of this study was to describe clinical, laboratory, and therapeutic outcomes of perianal fistulising CD in the pediatric age group.

MATERIALS AND METHODS

A total number of 149 children with an established diagnosis of IBD (63 CD, 84 ulcerative colitis, 2 unclassified IBD) who had been diagnosed before 18 years of age and followed in our tertiary center were revised. Clinical, endoscopic, laboratory, and radiologic data, recorded prospectively in our IBD database were compiled. Patients, whose follow-up was less than 18 months or those with

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an identified monogenic defect, were excluded. Fifty out of 63 CD patients who had a minimum of 18 months follow-up data, and underwent meticulous evaluation were enrolled in the study.

In Paris classification, perianal disease modifier "p" has been recommended to be used only for perianal disease with fistula, anal canal ulcer, or abscess.[4] Consistent with this description, fpCD was defined as the existence of either fistula and/or abscess in the perianal region. Patients with suspicious perianal findings such as non-inflamed but prominent skin tag, inflamed skin tag, notable anal fissure, or orifices around the perianal area all underwent a perianal magnetic resonance imaging (MRI). The images were obtained with a 1.5 T MR scanner (Magnetom Vision, Siemens, Germany) using the sequence of parameters as T1-weighted axial and coronal spin-echo (slice thickness, 4 mm; gap, 0.4 mm), T2-weighted axial, and coronal turbo spin-echo (slice thickness, 4 mm; gap, 0.4 mm), axial and coronal Short tau inversion recovery (slice thickness, 5 mm; gap, 0.6 mm), axial and coronal T1 weighted gradient echo with fat suppression (slice thickness, 5 mm; gap, 0.5 mm). Meglumin gadoterate was used as gadolinium-based contrast agent. The localization and characteristics of fistulae were categorized according to the Parks classification.[12] The Van Assche MRI score was used to delineate the anatomy and to assess the inflammatory activity at the time of initial diagnosis of fpCD.[13] Patients were stratified according to the presence or absence of fistulising perianal disease at diagnosis or developing one during the follow-up.

The disease phenotype was assessed by using the Paris classification, and disease activity was evaluated according to the parameters dictated by the Pediatric Crohn's Disease Activity Index (PCDAI).[4,14] Demographic data, growth parameters (z scores for the weight for age, height for age and body mass index), laboratory tests [leukocyte and platelet counts, C reactive protein (CRP), serum albumin and ferritin levels, erythrocyte sedimentation rate (ESR)] and disease activity were noted both at diagnosis and during the follow-up period. The cessation of drainage from the external orifice, healing of external orifices, and remission of clinical signs and symptoms were the criteria of response to the treatment. In case of unremitting clinical symptoms and aggravated perianal findings, patients underwent control MRI. The patient database was reviewed for the pharmacological agents used for induction and maintenance therapy as well as the surgical interventions (seton placement, drainage, resection), applied.

The study was approved by the local Ethics Committee of the university. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki.

Statistical Analysis

Descriptive analyses of the cohort were given as proportion, mean ± standard deviation (SD), or median (min; max). Continuous data were compared using Student's *t*-test or the Wilcoxon rank-sum test, as appropriate, for the distribution normality. Chi-square test or Fisher's exact test were applied for comparisons and categorical variables were reported as frequency and percentage. The Statistical Package for the Social Sciences (SPSS) version 22 was used for statistical analyses (IBM Corp.; Armonk, NY, USA). The statistical significance was considered as $P < .05$.

RESULTS

In our study group, 36/50 (72%) of the patients had the perianal disease. Most of the patients 23/36 (64%) had mild/moderate perianal signs and symptoms such as prominent skin tag, inflamed skin tag, notable anal fissure or mucosal tear with mild or moderate discharge, and induration along with the restriction of daily activities. Whereas 36% of the patients had fistulae orifices around the perianal area with or without undermining the skin and concomitant discharge, enduration, activity restriction, discomfort. Perianal MRI was performed all in those 36 patients with suspicious perianal findings. Fistula was verified in 56.5% (13/23) of patients with mild/moderate perianal signs and symptoms by perianal MRI.

Overall 26/50 (52%) of the patients with CD had fistulising perianal disease. Fistulising perianal disease (fpCD) was detected in 19 patients (38%) at diagnosis, while 7 patients (14%) developed fpCD during the course of the disease. Of 26 patients with perianal fistula, 19 (73%) were male, and the mean age at diagnosis was 14 ± 2.5 years. Disease location was ileocolonic in 65% of the fistulising patients, and most of them (66%) had upper gastrointestinal system involvement as well. The mean age at diagnosis and disease location were comparable between fistulising and non-fistulising patients. The rate of consanguinity among the parents in patients with fpCD was higher than in non-fistulising patients (30% vs. 12%, $P > .05$) (Table 1).

At diagnosis, the disease behavior was inflammatory in all of the patients with fpCD except 2 patients. MR enterography revealed stricturing and/or penetrating disease behavior in those 2 patients. Most of the

Table 1. Characteristics of the Patients at Diagnosis

	fpCD (+) (*n* = 26)	fpCD (–) (*n* = 24)	*P*
Gender (male)	73%	41%	**.025**
Age at diagnosis (years; mean ± SD)	14 ± 2.5	12 ± 4.6	.21
Duration of follow-up (months)	38 ± 21 (median = 28)	68 ± 36 (median = 66)	**.001**
Consanguinity (%)	30%	12%	.17
HFA Z score (mean ± SD)	–0.6 ± 0.9	–0.5 ± 0.9	.67
WFA Z score (mean ± SD)	–1.1 ± 0.9	–0.9 ± 1.6	.61
BMI Z score (mean ± SD)	–1.1 ± 1.3	–0.5 ± 1.5	.14
L1[1]	15.3%	12.5%	1.0
L2[1]	4%	8%	.6
L3[1]	65%	70%	.76
L4A[1]	61%	66%	.9
WBC × 10^3/μL (mean ± SD)	10.2 ± 2.9	11.3 ± 4.08	.29
PLT × 10^3/μL (mean ± SD)	594 ± 157	482 ± 163	**.03**
CRP (mg/L) (mean ± SD)	46 ± 39	37 ± 37	.44
ESR (mm/h) (mean ± SD)	53 ± 24	54 ± 25	.87
Albumin (g/dL) (mean ± SD)	3.2 ± 0.6	3.6 ± 0.4	**.015**
PCDAI scores (mean ± SD)	39 ± 10	29 ± 11	**.004**
Presence of granuloma (%)	50%	20%	**.03**
Rectal involvement	50%	41.6%	.55
Extraintestinal manifestations	19.2%	20.8%	.88

fpCD, fistulising perianal Crohn's disease; SD, standard deviation; HFA, height for age; WFA, weight for age; BMI, body mass index; WBC, white blood cells; PLT, platelets; CRP, C reactive protein; ESR, erythrocyte sedimentation rate; PCDAI, pediatric Crohn's disease activity index.
[1]Paris Classification/Location.

patients (77%) with fpCD had intersphincteric fistulae, and 4 of 26 patients had concurrent abscess formation (Figure 1). The characteristics of the fistulas according to MRI-based Van Assche classification were stated in Table 2. At enrollment, 23 out of 26 patients (88%) had moderate to severe disease activity, and the PCDAI score was higher in patients with fpCD compared to those without a fistula.

The median weight for age, height for age, and body mass index Z scores at diagnosis were –1.1 (range = –2.9 and 0.9), –0.6 (range = –2.6 and 1.5), and –1.1 (range = –4.5 and 0.8), respectively. There were no differences in weight for age, height for age, and body mass index Z scores between fistulising and non-fistulising CD patients. The number of patients with a moderate or severe growth delay (*Z* score <–1 SD) was comparable between the groups. Similarly, acute phase reactants such as leukocyte counts, CRP levels, ESR rates, rectal involvement, and the rate of extraintestinal manifestations were comparable between fistulising and non-fistulising CD patients. However, patients with fpCD had higher platelet counts and lower serum albumin levels compared to CD patients without any fistula. Furthermore, granulomas were detected in the histopathologic evaluation of the biopsy samples in half of the fistulising but only in 20% of the non-fistulising patients, and the difference between groups was statistically significant ($P < .05$) (Table 1). The duration of mean follow-up was 53 ± 26 months (median 51) in this cohort. Seven patients with CD developed fistulising perianal disease during the follow-up period, and all of them had had moderate to severe disease activity at diagnosis. The duration of median follow-up until the development of a fistula was 20 months (range = 13-48 months).

When non-fistulising CD patients (*n* = 24) were compared to the ones who developed fpCD during the follow-up (*n* = 7), there were no significant difference in age at

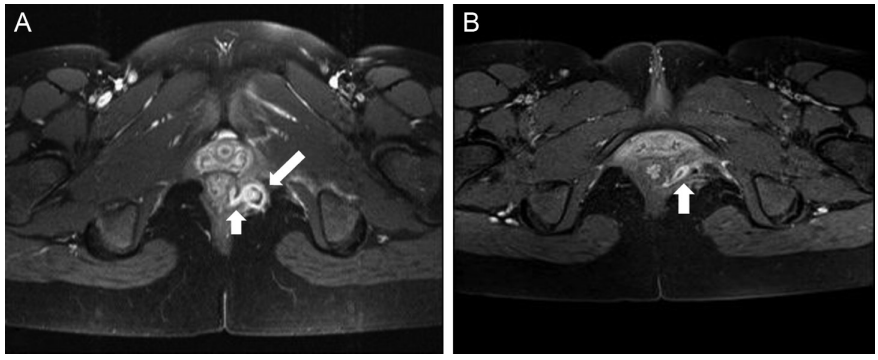

Figure 1. Axial contrast-enhanced T1W MRI images. (A) Abscess (long arrow) and intersphincteric fistula tract (short arrow). (B) Seton placed through the fistula (arrow), and a drained abscess is not visible.

diagnosis, growth parameters, and acute phase reactants. On the other hand, patients who developed fpCD during the follow-up period had higher PCDAI scores, and higher rates of granuloma in biopsy samples at diagnosis. The rate of remission in patients with fpCD at the end of the first year was lower than the CD patients without fistula, and the differences between the groups were statistically significant.

In this cohort, all patients with fpCD were consulted with the same surgeon who was specialized in IBD surgery, 1 of the patients presented with ileus at diagnosis, and underwent surgery for segmental resection of the ileocolonic stricture. Two patients with fpCD at diagnosis had concurrent abscess formations, and required surgical drainage as well. Patients with abscesses received intravenous antibiotics (metronidazole and/or ciprofloxacin) for 4-6 weeks at the initial stage of the treatment. Nine out of 19 (47.4%) patients who had fpCD at diagnosis required seton (non-cutting) placement on the account of active or complex fistula. All of the patients with fpCD were treated with infliximab eventually. A patient with fpCD who was treated with infliximab, underwent segmental bowel resection due to unresolved partial obstruction. All patients with fpCD who were given infliximab as induction treatment, received the combination of infliximab and an immune modulator for the maintenance except one. In that patient, infliximab was discontinued on the account of anaphylaxis, developed during the infusion. Despite the presence of fistulising perianal disease at presentation, 4 patients who refused infliximab therapy, received steroids for induction. Later, therapy had to be switched to infliximab due to the active disease and unremitting symptoms in 3 of them. Treatments, the follow-up data, and the outcome at the end of 18 months were given as a flow chart in Figure 2.

Table 2. The Characteristics of the Fistulae According to MRI-Based Van Assche Index

Descriptor	Categories	*n* (%)
Number of fistula tracts	Single, unbranched	19 (73)
	Single, branched	1
	Multiple	6
Location	Extrasphincteric or intersphincteric	20 (76.9)
	Transsphincteric	3
	Suprasphincteric	3
Extension	Infralevatoric	25 (96.1)
	Supralevatoric	1
Hyperintensity on T2-weighted images	Pronounced	8 (30.7)
Collections (cavities >3 mm in diameter)	Present	4 (15)
Rectal wall involvement	Thickened	3 (11.5)

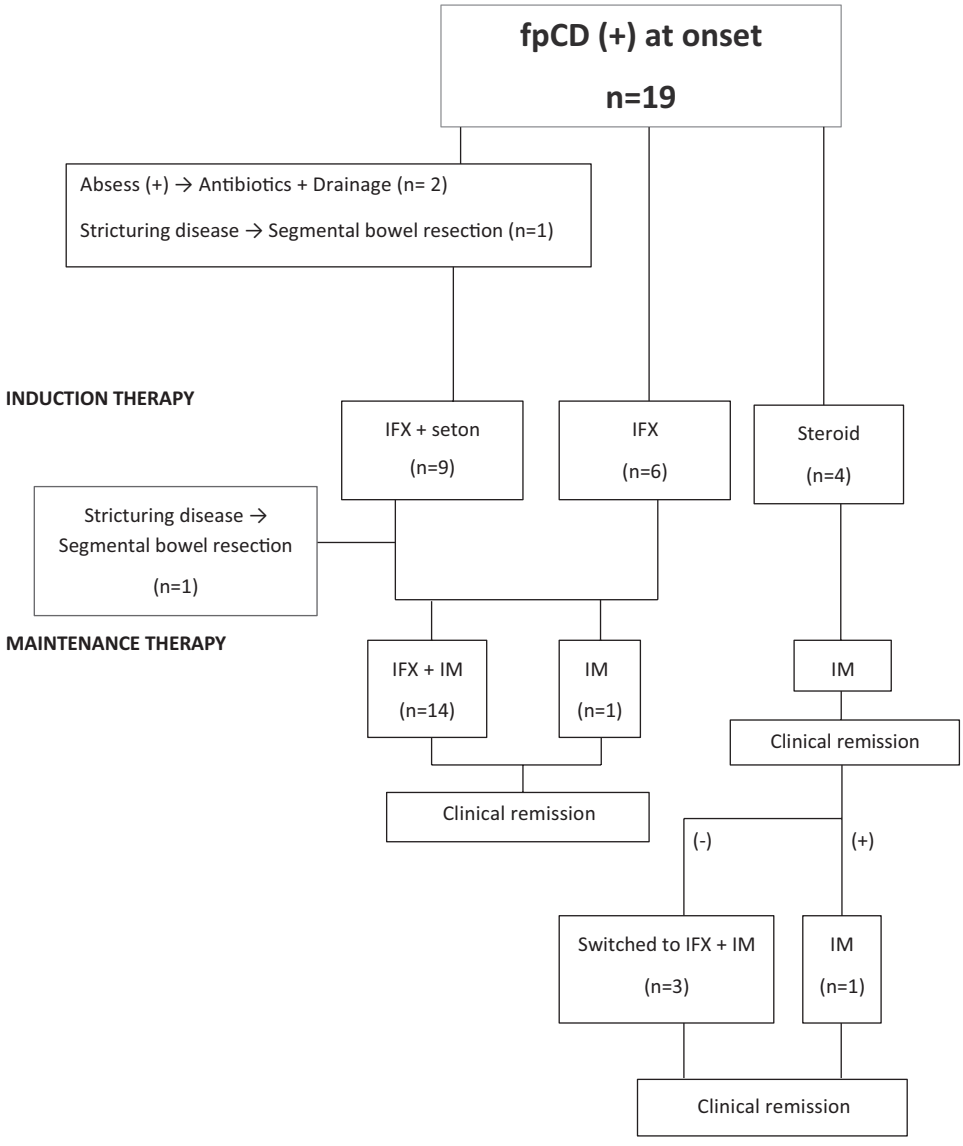

Figure 2. Treatment strategy and outcome at 18 months follow-up in patients with fpCD at the onset.

Patients, who developed fpCD during the course of the disease, had received steroids as induction treatment. Two of them had a concurrent abscess, and underwent surgical drainage while receiving antibiotic treatment. Seven patients who developed fpCD during the follow-up were treated with a combination of infliximab and immune modulator, and 3 out of 7 of them also required seton drainage (Figure 3).

In this cohort, healing of the fistula orifice took place within 6 months at the latest, at the end of infliximab induction therapy at the earliest. Since setons maintain the patency of the fistula tract and external cutaneous orifice, cessation of drainage has to be accepted as an indicator for monitoring the response to the treatment in those. Setons were usually removed 6-12 months after the placement. Patients with abscesses were the ones in whom setons were kept longer. All of the fistulising patients were free from perianal symptoms and abscess formation in the course of 18 months follow-up (Figure 1).

During the follow-up, 4 patients (8%) required major surgical intervention due to penetrating and/or stricturing disease. However, there was no statistically significant difference regarding the surgical requirement between patients with or without fpCD.

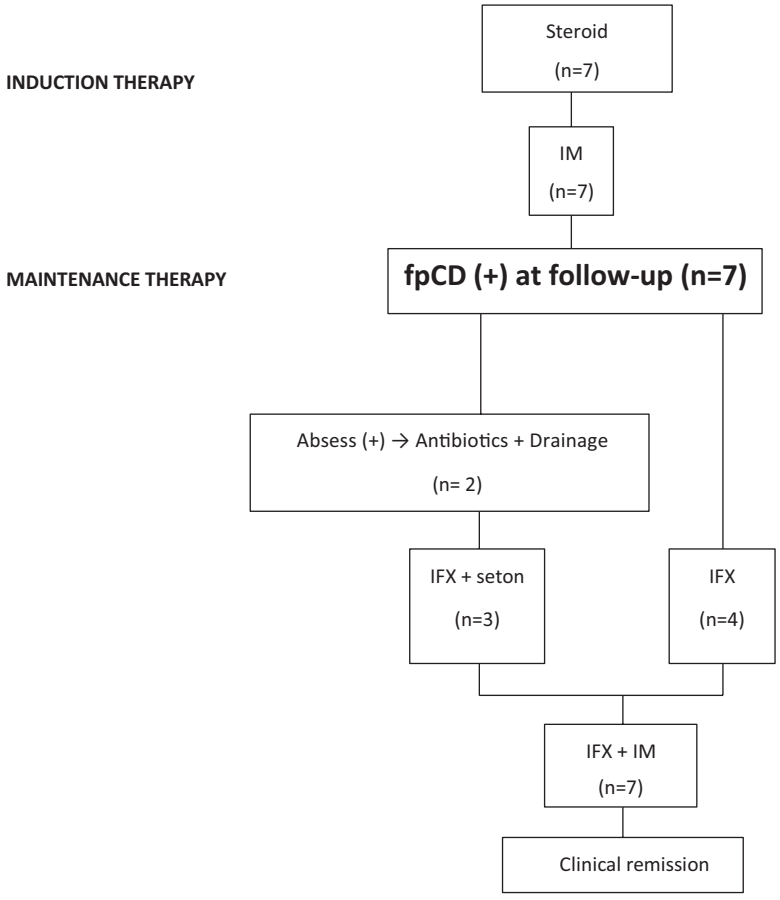

Figure 3. Treatment strategy and outcome at 18 months follow-up in patients who developed fpCD at the follow-up.

DISCUSSION

The perianal CD is associated with a rather aggressive and debilitating course in adults.[8,15] Furthermore, it has been stated in the pediatric guidelines that severe perianal disease is a precursor of poor outcome in the course of the disease.[16] However the prevalence, clinical features, phenotypes, and outcomes of perianal CD have scarcely been published in the pediatric age group.[17-21]

Evidence-based data suggest approximately 8% to 13% of children with CD have perianal fistula at diagnosis. However, there is a limited number of studies, looking into the development of perianal fistula during the course of the disease, and these figures vary between 5-27%.[21] In this cohort of 50 pediatric CD, fistulising perianal disease was discovered in more than half of the patients, and 38% of them had a fistula at diagnosis. The prevalence was obviously higher than the previously reported multi-center data.[17-24] This wide range of prevalence, reported in those multi-center studies might be due to the heterogeneity of both diagnostic approaches and the facilities of the centers. This study was carried out in a university hospital, which is a tertiary center for the referral of complicated IBD patients, and this might contribute to the higher rate of perianal fistulising disease in the study group.

There was a striking male predominance, consistent with the previous reports, in our patients with fistulising perianal disease.[17,23] Though inflammatory indicators such as leukocyte, CRP level, and ESR rate were similar in fistulising and non-fistulising patients; serum albumin level was lower, platelet count and PCDAI scores were higher in patients with fistula in the study group. Patients who developed fistulae during the course of the disease had higher disease activity at the onset, and had lower remission rate at the end of the first year of treatment. These data in children with CD emphasize the higher inflammatory activity at diagnosis was associated with the development of a fistula at follow-up. In contrast to previously published reports,[24,25] the indicators of growth were

comparable between the fistulising and non-fistulising CD patients in this study.

Non-caseating granulomas have been considered as one of the characteristics of histologic diagnosis of CD. Studies, investigating the clinical and prognostic significance of granuloma in CD have indicated rather aggressive disease phenotype, poor outcome in both adults and children.[17,23,25-28] The presence of epitheloid granuloma was verified in half of our patients with fistulising CD, which is consistent with the published data.[24,28] Furthermore, patients who developed fpCD during the follow-up, had a higher rate of granuloma at diagnosis compared to ones who did not develop fistulae.

The perianal region should be examined with a high index of suspicion and caution, since the recognition of CD with fistulising perianal disease is crucial for the management of treatment. In the pediatric age group, there is no evidence-based data regarding the diagnostic approach for fpCD. In the current Paris classification of pediatric IBD, "p" is an identifier for the perianal disease, and it has been recommended to be used in the presence of fistula, abscess, or ulcer in the perianal region.[4] On the account of this definition, the absence of an orifice around the perianal area might hinder the diagnosis. In our study group, more than half of the patients without any notable external orifice (i.e., mild/moderate perianal disease) had got the diagnosis of fpCD only after a perianal MRI imaging. At times, an attentive examination of the perianal area may be impossible particularly in reluctant adolescents. Therefore, the diagnosis of perianal disease should include imaging modalities along with physical and endoscopic examinations. In adult guidelines, examination under anesthesia (EUA), endoanal ultrasound (EUS), and fistulography have been stated as useful diagnostic modalities for fistulasing perianal disease, however, there are practical limitations in the pediatric age group. Perianal/pelvic magnetic resonance imaging (MRI), which is a highly accurate, non-invasive, and safe imaging technique, is considered the gold standard for the diagnosis of perianal CD.[10,11,28] We suggest that perianal MRI in patients with suspicious perianal lesions in this cohort doubtlessly facilitated the diagnosis, consequently this relatively high prevalence of the perianal disease.

Comprehensive radiological imaging and an experienced radiologist are obligatory not only for detection but also for the description of fistulae anatomy. Additional information regarding the presence of an abscess is also required for planning the medical and/or surgical therapeutic interventions. In this cohort, seton placement (12 patients) and concurrent abscess drainage (4 patients) were performed with the guidance of perianal MRI in fistulising patients. In 3 of those patients, abscesses were deeply located, and could only be identified by a perianal MRI. As expected, seton placement prevented the recurrence of the abscess and improved perianal symptoms. It has been reported previously that perianal fistulising CD is associated with a higher surgical resection rate, mostly in adults.[7,29] There are few studies in the pediatric age group, reporting a higher rate of intestinal resection in patients with perianal disease.[25,30] Even though a small number of patients required surgical interventions in our cohort, no difference was found between fistulising and non-fistulising groups.

In this single-center study, homogeneity of the clinical practice, close monitoring and prospectively recorded data potentiated our results. Fistulising perianal Crohn's disease seems to be more common than previously reported in the pediatric age group. A careful physical examination of the perianal area and a perianal/pelvic MRI in children with a high index of suspicion would enhance the rate of detection of fistulae. Besides, the severe course of the disease starting from the onset might serve as a warning for the development of fpCD. Prompt recognition of fistulising perianal disease might alter the treatment strategy and improve quality of life.

Ethics Committee Approval: The study was approved by the local Ethics Committee of the university.

Informed Consent: Informed consent was obtained from each patient included in the study.

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