Title:

Perianal Crohn's disease: clinical implications, prognosis and use of resources

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Perianal Crohn's disease: clinical implications, prognosis and use of resources

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List of abbreviations: Crohn's disease (CD), perianal disease (PD), inflamatory bowel disease (IBD), extra-intestinal manifestations (EIM), examination under anaesthetic (EUA), magnetic resonance of the pelvis (MRI pelvis), magnetic resonance enterography (MR enterography) computed tomography enterography (CTE).

Conflicts of interest: all authors declare that in the conception and development of this work there exists no conflict of interest.

ABSTRACT

Aim of the study: to investigate the prevalence of perianal disease, the associated phenotypical factors, its influence over prognosis and its impact in the use of health resources for patients with Crohn's disease.

Methods: a unicentric retrospective observational study in which we include 430 patients with Crohn's disease tracked through a monographical consultation of intestinal inflammatory disease.
We analysed demographic and phenotypical data of Crohn's disease, pharmacological and surgical treatments, complementary tests carried out and hospital admissions, carrying out also a comparative study between those patients without perianal disease and those with perianal disease in simple both form and complex form.

Results: the prevalence of perianal disease was 40.2%, with fistulas and abcesses being the most frequent manifestations. These appearences were associated with rectum affected and the existence of extra-intestinal manifestations. The patients with perianal disease most frequently required immuno-suppressant and biological treatment, but no further abdominal surgery. Amongst the patients with perianal disea-se there was also more frequently the need of biologics to luminal disease (42.8% vs. 30.7%). Furthermore, it required a greater use of explorations aimed at the studio of perianal disease and recto-colonoscopies, but not more MR/CT enterography.

Conclusions: perianal disease has a high prevalence among patients with Crohn's disease, especially when the rectum is affected. It is associated with a worse prognosis, requiring more frequently biological treatments as much because of perianal evolution such as luminal, especially in cases of complex perianal disease. This condition calls for more hospital admissions and the carrying out of complementary tests.

Keywords: Crohn's disease. Perianal disease. Health costs. Biological therapy.

INTRODUCTION

In patients with Crohn's disease (CD) one of the more debilitating complications is perianal disease (PD), whose prevalence fluctuates from 17-43% depending on the series (1). This varies in function to the luminal location, from 12% in patients with isolated ileum affected to 92% when the rectum is affected (2).

The terminology PD in the context of CD makes reference to a conjunction of anomalies either in an isolated form or in combination which appear in the anorectal region. The spectrum of lesions includes fissures, fistules, abcesses, cutaneous folds or 'skin tags' and stenosis. In clinical practice they are classified as simple and complex to make therapeutic decisions.

The timing of diagnosis of PD is usually after that of CD, however, up to 17% of patients with CD start with a perianal pathology which comes from years of intestinal symptoms.

PD is characterised as a prognosis factor in the detrimental progression of CD, as its presence at that very moment associates itself with a worse luminal evolution. It has been seen to be linked to a ra-pid progression, a more aggresive action of the disease, changes in the extent of its location, needing greater biological medication, hospitalisa-tions and surgery both perianal as wel as abdominal. It is estimated that up to 50% of CD cases with PD may require abdominal surgery, along side a greater risk of postoperative recurrence with a shorter time between these recurrences, especially in cases of complex PD.

All these factors entail a heavy economic burden, which in terms of health costs - pharmaceutical and hospital- compels us to optimise the

expenditure of available resources.

The main objective of our study was to quantify the expenditure of hos-pital resources among patients with PD associated CD and compare it with CD patients without that association, similarly correlating simple and complex forms in patients with PD. Next, we aimed to learn the prevalence of PD with CD within our own surroundings and the effect of its presence over the prognosis and evolution of CD.

MATERIALS AND METHODS

A unicentric retrospective descriptive study in which 430 patients with CD were included from a monographic consulta-tion of inflammatory bowel disease (IBD) from 2007 to 2019. The diagnosis of CD was carried out based on clinical, radiological, endoscopic and histopathologic clasical criteria of Lennard-Jones (11).

Clinical data were collected from the digital clinical history resource (SIDCA), analysing epidemological factors suc as age at diagnosis of IID, gender and smoking habit.

Phenotypical characteristics of CD were defined according to the Montreal classification (12), specifying the presence of rectum affected and extraintestinal manifestations (EIM).

PD was considered to be the presence of any of its manifestations (fissures, fistulas, abcesses, cutaneous folds/skin tags and stenosis, considering it to be complex the presence of high fistulas, with many ori-fices, abcesses, pain or fluctuation, rectovaginal tract or anal stenosis. Furthermore, the date of diagnosis of PD was recorded and its chronological relation with the diagnosis of CD.

We analyse the need for immunomodulator and biological treatments -including indication-, hospital admissions and surgeries related with PD during its development. As to the surgery it is specified if it was through luminal pathology (resection surgery, traffic reconstruction or reinter-vention) or perianal exploration under anaesthetic (EUA), the number of interventions, discharge ostomies and the requirement of local treatment of PD with stem cells or platelets.

Health resources expenditure was analysed in 187 patients whose diag-nosis took place from 2007 onwards, when registration of tests began, admissions and procedures on the digital platform of the hospital in or-der to avoid a loss bias of information.The number of edoanal ul-trasounds, pelvic magnetic resonances (MR enterography), EUA, colo-noscopies/rectoscopies were quantified, as well as imaging tests to eva-luate small intestine (MR/CT enterography), similarly the number of admissions for whatever CD related circumstance, the need for luminal surgery and biological treatments undertaken.

In patients with PD a further sub-analysis was taken between PD simple and PD complex as much in the necessity of treatment as for the ex-penditure of resources.

Statistical analysis was carried out with the statistic package SPSS, ver-sion 24 (SPSS Inc. Chicago, IL, EE.UU.). This finally led to a descriptive analysis and from the quantitative variables the statistics of centralization and dispersion were calculated: mean or median depending on said variables presented or not normal distribution after submission to the Kolmogorov-Smirnov test. Qualitative variables were analysed using either the Chi-squared or Fisher test following procedure, while quantatives

were used by the tests t of Student/ANOVA or non para-metric test (U Man-Whitney). In the posterior multivariant analysis lo-gistical regression means were employed. We consider the statistic significance to have an importance of ≤ 0.05.

The study concluded with agreement to the Declaration of Helsinki and followed the prevailing legal regulations (Royal Decree 223/2004). The approval of the Ethics Committee of Clinical Trials (CEIC) of our hospital was also secured.

RESULTS

We included 430 patients, whose baseline characteristics are reflected in Table 1. Regarding the location, among patients with colon disease (L2+L3) 125/220 had rectum affected (29.1% of total patients).

PD was present in 173/430 patients (40.2%), among those categorised as complex there were 126 ((72.8%) versus 47 cases (27.2%) with PD simple. The most frequent form of presentation was fistula (78.6%) and abcess(60.7%), the less frequent being fissures (30.1%), stenosis (15%), and flaps (4.6%).

The presence of PD regarding the diagnosis of CD was posterior in 79 cases (45.7%), simultaneous 73 (42.2%) and previous 21 (12.1%). The median of time between diagnosis of of PD and CD was 2.05 years when the diagnosis was previous (IQR 0.98-4.75) and 5.99 years when it was posterior (IQR 2.58-12.99).

In the univariate analysis of the factors involved in the development of PD, we see that at a younger age of CD, the presence of EIM and the rectum affected are associated with the presence of PD (Table 1). Multivariate analysis confirms rectal involvement and extraintestinal manifestations as independent factors of risk. With rectum affected, the probability of suffering PD increases 17.23 times (IC 95% 8.08-36.74) and in the case of EIM 2.38 times (IC 95% 1.22-4.63).

Patients with PD need more frequently immunosuppresant treatment (91.9% vs. 77.4%; p ≤).0001) and biological treatment (56.1% vs. 31.5%, p ≤ 0.0001). Luminal disease was the indication for biological therapy in 74/173 (42.7%) patients with PD (in 28 further cases there was deficient perianal control) versus 79/257 (30.7%) whom

had not PD (p 0.011) (Figure 1).

Analyzing the indication for biological treatment depending on the complexity of the PD, we encountered in PD simple, 21 patients who required it through luminal indication while, in the case of complex PD, in 25/76 (32.9%) was for luminal disease, in 23/76 (30.3%) due to PD and in 28/76 (36.8%) due to the combination of both conditions.

As far as the need for hospital admission through CD it was greater in patients with PD (138/173, 79.8% vs. 171/257, 66.5%; p 0.003); however, the need for intestinal resective surgery because of luminal pathology was similar in both groups: 76/173 (43.9%) in patients with PD versus 96/257 (37.4%) without PD (p 0.172).

When we compare these same variables depending on the complexity of PD we see that patients with complex PD in relation to PD simple equally need more biological treatment (76/126, 60.3% vs CD simple 21/47, 44.7%; p 0.065), more IS (122/126, 96.8% vs. 37/47, 78.7%; p ≤0.0001) but without differences in the need for hospitalisations (104/126, 82.5% vs. 34/47, 72.3%; p 0.137) or luminal surgery (56/126, 44.4% vs. 20/47, 42.6%; p 0.824).

Of the 187 patients included in the analysis of resource expenditure 117 did not have PD and 70 did indeed present it. Patients with PD required a greater number of endoanal ultrasounds, MR enterographies, IBDs, colonoscopies, biological treatments and hospital admissions. However, no significant differences were seen between both groups in MR/CT enterography and luminal surgery (Table 2).

The analysis separately of patients with PD complex (47 cases) and PD simple (23 cases) also revealed significant differences in endoanal ultrasounds, MR enterographies and EUA, these being more frequent in the case of PD complex compared to PD simple. We saw no differences in the number of colonoscopies, the use of biological treatments, admissions or intestinal surgery. (Table 2)

As far as additional treatments, these were only applicable to patients with PD, of the 173, 12 required discharge colostomy (6.9%), 4 stem cell treatment (2.3%) and 11 with platelet growth factors (6.4%).

DISCUSSION

Through this present study we confirm the great clinical impact of PD in patients in our midst, which entails a greater consumption of health resources.

The first fact to highlight is the high prevalence of PD. In the published series it is highly variable, up to 43% (1), this being one of the highest described and similar to that of our series. This could be justified because it is a monographic IBD consultation in a tertiary hospital compared to population cohort studies where the presence of PD is lower (7,13). Another reason is that in some series only fistulas are registered as PD, with a frequency between 13.7% and 26% (4, 14, 15) while our series includes all manifestations of PD.

Rectal involvement is the factor most clearly associated with the develop-ment of PD. Hellers et al (2) describe a 92% prevalence of PD in colonic disease with rectum affected, much higher than in other locations, as in our series (74%). In reference to the presence of EIM it has been described together with PD as a factor of bad prognosis of CD (17-21). However, there is scant evidence of relationship between EIM and PD. The young age at diagnosis of CD has been related in diverse studies to aggressive forms of the disease and the appearance of complications such as PD (5, 22, 23), however in our sequence it did not attain a statistical significance in the multivariant study. Based on these data and the frequent development of PD across the diagnosis of CD (5,7) we could propose immunomodular or biological treatment in an early form when these conditions coexist.

Regarding the prognostic implications of the PD we encounter that this patients required more frequently immunosuppressor treatment, biological treatment and hospital admissions, which reflects worse prognosis, rapid progression and/or more aggressive behaviour of CD, our results being consistent with previous evidence (4, 6, 7, 24, 25) where in series such as Zhao et al (7) the need for biological therapy in patients with PD is close to 50%, as in our serie. What is more, in our case, we found that among patients with PD the indication for biological treatment for luminal disease was higher, which indirectly reflects a worse evolution at the luminal level among

patients with PD, especially in complex forms, compared to simple ones.

However, we did not find a greater need for luminal resective surgery among patients with PD, unlike that described in other series (4, 7-10). This could be explained by the high response rate of luminal disease to biologics, most commonly used in patients with PD, although this cir-cumstance would be similar in previous studies.

Finally, regarding the consumption of other resources associated with PD, there are hardly any studies that analyse the impact in this regard as a primary or secondary objective (7, 25, 26). Chaparro et al (26) evaluated the costs associated with complex PE in CD by means of a multicenter study, concluding that pharmacological therapies, and in particular biological ones, are the main cost generator. It is logical to think that the worst evolution of the disease justifies the greater consumption of resources. This is reflected in our series with the significantly greater need for biologicals, admissions, and examinations aimed at the management of PD (pelvic MRI, endoanal ultrasound, EUA and colonoscopy). It is also greater in complex forms than in simple ones (pelvic MRI, EUA and endoanal ultrasound).

Among the limitations of our work, we highlight that, since it is a retrospective study, there may be an information bias. However, to minimise this in the assessment of resource consumption, we only analysed patients diagnosed since 2007, when the computerised registry of medical records began. However, in the registry of simple forms of PD, frequently asymptomatic, this bias was probably difficult to alleviate.

All in all, we can conclude that PD among patients with CD is very prevalent, especially if there is rectal involvement, and entails higher healthcare costs than patients without PD due to the worse evolution at the perianal and luminal level, especially in complex forms. All of this forces us to optimize treatment strategies in these types of patients.

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Table 1. Characteristics of patients at baseline and stratified by perianal disease.

Characteristic of the population	General population (n 430)	PD + (n 173)	PD – (n 257)	P
Male gender (n,%)	232 (54)	96 (55.5)	136 (52.9)	0.60
Age at CD diagnosis (years, median [IQR])	26 [20-30.25]	24 [18.5-32]	27 [20-40.5]	0.003
Active smoking habit (n,%)	137 (31.9)	53 (30.6)	84 (32.7)	0.59
CD evolution time (years, median [IQR])	12 [6.7-18.1]	13.8 [7.73-20.5]	11.04 [5.87-16.57]	0.004

CD Montreal classification				
Age at diagnosis				
A1 (≤ 16 años)	58 (13.5)	32 (18.5)	26 (10.1)	
A2 (17-40 años)	284 (66)	117 (67.6)	167 (65)	0.003
A3 (> 40 años)	88 (20.5)	24 (13.9)	64 (24.9)	
Location (n, %):				
L1 (ileal)	206 (47.9)	65 (37.6)	141 (54.9)	
L2 (colonic)	58 (13.5)	35 (20.2)	23 (8.9)	< 0.0001
L3 (ileocolonic)	162 (37.7)	73 (42.2)	89 (34.6)	
L4	54 (12.6) *	18 (10.4)	36 (14)	0.26
Behaviour (n, %):				
B1 (inflammatory)	183 (42.5)	69 (39.9)	114 (44.4)	
B2 (stenosing)	94 (21.9)	35 (20.2)	59 (23)	0.31
B3 (penetrating)	153 (35.6)	69 (39.9)	84 (32.6)	
Straight infection (n, %)	125 (29.06)	93 (53.8)	32 (12.5)	< 0.0001
Extraintestinal manifestations (n, %)	135 (31.4)	65 (37.6)	70 (27.2)	0.02

* 4 patients L4 exclusive

Table 2. Resource consumption based on the presence of PD and complexity

Resources consumed (median[IQR])	PD + (n 70)	PD − (n 117)	p	PD complex (n 47)	PD simple (n 23)	p
Endoanal ultrasound	0 [0-1.25]	0 [0-0]	<0.0001	1 [0-2]	0 [0-0]	<0,0001
MR entography	1 [0-3]	0 [0-0]	< 0.0001	2 [1-3]	0 [0-1]	< 0,0001
IBD	0,5 [0-2]	0 [0-0]	< 0.0001	1 [0-3]	0 [0-0]	< 0,0001
Colonoscopy	3 [2-4]	2 [2-3]	0.024	3 [2-4]	3 [2-4]	0,758
MR/CT enterography	3 [2-4]	3 [1-4]	0.738	3 [2-3]	3 [2-5]	0,344
Biológical	1 [0-2]	0 [0-1]	0.008	1 [0-1]	1 [0-2]	0,931
Admissions	2 [1-4]	1 [0-3]	0.004	3 [1-4]	2 [0-4]	0,227
Luminal Surgery	0 [0-1]	0 [0-0,5]	0.695	0 [0-1]	0 [0-1]	0,439

FIGURE

Figure 1. Immunosuppressive and biological treatment. Indication of biological treatment.