Mild clinical behaviour of Crohn disease in elderly patients in a Latin American country: A case-control study

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BACKGROUND: Crohn disease is characterized by fluctuating clinical behaviour, which is influenced by various factors. There are no data from Latin America that evaluate the clinical behaviour of Crohn disease in elderly patients.
OBJECTIVE: To evaluate the clinical course of elderly onset Crohn disease compared with younger onset in the Mexican population.
METHODS: The present analysis was a case-control study that included 132 patients with a histopathological diagnosis of Crohn disease between 1983 and 2013 in an inflammatory bowel disease clinic of a tertiary care centre. Statistical analysis was performed using SPSS version 17 (IBM Corporation, USA) and descriptive statistics, χ^2 and Fisher's exact test for categorical variables and Student's *t* test for numerical variables. Univariate and multivariate analysis were performed to identify associated risk factors and OR was calculated.
RESULTS: A total of 132 patients (73 men and 59 women) were divided into two groups according to age at diagnosis: 27 cases (>60 years of age) and 105 controls (≤60 years of age). Factors influencing the clinical course of Crohn disease in the elderly were: female sex (OR 2.55 [95% CI 1.06 to 6.10]; P=0.02); colonic location (OR 0.22 [95% CI 0.03 to 0.89]; P=0.02); mild clinical behaviour of disease (OR 10.08 [95% CI 3.74 to 27.17]; P=0.0001); response to medical treatment (OR 2.85 [95% CI 1.08 to 7.48]; P=0.02); frequent use of sulfasalazine (OR 4.46 [95% CI 1.22 to 16.28]; P=0.03); less use of azathioprine (OR 0.38 [95% CI 0.13 to 1.03]; P=0.04); and long-term remission (OR 4.96 [95% CI 1.70 to 14.48]; P=0.002).
CONCLUSION: Elderly patients with Crohn disease had a mild clinical course characterized by the lack of escalation to immunosuppressive and anti-tumour necrosis factor therapy, as well as long-term remission.

Key Words: *Clinical behaviour; Crohn disease; Elderly; Geriatric*

Le comportement clinique bénin de la maladie de Crohn chez les patients âgés d'un pays d'Amérique latine : une étude cas-témoins

HISTORIQUE : Le comportement clinique de la maladie de Crohn fluctue en raison de divers facteurs. Aucune donnée en provenance d'Amérique latine ne l'évalue chez les patients âgés.
OBJECTIF : Évaluer l'évolution clinique de la maladie de Crohn qui se manifeste chez les personnes âgées par rapport à celle qui se manifeste chez des personnes plus jeunes au sein de la population mexicaine.
MÉTHODOLOGIE : La présente analyse était une étude cas-témoins composée de 132 patients ayant obtenu un diagnostic histopathologique de maladie de Crohn entre 1983 et 2013 au sein de la clinique de maladies inflammatoires de l'intestin d'un centre de soins tertiaires. Les chercheurs ont procédé à l'analyse statistique au moyen de la version 17 du SPSS (IBM Corporation, États-Unis), ont établi les variables qualitatives au moyen des statistiques descriptives, du test du χ^2 et du test exact de Fisher et ont établi les variables numériques à l'aide du test *t* de Student. Ils ont effectué des analyses univariée et multivariée pour déterminer les facteurs de risque connexes et ont calculé le risque relatif.
RÉSULTATS : Au total, 132 patients (73 hommes et 59 femmes) ont été répartis entre deux groupes en fonction de leur âge au diagnostic, soit 27 cas (plus de 60 ans) et 105 sujets témoins (60 ans ou moins). Les facteurs qui influaient sur l'évolution clinique de la maladie de Crohn chez les personnes âgées étaient le sexe féminin (RR 2,55 [95 % IC 1,06 à 6,10]; P=0,02), le foyer dans le côlon (RR 0,22 [95 % IC 0,03 à 0,89]; P=0,02), le comportement clinique bénin de la maladie (RR 10,08 [95 % IC 3,74 à 27,17]; P=0,0001), la réponse au traitement médical (RR 2,85 [95 % IC 1,08 à 7,48]; P=0,02), l'utilisation fréquente de sulfasalazine (RR 4,46 [95 % IC 1,22 à 16,28]; P=0,03), la moins grande utilisation d'azathioprine (RR 0,38 [95 % IC 0,13 à 1,03]; P=0,04) et la rémission prolongée (RR 4,96 [95 % IC 1,70 à 14,48]; P=0,002).
CONCLUSION : L'évolution clinique de la maladie était bénigne chez les personnes âgées, ne s'aggravait pas jusqu'à nécessiter un traitement immunosuppresseur et la prise d'inhibiteur du facteur de nécrose tumorale alpha, et s'associait à une rémission prolongée.

Inflammatory bowel disease (IBD) includes Crohn disease (CD) and ulcerative colitis (UC). Little is known regarding its multifactorial and etiopathogenic mechanisms, of which three main factors – genetics, immunity and the environment – are involved (1). The course of CD is characterized by fluctuating clinical behaviour, which is influenced by various factors including hospitalization rates, treatment response, postsurgical recurrence, relapses, exacerbations and older age at diagnosis.

In 2014, the world's population was estimated to be 7.2 billion and, from this number, 8% appeared to be older adults (2); however, by 2050, the number of older persons worldwide is projected to more than double to two billion (3). Population aging is occurring in every country, although each country is at a different stage of this transition (4). For example, by 2050, Mexico's aged are projected to represent 27.7% of the population (5), while the same demographic in the United States is expected to represent 20.3% (6). This fast-growing elderly population represents part of an age group in which important physiological changes occur, including immune deficiency (peculiar to old age), increased frequency of comorbidities and polypharmacy. These characteristics place this age group at higher risk, which undoubtedly affects the clinical course of CD. Despite the fact that fewer than one-third of epidemiological studies have documented a bimodal distribution of IBD incidence with a second peak between 60 and 70 years of age (7), elderly patients with CD should not be treated with aggressive

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therapy because it has been proposed that the disease process may not represent the same disease process present in younger patients (8). Furthermore, 10% to 15% of patients with IBD will be diagnosed at >60 years of age (9-13) (65% during the sixth decade of life, 25% during the seventh decade and 10% during the eighth decade [12,13]). Women are more likely than men to be diagnosed with IBD after 60 years of age (14-18), and there is a higher incidence of UC than CD (14). These phenotypic differences among age groups reflect variations in mucosal immune response, composition of the microbiome, genetics and/or environmental risk factors that are not fully understood (18). Interestingly, very-early onset (zero to six years of age) and elderly onset CD are characterized by the predominance of pure colonic disease (L2, according to the Montreal classification) (18-26).

Several studies have proposed that elderly patients diagnosed with CD have a less aggressive clinical course compared with those diagnosed at a younger age. This suggests that gastrointestinal tract changes occur with aging and produce dietary shifts among older individuals, alterations in gastrointestinal motility and gastric pH due to mucosal atrophy, increased intestinal permeability and changes in the gut microbiota associated with aging that may influence host-inflammatory responses (27-30). For example, the risk for surgery decreases with older age at diagnosis, disease distribution and history of cigarette smoking (31). In CD, the prevalence of diarrhea, abdominal pain, extraintestinal manifestations, weight loss and fever decreases in older or elderly patients (18,32). A large population-based cohort study involving a French population that included 841 IBD patients concluded that the clinical course is mild in elderly onset IBD patients due to disease behaviour, and was reported to remain stable in 91% of patients with elderly onset CD after a median follow-up period of six years (33). Other studies have concluded that the clinical manifestations of the first flare of CD are similar in the >60 years of age and younger age groups (18), characterized by the predominance of inflammatory behaviour (18,21,34,35). To date, no data from genetic studies have been published regarding elderly onset IBD variants to further define the contribution of specific gene associations with elderly onset IBD; however, the role of genetic factors is believed to be greater in pediatric-onset than in late-onset IBD (18). It has also been found that older patients with IBD may have an increased susceptibility to gastrointestinal infection because the response to stress in the setting of acute inflammation may be altered or blunted (28,30,36).

There are some key features considered for elderly onset CD: inflammatory disease behaviour, colonic or ileocolonic disease location, uncommon family history of IBD, and reduced progression to penetrating or stricturing disease phenotypes (37). Prompted by the lack of data from Latin America evaluating the clinical behaviour of CD in the elderly, the aim of the present study was to evaluate the clinical course of elderly compared with younger-onset CD in the Mexican population.

METHODS

The present analysis was a retrospective case-control study that included 132 patients with histopathological diagnosis of CD between 1983 and 2013 in the IBD clinic of a tertiary care centre (National Institute of Medical Sciences and Nutrition "Salvador Zubirán", Mexico). Clinical records were reviewed and a database including the following variables was constructed: sex, age, place of birth, place of residence, weight, height and body mass index; family history of IBD and family or personal history of other immune-mediated diseases; pack-years of smoking (number of cigarettes smoked daily multiplied by the years of smoking divided by 20); history of appendectomy or tonsillectomy; intake of nonsteroidal anti-inflammatory drugs; thrombosis and its location (upper limbs, lower limbs, pulmonary thromboembolism, acute coronary syndrome or vascular brain disease); age at diagnosis; disease phenotype (inflammatory, stricturing or fistulizing); location (terminal ileum, ileocolonic, colonic, upper digestive tract); clinical course (initially active followed by long-term remission, intermittent activity (less or one relapse a year) or continuous activity (≥2 relapses per year); extraintestinal manifestations such as arthritis, arthralgia, ankylosing spondylitis, sacroiliitis, sclerosing cholangitis, pyoderma gangrenosum, erythema nodosum or uveitis; number of hospitalizations; treatment response and reasons for lack of response response and surgical treatment. Other variables included were: post-surgical recurrence; current CD treatment; and clinical activity or remission of the disease at the time of evaluation. The present research was approved by the local ethics committee.

Statistical analysis

Demographic, clinical, and laboratory characteristics are presented as mean ±SD, median and range. The Fisher's exact probability test was used to compare categorical variables when the number of expected subjects was <5 and by the χ^2 test otherwise. The unpaired *t* test was used to compare differences in the means of continuous variables. Nonparametric variables in independent samples were compared using the Mann-Whitney U test. ORs and 95% CIs were calculated using univariate and multivariate analyses adjusted for age, sex, extent of disease, Mayo Score, C-reactive protein level and current medical treatment. P≤0.05 was considered to be statistically significant and Bonferroni correction for P value was applied for multiple comparison calculated as α/n. All statistical analyses were performed using SPSS version 17.0 (IBM Corporation, USA).

RESULTS

A total of 132 patients were evaluated 73 (55.3%) men and 59 (44.7%) women divided in two groups: 27 (20.5%) who were diagnosed at >60 years of age (cases) and 105 (79.5%) who were diagnosed at ≤60 years of age (controls). Detailed demographic and clinical characteristics are summarized in Table 1 and 2, respectively.

CD patients >60 years of age

From the elderly patients, the case group consisted of 27 individuals (10 men and 17 women). The presence of steroid dependency was 3.8% and steroid resistance 0.8%; thiopurine-resistance 0.8% and intolerance to thiopurines 2.3%; and 72.7% undewent intestinal surgical resection. The reasons for surgery were bowel fibrostenotic stricturing (33.7%), bowel perforation (12.7%), intra-abdominal abscess (10.3%), penetrating disease (9%), dysplasia (5%), cancer (1.5%) and toxic megacolon (0.5%).

CD patients ≤60 years of age

The control group included 105 patients (63 men and 42 women). The presence of steroid dependency was 18.5% and steroid-resistance 7%; thiopurine resistance 15% and intolerance to thiopurines 2.5%. All patients underwent intestinal surgical resection for the following reasons: bowel fibrostenotic stricturing (35.2%), penetrating disease (28.57%), intra-abdominal abscess (20.5%), bowel perforation (10.5%), dysplasia (2.3%), cancer (1.5%) and toxic megacolon (1.43%).

Factors influencing the clinical course of CD in elderly patients

The univariate analysis found that the following factors influenced the clinical course of CD in elderly patients: female sex (OR 2.55 [CI 95% 1.06 to 6.10]; P=0.02); a less frequent colonic location (OR=0.22 CI 95% CI 0.03 to 0.89]; P=0.02); mild clinical behaviour of disease (OR 10.08 [95% CI 3.74 to 27.17]; P=0.0001) and a better response to the medical treatment (OR 2.85 [95% CI 95% 1.08 to 7.48]; P=0.02), frequent use of sulfasalazine (OR 4.46 95% CI 1.22 to 16.28]; P=0.03); low use of azathioprine (OR 0.38 [95% CI 95% 0.13 to 1.03]; P=0.04) and higher clinical remission rate (OR 4.96 [95% CI 1.70 to 14.48]; P=0.002) (Table 3).

Significant statistical trends were found in the following factors: elderly patients present pulmonary thromboembolism more frequently (OR 6.53 [95% CI 1.01 to 40.67]; P=0.05), as well as a predominant terminal-ileum location (OR 2.03 [95% CI 0.83 to 4.94]; P=0.09) and a more common inflammatory pattern (OR 0.48 [95% CI 0.18 to 1.24]; P=0.09).

TABLE 1
Demographic variables of patients with Crohn disease

Variable	Cases (n=27)	Controls (n=105)
Sex		
Male	10 (37)	63 (59.05)
Female	17 (63)	42 (40)
Family history of inflammatory bowel disease	0 (0)	1 (0.95)
Smoker	10 (37.03)	47 (44.76)
Autoimmune concomitant disease	3 (11.11)	13 (12.38)
Appendectomy	7 (25.92)	24 (22.85)
Tonsillectomy	3 (11.11)	18 (17.14)

Data presented as n (%)

In the multivariate analysis, the following factors influenced the clincal course of CD in elderly patients: a less frequent colonic location (P=0.021, OR=0.130), a mild clinical course of disease (P=0.0001, OR=0.151), less use of azathioprine (P=0.027, OR=0.255) and inflammatory pattern (P=0.01, OR=0.193).

DISCUSSION

The present study clearly showed a milder clinical course of CD in elderly patients, and was the first performed in the Latin American population. We found that women were predominantly affected, similar to a previous study (the EPIMAD registry [19]) and one study from the United States Military Health Care Population (38). Smoking was associated with increased risk for CD and worse outcomes over the disease course (18,39,40) and, interestingly, our study found a higher proportion of smoking patients in the young group than in the elderly group, which could have also influenced the different outcomes. In the present study, CD patients had a less frequent colonic location and had a more common inflammatory pattern, compared with the French registry, which found that pure colonic disease and inflammatory behaviour were the most frequent phenotypes (14). A study from Hungary (41) found pure colonic disease and a more common stenosing pattern. A retrospective study concluded that older and younger patients underwent surgery in similar percentages (83% versus 77%) (42), a finding similar to that reported in our population (66.6% versus 74.28%).

The elderly patients in the present study exhibited mild clinical disease behaviour, characterized by initially active disease followed by long-term clinical remission, better response to medical treatment and more use of sulfasalazine and less use of azathioprine. These findings were also reported in other studies. For example, the Hungarian study (41) found that their elderly population required less systemic steroids compared with their younger groups. A French study (43) concluded that immunosuppressants were more frequently required in the childhood-onset group than in the elderly onset patients. In this study, it was also found that older adults were less likely to require immunosuppressants or readmission for CD flares compared with younger patients (44). It has even been concluded that corticosteroid response is similar in older and younger patients hospitalized for IBD, but older corticosteroid-responsive patients are less likely to be treated with an anti-tumour necrosis factor agent than younger patients (45). Furthermore, care providers should be aware of polypharmacy and its potential for drug interactions because it has been shown that the prevalence of medication use is higher among patients with IBD than matched members of the general population, particularly the use of analgesic and psychiatric drugs (46). Regarding the extraintestinal manifestations of IBD, thromboembolic events represent a major cause of morbidity and mortality (47,48), and it is known that IBD is an independent risk factor for thromboembolic phenomena (49). One study also found a more frequent prevalence of venous thromboembolism (TE) in elderly patients with IBD (6.15%) compared with the control group (1.62%) (50). This correlates with the fact that our elderly patients tended to present with pulmonary TE more frequently. Other studies have concluded that the most frequent thromboembolic complications are deep vein thromboses and pulmonary emboli, and that this event can occur as a postsurgical complication or spontaneous event (48).

This less agressive clinical behaviour is gradually occupying an important place among the diverse factors that influence the decision-making process regarding the therapeutic approach to an elderly patient

TABLE 2
Clinical characteristics of Crohn disease (CD) patients

Variable	Cases (n=27)	Controls (n=105)
CD pattern		
Inflammatory	7 (25.92)	44 (41.9)
Fistulizing	10 (37.03)	30 (28.57)
Stricturing	10 (37.03)	37 (35.23)
CD location		
Terminal ileum	11 (40.74)	26 (24.76)
Ileocolonic	12 (44.44)	47 (44.76)
Colonic	2 (7.4)	27 (25.71)
Upper digestive tract	2 (7.4)	7 (6.6)
Clinical course		
Initially active followed by long-term remission	19 (70.37)	21 (20)
Intermittent activity	5 (18.51)	51 (48.57)
Continuous activity	2 (7.4)	27 (25.71)
Extraintestinal manifestations		
Arthritis	1 (3.7)	6 (5.71)
Arthralgias	3 (11.11)	23 (21.9)
Ankylosing spondylitis	4 (14.81)	8 (7.61)
Sclerosing cholangitis	0 (0)	1 (0.95)
Pyoderma gangrenosum	0 (0)	3 (2.85)
Erythema nodosum	0 (0)	2 (1.9)
Uveitis	1 (3.7)	0 (0)
Lack of response to medical treatment	10 (37.03)	70 (66.6)
Surgical treatment	18 (66.6)	78 (74.28)
Postsurgical recurrence	1 (3.7)	10 (9.52)
Current treatment		
Sulfasalazine	4 (14.81)	6 (5.71)
Mesalazine	4 (14.81)	23 (21.9)
Azathioprine	6 (22.22)	31 (29.52)
Prednisone	4 (14.81)	25 (23.8)
Methotrexate	0 (0)	1 (0.95)
Biologic therapy	0 (0)	2 (1.9)

Data presented as n (%)

TABLE 3
Factors influencing the course of Crohn disease in the elderly population

Variable	Univariate analysis	Multivariate analysis
Female sex	P=0.02	P=0.54
	OR=2.55	
Colonic location	P=0.02	P=0.03
	OR=0.22	OR=0.13
Mild clinical course of disease	P=0.0001	P=0.0001
	OR=10.08	OR=0.15
Response to medical treatment	P=0.02	P=0.31
	OR=2.85	
Use of sulfasalazine	P=0.03	P=0.54
	OR=4.46	
Use of azathioprine	P=0.04	P=0.02
	OR=0.38	OR=0.25
Clinical remission	P=0.002	P=0.22
	OR=4.96	

diagnosed with CD. Nevertheless, it should not be considered without taking into account all other aspects that play a role in each specific case. For example, one current approach to drug therapy in the elderly is to 'start low; go slow' and then reassess their candidacy for more aggressive therapy (biologics, apheresis, surgery), and not treat or exclude patients on the basis of age alone (51). In conclusion, elderly patients with CD had a mild disease course characterized by long-term remission, less use of aggressive therapy, such as thiopurines and anti-tumour necrosis factor agents, and better response to medical treatment.

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CONCLUSIONS

Elderly patients had a less aggressive clinical course compared with younger patients, and commonly achieved remission without the need of escalating the treatment beyond aminosalycilates.

There are no data from Latin America that evaluate the clinical behaviour of CD in elderly patients. The present study showed that elderly patients with CD had a mild clinical course characterized by the lack of escalation to immunosuppressive and anti-tumour necrosis factor therapy, as well as long-term remission.

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