



## THE INFLUENCE OF AGE AT DIAGNOSIS ON CLINICAL FEATURES IN ELDERLY PATIENTS WITH CROHN'S DISEASE

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### ABSTRACT

Inflammatory bowel diseases are chronic recurrent bowel disorders. They usually occur in children and young adults. It is an uncommon condition in the elderly. This work is aimed to evaluate the clinical characteristics and disease course of Crohn Disease in the elderly patients and to compare them with the clinical characteristics of younger patients in a population from Western Algeria region. It was a retrospective comparative survey of 35 elderly patients whose age was >60 years diagnosed during the period from 2007 to 2020 at the level of general surgery departments and university hospital centers in the Western Algeria region. The study included 437 Crohn Disease patients involving 35 elderly and 402 young adults. The mean age of the elderly patients was 65.48±11.43. The most noted localization was colonic in Elderly with a rate of 23 (65.7%)/P= 0.002, while it was ileo-caecal in 236 Young patients (58.7%)/P= 0.005. The majority of elderly patients, complained of abdominal pain 28 (80%), cessation of matter and gas 18 (51.4%), vomiting 13 (37.1%), weight loss 06 (17.1%), and diarrhea 05 (14.3%). During the follow-up period, medical therapy was the same for both groups. Moreover, 29 (82.8%) of the elderly patients underwent surgical treatment compared to 295 (73.4%) of the young patients. The number of patients with extra-intestinal manifestations in the elderly group was significantly higher than in the young group. Through our results, it seems that Crohn's disease in the elderly generally follows the same clinical pattern as in young people, with some exceptions.

**Key words:** Crohn, elderly, young, clinical, treatment.

### INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic recurrent bowel disorder. It usually occurs in children and young adults. With the growth of the world's aging population, elderly patients have become a new subgroup, particularly because of the often concomitant multimorbidity and delay in diagnosis (Cantoro et al. 2017; Song et al. 2018; Corazza et al. 2019).

Several studies on Crohn's disease (CD) have been done in the elderly, the oldest of which was conducted in Belgium and found similar characteristics between patients diagnosed at an age of more than 60 years and less than 60 years, with the exception of those over 60 years of age who had less diarrhea, weight loss and extra-intestinal symptoms (Song et al. 2018).

CD remains a challenging medical problem for gastroenterologists. Its diagnosis in the elderly can be difficult because the clinical presentation may differ from that of younger patients, as they may complain of fewer symptoms (Duncan et al. 2010; Kim et al. 2019) or have fewer of the typical symptoms seen in younger patients, namely diarrhea, weight loss, and extraintestinal symptoms (Katz et al. 2008).

Other co-morbidities associated with advanced age may lead to conditions that resemble to CD (Gajendran et al. 2018). Elderly patients may be asymptomatic, and failure to consider Crohn's disease as a possible diagnosis can lead to a significant delay in diagnosis and appropriate therapeutic management (Triantafillidis et al. 2000; Kim et al. 2019). Clinically, elderly patients may present with

nonspecific symptoms, such as constipation, fever, malaise, and gastrointestinal bleeding, without observing the usual symptoms of the young, such as abdominal cramps, diarrhea, or weight loss (Katz et al. 2008; Sturn et al. 2016; Raddawi et al. 2020).

The phenotype of Crohn's disease is often inflammatory or penetrative, although some studies report more stringent activity in younger people (Charpentier et al. 2014; Everhov et al. 2018; Mañosa et al. 2018; Kim et al. 2019). However, other studies have shown that the clinical course of Crohn's disease in older age has been identified by more frequent colonic involvement compared to those under 60 years of age at diagnosis (Heresbach et al. 2004; Song et al. 2018; Kim et al. 2019). Characteristics such as atypical presentation, slow progression of the disease, and the presence of multiple comorbidities in the elderly make the diagnosis more difficult (Raddawi et al. 2020). The treatment of CD in the elderly is more complicated compared to those in younger patients. Indeed, multiple comorbidities, polypharmacy, health problems, and reduced physical activity may occur in the elderly (Taleban, 2015; Fumery et al. 2016).

In this study, we sought to evaluate the clinical features of CD in elderly patients of Algerian population "Algerian West region" and to compare them with the clinical features of a younger group patients, in order to identify features that might characterize the disease in the elderly. The therapeutic management, in particular the risk of surgery, was also evaluated.

## MATERIALS AND METHODS

### Study design:

A retrospective comparative survey was conducted from 2007 to 2020, on a cohort of adults and elderly diagnosed with CD whose age at diagnosis was <60 years (Young group) and >60 years (Elderly group). Clinical and demographic data of all enrolled patients were retrieved and analyzed from the registries of the gastrology and general surgery departments of the University Hospitals of Western Algeria region, namely "Dr. Hassani Abdelkader"; of Sidi Bel Abbes and "First November" of Oran, which included 437 CD patients, 35 of whom were elderly and 402 young.

All patients were diagnosed with CD on the basis of conventional clinical, radiological, endoscopic and pathological criteria (Park et al. 2014). Data included age, sex, smoking status, location, family history, and disease behavior at diagnosis, as well as medical and surgical treatment. We compared the clinical characteristics and disease course between Young and Elderly patients according to age at diagnosis. Ethical approval was obtained from the department in which the study was carried out.

### Statistical Analysis:

Categorical variables were evaluated as absolute frequencies and percentages, whereas quantitative variables were summarized by means and standard deviations.

Continuous variables were compared using the Pearson Chi-square ( $\chi^2$ ) test and the student test. Results were presented using the p value, and its significance level was limited by the 5% level. All conventional analyses were performed using IBM SPSS Statistics 22 [IBM Corp. (2013). IBM SPSS Statistics for Windows (Version 22.0) [Computer software]. IBM Corp].

## RESULTS

Of 437 patient records reviewed, 242 (55.4%) were male and 196 (44.6%) female. Thus we found an overall male predominance with a sex ratio M/F of 1.3, the median age at diagnosis was (37.99±14.08).

The epidemiological characteristics of elderly and young patients with Crohn's disease are presented in Table 1. Of the 437 patients, 402 were young patients (219 male, 183 female) and 35 were elderly patients (23 male, 12 female). The mean age at diagnosis in young patients was 40.37±139.75 while it was 65.48±11.43 in elderly patients with a P= 0.01. (Table 1).

Regarding localization, a significantly high ileo-caecal and colonic localization (0.002/0.005) was observed in both young and old patients. However, there was a predominance of colonic location in the elderly and caecal location in the young patients. (Table 1).

According to the phenotype of the disease, no significant differences were found between the young/old group. It was mainly inflammatory in both groups (Young=243

(60.4%)/Elderly=48.6%)(Table 1).

In contrast, the duration of symptom onset at diagnosis in elderly patients was significant at  $p=0.013$ .

Our comparative study showed that family history of IBD was more frequently noted in the younger group than in the older group of patients. Nevertheless, 31 (88.6%) of the elderly patients with a previous medical history presented a

significant association ( $P=0.004$ ) compared to the young patients.

The incidence of appendectomy in the young group was significant, in fact we recorded 87 (21.6%) of the young patients ( $P=0.008$ ) against only one elderly patient. However, we found that 33 of the elderly patients (94.3%) were non-smokers with a  $P=0.002$  and 02 (5.7%) were ex-smokers (Table 1).

**Table 1 : Characteristics and evolution of the disease in all age groups (Elderly /Young).**

Characteristics :	Young (n= 402) <60 years	(n= 35) ≥ 60 years	Value P
Age at onset	35.33±11.08	68.48±7.32	0.5 <sup>a</sup>
Age at diagnosis	40.37±139.75	65.48±11.43	<b>0.01<sup>a</sup></b>
<b>Sex :</b>			
Male	219(54.5%)	23 (65.7%)	0.20 <sup>b</sup>
Female	183 (45.5%)	12 (34.3%)	
<b>Location :</b>			
Colic	158 (39.3%)	23 (65.7%)	<b>0.002<sup>b</sup></b>
Ileo-caecal	236 (58.7%)	12 (34.3%)	<b>0.005<sup>b</sup></b>
Upper digestive tract	30 (7.5%)	03 (8.57%)	0.81 <sup>b</sup>
<b>Behavior :</b>			
Inflammatory type	243 (60.4%)	17 (48.6%)	0.17 <sup>b</sup>
Stenosis type	145 (36.1%)	14 (40%)	0.64 <sup>b</sup>
Fistuleux type	43 (10.7%)	05 (14.3%)	0.51 <sup>b</sup>
Ano-perineal	13 (3.2%)	00 ( 0.0%)	0.28 <sup>b</sup>
Duration from symptom onset to diagnosis by months	46.90±74.51	22.77±43.83	<b>0.013<sup>a</sup></b>
Family history	56 (13.9%)	07 (20%)	0.32 <sup>b</sup>
Surgical history	252 (62.7%)	23 (65.7%)	0.72 <sup>b</sup>
Medical history	261 (64.9%)	31 (88.6%)	<b>0.004<sup>b</sup></b>
Appendectomy	87 (21.6%)	01 (2.9%)	<b>0.008<sup>b</sup></b>
Former smoker	69 (17.2%)	02 (5.7%)	<b>0.07<sup>b</sup></b>
Current smoker	50 (12.4%)	00 (0.0%)	<b>0.02<sup>b</sup></b>
No smoking	283 (70.4%)	33 (94.3%)	<b>0.002<sup>b</sup></b>
Alcoholism	28 (7%)	00 (0.0%)	0.10 <sup>b</sup>

Data analyzed by Sample *t*-test<sup>a</sup> and chi-square test<sup>b</sup>.

The 35 elderly patients identified had clinical symptoms of abdominal pain, cessation of matter and gas, vomiting, diarrhea, weight loss and altered general condition (Table 2). As shown in Table 3, occlusive and subocclusive Sd were the most frequent diagnostic symptoms in the elderly group with a significant association.

Medical therapy was the same for both groups as shown in Table 2. However, we noted an

administration of immunosuppressants and 5-aminosalicylic acid 5-asa in the elderly patients. During the follow-up period, 29 (82.8%) elderly patients underwent surgical treatment compared to 295 (73.4%) young patients.

Sigmoid resection was the most common indication significantly higher in the elderly group with a  $P < 0.001$ , followed by ileocaecal resection with ileocolic anastomosis.

**Table 2: Medical and surgical treatment of the disease in elderly and young people with Crohn's disease.**

	<60 years (n= 402)	≥60 years (n= 35)	P-value
<b>Symptom :</b>			
Abdominal pain	318 (79.1%)	28 (80%)	0.90 <sup>b</sup>
Material and gas shutdown	110 (27.4%)	18 (51.4%)	<b>0.003<sup>b</sup></b>
Vomiting	88 (21.9%)	13 (37.1%)	<b>0.04<sup>b</sup></b>
Diarrhea	185 (46.0%)	05 (14.3%)	<b>&lt;0.0001<sup>b</sup></b>
Constipation	41 (10.2%)	01 (2.9%)	0.15 <sup>b</sup>
Fever	53 (13.2%)	02 (5.7%)	0.20 <sup>b</sup>
Slimming	120 (29.8%)	06 (17.1%)	0.11 <sup>b</sup>
Alteration of the general condition	73 (18.1%)	02 (5.7%)	0.06 <sup>b</sup>
<b>Treatment :</b>			
5-aminosalicylic acid	85 (21.1%)	06 (17.1%)	0.57 <sup>b</sup>
immunosuppressive Corticotherapy	104 (25.9%)	06 (17.1%)	0.25 <sup>b</sup>
Biotherapeutic	62 (15.4%)	04 (11.4%)	0.52 <sup>b</sup>
Surgical	50 (12.4%)	07 (20%)	0.20 <sup>b</sup>
Surgical	295 (73.4%)	29 (82.8%)	0.22 <sup>b</sup>
<b>Indication :</b>			
-Ileocaecal resection with ileocolic anastomosis	112 (27.9%)	06 (17.1%)	0.17 <sup>b</sup>
-Sigmoid resection	29 (7.2%)	09 (25.7%)	<b>&lt;0.0001<sup>b</sup></b>
-Ileal resection with ileo-leal anastomosis	54 (13.4%)	03 (8.6%)	0.41 <sup>b</sup>
-Right hemi- colectomy	44 (10.9%)	04 (11.4%)	0.93 <sup>b</sup>
-Fistula resection	24 (6%)	02 (5.7%)	0.95 <sup>b</sup>
-Total coloprotectomy	06 (1.37%)	01 (2.9%)	0.53 <sup>b</sup>

<sup>b</sup>Data analyzed by Chi-square test

The most common radiological features in the elderly group compared to the young group were: X-ray of the abdomen without preparation (AWP), Fibroscopy, Barium Enema, Recto-sigmoidoscopy, Ultrasound and hail transit Hailstorm (Table 3).

The patients with the occurrence of extra-intestinal manifestations in the elderly group were

significantly higher than that of young people. The most frequent were joint (P=<0.0001), dermatological and eye(P=0.007).

In the elderly group, 13 patients had complications of anal fistulas and 11 of anal fissures, while a lower proportion of patients were more likely to develop anoperianal abscesses than those in the young group. (Table 3).

**Table 3: Clinical outcomes and complications in the elderly and young.**

	<60 years (n= 402)	≥60 years (n= 35)	P-value
Radiography	150 (37.3%)	08 (22.8%)	0.08 <sup>b</sup>
Ultrasound	182 (45.3%)	14 (40%)	0.54 <sup>b</sup>
Hail transit	221 (55%)	21 (60%)	0.56 <sup>b</sup>
Barium Enema	289 (71.9%)	29 (82.8%)	0.16 <sup>b</sup>
Scanner	219 (54.5%)	15 (42.8%)	0.18 <sup>b</sup>
Telethorax	296 (73.6%)	21 (60%)	0.08 <sup>b</sup>
X-ray	375 (93.3%)	32 (91.4%)	0.67 <sup>b</sup>
(AWP)Fibroscopy	327 (81.3%)	29 (82.8%)	0.82 <sup>b</sup>
Coloscopie	79 (19.6%)	10 (28.6%)	0.20 <sup>b</sup>
Rectosigmoidoscopy	325 (80.8%)	20 (57.1%)	<b>0.001<sup>b</sup></b>
Hospitalization	352 (87.6%)	35 (100%)	<b>0.02<sup>b</sup></b>
<b>Biological test:</b>			
Hyperleukocytosis	116 (28.9%)	11 (31.4%)	0.74 <sup>b</sup>
Sd anemic	134 (33.3%)	13 (37.1%)	0.64 <sup>b</sup>
Hypo-albumin	123 (30.6%)	16 (45.7%)	0.06 <sup>b</sup>
CRP positive	185 (46.0%)	19 (54.3%)	0.34 <sup>b</sup>
Accelerated VS	145 (36.1%)	17 (48.6%)	0.14 <sup>b</sup>
<b>(EIM):</b>			
M.Articular	93 (23.1%)	23 (65.7%)	<b>&lt;0.0001<sup>b</sup></b>
M.Eye	22 (5.4%)	06 (17.14%)	<b>0.007<sup>b</sup></b>
M.Dermato	49 (12.2%)	10 (28.6%)	<b>0.007<sup>b</sup></b>
Relapse	200 (49.7%)	21 (60%)	0.24 <sup>b</sup>
<b>Complication:</b>			
Anal fissures	83 (20.6%)	11 (31.4%)	0.13 <sup>b</sup>
Anal fistulas	89 (22.1%)	13 (37.1%)	<b>0.04<sup>b</sup></b>
Anoperineal Abscess	62 (15.4%)	02 (5.7%)	0.11 <sup>b</sup>
Anoperineal Stenosis	25 (6.2%)	00 (0.0%)	0.12 <sup>b</sup>
Cancer	01 (0.2%)	00 (0.0%)	0.76 <sup>b</sup>
<b>Diagnostic information:</b>			
Occlusive Sd	111 (27.6%)	17 (48.6%)	<b>0.009<sup>b</sup></b>
Sub-Occlusive Sd	74 (18.4%)	12 (34.3%)	<b>0.02<sup>b</sup></b>
Abscess	50 (12.4%)	02 (5.7%)	0.23 <sup>b</sup>
Fistula	67 (16.7%)	04 (11.4%)	0.42 <sup>b</sup>
Abdominal pain	113 (28.1%)	02 (5.7%)	<b>0.004<sup>b</sup></b>
Peritonal Sd	20 (5.0%)	00 (0.0%)	0.17 <sup>b</sup>

<sup>b</sup>Data analyzed by Chi-square test, Sdanemic : Syndrome anemic, CRP positive : C Reactive Protein positive, Accelerated ESR : Accelerated Erythrocyte Sedimentation Rate, EIM: extra-intestinal manifestations, Occlusive Sd: occlusive syndrome, Sub-Occlusive Sd: sub-occlusive syndrome, Peritonal Sd : Peritonal syndrome

## DISCUSSION

The elderly represent an increasing proportion of the IBD population (Nguyen et al. 2017). Crohn's disease (CD) in the elderly is a special entity, characterized by its occurrence in a frail subject, often with associated comorbidity and sometimes a severe course. It can be difficult to make a definitive diagnosis in these patients, as many gastrointestinal diseases that are more common in this age group (Song et al. 2018; Cantoro et al. 2020).

Nevertheless, studies have shown that some features of CD in older versus younger individuals could even be attributed as two different diseases (Cantoro et al. 2020). Because of the different enrollment parameters, others have noted that it is not possible to compare the characteristics of "Elderly" versus "Young" CD (Duncan et al. 2010; Kim et al. 2019).

In our study we evaluated the clinical characteristics and long-term outcomes of elderly patients and the influence of age at diagnosis on baseline characteristics and disease course. Indeed, the survey of 437 patients with CD where the age of young patients is <60 and the age of elderly patients is >60 (Hwang et al. 2017) yielded the following respective proportions: 402 (92%) with an age of diagnosis of  $40.37 \pm 139.75$  in young patients and 35 (8%) with an age of diagnosis of  $65.48 \pm 11.43$  in elderly patients which is similar to literatures data (Triantafyllidis et al. 2000; Cantoro et al. 2020). Our study showed that the estimated frequency in the elderly is close to the 9-23% reported in European studies (Mañosa et al. 2018).

Although elderly patients showed different clinical characteristics, our study revealed a male predominance in young patients compared to elderly patients. However, in other studies the predominance was female (Song et al. 2018). Compared with elderly patients, young patients with CD are much more likely to have a family, surgical, and medical history (with significance that could develop aggressive disease (Cantoro et al. 2020).

Our study showed that 33 non-smoking elderly patients had a significant association ( $p=0.002$ ) compared to young patients. It was noted in the study by Song et al. (2018) that the number of current smokers appears to be lower in

the elderly than in the young. Therefore, further studies are needed (Song et al. 2018). In addition, different age-related immune responses and different gut microbiota may play a role in pathogenesis (Taleban et al. 2015). In contrast, other studies have found that smoking, alcoholism, and appendectomy were risk factors in patients with CD (Feuerstein et al. 2017; Chen et al. 2019).

In France, Hungary and the United States it has been shown that the involvement of the colon was at the time of diagnosis in the elderly (Fumery et al. 2016; Saad et al. 2016; Nguyen et al. 2017). Indeed, the most common location in the elderly was much more the colonic location followed by the ileo-caecal location with a significant association  $P=0.002$ . In contrast to younger patients, the most common location was ileo-caecal (Fumery et al. 2016; Cantoro et al. 2020; Benaissa et al. 2020) followed by colonic location as shown in the study by Charpentier et al where colonic involvement was observed in almost 90% of elderly patients in Northern France, although the difference was statistically insignificant at the upper gastrointestinal tract location and less frequent in the elderly (Charpentier et al. 2014). In Western countries, CD in the elderly is well characterized by the predominance of pure colonic location (Fumery et al. 2016; Hwang et al. 2017). In contrast, some studies of Korean patients found that the small intestine was the most common location in all age groups (Hwang et al. 2017).

In our study the difference in diagnosis was not significant since in 35 elderly patients with Crohn's disease the disease behavior was the inflammatory phenotype which is similar with the study of Geoffrey et al where it was noticed that the most frequent behavior in both groups was inflammatory phenotype (Fumery et al. 2016; Nguyen et al. 2017). Others have suggested that it is possible to have isolated colonic disease and an inflammatory phenotype of the disease with less penetrating complications or perianal disease (Nguyen et al. 2017).

Early diagnosis of Crohn's disease is relatively difficult (Song et al. 2018). It is most often evoked in the elderly by symptoms similar to those of the young. We observed a significant association of 0.003 and 0.04 of elderly patients

who had symptoms of cessation of matter and gas as well as vomiting compared to young patients where the association was highly significant  $<0.001$  (Triantafillidis et al. 2000). Similarly both groups suffered from abdominal pain as presented in the studies of Song et al. 2018. On the other hand, the duration between the onset of symptoms and diagnosis in months was 0.013.

With regard to medical therapy, no significance was shown in either group. However, bi o t h e r a p y ( 5 0 v s . 7 ,  $p = 0 . 2 0$ ), immunosuppressants (104 vs. 6,  $p=0.25$ ) and 5-asa (85 vs. 6,  $p=0.57$ ) were used most in the older group. The low use of corticosteroids in the older group could be explained by the higher risk of drug-related complications (Cantoro et al. 2020). In CD, thiopurines and anti-TNF agents are often used in the postoperative setting for the prevention or treatment of postoperative recurrence (Domènech et al. 2017; Mañosa et al. 2018). Some studies have persuaded that thiopurine used in the elderly group may be a marker of aggressive disease progression, on the other hand others have found that it may imply a milder course. However, this should be interpreted with caution; thiopurines are generally not recommended for elderly patients (Mazor et al. 2013; Taleban et al. 2016).

Medical treatment is the primary therapy in the majority of affected patients (Argeny et al. 2016). However, surgery remains the last resort in patients who do not respond to medication (Riss et al. 2014; Kristo et al. 2015). In our case, the risk of surgery was roughly similar in both groups (73.4% vs. 82.8%,  $p = 0.22$ ). The elderly had higher cumulative rates of surgery than their younger counterparts (Cantoro et al. 2020). Thus, the most frequent resection in elderly patients was sigmoidal resection ( $p = <0.001$ ) followed by ileocaecal resection with ileocolic anastomosis whereas younger subjects had much more frequency to ileocaecal resection with ileocolic anastomosis. Therefore, the risk of bowel resection may reflect the prognosis of patients with Crohn's disease (Jeuring et al. 2016). These results are similar to those revealed in studies of French and Hungarian populations with CD diagnosed at age  $\geq 60$  years and  $< 60$  years (Hwang et al. 2017).

Regardless of age, medical and surgical ant

therapies carry some risk and potential adverse effects that must be carefully evaluated and discussed with patients (Cantoro et al. 2020). Regarding laboratory investigations (biological tests, inflammatory Sd mostly positive with anemic Sd, hypoalbumin and hyperleucocytosis), it was found that there was no significant difference between those of the young and the elderly except for the most frequent examinations such as (AWP, Barium enema, telethorax as well as fibroscopy). This is consistent with other results (Cantoro et al. 2020).

Among the 35 elderly patients, the majority suffered from extra-intestinal pain, including (23 vs 93,  $P=<0.0001$ ) joint pain, (6 vs 22,  $p=0.007$ ) eye problems (10 vs 49,  $P=0.007$ ) as well as dermatological problems as shown in the study by Triantafillidis et al. (2000).

Other studies have suggested that there are complications and that the need for surgery is not directly proportional to the severity of the disease. It is still necessary in case of complications, strictures or abscesses (Cantoro et al. 2020). We also found other complications in our patients, such as anal fistulas, which were more frequent in both young and old patients with a  $P=0.04$ , followed by anal fissures and anoperineal abscesses (Triantafillidis et al. 2000; Song et al. 2018).

## CONCLUSION

In conclusion, CD is heterogeneous by age at diagnosis. It seems that Crohn's disease in the elderly generally follows the same clinical pattern as in young people, with some exceptions related mainly to the type of onset of symptoms and the evolution of the disease.

The management of this group of patients is becoming more and more important, as our results have highlighted a colonic localization and extra-intestinal manifestations in the elderly. We also found that depending on the age and the time of diagnosis, the intestinal resection was sigmoidal and could develop a more aggressive disease with anal fistula involvement.

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