Aims — Jejunoileitis might be a severe form of Crohn’s disease (CD). The aim of the study was to evaluate clinical characteristics, therapeutic modalities and long-term outcome in CD patients with jejunoileitis (CDJI).

Methods — All patients with CDJI followed in the department of Gastroenterology from 1963 to 1999 were included and compared to matched (on year of CD diagnosis) CD controls without jejunoileitis. Data were obtained from retrospective review of medical charts.

Results — Eighteen patients with CDJI were compared to 36 matched CD controls. Median follow-up was 7.65 years in both groups. At time of CDJI diagnosis the following signs were significantly more frequent in patients with jejunoileal CD than in controls: malnutrition (39% vs 3%), pain suggesting obstruction (33% vs 8%), vomiting (28% vs 5%). Patients with CDJI were more frequently male: M/F ratio = 2.0/1.1 (P = 0.03). Upper digestive involvement (esophagus, stomach and duodenum) (67% vs 36%, P = 0.04) and small intestine strictures (61% vs 19%, P = 0.06) were more frequent in CDJI. Initial management was more “aggressive” in CDJI than in controls: steroids in 62% vs 30%, azathioprine in 39% vs 3%, total parenteral nutrition in 28% vs 8% and surgery in 33% vs 17%. During follow-up, the need for azathioprine therapy and surgery were more frequent in CDJI than in controls (extensive small bowel resection in two patients). In 10 of 18 patients, jejunoileitis involvement was diagnosed with a median delay of 3.6 years (range: 0.5-14.5) after CD diagnosis and at time of CDJI diagnosis in the 8 others; outcome after CDJI diagnosis was similar in these 2 groups.

Conclusion — The main revealing signs of jejunoileitis in CD patients are obstruction and malnutrition. Patients with CDJI require more often azathioprine and surgery than CD patients without jejunoileitis. Jejunoileitis is a severe form of CD more frequently complicated by extensive small bowel resection.

SUMMARY

Maladie de Crohn jéjuno-iléale : étude cas-témoins
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C rohn’s disease (CD) is a chronic disorder of the gastrointestinal tract related to a still undetermined pathophysiological mechanism involving hereditary and environmental factors [1]. The clinical course is unpredictable and includes acute episodes followed by periods of remission. In an attempt to better predict the long-term course of the disease and adapt management decisions to the risk of relapse, it would be useful to define subgroups of patients with clinically homogeneous presentations based on demographic and clinical findings and on the initial course of the disease.

Involvement of the ileum and the ascending colon is frequently observed in CD (45-48% of patients), but the disease can involve any part of the gastrointestinal tract. Clinical patterns have been described on the basis of the initial localization and associations with symptoms and complications [2, 3]. Diffuse jejunoileal Crohn’s disease (CDJI), first reported by Crohn and Yonich [4] is an uncommon and poorly described entity which is nevertheless considered to be a severe form of the disease. CDJI is generally...
observed in young patients at diagnosis, with higher mortality compared with other localizations [5] and more frequently requires surgery [6] and azathioprine [7].

The purpose of this retrospective review was to compare the clinical presentation, initial and long-term management practices, and prognosis of all patients with CDJI followed in a single center in comparison with control cases of CD matched for the time of diagnosis. In addition, patients with initial manifestations of CD involving the jejunum-ileum (early CDJI) were compared with patients with CDJI during the course of recognized CD (late CDJI).

Results

Among 335 patients with a diagnosis of CD who attended the unit between 1963 and 2000, 199 had been seen at least 3 times. Among these, the diagnosis was certain CD in 101, probable CD in 88, and possible CD in 10. The medical files of 189 patients with certain or probable CD were thus retained for analysis. None of the patients excluded from the analysis had known jejunoileal involvement. Among the entire series of 335 patients, 18 (5.4%) had jejunoileal involvement. Jejunoileal disease was diagnosed at the initial inflammatory episode in 8 patients and during the course of recognized CD in 10 others (late CDJI) 3.6 years (median, range 0.5-14.5) after initial diagnosis of CD. The 18 patients with CDJI were compared with 36 patients matched for year of diagnosis among the group of patients with certain or probable CD.

Initial features

All results for the CDJI group are expressed using the date of diagnosis of jejunoileal involvement as the reference date. For the control group, the reference date was the date of CD diagnosis.

Demographic data and clinical features at the time of diagnosis are given in tables I and II. There were more males in the CDJI group compared with the control group (M/F sex ratio = 2 vs 1.1). Malnutrition, pain suggestive of obstruction, and vomiting were more frequent in patients with CDJI than in the controls. Upper digestive involvement was more frequent in CDJI patients (67%) than in controls (36%) (P = 0.04) and involvement of the terminal portion of the ileum was less frequent (78% and 97%, respectively) (P = 0.037) (table III). Stricture of the small bowel was significantly more frequent in patients with CDJI than in controls (61% vs 19%) (P = 0.006). Epithelioid and giant-cell granulomas were observed in 78% of the CDJI patients and in 53% of the controls (P = 0.75).

The initial treatment was different for patients with CDJI compared with the controls in that the following treatments were given significantly more often: corticosteroids (62% vs 30%), azathioprine (39% vs 3%), total parenteral nutrition (28% vs 8%) (table IV). None of the patients whose CDJI was diagnosed after diagnosis of CD was given azathioprine before discovery of the jejunoileal lesions. The median year of diagnosis of CDJI was more recent in the 7 patients with CDJI who were given azathioprine at diagnosis of CDJI (1998, range: 1986-1999) compared with the 11 patients with CDJI who were not given azathioprine at diagnosis of CDJI (1990, range: 1970-1999). Seventy-five percent (9/12) of the patients with CDJI given azathioprine were also treated with corticosteroids compared with 92.3% (12/13) of the controls.

Six of the 18 patients (33%) with CDJI underwent first-line surgery (excluding anoperineal surgery) versus 17% of the controls (P = 0.18). Five patients with CDJI underwent small bowel resection (associated with stricturoplasty in one patient and segmentary colectomy for another); ileocecal resection was performed in the sixth. Resection of the ileum and the ascending colon was performed in 4 of the 6 controls with first-line surgery (including one who also had small bowel resection), ileocecal resection in one and small bowel resection in the other. Two patients with CDJI had undergone surgery before diagnosis of the ileojejunal involvement.

Clinical course after the first acute episode

Mean duration of follow-up was the same in the two groups: 7.65 years (range: 1-19) for the CDJI group and 1-30 for the
controls. Two patients with CDJI (11%) and 8 controls (22%) were lost to follow-up. One control died of AIDS 16 years after the diagnosis of CD. Irrespective of the type of management (medical or surgical), all patients achieved remission after the first acute episode except one patient with CDJI. Four patients with CDJI (22%) and 5 controls (14%) did not experience relapse during the follow-up (P = 0.46). Median follow-up for these patients, 80 and 110 months respectively, was longer than the median time to the first relapse in the other patients (13 months for CD patients and 18 months for CDJI patients). The 4 patients with CDJI who did not experience relapse had been given azathioprine as the initial treatment and 3 of the 4 were still taking azathioprine at last

Table I. – Demographic characteristics of patients with CDJI compared to CD controls.
Caractéristiques démographiques des malades avec MCJI et des témoins appariés atteints de MC de localisation autre que jéjuno-iléale.

<table>
<thead>
<tr>
<th></th>
<th>CDJI (n = 18)</th>
<th>CD controls (n = 36)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men/women</td>
<td>12/6</td>
<td>19/17</td>
<td>0.33</td>
</tr>
<tr>
<td>Age at diagnosis of CD*, years</td>
<td>20.8 (12.4-80)</td>
<td>22.6 (14.5-51)</td>
<td>0.91</td>
</tr>
<tr>
<td>Age at diagnosis of CDJI*, years</td>
<td>24.1 (14.5-80)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Time to diagnosis** of CD, months*</td>
<td>4.4 (0-137)</td>
<td>5.3 (0-141)</td>
<td>0.52</td>
</tr>
<tr>
<td>Disease course in years *</td>
<td>7.65 (1-19)</td>
<td>7.65 (1-30)</td>
<td>NS</td>
</tr>
<tr>
<td>Smokers, %</td>
<td>50</td>
<td>44***</td>
<td>0.9</td>
</tr>
</tbody>
</table>

* median (range)
** period between symptom onset and establishment of diagnosis
*** data missing in 7 controls

Table II. – Initial clinical characteristics of patients with CDJI compared to CD controls.
Caractéristiques initiales des malades avec MCJI et des témoins appariés atteints de MC de localisation autre que jéjuno-iléale.

<table>
<thead>
<tr>
<th></th>
<th>CDJI (n = 18)</th>
<th>CD controls (n = 36)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malnutrition</td>
<td>7 (39)</td>
<td>1 (3)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Vomiting</td>
<td>5 (28)</td>
<td>2 (5)</td>
<td>0.03</td>
</tr>
<tr>
<td>Symptoms suggesting obstruction</td>
<td>6 (33)</td>
<td>3 (8)</td>
<td>0.04</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>13 (72)</td>
<td>24 (67)</td>
<td>0.67</td>
</tr>
<tr>
<td>Weight loss</td>
<td>8 (44)</td>
<td>12 (33)</td>
<td>0.99</td>
</tr>
<tr>
<td>Fever</td>
<td>3 (17)</td>
<td>11 (30)</td>
<td>0.33</td>
</tr>
<tr>
<td>Anoperineal manifestations</td>
<td>4 (22)</td>
<td>8 (22)</td>
<td>0.4</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>9 (50)</td>
<td>24 (67)</td>
<td>0.23</td>
</tr>
</tbody>
</table>

Table III. – Initial inflammatory involvement in patients with CDJI compared to CD controls.
Topographie initiale des lésions liées à la MC des malades avec MCJI et des témoins appariés atteints de MC de localisation autre que jéjuno-iléale.

<table>
<thead>
<tr>
<th>Topology</th>
<th>CDJI (n = 18)</th>
<th>CD controls (n = 36)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper digestive tract</td>
<td>8 (67)*</td>
<td>5 (36)*</td>
<td>0.04</td>
</tr>
<tr>
<td>Terminal ileum**</td>
<td>14 (78)</td>
<td>35 (97)</td>
<td>0.037</td>
</tr>
<tr>
<td>Terminal ileum alone **</td>
<td>5 (28)</td>
<td>15 (42)</td>
<td>0.31</td>
</tr>
<tr>
<td>Colon**</td>
<td>12 (67)</td>
<td>17 (47)</td>
<td>0.10</td>
</tr>
<tr>
<td>Colon alone**</td>
<td>3 (17)</td>
<td>1 (3)</td>
<td>0.10</td>
</tr>
<tr>
<td>Terminal ileum and colon**</td>
<td>9 (50)</td>
<td>16 (44)</td>
<td>0.69</td>
</tr>
<tr>
<td>Rectum**</td>
<td>4 (22)</td>
<td>6 (17)</td>
<td>0.71</td>
</tr>
<tr>
<td>Anoperineal**</td>
<td>4 (22)</td>
<td>8 (22)</td>
<td>0.99</td>
</tr>
</tbody>
</table>

* searched for in 12 of the 18 patients with CDJI and in 14 of the 36 controls
** in addition to the jejunoileal involvement in the CDJI group
follow-up. The 5 controls who did not experience relapse had never been given azathioprine. The relapse-free curve was similar in the two groups (figure 1). Median time interval between acute episodes was similar in the two groups, 15 months (range: 10-23) for CDJI patients and 14 months (range 6-21) for controls. Symptoms of intestinal obstruction were more frequent for acute exacerbations in the CDJI patients, 39% at first relapse, 60% at second relapse and 38% at third relapse versus 13%, 18% and 18% respectively for the controls.

**Therapeutic management during follow-up**

The cumulative percentage of operated patients was similar in the two groups (56% for CDJI and 53% for controls). The Kaplan-Meier survival curve showed that the probability of at least one operation was not significantly different for the two groups (P = 0.14) (figure 2). The median time to surgery was 4 months in CDJI patients after diagnosis of the ileojejunal involvement and 8 months for controls. The percentage of patients requiring surgery (excluding anoperineal surgery) was higher in the CDJI group (28%) than in the control group (11%). Median time to relapse after the first surgery was 26 months for patients with CDJI versus 38 months for controls (P = 0.16). For patients with CDJI, the indication for initial surgery was small bowel stricture in 90% of the cases; small bowel resection was performed in 59% and ileocecal resection in 25%. For the controls, the indication for initial surgery was stricture of the terminal ileum in 56% and terminal ileitis without stricture in 37%. Ileocecal resection was performed in 87% of the patients.

**Table IV.** – Initial therapeutic management of patients with CDJI compared to CD controls.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>CDJI (n = 18)</th>
<th>CD controls (n = 36)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticosteroids</td>
<td>11 (62)</td>
<td>11 (30)</td>
<td>0.03</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>7 (39)</td>
<td>1 (3)</td>
<td>0.001</td>
</tr>
<tr>
<td>Total parenteral nutrition</td>
<td>5 (28)</td>
<td>3 (8)</td>
<td>0.04</td>
</tr>
<tr>
<td>5-ASA and/or antibiotics</td>
<td>3 (17)</td>
<td>25 (69)</td>
<td>0.03</td>
</tr>
<tr>
<td>Surgery*</td>
<td>6 (33)</td>
<td>6 (17)</td>
<td>0.18</td>
</tr>
</tbody>
</table>

* anoperineal surgery excluded
5-ASA: 5-aminosalicylic acid

The cumulative rate of corticosteroid therapy was not significantly different between the two groups, 60% and 40% at one year, 78% and 56% at five years and 78% and 62% at ten years for CDJI and CD patients, respectively.

Azathioprine was the only immunosuppressor drug given to the patients in this study population. Azathioprine was prescribed during the follow-up significantly more often for CDJI patients (64%) than controls (36%) (P = 0.01). The most frequent indications for azathioprine were extensive small bowel involvement (67%) and corticosteroid dependence (42%) for CDJI patients and recurrent relapse (23%) and perineal involvement (23%) for controls. The probability of azathioprine treatment was higher among patients with CDJI than among controls (P = 0.028) (figure 3). At one year, 39.4% (95% confidence interval CI 95; 17-62) of the CDJI patients had been given azathioprine versus 9.7% (CI 95: 0-20) of the controls. At five years, these percentages were 64.6% (CI 95: 41-88) in CDJI patients versus 23.6% (CI 95: 8-39) in controls. Median time to administration of azathioprine was 5.2 months after diagnosis of CDJI in the CDJI patients versus 32.5 months after diagnosis in the CD patients (P = 0.25). The rate of persistent remission with immunosuppressor treatment was not significantly different between the two groups, 64% and 64% for CDJI and 77% and 38% for controls at one and three years, respectively (NS).

At last follow-up, corticosteroid dependence and extensive small bowel resection were more frequent among patients with
surgery, but did not mention the pattern of the clinical course [6]. In 1993, Tan et al. reported some information concerning at first diagnosis of CD and subsequent first-line management [6, 7]. In 1993, Tan et al. reported some information concerning at first diagnosis of CD and subsequent first-line management [6, 7]. The corresponding figures for controls were: asymptomatic, 52.7% (5 of 31 patients taking azathioprine), 33.3% without treatment; and symptomatic 14% (1 of 5 patients taking azathioprine). The corresponding figures for controls were: asymptomatic, 52.7% (5 of 31 patients taking azathioprine), 33.3% without treatment; and symptomatic 14% (1 of 5 patients taking azathioprine).

Comparison between early and late diagnosis of CDJI
The demographic data (sex ratio, age at diagnosis of CDJI, year of diagnosis of CD and CDJI and duration of follow-up (counting from diagnosis of CD and from diagnosis of CDJI) were similar in the two subgroups of patients with CDJI (jejunoileal involvement diagnosed early or late). The initial gastrointestinal involvement of late CDJI concerned the terminal ileum in 7 patients, the colon in 7, the rectum in 3, the anoperineal region in 1 and the upper digestive tract in 1. Seventeen of the 10 patients with late CDJI had not experienced an acute episode before the diagnosis of jejunoileal involvement. Before the diagnosis of CDJI, none of the 10 patients with late CDJI had been given azathioprine and only 2 had undergone surgery. After the diagnosis of CDJI, the probability of remaining in remission was similar for patients with early and late CDJI (P = 0.98) (figure 4). At last follow-up, the percentage of patients taking immunosuppressor drugs was similar, 75% of the early CDJI patients and 60% of the late CDJI patients (NS). Three patients with early CDJI (37.5%) and 7 patients with late CDJI (70%) underwent surgery (NS), with extensive resection of the small bowel in one patient in each subgroup.

Discussion
There are few data in the literature concerning CDJI, undoubtedly due to the low prevalence of jejunoileal involvement. In our series, the prevalence of jejunoileal involvement was 5.4%, similar to the rates (3-6%) reported by others [3, 6, 7, 9, 10]. The most recent reports describe patients with jejunoileal involvement at first diagnosis of CD and subsequent first-line management [6, 7]. In 1993, Tan et al. reported some information concerning long-term prognosis among CDJI patients mainly treated with surgery, but did not mention the pattern of the clinical course [6]. In 1999, Touzé et al. published data from the EPIMAD registry after a median 34 months follow-up [7]. The long follow-up in our patients (median 7.65 years) is exceptional and allowed us to evaluate early and long-term management schemes separately.

The main methodological limitation of this study is the retrospective nature of the recruitment over a long period (1963-2000). The fact that all the patients were treated in the same unit and the case-control matching scheme (according to year of diagnosis of CD) however limits bias caused by changes in management options over time. We have been unable to find any precise data in the literature concerning the diagnosis of jejunoileal involvement during the course of follow-up after diagnosis of CD (late CDJI). Tan et al. [6] reported late CDJI in 34.7% of their patients. In our series, the patients with late CDJI probably did not have jejunoileal involvement at the time of diagnosis of CD; a barium study of the small bowel had been performed in 7 of 10 patients at the time of the initial diagnosis. In addition, the clinical course of the disease in late CDJI patients was less severe before development of jejunoileal involvement; thereafter the clinical expression was similar to that in patients with early CDJI (figure 4).

The clinical manifestations of CDJI were dominated by symptoms of obstruction (observed in 33% of patients versus 8% of controls) and malnutrition (39% versus 3% in controls). This type of inaugural manifestation is different than reported in earlier series [6, 7, 11] where the main symptoms were abdominal pain, weight loss and diarrhea. This type of presentation is however similar to that noted in two series of patients with CD of the proximal portion of the small bowel where proximal obstruction was observed in 56% and 71% of the patients [10, 12]. The high frequency of esophagogastroduodenal involvement in our patients with CDJI (67%) was higher than in earlier series (30% and 55%) [6, 7]. However, search for upper digestive tract involvement was performed in only 66% of the patients with CDJI and in 39% of the controls. At diagnosis, 78% of the patients with CDJI also had terminal ileitis, an expression of the diffuse nature of the small bowel involvement. Median age at diagnosis of CDJI was 20.8 years. Young age at diagnosis was also reported in earlier series [6, 7, 11]. The influence of age at disease onset on the localization of CD has been demonstrated in hospital series where proximal lesions were more frequent among young subjects [2, 10] particularly children and adolescents [13-15].

Despite the lack of significant difference compared with controls, probably because of the small sample size, we noted the trend towards male predominance in CDJI (sex ratio 2 vs 1.1) reported by others [6, 7, 11, 12] which is the contrary to the female predominance observed in epidemiological series of unselected patients with CD [2, 8, 16-23]. As was demonstrated in two recent studies [24, 25], smoking, at diagnosis or during the course of the disease, does not influence disease localization.

In series of CD patients treated medically or surgically where extension is clearly described, there has been no difference in the frequency of granulomas in different intestinal segments during the course of the disease. Conversely, granulomas are more frequent among younger patients at diagnosis (26 to 73% in the most recent series with 73% concerning young subjects) [26]. The high prevalence of granulomas in our patients (78%) would be related to the young age of our population and not disease localization.

One of the original features of our study concerns evaluation of the management modalities implemented at diagnosis. Initial treatment was more “aggressive” for patients with CDJI compared with CD controls, the initial treatment using corticosteroids in 26% (versus 30%), azathioprine in 39% (versus 3%), total parenteral nutrition in 28% (versus 8%), and surgery in 33% (versus 17%). Small bowel stricture was the most frequent...
indication for surgery. Management during follow-up was also more aggressive for CDJI patients with surgery and immunosuppressors being more frequent. Compared to controls, patients with CDJI underwent several surgical procedures more often (28% versus 11%) and appeared to experience relapse earlier after initial surgery (26 months versus 58 months) (P = 0.16). This would most likely be explained by the principal indication for surgery in the CDJI patients: stricture (jejunoileal stricture in two-thirds of the patients). Surgical series studying factors favoring postoperative recurrence have demonstrated that indications for second procedures were similar to indications for the first procedures [27-29], that the rate of repeated resections was higher when the indication was intestinal obstruction [28], and that multifocal involvement increases the risk of recurrence [30]. In our series, patients with CDJI underwent surgery less often than the patients reported by Tan et al. [6] where the recruitment period ran from 1960 to 1991: 82% of the patients at last follow-up and 62% with more than 2 operations. Nevertheless, only 21% of the patients in Tan’s population were given immunosuppressors (for partial response to steroids), noting that the demonstration of the efficacy of azathioprine given for prevention of postoperative recurrence was published in the 90s [31-32]. Like our colleagues from Lille [7] we observed more frequent requirement and earlier use of azathioprine after diagnosis of jejunoileal involvement. The probability of immunosuppressor prescription in patients with CDJI and controls was 39.4% and 9.7% and 64.6% and 23.6% at 1 and 5 years, respectively (figure 3). The main indication for prescription of azathioprine was extensive small bowel involvement [67%]. This is in line with the current trend towards wider indications for azathioprine in patients who have a risk of extensive small bowel resection due to repeated resections. The relapse rate in patients given azathioprine was similar in CDJI and control patients, 36% and 23% at one year respectively. These results are in agreement with recent data [31, 33-35] showing that the topography of the lesions has no influence on the long-term efficacy of azathioprine [36, 37]. None of our patients were given anti-TNFα antibodies, because of the recruitment period (1963-2000) and the frequency of strictures (61% of the patients with CDJI), a contraindication to azathioprine.

To our knowledge, the rate of persistent remission after a first acute episode of CDJI has not been studied to date. In our work, 22% of the patients with CDJI remained in remission after the first flare-up (median follow-up 80 months). A similar rate was found in controls (14%, NS). These rates are similar to those reported in a series of patients with colonic CD (1.4%, median follow-up 13.4 years) [38], and of non-selected patients with CD (24%, 5-year follow-up) [39]. The data collected at last follow-up by Tan et al. showed that 75% of the patients were in remission without treatment after a mean 16 years follow-up [6]. These figures are in agreement with those reported by Etienney et al. [40] who found that half of the population of 177 non-selected patients with CD followed for 20 years were in remission with medical treatment, one quarter were in remission without treatment, and one quarter relapsed despite treatment. In light of these reports, we suggest that with adapted management, particularly more aggressive treatment in the event of jejunoileal involvement, the pattern of the disease course of CDJI is similar to that of CD without jejunoileal involvement.

In conclusion, CDJI is observed in twice as many men as women. About half of the patients do not have jejunoileal involvement at the time of diagnosis of CD, the jejunoileal involvement developing later during the course of the disease. Esophagogastroduodenal involvement is associated with jejunoileal involvement significantly more often. Disease manifestations involve obstruction and malnutrition more often and lead to extensive resection of the small bowel more frequently due to the requirement for repeated resections. The risk of a second surgical intervention might be decreased by systematic use of immunosuppressors at diagnosis of CDJI and the risk of extensive resection by performing stricturoplasty rather than resection whenever technically possible.

REFERENCES


