Incidence of inflammatory bowel disease in Corsica from 2002 to 2003

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SUMMARY

Objectives — The aim of this prospective epidemiological study was to determine the incidence of inflammatory bowel diseases (IBD) in Corsica using the same methodology as that of the EPIMAD registry.

Methods — Between January 1st, 2002 and December 31, 2003, all gastroenterologists in Corsica (N=19) enrolled patients consulting for the first time with clinical symptoms compatible with IBD. Each case was reviewed by another expert gastroenterologist to assign a diagnosis of definite, probable, possible Crohn’s disease (CD), ulcerative colitis (UC) or unclassified/able chronic colitis.

Result — Eighty-one new cases were recorded, including seventy-one diagnoses of IBD (definite and probable cases), with 20 (28%) CD, 49 (69%) UC and 2 (3%) unclassifiable chronic colitis. The age-adjusted incidence (per 10^5 inhabitants/year) was 4.05 for CD and 9.5 for UC. The female/male ratio and median age at time of diagnosis were 1.3 and 29 years for CD and 0.63 and 44 years for UC, respectively. The median time from symptom onset to diagnosis was five months for both diseases.

Conclusion — In Corsica, the observed incidence of CD is close to that observed in other metropolitan French regions. These data are contrary to the north-south gradient reported for this disease. Our figure of 9.5/10^5 for UC in Corsica is two-fold higher than reported in other metropolitan French regions. Genetic and/or environmental factors may explain these findings.

Original Article

RÉSUMÉ

Incidence des maladies inflammatoires cryptogénétiques intestinales en Corse en 2002 et 2003

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Objectifs — Évaluer de manière prospective l’incidence des maladies inflammatoires cryptogénétiques intestinales (MICI) en Corse selon la méthodologie du registre EPIMAD.

Méthodes — Du 1er janvier 2002 au 31 décembre 2003 tous les gastroentérologues (N=19) de Corse ont recensé les cas incidents de MICI. Tous les dossiers de maladie de Crohn (MC), de rectocolite hémorragique (RCH) et de colites chroniques inclassables (CCI) étaient classés par un gastroentérologue référent en cas certains, probables ou possibles.

Résultats — Quatre-vingt-un cas ont été répertoriés dont 71 cas de MICI incluant uniquement les cas certains et probables. Ces 71 cas étaient repartis en 20 (28 %) MC, 49 (69 %) RCH et 2 (3 %) CCI. L’incidence standardisée à l’âge (pour 10^5 habitants/an) était de 4,05 pour la MC et de 9,5 pour la RCH. Le sex-ratio (féminine/homme) était de 1,3 pour la MC et de 0,63 pour la RCH. L’âge médian au moment du diagnostic était de 29 ans pour la MC et de 44 ans pour la RCH. Le délai médian entre le début des symptômes et le diagnostic était de 5 mois pour les deux affections.

Conclusion — En Corse, l’incidence de la MC est proche de celle observée dans les autres régions de France métropolitaine, ce qui va contre la notion de gradient nord-sud pour cette affection. L’incidence de la RCH est plus de deux fois supérieure à celle des autres régions de France. Il pourrait donc exister en Corse des caractéristiques génétiques et/ou environnementales particulières favorisant l’émergence de la RCH.

Introduction

In France, inflammatory bowel disease (IBD) exhibits distinctive epidemiological features not observed in other countries, with a particularly high incidence of Crohn’s disease (CD) and a low incidence of ulcerative colitis (UC). The current trend is a widening difference in the incidence rates for these two diseases due to an increasing incidence of CD and, inversely, a decreasing incidence of UC [1].

Recent work based on national healthcare fund data [2] has demonstrated a north-south gradient in France (including Corsica) for CD but not for UC. The epidemiology of IBD in Mediterranean countries is not well known.

We thus undertook a prospective evaluation of incidence cases of IBD in Corsica, a French island in the Mediterranean Sea. Corsica is particularly adapted for this type of epidemiological study because the small population (260,196 inhabitants according to the 1999 Insee census) is relatively isolated from neighboring regions and migratory flow is minimal.

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Materials and methods

This prospective study was conducted over a two-year period from January 1st 2002 to December 31st 2003. All incident cases of IBD were recorded during this period. In order to compare findings with those in other French registries, the EPIMAD methodology was used [3].

Before initiating the survey, the nineteen gastroenterologists practising in the island of Corsica were informed of the objectives and the methodology of the study via information meetings, regular postal letters and personal contact with the investigators. Data were collected using a standard form designed from the EPIMAD registry. Data items collected were: patient age, gender, time from symptom onset to diagnosis, and clinical, endoscopic, histological and radiographic findings at diagnosis. The date of diagnosis was defined as the date of the first examination providing evidence of lesions compatible with the diagnosis of IBD.

Patients included in this study consulted for the first time for symptoms of suspected IBD. The exclusion criteria included positive stool culture or antibiotic or nonsteroidal inflammatory drug treatment during the month preceding the symptoms, except when symptoms persisted for more than one month after treatment withdrawal or recurred after a symptom-free period.

The definition of IBD was descriptive, based on clinical, endoscopic and histological evidence [4, 5]. Patients were considered to have definite, probable or possible CD or UC depending on symptom agreement with established diagnostic criteria (see appendix 1). Patients with symptoms compatible with both UC and CD constituted a subpopulation of patients considered to have unclassified/able chronic colitis. Cases of acute colitis (clinical course less than six weeks) were excluded.

Mean annual incidence rates were expressed using a standardized protocol, grouping together definite and probable cases of each disease (UC, CD) and excluding possible cases.

The survey concerned only patients residing on Corsica. Students, sailors and military personnel where included if their permanent residence was on the island. The study was reported to the national commission for the protection of personal rights 1 and all patients gave their informed consent before inclusion.

For each patient with a suspected diagnosis of IBD, the participating gastroenterologist filled out an anonymous report form. Each case report was then analyzed by an expert in IBD from the Nice University Hospital who established an independent diagnosis which was later compared with the initial diagnosis reported by the Corsica gastroenterologist. In the event of disagreement between the two opinions, a second expert in IBD from the Nice University Hospital was called in to establish a final consensus diagnosis.

Results

During the two-year study period (2002-2003), 81 new cases of IBD were recorded, including 71 (87.6%) with a definitive or probable diagnosis of IBD: 49/71 patients (69%) had UC, including 13 with isolated rectal involvement and 20/71 patients (28%) had CD, including four under 16 years old and two (3%) with unclassifiable chronic colitis (figure 1). Six patients (7.4%) had acute colitis.

Incidence and geographical distribution

Based on raw data the annual incidence per 100,000 inhabitants was 3.84 new cases of CD and 9.41 new cases of UC. After adjusted for age, the figures were 4.05 cases per 10^5 inhabitants for CD and 9.50 for UC. Urban inhabitants accounted for 62% of the cases and rural inhabitants for 38%.

Incidence by gender and age

Among the 20 patients with CD, eleven were women and nine were men. Among the 49 patients with UC, 19 were women and 30 were men. The F-M ratio, determined for comparison with other French registries, was 1.3 for UC, but with male predominance among patients aged over 50 years, and 0.63 for UC, with male predominance in all age groups (figures 2 and 3). Median age at diagnosis was 29 years (range 11-58 years) for CD and 44 (range 18-80 years) for UC.

Smoking and appendectomy

For the CD patients, 30% were smokers and 5% former smokers. For the UC patients, 6% were smokers and 16 former smokers (table I). Appendectomy was noted in the medical history of 4% of the patients with UC and in none of those with CD.

Clinical findings

Diarrhea was the most common symptom, observed in 85% of patients. Abdominal pain was the second most common complaint, observed in 65%. Median time from symptom onset to diagnosis was five months (range 1-58 months) for both diseases. Coloscopy was performed in 98.7% of patients, and had visualized the entire colon (including the cecum) in 97.5% of patients. Tissue biopsies for histology were obtained in all procedures. Twenty percent of the endoscopy reports failed to provide any information concerning exploration of the ileum. When mentioned, the ileum had been explored in one-third of the patients, basically those with CD (the ileum was explored in 14 of the 20 patients with CD (70%). Among the entire cohort, a small bowel study was performed in seven patients and in four patients with CD disclosed an ileal anomaly which was later confirmed at ileoscopy. A history of IBD in a first-degree relative was noted in 7.9% of patients.

Disease localization

Three quarters of the patients with CD exhibited ileal involvement, 15% with ileal stricture. Involvement was limited to the ileum in 20% of patients and to the ileocecal region in 20%. The other 35% of the CD patients had ileal involvement associated with pancolitis (30%). One-quarter of patients exhibited isolated colonic involvement. Four patients presented anopereineal lesions (two fissures, one fistula and one anal stricture).

Among the patients with UC, localizations were: left colon alone (56%), rectum alone (27%), pancolitis (12.5%), right colon (4.5%).

Discussion

By recording all incident cases, this survey probably enabled nearly exhaustive data collection since the study population was geographically isolated on an island known to have a limited migratory flow (the number of island residents who consulted on the mainland for first manifestations was probably negligible). This methodology, which has been evaluated and validated by the EPIMAD registry [3], might underestimate the real incidence of UC by not recording patients diagnosed by practitioners other than gastroenterologists. In our study a coloscopy was performed in 98.7% of patients, necessarily by a gastroenterologist who reported the case. The proportion of patients with rectal involvement alone can be used to estimate the quality of data collection. This proportion varies from 22 to 59% in the literature [3] and reaches 27% in our study. In order to enable a valid comparison of our findings with those reported by other French
registries, we adopted the methodology used by the EPIMAD registry.

In our study, the age-adjusted incidence was 9.5 for UC and 4.05 for CD. Both of these figures might be underestimates considering that patients with a possible diagnosis of IBD and those with acute colitis were excluded. In certain registries, acute colitis is noted in up to 37% of incident cases [6] which, according to the literature [7], corresponds to a first manifestation of IBD in 35-50% of patients. Among our six patients with acute colitis, at three years follow-up, one had overt UC, one had an unclassifiable chronic colitis and four were lost to follow-up (these four patients were not retained for determining incidence figures). In Corsica, the incidence of UC is clearly higher than that of CD. The inverse is observed in other areas of metropolitan France (excepting the Midi-Pyrénées). The incidence of UC in Corsica is twice that observed in other French registries while the incidence of CD is not very different from that in other regions (figure 4).

Median age at diagnosis was 29 years for CD, comparable with data in the literature. Conversely, for UC, median age at diagnosis was 44 years while in most series it is reported around 35 years [1, 6-11]. This older age at diagnosis might be related to more pronounced student migration to the mainland. There might also be a geographical effect since the incidence pattern observed in Corsica, an island off the south coast of France, is similar to that observed in the Midi-Pyrénées region which is located in southwestern France. This might correspond to a “frontier” between northern regions, with a higher incidence of CD than UC, and southern regions, with a higher incidence of UC than CD.

Like most reports, we found a clear male predominance for UC (F-M ratio 0.63) in all age groups (figure 3). Certain authors [8], suggest that this male predominance could be related to smoking, in addition to other environmental factors including hormonal effects. The male-female difference is also seen in the incidence peaks. A second peak, observed in the 50-60 year age group in men for both CD and UC was not found in women. For UC, this second peak was even greater than the first peak. Another study also found a higher second peak for men [12] and in more recent work [8, 13], the trend is toward a peak incidence in the 20-40 year group with a slower regular decline thereafter in men.

<table>
<thead>
<tr>
<th></th>
<th>Crohn</th>
<th>UC</th>
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<tr>
<td>Median age in years</td>
<td>29</td>
<td>44</td>
</tr>
<tr>
<td>(range)</td>
<td>(11-58)</td>
<td>(18-80)</td>
</tr>
<tr>
<td>Sex-ratio (F/M)</td>
<td>1.30</td>
<td>0.63</td>
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<tr>
<td>Median time from symptom onset to diagnosis (range)</td>
<td>5 months (1-58)</td>
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<tr>
<td>Smoking status</td>
<td>Smoker</td>
<td>30%</td>
</tr>
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<td></td>
<td>Former smoker</td>
<td>5%</td>
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<tr>
<td></td>
<td>6%</td>
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<td></td>
<td>16%</td>
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<td>History of appendectomy</td>
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<td></td>
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<tr>
<td></td>
<td>4%</td>
<td></td>
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<tr>
<td>Geographic distribution</td>
<td>North</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>37</td>
<td></td>
</tr>
<tr>
<td></td>
<td>South</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td></td>
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<tr>
<td>Standardized incidence (per 100,000 habitants/year)</td>
<td>4.05</td>
<td></td>
</tr>
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<td></td>
<td>9.50</td>
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Fig. 1 – Definitive and probable diagnosis of Crohn’s disease, ulcerative colitis, and unclassifiable chronic colitis in Corsica.

Répartition des cas certains et probables de MC, RCH et CCI en Corse.

Fig. 2 – Annual incidence of Crohn’s disease by age group and gender in Corsica (2002-2003).

Incidence of inflammatory bowel disease in Corsica from 2002 to 2003

Our incidence rates were slightly higher than the average rates for southern Europe determined in a multicentric European study [8] which included 2201 patients (8 for UC and 3.6 for CD). They were also lower than the average rates for northern Europe (11.4 for UC and 8 for CD). Thus the Corsica rates are intermediary between those reported for northern and southern Europe and are close to the European average (9.8 for UC and 5 for CD). If the north-south gradient is real, this is a paradoxical finding for an island situated in the very southern part of Europe.

The epidemiology of IBD in Mediterranean countries is highly variable depending on the geographical area, but there is a general trend towards a lower incidence for CD and a higher incidence for UC. Nevertheless, in recent years in southern Europe the trend has moved towards an increase in the incidence of IBD, particularly UC [14-16] (figure 5). Although solid evidence is still lacking, it would be reasonable to attribute a protective effect to the components of the traditional Mediterranean diet. As has been suggested for Japan [17], changing eating habits in Mediterranean countries might have a favoring effect on the development of IBD. In the Heraklion region in Crete, where the epidemiological features are similar to those in Corsica, incidence rates for UC and CD are 8.9 and 3 respectively [15, 16]. Median age at diagnosis of UC is also high, between 45 and 64 years, while for CD, the average is situated in the 25-34 rage also found for other regions.

As expected, the proportion of smokers was higher in CD (30%) than in UC (6%). While smoking has an impact on the disease course [18, 19], it does not appear to affect disease severity at the initial presentation since we were unable to observe any difference between smokers, non-smokers, and former smokers. The proportion of former smokers was higher in UC (16%) than CD (5%), in agreement with now well documented evidence that smoking cessation improves the prognosis of CD while inversely is a risk factor during the course of UC [20].

We also noted a history of appendectomy in 4% of the UC patients and none of the CD patients. The role of appendectomy during the course of UC is an open issue, but most studies are in favor of a protective effect. The meta-analysis reported by Koutroubakis et al. [21] noted that a history of appendectomy was observed in 10% of controls and 4% of patients. We found this same 4% figure in our UC patients but the absence of a control group prevents any conclusion concerning a relationship between appendectomy and UC.

Median time from symptom onset to diagnosis was five months in our study, a longer delay than reported in other French
series: two months for the Nord-Pas-de-Calais and French Antilles registries, three months in Puy-de-Dôme and Brittany. Longer delays up to 13 months have also been reported [22].

Ileal involvement was noted in 75% of the CD patients and was the only zone involved in 20%. These figures are quite similar to those from the EPIMAD and ABERMAD registries. Variable patterns of evolving localizations have been reported. Endoscopic exploration of the ileum had been performed in only one-third of the 81 patients with suspected IBD. Among the explored patients, 70% had definitive or probable CD. This finding suggests that during a first-line colonoscopy, gastroenterologists pursue the exploration to the ileum when the colonic involvement is compatible with CD or an unclassifiable chronic colitis but rarely when the colonic lesions are suggestive of UC.

We observed pancolitis in 12.5% of patients with UC, a finding comparable with data from other French studies. The disease course is again variable: during the EPIMAD study the rate of pancolitis increased from 10% to 17.5% while the trend was towards a decline in other studies [23, 24]. There was also a family history of IBD in 7.9% of our patients, a rate which is higher than in other French series.

In conclusion, this prospective epidemiological study, the first conducted in Corsica, demonstrated a high incidence of IBD. The incidence of CD was similar to that observed in other regions of France where data are available, a finding which does not favor a north-south disease gradient. The incidence of UC was more than twice that observed in other French registries. Considered globally, our data suggest that certain genetic and/or environmental factors could affect the development of IBD in Corsica, particularly for UC.

REFERENCES


Appendix 1. — Diagnostic criteria for the classification of inflammatory bowel disease.

**Crohn's disease (CD)**

- Certain CD
  - Presence of epithelioid and giant-cell granulomas on endoscopic biopsy or surgical specimens.

- Probable CD
  - History of diarrhea and/or abdominal pain for at least six weeks and at least two of the following three criteria: a) cobblestone aspect or colonic stenosis observed radiologically or endoscopically; b) histology compatible with CD; c) fistula and/or abscess arising from the intestine.

Small bowel lesions, and, irrespective of the symptoms or their duration, presence of at least two of the three criteria listed above.

- Possible CD
  - Small bowel lesions with a history of diarrhea (and/or abdominal pain) for at least six weeks, and presence of one of the three criteria listed above.

Small bowel lesions with or without colonic involvement and presence of one of the three criteria listed above, irrespective of the duration of the symptoms.

**Ulcerative colitis**

- Certain UC
  - History of diarrhea and/or proctorrhagia for at least six weeks, and at least two of the following criteria: a) characteristic endoscopic aspect (granulous mucosa which is fragile or ulcerated or both); b) characteristic radiologic aspect (ulcerations, narrowing, shortening); c) typic histology on endoscopic, surgical or autopsy specimens.

- Probable UC
  - History for at least six weeks, but non typical UC, and at least one of the three criteria listed above.

  Surgical or autopsy sample presenting a typical gross aspect but without the characteristic histologic aspect.

- Possible UC
  - Typical history for at least six weeks, but with no morphological or histological argument compatible with this diagnosis.

  - Certain, probable, possible rectitis

  These conditions are defined by the same criteria as used for UC, with certain proof that the sigmoid is normal above the pathological rectum. The rectosigmoid junction is arbitrarily situated 20 cm above the anal margin.

**Unclassifiable chronic colitis**

Patients with a history of chronic colitis compatible with either diagnosis (CD and UC) are considered as having unclassifiable chronic colitis.

**Acute colitis**

Patients with a history of colitis for at least six weeks are classified as having acute colitis.