ABSTRACT

Backgrounds: standardisation of subgroups in Crohn’s disease (CD) could help to design, and interpret the results of clinical trials and to compare studies performed in different populations. However, due to the lack of a uniformly used classification, data is scarce and difficult to interpret on the frequency of specific subtypes and disease behaviour in different ethnicities.

Methods: analysis was performed using the “Vienna classification” on an unselected Hungarian population of 100 CD patients diagnosed according to Lennard-Jones criteria at least three years before the data was collected.

Results: disease behaviour and location was strongly associated (p=0.008); ileocolonic location presented most commonly with penetrating disease (49%), while colonic location with non-stricturing, non-penetrating disease behaviour (48%). Operations were more frequent in patients with penetrating disease (p<0.0001). Among patients with extraintestinal manifestations penetrating disease was more common (49 vs 30%) and strictureing less frequent (16 vs 38%) than in the group of patients who did not have extraintestinal symptoms (p=0.001). In patients whose disease involved the colon, among those with an earlier age of onset, women presented more often with strictureing disease, than in men (OR=4.18 CI=1.07-16.32). Moreover, less operation were performed in women, than in men (OR=2.3 CI=1.02-5.19). Smoking had influence on the disease location and severity, while not on the disease behaviour.

Conclusions: these results point to different disease characteristics between men and women. They support the concept that distinct phenotypes have different complications and prognosis. Therefore, the Vienna classification provides a simple tool to standardise patients subgroups with Crohn’s disease.


INTRODUCTION

Crohn’s disease (CD) is a chronic transmural granulomatous inflammatory bowel disease (IBD) of unknown aetiology. Evidence is accumulating that CD consists of different subgroups, based on the location of macroscopic disease, clinico-pathological features, and a dissimilar course of the disease. There is some support for the concept that these subgroups could be genetically determined (1-5). Previous studies have shown that the incidence of the disease may greatly differ between different ethnicities (6-10). However, there is no sufficient information if and how the disease behaviour and the clinical course of CD vary in different ethnic groups. In order to progress on the search for the etiological agents and genetic markers as well as to provide homogenous subgroups for clinical trials there is an increasing need to standardise the description of CD patients’ groups. At the World Congresses of Gastroenterology in 1998, in Vienna, a new classification was recommended for these and another purposes (11). This classification is in many respects a revised and a more complete effort of the classification proposed in Rome in 1992 by Sachar and co-workers (12). From eight outcome variables, three were found to be the most informative: a) the age of disease onset (younger than the age of 40 A1, equal to or above the age of 40 A2); b) the disease location (terminal ileal I1, colonic L2, ileocolonic L3, upper gastrointestinal L4); and c) the disease behaviour (non-penetrating, non-stricturing disease B1, stricturing disease B2, penetrating disease B3).
Earlier studies have indicated that anatomic involvement at the time of diagnosis (13), disease behaviour (14-16), the age of disease onset (17,18) and gender (19,20) might be predictive of clinical outcome, complications, and prognosis. Though due to the lack of a uniform agreement on the use of “site of disease” and “age of onset” these characteristics were of limited value. Also, smoking has been found to be a severity factor in Crohn’s disease, with-thout stratification on its effect on the disease behaviour (21,22). Therefore the aims of our study were:

1. To present information on the disease characteristics of an ethnically different CD population than the ones studied so far.
2. Another goal was to investigate if disease behaviour, location or the age of disease onset have an impact on the presence of extraintestinal manifestations, on the need of operation, or on medical management, in particular immunosuppressive drugs.
3. Finally, the study was aimed to answer the question whether the history of smoking or the gender has an influence on the disease characteristics.

MATERIALS AND METHODS

Patients

Hundred patients (58 women, 42 men) with Crohn’s disease attending one of three IBD centres in two regions of Hungary were included in the study. All patients were unrelated adults of Hungarian ethnicity. Previous studies and our earlier results suggested no genetic differences between these regions in Hungary (4,23). Diagnosis was based on standard clinical, radiological, and endoscopic criteria as defined by Lennard Jones (24). Patients were diagnosed at least three years before the data was analysed using the classification (median: 7 years). Data was completed from medical records preceding the first resection and was reviewed on the basis of the same questionnaire in all the three centres. If a newer complication was suspected during the follow-up period, or the clinical course was not typical, the relevant diagnostic examinations were repeated. Disease behaviour and location was based on the results of upper and lower endoscopy and/or enterocolitis. Additionally, in uncertain cases leukocyte scintigraphy and spiral CT, and in case of non-total colonoscopy double-contrast enema was performed. The presence of inflammatory masses and abscesses was additionally investigated by ultrasound and CT.

Classification

Division of patients into subgroups was carried out according to criteria of the Vienna classification, based on the consensus of the International Working Party for the World Congresses of Gastroenterology 1998 (11). Shortly summarised:

- The age (A) when diagnosis of CD was first definitively established by radiology, endoscopy, pathology or surgery. If it was before the age of 40, the patient is defined to belong to group A1, while when it was established at or later than the age of 40 group A2.
- Location (L) was assessed on the maximum extent of disease involvement at any time before the first resection. Minimum involvement for a location defined as any aph-thous lesions or ulceration, mucosal erythema and oedema are not sufficient. For classification at least both small and large bowel examination are required. If the maximum extent of disease is restricted to the lower third of the small bowel (terminal ileum), with or without a spill over into the cecum, the patient belongs to subgroup L1. If the patient presented with any colonic location between cecum and rectum with no small bowel or upper GI involvement he belongs to the group L2. Disease of the terminal ileum and any location between ascending colon and rectum is defined as L3, while patients with any disease location proximal to terminal ileum regardless to any additional involvement of the terminal ileum or colon are considered as L4.
- Disease behaviour (B): patients with inflammatory disease, that presented neither structuring nor penetrating symptoms are defined as group B1. B2 patients are the ones that have structuring disease defined as the occurrence of constant luminal narrowing demonstrated by radiological, endoscopic or surgical-pathologic methods with prestenotic dilatation or obstructive signs/symptoms without presence of penetrating disease at any time in the course of disease. Penetrating disease (B3) is defined as the occurrence of intra-abdominal or perianal fistulas, inflammatory masses and/or abscesses at any time in the course of disease, including perianal ulcers. Excluded are postoperative intra-abdominal complications and perianal skin tags.

Statistical analysis

Patient’s subgroups were compared by χ2 statistics and when appropriate Fisher’s exact test was used.

RESULTS

The average age of disease onset was 30±0.8 yrs in our population; the disease has only been in 16% of all patients diagnosed later than the age of 40 yrs (Table I). shows the allocation of patients with Crohn’s disease in the 24 subgroups of the Vienna Classification. The disease location was in 17% of the patients L1 (terminal ileum), 29% L2 (colon), 50% L3 (ileo-colon) and 4% L4 (upper gastrointestinal). All L4 patients had also ileo-
colonic disease. CD presented in 30% of the patients as B2 (stricturing), 37% as B3 (penetrating) and 33% as B1 (non-stricturing, non-penetrating). Concerning the disease duration there were no significant differences between the subgroups of any of the classifying variables.

A strong association between disease behaviour and disease location (p=0.008) was found (Table I). This was true in patients in both the younger and older age of onset group. Ileocolonic location and penetrating disease behaviour often presented together (24%), while patients with a disease location restricted to terminal ileum rarely had a penetrating disease course (1%). Non-stricturing, non-penetrating disease was in L2 patients the most common. Disease behaviour was different in patients with a late disease onset (A2) from the patients with a younger age of onset (A1). Overall, A2 patients tended to present more often with stenosing course, than A1 patients (50 vs 26%). This trend was most apparent in patients with ileocolonic location (31 vs 13%). However the association, probably due to the small number of patients in the A2 group, did not reach the level of significance (p=0.08).

Among patients with extraintestinal manifestations penetrating disease behaviour was significantly more prevalent (49 vs 30%) and stricturing less frequent (16 vs 38%) than in the group of patients who did not have extraintestinal symptoms (p=0.001). In comparison with the groups of patients with other location, A1 patients with only ileal disease rarely presented extraintestinal symptoms (L1:15 vs L2:41%, L3:34%, L4:33%).

The need of immunosuppressive therapy was strongly associated with the disease behaviour (p<0.0001). In the group of patients that needed immunosuppressive therapy B3 (the penetrating type) behaviour was the most common (53%), while among those patients whose disease was possible to control without immunosuppressive drugs the B1 disease behaviour (43%). Only 16% of the patients with B1 disease course needed due to steroid dependency immunosuppressive therapy. Considering the location, disease of the terminal ileum was the least frequently associated with immunosuppressive therapy (17 vs L2:38%, L3:38%, L4:25%).

Similarly, operated patients had significantly more often B3 disease behaviour (62 vs 12%, p<0.0001) and L3 location (63 vs 35%, p=0.038) than non-operated ones. Overall 63 operations of 49 patients were performed: 37 patients had one operation, 11 had two, while one patient was three times operated. Among the surgical interventions there were 40 resections, 12 fistulotomies, 8 abscess drainage and 3 fissurotomies.

Disease behaviour was different between the two genders: among patients with an isolated ileal involvement in women the non-stricturing, non-penetrating disease was the most common (56%), while in men the stricturing form (75%). On the other hand, in A1 patients, women whose colon was also affected by the disease (L2, L3, L4), presented more often with stricturing disease behaviour than men (p=0.03 OR=4.18 CI=1.07-16.32). There was also a significant difference among the genders in the number of operations, as defined above,: 62% of the men, while only 41% of women had surgical treatment (p=0.04, OR=2.3 CI=1.02-5.19).

All our smoker patients have been smoking not less than of 3-5 cigarettes/day since at least 3 years before the study. In comparison to non-smoking patients in smoking patients there were more operations performed (46 vs 57%, p=0.048), and tended to have more patients with extensive disease (L3+L4: 46 vs 69%) and the need of immunosuppressive therapy (30 vs 41%).

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Table I. Patients’ distribution in the subgroups determined by the Vienna classification. Data is given as % of all patients

<table>
<thead>
<tr>
<th></th>
<th>A1 Age at diagnosis &lt;40 years</th>
<th>A2 Age at diagnosis ≥40 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B1 Non-stricturing, non-penetrating</td>
<td>B2 Stricturing</td>
</tr>
<tr>
<td>L1 Terminal ileum</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>L2 Colon</td>
<td>13</td>
<td>10</td>
</tr>
<tr>
<td>L3 Ileocolon</td>
<td>10</td>
<td>11</td>
</tr>
<tr>
<td>L4 Upper GI tract</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Σ</td>
<td>31</td>
<td>22</td>
</tr>
</tbody>
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Vol. 95. N° 8, 2003 PHENOTYPES DEFINED BY THE “VIENNA CLASSIFICATION” IN 100 HUNGARIAN PATIENTS WITH CROHN’S DISEASE 535
DISCUSSION

Clinical research of the last decade has indicated that Crohn’s disease represents a heterogeneous spectrum of manifestations that result in different subgroups (1,3). The clinical heterogeneity is indicated by differences in the course of disease (inflammatory, fibrostenotic, fistulising), the various extension of the inflammation (localised or diffuse), localisation (any part of the gastrointestinal tract from mouth to anus) or by the divergent intervals of relapse and remission. The presence of an extraintestinal manifestation, and in some cases, granulomatous inflammation of an extraintestinal organ—metastatic CD—might colour further the clinical picture. Data is accumulating that this phenotypic variety is associated with differences in the genetic background (4,5,25). Moreover, revision of the literature suggests that the frequency of the disease patterns—location (8,26-28), extraintestinal manifestations (27,29-31)—or the severity of CD (8) vary among different ethnicities. However, in the lack of a broadly used, uniform classification, so far it was difficult to compare the disease characteristics of different populations.

In this Hungarian population of CD patients disease behaviour and location was significantly associated. Penetrating disease was linked with more severe course of disease. Although the larger frequency of immunosuppressive therapy observed in this group of patients can be partly due to the current indications; the number of operations, extraintestinal manifestations as well as the more extensive ileocolic location were all more frequent among these patients. The most favourable course was experienced by those with segmental involvement of the terminal ileum: the frequency of operation, the need of immunosuppressive therapy as well as the presence of extraintestinal manifestations were as well as the more extensive ileocolic location were all more frequent among these patients. The most favourable course was experienced by those with segmental involvement of the terminal ileum: the frequency of operation, the need of immunosuppressive therapy as well as the presence of extraintestinal manifestations were the lowest in this latter group. Our results are largely in consistence with earlier findings suggesting a benevolent course in ileal-only disease (14), and a frequent association of fistulising course and ileocolic disease (15,16,32). Earlier studies have also indicated that the group of patients with perianal disease have more frequently colitis and ileocolitis, than a location restricted to the small bowel. In comparison with patients who did not have such symptoms, this group was described to be more prone to extraintestinal manifestations (32). These observations of clinical similarities are supportive of a similar pathogenic mechanism of the perianal disease and the fistulising disease behaviour. Recent results indicate that patients with perianal disease may have particular genetic background (2). In our group of patients extraintestinal complications—typified sometimes earlier as colitis related (15,33)—were rather associated with ileocolitis as reported by Farmer et al. (14). However, extraintestinal manifestations and the need of operation were more typically disease behaviour—associated than disease location-associated.

Data in the literature is somewhat controversial concerning an association between the age of disease onset—the first Vienna classifying variable—and the prognosis of disease. Some results show a more severe (34), some milder (17) or similar course (35) than in patients with a younger age of onset. In our Hungarian IBD population patients with an onset not earlier than 40 years of age had a different, however not milder or more severe disease, than the ones with an earlier onset. In the A2 (the older age) subgroup there were fewer patients with non-stenosing, non-penetrating, while more with stenosing disease when compared to patients in the A1 group, however our A2 group was relatively small. Concerning the disease location some studies have suggested a more frequent small bowel disease in individuals with an earlier age of disease onset while more often colonic disease in older-onset populations. Our study, similarly to the one based on the Olmsted county population and a recent Greek study could not confirm these findings (34,36). An explanation might be the low number of patients diagnosed earlier than the age of 18 in our study population or alternatively, the influence of divergent environmental and genetic factors.

The International Working party has also performed an internal validation on the final, presented Vienna classification. Three populations from Northern Europe and North America and additionally two referral centres from North America were classified using the three variables (11). Concerning the allocation of the variables our results in the group “age of diagnosis” was comparable with the results of the displayed, unified database. On the other hand, we had more patients that presented with ileocolic disease and less, whose disease behaviour was non-penetrating, non-penetrating. These differences are not surprising as the working group has also described a distinct allotment between referral centres and specific populations, as well as in-between populations, especially regarding the disease behaviour. However, the cross table analyses have provided similar results, showing a strong association between disease behaviour and location in general, and also specifically between L2 and B1 and L1 and B2. In the population examined by us, in contrast to the results of the International Working party there was no significant association between the age of onset and the disease location, but there seemed to be a comparable trend as found by them between the age of disease onset and the disease behaviour. These results suggest that although there are wide distinctions in the presentation of Crohn’s disease between different populations, there are certain well-definable, general disease patterns, that could be categorised by the Vienna classification.

The idea of a role of genetic and environmental factors in influencing the course of CD is strengthened by our finding of a distinct pattern of disease between men and women. Although the number of female and male patients in the different behavioural patterns and in the four loca-
tions are comparable, the allocation to the subgroups differ (Table II). This is most apparent when considering the presence of stenosing disease in patients with different disease locations. A dissimilarity in the genetic background of stenosing disease in comparison with the other two forms was also suggested by previous results of the interleukin-1 gene polymorphisms (4). The assumption of a distinct disease course of the two genders accords with an earlier study by Griffiths et al., who found that in childhood CD boys have a more severe course than girls (20). A larger prevalence of Crohn’s disease in Turner syndrome (37), the reported higher transmission rate from mothers to children than from fathers to children (38), and the more severe course in smoking women in comparison with men (22) further supports the idea of an influence of the gender. In many of these diseases not only a different prevalence rate can be observed between the genders, but also different prognosis and clinical course (39,40). The reasons for the sex bias are unclear, but might include such factors as gender-related differences in the immune responsiveness, sex steroid effects, and gender-related genetic factors. For example estrogens were demonstrated to decrease interleukin-1 bio-responsiveness in certain cell types (41).

Beside an individual susceptibility, environmental and lifestyle factors are probably necessary for the development of Crohn’s disease. An established risk factor for relapse and recurrence in CD is smoking that is also associated with a worse disease prognosis (21,22). In consistence with these results we observed a more severe course of disease in smoking patients: there were more operations performed among them (57 vs 46% p=0.048). The relative number of individuals with the need of immunosuppressive therapy was also higher (41 vs 30%) in comparison to the non-smoking patients’ group. The proportion of patients with a more extensive location—the disease involving at least both the colon and ileum—was also higher in smoking patients (69 vs 46%), while the ratio of restricted small bowel and colonic involvement did not vary between smokers and non-smokers. Some earlier studies have suggested that non-smokers have more often colonic disease, while smokers small bowel involvement (21,42). However, the assignment of the ileocolic location has not always been clear and the definition of terminal ileal disease might or might not have included those with a spill into the cecum. In relation to the disease behaviour we did not find significant differences between smoking and non-smoking patients.

Our results suggest that there is an “intrinsic disease behavioural pattern” that is probably determined by the individual genetic background, while environmental and lifestyle factors can additionally influence the severity of disease—by expanding the location or by aggravating the inflammatory symptoms.

The knowledge of these clinically relevant behavioural patterns that can be categorised by the Vienna classification will probably help to make more specific therapeutic decisions and set the stage to study genetic markers. Our results point strongly to significantly different disease characteristics between men and women. We hope that further studies will help to validate these results and perhaps gender should form another parameter to add to the Vienna classification.

ACKNOWLEDGEMENTS

We would like to thank for Prof. D.B. Sachar and Prof. C. Gasche for their valuable comments. We would like to acknowledge the financial support received from “NUF-FIC” and the “Vrije Universiteit Vrouwenfonds” who supported A.N. and Ferring Hungary who supported T. M. while in Amsterdam.

| Table II. Disease behaviour and location in male and female CD patients with an earlier age of disease onset (A1) |
|-------------------------------------------------|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Women (n=48) | | | | | | | | | |
| | B1 | B2 | B3 | Σ | B1 | B2 | B3 | Σ | | |
| | Non-stricturing | non-penetrating | Stricturing* | Penetrating | | Non-stricturing | non-penetrating | Stricturing | Penetrating | | |
| L1 Terminal ileum | 10,2 | 4,1 | 2,0 | 16,3 | 2,9 | 11,4 | 0 | 14,3 | | |
| L2 Colon | 14,3 | 8,2 | 10,2 | 32,7 | 17,1 | 0 | 14,3 | 31,4 | | |
| L3 Ileocolon | 8,2 | 16,3 | 20,4 | 44,9 | 17,1 | 8,6 | 28,6 | 54,3 | | |
| L4 Upper GI tract | 4,1 | 2,0 | 0 | 6,1 | 0 | 0 | 0 | 0 | | |
| Σ (%) | 36,8 | 30,6 | 32,6 | 100 | 37,1 | 20,0 | 42,9 | 100 | | |

Data is given in %. *OR = 4,179
REFERENCES


