Changes of Crohn's disease phenotype over time

Le changement du phénotype de la maladie de crohn au cours du temps

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RÉSUMÉ

Introduction: La maladie de Crohn est une affection qui se caractérise par une expression clinique hétérogène. Notre objectif était d'étudier les modifications du phénotype de la maladie de Crohn dans le temps selon la classification de Montréal et de déterminer les facteurs prédictifs de recours aux immunosuppresseurs ou à la chirurgie.

Méthodes: Nous avons inclus les patients porteurs de maladie de Crohn qui ont été suivis durant une période minimale de 5 ans. Les patients qui ont été perdus de vue avant 5 ans de suivi ont été exclus. Le phénotype de la maladie de Crohn a été apprécié selon la classification de Montréal au moment du diagnostic et 5 ans après. L'évolution du phénotype au cours du temps et le recours aux immunosuppresseurs, aux immunomodulateurs ou à la chirurgie ont été relevés.

Résultats: Cent vingt patients consécutifs ont été colligés. Il s'agissait de 70 hommes et de 50 femmes. Au moment du diagnostic, 68% des patients étaient classés A2 selon la classification de Montréal. La maladie était le plus souvent localisée au colon. La localisation de la maladie de Crohn était relativement stable au cours du temps, avec 93,4% des patients n'ayant présenté aucun changement dans la localisation de la maladie. Le phénotype de la maladie de Crohn a changé au cours du temps avec un passage fréquent vers les formes sténosantes et fistulisantes de 6% à 11% en 5 ans. Le seul facteur prédictif du changement du phénotype était l'atteinte de l'intestin grêle (OR :3,7 [1,2–7,6]). Au cours du suivi, 82% des patients ont présenté une poussée sévère attestée par le recours aux immunosuppresseurs ou à la chirurgie. Les facteurs associés à la sévérité de la maladie étaient: l'atteinte de l'intestin grêle (L1), les phénotypes sténosant (B2) et fistulisant (B3) de la maladie et la présence de lésions périnéales (OR :17,3 [8,4-19,7]; 12 [7,6–17,2] ; 3[1,7- 8,3] et 2,8 [2,2–5,1] respectivement). Il n'y avait pas de lien entre la sévérité de la maladie et l'âge, le sexe et le tabagisme.

Conclusion: La maladie de Crohn évolue au cours du temps: d'un phénotype inflammatoire vers les phénotypes sténosant et fistulisant, plus agressifs. L'atteinte iléale, les phénotypes sténosant et fistulisant et la présence de lésions périnéales étaient associés au recours aux traitements immunosuppressseurs ou immunomodulateurs et à la chirurgie.

Mots-clés

maladie de Crohn; phénotype; évolution

SUMMARY

Background: Crohn's disease is a clinically heterogeneous condition. Our aim was to identify the phenotype evolution of Crohn's disease over time according to the Montreal Classification and to precise predictive factors of the need for immunosuppressant treatment or surgery.

Methods: We included Crohn's disease patients who were followed up for at least 5 years. We excluded patients who were lost to follow up before five. Patients were classified according to the Montreal classification for phenotype at diagnosis and five years later. The evolution of phenotype over time and the need for surgery, immunosuppressive or immunomodulatory drugs were evaluated.

Results: One hundred twenty consecutive patients were recruited: 70 males and 50 females. At diagnosis, 68% of patients belong to A2 as determined by the Montreal classification. Disease was most often localized in the colon. The disease location in Crohn's disease remains relatively stable over time, with 93.4% of patients showing no change in disease location. Crohn's disease phenotype changed during follow up, with an increase in stricturing and penetrating phenotypes from 6% to 11% after 5 years. The only predictive factor of phenotype change was the small bowel involvement (OR=3.7 [1.2-7.6]). During follow-up, 82% of patients have presented a severe disease as attested by the use of immunosuppressive drugs or surgery. The factors associated with the disease severity were: small bowel involvement (L1), the stricturing (B2) and penetrating (B3) phenotypes and perineal lesions (OR=17.3 [8.4-19.7]; 12 [7.6-17.2]; 3[1.7-8.3] and 2.8 [2.2–5.1] respectively), without association with age, sex or smoking habits.

Conclusion:

Crohn's disease evolves over time: inflammatory diseases progress to more aggressive stricturing and penetrating phenotypes. The ileal location, the stricturing and penetrating forms and perineal lesions were predictive of surgery and immunosuppressant or immunomodulatory treatment.

Key-words

Crohn's disease; phenotype; evolution

Crohn's disease (CD) is a heterogeneous disorder with variable manifestations and outcomes. Classification of CD using phenotypic features has been proposed to assist in recruiting patients into clinical trials, to predict their natural history and to assist correlation with genotype. In 2005, the Montreal revision of the Vienna classification system was introduced (1). The CD behaviour has a tendency to change over time, with increasing proportion of patients that develop fistulising and stricturing complications, indicating that CD is a dynamic process in evolution. The aims of this study were to describe the evolution of CD phenotype in a population that was followed up for at least 5 years, to precise the predictive factors of phenotype changes and the CD phenotype associated to a severe form defined by need for immunosuppressant or immunomodulatory therapy or surgery.

METHODS

We included hospitalised patients whom Crohn's disease was diagnosed between 1998 and 2003. Patients who were lost to follow up before 5 years were excluded. The diagnosis of Crohn's disease was made according to clinical, endoscopic, histopathological and radiological findings. Information on date of onset of symptoms and diagnosis, type of clinical onset, location, familial occurrence of inflammatory bowel disease (IBD), clinical course, need for immunosuppressive and/or biological treatment, as well as abdominal surgery (intestinal resection) were collected. The disease phenotype (age at onset, duration, location, and behaviour) was determined according to the Montreal Classification at diagnosis and 5 years after.

Statistical Package for Social Science (SPSS) software version 20.0 was used for analysis of data. Data were summarized as mean and percentage. Both study groups were compared using the $\chi 2$ test for qualitative variables. Student's t and ANOVA tests were used for analysis of parametric data. Mann –Whitney U and Kruskal –Wallis H tests were used for analysis of non-parametric data. P-value less than 0.05 was considered significant.

RESULTS

One hundred and twenty-two patients were included (70 men and 52 women) with a median follow up of 8 years. A detailed clinical description of patients is presented in *table 1.*

Location: Disease location remained relatively stable after 5 years of follow up : only 6.6 % of patients have changed their location with a decreasing L1 location: 32 (26.2%) to 27 (22.1%) and an increasing L3 location : 42 (34.4%) to 48 (39.3%) *(Table 2).*

Behaviour: CD behaviour changed significantly 5 years after diagnosis. Among patients, 41/122 (33.6 %) had changed their behaviour. The non stricturing, non penetrating phenotype had a tendency to progress into stricturing or penetrating disease (*Table 3).* The proportion of penetrating disease (B3) increased from 6 (5%) to 10 (8.2 %), and stricturing disease (B2) increased from 13(10.7 %) to 23(19%) after 5 years. Perineal lesions were more frequent after a 5 year follow up.

Table 1 : Characteristics of the study population at Diagnosis of Crohn's disease

	At Diagnosis	After 5 years
L1 (ileal) (n)	32	27
L2 (colic) (n)	45	44
L3 (ileocolic) (n)	42	48
L4 (upper GI disease) (n)	3	3

Table 2 : Changes of Crohn's disease location over time

Parameter	N°
Male/female	70/52
Age at diagnosis	32.39
A1	6 (4.9 %)
A2	83 (68 %)
A3	33 (27 %)
Familial IBD	0
Smoking	36 (29.5%)
Location at diagnosis	
L1	32
L2	45
L3	42
L4	3
Behaviour at diagnosis	
B1	85
B2	13
B3	6
Perineal location	18

Table 3 : Characteristics of the study population at Diagnosis of Crohn's disease

	At diagnosis	After 5 years
B1 (non stricturing, non penetrating) (n)	85	56
B2 (stricturing) (n)	13	23
B3 (penetrating) (n)	6	10
P (perineal lesions) (n)	18	33
B2 + B3 (n)	19	33

Factors associated with phenotype changes: In a univariate and multivariate analysis, the only factor that was associated with phenotype changes was the ileal location (hazard ratio = 3.7 [1.2-7.6]). No correlation with age, history of smoking and sex at diagnosis was found *(Table 4).*

Table 4 : Predictive factors of phenotype changes

Factor	Yes	No	p	Odd ratio
Age at diagnosis (year)				
-< 16 ans (n)	2	4		
- between 17 and 40 (n)	30	53	0.46	-
- > 40 (n)	8	25		
Smoking				
Yes (n)	12	24	0.93	-
No(n)	28	58		
Location				
- ilécolic (n)	13	19	0.84	
- iléal (n)	18	24	0.013	3,7 [1.2-7.6]
- colonic (n)	7	38		
Sex				
Men (n)	22	48	0.7	-
Women (n)	18	34		

Severity: During follow up, 100 patients (82%) have developed a severe form as attested by the need for immunosuppressants and for surgery. The stricturing phenotype (Odds ratio = 12 [7.6-17.2]) and the ileal location (OR = 17. 3[8.4-19.7]) were the main predictive factors of a severe form (81% of patients with ileal location underwent surgery during 5 years of follow up). The penetrating phenotype (OR = 3[1.7- 8.3]) and the perineal involvement (OR = 2.8 [2.2 – 5.1]) were also associated with severe forms of CD *(Table 5)*

Table 5 : Factors associated with disease severity

Parameter	Odd ratio
Ileal Location	17.33 [8.4-19.7]
Perineal lesions	2.8 [2.2–5.1]
Penetrating phenotype	3 [1.7–8.3]
Stricturing phenotype	12 [7.6–17.2]

DISCUSSION

This study revealed that CD evolves over time: 33 % of patients have changed their phenotype during the 5 years of follow up. The disease location did not show significant change over time, it occurs only in 6.6% of our patients. By contrast, regarding disease behaviour, the nonstricturing, nonpenetrating phenotype had a tendency to progress into stricturing or penetrating disease especially when ileum is involved (p= 0.013). This is in agreement with previous studies which reported an increase from the inflammatory to the complicated forms of CD with a relatively stable location over time (2, 3).

Previous studies have suggested that the phenotypic clinical expression of Crohn's disease depends on the age of initial diagnosis : disease developing earlier during childhood tends to be more severe (4, 5): this age dependant phenotypic clinical expression was not shown in our study because of the patient selection bias : only 6 patients belonged to A1class. Freeman et al reported that CD is a chronic and progressive disorder, although the rate of progression may be altered or slowed by the use of some therapy, such as steroids, antibiotics, or resective surgery, at least for a period of time. It appears that the disease begins as an inflammatory process that progressively develops over time to a more complex disease with stricture and fistula formation (6).

In our study, only a minority of patients (18%) did not need either immunosuppressants or abdominal surgery. In fact, Immunosuppressive drugs were taken by 55.7% of patients and surgery was performed in 52.5% of cases. These figures are quite similar to those reported in previous studies: Magro et al has reported that 49 % of their patients (cohort of 1692 patients) had taken immunosuppressants at some point during the course of their disease and at least, 48% underwent surgery (7), and so reported series published from North America and from Denmark (8, 9). Louis et al reported a proportion of 30.4% of patients that underwent surgery after 10 years of follow up (3).

The main factors that have been associated with the severity of disease were: the ileal location and the stricturing behaviour. This is similar to previous studies that showed patients with small bowel disease experienced a more severe form than those with colonic disease (10). Magro et al reported that ileal involvement in CD was associated with the need for resective surgery, as opposed to ileocolonic involvement (7).

CONCLUSION:

In conclusion, this study has shown the benefits of a careful phenotyping of Crohn's disease at diagnosis in order to determine the risk of disease progression. Inflammatory bowel diseases progress to more aggressive stricturing and penetrating phenotypes. The ileal location and the stricturing phenotype predict the severity of the disease. Introducing Montreal Classification in routine clinical practice may be helpful for clinicians in determining the appropriate treatment and prognosis for their IBD patients.

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