

Disease Behaviour in Patients with Crohn's Disease: A Review

Abstract

The disease behaviour is one of the three phenotypic criterion in Vienna, Montreal and Paris classification and important for the management of Crohn's disease (CD). This article reviews following aspect of disease behaviour in CD: temporal change in disease behaviour, changing phenotype at presentation over decades, difference in disease behaviour in childhood onset as compared to adult onset CD, changing natural history, the effect of therapy on the natural history of the disease and factors responsible for change in disease behaviour.

The disease behaviour changes over time to more complicated phenotype, although the proportion may be less than that in earlier studies. There is mixed data about the change in disease phenotype at presentation over decades although some of the recent data suggests more inflammatory phenotype at presentation. Earlier studies suggested more severe disease behaviour in pediatric onset disease than adult onset but the recent data suggests that the course in pediatric onset CD may be similar to that in adult onset CD. Studies suggest that the disease behaviour may change as early as 90 days but it needs to be confirmed that they did not have subclinical stricturing or penetrating disease. There is some evidence that more patients are presenting with inflammatory behaviour, the progression to complicated disease is decreased and surgery rates are decreased before era of biologics. Finally there is evidence that surgery is delayed due to use of azathioprine and the disease progression may be delayed due to azathioprine and biological agents.

Keywords: Crohn's disease complications; Disease phenotype in Crohn's disease; Disease behaviour in inflammatory bowel disease; fistulae; Montreal classification; Strictures

Mini Review

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Introduction

Vienna and Montreal classifications classified disease behaviour in Crohn's disease (CD), along with age at presentation and location of disease, as an important criterion to predict outcome. The location of the disease tends to remain relatively constant but the disease behaviour is a dynamic over time. The Vienna classification divided the disease behaviour into non-stricturing, non-penetrating, stricturing and penetrating phenotypes and this was maintained in Montreal classification [1,2]. Montreal classification recognized different behaviour of perianal fistulizing disease as compared to intestinal fistulizing disease. Pediatric modification of Montreal classification, termed as Paris classification, in addition had the option of combined both stenosing and penetrating disease and added growth retardation (B2B3) [3]. This article reviews the change in the disease behaviour over a period of time along with other issues related to disease behaviour.

Temporal change in the disease behaviour

Table 1 shows the hospital and population based studies which shows the temporal changes in disease behaviour in Crohn's disease [4-14]. There are 6 hospital-based studies with 3617 patients and 5 population based studies with 1724 patients. At diagnosis 73% to 83% in hospital based (with the exception of Study by Freeman [6] in which only 41% had non stricturing, non penetrating disease) and 62 to 81% of population based patients had non-stricturing, non-penetrating disease. At 5

years, 11 to 35%, at 10 years 15 to 43%, at 20 years 32 to 55% and at 30 years, 45 % of patients had progressed to stricturing or penetrating behaviour. So there is seems linear progression of patients into complicated behaviour, although it may not be case in individual patient. In general, population based studies suggest lower proportion of patients with B3 disease over period of time than the hospital based study and probably give a more balanced picture. The changing natural history is discussed below in the section on changing natural history.

Vienna classification vs. Montreal classification in deciding disease behaviour over time

It is important to realize that some studies have used Vienna classification where as the recent studies have used Montreal classification. The Vienna classification classifies perianal disease as B3 whereas Montreal classification uses perianal disease as modifier, which is added to B1, B2 or B3. Hence classifying same group of patient with both classification, B3 disease is more in Vienna and less in Montreal as perianal disease re classified as B1p or B2p. The study by Chow et al. [8] exemplifies this point well [8]. In this study, at presentation, the proportion of non-stenosing non-penetrating, stenosing and penetrating disease by Vienna classification was 46%, 26% and 28 % respectively. When this was reclassified by Montreal classification, the proportion of non-stenosing non-penetrating, stenosing and penetrating disease changed to 67%, 30% and 3% respectively. This needs to be remembered when we are comparing the disease behaviour studies.

Table 1: Hospital and population based studies showing disease behaviour at baseline and on follow up.

| Author and Year | No of Patients | Behaviour at Diagnosis (%) | | | Behaviour Later | | | Surgery (%) | Comment |
|------------------|----------------|----------------------------|-----------------|----------------|------------------------------|------------------|--------------------------------------|----------------|-----------------------|
| | | I [^] | S ^{^^} | F ⁺ | I | S | F | | |
| Hospital based | | | | | | | | | |
| Louis [4] | 297 | | | | 52 | 21 | 27 (5 y ^{**}) | 30 (10 y) | Vienna classification |
| | 187 | | | | 31 | 32 | 37 (10 y) | | |
| | 125 | 74 | 11 | 15 | 22 | 35 | 43 (15 y) | | |
| | 74 | | | | 19 | 32 | 49 (20 y) | | |
| | 32 | | | | 13 | 31 | 56 (25 y) | | |
| Cosnes [5] | 2002 (R) | 83 | 3 | 14 | 48 | 12 | 40 (5 y) | 72 | Vienna |
| | 646 (P) | 36 | 13 | 52 | 12 | 18 | 70 (20 y) | | |
| | | | | | 23 | 15 | 63 (5 y) | | |
| Freeman [6] | 150 | 41 | 38 | 21 | 13 | 48 | 39 (10 y) | 30 | Vienna |
| | | | | | 9 | 39 | 52 (20 y) | | |
| Nos [7] | 73 (B1) | | 73 | | 64 | 14 | 22 (Mean FU ⁺⁺ 93 months) | 30 | Vienna |
| Chow [8] | 109 | 46 | 26 | 28 | 33 | 31 | 36 (5 y Vienna) | 31 | Vienna and Montreal |
| | | | (Vienna) | | 50 | 45 | 5 (5 y Montreal) | | |
| | | 67 | 30 | 3 | 24 | 33 | 43 (10 y Vienna) | | |
| | | | (Montreal) | | 43 | 43 | 14 (10 y Montreal) | | |
| Lakatos [9] | 340 | 58 | 19 | 23 | B1 to B2/B3 30% (9.7± 7.5 y) | | | 47 | Montreal |
| Population Based | | | | | | | | | |
| Wolters [10] | 358 | 74 | 16 | 8* | | | | 25 (89 months) | Vienna |
| Solberg [11] | 197 | 62 | 27 | 11 | 51 | B2 +B3= 49%(5 y) | | 27 (5 y) | Vienna |
| | | | | | 47 | 31 | 22 (10 y) | 40 (10 y) | |
| Tarrant [12] | 715 | 73 | 17 | 10 | 56 | 25 | 20 (5 y) | - | Montreal |
| | | | | | 44 | 31 | 25 (10 y) | | |
| Thia [13] | 306 | 81 | 5 | 14 | 64 | 12 | 24 (5 y) | 16 (half y) | Montreal |
| | | | | | 58 | 15 | 27 (10 y) | | |
| | | | | | 41 | 22 | 37 (20 y) | | |
| | | | | | 36 | 22 | 42 (30 y) | | |
| Lovasz [14] | 506 | 57 | 20 | 23 | 42 | 20 | 38 (5 y) | 41 | Montreal |
| | | | | | 30 | 20 | 50 (10 y) | | |

Decimal point rounded; * Remaining patients (7/358) had stricturing and penetrating disease; **years; ^inflammatory (non stricturing, non penetrating, ^^stenosing; + penetrating; ++ Follow up; (R) retrospective; (P) prospective

Is initial disease behaviour phenotype (at presentation), changing over time?

Cosnes et al. [5] studied 2 groups of patients: a retrospective group of 2002 patients (from 1974 to 2000) and a prospective group of 646 patients (from 1995 to 2000) [5]. The proportion of patients with B1, B2 and B3 disease at presentation were 83%, 3% and 14% in the retrospective group (from 1974 to 2000) and 36%, 13% and 52% in the prospective group (from 1995 to 2000). This hospital-based study suggested that the phenotype of disease behaviour at presentation is changing with more B2 or B3 phenotype at presentation. Similar results were reported from ISBEN study [11].

Other studies came to opposite conclusions. Zhulina et al. [15] in a retrospective study, examined the phenotype at presentation in Örebro University, Sweden from 1963 to 2010 [15]. In this population-based study, at diagnosis, the proportion of patients with B1 (non stricturing, non penetrating) CD was 12.5% in the period between 1963 and 1965. This increased to 82.3% during the period 2006 to 2010. The authors attributed this to early diagnosis of CD. In the other study by Lovasz et al. [14] the proportion of B1, B2 and B3 was 50%, 22% and 28% respectively during the period 1977 to 1998 and 65%, 17% and 18% during the period 1999 to 2008 [14]. Two recent articles show mixed results – In a hospital-based study by Lakatos et al. [11] the proportion of B1, B2 and B3 at presentation was 58%, 19% and 23% respectively [11]; in the population-based study by Thia et al. [13] the proportion of B1, B2 and B3 was 81%, 5% and 14% respectively [13]. Thus there is a mixed trend of disease phenotype at presentation.

How early can the disease behaviour phenotype change?

Louis et al. [16] found that significant proportion of patients in their study had change in disease behaviour by one year [16]. Chow et al. [8] found that disease behaviour changed after 3 years [8]. However, Thia et al. [13] found that 18.6% of their patient had change in disease behaviour in 90 days [13]. Hence the disease behaviour can change significantly in few months. However it needs further study- how do we know that patient did not have subclinical B2 or B3 disease, which may have manifested at the time of complication? A recent study by Greener et al. exemplifies this point [17]. In this prospective study presented in an abstract form, they studied the impact of adding Video capsule endoscopy and Magnetic resonance enterography in patients with Crohn's disease to see the change in phenotypic classification. They found that the adding both these tests changed the Montreal classification in 64% of patients by new disease extent (in proximal small bowel) and discovering more B2/B3 disease.

Is there a difference in disease behaviour in adult onset and pediatric onset CD?

Initial studies in pediatric population suggested that the disease behaviour in pediatric population was severe as compared to that in adults (Table 2). A study of 404 pediatric CD by Vernier-Massouille et al. [19] from France reported that at diagnosis, 29% of patients had complicated behaviour (25% B2 and 4% B3). At follow up (> 2 years) additional 31 % had complicated behaviour (B2 increased from 25% to 44% and B3 from 4% to 15%. Surgery was required in 20% in 3 years and 34% at 5 years from diagnosis.

They concluded that pediatric CD was characterized by frequent occurrence with severe phenotype. In another study from France, Pigneur et al. [21] compared natural history of CD in 206 pediatric and 2992 adult onset disease. They reported that patients with childhood onset disease had more active disease course and required more immunosuppression due to intrinsically more severe disease phenotypes. Thia et al. [13] found that the risk of complications was non significantly increased in age group 17 to 40 years as compared to the patients diagnosed at 16 years of age (Hazard ratio 2.07 95% confidence interval 0.85 -5.22). In a recent article by Lovasz et al. [14] 74 pediatric onset IBD patients were compared with 432 adult onset IBD. Other recent studies published by De Bie in [23] (Eurokid registry), Gower-Rousseau et al. in [24] (EPIMAD registry), and Isreali et al. [25] have suggested that there was no significant difference in the likelihood of developing complicated disease behaviour and time to change the disease behaviour. Thus pediatric onset CD behaves similar to adult onset IBD in majority of recent studies. The disease location is extensive in pediatric onset CD.

Factors responsible for change in disease behaviour

Disease location at baseline is probably most important factor associated with disease progression and intestinal complication. Ileal and UGI disease are associated with progression towards complicated disease [13,16,26]. A large study of 715 patients by Tarrant et al. [12] suggested that perianal disease was a strong predictive factor for the development of complicated CD [12]. Need for steroid therapy at diagnosis has been suggested as another factor associated with disease progression [27,28]. Age < 40 years has been considered as a factor associated with progressive disease [10,11,27] but a study by Loly et al. [28] failed to confirm this association [28]. In the postoperative setting, smoking, resection during previous surgery and severity and timing of post-operative recurrence are the factors with symptomatic recurrence [29].

Is the natural history changing? Can any treatment improve the phenotype of CD?

Since Crohn's disease has existed for more than a century and many treatment modalities are available over time, it would be interesting to know the changes in natural history of the disease. In a 2010 review of natural history of adult CD in population based cohort studies, Peyrin-Birolet et al. [30] found that up to one-third of patients had stricturing or penetrating disease at presentation and half had an intestinal complication in 20 years (with half requiring surgery in 10 years) [30]. However Golovics et al. [31] in the review of natural history of CD, suggested that more patients are presenting with inflammatory behaviour, the progression to complicated disease is decreased and surgery rates are decreased before era of biologics (reduced surgery rates are probably related to azathioprine use) [31].

A recent study by Magro et al. [32] has addressed the issue of change in natural history by immunosuppressants and biological agents. They found that the disease progression was delayed in patients on azathioprine therapy commenced before the change in phenotype (median 361 months in patients on azathioprine vs. 71 months in patients not on azathioprine; $p < 0.001$). The disease progression was also delayed in patients on combination therapy with azathioprine and anti TNF- α .

Table 2: Summarizes studies and reviews on disease behaviour in pediatric CD.

| Author and Year | Study Characteristic | No. of Patients | Comparison of Disease Behaviour in Childhood Onset and Adult Onset Groups | Other Comment/s |
|-------------------------|----------------------------------|--|---|--|
| Limbergen [18] | Retrospective 3 Scottish centers | 276 childhood & 596 adult onset | No difference at 5 years | Less ileum- and colon-only location; more ileocolonic and UGI involvement |
| Vernier-Massouille [19] | EPIMAD registry | 404 childhood onset CD | Severe phenotype in childhood onset | Extensive and complicated disease; increased need for immunosuppression; |
| Levine [20] | Review | | Disease course parallel | |
| Pigneur [21] | Retrospective | 206 pediatric onset 2992 adult onset CD | Severe disease in pediatric onset | More active disease; increased need for immunosuppression However; cumulative B2/B3 and surgery same |
| Thia [13] | Retrospective | 306 | Similar behaviour | Risk of complications non significantly more in 17 to 40 as compared to, 16 years |
| Abraham [22] | Review | 41 studies with 3505 patients | Less patients needed surgery in pediatric onset CD | Pediatric onset CD more extensive disease as compared to adult onset |
| Lovasz [14] | Prospective | 74 pediatric onset and 432 adult onset | No difference | |
| De Bie [23] | Eurokid registry (18 countries) | 582 pediatric onset CD | No difference | Extensive disease in pediatric onset |
| Gower-Rousseau C [24] | EPIMAD registry | 689 pediatric, 5853 adult, 367 elderly onset | No difference | Pediatric onset CD had more B2 and B3 disease than elderly onset CD |
| Israeli [25] | Retrospective, | 115 childhood onset, 336 adult onset | Similar disease behaviour | More pan enteric disease in pediatric onset |

UGI- upper Gastrointestinal

Do the present classifications allow downgrading of disease?

Vienna, Montreal and Paris classification are based on assumed progression of the disease. However some studies have shown that the disease severity can decrease. For example, in the ISBEN study reported by Solberg et al. [11] 43% patients had reduction in disease severity during follow up. The present classification do not clearly state if the downgrading of the disease is permitted.

Conclusion

The disease behaviour phenotype changes over time to more complicated phenotype, although the proportion may be less than that in earlier studies. There is mixed data about the change in

disease phenotype at presentation over decades although some of the recent data suggests more inflammatory phenotype at presentation. Earlier studies suggested more severe disease behaviour in pediatric onset disease than adult onset but the recent data suggests that the course in pediatric onset CD may be similar to that in adult onset CD. Studies suggest that the disease behaviour may change as early as 90 days but it needs to be confirmed that they did not have subclinical stricturing or penetrating disease. There is some evidence that more patients are presenting with inflammatory behaviour, the progression to complicated disease is decreased and surgery rates are decreased before era of biologics. Finally there is evidence that surgery is delayed due to use of azathioprine and the disease progression may be delayed due to azathioprine and biological agents.

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