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Disease Behavior in Adult Patients: Are There Predictors for Stricture or Fistula Formation?

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Key Words
Serologic markers · Glycans · Prognosis

Abstract
In the current era, in inflammatory bowel disease step-up vs. top-down therapeutic approaches for the treatment of Crohn's disease (CD) are evaluated. As a consequence, we need to be able to differentiate between patients who will have more aggressive phenotypes to those with potentially more benign CD course. The former would require closer follow-up; however, more important might be the subgroup of patients to whom we want to offer biologic and immunomodulator therapy early on. This strategy is the only one supposed to prevent hospitalization and surgical intervention, specifically in patients with fistulae. Patients with expected fibrostenotic disease phenotype require early identification as well. The data regarding primary prevention of fibrostenosis are scarce; however, the association of biologic therapy with fewer surgeries might suggest that at least a subgroup of these patients would benefit from early, step-up therapeutic strategy. They might also benefit more from early immunomodulator therapy, as this was shown to have a secondary (though modest) preventive effect. The patients with fibrostenotic phenotype are also candidates for the most needed but still practically nonexistent anti-fibrotic therapies. In any case where patients are identified as having a higher chance to develop the more aggressive phenotypes, fibrostenotic and perforating, recommendation to avoid triggers/accelerators of disease progression (smoking, NSAIDS use) should be kept rigorously. Until recently, we based our attempts to predict disease phenotype mainly on clinical characteristics. As would be the case with many clinical features, some of them are not even predictors, but already manifestations of the condition we are trying to predict. Intervention at this stage might be too late for this patient. In addition to known demographic and clinical predictors reported, more recently sophisticated predictors shall be described. These predictors belong to three major groups: serologic markers, genetic markers, mucosal disease/healing. The major serologic markers used: anti-*Saccharomyces cerevisiae* antibodies (ASCA), anti-neutrophil cytoplasmic antibodies (ANCA), outer membrane porin C (OmpC), CBir1-flagellin, antibodies against I2 protein and the anti-glycan antibodies: anti-laminaribioside carbohydrate (ALCA), anti-chitobioside carbohydrate (ACCA) and anti-mannobioside carbohydrate (AMCA) and their associations with penetrating and fibrostenotic disease shall be discussed. The associations of genetic polymorphisms such as CARD15 and TLR4 variants and more aggressive disease phenotype will be described as well. Finally, the data supporting the relationship between inflamed, in contrast to healed intestinal mucosa and more aggressive disease course will be illustrated. These predictors may be used in clinical practice and/or research in order to better stratify CD prognosis. Thus they may be significant in our therapeutic decisions. Models for using these predictors would be presented.

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Crohn's Disease Phenotype and Behavior: Not All Patients Are the Same

Crohn's disease (CD) is an inflammatory disorder with heterogeneous manifestations and complications. The notion that it is probably a syndrome or several diseases with intestinal manifestations piled into one sack lends support from its many phenotypes, and the recently reported many possible genotypes [1]. Thus, there are repeated attempts to stratify CD into more homogeneous groups. Examples are the Vienna and the Montreal classifications (table 1) [2, 3]. This paper will focus on disease behavior (B section of both classifications). The most common presentation of CD is the inflammatory type, manifested mainly as diarrhea, abdominal cramps, possible fever and extraintestinal manifestations such as arthralgia, but no fibrostenotic or perforating (fistulizing) complications. However, disease behavior is not a constant given. Rather, more than 70% of CD patients would develop the more aggressive disease behaviors (fibrostenotic and perforating) within 10 years. This was shown by Cosnes et al. retrospectively assessing well-characterized CD patients in one center, as well as by the EC-IBD collaboration [4, 5].

This change in behavior with time is specifically striking as disease location (section L in the Vienna and Montreal classifications) does not tend to similarly change with time [6]. The implications of developing a more aggressive disease behavior type are significant. These phenotypes are associated with more surgical interventions, more hospital admissions and a greater personal and economic burden [7]. Moreover, stricture (i.e. the fibrostenotic disease behavior type) or fistula (i.e. the penetrating disease behavior phenotype) are not only manifestations of aggressive disease, they also predict a more aggressive disease, whether defined as the need for surgery or more hospitalizations and the use of steroids, as shown in both adult and pediatric populations [8, 9]. Having mentioned the need for surgery it is important to point out the well-known diagrams of timing to first surgery in CD patients. While several studies show that 50–70% of CD patients would require surgery within 10 years of diagnosis, Veloso et al. [10] have shown that the major contribution for this increased risk is on account of the aggressive phenotypes: fibrostenotic and penetrating. In a recent population-based study, Romberg-Camps et al. [11] showed that stricturing and penetrating phenotypes at diagnosis were important predictors for surgery, and stricturing phenotype, together with a young age <40 years and small bowel disease location, was a predictor of disease recurrence.

Table 1. Vienna and Montreal classifications of Crohn's disease

Vienna	Montreal
Age at diagnosis (A)	*Age at diagnosis (A)*
A1 <40 years	A1 <17 years
A2 >40 years	A2 17–40 years
	A3 >40 years
Location (L)	*Location (L)*
L1 terminal ileum	L1 ileal
L2 colonic	L2 colonic
L3 ileocolonic	L3 ileocolonic
L4 upper gastrointestinal	L4 isolated upper
Behavior (B)	*Behavior (B)*
B1 nonstricturing-nonpenetrating	B1 nonstricturing-nonpenetrating
B2 stricturing	B2 stricturing
B3 penetrating	B3 penetrating
	P perianal disease

All these observations stress the point that the stricturing-fibrostenotic and penetrating-fistulizing phenotypes are not only aggressive phenotypes per se, but they also predict an aggressive course.

Disease Phenotype Predictors: Why Are They Required?

As intuition and data support the notion that stricture and fistula represent and predict aggressive disease behavior and course, one might ask why we need predictors for such disease behavior. There are several important reasons for that in addition to our wish and need to better understand the disease pathophysiology. The main reasons for the need to have predictors for disease behavior are:

(1) Patient information: Upon diagnosis patients wish to know what their disease course will be.

(2) Closer follow-up of patients with worse prognosis: Knowing which patient might have a worse disease course would enable to put that patient under closer follow-up and to intervene earlier in case symptoms worsen.

(3) Modifying disease course: In the last decade traditional step-up vs. top-down therapeutic approaches for the treatment of CD are being evaluated. It has been shown by several authors, in both adult and pediatric populations, that top-down therapy, i.e. earlier use of biologic and immunomodulator therapies, might modify disease course, decrease hospitalizations, prevent surgeries and decrease the need for steroid treatment [9, 12].

These potent treatments might, however, be associated with significant side effects, specifically serious infections and the risk of malignancies. In addition, they might not be needed for the subgroup of patients destined to have a benign course. Their high cost also justifies optimal treatment-to-patient adjustment.

As a consequence, we need to be able to differentiate between patients who will have more aggressive phenotypes to those with potentially more benign CD course. The former would require closer follow-up, but, more importantly, is the subgroup of patients to whom we would offer biologic and immunomodulator therapy early on. As mentioned, this strategy is the only one currently known to prevent hospitalization and surgical intervention, specifically in patients with fistulae [13].

Patients with expected fibrostenotic disease phenotype require early identification as well. The data regarding primary prevention of fibrostenosis are scarce; however, the association of biologic therapy with fewer surgeries might suggest that at least a subgroup of these patients would benefit from early, step-up therapeutic strategy. They might also benefit more from early immunomodulator therapy as this was shown to have a secondary (though modest) preventive effect on postoperative disease recurrence [14]. The patients with fibrostenotic phenotype are also candidates for the most needed but still practically non-existent antifibrotic therapies.

In any case where patients are identified as having a higher chance to develop the more aggressive phenotypes (fibrostenotic and perforating), it is recommended to avoid triggers/accelerators of disease exacerbation and progression (e.g. smoking, NSAIDS use).

What Are the Current and Near-Future Tools for Disease Phenotype Prediction?

Three major factors might assist in predicting CD behavior: clinical, serologic and genetic.

Until recently, we based our attempts to predict disease phenotype mainly on clinical characteristics. As would be the case with many clinical features, some of them are not even predictors but already manifestations of the condition we are trying to predict. Intervention at this stage might be too late for this patient. Still, important observations made through the years might and should be used to stratify patients into subgroups. When Cosnes et al. [4] retrospectively assessed a cohort of CD patients in a single center and asked the question we are asking, i.e. what clinical factors might predict stricture formation, they identified several factors that intuitively make sense: jejunal involvement and ileal involvement had HRs of 3.2 [2.2–4.7] and 2.5 [1.9–3.3], and no colonic involvement had a HR of 2.0 [1.6–2.4]. No anoperineal disease and a recent diagnosis had a modest association with stricture formation (HRs 1.4 [1.1–1.8] and 1.3 [1–1.6], respectively). Predicting fistula formation was even harder, as only anoperineal disease, now considered an inherent part of the perforating phenotype, predicted fistula formation (HR 2.6 [2.3–3]) [4], while age <40, non-Caucasian origin and no upper gastrointestinal tract involvement had only modest effects (HR ~1.3). As specifically and directly addressing the question of stricture or fistula formation was usually part of larger-scale studies assessing different predictors of disease outcome, we might use data from studies looking at predictors for complicated/disabling disease. While the definition of 'complicated/disabling disease' is not unanimous amongst authors, it usually includes the use of steroids, hospital admission and surgery. As mentioned, stricture or fistula are often associated with this disease course. Interestingly, independent studies from several centers observed that >50% of CD patients would have a disabling disease course within 5 years [8, 15]. Beaugerie et al. [15] found that having 2 or more of the factors age <40 years, steroid treatment or perianal lesions had a ~90% positive predictive value for disabling disease. Thus, these might be used as indirect predictors also for stricture or fistula formation. As described, several clinical factors might be used to stratify CD patients into a 'higher-risk' group to develop stricture or fistula. However, most data come from retrospective studies, and are mainly associations, expressed as hazard ratios. Thus, stronger, more sophisticated predictors are required in order to 'fine-tune' our predictions. Here, attention should be given to the reports connecting mucosal healing or non-healing to CD postoperative recurrence, chances of surgery and disabling disease. While not specifically assessing stricture or fistula formation, these might be important predictors of the more aggressive disease phenotypes and course [16, 17]. They may specifically aid in the prediction (and thus potential prevention) of strictures, as the finding of significantly diseased mucosa in the small bowel equals small bowel disease, already associated with an increased risk for strictures.

Comment: Smoking, an important risk factor for postoperative CD recurrence and a negative prognostic factor in CD, was not addressed in this section as few studies

Table 2. Serologic markers and prognostic associations

Antibody	Directed against	Sensitivity/specificity (%)	
pANCA	neutrophil cytoplasm (colonic bacteria?)	60–70 in UC	
ASCA	mannans, *Saccharomyces cerevisiae*	60–70 (can be as low as 35) 95	young diagnosis age
OmpC	outer membrane porin C, *Escherichia coli*	31–55	IP disease, need for surgery
Anti-I2	I2 protein, *Pseudomonas fluorescens*		FS disease, need for surgery
CBir1	flagellin of commensal bacteria (clostridium?)		SB IP FS
gASCA	covalently bound mannan	50–56	young diagnosis age shorter duration
ALCA	laminaribioside	15–27	young diagnosis age FS/IP
ACCA	chitobioside	11–20	longer duration (high levels) noninflammatory behavior
AMCA	mannobioside	11–28	NOD2 association

See references 9, 18, 19, 21, 25 and 30–37.

directly assessed and reported on its association with stricture or fistula formation. However, its relation to worse-prognosis CD in general should be acknowledged.

Serologic Markers as Predictors for Stricture or Fistula Formation

In addition to known demographic and clinical predictors, more sophisticated predictors might be used to aid in stratifying CD patients. One such group of markers is the serologic one, gaining increasing support as important prognostic markers in CD.

The major serologic markers available are: anti-*Saccharomyces cerevisiae* antibodies (ASCA), anti-neutrophil cytoplasmic antibodies (ANCA), outer membrane porin C (OmpC), CBir1-flagellin, antibodies against I2 protein and the recently described anti-glycan antibodies: anti-laminaribioside carbohydrate (ALCA), anti-chitobioside carbohydrate (ACCA) and anti-mannobioside carbohydrate (AMCA). Table 2 shows these serologic markers and some of the reported prognostic associations reported for each one. As seen, several serologic markers that are associated with CD were associated with small bowel location, need for surgery, fibrostenotic, penetrating disease or a noninflammatory phenotype. Consistent associations reported by >1 groups include ASCA and gASCA, OmpC, I2, CBir1-flagellin, ALCA and ACCA. The serologic markers associated with both stricturing and penetrating behavior are ASCA and gASCA, CBir 1-flagellin, ALCA and ACCA (noninflammatory behavior). Importantly, it is not only the qualitative serologic response that counts but the quantitative one, i.e. higher titers and several seroreactivities pose an increased risk. Thus, higher titers or cumulative seroreactivities were associated with stricturing or penetrating disease behavior in adult and pediatric populations, small bowel location, need for surgery, and a relapsing course of pediatric CD [18–25]. Different serologic panels were thus tested in pediatric and adult populations. Ferrante et al. [19] showed that gASCA, ACCA, AMCA and OmpC were independently associated with non-inflammatory behavior (stricture or fistula) and Dubinsky et al. [20] showed that the frequency of structuring/penetrating disease increased with increasing numbers of immune responses against OmpC, CBir1-flagellin and ASCA.

Interestingly, seroreactivities determined not only an increased risk for stricture or fistula formation. Pediatric patients having multiple seroreactivities progressed to stricturing or penetrating disease sooner after diagnosis as compared to seronegative patients [20].

Genetic Markers as Predictors for Stricture or Fistula Formation

Several genetic variants were reported as predictors of CD phenotypes. Specifically, NOD2 variants were associated with strictures in the adult population [26], and synergism between NOD2 genotype and seroreactivity predicted fistulizing disease as well [27].

A study in the pediatric population has reported that variants of the OCTN and DLG genes were associated with fistulizing disease [28].

Not surprisingly, a genotype-serotype-dosage effect existed. gASCA, AMCA, ALCA and ASCA combinations were positively associated with NOD2/CARD15 genotype. Moreover, seropositivity increased with increasing positive NOD2/CARD15 variants [23–25].

As more genetic variants are identified in CD patients, more genotype-phenotype associations are reported. Thus, Weersma et al. [29] assessed known risk allele for CD in 1,684 patients from The Netherlands. In addition to adding support to the notion that more risk alleles were associated with stricturing or penetrating disease, they added that the autophagy gene ATG16L1 had an independent significant association with stricturing and perianal disease.

Summary and Conclusions

Complicated disease behavior manifested as stricturing, fibrostenotic disease or fistulizing penetrating disease is common in CD patients and increases in prevalence in parallel to disease duration. Attempts to predict complicated disease behavior are important for informing patients regarding their potential prognosis, closer follow-up of patients at risk and, more importantly, trying to modify disease course, using the powerful tools currently available such as biologic treatments. Adopting a 'risk-stratified approach' in the treatment of CD patients is recommended. Such a tailored approach would combine clinical, serologic and genetic markers so that high-risk patients could be identified before significant complications occur. Then, at an early disease stage, therapeutic interventions are expected to be most efficacious and optimally administered. Such an approach should be prospectively evaluated in large independent well-characterized patient cohorts. This way, the true-positive predictive value of clinical, serologic and genetic panels (as it is clear that single predictors are of little value) could be evaluated. As several of the potential predictors, specifically recently identified genes, are not widely available, and as time from prediction to complication (or avoiding it) might be protracted, acquiring the data is expected to be a lengthy process. Yet, its significance for CD patients and their physicians is invaluable, as it will enable evidence-based, high-quality predictions and interventions that might change the disease course of the patients.

Disclosure Statement

The author declares that Glycomids Ltd., Lod, Israel supplies IBDx® kits for serologic research at TASMC.

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