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Confirming complexity: Assessing environmental and genetic risk factors for inflammatory bowel disease

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The incidence of inflammatory bowel disease (IBD) is increasing worldwide with the highest incidence rates in westernized countries such as those of northern Europe, the United Kingdom and North America. These countries share many possible environmental risk factors and similar genetic backgrounds, all of which may contribute to the risk of developing IBD. The prevalence of IBD is especially high in Canada. In 2018, 267,983 Canadians (0.73%) were estimated to be living with IBD, with a forecast growth to 402,853 by 2030 (1). In previous studies, Bernstein and colleagues have endeavored to understand the risk factors for IBD, particularly during the neonatal period and in the first year of life (2-6). They and others have performed multiple studies on the effects of mode of childbirth, antibiotic use, rural compared with urban environments, breastfeeding, parental smoking and other hygiene and dietary factors on the development of IBD (7-15). Their paper in this issue of Gastroenterology is the most comprehensive analysis to date to examine the impact of demographic variables at birth and early life events on the risk of developing IBD (16). The authors at first focus on events which would likely lead to alterations in the gut microbiome but, even more importantly, they then report the potential genetic risks by examining the impact of a maternal history of IBD.

The University of Manitoba Epidemiology Database contains records of all Manitobans diagnosed with IBD between 1984-2010 and is uniquely suited to study risk factors (16). Identification of cases is based on an administrative definition of IBD based on frequency of health system contacts, and this approach was validated in 1995. In this study, a total of 825 IBD cases were matched to 5999 controls, although it is not detailed from which
study population the controls are found. The authors used 994 siblings unaffected by IBD as additional controls.

The authors performed multiple regression models, which make it challenging to interpret and compare all results. The main results show that maternal IBD diagnosis is the predominant factor for development of IBD for the risk of development of IBD in general (OR=4.53, 95% CI 3.08-6.67), for CD (OR=5.98, 95% CI 3.72-9.63), for UC (OR=2.71, 95% CI 1.34-5.51), for development of IBD under age 10 (OR=5.92, 95% CI 1.76-19.98), and for IBD under age 20 (OR=4.95, 95% CI 3.18-7.71). As suggested in their manuscript, the most important predictor(s) for subsequent diagnosis of IBD is evidence of a strong genetic effect and/or evidence of a close environmental mother-child relationship.

Using population controls, the authors also identify that infections during the first year of life are associated with an increased risk of IBD at any age (OR=1.39, 95% CI 1.09-1.79). However, this association was not statistically significant when examining CD and UC patients as separate groups. Additionally, infections during the first three years of life were not associated with a significantly increased risk of IBD at any age. The role of infections in the subsequent development of IBD under 10 and 20 years of age, however, might have a more important role (OR =3.06, 95% CI 1.07-8.78 and OR=1.63 95% CI 1.18-2.24, respectively). The authors eliminated the impact of maternal diagnosis of IBD by using siblings as controls, and found that infections during the first year of life are not
associated with a significantly increased risk of IBD at any time. This finding emphasizes that maternal IBD is more important than any examined environmental influence.

One of the challenges of this study is whether infections themselves are the risk factor for subsequent IBD or whether it is instead the exposure to antibiotics to treat the infections that incur the most risk. The authors hypothesize that infections and/or antibiotics might change the composition of the gut microbiome and thereby contribute to the cause of IBD. To evaluate infections requiring antibiotics, sub-analyses were performed after exclusion of children with viral infections. These results suggest that bacterial infections during the first year of life were not significantly associated with an increased risk of IBD. In our opinion, several of the authors’ sub-analyses thus failed to support a statistically significant importance of early infections for the development of CD and UC. The authors, however, found a statistically significant association between early infections and early onset of IBD. The complex influence of early infections and antibiotics has been underscored in a recent publication by other investigators and reported that exposure to antibiotics during pregnancy, but not in infantile age, is associated with an increased risk of very early onset IBD regardless of gastroenteritis (14).

A large case control study, like this one, is the most appropriate design for examining risk factors, but the limitations must be kept in mind. Methodological challenges can be linked to case control studies and confounding can never be ruled out in observational studies. In this study, although the regression models included factors such as
socioeconomic class, rural versus urban geography, birth weight, gestational age, neonatal intensive care unit admission, mode of delivery and Apgar score, a more complete picture of potential risk factors would have included data about paternal diagnosis of IBD, parental smoking, and the diets of the affected and unaffected children.

When compared to environmental factors, maternal inheritance was found to have a greater influence in this study, although there is no doubt of a complex interaction between specific early life events, exogenous exposures, epigenetic mechanisms, and genetics. Genetic risk for IBD has been known for decades with an approximately 4-fold increased risk of UC in the children of mothers and fathers with UC and an almost 8-fold increased risk of CD in the children of mothers and fathers with CD (17-20). This important paper by Bernstein and his colleagues have set the standard in a single study for considering both genetic and environmental influences of IBD. Although genetic factors are more powerful in this study, they are likely only a piece of the puzzle. Future studies should consider both environmental factors and genetic susceptibility, as it is likely a combination of these elements that influence the development and phenotypic manifestations of IBD.
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