Risks for Celiac Disease: Bacteria Make It Three

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Although the pathogenesis of celiac disease is now well-described [1], key factors contributing to the timing and pattern of its onset in an individual remain unclear. Thus, despite evidence that nearly every person who develops overt celiac disease expresses human-leucocyte antigen (HLA)-DQ2 or HLA-DQ8, there is still no clear explanation of why only a small number of these genetically predisposed individuals will develop celiac disease when exposed to gluten in their diet. This observation strongly suggests that other risk factors are also involved in the aetiology of this disease. In this issue of *Digestive Diseases and Sciences*, Riddle et al. [2] report the association between recent campylobacter infection and subsequent development of celiac disease that did not generalize to other antecedent infections, as monitored by a medical encounter database.

Several lines of evidence support the hypothesis that infectious insults may contribute to the development of celiac disease. The presence of adherent rod-shaped bacteria in small intestinal biopsies from children with celiac disease, not present in healthy controls, is suggestive of a microbial etiology [3]. Moreover, an association has been reported between infections occurring during the perinatal period [4] and in the first six months of life [5] with a subsequent increased risk of celiac disease. Intriguingly, one of these studies also reported data that disease risk rose synergistically with increasing exposure to gluten [5].

Breast-feeding reduces rates of enteric infections in early life by several mechanisms [6]. Furthermore, breast-feeding may affect the onset of celiac disease, particularly when gluten is introduced during breast-feeding. Potential confounders include the beneficial effects of breastfeeding on acute infections and on the development of the intestinal microflora, the consequence of replacing breastfeeding as the exclusive source of nutrition, and other small intestinal host protective factors.

Campylobacter species are the most common bacterial cause of acute enteric infections worldwide [7] with high infection rates in children under five years of age [8]. Thus, an environmental factor such as an increased incidence of campylobacter infections could explain, in part, the increasing prevalence of celiac disease, such as was recently reported in Finland [9].

The finding by Riddle et al. [2] that recent campylobacter infection is associated with an increased risk of developing celiac disease adds to a growing body of evidence that antecedent campylobacter infection increases the risk of a number of diseases, for example irritable bowel syndrome (IBS) [10]. Furthermore, their description of altered permeability consequent to an infectious insult as a potential mechanistic factor in the development of celiac disease [2] reflects a growing awareness that campylobacter compromises the integrity of the intestinal barrier [11]. Thus, increased permeability following campylobacter infection in an HLA-DQ2 or HLA-DQ8-positive person exposed to gluten may initiate the onset of celiac disease whereas a loss of epithelial integrity in an infected but genetically different individual may increase the risk of developing other sequelae or, indeed, have no effect. The duration of campylobacter infection could contribute to some of this variability of outcome.

Campylobacterial infections are usually self-limiting, partly because of activation of host innate immune

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responses to infection. *Campylobacter* infection involves bacterial adherence to gut epithelial cells, leading to cell invasion and consequent initiation of innate immune responses. These in turn lead to recruitment of specific inflammatory cells, including neutrophils and monocytes [11]. This host immune response to the infection is marked by the production of *campylobacter*-specific antibodies in most infected individuals. These antibodies are able to bind to adherent and invasive bacteria, thereby limiting their spread, either by removing them from the epithelial surface or by targeting internalised bacteria to lysosomes where they are killed. These innate and acquired immune responses generally ensure timely elimination of the infecting *campylobacter* organisms.

Nevertheless, it seems that a subset of individuals fails to produce antibodies to infection [12], indicative of an immune response not recognising or appropriately responding to the bacterial insult. It is currently unknown if seroconversion failure is associated with persistent infection, although likely, given the importance of anti-*campylobacter* antibodies in bacterial clearance. Regardless, the apparent tolerance of the host immune system to *campylobacter* infection may be another risk factor that augments the subsequent development of such long-term complications as celiac disease in a genetically susceptible host.

At present the findings outlined by Riddle and colleagues are suggestive but not yet conclusive. Prospective population-based studies are now required to fully define the consequences of acute *campylobacter* infections on the development of celiac disease in at-risk populations. Furthermore, mechanistic studies are required to better understand the interactions between the host and the pathogen that contribute to such specific outcomes.

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