Abstract

Celiac disease, a chronic immune-mediated disorder of the small intestine, manifests in a fraction of individuals with genetic predispositions consuming gluten. Environmental factors play an essential role in its triggering. The environmental stimuli may include dietary factors, infections etc. Identification of specific triggers could help in celiac disease prevention.

Our research project focused on common intestinal infections in infancy. We investigated adenoviruses and enteroviruses in stool specimens of children carrying a high-risk HLA genotype for celiac disease. We aimed to determine whether these infections are associated with early markers of celiac autoimmunity, and to identify virus genotypes. To distinguish multiple infections, massive parallel amplicon sequencing was utilized.

During 2001-2007, nearly 50.000 Norwegian newborns were screened within the MIDIA study for the presence of the HLA DR3-DQ2/DR4-DQ8 genotype, which is known to significantly increase the risk of celiac disease. The risk genotype was identified in 912 babies. Up to three years of children´s age, monthly stool specimens were collected and archived. Blood sampling was done every three months up to the age of a year, and then annually. Periodical questionnaires on children´s thrive were collected. During 2014-2016, the cohort was offered participation in a celiac disease study. A total of 220 individuals underwent a celiac disease screening, which led to the diagnosis in 27 cases. Each of patients was matched to two most similar healthy controls from the same cohort. A total of 2.161 stool samples were tested by real-time quantitative PCR for adenovirus and enterovirus and viruses were genotyped. The data were statistically analyzed by mixed effects logistic regression which took into account most of potential confounders.

The development of celiac disease antibodies was preceded by more enterovirus infections than was observed in matched controls. Also, prolonged infections and specimens of high viral load were significantly more frequent before the celiac disease antibody development. Both common enterovirus species, *Enterovirus A* and *Enterovirus B,* were significantly associated with celiac disease. Notably, there was a significant synergistic interaction between the enterovirus effect and the introduction of gluten into infant diet. Adenovirus, the second most frequent enteric virus, was not associated with celiac autoimmunity. The findings may have implications for designing future prevention strategies.