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POSSIBLE PATHOGENETIC ROLE OF VASCULAR, IMMUNOLOGICAL AND GENETIC FACTORS IN CERTAIN GASTOENTEROLOGICAL DISORDERS

Clinical presentations of the celiac disease and inflammatory bowel diseases (IBD) are highly variable but little is know about those factors determining disease phenotype. Since differences in the antioxidant, scavenging and immunomodulatory properties were found among three major haptoglobin (Hp) phenotypes, Hp polymorphism was reported to be associated with the risk and clinical course of inflammatory diseases. The *1-1* genotype of Hp α-chain results in production of low molecular weight dimers, while the *2-1* and *2-2* genotype are associated with variable length of linear polymers and cyclic polymers, respectively. The aim of our study was to investigate the distribution of Hp polymorphisms in large cohort celiac patients and in patients with IBD, and also their possible association with the clinical presentation of these diseases. Hp phenotypes were determined by SDS-PAGE and immunoblotting of the sera, which clearly identifies the genotype of the patients. The Hp results were compared to a group of healthy individuals representing the normal Hungarian population. In celiac patients, the frequency of Hp*2-1* phenotypes was significantly higher compared to the control population. The occurrence of Hp*2-2* phenotype was lower; however patients having this phenotype were at an increased risk of severe malabsorption as a clinical presentation of the disease but reduced risk of silent disease. The Hp phenotype distribution showed no difference in IBD group as compared to control population. In Crohn's disease (CD), patients with Hp *2-1* type carried a higher probability for inflammatory (non-stricturing, non-penetrating) form compared to the other two phenotypes, while the stricturing form developed less frequently. Regarding extraintestinal manifestations of the disease, we found no Hp*1-1* expression in patients with primary sclerosing cholangitis. The role of Hp molecules may be contributed to their distinct immunomodulatory properties and structural characteristics.

Sero-reactivity to microbial components or perinuclear components of neutrophils (P-ANCA) is reported to be associated with disease phenotype and may be of diagnostic importance in IBD. The aim of our study was to investigate the prevalence of serological markers in a large cohort of IBD patients. We also assessed the possible interaction with the disease phenotype and studied the relationship between serological response and genetic factors. We analyzed the feasibility of using the combination of ethanol- and formalin-fixed neutrophil substrates in the identification of IBD associated atypical P-ANCA. Sera were assayed for *Saccharomyces cerevisiae* (ASCA) and outer membrane porin protein of *Escherichia coli* anti-Omp by ELISA and ANCA by indirect immunofluorescence method. ASCA and anti-Omp positivity were associated with increased risk for CD. In addition, atypical P-ANCA was associated with increased risk for ulcerative colitis. The combined application of ethanol- and formalin-fixed substrates did not facilitate the differentiation between P-ANCA and atypical P-ANCA. Combining all P-ANCAs (typical and atypical) together ensures the highest sensitivity and specificity in differentiating ulcerative colitis from CD. In a logistic regression analysis, ASCA and anti-Omp were independently associated with ileal and non-inflammatory disease, but not with a risk for surgery. The number of antibodies produced against microbial antigen and their titers in CD showed a positive correlation with the small bowel involvement and the severity of the disease course (serology dosage effect). Reactivity to microbial components was associated with NOD2/CARD15 genotype. Positive correlation was found between the number of mutations and the prevalence of antimicrobial antibodies (gene dosage effect), further supporting the role of altered microbial sensing in the pathogenesis of CD.

Keywords: celiac disease, inflammatory bowel diseases, haptoglobin polymorphism, anti-microbial antibodies, anti-neutrophil cytoplasmic antibodies