Gluten Sensitivity is Associated with the Activation of The Innate Immune Response to Gluten Exposure, But Not the TH1/TH17 Response.

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Background: There are cases of gluten reaction defined as gluten sensitivity (GS) in which neither an allergic (wheat allergy) nor an autoimmune [celiac disease (CD)] mechanism can be advocated. Recent evidences suggest that early changes in intestinal permeability (IP) and activation of both innate and adaptive immune responses are involved in CD pathogenesis. Conversely, no data are available on the mechanisms leading to GS.

Aims: To investigate the changes in IP, TJ protein genes expression, and innate and adaptive immune responses in GS.

Methods: Biopsy samples were obtained from 28 GS patients, 53 pts with active CD, 16 patients with CD in remission, and 37 healthy controls (age range: 5 years -50 years). Claudin (CL) 1, CL2, CL3, CL4, ZO-1, and TLR1, TLR2 and TLR4, FOXP3, and TGF-β gene expression were measured by Real-time PCR. IP was evaluated by means of the lactulose/mannitol test. ELISA analysis of IL6, IL8, TNFα, and IL17 was conducted on PBMC of all patients.

Results: CL3 and CL4 expressions were significantly increased in GS subjects compared to CD patients ($p<0.01$). In GS patients, these changes were associated to a lower IP (0.010±0.008) that inversely correlated to CL4 gene expression ($r= -0.6318$; $p<0.05$) compared to healthy controls (0.018±0.009). Conversely, in CD patients an over-expression of CL2 was observed that was associated to increased IP (0.053±0.048). In a subgroup of GS pts, intestinal TLR1 and TLR2 expression was increased and these changes were associated to increased production of cytokines related to innate but not adaptive immune responses. IL 17 was elevated in CD but not in GS patients.

Conclusions: Compared to CD patients, GS subjects showed normal IP and activation of the innate but not TH1 and TH17 adaptive immune responses. These changes cause only minimal gut inflammation, suggesting that in GS lack of adaptive immune response involvement prevents the autoimmune gut insult typical of CD.