Title: A Novel Mechanism in Pediatric Chronic Enteropathies

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Background: Among the most common non-infectious causes of chronic diarrhea in pediatric age group are milk-protein allergy, gluten enteropathy, inflammatory bowel diseases, and autoimmune enteropathy. These conditions lead to the shared histopathology of blunting of the intestinal villi and/or lymphocytic infiltration of gut tissue. A subset of infants and children with chronic diarrhea, however do not fit any of these disease processes; lack food allergies, do not respond to elimination diets, have no serological or histological findings of inflammatory bowel disease or autoimmune enteropathy.

Objective: To investigate the underlying immunologic mechanisms in patients with chronic diarrhea and villus blunting of unknown etiology.

Design/Methods: We studies three patients (2M: 1F), presenting in infancy with diarrhea, vomiting, abdominal cramping, and failure to thrive. These children lacked anti-enterocyte antibodies in serum and had normal FOXP3 expression. Flow cytometry and standard immunohistochemistry techniques were used to assess early and late lymphocyte activation markers in serum and small bowel biopsies.

Results: In all, there was a significant elevation of both early (CD 25 and CD 69) and late T-cell activation markers (CD 71 and HLA-DR) in peripheral blood and small bowel biopsies compared to controls. These patients were unresponsive to elemental formulas, and were placed on intravenous steroids at 3mg/kg/day with a taper over 3 month course. Once clinical remission was established, the immunosuppressive regimen was switched to Azathioprine. On follow-up flow cytometry analysis, even though the early activation markers normalized, late activation markers were still elevated, despite remission and healing of the intestinal villi on the repeat biopsies.

Conclusions: In immune mediated enteropathies, antigen specific T-cells mediate tissue injury. Since the frequency of these antigen-specific T-cells are low, even though they express activation markers, it will only lead to a minimal rise in the percentage of activated T-cells. Autoimmune enteropathy is an exception to this, where there is a global rise in the lymphocyte activation markers. We describe a patient population that resembles autoimmune enteropathy with global lymphocyte activation, but lacks the anti-enterocyte antibodies and FOXP3 mutations. These patients represent a cohort of either a new disease entity or a stage in the development of classical autoimmune enteropathies.