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OBSERVER

Adult autoimmune enteropathy

Hugh James Freeman

Hugh James Freeman, Department of Medicine (Gastroenterology), University of British Columbia, Vancouver, BC, Canada
Correspondence to: Dr. Hugh James Freeman, MD, FRCPC, FACP, Department of Gastroenterology, University of British Columbia, Hospital, 2211 Wesbrook Mall, Vancouver, BC V6T 1W5, Canada. hugfree@shaw.ca
Telephone: +1-604-8227216 Fax: +1-604-8227236
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Abstract

Recent reports have suggested that autoimmune enteropathy involving the small bowel may occur in adults as well as in children. Apparently, the endoscopic and histological changes are similar to celiac disease before treatment, but these are not altered by any form of dietary restriction, including a gluten-free diet. As in celiac disease, histologic changes in gastric and colonic biopsies have also been recorded. Anti-enterocyte antibodies detected with immunofluorescent methods have been reported by a few laboratories, but these antibodies appear not to be specific and may simply represent epiphenomena. A widely available, reproducible and quantitative anti-enterocyte antibody assay is needed that could be applied in small bowel disorders that have the histological appearance of celiac disease, but fail to respond to a gluten-free diet.

Key words: Celiac disease; Autoimmune enteropathy; Anti-enterocyte antibodies; Anti-goblet cell antibodies; Antibodies in celiac disease

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COMPONENTS OF DIAGNOSIS

A number of reports in adults[1-7], similar to prior publications in children[8-10], have described an entity, termed autoimmune enteropathy (AIE), that appears to involve mainly, but not exclusively, the small intestine[4,7]. Some of the histologic changes, at least in adults, have been reported to permit pathological distinction from other disorders characterized by severe small bowel mucosal architectural abnormalities, specifically untreated celiac disease (Table 1). Specifically, reduced numbers of intra-epithelial lymphocytes, especially in surface epithelium, may be evident in AIE compared to adult celiac disease[7]. In AIE, the diarrhea fails to respond to any form of dietary restriction, including a gluten-free diet[8]. Circulating anti-enterocyte and/or anti-goblet cell antibodies are generally present in diagnosed AIE[7], but their precise significance in the pathogenesis of this disorder is not clear. It has been postulated elsewhere that these antibodies likely only represent epiphenomena since these appear after the onset of mucosal damage and then disappear following treatment, but before return to normal mucosa[11]. In some, pathological changes in gastric and colonic biopsies have also been recorded[7].

The antibodies are reported to appear as a linear pattern along the apex or brush border of the enterocytes, sometimes with an extension along the baso-lateral membrane[10]. Usually, the antibodies are IgG in type, sometimes complement-fixing, while in some, IgM and IgA antibodies occur[7,10]. These anti-enterocyte antibodies do not appear in celiac disease, Crohn's disease or ulcerative colitis[10]. Antibodies may also react with mucus in goblet cells, but these seem to be even less specific than anti-enterocyte antibodies[10]. For example, antibodies to goblet cells have been detected in chronic inflammatory bowel disease patients and their first-degree relatives[12].

Other co-existent autoimmune disorders as well as antibodies of different types have been observed in AIE. Indeed, even antibodies to tissue transglutaminase (tTG) have been described in over 30% of the largest series of reported AIE patients[7]. However, the presence of an associated autoimmune disorder is not a truly distinctive or differentiating clinical feature as autoimmune disorders have been commonly reported in several small bowel disorders, particularly in celiac disease, regardless of duration of gluten exposure[13-16].

DIAGNOSTIC DIFFICULTIES AND THE FUTURE

Most clinicians are likely to encounter significant difficulties in securing a definite diagnosis of AIE, because its precise differentiation from other small bowel disorders may be very difficult, at least based on current suggested criteria for diagnosis of adult AIE[7]. A number of factors have come into play. First, dietary compliance, even in an

Table 1 Comparison of celiac disease and autoimmune enteropathy in adults

	Celiac disease	Autoimmune enteropathy
Diarrhea	Responds to gluten-free diet	No response to diet therapy
Endoscopic and microscopic changes	Not specific, responds to gluten-free diet	Not specific, similar to celiac disease (pre-gluten-free diet)
Gastric and colon microscopic changes	May be abnormal	May be abnormal
Ages reported	All ages	All ages, mainly children
Autoimmune phenomena	Present	Present
TTG antibodies	Usually present	Present in 30% or more
Prognosis	Good with gluten-free diet	Unknown, anecdotal results

adult, may be exceedingly difficult to define. If dietary indiscretion is intentional or unavoidable, it may be very obvious. However, most experienced clinicians know that it may be very difficult to confirm that a specific diet has been continuously followed for prolonged periods (eg., gluten-free diet in celiac disease). Alternative "markers" have been suggested. For example, reduced antibodies to tTG in celiac disease have been suggested by some to provide a marker of compliance to a gluten-free diet, but others dispute this claim[17-19]. Second, failure to resolve symptoms with dietary restriction (eg., gluten) should not necessarily translate into a diagnosis of a persistent or refractory disorder. Other concomitant causes for symptoms, including functional disorders, may co-exist. Third, evidence for persistent histopathological changes in spite of dietary restriction may be more reflective of an inadequate duration of dietary restriction in order to detect a response or an inadequate method of assessment. In celiac disease, for example, histological evidence of normalization of pathological changes may require months or years, and usually occurs first in the most distal sites of involvement. Only later, sometimes much later, can a definite histopathological response to a gluten-free diet be documented in the most proximal small bowel (where endoscopic biopsies are generally taken). Fourth, only a limited number of laboratories claim to be able to detect anti-enterocyte antibodies, even though required methodology is straightforward, i.e., immunofluorescence microscopy. While anti-enterocyte antibodies are apparently not present in celiac disease[10], it appears that some of the histopathologic features of adult AIE may co-exist with those of celiac disease[7], further confusing the clinical picture.

In addition, these anti-enterocyte antibodies are not specific for AIE being reported in HIV-associated immunodeficiency syndromes without intestinal symptoms[20]. As noted earlier, anti-goblet cell antibodies which may be even less specific have been described in inflammatory bowel disease patients and their relatives[12]. Finally, and most importantly, immunofluorescent methods for serum antibody detection are very subjective, and observer-dependent. Use of immunofluorescent methods for screening (eg. anti-endomysial antibodies for celiac disease) are often based on "in-house" assays and may be difficult to reproduce between different laboratories, even if the same sources of sample material are used.

Further studies are needed to determine if AIE in adults is truly a separable clinical entity that may be amenable to other treatments. The most critical element needed is a widely available, reproducible, sensitive and specific assay for anti-enterocyte antibodies that might permit separation of AIE from other small bowel disorders and be an important addition to the investigative methods currently available for persistent diarrhea disorders in adults. To date, different therapeutic options have been used in an anecdotal fashion in adults diagnosed with AIE[7], but a conclusive approach to treatment still requires further evaluation.

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