

Immune and Autoimmune Enteropathies

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Key Words

Diarrhea, children and infants · Enteropathy, immune and autoimmune · IPEX syndrome · Autoimmunity

Abstract

Autoimmune enteropathy characteristically presents in infancy with protracted diarrhea. Underlying disorders of immune function, including regulatory T cells, must be excluded. Treatment options include nutritional rehabilitation, immune suppression, and, in select cases, bone marrow transplant.

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Introduction

Autoimmune enteropathy and enteropathies due to primary immune deficiencies are relatively uncommon causes of protracted diarrhea during infancy. When confronted with an infant or young child with chronic unexplained diarrhea, the differential diagnosis is quite extensive [1] and distinct from the considerations in assessing an adult with the same clinical symptoms [2, 3]. In most parts of the world, infectious and post-infectious enteropathies remain the most common causes of protracted diarrhea [4]. Some investigators contend that allergic enteropathies also are common in young children, even in

the absence of other atopic symptoms or a family history of an allergic predisposition. Much more commonly, milk and soy protein-induced allergic colitis develops in newborns and infants, including those receiving breast milk as their sole source of nutrients. In an older child who has received gluten in the diet, it is important to consider celiac disease as the underlying cause of symptoms since it is increasingly apparent that gluten-sensitive enteropathy has protean manifestations and is a life-long condition that can be treated effectively and safely with appropriate dietary adjustments [5].

One helpful way to consider alternative etiologies is to differentiate those causes of chronic diarrhea in which there is a relatively intact villus-crypt unit from those with abnormal villus-crypt architecture (i.e. an enteropathy). In the former scenario, conditions such as congenital disorders of ion transport and secretory diarrhea, due to bacterial enterotoxins and hormone-secreting tumors, need to be considered [1]. By contrast, an enteropathy with a reduction in villus height should bring to mind a completely different set of diagnostic considerations. After infectious and allergic etiologies have been excluded, chronic high volume diarrhea beginning in the first few days of life should raise microvillus inclusion disease for diagnostic consideration [6]. This latter condition also is referred to as familial microvillous atrophy [7] or Davidson's syndrome.

With slightly later onset of chronic diarrhea, a condition that can present much like autoimmune enteropathy is tufting enteropathy [8], which also is referred to as intestinal epithelial dysplasia [9]. Interestingly, many of the infants reported from both Europe and North America with this enteropathy are from families originally from North Africa, Turkey and, especially, the island of Malta. As a result, tufting enteropathy certainly should be considered seriously in infants of these backgrounds.

Clinical Presentation

Children with autoimmune enteropathy typically present after the neonatal period, but within the first year of life. A history of maternal polyhydramnios during the pregnancy and/or a family history of other affected children should direct a search for other causes of protracted diarrhea of neonatal onset including, for example, congenital chloride-losing enteropathy [1].

Most cases of autoimmune enteropathy begin with chronic, watery and unremitting diarrhea between 2 and 4 months of age after an uneventful pregnancy and neonatal period. However, the later onset of symptoms is well described, including isolated case reports of initial manifestations of diarrheal disease during adolescence [10] and the adult years [11]. These older-onset patients typically carry the diagnosis of refractory sprue, until an analysis for the presence of anti-enterocyte antibodies is carried out. It remains to be established whether the later onset of symptoms is due to the same molecular basis of disease as for those with the development of diarrhea during the first year of life.

Although such autoimmune conditions primarily manifest as enteropathies, the colon often is involved as well. Signs and symptoms of colitis (for example: urgency, tenesmus, hematochezia and mucus in the stools) accompanying protracted diarrhea that is unresponsive to a trial of elemental feeding – particularly in association with impaired growth and undernutrition – should raise the suspicion of an autoimmune enteropathy.

The presence of other autoimmune conditions also raises the risk of autoimmune enteropathy. Initial cases of autoimmune enteropathy described in the scientific literature were associated with type-1 diabetes mellitus, autoimmune thyroiditis, autoimmune hemolytic anemia and skin conditions that likely had an autoimmune basis. Many of the affected cases reported also were associated with tubulonephropathy.

Histopathologic Findings

Small bowel biopsies in infants and children with protracted diarrhea are extremely helpful. Results of morphology and immunohistochemistry are not only helpful in establishing a specific diagnosis, but frequently also can exclude other conditions when such evaluations are not definitive [12].

In cases of autoimmune enteropathy, light microscopy findings (fig. 1a) often resemble many of the features associated with gluten-sensitive enteropathy even when affected children have not been challenged with gluten. Examinations of sections stained with hematoxylin and eosin often reveal total villus atrophy and crypt hyperplasia. In addition, there often is marked immune cell infiltration including activated T cells [13], into the lamina propria of the intestinal mucosa. There also can be morphological evidence of intraepithelial lymphocytes, but not to the same degree as that observed in children with total villus atrophy caused by celiac disease [14]. Immunohistochemistry, with relevant antibodies as markers, provides evidence of a marked infiltration of CD3+ T cells into the lamina propria (fig. 1b). Recent findings indicate that the cytokine interleukin-21 may mediate T-cell activation, impaired survival of the cells and ultimately predispose the affected host to autoimmune diseases [15].

Colonic biopsies also show evidence of immune cells infiltrating the lamina propria in children with autoimmune enteropathy. This finding is in contrast to other causes of protracted diarrhea in infants in whom evidence of immune activation other than in the small bowel is not observed [14].

Autoantibodies

A hallmark of autoimmune enteropathy is the presence in serum of immunoglobulin G antibodies, usually circulating in low titer, which bind to apical aspect of enterocytes (fig. 2). In one report on 25 children with unexplained chronic diarrhea, anti-enterocyte antibodies were detected in 14 (56%) subjects, compared with positive test results in 3 (5%) of 53 patients with chronic inflammatory bowel diseases, 0 of 10 with celiac disease and none of the 50 children with other conditions unrelated to the gastrointestinal tract [16]. The antibody is not specific to an epitope on human enterocytes, because the autoantibodies also bind to small bowel epithelial cells in intestinal sections obtained from rats, mice and guinea pigs. The antigen also is detected in renal epithelium.

Fig. 1. a Biopsy of the small bowel mucosa obtained from a child with protracted diarrhea. The biopsy shows total villus atrophy with crypt hyperplasia and infiltration of the lamina propria by a mixed chronic inflammatory cell infiltrate. HE. Approximate original magnification $\times 20$. **b** Immunohistochemistry with anti-CD3 antibody demonstrates infiltration of the lamina propria by numerous CD3+ T cells. Approximate original magnification $\times 20$.

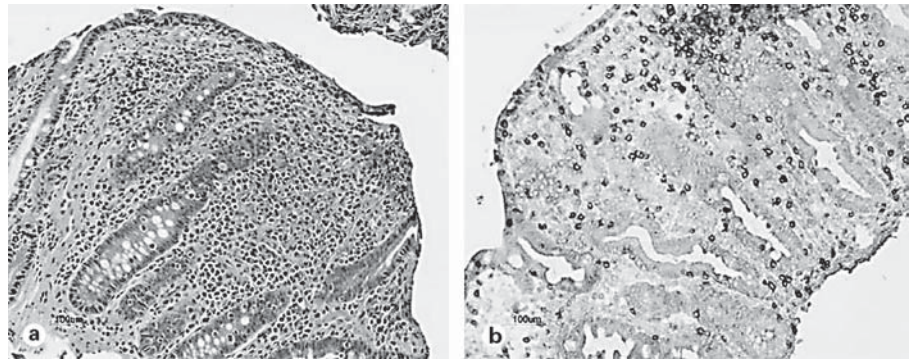
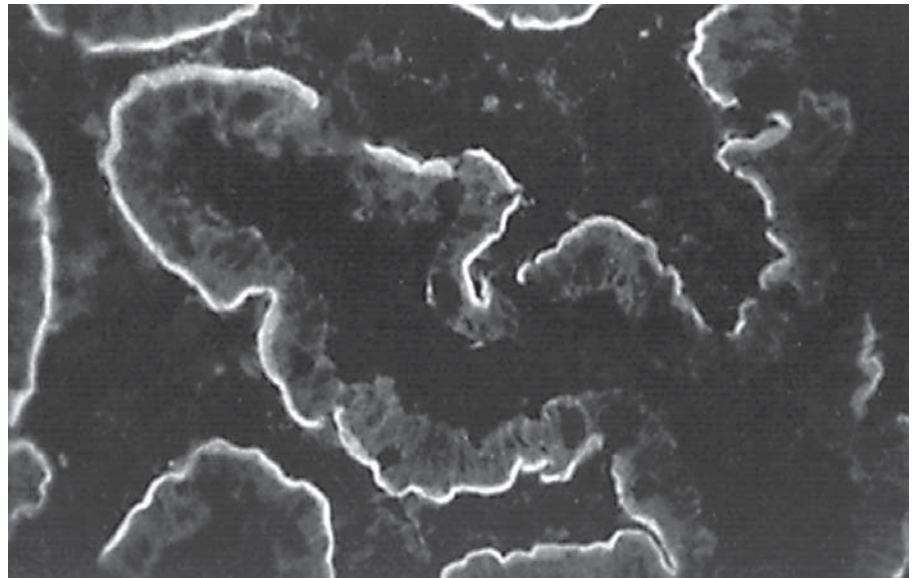


Fig. 2. Indirect immune fluorescence demonstrates the presence of anti-enterocyte antibodies in the serum of a child with autoimmune enteropathy. Fluorescent staining outlines the apical surface of enterocytes along the villus-crypt unit.



Western blots show that autoantigens are either 55 [17] or 75 kDa [18, 19]. The 75-kDa autoantigen is expressed in the small bowel, large intestine, pancreas and kidney [20]. With therapy (considered below), titers of circulating anti-enterocyte antibodies are reduced, or disappear progressively and completely with clinical improvement. Therefore, systemic autoantibody levels can be monitored as an objective measure of responsiveness to clinical interventions [17].

Even though molecular targets for anti-enterocyte antibodies have been described, other investigators observed that the test may not be sufficiently specific. For instance, Martin-Villa et al. [21] noted the presence of such autoantibodies in the systemic circulation of subjects without villous atrophy and with no history of diarrhea. Thus as with any other screening tests, these anti-enterocyte antibody assessments must be placed in appropriate clinicopathological contexts.

A few case reports describe an autoimmune enteropathy in which systemic autoantibodies are directed against the goblet cell lineage rather than apical regions of enterocytes [22]. Intestinal biopsies in these cases show a lack of goblet, Paneth and enteroendocrine cells [23]. This may reflect a deficiency in the transcription factor, Math1 [24]. The clinical and pathological findings are otherwise similar to those in other cases of autoimmune enteropathy. This finding supports the view that infiltrating T cells, rather than the systemic autoantibodies, are involved in mediating the disease's pathobiology. Thus, autoantibodies likely provide markers of an underlying condition which develops as a result of mucosal inflammation and injury, rather than being specifically involved in disease pathogenesis [13, 14].

Primary Immune Deficiency Disorders

A variety of immune disorders of genetic origin can cause intestinal injury resulting in enteropathy, malabsorption of nutrients, and protracted diarrhea [25]. For instance, chronic granulomatous disease and glycogen storage disease type 1b both have been associated with mucosal inflammation along the length of the gastrointestinal tract, with clinical, radiological, and endoscopic features that can mimic those observed in chronic inflammatory bowel diseases. Eosinophilic gastroenteritis also should be considered in the differential diagnosis.

It is now clear that there are multiple causes of what previously had been lumped together in the single entity referred to as autoimmune enteropathy. For example, primary T-cell immune deficiencies are reported to present with features of autoimmune disease. For instance, Arniaz-Villena et al. [26] reported a kindred in which there was a congenital defect in the expression of the CD3- γ subunit of the T-cell receptor complex. The affected proband presented with protracted diarrhea in association with autoantibodies against gut epithelial cells, smooth muscle and mitochondria, as well as autoimmune hemolytic anemia and a selective IgG2 subclass deficiency.

Two children with Schimke immuno-osseous dysplasia and abnormal T-cell immune function were described in the literature [27, 28]. Both children presented with chronic diarrhea and signs and symptoms consistent with autoimmune enteropathy. However, autoantibodies were not present and atypical *Mycobacteria* were identified in the small bowel mucosa in one child [28]. This observation serves to reinforce and highlight the importance of excluding chronic infection and underlying immunodeficiency state in a child with unexplained protracted diarrhea.

IPEX Syndrome

Immune dysregulation, polyendocrinopathy, enteropathy, and X-linked (IPEX) syndrome is the most specific and well-documented underlying cause of autoimmune enteropathy. The disease is caused by mutations in the *Foxp3* gene carried in the peri-centromeric region of the X chromosome: Xp11.23–Xp13.3 [29, 30]. *Foxp3* (also variously referred to as *JM2* and *scurfin*) is a transcription factor that is critical for control of the normal development of regulatory T cells [31, 32]. When mutated, the normal control of CD25+ T cells is lost [33, 34] and there

is an inappropriate activation and dissemination of activated immune cells to multiple organs, including the intestinal tract (fig. 3).

Several *FoxP3* gene mutations have been reported that cause human disease. There is probably a genotype-phenotype relationship explaining differences observed in terms of clinical expression, disease severity, number of extra-digestive autoimmune manifestations, and prognoses [35]. As a result, autoimmune enteropathy can be subdivided into those cases due to IPEX, affected males without evidence of a mutation in the *FoxP3* gene, and affected girls [36].

Male infants with IPEX syndrome present in infancy with type-1 diabetes mellitus, autoimmune thyroiditis, autoimmune hemolytic anemia (positive direct Coomb's test) and a variety of skin lesions, including eczema, an ichthyosiform dermatitis, psoriatic dermatitis and alopecia universalis [37]. Protracted high-volume diarrhea, due to an autoimmune enteropathy, is generally a prominent presenting feature. These children also may present with atopic features, including food allergies, peripheral eosinophilia and raised levels of immunoglobulin E [38]. Cases of autoimmune enteropathy occurring in boys (especially if there are multiply affected siblings in the same family) with evidence of autoantibodies directed against other organs and evidence of systemic autoimmune diseases, which have been published previously in the medical literature, should be considered as possible cases of IPEX syndrome.

Therapeutic Considerations

The initial management of infants with chronic diarrhea in whom autoimmune enteropathy is a diagnostic consideration is precisely the same as that for all other affected individuals. The initial focus should target the maintenance of intravascular volume and nutritional rehabilitation, which generally requires either continuous elemental, enteral venous infusion or total parental alimentation. Children often are left dehydrated and undernourished during extensive in-hospital diagnostic evaluations. This approach is deplorable: fluid and nourishment are among the first priorities [39]. Only after these are provided should health care providers pause to consider the long list of potential considerations in the differential diagnosis.

Autoimmune enteropathy generally responds well to potent suppression of the hosts' immune system. High-dose systemic corticosteroids frequently will reduce mu-

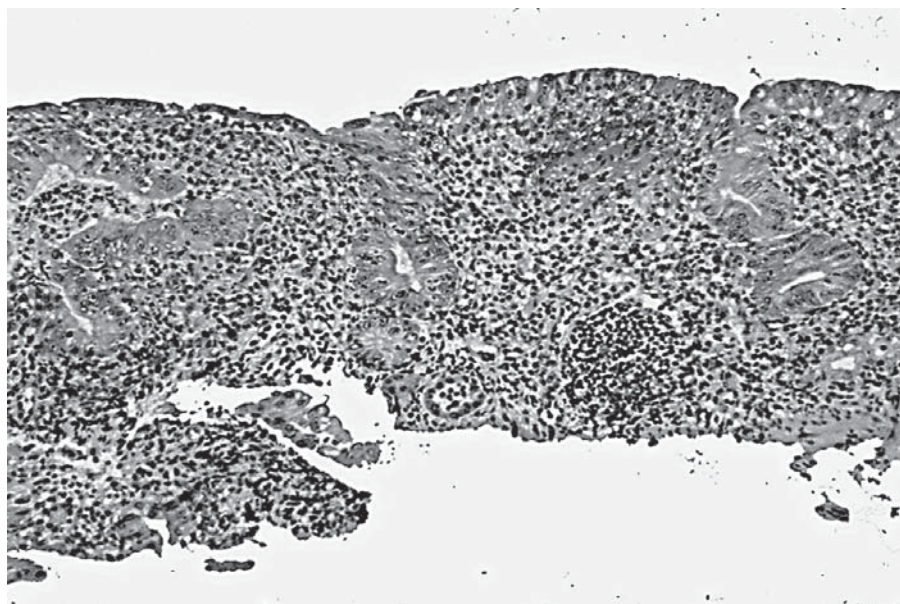


Fig. 3. Histology of the small bowel in a child with IPEX syndrome shows evidence of total villous atrophy and marked inflammation of the lamina propria with a chronic inflammatory cell infiltrate.

cosal inflammation, lower stool output and permit increased enteral delivery of calories. Autoantibody titers are reduced in parallel with clinical responses to medical therapies. However, steroid dependence (that is, recurrence of symptoms following a tapering of the corticosteroid dose) is the norm. Steroid resistance (i.e. absence of an apparent response to therapy) is also common. As a result, a number of other potent immune-suppressive agents have been employed. Case reports indicate apparent clinical benefits of a variety of therapies such as cyclosporine [40, 41], tacrolimus [42], sirolimus [43], mycophenolate mofetil [44], cyclophosphamide [45] and biologic agents such as the chimeric monoclonal antibody against tumor necrosis factor- α , infliximab [46].

Most affected children respond to potent suppression of the immune system and, ultimately, tolerate advancing enteral feedings and concurrent reductions in parenteral nutritional supports. As a result, autoimmune enteropathy should not be considered as an indication for undertaking small bowel transplant. This clinical prognosis stands in stark contrast to most cases of microvillus inclusion disease where there is no response to potent immune suppression and the outcome is guarded in the absence of intestinal transplantation, at least as a therapeutic option [1, 6, 12].

Whether these children may benefit from alternate therapeutic strategies, such as bone marrow transplantation, is not known. Reported benefits of transplanting bone marrow-derived cells in children with IPEX syn-

drome [47] suggest that this approach is worth further consideration in severely affected cases with a limited or partial response to potent suppression of the immune system. Positive responses of children with IPEX syndrome to allogeneic bone marrow transplantation also emphasize the critical importance of establishing the correct underlying diagnosis of protracted diarrhea in infants and young children. Lumping affected cases together as so-called intractable diarrhea of infancy is unhelpful and may impair consideration of appropriate therapeutic options.

Careful consideration of the precise etiology of protracted diarrhea is also essential in considering genetic counseling of families with affected children. Most cases of autoimmune enteropathy appear to be sporadic without other affected family members or evidence of parental consanguinity. On the other hand, IPEX syndrome is an X-linked condition. This raises other issues related to risk in affected families that are beyond this review.

Conclusions

Autoimmune enteropathy is a term used to describe a relatively uncommon cause of protracted diarrhea in infants. This is a severe inflammatory condition, which generally is responsive to immune suppression therapy. It is quite likely that autoimmune enteropathies encompass a number of etiologies that require better definitions

to enable future targeting of appropriate therapies and genetic counseling. Further research should define underlying immune disorders and pathophysiological processes that result in the disease's clinical manifestations. Appropriate relevant animal models likely will prove to be exceptionally helpful in the disease processes' delineation.

To identify genetic mutations accounting for autoimmune enteropathy, fibroblasts from a skin biopsy should be immortalized for cell culture. Similarly, messenger RNA should be isolated from intestinal biopsies for use in whole genome scanning, which is already technologi-

cally feasible and economically viable as a powerful research tool [48]. An international collaborative research effort also will improve the current understanding of the molecular basis of chronic immune-mediated enteropathies.

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