Current Paediatrics (2006) **16**, 305–316

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Advances in the understanding and management of autoimmune enteropathy

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KEYWORDS
Autoimmune enteropathy;
IPEX syndrome;
Foxp3;
APS-1;
Aire;
Bone marrow transplantation

Summary
There have been real advances in understanding the pathogenesis of autoimmune enteropathy, including determination of specific autoantigens. The most important clinical association is with IPEX (X-linked immune polyendocrinopathy) syndrome, which is due to mutation in the *Foxp3* transcription factor, a molecule critical in generation of regulatory T cells. Association of non-IPEX autoimmune enteropathy with T cell activation defects further point to impairment of T cell tolerance mechanisms as the primary underlying cause of autoimmune enteropathy. This also explains the frequency of other autoimmune manifestations. The centrality of T cell responses in autoimmune enteropathy, rather than B cell autoantibody production, as previously thought, is further suggested by the finding of late-onset gut autoimmunity in APS-1 (autoimmune polyglandular syndrome-1), a condition where negative selection of T cells within the thymus is disrupted due to mutation in the *Aire* (autoimmune regulator) gene. However, this form of autoimmune enteropathy is milder because the immune target is within entero-endocrine cells rather than absorptive enterocytes. There have also been important changes in management, with introduction of more potent immunoregulatory therapy, and more recently the use of bone marrow transplantation, which may theoretically offer hope of a cure in what frequently used to be a fatal condition.

Practice points

- Autoimmune enteropathy is an important cause of childhood intestinal failure
- Careful clinical assessment—including stool analysis while nil by mouth and on carbohydrate challenge—is a cornerstone of diagnosis
- There are now recognized autoimmune enteropathy syndromes with identified gene mutations
- Scrupulous long-line care may be life-saving if parenteral nutrition is needed long-term
- Full immunological work-up including T cell activation is necessary
- Therapeutic options may now include bone marrow transplantation in selected cases

Introduction

Autoimmune enteropathy is a rare but important cause of severe persistent diarrhoea caused by an autoimmune

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doi:10.1016/j.cupe.2006.07.008

response to intestinal epithelium.[1–7] It presents classically in the first months of life with chronic diarrhoea, and is frequently thought to represent post-enteritis or food-sensitive enteropathy in the early stages. However, the diarrhoea fails to resolve despite all dietary exclusions, and weight loss is often so significant that parenteral nutrition is required. Diagnostic criteria are based on small intestinal villous atrophy, unresponsiveness to dietary restriction, circulating enterocyte antibodies and/or associated autoimmune conditions.[4]

The disease may be confined to the small intestine,[1] and sometimes also the colon,[8] or it may be part of a multisystem autoimmunity, most commonly in association with renal disease or polyendocrinopathy.[2–5] The lesion of autoimmune enteropathy, crypt hyperplastic villous atrophy, is induced by uncontrolled activation of T cells within the intestinal mucosa.[7] The main diagnostic test, detection of enterocyte autoantibodies, is, however, based on an associated B cell response. Several cases have been reported in which enterocyte autoantibodies have been undetectable or variable, and their titre often bears little relationship with clinical disease activity.[3,5,7–9] Thus the disease is now primarily viewed as T cell associated.[7,9]

The outcome of autoimmune enteropathy has often been poor, with many children dying from complications of long-term parenteral nutrition or because of involvement of other organs by the autoimmune process.[10–14] Recent trends have been towards more aggressive immunotherapy, or even bone marrow transplantation if an underlying constitutive immunodeficiency is identified.[9]

Presentation of autoimmune enteropathy

The classic presentation of autoimmune enteropathy is with chronic diarrhoea, beginning within the first months of life, and proceeding relentlessly despite all dietary manipulations.[6,11,12,15,16] The age at first onset is an important part of the history, as the primary epithelial enteropathies, the other major causes of intractable diarrhoea, usually present in the early neonatal period.[15,16] Perinatal onset may rarely occur in autoimmune enteropathy, but there is normally a history of good growth before the onset of symptoms. It is more common in males (often X-linked) and in consanguineous families. Affected children may develop autoimmunity in other organs, most commonly the pancreas and the kidney.[6] There is recent evidence that autoimmune enteropathy may occur in adults, sometimes enterocyte antibody negative[17,18] and potentially associated with thymoma.[19,20] Findings of gastric and colonic involvement in some cases have led to the introduction of the term generalized autoimmune gut disorder (GAGD).[8,18]

Autoimmune enteropathy may have either an aggressive or relatively insidious onset, and may not initially appear different to other diarrhoeal diseases. Primary immunodeficiency or autoimmune predisposition may be unmasked by enteric pathogens, and the disorders often considered initially are infective gastroenteritis and post-enteritis syndrome/cow's milk sensitive enteropathy.[6,21] Initial management includes milk exclusion with use of lactose-free oligoallergenic formulae, which may induce slight improvement in osmotic diarrhoea as secondary deficiency of lactase is common in enteropathy.[7] However, the loose stools and weight loss essentially continue.

Differential diagnosis of autoimmune enteropathy

There is a wide differential diagnosis for persistent diarrhoea in infants and young children, including common and rare diseases (Table 1).[21] The most common cause at this age is food-sensitive enteropathy, and appropriate exclusion diets should be performed for an adequate period. Chronic diarrhoea due to primary carbohydrate malabsorption syndromes (e.g. glucose–galactose malabsorption), will remit while nil by mouth, underlining the importance of this manoeuvre.[21]

Disorders of other transport systems induce malabsorption of lipids and fat-soluble vitamins (abetalipoproteinaemia, hypolipoproteinaemia, Anderson's disease, ileal bile-salt receptor deficiency), neutral amino acids (Hartnup disease), tryptophan, basic amino acids (cystinuria), electrolytes (chloridorrhoea, defective jejunal Na^+/H^+ exchange) and zinc (acrodermatitis enteropathica). Although vacuolated enterocytes and an abnormal blood film may be

Table 1 Causes of persistent diarrhoea in early life.

1. *Failure of specific absorption pathway* (e.g. Glucose-galactose malabsorption, primary alactasia, bile salt malabsorption).
2. *Food sensitive enteropathy or enterocolitis* (e.g. cow's milk sensitive enteropathy, coeliac disease, Food protein induced enterocolitis)
3. *Pancreatic malabsorption* (e.g. cystic fibrosis, Shwachman syndrome)
4. *Dysmotility with bacterial overgrowth* (potentially related to anatomical abnormality or pseudo-obstruction syndrome)
5. *Inflammatory bowel diseases* (classic inflammatory bowel disease is very rare in infancy—underlying systemic causes such as immunodeficiency should be sought)
6. *Immunodeficiency* (even severe immunodeficiencies may be clinically silent until unmasked by a pathogen—if a gut pathogen, this may prompt referral to the gastroenterologist rather than immunologist in the first instance)
7. *Systemic diseases* (e.g. mitochondrial cytopathy)
8. *Primary epithelial causes of intractable diarrhoea* (e.g. microvillous inclusion disease, tufting enteropathy, heparan sulphate deficiency)
9. *Cryptogenic enteropathies* (Syndromatic intractable diarrhoea)
10. *Autoimmune enteropathy*