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Diarrhoea due to small bowel diseases

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Abstract

Small intestinal diseases are a common, though often overlooked cause of diarrhoeal illness. Fully 1% of the Caucasian population are affected by coeliac disease and a substantial portion of children living in poverty in the developing world are affected by environmental enteropathy. These are but two examples of the many diseases that cause mucosal injury to the primary digestive and absorptive organ in our body. While diarrhoea may be a common, though not universally seen symptom of small bowel mucosal disease, the consequent malabsorption can lead to substantial malnutrition and nutrient deficiencies. The small intestine, unlike the colon, has been relatively inaccessible, and systematic evaluation is often necessary to identify and treat small intestinal mucosal diseases that lead to diarrhoea. Immunodeficiency states, including HIV enteropathy, adult autoimmune enteropathy, drug-associated enteropathy, and tropical sprue continue to occur and require specific therapy. All patients with severe diarrhoea or diarrhoea associated with features suggestive of malabsorption may have a disease of the small intestinal mucosa that requires careful evaluation and targeted management.

Keywords

Autoimmune enteropathy; Coeliac disease; HIV enteropathy; Malabsorption; Tropical sprue steatorrhoea

Introduction

This chapter will cover the clinical features of small intestinal diseases that can result in chronic diarrhoea (Table 1). A major focus will be on coeliac disease and other disorders that can mimic the clinical features, pathologic changes, and occasionally overlap with coeliac disease. We will address small intestinal overgrowth, tropical sprue, Whipple's disease and briefly discuss common variable immunodeficiency and other miscellaneous disorders.

Clinical clues for small bowel origin of diarrhoea

The small intestine is both a secretory and absorptive organ. Disorders of the small intestine can be primarily malabsorptive or secretory in nature but most disorders on the small intestine mucosa result in both excess secretion and failure of absorption. Diarrhoea of small

bowel origin is more often noninflammatory and high output. Improvement of diarrhoea after fasting suggests an osmotic component of the symptoms. Postprandial diarrhoea, bloating, malodorous flatus, and pale stools which leave an oil slick or are difficult to flush suggest malabsorption. Weight loss despite a normal appetite might suggest malabsorption though loss of appetite due to pain on eating can also be a cause. Pain is a common symptom of small bowel diseases including coeliac disease. The pain may be focal or diffuse; it is often associated with meals, bloating and/or distension. Generalized malaise or fatigue are also common though nonspecific.

Coeliac disease

The most common inflammatory disorder of the small intestine in the Western world is coeliac disease. This is a chronic inflammation due to an immune reaction to dietary gluten which is present in wheat, barley, and rye.

Epidemiology

The disorder affects 1% of Caucasians, with some variation in geographic locations. It occurs worldwide, but some racial groups are less likely to develop it either because of low genetic susceptibility or low consumption of wheat. While these numbers reflect the results of screening studies, fewer patients are diagnosed; as many as 83% of persons with coeliac disease in the United States may remain unrecognized [1]. The rate of diagnosis clinically is rising in all areas and the disease can be detected at any age, usually at an early age but even in the very elderly [2].

Clinical manifestations

There is a broad spectrum of presentation from the classic malabsorption (diarrhoea, weight loss, steatorrhea, and multiple deficiencies - particularly iron, folic acid, B₁₂ and fat-soluble vitamins) to much less common or even absence of symptoms [3]. These include iron-deficiency anaemia, isolated diarrhoea or symptoms that can mimic irritable bowel syndrome as well as extra gastrointestinal manifestations, which can affect virtually any system in the body from infertility, neurologic syndromes, and bone disease. Diarrhoea appears to be less frequent today than 20 years ago. [4]. Coeliac disease can occasionally present with life threatening severity requiring hospitalization and parenteral support [5] (Table 2).

Diagnosis

Coeliac disease is usually initially detected by specific serology, including tissue transglutaminase or endomysial antibodies [6] and less commonly during endoscopy. Both of these antibodies are usually of the immunoglobulin (Ig) A isotype. In a few patients, there may be IgA deficiency, in which case IgG isotype antibodies directed against tissue transglutaminase may be helpful. Gliadin antibodies are not particularly helpful in diagnosis due to poor specificity and sensitivity. Deamidated gliadin antibodies are a substantial advance over the standard gliadin antibodies within improved specificity and sensitivity [7]. They provide little incremental benefit beyond tissue transglutaminase IgA antibodies, though it may be helpful when there are borderline tissue transglutaminase antibodies results. The combination of tests in panels may increase the sensitivity but can negatively affect specificity [8]. A more rational approach to the serological testing may consist of a cascade of testing determined first by the level of IgA (Fig. 1). A stepwise approach to the detection and confirmation of coeliac disease is most efficient (Fig. 2). Intestinal biopsies are the gold standard for the diagnosis of coeliac disease [9]. Coeliac disease can produce a whole spectrum of injury to the proximal small intestine from inflammation only to several degrees of villous atrophy (Marsh classification) [10]. There are many important disorders

that can mimic this enteropathy, and are important to consider when seeing a patient with malabsorption and/or villous atrophy (Table 1).

Recently, the European Society for Paediatric Gastroenterology and Hepatology and Nutrition have suggested that biopsies may be avoided in children in whom there is strongly positive tissue transglutaminase antibodies (at least 10 times the upper limit of normal), positive endomysial antibodies in a different blood sample, carriage of the appropriate human leukocyte antigen (HLA) genotype for coeliac disease (DQ2 and/or DQ8) and response of characteristic symptoms to a gluten-free diet [11]. Further prospective data are necessary before this recommendation can be affirmed elsewhere or applied to adults.

Most patients with coeliac disease carry the gene pairs encoding the HLA types DQ2 or DQ8 [12]. Rare exceptions can occur and when biopsies and serology are both positive a diagnosis can be made in absence of the genotype. Caution is suggested when there are positive biopsies but negative serology suggesting that other causes of enteropathy be considered even when the HLA type is permissive. The major value of HLA typing is that when it is absent it makes the diagnosis very unlikely (high negative predictive value) [12].

Treatment

The treatment of coeliac disease is lifelong adherence to a gluten-free diet (elimination of wheat, barley and rye) [13]. When a patient with what seems to be a coeliac syndrome does not respond to a gluten-free diet, alternative or additional diagnoses need to be sought [14]. The most frequent cause of nonresponsive coeliac disease is inadvertent gluten contamination. There are several experimental approaches in development that have promise as adjunctive or perhaps even alternative approaches to the management of coeliac disease though none of them have been approved for use.

Non-responsive coeliac disease

Approximately 10–20% of patients with coeliac disease will continue to have frequent symptoms or will have a relapse of symptoms despite an initial response to a gluten-free diet. The most common persistent symptoms are diarrhoea, and the most common explanation is continued contamination of the diet with gluten, either advertent or inadvertent [15]. A systematic approach to these patients is most valuable and will often reveal causes (Fig. 3). A systematic evaluation by an expert dietician is invaluable for identifying inadvertent sources of gluten in the diet. In the past, one of the most common sources was that of commercial cereal ingestion by patients whose education on the gluten-free diet had occurred many years before recognition of the trace additives, such as malt, as a gluten source in corn- or rice-based cereals. Inadequate education, motivation, or sometimes even deliberate ingestion of gluten are well recognized. Serologic tests are not especially sensitive, except for the largest quantities of gluten contamination. Once gluten contamination has been identified or ruled out, the next step is to consider the presence of an alternative diagnosis. A small proportion of subjects assumed to have coeliac disease on the basis of initial biopsies ultimately turn out not to have coeliac disease and instead have one of many other disorders associated with villous atrophy. Most commonly these patients do not have specific positive coeliac serology or did not have serology done [16,17].

Once alternative diagnoses have been ruled out, associated disorders should be sought. Bacterial overgrowth, microscopic colitis, exocrine pancreatic insufficiency and motility disorders, such as rapid transit diarrhoea, should be tested for and managed. If these diagnoses have been excluded, patients with persistent villous atrophy may then be classified as refractory coeliac disease and managed appropriately.

Refractory coeliac disease

Refractory coeliac disease probably affects no more than 1–2% of patients. It is defined as severe malabsorptive symptoms that have persisted or recurred despite verified strict adherence to a gluten-free diet for at least 6 months in whom other causes of non-response (see above) have been either ruled out or adequately treated and who do not have overt lymphoma [16]. Much of what is known about refractory sprue comes from case series in national and international referral centres. The disorder is characterized by severe villous atrophy, often appreciable endoscopically (Fig. 4). Patients may develop extensive ulceration within the proximal small intestine that also may be visually apparent endoscopically. Histology usually reveals severe villous atrophy in the context of ongoing inflammation, including increased intraepithelial lymphocytosis. Often the degree of injury is as severe or more severe than that at the initial diagnosis. The immunopathogenesis of the disease probably relates to excess inflammation driven by IL15-stressed epithelial cells and also by cells with the innate immune system in the lamina propria. The intraepithelial lymphocytes are activated cytotoxic T cells that produce cellular injury of the epithelial cells [18]. The most typical clinical scenario is severe malabsorption with diarrhoea and abdominal pain. There is often hypoalbuminemia, anaemia, and advanced metabolic bone disease. Other common deficiencies include vitamin B12, folic acid, zinc and copper. Some of these deficiencies individually can produce substantial impact or morbidity – for example, there can be neurologic complications with copper deficiency. Refractory coeliac disease can be primary, when there has never been a response to a gluten-free diet or secondary when symptoms recur many years after an initial response [19]. Typically, a diagnosis of refractory coeliac disease would not be made until at least 12 months of a strictly-enforced gluten-free diet; however, in patients with primary disease, their disease may be so severe as to require earlier intervention and the authors will institute this after 6 months in such patients. Cross-sectional body imaging is largely used to identify malignant complications, though occasionally non-malignant complications, such as giant mesenteric lymphadenopathy, may be seen with cystic cavitation of giant mesenteric lymph nodes [20]. Often patients have splenic atrophy and may be prone to infections. Other findings, such as moderate mesenteric lymphadenopathy, small bowel wall thickening, and intussusception are commonly seen in patients with complicated refractory coeliac disease. One of the initial steps in the evaluation of a patient with refractory coeliac disease is to evaluate for enteropathy-associated lymphoma with radiologic imaging (Fig. 5). Once the diagnosis of refractory coeliac disease has been established, it is important to determine if the patient has developed clonal T cell expansion of aberrant T cells, which is known as Type 2 refractory coeliac disease. Type 1 refractory coeliac disease is essentially defined as similar clinical scenario as Type 2, except there is no evidence of aberrant T cells present. These patients are at especially high risk of mortality and progression to lymphoma [21]. The survival of refractory coeliac disease depends on the type. Those patients with type 1 refractory coeliac disease have an 80% 5-year survival, though the 5-year survival in those with type 2 in one series is <50%. The most helpful prognostic factors of older age, anaemia, hypoalbuminemia, and the presence of a T cell clone are all suggestive of an increased risk of mortality. The management of patients with refractory coeliac disease is largely based on case series and small case studies. A common approach for both types of refractory coeliac disease include strict adherence to a gluten-free diet, institution of vigorous nutritional support often requiring parenteral nutrition, the use of potent topically-active steroids followed if necessary by systemically-active steroids, often administered intravenously and, in patients with type 1 coeliac disease lacking clonal T cell gene rearrangement, azathioprine may be used for steroid-sparing effect. In patients with type 2 refractory coeliac disease, our practice has been to avoid the use of azathioprine.

Small intestine bacterial overgrowth

Small intestine bacterial overgrowth occurs when symptoms are related to increased numbers of small bowel bacteria – by definition, $>10^5$ bacteria/mm³ in small bowel fluid culture [22]. These bacteria are usually but not exclusively anaerobic.

Epidemiology

The prevalence of small bowel bacterial overgrowth is unknown. It can occur as an isolated disorder or coexist with other gastrointestinal disorders with abnormal mucosal integrity, prior surgery, reduced gastric acid or abnormal motility.

Clinical manifestations

Small intestinal bacterial overgrowth may cause a wide spectrum of symptoms that mimic irritable bowel syndrome or cause severe malnutrition and diarrhoea [23]. The finding of small intestinal bacterial overgrowth should prompt the search for other underlying causes unless something is obvious in the history. Small intestine bacterial overgrowth has been associated with scleroderma, motility disorders, gastrointestinal surgery, and conditions with reduced gastric acid secretion [24].

Recent studies suggest that pharmacological suppression of gastric acid with proton pump inhibitors does not increase bacterial overgrowth [25].

Surgeries that disrupt the flow of intestinal contents such as intestinal bypass surgery frequently results in bacterial overgrowth, and occasionally produces severe malabsorption and diarrhoea. Small intestinal diverticulosis often associated with motility abnormalities can result in recurrent bacterial overgrowth.

Immune deficiencies also can lead to bacterial overgrowth. For example, selective IgA deficiency and combined variable immunoglobulin deficiency can all lead to bacterial overgrowth, which can be quite difficult to treat and often may be associated with parasitic diseases.

Diagnosis

The diagnosis of small intestinal bacterial overgrowth is controversial and consists of either breath testing or direct culture of intestinal fluid using aerobic and anaerobic methods. However, this technique is not widely available. A bacterial count $>10^5$ bacteria/mm³ in the small bowel is abnormal. Specific identification of bacteria is not performed as there are often multiple types of bacteria present.

Hydrogen breath testing is widely used for the detection of bacterial overgrowth [26]. Lactulose is frequently used, with small intestinal bacterial fermentation of lactulose with release of hydrogen that is expired in the breath. This typically would show a peak within 1 hour. Over time, lactulose reaches the colon where colonic bacteria metabolize it leading to a second peak, which will be prolonged into a plateau of hydrogen production. This test has both a low sensitivity and high rate of false positives [27]. There is no consensus about criteria for a positive test, although the “double peak” phenomenon is often used as indicative of small intestinal bacterial overgrowth [26].

Glucose is another substrate that may have a somewhat higher sensitivity and specificity than lactulose test [26]. It is important to recognize that glucose can reach the colon within 90 minutes and, if there is rapid or accelerated small bowel transit, it may reach it even faster giving a false positive reading. Methane is also commonly measured but the

interpretation of elevated methane levels is controversial and, when found in large quantities, renders the test unreliable.

Finally, small intestine bacterial overgrowth as a clinical syndrome may be diagnosed on the basis of a clear response to an empiric trial with an antibiotic [24]. However a single trial of antibiotics alone would not be sufficient to justify long term or repetitive therapy except in patients with very high risk anatomy or immunodeficiency.

Treatment

Treatment of small intestine bacterial overgrowth starts with treating the underlying condition if there is the motility disorder, if feasible. Suppression with antibiotics with anaerobic coverage is often used with either a nonabsorbable antibiotic such as rifaximin or other broad-spectrum antibiotic (e.g., tetracycline, penicillin, and cephalosporin) [24,28]. The effect is intraluminal and does not require systemic absorption. Metronidazole is often quite effective, but may not be well-tolerated if repeated courses are needed [29]. As none of the diagnostic tests are 100% specific, it is reasonable to start with a single course to identify either a clear-cut response; if there is a remediable underlying cause, further suppressive therapy may not be needed. Many patients will need ongoing suppressive therapy, either with continuous therapy or cycling different antibiotics on 10 days of each successive month.

Whipple's disease

Whipple's disease is a rare disorder, primarily affecting the intestine but also affecting extraintestinal locations including the joints, lungs, central nervous system, heart and the eyes [30]. It is a chronic infection by *Tropheryma whipplei*, a fastidious intracellular organism. The modes of infection, transmissibility and predisposition to infection are poorly understood.

Epidemiology

Whipple's disease is rare, with about 1000 cases reported in the literature. It affects middle-aged individuals with predominance among males.

Clinical manifestations

Whipple's disease presents with diarrhoea weight loss, general malaise, fevers, joint pains, cognitive impairment, ataxia, and eye involvement. It is often gradual in onset. Intestinal biopsies will show villous atrophy [31]. Intracellular organisms can be identified by periodic-acid Schiff stain, identifying inclusions within macrophages (Fig. 6). Electron microscopy can also demonstrate the organisms. Currently, the diagnosis is confirmed by polymerase chain reaction on biopsies, blood or cerebrospinal fluid [32]. Cases may only involve the central nervous system, heart (e.g., endocarditis), or other extraintestinal sites without gut involvement (localized infection) [33].

Treatment

The disease is fatal if untreated. Treatment must be long term with antibiotics that can penetrate the blood brain barrier. Although the optimal treatment for Whipple's disease has not yet been determined, a combination of 2-weeks of either ceftriaxone or meropenem intravenously followed by 1 year of oral trimethoprim-sulfamethoxazole is a reasonable initial therapy [34]. Despite initial clinical response, relapses can occur and central nervous system relapses can be severe [35].

Tropical sprue

While coeliac disease is the most common chronic enteropathy in the developed world, tropical sprue is one of the most common disorders in certain parts of the developing world. The cause has never been identified [36] but is assumed to result from exposure to enteric bacteria.

Epidemiology

The prevalence of tropical sprue is unknown. It occurs in residents or visitors to particular geographic areas where tropical sprue occurs – in Mexico and Central America and South and Southeast Asia, but rarely in Africa [37]. It appears to be decreasing in frequency in residents in these locations, but it seems to be increasing in the U.S. in patients who are returning from visits to these locations.

Clinical manifestations

Tropical sprue can cause symptoms of weight loss, diarrhoea, fatigue, steatorrhea and nutritional deficiencies. Folate deficiency is frequent. Histopathology may be indistinguishable from coeliac disease with varying degrees of villous atrophy and intraepithelial lymphocytosis (Fig. 7). Coeliac-specific serology is usually negative and these patients do not have an enriched background of the coeliac associated HLA genotypes. Antigliadin antibodies can be positive in a third of patients with tropical sprue [38]. Secondary exocrine pancreatic insufficiency can be a cause of persistent symptoms after treatment [38]. Tissue transglutaminase and endomysial antibodies are negative. In evaluating patients with possible tropical sprue, we recommend testing with coeliac serology; if negative, we recommend treatment for presumed tropical sprue without using a gluten-free diet.

Treatment

The treatment of choice for tropical sprue is a combination of antibiotics (e.g., oral tetracycline) and folic acid supplementation for 3–6 months [39]. Recurrences are possible for patients living in endemic areas, and may be delayed for months.

Miscellaneous conditions

Adult autoimmune enteropathy

Autoimmune enteropathy was first described in young children, often neonates who have a syndrome characterized by 1) severe diarrhoea with malabsorption, 2) total villous atrophy, and 3) anti-enterocyte antibodies. By definition, this condition does not respond to any form of food exclusion diet, and the patients lack obvious immunodeficiency [40]. The disorder also occurs in adults. It is thought that the immune system targets the components of the enterocyte via activation of the innate and adaptive immune system. This results in an enteropathy characterized largely by a lymphoplasmacytic infiltration of the lamina propria, loss of goblet cells, villous atrophy that may be partial or complete, and often a lack of intraepithelial lymphocytosis in the surface (Fig. 8). Patients often have anti-enterocyte antibodies. These antibodies are directed against surface components of the enterocytes or goblet cells. While these antibody tests are not entirely specific to autoimmune enteropathy (for example goblet cells antibodies can be seen in ulcerative colitis) in the context of a patient with severe unexplained enteropathy they are quite supportive of the diagnosis. This testing can be performed by ELISA tests against extracted antigens or by indirect immunofluorescence (Fig. 9). Autoimmune enteropathy can also be associated with colitis and gastritis, also characterized by the absence of goblet cells. In some cases, there can be overlap with coeliac disease. The diagnostic criteria for adult autoimmune enteropathy have

been proposed (Table 3). A common feature of patients with autoimmune enteropathy is association with other autoimmune diseases, typically thyroid disease, myasthenia gravis, SLE lupus, Sjögren's syndrome, as well as immune deficiencies that predispose to infections or parasitosis. Typically patients have substantial diarrhoea. Prominent mesenteric lymphadenopathy can be seen in a minority of patients. Diagnosis is based on the criteria above and is often first suggested in patients who have severe villous atrophy, negative coeliac serology and failure to respond to a gluten-free diet.

Treatment

Treatment is largely based on anecdote as there have been no define trials for this very rare condition, and the treatment is largely based on immunosuppression. The authors' first choice is that of budesonide in which the dosing regimen is altered in order to achieve topical exposure of the affected small intestine to the drug, taking care to avoid any foods or medications that inhibit cyp3A4 activity. This is necessary in order to reduce the risk of systemic steroid effects of budesonide that has a high first pass inactivation in the liver.

The ultimate outcome is uncertain, though many patients do have an initial response to steroids or immunomodulatory therapy. Differentiating autoimmune enteropathy from other conditions, particularly inflammatory bowel disease, true refractory coeliac disease, diffuse lymphoma, drug-associated enteropathy, or rare genetic disorders such as IPEX syndrome is important [41].

Autoimmune enteropathy may also occur in the context of thymoma, an extremely rare syndrome, and can be a clue for myasthenia gravis [42].

Collagenous sprue

Collagenous sprue refers to a pathologic entity characterized by mucosal villous atrophy that is similar coeliac disease but with clear-cut layer of subepithelial collagen which extends into the lamina propria. The spectrum of disease varies somewhat; however, the majority of the patients have complete villous atrophy with partial villous atrophy in approximately one third. The collagen layer is usually readily visible on H&E, but can be better seen with special stains for collagen (Fig. 10B). Mild collagen thickening ($<20\text{ }\mu\text{m}$) can be seen in patients with untreated coeliac disease, especially in a patchy fashion; this does not meet the criteria for true collagenous sprue [43,44]. The deposition of a thick band of collagen itself may result from any form of chronic inflammation of the small intestine and, indeed, collagenous sprue can often occur as a sequelae or end result of several pathologic processes, including coeliac disease, autoimmune enteropathy or drug-associated enteropathy (Fig. 10). The disorder typically occurs in older women. This pathologic entity is associated with a clinical syndrome of severe malabsorption with diarrhoea, weight loss and abdominal pain, and failure to respond to a gluten-free diet [44]. It is associated with a substantial fat malabsorption, frequent hospitalization, and often substantial impact nutritionally on the patient [43]. The mechanisms for collagenous sprue are variable and start with some usually primary disease (Fig. 11).

The treatment of collagenous sprue is largely directed at the underlying disorder, be that coeliac disease, drug-induced enteropathy, etc. Most frequently patients also need to be treated with corticosteroids and typically potent topical agents, such as budesonide, are preferred, though patients may require parenteral steroids initially. Occasionally, reversal of the enteropathy, including reversal of fibrosis, can be seen. This is particularly common when the underlying aetiology is readily reversible, such as drug-associated enteropathy. If immunosuppressive medications are used, anecdotally it seems important to measure levels of the drug or metabolites to insure that adequate absorption has been obtained, particularly

important for azathioprine. Maintenance therapy is often required in idiopathic cases, though our recent experience in patients in whom a drug-associated disorder is suspected is that patients can be weaned off steroid therapy after several weeks or months.

Drug-associated enteropathy

Medications are a frequent cause of diarrhoeal illness. Many of these disorders are acute and occur while the patient is on antibiotics, such as erythromycin, or shortly after it is completed, such as *C difficile* infection. However, small intestinal injury has also been reported in association with the chronic use of several medications. Perhaps best known amongst these is the drug-induced villous atrophy associated with the use of mycophenolate mofetil first described in patients post-transplantation [45]. Other medications, including azathioprine and non-steroidal anti-inflammatory drugs, have been described as causing enteropathy, though they are less likely to cause diarrhoea. We recently reported a series of patients referred with a severe enteropathy-associated diarrhoea associated with olmesartan therapy. It had been assumed to be refractory coeliac disease; however, these patients lacked the typical coeliac-specific serology, and most lacked autoantibodies characteristic of autoimmune enteropathy [46]. This syndrome was often clinically quite severe with dramatic weight loss, severe diarrhoea, and electrolyte abnormalities. Patients often required hospitalization for acute dehydration (Table 4). Patients frequently, in addition to severe enteritis, had microscopic colitis and lymphocytic gastritis. A significant portion of these patients had collagenous deposition consistent with collagenous sprue. While steroid therapy was successful in some patients, the disorder did not remit until after the medication, olmesartan, was discontinued [46]. While cause and effect has not been proven, it does appear clinically that recovery does not occur until the medication is withdrawn and may take weeks or months. This form of medication-induced diarrhoea is unusual in the long lag time between the initiation of therapy, which is often years, and the development of diarrhoea. This is likely an extremely rare association of olmesartan therapy as this was not reported in any of the clinical trials, which have often included thousands of patients. However, when faced with a patient with severe diarrhoeal illness and unexplained enteritis, discontinuation of any non-essential medications should be contemplated as some of these responses may be idiosyncratic.

Environmental enteropathy

Environmental enteropathy, previously termed tropical enteropathy, primarily affects young children in severe poverty [47]. It is estimated that 145 million children are affected worldwide, not exclusively in the tropical areas. It is associated with multiple infectious insults in the first year of life. The intestine looks indistinguishable from tropical sprue but the presentation may be more subtle, primarily affecting growth and intellectual development [47]. The treatment currently focuses on improved nutrition and hygiene.

Enteropathy associated with immunodeficiencies

Common variable immunodeficiency is a relatively rare disorder in which there is a defect which can be congenital or acquired in which there is impairment of the production of immunoglobulins by plasma cells [48]. These patients frequently have diminished or absent IgA and often diminished or absent IgG subclasses. IgM may also be diminished. There is a blunted immune response to infections and vaccinations. These patients often give a long history of infections affecting mucosal surfaces – sinusitis and bronchiectasis in particular are common. Within the intestine, they are prone to giardiasis and small intestinal bacterial overgrowth.

There may be dysregulation of gut immune homeostasis, and this can lead to chronic inflammation in the intestine that can mimic inflammatory bowel disease or coeliac disease

[49]. One important histologic feature is the absence or paucity of plasma cells in the biopsy that occurs in common variable immunodeficiency [50] (Fig. 12). However, this absence may be overlooked as usually coeliac disease, tropical sprue, and other entities are associated with normal or increased number of plasma cells. The diagnosis is initially made by measuring quantitative immunoglobulins and then specific immune testing on these cell subsets in the circulation by flow cytometry. From a management perspective, the response to pneumococcal vaccination is important; it is usually considered an indication for intravenous immunoglobulin therapy. The management of small intestinal bacterial overgrowth in these patients usually needs to be either continuous or repeated courses of antibiotic therapy chronically in order to minimize symptoms. Patients who have inflammatory conditions despite the treatment for bacterial overgrowth may require anti-inflammatory therapy such as budesonide and occasionally even biologic therapy may be necessary [49]. It is important to recognize that common variable immunodeficiency can occur at any age, but an early onset may be associated with an increased risk of gastric cancers and lymphoma, particularly of the intestine. Patients with common variable immunodeficiency should be managed by an immunologist with experience in primary immunodeficiency states, given the complications of these patients. The commonly used parenteral immunoglobulin therapy does not seem to help the GI manifestations though it is important for prevention of severe infection. Patients are also prone to autoimmune disorders including pernicious anaemia, further increasing the likelihood of bacterial overgrowth.

Giardiasis

Small intestinal parasitosis can cause substantial diarrhoea [51]. Of these, only giardiasis causes significant morphologic change in a small intestine. Transmission of Giardiasis occurs throughout the United States, most often affecting young children [52]. When *Giardia* is identified on biopsies, the careful scrutiny of the lamina propria for the absence of plasma cells should be undertaken by the pathologist. If plasma cells are absent, this may represent combined variable immunoglobulin deficiency and testing quantitative measures of the different immunoglobulin isotypes should be undertaken [49]. In patients with IgA deficiency, giardiasis may be severe and persistent and indeed recurrent. The nitroimidazole compounds are highly effective for treatment of Giardiasis [51].

Human immunodeficiency virus (HIV) enteropathy

HIV infection now in the era of highly active antiretroviral therapy has become eminently managed and indeed many patients will survive now decades with HIV infection. HIV targets CD4 cells. It appears to be particularly destructive of the intestinal CD4 cells. Despite a rise in circulating CD4 cells in patients on active treatment, CD4 cells remain virtually absent from the small intestine. Patients do get a syndrome of scarring of the lymphoid structures within the gastrointestinal tract and lymph nodes. This can lead to chronic malabsorption and weight loss as well as peculiar changes in the distribution of fat which tends to be a substantial increase in visceral fat. [53]. Unfortunately, little is known about the treatment of this condition although highly active antiretroviral therapy, nutritional supplementation, and medications to control symptoms may be helpful [54]. Acute HIV infection can also present with an enteric syndrome and consideration of this condition should be considered as most cases are now acquired through heterosexual transmission in otherwise healthy young adults. The centers for disease control recommendations are that all individuals between 13 and 64 should be routinely tested for HIV as the most effective way of detecting that infection need to be considered by all practitioners [55].

Conclusion

In summary, coeliac disease and these other disorders with malabsorptive symptoms can overlap or can be confused with each other. In particular, coeliac disease can be associated with small intestine bacterial overgrowth and in the context of IgA deficiency coeliac disease also with giardiasis. Small intestinal bacterial overgrowth itself can be seen in patients with immune deficiencies. Tropical sprue must always be considered in residents in or who travel to tropical sprue areas and travel history should be sought. Serology and occasionally HLA testing should be done before any change in the diet in order to differentiate coeliac disease from these other causes. Whipple's disease, albeit rare, should be considered in patients with diarrhoea and systemic organ involvement.

Abbreviations

HIV	human immunodeficiency virus
HLA	human leukocyte antigen
Ig	immunoglobulin.

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Practice points

- Coeliac disease is an increasingly common disorder in both the developed and now the developing world. It is best first detected by sensitive and specific serologic tests and confirmed by biopsy.
- Other disorders account for 10% of cases of villous atrophy. They should be suspected in patients in whom serologic tests for coeliac disease are negative or in those who do not respond to a gluten-free diet.
- Severe malabsorption can result from mucosal disease. This severe mucosal disease can have multiple aetiologies that include drug-associated enteropathy, adult autoimmune enteropathy, and collagenous sprue.
- A travel history to areas at risk for tropical sprue should be sought in all patients with a malabsorptive disorder.
- Immunodeficiency states should be sought in patients with seronegative enteropathy.

Research agenda

- It is crucially important to understand why coeliac disease is becoming more frequent, which is not simply due to increased detection.
- The mechanisms by which various medications could be associated with enteropathy need to be further elucidated.
- Understanding the role of the humoral immune system in mucosal immune homeostasis will be crucial to understand not only the GI complications of the rare primary immunodeficiency states, but also may provide insight into inflammatory bowel disease.
- The cause of tropical sprue has eluded much investigation for over 100 years. This condition, especially the association with what used to be termed tropical enteropathy or now known as environmental enteropathy, has probably the largest single impact of a small bowel disease. It affects over 140 million children, leaving consequences of reduced growth and intellectual potential that have devastating consequences on entire cultures or populations. Understanding the mechanism of this disease so that effective interventions/preventions can be instigated would be crucial to the health of the young poor of the world.

Fig. 1.
Coeliac disease serology cascade based on total IgA measurement. [Courtesy of Melissa M. Snyder, PhD, Antibody immunology laboratory, Mayo Clinic].

Algorithm for diagnosis of coeliac disease

Fig. 2. Confirmation of the diagnosis of coeliac disease by using combined serology and histology. [Reprinted from Walker MM, Murray JA. An update in the diagnosis of coeliac disease. *Histopathology* 2011; 59:166–179].

Fig. 3.

A systematic approach to the evaluation of non-responsive coeliac disease. The outline of a systematic approach to the patient with non-responsive coeliac disease (NCD).

LC=lymphocytic colitis. CC=collagenous colitis. GC=gluten contamination. RS=refractory sprue. PLE=protein-losing enteropathy. [Reprinted from Abdulkarim AS, Burgart LJ, See J, Murray JA. Etiology of nonresponsive coeliac disease: Results of a systematic approach. *Am J Gastroenterol* 2002; 97:2016–21].

Fig. 4. Endoscopic appearance of villous atrophy in a patient with refractory coeliac disease. These findings are essentially indistinguishable from standard coeliac disease or indeed other causes of severe villous atrophy. [Reprinted from Rubio-Tapia A, Murray JA. Classification and management of refractory celiac disease. *Gut* 2010; 59:547–57].

Fig. 5. Protocolized approach to the evaluation and management of patients with refractory coeliac disease. [Reprinted from Rubio-Tapia A, Kelly DG, Lahr BD, Dogan A, Wu T-T, Murray JA. Clinical staging and survival in refractory celiac disease: a single center experience. *Gastroenterology* 2009; 136:99–107].

Fig. 6. Periodic-acid Schiff (PAS) positive macrophages and partial villous atrophy of the duodenum characteristic of Whipple's disease (magnification: 10×).

Fig. 7. Partial villous atrophy in a patient with tropical sprue is indistinguishable from mild gluten sensitive enteropathy on the basis of histology. Courtesy of Tsung-Teh Wu, M.D., Ph.D.

Fig. 8.

Photomicrograph of duodenal biopsies in a patient with autoimmune enteritis demonstrating near total villous atrophy. Note the dense lymphoplasmatic cellular infiltration of the lamina propria. (B) At a higher power, there is disruption of the brush border and neutrophilic infiltration of the crypts producing abscess. Note the absence of any surface lymphocytosis. [Reprinted from Akram S, Murray JA, Pardi DS, Alexander GL, Schaffner JA, Russo PA, Abraham SC. Adult autoimmune enteropathy: Mayo Clinic Rochester experience. *Clin Gastroenterol Hepatol* 2007; 5:1282–90].

Fig. 9.

This is an indirect immunofluorescence assay utilizing the serum from a patient with autoimmune enteropathy. The substrate used is small intestine. The pattern is a linear fluorescence pattern of the brush border of the enterocytes. Magnification: 300 $\times$. [Reprinted from Akram S, Murray JA, Pardi DS, Alexander GL, Schaffner JA, Russo PA, Abraham SC. Adult autoimmune enteropathy: Mayo Clinic Rochester experience. *Clin Gastroenterol Hepatol* 2007; 5:1282–90].

Fig. 10.

These photomicrographs illustrate total villous atrophy and features that are inherently similar to that of coeliac disease with crypt hyperplasia, mixed inflammatory infiltration involving the lamina propria, and a clear lucent area under the surface epithelium. (B) A trichrome stain highlights the collagen layer (arrows). Original magnification: 200 $\times$.

[Reprinted from Rubio-Tapia A, Talley NJ, Gurudu SR, Wu TT, Murray JA. Gluten-free diet and steroid treatment are effective therapy for most patients with collagenous sprue. *Clin Gastroenterol Hepatol* 2010; 8:344–9].

Fig. 11.

Collagenous sprue represents a common pathologic endpoint to many particular triggers, which may consist of other primary inflammatory conditions, immune deficiencies, environmental exposures, particularly medications. [Reprinted from Rubio-Tapia A, Talley NJ, Gurudu SR, Wu TT, Murray JA. Gluten-free diet and steroid treatment are effective therapy for most patients with collagenous sprue. *Clin Gastroenterol Hepatol* 2010; 8:344–9].

Fig. 12.

Immunoglobulinemic sprue is a common gastrointestinal manifestation of combined variable immunoglobulin deficiency (CVID) (A; magnification: 4×). A distinguishing feature of this enteropathy is the absence of plasma cells (B; magnification 20×). Courtesy of Tsung-Teh Wu, M.D., Ph.D.

Table 1

Small intestinal mucosal diseases that cause chronic diarrhoea.

Coeliac disease
Tropical sprue
Environmental enteropathy
Drug associated enteropathy
Ischaemic enteropathy
Immunodeficiency sprue
Whipple's disease
HIV enteropathy
Collagenous sprue
Infectious enteritis
Tuberculosis
Giardiasis (especially in immunodeficiency (IgA deficiency))
Bacterial overgrowth

Table 2

Presentations of coeliac disease.

Gastrointestinal symptoms	Non-gastrointestinal symptoms
Diarrhoea	Iron deficiency anaemia
Bloating	Chronic fatigue
Postprandial abdominal pain	Itching skin rash (dermatitis herpetiformis)
Steatorrhoea	Aphthous ulceration
Constipation	Dental enamel defects
Vomiting (especially nocturnal)	Short stature/growth failure
Dyspepsia/GERD	Unexplained infertility
Rare presentations	Poorly-controlled type I diabetes
Acute abdominal pain	Unexplained weight loss
Intussusception, often multiple	Pica (due to deficiencies)
Intestinal lymphoma	B ₁₂ deficiencies
Ulcerative jejunal ileitis	Bleeding from Vitamin K deficiency
Perforation	Non-Hodgkins lymphoma
	Neurologic syndromes
	Ataxia
	Peripheral neuropathy
	Seizure disorders
	Premature dementia/cognitive impairment
	Mononeuritis multiplex
	Bone disorders
	Osteomalacia
	Premature osteoporosis
	Arthralgias
	Family history of coeliac disease
	Multiple autoimmunity

Table 3**Diagnostic criteria for adult autoimmune enteropathy.^a**

-
1. Adult-onset chronic diarrhoea (>6 weeks' duration)
 2. Malabsorption
 3. Specific small bowel histology
 - Partial/complete villous blunting
 - Deep crypt lymphocytosis
 - Increased crypt apoptotic bodies
 - Minimal intraepithelial lymphocytosis
 4. Exclusion of other causes of villous atrophy including CD, refractory sprue, and intestinal lymphoma, absence of response to gluten exclusion or withdrawal of medications.
 5. AE and/or AG antibodies
-

Note. Criteria 1-4 are required for a definite diagnosis of adult autoimmune enteropathy. Presence of AE and/or AG antibodies is an important diagnostic support, but their absence does not exclude the diagnosis of adult autoimmune enteropathy.

^a Adapted from Akram S, Murray JA, Pardi DS, Alexander GL, Schaffner JA, Russo PA, Abraham SC. Adult autoimmune enteropathy: Mayo Clinic Rochester experience. *Clin Gastroenterol Hepatol* 2007; 5:1282-90.

Table 4Clinical features of sprue-like enteropathy associated with olmesartan.^a

Gastrointestinal symptoms (e.g., chronic diarrhoea, weight loss, steatorrhea)
Negative IgA tissue transglutaminase antibodies (or endomysial antibodies)
Evidence of enteropathy (villous atrophy) with or without collagen deposition or intraepithelial lymphocytosis
Lack of clinical response to gluten exclusion
Exclusion of other causes of enteropathy (e.g., coeliac disease)
Evidence of clinical and histologic improvement after suspension of olmesartan

^aReprinted from Rubio-Tapia A, Herman ML, Ludvigsson JF, Kelly DG, Mangan TF, Wu T-T, Murray JA. Severe sprue-like enteropathy associated with olmesartan. *Mayo Clin Proc* 2012 Aug; 87(8):732-8.