In fasting state, mucosal biopsy is obtained with a Crosby-Kugler capsule. Enough care should be taken for proper orientation of the specimen on a paper. Under dissecting microscope (or a magnifying glass), finger-like villi (normal) (Fig 9.14), leaf-like villi, convoluted pattern or flat mucosa (abnormal) can be identified. Flat mucosa is characteristic of gluten induced enteropathy (coeliac disease). On histology, partial villous atrophy (tropical sprue) (Fig 9.15) or subtotal villous atrophy (coeliac disease) is often seen with malabsorption syndrome. Intestinal lymphangiectasia, Whipple’s disease, Mediterranean lymphoma and abetalipoproteinemia are also diagnosed on jejunal biopsy.

The diagnosis is suspected in patients complaining of diarrhoea and weight loss and showing malabsorption of d-xylene, fat and vitamin B12. Normal jejunal biopsy and diabet curve on glucose tolerance test indicate pancreatic disease.

**TREATMENT**

Oral antibiotic (tetracycline 1 g/day for 15 days) and lactose acid (5 g tds) for one month are highly effective in tropical sprue. Parenteral vitamin B12 (500 μg) once a week corrects macrocytic anaemia. Gluten-free diet is recommended for patients with coeliac disease; weight gain is observed in one month and histological improvement in jejunal biopsy within 3 months. A few who fail to respond despite strict gluten-free diet are administered prednisolone 30 mg/day for a few weeks.

Patients with lactose malabsorption are advised to take milk as curd or buttermilk. Patients with cholehaemorrhoea (bile acid malabsorption) are given cholestyramine (5 g three times a day) and aluminium antacids to bind bile acids in the lumen. Blind loop syndrome patients are administered antibiotics (tetracycline or lincomycin) effective against anaerobic bacteria. Medium chain triglycerides (coconut oil) is recommended to patients with intestinal lymphangiectasia.

**RECOMMENDED READING**


### 23. TROPICAL SPRUE AND COELIAC DISEASE

**VI MATHAN**

Many diseases can affect the small intestine and cause malabsorption. Among these, tropical sprue and coeliac disease (non-tropical sprue) are due to abnormalities in enterocytes. However, there are fundamental differences between these two conditions in their epidemiology, pathogenesis, although the clinical presentation with diarrhoea, malabsorption and consequent malnutrition is similar.

**TROPICAL SPRUE**

Tropical sprue is defined as a primary malabsorption syndrome, presenting clinically with chronic diarrhoea, wasting, affecting visitors to or residents of tropical regions. It was initially described in expatriates from temperate climates to tropical regions in South and South-East Asia and Caribbean islands during the colonial era, and was then a mainly a problem of adults. During the last three decades a high prevalence of the syndrome in the indigenous populations of endemic regions has been documented, and children and adults are known to be affected. Tropical
Gastroenterology

The tropical sprue has been reported from most of South-East Asia, there have been no reports from South America. There were reports from China in the 19th century and in recent years it appears to have disappeared. Cases have been reported from several of the Caribbean islands, but not from Jamaica. There is also a paucity of reports from Saharan Africa. In the majority of regions the syndrome has been described almost exclusively in adults.

Two major factors may explain the paucity of reports of tropical sprue in children and from certain tropical regions. Facilities for extensive investigations necessary for the diagnosis, by exclusion of diseases which can give rise to secondary malabsorption, are not generally available in tropical developing areas where the disease may be endemic.

Secondly, if the possibility of tropical sprue is actively considered in all patients with chronic diarrhoea and all available investigative facilities are mobilised, the diagnosis of tropical sprue is less likely to be missed.

In southern India, tropical sprue is encountered in two epidemiologically distinct forms. (i) Endemic tropical sprue is diagnosed in patients who present without temporal or spatial association with other similar patients. (ii) Other patients develop the syndrome in large epidemics of diarrhoea, the largest of which affected at least 100,000 people with nearly 1000 deaths. Overall, the attack rate in adults is significantly greater than in children.

The aetiology of tropical sprue is not yet known. The basic lesion, enterocyte damage, may be the result of infections, nutritional deficiency or toxins. Data from southern Indian epidemics suggest an as yet unidentified infectious aetiology; however possible that more than one aetiologic agent may be involved. In addition to the primary agent responsible for causing enterocyte damage, there are also likely to be a variety of factors which help to perpetuate the lesion and give rise to chronic persistent problems. Microbial colonisation of the small intestine, immunologic alterations, and changes in endocrine peptide hormones as well as increasing malnutrition as a sequel of malabsorption, may all contribute to the pathogenesis of the disease.

The pathogenesis of the jejunal mucosal lesion in tropical sprue involves the initial event is damage to enterocyte stem cells, which produce damaged progeny which are rapidly exfoliated from the epithelial layer. Accelerated turnover of the protective epithelial layer occurs to compensate for the loss of functional absorptive cells leading to crypt hypertrophy. The balance between the crypt cell damage with defective progeny expansion and the accelerated turnover determines the profile of final mucosa with crypt hypertrophy and villus shortening.

The enterocyte stem cell lesion in the crypts has only been demonstrated in patients with tropical sprue in southern India. In African patients colonisation of the upper small intestine by toxin producing coliforms appears to be causative and their eradication with appropriate antibiotics is effective. Bacterial colonisation to a significant extent has been demonstrated in southern Indian patients. It is difficult to say whether these differences are the result of regional differences only or whether they denote entirely different clinical syndromes.

The cause of diarrhoea in patients with tropical sprue is not only impaired water absorption or secretion in the small intestine, but also a defect in the function of the colon. A colonic lesion which resembles the small intestinal lesion also occurs in these patients. In addition, unabsorbed unsaturated fatty acids in the faeces have an inhibitory effect on sodium-potassium adenosine triphosphatase, the biochemical equivalent of the sodium pump on the basolateral membranes of the colonocytes. This appears to be an important mechanism in the pathogenesis of diarrhoea in tropical sprue.

CLINICAL FEATURES

The majority of patients present with a history of chronic diarrhoea of several months' duration and the nutritional sequelae of malabsorption.

Clinical features of nutritional deficiency (wasting, oedema, megaloblastic anaemia, thrombocytopenia, cutaneous and hair changes of hypoproteinaemia, xerosis of conjunctivae, keratomalacia, etc.) are the major findings at the time of presentation. The prevalence of signs and symptoms of nutritional deficiency correlates well with the duration of illness.

The stools in the chronic stage of the illness are often large in bulk, unformed, frothy and may float in the toilet. The volume of diarrhoea in the chronic stage is usually not sufficient to cause major problems of dehydration. In contrast, early in the course of the illness, especially in epidemics, watery diarrhoea and dehydration are widespread and dehydration is a major cause of death.

Intercurrent infections are common in malnourished patients and in the tropical environment cutaneous and respiratory infections are the most important, the latter often contributing to morbidity and mortality. Concurrent specific enteric infections do not have a frequency higher than in a comparable population.

DIAGNOSIS

The diagnosis of tropical sprue in the individual patient is dependent on confirming malabsorption of nutrients and excluding the many conditions which can cause malabsorption by defined mechanisms. Usually in the clinical situation the absorption of fat, d-xylose and vitamin B12 are the three tests which are widely used. Malabsorption of at least two nutrients is usually present. Once malabsorption has been established, detailed investigations to find the underlying cause, if any, are necessary. Small intestinal mucosal biopsy, careful search for intestinal parasites (giardia, strongyloides, etc.), estimation of immunoglobulins, pancreatic function studies and careful radiological examination in selected patients, may all be indicated.

The changes in the jejunal mucosa, viz. shortening of villi with crypt hypertrophy, increased mononuclear infiltration of the lamina propria and epithelial layer, and damaged enterocytes in the surface and crypt layers, are only suggestive and not diagnostic. The major importance of jejunal biopsies is to exclude a number of conditions like coeliac disease, intestinal lymphoma, nodular lymphoid hyperplasia, with hypogammaglobulinaemia, abetalipoproteinaemia and parasitic infestations, which can give rise to secondary malabsorption syndromes.

An important part of the diagnostic workup is the evaluation of the nutritional status of the patient. Haematological
CLINICAL FEATURES

Symptoms and signs are the result of intestinal malabsorption and are similar to other diseases with malabsorption, with abdominal symptoms such as diarrhea and flatulence and the nutritional sequelae of malabsorption. The extent of involvement of the small intestinal mucosa determines the severity of the clinical features. Symptoms usually appear in infants with the introduction of the appropriate cereal in the diet, may persist throughout childhood if the cereals are continued, but usually diminish or disappear during adolescence to reappear in early adult life. There are other patients who are asymptomatic during childhood and the diagnosis is established only during middle or old age. The finding of typical intestinal lesions in asymptomatic relatives suggests that there might be a large number of clinically inapparent patients.

The extraintestinal symptoms of coeliac sprue are primarily the result of nutritional deficiency and, as in tropical sprue, anaemia, bleeding diarrhoea, osteoporosis, wasting, peripheral neuropathy and skin changes, may be present.

DIAGNOSIS

The diagnosis of coeliac disease must be kept in mind especially in children with chronic diarrhoea, whose symptoms have started soon after the introduction of cereals during weaning. In adults in India, the diagnosis must be considered if a flat jejunal biopsy with total villous atrophy is encountered.

Peroral jejunal mucosal biopsy is an invaluable procedure in the diagnosis. A mucosal suction biopsy of the distal duodenum or jejunum is preferable to a biopsy of the proximal duodenum at upper gastrointestinal endoscopy, since the latter is likely to be distorted due to the presence of Brunner’s gland. A flat mucosal surface with complete absence of villous structures is the characteristic appearance if the surface of the biopsy is examined with a magnifying lens. On examining sections, the loss of villi is confirmed, with extensive hypertrophy of the crypts and normal mucosal thickness. The crypts appear to open directly on the flat surface. The luminal surface is lined by abnormal enterocytes which appear to have lost the glycocalyx and may be cuboidal or squamoid in appearance. The enterocyte cytoplasm is more basophilic and there may be loss of nuclear polarity. Striking abnormality of surface enterocytes is found on electron microscopic examination. The undifferentiated crypt cells are markedly increased and are normal morphologically although there is an increase in mitosis. Paneth cells and goblet cells are present in normal numbers while endocrine peptide cells appear increased. The cellularity of the lamina propria is increased and there is increased infiltration of the surface epithelium by lymphocytes.

The length of the small intestine involved is variable and the lesion is most marked in the proximal small bowel. The greater the clinical severity, the more the extent of involvement of the small intestinal mucosa.

The characteristic improvement of the small intestinal lesion on strict withdrawal of gluten from the diet and the prompt recrudescence of the mucosal damage with gluten challenge are useful in confirming the diagnosis. While the response to gluten challenge occurs within a matter of days, the improvement on gluten withdrawal is much slower and may take several weeks of months.

MANAGEMENT

Removal of toxic gluten from the diet is the most important single step in the management of these patients. In western countries many special foods which are guaranteed free of
GRANULOMATOUS DISEASES OF THE INTESTINE

PHILIP ABRAMIAH

CROHN'S DISEASE

This is a slowly progressive, idiopathic, inflammatory disease, extending into all layers of the intestine, affecting disease regions anywhere from the mouth to the anus, with systemic complications and a high tendency to recur. The disease is relatively uncommon in India.

PATHOLOGY

Pseudopolypoid ulcers are an early feature of this condition. In the established disease, the bowel is thickened and leathery, with multiple segments alternating with grossly normal regions. Obvious tracts may be seen penetrating into adjacent organs or blindly into abscesses. Fingerprint projections of edematous, fatty mesentery are suggestive of the abnormal mesenteric border. The mesentery is often contracted and the bowel at angles. Mesenteric nodes are enlarged, firm, and often matted together. The opened bowel has a characteristic cobblestone appearance because of deep mucosal spatulation and submucosal thickening.

The small intestine and colon are involved in about one-half patients, another 30% have only small bowel lesions, and 10% only the colon is involved.

Microscopically, lymphocytes aggregate, some with germinal centers, scattered transversally, are a characteristic finding in most patients. Typical noncaseating granulomas, which consist of epithelioid cells and a few multinucleated Langhans cells, are found in the lamina propria of lymphoid follicles, and may spread into all bowel layers, especially in the submucosa, lamina propria, and also in extraintestinal sites. The other granulomatous changes may arise, extend into adjacent lymph nodes and mesenteric lymph nodes. At times, this transmural inflammation is replaced by vascular dilatation and fibrosis. Microscopic ulcers, fissures, and occasional crypt abscesses may be seen. Axonal necrosis of autonomic nerves on electron microscopy has been described recently.

AETIOLOGY AND PATHOGENESIS

Among the factors implicated in this condition are infectious agents, especially mycobacteria; altered host susceptibility including specific HLA haplotypes; dietary factors including reduced intake of fibres as well as increased intake of refined sugars and chemical food additives like carrageenan; and finally psychological factors. The evidence in one of these cases is conflicting.

CLINICAL FEATURES

The manifestations depend on the site, severity, and extent of disease. The onset of symptoms may be related to mental or physical stress; upper respiratory and enteric infections may precipitate a relapse. A majority of patients present as young adults with recurrent episodes of diarrhea, abdominal pain and fever lasting several days each time. Local symptoms and signs depend on the site of involvement in the intestine. Features of intestinal obstruction or perforation may be present in addition to other evidence of inflammation in the form of abscesses or fistulae. A rare patient may present as acute appendicitis.

Significant weight loss is a complicating feature in about a third of patients. Severe nutritional deficiencies may occur. Joint symptoms are present in 20–25% of cases; a variety of liver, skin, eye, lung, vascular and neurological lesions are present in 5–10%.

INVESTIGATIONS

One of the main purposes of investigation especially in India is to rule out other more common conditions with which Crohn's disease may be confused. A thorough stool examination is mandatory in patients with suggestive symptoms, to rule out parasitic infestation and bacterial enterocolitis. Leucocytosis, thrombocytosis, and elevated erythrocyte sedimentation rate and levels of various acute phase reactants are not specific. A deficiency anaemia and stools positive for occult blood may be present. Liver function tests and malabsorption tests are helpful to indicate the overall status.

A chest X-ray must be done for evidence of tuberculosis. Plain X-ray of the abdomen may show air-fluid levels or soft tissue masses; thumb-printing of the bowel wall may be present. Barium enema, especially a double-contrast study, and a small bowel study, preferably enterocystoscopy (small bowel enema), show a cobblestone appearance, deep ulceration, narrowing, fistulae and skin lesions. In patients with diagnosed disease, radionuclide scanning can be useful for finding lesions. For example with indium-111 labelled leucocytes, may help to locate and determine the extent of disease. In over one-half of patients, the distal colonic mucosa appears normal on endoscopy. In those with involvement, the mucosa has a cobblestone appearance with distinct ulcerations; the characteristic interrupted involvement is seen in only about 25% of cases. A suction biopsy particularly useful for histological studies and may be obtained from the rectum even when that region is not grossly involved. Recently, flexible endoscopy in rectal mucosa has been suggested as a reliable test. Histological examination should pay special attention to evidence of parasites, and issue should be studied for acid-fast bacilli.