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Chronic Diarhoea – An Approach

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INTRODUCTION

Diarrhoea is a common human experience. The word diarrhoea originates from the Greek terms dia (through) and rhein (to flow).For many, episodes of diarrhea last a day or 2 and rapidly subside without medical intervention. While for few others, diarrhoea will last for more than a few days or is complicated by fever, prostration, or rectal bleeding. Diarrhoea lasting for more than 4 weeks is termed as chronic diarrhoea. An acute diarrhoeal episode occurs once in every 18 months in an individual in developed countries. Chronic diarrhoea can occur in 3–5% of the population in any given year.

Diarrhoea is defined as the passage of abnormally liquid or unformed stools at an increased frequency, i.e. more than three times in a 24 hour period. In Western populations,

Table 1: Classification of Chronic Diarrhoea

1. Osmotic

- Medications

  Laxatives (Mg SO_4, PO_4), elixirs
- Undigested sugars

  Diet foods/drinks/gum (sorbitol, mannitol, others); Enzyme dysfunction (e.g. lactose, fructose)

2. Secretory

- Medications

  Non-osmotic laxatives, antibiotics
- Small intestinal bacterial overgrowth
- Endocrine:

  Tumors: Carcinoid, Gastrinoma, Medullary thyroid cancer, VIPoma

  Systemic: adrenal insufficiency, hyperthyroidism
- Bile salt malabsorption (ileal resection, idiopathic, postcholecystectomy)
- Non-invasive infections: Giardiasis, Cryptosporidiosis

3. Steatorrhoea

- Maldigestion

  Decreased bile salts (cirrhosis, bile duct obstruction, ileal resection)

  Pancreatic dysfunction (chronic pancreatitis, cystic fibrosis, ductobstruction)
- Malabsorption

  Celiac sprue, Tropical sprue, Giardiasis, Whipple's disease

  Chronic mesenteric ischemia

  Short bowel syndrome

  Bacterial overgrowth (diabetes mellitus, scleroderma, prior bowel surgery)

  Lymphatic obstruction

4. Inflammatory

- Inflammatory bowel disease: Ulcerative colitis, Crohn's disease,Microscopic colitis
- Malignancy: colon cancer, lymphoma
- Radiation colitis/enteritis
- Mastocytosis

  Invasive or inflammatory infections: C.difficile, Cytomegalovirus, E.histolytica, Tuberculosis
- Ischemia

5. Motility disorders

- Post-surgical (vagotomy, dumping)
- Scleroderma
- Diabetes mellitus
- Hyperthyroidism

6. Miscellaneous

- Irritable bowel syndrome
- Functional diarrhoea
- Factitious

Table 2: Drugs Causing Diarrhoea

More Common
Antacids, PPI
Cephalosporins, Clindamycin, Ampicillin, Amoxycillin, Erythromycin
Colchicine
Metformin
Non-steroidal anti-inflammatory drugs, 5-aminosalicylates
Cholesterol-lowering agents (Clofibrate, Gemfibrozil, Lovastatin)
Anti Neoplastic drugs
Less common
Angiotensin converting enzyme inhibitor
Angiotensin receptor blocking agents
Beta-adrenergic receptor antagonists, other antiarrhythmics
Carbamazepine
Lithium
Vitamin and mineral supplements

daily faecal weight does not exceed 200g, but in Indians this figure is somewhat higher and up to 400g per day may be acceptable.

CLASSIFICATION OF CHRONIC DIARRHOEA

The list of differential diagnosis for chronic diarrhoea is extensive. Depending on the Patho physiology, chronic diarrhoea can be broadly classified into six categories.

Osmotic diarrhoea is suspected in a patient whose diarrhoea occur after meals but resolves with fasting.

Secretory diarrhoea is suggested in a patient with large-volume watery diarrhoea which is painless and that persists even after fasting. It can be confirmed by demonstrating an increase in stool volume in absence of increased osmotic gap.

Steatorrhoea is suggested by the occurrence of greasy or oily stools that have an offensive odour and float on the toilet water. Steatorrhoea can be confirmed by stool analysis. Quantitatively, steatorrhoea is defined as stool fat exceeding the normal 7 g/day.

The presence of blood or pus in the stools, pain abdomen and fever is suggestive of inflammatory diarrhoea. It can be confirmed by the demonstration of leukocytes in stool or leukocyte proteins (such as lactoferrin or calprotectin), or by the visualisation of inflammatory changes in the colonic mucosa by endoscopy and biopsy.

Inflammatory bowel disease, may have extra intestinal manifestation like uveitis, polyarthralgia, erythema nodosum etc. Microscopic colitis mostly occur in middle-aged women and those on NSAIDs, statins, PPIs and SSRIs. Biopsy of a normal appearing colon is required for histologic diagnosis.

Motility disorders cause diarrhoea through either increased GI transit (e.g. post-vagotomy diarrhoea) or by slowing transit, thereby predisposing to small intestinal bacterial overgrowth (e.g. scleroderma).

Diabetic diarrhoea may result from abnormal gut motility due to autonomic neuropathy, bacterial overgrowth and bile salt malabsorption. Irritable bowel syndrome (IBS) and functional diarrhoea are the common causes of chronic diarrhoea in Western countries. IBS is defined by the Rome Committee as a chronic condition characterized by abdominal pain and altered bowel habits; the pain characteristically is in association with a change in stool form or frequency, and is relieved by defaecation. Functional diarrhoea is defined as recurrent or continuous passage of loose or watery stools without abdominal pain or discomfort. Factitial diarrhoea accounts for up to 15% of unexplained diarrhoeas referred to tertiary care centers. It can occur as a part of Munchausen syndrome. Some patients may self-administer laxatives or adulterate the stool sample with water or urine to increase its volume.

CLINICAL APPROACH TO CHRONIC DIARRHOEA

History and examination-

A detailed history and thorough examination are crucial in the work up of patients with chronic diarrhoea. IBS commonly occur in the third and fourth decade, AIDS-related diarrhoea is common in younger patients whereas the peak incidence of microscopic colitis is in the seventh and eighth decade of life. Colon cancer should be excluded in a patient with new onset of diarrhoea over the age of 50 years. IBS and microscopic colitis are more common in females.

The presence of lymphadenopathy or significant weight loss could suggest chronic infection or malignancy. Family history is important in cases of inflammatory bowel disease, coeliac disease or neoplastic diseases.

History and clinical examination should exclude systemic diseases like thyrotoxicosis, diabetes mellitus, parathyroid and adrenal disease which may cause chronic diarrhoea through various mechanisms. A detailed drug history should be obtained in all patients. History of alcohol abuse is important. Alcohol can cause diarrhoea by increasing gut motility, reducing activity of intestinal disaccharidases and decreased pancreatic function. The presence of malabsorption is usually evident by steatorrhoea which include pale, bulky malodorous stool. Fat laden stools float, are sticky and difficult to flush away.

Patients with IBS have erratic stool pattern. Patients' complain of abdominal cramps accompanied by either with diarrhoea or constipation. Abdominal pain is often relieved by defaecation. The symptoms of IBS as defined by the Rome IV criteria include recurrent abdominal pain that is present at least three days per month in the last three months, associated with a change in stool frequency or form which improves with defecation. Psychiatric symptoms like anxiety and depression are frequently associated with IBS and may be present in upto 67% cases.

Table 3: Physical Finding in Some of the Causes of Chronic Diarrhoea

Findings	Implications
Muscle wasting, oedema --	Malnutrition
Urticaria pigmentosa, dermatographism --	Mast cell disease (mastocytosis)
Pinch purpura, macroglossia --	Amyloidosis
Hyperpigmentation --	Addison's disease
Migratory necrotizing erythema --	Glucagonoma
Malignant atrophic papulosis -	Kohlmeier-Degos disease
Dermatitis herpetiformis--	Celiac disease
Thyroid nodule, lymphadenopathy --	Medullary carcinoma of the thyroid
Tremor, lid lag--	Hyperthyroidism
Right-sided murmur, wheezing,flushing --	Carcinoid syndrome
Hepatomegaly --	Endocrine tumor, amyloidosis
Arthritis --	Inflammatory bowel disease, yersinosis
Lymphadenopathy--	HIV, lymphoma, cancer
Abdominal bruit --	Chronic mesenteric ischemia
Anal sphincter weakness--	Faecal incontinence

Table 4: Small Bowel Radiography

Celiac disease - Dilated calibre; increased fluid; thin, effaced folds (moulage), segmentation of barium column, painless intussusception
Whipple's disease - Normal calibre; thick, wild fold pattern; patchy micronodularity
Scleroderma - Dilated, esp. duodenum; delayed peristalsis, hypomotility
Lymphoma - Variable calibre; coarse folds; wall infiltrated, stiff; extraluminal masses; micronodularity
Amyloidosis- Normal caliber; symmetrical fold thickening, no oedema; stiff walls; micronodularity
Lymphangiectasia- Increased luminal fluid; thick, oedematous folds
Crohn's disease - Stenotic (string sign); deformed/ thickened folds; rigidity/ulceration of walls;
Sometimes extraluminal mass
Dysgammaglobulinemia- Increased luminal fluid; nodular lymphoid hyperplasia
Giardiasis- Dilated duodenum; thick duodenal folds; spasm, rapid transit
Zollinger–Ellison Syndrome - Dilated duodenum; thick duodenal folds; peptic ulcer; reticulated pattern
Cystic fibrosis - Thick folds; nodularity in duodenum
Abetalipoproteinemia- Fine mucosal graininess
Mastocytosis- Thick gut wall; mucosal nodularity

Crohn's disease is associated with pain in the right iliac fossa, while patients with malabsorption complain of dull, poorly localized abdominal discomfort. The presence of blood in stool necessitates further examination, usually by colonoscopy, although minor bleeding because of trauma is common in all diarrhoeal diseases.

Dietary history is important to identify foods which may cause diarrhoea. Increased consumption of wheat fibre and certain fruits (grapes, plums, mangos, and cherries) can cause diarrhoea. Lactose is a disaccharide present in milk and is a common cause of diet induced diarrhoea. Diarrhoea due to lactose intolerance occurs if the patient consumes more than 12 g/day (240 ml of milk or its equivalent in other dairy foods). Physical examination should include evidence of weight loss, signs of malnutrition, anaemia, clubbing, or lymphadenopathy. Rectal examination is useful to exclude local tenderness that might suggest Crohn's disease and rectal tone to rule out any sphincter defect which can cause incontinence. Moreover, it is important to differentiate between small and large bowel diarrhoea. In small bowel involvement, usually the frequency is less than 4 per day, large volume, bulky, frothy and greasy. In large bowel involvement, the frequency is more than 4 with small volume. Blood, mucous, pus may be present.

LABORATORY WORK-UP TO EVALUATE CHRONIC DIARRHEA

Routine Blood tests

Complete blood count, serum albumin, erythrocytes sedimentation rate, liver and kidney function tests, blood glucose and electrolytes. The presence of iron deficiency anaemia may indicate Coeliac disease.

Serological tests

Immunoglobulin A (IgA) anti-TTG is the preferred single test for detection of celiac disease in individuals over the age of 2 years. Total serum IgA should be measured at the same time to rule out IgA deficiency that might cause a falsely negative test. Anti- Saccharomyces cerevisiae antibodies are measured to diagnose IBD.

Stool examination

Fecal electrolytes can help to differentiate between osmotic and secretory diarrhoea. It is based on calculation of the osmotic gap.

The stool osmotic gap: serum osmolarity (typically 290 mosmol/kg) - (2 x [fecal sodium + potassium concentration]).

A faecal osmotic gap of < 50 mosmol/kg indicates a secretory diarrhoea while a gap of > 75 mOsm/kg indicates an osmotic diarrhoea.A low fecal pH (<7.0)) is suggestive of carbohydrate malabsorption.

Leucocyte enzyme, lactoferrin or calprotectin are used as surrogate markers of faecal leukocytes to diagnose mucosal inflammation. Fecal calprotectin has been found to be more sensitive.

Imaging tests

A plain abdominal radiograph showing pancreatic calcifications is diagnostic of chronic pancreatitis. Barium studies have been used extensively in the past in the diagnosis of chronic diarrhoea. With the introduction of abdominal CT scans, the role of barium studies has become limited.

CT and magnetic resonance enterography

CT and magnetic resonance (MR) enterography are useful in the diagnosis of chronic diarrhoea because of small bowel Crohn's disease, eosinophilic gastroenteritis and in the detection of small bowel tumors, such as carcinoids.

Nuclear medicine imaging

Radio ligand scintigraphy is useful in detecting neuroendocrine tumors that express somatostatin receptors, such as gastrinomas and carcinoid tumors. SPECT-CT provides better localization of these tumours.

Endoscopy

Colonoscopy with biopsy is helpful for the diagnosis of IBD, neoplasia and microscopic colitis. Upper GI Endoscopy and duodenal biopsy can confirm a diagnosis of celiac disease. Duodenal biopsy may also aid in diagnosis of giardiasis and other protozoal infections and Whipple's disease. Upper endoscopy also helps in collection of duodenal aspirate for quantitative for a diagnosis of small intestinal bacterial overgrowth.

Colorectal and terminal ileal biopsy

Colonoscopy and biopsy have a significant role in diagnosing conditions like IBD, microscopic colitis, inflammatory conditions and neoplasia. Multiple studies have evaluated the role of colonoscopy stating the yield of specific diagnoses of chronic diarrhoea in 15 – 31%.

Breath tests

Hydrogen Breath Tests (HBT) The breath tests help in diagnosing carbohydrate malabsorption and small intestinal overgrowth. However, the sensitivity and specificity however varies widely.

Pancreatic function tests

The standard secretin stimulation test is rarely used now a days whereas the modified endoscopic secretin stimulation test done using ERCP has limited diagnostic yield. Various other tests for pancreatic function include serum trypsin, faecal chymotrypsin and faecal elastase which again show limited utility in mild insufficiency. Pancreatic imaging using endoscopic ultrasound and MRI is used invariably to detect abnormal anatomy.

Bacteriology/Microbiology

In developing countries chronic bacterial, mycobacterial, and parasitic infections are common. Additionally some clinical situations require extensive search for a source of infection in case of diarrhoea of chronic origin. They include diarrhoea in immigrants from endemic areas, immunocompromised subjects, patients with HIV/ AIDS infection, men who have sex with men, and in individuals with chronic travellers' diarrhoea. Giardiasis, amebiasis, yersinosis, and C. difficile infections are frequent causes of chronic diarrhoea in immunocompetent hosts.

Strongyloides is occasionally seen but is quite unusual. These five pathogens should be sought in such patients. Giardia is most reliably detected with a stool enzyme-linked immunosorbent assay (ELISA) assay. Amoeba and Strongyloides are sought with serological tests and stool examination for ova and parasites. Three stool samples should be sent for microscopic examination. C. difficile is most reliably detected with a stool DNA amplification assay.

Patients on immunosuppressant medications or those with HIV/AIDS infection have a greater likelihood of chronic infections. Enteropathogens that can cause acute, self-limited diarrhoea in immunologically normal individuals can cause chronic diarrhoea in these patients. These pathogens are Salmonella, Shigella, Campylobacter, E. coli, Yersinia, and others. These infections can last many weeks in the immunosuppressed host. Traditionally, these infections are detected with standard stool cultures. However, new molecular techniques may prove to be better in time, making standard stool cultures obsolete. Patients with HIV/AIDS suffer from potential infectious aetiologies related to their degree of immunosuppression. With lesser degrees of immunosuppression(CD4 count > 200 cells/mm3),the usual pathogens predominate. However if the CD4 count is < 200 cells/mm3, the spectrum includes mycobacterial and protozoan infections also along with the enteropathogens. These include MAC, cryptosporidium, cyclospora, isospora belli and microsporidium. Viral infections, such as CMV and Herpes simplex virus, and fungal infections, such as candidiasis and histoplasmosis, should be considered if other pathogens are not found.

MANAGEMENT ISSUES

The aetiology of chronic diarrhoea should be identified and treated accordingly. Dietary measures include the restriction of unabsorbed carbohydrates and sweets, avoidance of milk and milk products in patients with lactose intolerance, and fat restriction and supplementation of fat soluble vitamins and calcium in patients with steatorrhoea. Empirical therapy for chronic diarrhoea may be used when the diagnostic workup has failed to confirm the diagnosis, if no specific treatment is available or if the treatment has failed. Opiate anti diarrhoeal agents such as loperamide are frequently used. They are safe and effective but should not be used in infectious diarrhoea or in severe inflammatory bowel disease. Bile acid sequestrate like cholestyramine are useful in diarrhoea caused by bile acid malabsorption. Octreotide is used to control diarrhoea occurring in carcinoid syndrome, VIPomas and neuroendocrine tumors. Alpha2-adrenergic agonist, clonidine,is used to treat diabetic diarrhoea.

Eluxadoline, a μ opioid receptor agonist is a new drug approved for use in patients with IBS. Diarrhoea in Zollinger-Ellison syndrome respond to treatment with proton pump inhibitors. Bacterial overgrowth is treated with antibiotics.

CONCLUSION

In conclusion, it is prudent to emphasize that the umbrella of chronic diarrhoea covers a vast range of disorders. A thorough history and clinical examination is absolutely necessary to arrive at a diagnosis.

Though quite a number of laboratory investigations including imaging are available, judicious use of these investigations is the key. Examination of stool sample is vital. The management depends upon the aetiology.

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