

Review Article

Chronic diarrhea in children

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Abstract

Acute diarrhea is a leading cause of under-five mortality in developing countries like India. Most of the diarrheal episodes recover within 14 days. However in certain cases acute diarrhea may last for more than 14 days in which it is termed as persistent diarrhea if presumed to be of infectious origin. Various malabsorptive syndromes due to carbohydrate, fat and protein malabsorption can result in chronic malnutrition in a child. This entity is known as chronic diarrhea.

Definitions

Diarrhea is defined as stool volume >10 g/kg per day in infants and toddlers, and >200 g/day in older children. [1]. Persistent diarrhea is an episode of diarrhea which is of presumed infectious etiology, which starts acutely and it lasts for more than 14 days. Chronic Diarrhea is one which lasts for more than 14 days, is usually noninfectious and associated with malabsorptive features.

Epidemiology

The exact incidence of chronic diarrhea is not known in India, however large-scale studies indicate that the prevalence of chronic diarrhea illnesses worldwide ranges from 3% to 20%, and the incidence is around 3.2 episodes per child year [2]. The causes of chronic vary amongst different age of children. In an Indian study on 137 children with chronic diarrhea, celiac disease was most common causes accounting for 26%, parasitic infections in 9% and tuberculosis in 5% of children [3].

Patho-physiology

The basic patho-physiology is incomplete absorption of water from the intestinal lumen either because of a reduced rate of net water absorption (related to impaired electrolyte absorption or excessive electrolyte secretion) or because of osmotic retention of water in the lumen. It is seen that reduction of net water absorption by as little as one percent may be sufficient to cause diarrhea [4].

Hence even modest compromise of absorptive function can lead to loose stools and many conditions can be associated with diarrhea, the frequencies and characteristics of which vary depending on age and socioeconomic status.

Osmotic diarrhea is caused by a failure to absorb a luminal solute and hence osmotic retention of water in the lumen. It can be seen because of disaccharidase deficiencies or because the absorptive capacity of the intestine for that sugar may be overwhelmed by excessive consumption [5], eg, fructose and sorbitol. It is seen in young children with excessive intake of simple sugars like fruit juices. Disaccharidase deficiencies, such as lactase deficiency are usually seen as a result of gut mucosal injury secondary to some process later in infancy, like acute enteritis (bacterial/viral). The osmotic diarrhea usually cease when the offending dietary nutrients are removed or after fasting within 24 hours.

On the contrary secretory diarrhea occurs when there is a net secretion of electrolyte and fluid from the intestine. Children with a pure secretory diarrhea will continue to experience diarrhea even while fasting. Examples include multiple congenital diarrheal disorders associated with identified genetic mutations that affect gut epithelial ion transport like congenital chloride diarrhea (Table 1).

Common causes of chronic diarrhea in children

Causes of chronic diarrhea can be divided into following subgroups (Table 2).

Infections

Infective causes: Infective causes of chronic diarrhea can be seen in any age and common organisms implicated includes *Salmonella*, *Yersinia*, *E.coli*, *Campylobacter*, *Aeromonas*, *Plesiomonas*, *Giardia*, *Cryptosporidium*, viral causes (Rota, Enterovirus, Norwalk). They have associated fever, abdominal pain, exposure history, blood/mucus in stool. The protozoa *Giardia intestinalis* may affect immunocompetent as well as immunodeficient children and adolescents. The resultant infection affects the duodenum and upper small bowel, leading to mild villous blunting, disaccharidase deficiency, and resultant osmotic and secretory diarrhea. Infections are linked to contaminated food and water. Many such outbreaks may occur in childcare centers. Microscopic examination of a freshly passed stool on three consecutive

Table 1. Difference between osmotic and secretory diarrhea.

Secretory diarrhea	Osmotic diarrhea
Volume of stool >200 ml/24 hr	<200 mL/24 hr
Response to fasting : Diarrhoea continues	Diarrhoea stops
Stool Na : >70 mEq/L	<70 mEq/L
Reducing substances : Negative	Positive
Stool pH >6	<5
Stool osmotic gap {Stool osmolarity – 2(stool Na + K)} : < 100	>100

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Table 2. Causes of chronic diarrhea.

Infective
Due to exogenous substances
Abnormal digestive processes
Nutrient malabsorption
Immune and inflammatory
Structural defects
Defects of electrolytes and metabolite transport
Motility disorders
Neoplastic
Chronic non specific diarrhoea

days is recommended for detection of Giardia trophozoites. Giardiasis should be treated with metronidazole, tinidazole, or nitazoxanide.

Emphasis should be laid on maintenance of health and hygiene especially cleans portable drinking water.

Small bowel bacterial overgrowth: Overgrowths of aerobic and anaerobic bacteria in the small bowel like in condition as in short bowel syndrome, bowel strictures, pseudo-obstruction, malnutrition. There is enhanced bile acid deconjugation and fatty acid hydroxylation by bacteria. The patients present with abdominal pain and diarrhea.

Whipple's disease: Whipples disease is caused by Gram +ve bacteria: Tropheryma whippelii. The patients have Malabsorption, central nervous system, joints and cardiovascular involvement. It is a rare condition and carries a poor prognosis.

Tropical sprue: It is a rare condition in children and coliform organisms are implicated in its etio-pathogenesis.

Abnormal digestive processes

Cystic fibrosis: In Cystic fibrosis diarrhea occurs as a result of pancreatic insufficiency. Ninety percent of patients suffering from cystic fibrosis have pancreatic insufficiency [6].

The patient suffering from cystic fibrosis has repeated chest infections, abdominal bloating along with passage of large greasy rotten smelling stools with failure to thrive Sweat chloride estimation is done for screening and mutation studies are diagnostic.

Other rare causes like Shwachman Diamond syndrome, Pearson syndrome, Johanson- Blizzard Syndrome

Nutrient malabsorption

Carbohydrate malabsorption: Carbohydrate malabsorption is seen in condition like intestinal lactase deficiency which can be congenital, adult-onset and secondary lactase deficiency. Congenital lactase deficiency is rare entity. Adult onset is extremely common and 'normal' for most humans and has racial distribution being common among Asians. Secondary lactase deficiency is seen after infectious gastroenteritis or injury to small intestinal mucosa caused by gluten or other sensitizing substances.

Lipid malabsorption: Lipid malabsorption is seen in diseases like cystic fibrosis, Shwachman Diamond syndrome, Pearson syndrome, Johanson- Blizzard Syndrome, celiac disease, cholestatic liver disease, beta lipoproteinemia, lymphangectasia and short bowel syndrome.

Protein malabsorption: Protein malabsorption is seen in condition like pancreatitis, cystic fibrosis, trypsinogen deficiency, enterokinase deficiency, hartnup disease, lymphangectasia, lowes syndrome and lysinuric protein intolerance.

Immune and inflammatory

Celiac disease: Celiac disease is an immune-mediated systemic disease that occurs in the setting of gluten ingestion in a genetically susceptible individual. It is very common in India, especially in North India with prevalence approaching 1% [7].

It is most common cause of chronic diarrhea and malabsorption in more than 2 years age group patients [8].

The typical presentation of celiac disease in children is failure to thrive, diarrhea and abdominal distension. However, the presentation of disease seems to have changed over the past few years. The typical presentation is now seen in less than 50% of newly diagnosed cases of Celiac disease. Diagnosis should begin with establishing the presence of anti-tissue transglutaminase antibody/anti endomyseal antibody and is confirmed by histologic findings in the duodenum which is graded according to Marsh Criteria. The management of celiac disease is lifelong restriction of food containing gluten in diet which includes wheat, rye, and barley. Multivitamin and mineral deficiency should also be managed appropriately.

Cow's milk protein allergy (CMPA): Cow's milk protein allergy present in first yr of life, but may present up to two years of age. The child present with streaks of blood and mucus in stool, in otherwise healthy infant. It typically occurs in child on top milk, however 0.5% may present in exclusive breast fed infants. CMPA is increasing being recognised in India over past decade [9].

The disease can be IgE and non IgE mediated, most of the gastrointestinal symptoms are non Ig mediated. Double blinded placebo control trial is diagnostic for the disease, however it is cumbersome and an open challenge is done in practice [10]. In open challenge the patient is advised to stop all milk and milk products and is started on extensively hydrolysed formulae for 4-6 weeks and after improvement of symptoms the child is challenged with normal milk, if the symptoms reappear it confirms the diagnosis. Treatment is extensively hydrolysed formulae (eHF) or amino acid based formulae. In exclusive breast fed infants below 6 months of age, the mother is stopped of all milk and milk products and breast feeding is continued. Soy protein-based formula may be an option in infants older than 6 months who do not accept the bitter taste of an eHF, or in cases in which the higher cost of an eHF is a limiting its factor, provided that the tolerance to soy protein has been established [10].

Inflammatory bowel disease: Inflammatory bowel diseases (IBD) can present in children and adolescents with chronic diarrhea with passage of blood or mucus in stools. The child can have weight loss, anemia, tenesmus, joint pains, and redness of eyes. In Crohn's disease, stool may contain microscopic blood but may not be grossly bloody. In ulcerative colitis, diarrhea is a more consistent presenting feature. The patients will have raised inflammatory markers like ESR, CRP, Platelet counts, and low albumin. Evaluation involves hematological markers, serology, upper GI endoscopy and colonoscopy. Treatment includes anti-inflammatory agents like steroids, 5ASA, Azathioprine etc.

Autoimmune enteropathies: Autoimmune enteropathies are rare disorders that may present as severe diarrhea during infancy or toddlerhood. The diarrhea may be isolated, or may occur in association with diabetes mellitus as part of the IPEX syndrome.

Immunodeficiency: Patient with chronic diarrhea should be evaluated for primary or secondary immunodeficiency such as HIV disease. In this case, the evaluation should focus on potential infectious

causes of the diarrhea, particularly parasites and opportunistic infections such as *Cryptosporidium*, *Isospora*, and *Cyclospora* [10].

Structural defects: These include disease like tufting enteropathy, microvillous inclusion disease, phenotypic diarrhea, lymphangiectasia, intergrin deficiency, heparan sulphate deficiency. These are rare diseases and cause neonatal diarrhea and carries a poor prognosis.

Defects with effects of electrolytes of electrolytes and metabolite transport: It includes congenital chloride diarrhea (CCD) and congenital sodium diarrhoea (CSD), these disorders cause secretory diarrhea and present in 1-2 week of life and carry a poor prognosis.

Chronic non specific diarrhea

Chronic non specific diarrhea of infancy/Toddler's diarrhea: Toddler's diarrhea is most commonly seen in first 3 years after birth. It present with varied stool frequency and consistency without blood or mucus and stool contain undigested food particles. There is no failure to thrive and treatment includes decreased fruit juices (fructose) and reassurance along with liberalization of fat to encourage normal caloric intake and to slow intestinal transit time is also important [12].

Monitoring growth parameters in child with chronic diarrhea is important as disease like toddler's diarrhea have normal growth parameters.

Neoplastic causes: Neoplastic causes of chronic diarrhea are rare and includes diseases like gastrinoma, vipoma, mastocytosis, Zollinger Ellison syndrome, pheochromocytoma, lymphoma.

Motility disorders

Hirschprung's disease

Hirschsprung's disease may present enterocolitis and diarrhea, and may progress to life-threatening toxic megacolon. Infant presents with history of delayed passage of meconium, constipation, failure to thrive. Per rectal examination will reveal an empty rectum and gush of air and stool following withdrawal of finger. Infants with Hirschsprung's disease should be evaluated promptly with abdominal plain films, barium contrast studies and/or rectal suction biopsies.

Evaluation

Evaluation of chronic diarrhea includes detailed history and physical examination: As with all diseases in medicine, a detailed history and examination is must to diagnose the cause of chronic diarrhea. Characteristics of the stool are very important in assessing the cause and severity of the illness. It is important to differentiate small bowel diarrhea from large bowel type of diarrhea. Large bowel type of diarrhea has blood, mucus, tenesmus, urgency and high frequency. Small bowel diarrhea has large volume, foul-smelling stools with undigested food particles and often associated with features of lactose intolerance like explosive diarrhea and bloating. Stool frequency and volume along with appearance; the presence of blood or mucus; and the relationship to feeding or dietary intake should be asked. Patients with toddler's diarrhea often have loose stools with undigested food particles; frequent loose watery stools may indicate carbohydrate intolerance and pasty or loose foul-smelling stools indicate fat malabsorption. Extraintestinal symptoms should be asked like presence or absence of weight loss, rash, fatigue, vomiting, joint aches, or oral ulcers.

A detailed history of source of drinking water, family history, and sick contacts should be evaluated. History of complementary feeding is important and should be asked and onset of diarrhea after introduction

of specific foods like seen in celiac disease and Cow's milk protein allergy is noted. History of repeated infections may be seen in cystic fibrosis or immune deficiency syndromes.

Physical examination should include anthropometry assessment and evaluation of dehydration. Clubbing can be seen in celiac disease and IBD. Joint pain, swelling and erythema can be extra-intestinal manifestations of IBD. Signs of nutrient and vitamin deficiencies should be evaluated such as perianal dermatitis in zinc deficiency, bone deformity in vitamin D deficiency, night blindness and keratomalacia in Vitamin A, bruising in Vitamin K deficiency and other changes associated with B complex deficiency. The abdomen may be distended in malabsorption syndromes or small bowel bacterial overgrowth. Examination of the rectum is important also and may reveal perianal disease in IBD and findings suggestive of Hirschsprung's disease.

Laboratory evaluation: A detailed history and examination is needed so that unnecessary investigations are better avoided. Initial investigations include a complete hemogram to evaluate anemia, total counts and platelets. Stool routine and culture with urine routine should be done in all cases of chronic diarrhea. Stool may contain rbc, wbc and mucus indicating a mucosal inflammation in large bowel. Serum electrolytes with renal function test should also be done. Serology for celiac disease ie Ttg with total IgA should be done in cases of small bowel diarrhea. Upper GI endoscopy and when required colonoscopy with mucosal biopsy are required in many diseases like celiac disease, IBD, eosinophilic enteropathy, microvillous inclusion disease, tufting enteropathy, giardiasis, Intestinal lymphangiectasia. In special cases fecal fat estimation, fecal elastase, fecal a1 antitrypsin levels, H2 breath test, hormonal assays may be required.

Treatment

It depends on primary cause of chronic diarrhea; it may vary from just reassurance in cases of chronic nonspecific diarrhea to bowel transplant in structural enteropathies. In addition to specific disease oriented therapy the patients should be given vitamin and mineral supplement.

Disease like Cow's milk protein allergy, celiac disease, and giardiasis are easily treatable. Celiac disease management includes a lifelong strict adherence to gluten free diet and nutritional counseling. For CMPA, the ideal management is extensively hydrolysed formulae, unfortunately they are not still available in India and are to be imported thereby increasing their cost.

Conclusion

Chronic diarrhea is important cause of morbidity in developing countries. Timely evaluation and management is of paramount importance to prevent complications. The patient should be referred to a tertiary care center in time for appropriate diagnosis and treatment.

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