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REVIEW ARTICLE

Understanding and Management of Persistent Diarrhoea

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The diarrhoea that follows an attack of acute episode and continues for more than two weeks is defined as persistent diarrhoea. In Bangladesh, the incidence of persistent diarrhoea is about 7%. Determinants of persistant diarrhoea are poorly understood. However, malnutrition, poor enviromental sanitation, genetic and familial factors have been incriminated. Exact etiology and pathophysiology is also not known in most of the cases,but in some cases pathogens causing acute diarrhoea such as enterotoxigenic and enteropathogenic E. coli, shigella spp., non- typhoidal salmonella, Aeromonous, Campylobacter and rotavirus can be isolated. Abnormal bacterial colonisation of intestine with enteroadherent and enteropathogenic E coli, Klebsiella, Enterobacter, Staph aureus, Streptococci, C. defficile, B. fragilies may be responsible in it's pathophysiology. Parasites such as giardia, cryptosprodium, entamoeba histolytica may also be associated with persistent diarrhoea. Malabsorption of nutrients, particularly lactose and fat is marked which in turn may aggravate the diarrhoea by increasing osmotic load. Cows milk protein allergy may also cause enteropathy giving rise to persistent diarrhoea. Important investigations that may aid in diagnosis of persistent diarrhoea include stool for microscopy, culture, ELISA for rota virus, pH, glucose, reducing substances, electrolytes and osmolarity. If facilities are available, microscopy and culture of intestinal luminal fluid, thin layer chromatography and gas- liquid chromatography to identify and quantitate disaccharides, total bile acid concentration of stool can be done. Management of persistent diarrhoea remains problematic because of inadequate knowledge of it's pathophysiology. However,dietary manipulation remains the principle therapy in the management of persistent diarrhoea along with treatment of systemic infections. Lactose intolerance and cows milk protein enteropathy can be managed with cereal base diets. Rice-suji,a recently developed local and simple cereal based lactose-free inexpensive diet has been proved to be a successful therapeutic diet for management of persistent diarrhoea in ICDDR,B. Difficult cases may need diets such as comminuted chicken, soy-based or semi-elemental diets like pregestimil. Antibiotics may be needed in a few cases to treat abnormal bacterial overgrowth of intestine.

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With the advancement of management and investigations, acute diarrhoea is not considered to be dreadful when appropriate antibiotics and rehydration fluid are available. But considerable difficulty is encountered to handle a case of protracted diarrhoea bacause of lacking in straightforwad answer.

Diarrhoea whcih continues for more than 2 or 3 (in ICDDR,B, 2 wks) weeks is generally considered as chronic or protracted diarrhoea. Unfortunately without classifying into several categories, it is very difficult to outline management of protracted diarrhoea.

Apparently classification can be done according to the mode of onset and clinical features although considerable overlapping is possible.

- **Persistent diarrhoea of children (PPD):** This diarrhoea follows an attack of acute episode of diarrhoea and continues for longer time with growth failure. A considerable number of pathogens for acute diarrhoea may be isolated from this entity.

- **Chronic non-specific diarrhoea (CNSD):** Cohlan defined it in 1956 as a continued diarrhoea between 6 and 30 months of age without any psychological syndrome (1). The features include absence of nutrient malabsorption,growth retardation and dehydration. There are disagreement on accepting it as irritable bowel syndrome which has psychological syndrome and spontaneously resolves by 3 years of age.

  Intractable diarrhoea of infancy: Of all variety of protracted diarrhoea this is the most difficult one to manage. In 1968 Avery et al. defined it with the following criteria, lasting more than 2 weeks and onset before 3 months of age with no pathogen isolated on 3 repeated stool microscopy or culture (2).

- **chronic diarrhoea of specific etiology:** The clinical course and underlying causes are better known and the management includes specific therapeutic intervention.

  Common diseases are listed below:

  1. Coeliac disease
  2. Tropical sprue
  3. Tropical enteropathy
  4. Cystic fibrosis of the pancreas
  5. Congenital sucrose- isomaltase deficiency
  6. Lymphangiectasia
  7. Congenital chlorodiarrhoea
  8. Cows milk protein/ soy protein enteropathy
  9. Exudative enteropathy
  10. Acrodermatitis enteropathica
  11. Selective IgA deficiency, T cell deficiency
  12. Crohns disease
  13. Ulcerative colitis

Epidemiology

Community based studies showed that in Ethiopia 1-27% of acute diarrhoea continued to be protracted for more than 3 weeks in children between 12-23 months (3). In Bangladesh, Guatemala and other children in Ethiopia, the incidence is around 7%. During hospital treatment of diarrhoea quite a good number of children goes on to chronic diarrhoea.

Determinants:

To date there have been no study on

identifying the predisposing factors for chronic diarrhoea. But it is known that malnutrition has strong relationship with increased duration and severity of diarrhoea, reduced intestinal enzyme activity and loss of normal mucosal integrity.

prolonged intestinal mucosal injury has been postulated to maintain a vicious cycle of malnutrition-diarrhoea-malabsorption(4). Supplementary feed, bacterial contamintion and environmental sanitation have also been considered to be important.

Genetic disorders like histocompatibility antigen-(HLA) are responsible in some chronic cases. Familial diseases are also known in this group,such as, lymphangiectasia, chloridiarrhoea, congenital enzyme deficiency like sucrose-isomaltase deficiency, glucose-galactose malabsorption and congenital lactase deficiency (primary).

Persistent diarrhoea due to enteropathogens:

a. PARASITIC:

Giardiasis is a frequent cause of chronic diarrhoea in developing countries. Prolonged adherence to duodenojejunal mucosa, mucosal damage, mechanical barrier, competition for nutrients and toxin secretion may be the mechanism of diarrhoea. Small intestinal bacterial overgrowth is frequently associated with malabsorption of nutrients during giardiasis (5).

Cryptosporidium has been identified to be associated with chronic diarrhoea.

Amoebiasis is a known cause of mucoid diarrhoea which may continue more than 2 weeks.

Strongyloides stercoralis can cause protracted diarrhoea.

b. BACTERIAL:

Shigellosis, Salmonella enteritis, ETEC, EPEC, Campylobactor jejuni, Yersinia enterocolitica, Aeromonas hydrophilia and Clostridium defficile have been responsible for prolonged diarrhoea.

c. VIRAL:

Rotavirus diarrhoea is very frequent in children. 3% of rotavirus diarrhoea lasted more than 3 weeks in Bangladesh(6). Astrovirus has been isolated in UK (7). Measles infection may be followed by prolonged diarrhoea due to mucosal damage.

Malabsorption of Nutrients:

Carbohydrate, protein and fat digestion and absorption can be seriously disturbed and produce protracted diarrhoea by several mechanisms.

Carbohydrate:

Digestion can be impaired due to reduced exocrine pancreatic function leading to reduced luminal (-amylase which helps to hydrolyse oligosaccharides with more than 10 monosaccharide molecule. Decrease in brush border enzyme (-glucoamylase leads to inability of breaking oligosaccharide bands in less than 10 sugar molecules.

The commonest problem is brush border disaccharidase deficiency of which lactase, sucrase, maltase,and isomaltase are important. Lactase is the most vulnerable enzyme though sucrase is closer to it. Lactose malabsorption is frequent after gastrointestinal infection like Rotavirus diarrhoea when villus tip cells are partially damaged. This phenomenon is called secondary disaccharidase deficiency or transient lactose malabsorption. In most occasion the repair of the villus is quick and malabsorption improves. Some of these cases

suffer from ineffective repair of mucosal damage leading to persistent malabsorption. Lactose from milk cannot be digested or absorbed and so passes on to colon, resulting in osmotic diarrhoea. Moreover, in colon, bacterial fermentation produces lactic acid and gas. Similarly other carbohydrates are fermented in colon into short chain organic acids with secretory properties. Sucrose malabsorption can also be a cause of chronic diarrhoea. Monosaccharide malabsorption has been reported in many occasion.

Ineffective villous repair or prolonged mucosal injury in malnourished children can be potential cause for protracted diarrhoea. Even without diarrhoea malnourished children have been found to have lactase deficiency in Bangladesh (8) and in India (9). Studies in PEM children have shown that mucosal damage and enzymatic deficiency are common in them(10).

Fat:

Steatorrhoea can be due to insufficient pancreatic lipase or absorptive defect of fatty acid from the gut due to disturbance in bile acid metabolism. Below a critical concentration of bile salt (2 mmol/L) micelle formation cannot happen. In malnutrition with reduced bile acid pool fat absorption is incomplete in addition to the fact that fat absorption below one year of age is 80% at it's best.

Protein:

During malnutrition protease activity in pancreatic secretion is reduced. Reduced trypsin, chymotrypsin and carboxypeptidase A have been reported from patients with exocrine pancreatic disorder other than cystic fibrosis. In cystic fibrosis and other exocrine deficiency lipase is consistently decreased.

Cows milk protein enteropathy (CMPE) and Soyprotein allergy:

Cows milk allergy usually occurs before 6 months of age. B- lactoglobulin fraction in the milk is responsible in most cases. During malnutrition or diarrhoeal episodes mucosal permeability (paracellular) increases and in children with low SIgA in the gut, antigen uptake is enhanced and it causes local inflammation. It can lead to mucosal damage to deeper layer and inflammatory cells appear in submucosa. Circulatory milk protein antigen can stimulate further systemic manifestations. Soyprotein has also been reported to cause such allergy with diarrhoea with blood and mucous. Withdrawal of milk responds with recovery. Milk antibody and IgE are increased in the mucosa in this enteropathy. In Malaysia and Indonesia milk protein enteropathy is frequently encounterd (11). Even in UK CMPE is frequently reported to be a cause of protracted diarrhoea.

Defective bile acid metabolism:

Bile acids can cause purgation even can induce diarrhoea by stimulating fluid and electrolyte secretion from jejunum, ileum and colon. Di-hydroxylated (chenodeoxycholic acid or deoxycholic acid) bile acids induce cholera like secretion through cAMP mediated mechanism. It can increase membrane permeability and also causes damage to the mucosal cells. Formation of dihydroxy bile acids reduces enterohepatic circulation and leads to reduced bile acid pool. Increased presence of bile acid in the colon produces choleric enteropathy with diarrhoea with an additional risk of cholesterol gallstone disease, renal stone formation and steatorrhoea (12). Obligate anaerobes are capable of 7 dehydroxylation of bile acids. In addition, deconjugation of bile acids catalysed by bacterial cholylamidases liberates

unconjugated compounds preventing micellar solubilization. Bacterial overgrowth and patchy mucosal lesions in the jejunum was well correlated (13).

Abnormal bacterial colonisation of intestine:

An important aspect of the pathophysiology of chronic diarrhoea includes bacterial colonisation of the jejunum, ileum and colon. In breast-fed babies lactobacilli and bifidus bacteria are present which suppress overgrowth of other abnormal bacteria. They are protective by bactericidal and neutralising capacity. With supplementary feeding or weaning process abnormal bacterial colonisation (E. coli, Klebsiella, Enterobacter, Staph aureus, Streptococci) may occur. Aerobic organisms predominates in upper small intestine and anaerobic bacteria grows in colon. Among anaerobic bacteria Clostridium defficile and bacteroies fragilis are frequent. The upper limit of bacterial population in upper GI tract is below 10^5ml, but in colon, 10^7ml- 10^9ml. Protracted diarrhoea can be due to this abnormal bacterial population through several mechanisms such as, competitive utilization of micronutrient, release of toxins, stimulation of secretion, deconjugation of bile salts, inhibition of nutrient absorption, enzymatic degradation of brushborder enzymes and mucosal structures. Malnutrition and depressed immune capacity are two predisposing factors of this process though congenital, surgical and infective caurses are also important.

Tropical enteropathy and tropical sprue:

Tropical sprue is characterised by chronic diarrhoea with severe weight loss, glossitis and anaemia but most studies are done on adults. It seems likely that enteropathogens are responsible for abnormalities of intestinal structure and functions. Most of the western visitors have changed in intestinal flora during their stay in tropical countries. This syndrome is again termed as post-infective tropical malabsorption.

Diagnosis of the underlying causes

History:

Detailed history of onset of diarrhoea in relation to age, previous diarrhoeal episodes including measles, previous dietary regime, introduction of supplementary feeds, history of diarroea in the family, duration of diarrhoea, character of stool, hygiene and sanitation of the family, socio-economic status of the parents and breast feeding.

Physical Examination:

Assessment of nutritional status, signs of protein energy malnutrition, assessment of dehydration, vital signs, signs of deficiency diseases, systemic examination and presence of underlying infection.

Laboratory investigations:

Blood: Total and differential count of WBC, electrolytes, serum albumin, serum zinc and serum folate.

Stool: M/E for parasites, formol ether concentration method for Giardia lamblia, Zeel Nelson stain for Cryptosporidium, Pus cells/HPF, RBC/HPF.

Sudan III stain for stool fat (Qualitative).

Stool culture for: **Salmonella, Shigella, Cholera, E. coli (ST, LT) EPEC, Klebsiella, Campylobactor, Aeromonas hydrophilia, Yersinia enterocolitica.**

ELISA for Rotavirus. Electron microscopy for other virus particles (astro and calci virus).

Stool: examination (Biochemical): pH, glucose - prehydrolysed and posthydrolysed or reducing substance. Thin layer chormatography (TLC) to identify disaccharides, gas-liquid chromatography (GLC) to quantitate sugars.

Stool: electrolytes and osmolality can reveal nature of diarrhoea.

Functional test of enzyme activity: Collection of luminal fluid from jejunum by intubation with Crosby capsule, Watson capsule or String capsule.

Luminal enzymes: Pancreatic carboxypeptidase A, Lipase, amylase, trypsin and chymotrypsin.

D-xylose test: one hour D-xylose level in blood after intake of oral dose.

Sucrose tolerance test will exclude specific disaccharidase deficiency.

Fat tolerance test : 24 hour stool fat >5g is abnormal.

Total bile salt concentration may be estimated, critical miceller concentration (CMC) is 2 mmol/1.

M/E of luminal fluid for giardia, cryptosporidium and Strongloides.

Culture of luminal fluid for aerobic and anaerobic organisms, quantitative culture of bacteria. ($>10^4$/ml)

Sweat test: Chloride conecentration > 60 mmol/L (cystic fibrosis), secretory IgA level can be determined from luminal fluid.

Biopsy: mucosal biopsy can be obtained by Crosby or Watson Capsules, examination under dissecting microscope reveals 3 dimensional appearance for mucosal atrophy, histology by light microscopy reveals extent of mucosal damage, infiltration into lamina propria, change in crypt villus ratio, shape of villi and depth of crypts.

Barium follow through: Crohn's disease, abnormal mass, intestinal T. B.

Barium enema: abnormality in colonic haustrations, Hirschprung disease.

Urine examination: routine analysis and culture to exclude UTI.

Assessment of present diet:

Solute content, digestibility, osmolality adequacy of major nutrients, volume/kg vitamins and minerals.

Management of Protracted Diarrhoea

There is no scheduled outline for management of chronic diarrhoea. But few simple principle may be planned before establishing the specific underlying causes:

1. Correction of dehydration:

Mild to moderate dehydration can b rehydration with oral rehydration solution WHO ORS contains 111 mmoles of gluco with a total osmolality of 330 mmol/L. I osmotic diarrhoea with malabsorption nutrients (e. g. , Lactose), administration ORS may precipitate diarrhoeal loss. Ri powder containing oral rehydration soluti (rice ORS) has low osmotic load and can better (14). But young infants who suffer fr prolonged diarrhoea with associat malnutrition may not have adequa pancreatic amylase before 6 months of age, l brush border glucoamylase can split oligosaccharides up to 10 molecules monosaccharide where there is no sev damage in epithelium. Further more gast acid helps in hydrolysis of carbohydra

Infants below 3 months with PEM may require attention to this fact. Intravenous rehydration can be an alternative approach to these cases. Children who are receiving carbohydrate diet may receive rice based ORS because of its superiority.

2. Control of infection

Common infections encountered are, respiratory tract infection, bronchopneumonia, urinary tract infection and septicemia, Appropriate antibiotics should be used without delay. Underlying tuberculosis should be excluded in unexplained fever and malnutrition.

3. Nutritional management:

Adequate energy, protein and fat intake should be ensured in order to recover from malnutrition. But this can be very difficult during the early part of management.

4. Use of antibiotics to control small intestinal bacterial over growth:

a. Anaerobes (e. g. by metronidazole)

b. Aerobes (e. g. by Co-trimaxazole)

5. Use of anion exchange resin (e. g. cholestyramine):

To bind deconjugated bile acids in cases of bile acid induced diarrhoea with higher amount of those acids in stool or luminal fluid.

Feeding

Appropriate feeding is an important tool for control of persistent diarrhoea and of fundamental importance for the recovery of the patients. Two management regimes are at current practice: 1. Total parenteral nutrition (TPN) and 2. Dietary manipulation.

1. Intravenous alimentation:

This is indicated in cases of intractable diarrhoea when diarrhoea continues despite nil by mouth. It should be continued for a period till the diarrhoea ceases.. Prolonged intra-venous feeding reduces recovery of mucosal enzymes and leads to atrophy of intestinal mucosa. Intravenous alimentation can be done by opening a central vein line through cannula (e. g. subclavian vein or superior vena cava). Parenteral fluid contains mixture of aminoacids providing 4-6 g protein per kg body weight per day, Major amount of energy is supplied from emulsion of fat (e. g. intralipid) containing essential fatty acids and from 50% dextrose solution. Additional vitamins and minerals are given in biweekly schedules. This regime is difficult to manage in a general hospital setup. Frequent infection, requirement of additional manpower, maintenance of sterile environment and surgical help for opening line and isolation of the patient are the main constraints in addition to high expense. In spite of those technical disadvantages there are severe cases of protracted diarrhoea who require TPN as a measure for saving their lives.

2. Dietary manipulation:

Patients who do not require TPN can be managed with formulated diets. Diet should be selected with consideration to the underlying cause of diarrhoea. Lactose intolerance can be easily managed with lactose free diet such as soybased milk formula. Prosobee or Isomil can be used with satisfactory outcome. Duration of feeding varies from 3-8 weeks before going back to milk formula. Rice based diet has been successfullyt used in ICDDR, B.

Most commonly used in the west for intractable diarrhoea of infancy is comminuted chicken formula (15). A full strength feed contains (per 100 ml) comminuted chicken 50 g, gastrocaloreen (glucose polymer) 10g,

prosparol (fat) 4gm, metabolic mineral mixure 1g, with added calcium (1.25 mmol/100 ml). Initially this formula is given as a quarter strength feed with added sugar (5% dextrose) from which prosperal is omitted and in small frequent feeds with disaccharide free complete vitamin supplements. The feed is then slowly build up over 10-30 days. Prosperal is added after full strength feeds in 2 to 5 ml increments. Feed volume may reach 200 ml/kg/ day and energy 750 KJ/ kg/ day.

Less severely ill patients may be managed with formula like Pregestimil which contains glucose polymer, medium chain triglycerides and casein hydrolysate. Some children with monosaccharide malabsorption and glucose polymer intolerance will not respond to this formula. This formula has the advantage of being free of disaccharide, milk protein, soyprotein and long chain fatty acids.

Another therapeutic diet (rice suji) has been developed and been successfully used (81% cure rate) in persistent diarrhoea patients in ICDDR, B. This has been formulated with rice powder, glucose, oil and egg-white (16). The advantage of this diet is to avoid lactose, sucrose, milk protein and soyprotein.

Energy and protein supplied should be at least 100 Kcal /kg per day and 4-5 gm/kg/ day respectively. Protein calorie at 8% of the diet would provide growth and energy over 100 Kcal/kg will enhance growth above maintenance.

REFERENCES

Cohlan SQ. Chronic non-specific diarrhoea in infants and children treated with dicodohydroxyquinoline. Pediatrics 1956; 18: 424.

Avery GB, Villa Vicencio O, Lilly JR' Randalph JG. Intractable diarrhoea in early infancy. Pediatrics 1968; 41:712-722.

3. Gordon JE. Diarrhoeal disease of early childhood -world wide sign of the problem, Ann N. Y. Acad Sci 1971; 176: 9-15.

4. Labenthal E. Chronic diarrohea in children, Labenthal E. ed. Nestle, Raven press, New York 1984;.

5. Tomkins AM, Wright SG, Drasar BS, James WPT. Bacterial colonisation of jejunal mucosa in giardiasis. Trans Roy Soc Trop Med Hyg 1978; 72: 33-36.

6. Black et al. Chronic dirrhoea. Soreham, June 8, 1983.

7. Walker-smith JA, Cows milk protein intolerance. Arch Dis Child 1977;50: 347-350.

8. Brown KH, Parry L, Khatun M, Ahmed G. Lactose malabsorption in Bangladeshi village children: relation with age, history of recent diarrhoea, nutritional status and breast feeding. Am J Clin Nutr 1979; 32: 1962-1969.

9. Chandra RK, Pawa RR, Chai OP. Sugar intolerance in malnourished infants and children. Brit Med J 1968; 4: 611-613.

10. Alleyene GAO, Hay RW, Picou DI, Stantield JP, Whitehead. The pathology of protein energy malnutrition. Edward Arnold, London. 1977; pp.244-245.

11. Iyankaran N, Robinson MJ, Sumithran E, Lam SK, Puthucheary SD, Yadav M. Cows milk protein-sensitive enteropathy. An important factor in prolonging diarrhoea of acute infective enteritis in early infancy. Arch Dis Child 1978; 53: 150-153.

12. Heaton KW. Disturbances of bile acid metabolism in intestinal disease. Clin Gastroent 1977; 6: 69-85.

13. Ament ME, Shimoda SS, Saunders DR. Rubin CE. Pathogenesis of steatorrhoea in

three cases of intestinal stasis syndrome. Gastroenterlogy 1972; 63:728-47.

14. Molla AM, Ahmed SM, Greenough III WB. Ricebased oral rehydration solution decreases the stool volume in acute diarrhoea. Bull WHO 1985;63 (4): 751-756.

15. Harries JT. Infective diarrohea and vomiting. In. Harried JT. Ed. Essentials of pediatric gastroenterology.

Churchill Living Stone. Edinburgh London, New York. 1977;164-198.

)y SK, Haider R, Akbar MS, Khatun M, lam AN and Eeckels R, Persistent iarrhoea: Clinical efficacy and nutrient sorption with a rice-based diet. (in press) rch Dis Child 1989.