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Pathology of Infantile Diarrhoe

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Introduction

The leading cause of morbidity in infants is gastrointestinal infection and diarrhoe, the causes of infantile diarrhoe are various and different in countries according to their socio-economic differences. Children younger than 2 years of age with acute diarrhoe requiring hospitalization are about 5% of cases. Viral pathogen involving rotavirus or enteric adenovirus is about 26%, and bacterial one by Salmonella and so forth is about 14% in Baltimore, USA¹. In Germany infantile diarrhoe is often caused by rotavirus infection, but only 20% of cases by bacterial origin². In Europe and America, the main cause of infantile diarrhoe is rotavirus infection and not so many by bacterial infection. In Japan many children were died of infantile diarrhoe with malnutrition by bacterial infection at 1940 to 1950 by bad hygienic condition and economic state after the 2nd World War. With improvement of socio-economic state and hygienic environments, infantile diarrhoe by bacterial infection has reduced in number, which causes only a few cases of death by use of antibiotics. However, some enteropathogenic bacteriae are the main cause of protracted diarrhoe more than 58.6% in Brazil³. In chronic diarrhoe of infants showed the presence of microorganism and malnutrition more than 85% in Chinese⁴. In

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India, 1.4 million children die especially in summer each year from diarrhoe excluding death cases by cholera infection⁵, but more in some African countries. Iwanaga et al⁶ examined the stool of 264 children under 2 years of age in Surabaya, Indonesia, and positive isolation of enteropathogens 61 in pediatric inpatients (47%) and of 48 outpatients (38%). It was composed of 83 diarrheagenic E.coli (31.4%), Shigella and Salmonella were 1.5% respectively, V.cholerae 3.0%, Aeromonas 2.7%. Rotavirus was examined about half of cases, and rotavirus plus diarrheagenic E.coli or others were also found there. Prevailing the new serovar of non-O1 vibrio cholerae and disappearance of V.cholerae O1 are seen recently in India⁷ and Bangladesh⁸.

Classification

Infantile diarrhoe is classified clinically acute and chronic diarrhoe. Acute diarrhoe is essentially infective, by virus, bacteria and protozoa and others. Many cases of acute infantile diarrhoe get well naturally or after medication, but show poor prognosis if they have malnutrition or low hygiene condition, poverty and limited education of their family.

Chronic diarrhoe showing malabsorption syndrome is caused by various agents; abnormal microvilli of the intestinal canal⁸⁻¹¹, tuberculous infection, giardia infection¹², abnormalities of enzymatic or chemical metabolism¹³⁻¹⁵ drugs¹⁶, acquired

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4. Jiang T.A.: Ultrastructural changes in the intestinal mucosa of children with chronic diarrhea. *Chung. Hua. I. Hsueh. Tsa. Chih. Taipei.* 1991, 71:pp.68-71.
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 12. Garcia-La-Osa I.C., Dehesa-Enriquez A., Gonzalez-Perez T., Fragoso-Arbelo T., Gra-Oramas B.: Morpho-functional aspects of the mucosa of the small intestine in children with chronic diarrhea caused by giardiasis. *Rev. Cubana. Med. Trop.* 1987, 39:pp.93-99.
 13. Jiang T.A., Ye R.Y.: Studies in small intestinal mucosal morphology lactase activity and lactose hydrolysis rate in childhood with diarrhea. *Chin. Med. J. Engl.* 1991, 104:pp.476-479.

abnormalities^{17,18}, and others¹⁹⁻²⁴. The cause of chronic diarrhoe in infants is often difficult to ascertain.

I. Acute infective diarrhoe in infants

Although causes of infantile acute diarrhoe are different in countries and various according to an era, approximately half cases of hospitalized patients are derived from rotavirus, an by adeno- and ECHO viruses, and by parvovirus about 10%, respectively. Cases less than 10% are occupied by disturbance of the autonomic nerve, extra-intestinal infection and bacterial one, but remaining cases about 30% are uncertain origin.

a. Rotavirus infection

Rotavirus infection causes infantile watery diarrhoe and self-limited vomiting. Patients are rarely biopsied and diagnosed by enzyme-linked immunosorbent assay from their blood serum²⁵, or by electron-microscopic positivity of viral particles in the intes-

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16. Sullivan P.B., Lunn P.G., Northrop-Clewes C., Crowe P.T., Marsh M.N., Neale G.: Persistent diarrhea and malnutrition - the impact of treatment on small bowel structure and permeability. *J. Pediatr. Gastroenterol. Nutr.* 1992, 14:pp.208-15.
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23. Phillips A.D., Jenkins P., Reafat F., Walker-Smith J.A.: Congenital microvillous atrophy: Specific diagnostic features. *Arch. Dis. Child.* 1985, 60:pp.135-140.
24. Phillips A.D., Schmitz J.: Familial microvillus atrophy: a clinicopathological survey of 23 cases. *J. Pediatr. Gastroenterol. Nutr.* 1992, 14:pp.380-396.
25. Hasegawa A., Mukoyama A., Akatani K., Ikegami N., Urasawa S., Ushijima H.: Serotyping of human rate virus enzyme immunoassay with monoclonal antibodies. *Jpn. J. Med. Sci. Biol.* 1993, 46:pp.221-226.

tinal mucosae or stools. Pathological characteristics of acute rota virus enteritis are lymphocytic infiltration in the duodenal mucosae and hyperaemia, "so-called duodenitis" at early phase. Pathological changes in the gastric and colonal mucosae are slight in general. At the autopsied cases, pathological changes are mostly restricted in the intestine, showing various degree of enteritis with lymphocytic infiltration and reactive lymphadenitis in peyer's patches and mesenteric nodes, and flattening of intestinal mucosae. Poley J.R reported²⁶ 230 children with chronic diarrhea by rotavirus infection and often many diseases, who showed visceral myopathy and villous asthenia. Scanning electron microscopy (SEM) is a good method to detect microorganisms and change of ultrastructural structure. Only a few cases with convulsions was positive for rotavirus in the nervous system on latex agglutination or enzyme immunoassay in their cerebro-spinal fluid²⁷. The rotavirus can be proved in the stool of infected children by transmission electron microscopic examination (TEM) also. Rotaviremia or lymphadenitis may cause "viral dysentery" (Reiman,1952), causing disturbance of autonomic nerve followed to accelerated peristalsis and diarrhoe. Ushijima H.,et al studied serotyping of human rotavirus in the Tokyo Area, at 1990-1993, by enzyme immunoassay against VP4 and VP7²⁸. Direct rotavirus serotyping in stool specimen by reverse transcription polymerase chain reaction amplification is more sensitive 70.4% than enzyme immunoassay with monoclonal antibodies 35.6% positivity²⁹. Furthermore, sequence analysis of gene encoding the major glycoprotein (VP7) was performed on 12 human isolates of serotype 1 of rotavirus in Japan and China³⁰.

26. Poley J.R.: The scanning electron microscope: How valuable in the evaluation of small bowel mucosal pathology in chronic childhood diarrhea? *Scanning Microsc.* 1991, 5:pp.1037-1063.

27. Nishimura S., Ushijima H., Nishimura S., Shiraishi H., Kanazawa C., Abe T., Kaneko K., Fukuyama Y.: Detection of rotavirus in cerebrospinal fluid and blood of patients with convulsions and gastroenteritis by means of the reverse transcription polymerase chain reaction. *Brain & Development.* 1993, 15:pp.457-459.

28. Ushijima H., Mukoyama A., Hasegawa A., Nishimura S., Konishi K., Kim B.: Serotyping of human rotavirus in the Tokyo area (1990-1993) by enzyme immunoassay with monoclonal antibodies and by reverse transcription and polymerase chain reaction amplification. *J. Med. Virol.* 1994. In press.

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b. Adeno-, ECHO, parvo-virus

Adenovirus has been incriminated as the most important pathogen of viral diarrhea until the discovery of rotavirus. This virus affects at first respiratory tract and secondary causes enteritis with diarrhea. This DNA virus particles sized 80-90nm can be found electron microscopically in diarrhoic stool but sometimes positive in non-diarrhoic stools of children. Latex agglutination in diarrhoic stool and their inoculated cell cultures are effective for the examination of adenovirus. Positive antibody levels to enteric adenovirus type 40 and 41 sera are about 20% from umbilical cord, neonates and infants, but 40% or more in adults³¹. Adenovirus infection with diarrhea can be seen from May to October, not so severe clinically. However, children with malnutrition or immuno-insufficiency die of adenovirus infection³².

ECHO and coxsackie viruses in enterovirus group have been examined in diarrhoic feces of children. These RNA viruses are 20-30nm in size. Children infected by ECHO or coxsackie virus show diarrhea and sometimes vomiting and pharyngitis by viremia, but most of cases are recovered without specific treatments. Infected site is the small intestine with mild erosion but no ulcer formation.

Parvo-virus consists of many agents such as Norwalk agent (Adler 1969), Wallon agent (Clarke 1972), Montgomery County agent (Wyatt 1974), Hawaii agent (Wyatt 1974), Ditchling agent (Appleton 1977) and others. Norwalk agent include RNA viruses of about 70-80nm in diameter, both in children and adults. Infection is transmitted to healthy children from affected individuals, and associated with intestinal erosion but with intact gastric mucosae³³. Many other viruses such as reovirus, astrovirus, picorna virus and so forth³⁴ can cause infantile diarrhea.

c. Bacterial infection

The commonest bacterial pathogens are enteropathogenic *E. Coli*, *Salmonellae* and

31. Shinozaki T., Araki K., Ushijima H., Fujii R.: Antibody response to enteric adenovirus types 40 and 41 in sera from people in various age groups. *J. Clin. Microbiol.* 1987, 25:pp.1679-1682.

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Shigellae and *Vibrio cholerae*. In developing countries mortality rate for bacterial enteritis and diarrhoe in younger children is still higher. Furthermore, about half of travelers suffer from diarrhoe by bacterial infection in these developing countries³⁵.

Escherichia coli is gram-negative bacilli ordinary in the intestine. It is subclassified to enteropathogenic *E. Coli* with adherence factor (EPEC), which is composed of enterotoxigenic *E. Coli* (ETEC) and enterohemorrhagic *E. Coli* (EHEC). ETEC elaborates heat-labile (LT) and heat-stable enterotoxins in the small intestine without mucosal destruction and causes diarrhoe³⁶. LT causes diarrhea and bloody excrement of which gene is derived from cholera enterotoxin gene. LT activates adenylyl cyclase and results elevation of cAMP titer, but ST activates guanylate cyclase and elevates the titer of cGMP. EHEC produces Vero toxin like shigellae toxin causing intestinal hemorrhage. In ETEC infection, LT and ST are elaborated in the small intestine causing diarrhoe without mucosal destruction. Other subtype, enteroinvasive *E. Coli* (EIEC) invades to the mucosae and destructs epithelial cells.

Fagundes-Neto U., et al examined stools and biopsy specimens of the small bowel and the rectum affected by EPEC of 29 children, and showed subtotal villous atrophy of the small bowel and colitis in 44.8% at Brazil³⁷. Electron microscopy of jejunal mucosae affected by EPEC revealed effacement of the brush border and attachment of bacteria by pedestal formation. Brush border enzymes showed marked depression of disaccharidases, zinc-resistant alpha-glucosidase, and alkaline phosphatase³⁸. Rothbaum R.J., et al reported jejunal and rectal biopsy of EPEC infection with chronic inflammatory cell infiltration and villous atrophy, in which *E. coli* adhered to the luminal surface of the rectum by electron microscopic observation³⁹.

Salmonella enteritis is an another pathogen of infantile bacterial diarrhoe. Concern-

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37. Fagundes-Neto U., Ferreira V., de-C, Patricio, F.R., Mostaco V.L., Trabulsi L.R.: Protracted diarrhea: The importance of the enteropathogenic *E. Coli* (EPEC). *J. Pediatr. Gastroenterol. Nutr.* 1989, 8:pp.207-211.

38. Taylor C. J., Hart a., Batt R.M., McDougall C., McLean, L.: Ultrastructural and biochemical changes in human jejunal mucosa, associated with enteropathogenic *Escherichia coli* (0111) infection. *J. Pediatr. Gastroenterol. Nutr.* 1986, 5:pp.70-73.

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ing to type of salmonella and clinical figures, gastroenteritis is often seen in the infection by *S. typhimurium*, *S. montevideo*, *S. oranienberg*, *S. newport*, *S. muenchen*, *S. manhattan*, but *S. choleraesuis* shows bacteremia with abscess formation or osteomyelitis less than 15% of occurrence of gastroenteritis. Focal infection is seen in *S. bredeney* and *S. panama*. Carrier patients by *S. tennessee* are many but without clinically obvious signs of infection. *Salmonella typhosa* causes bacteremia and typhoid nodule in reticulo-endothelial system, but recently rare in number. *S. paratyphi* A. and B, especially B-type infection induce diarrhoe with diffuse erosion of mucosae in the ileum and left flexure of the colon. *S. typhi* murium and *S. enteritidis* occur from food poisoning and cause sometimes mass food poisoning especially in the rainy season in Japan and nosocomial infection.

Shigella dysenteriae (A-group) cause typical colitis with severe and hemorrhagic diarrhoe. *S. dysenteriae* invade to the submucosa of the colon and cause pseudomembranous necrosis and ulcer formation in severe cases. Lymph apparatus in the intestine is easily effected and form follicular dysentery. These severe cases seen in children between 2 and 6 years of age are called as ekiri, associated with convulsion, coma and drowsiness, circulatory disturbance, often with their death.

Vibrio cholerae are popular in east-southern countries and infective in dry winter months in their many urban areas. Duodenum and jejunum are affected sites, but their mucosae are almost intact by light- and electron-microscopies. *V. cholerae* induce enterotoxin or cholera toxin, which invade through intestinal mucosae and reach to the vessels. This cholera toxin binds to susceptible cells by high-affinity binding of the B-subunits to a membrane receptor, and results translocation of the A1 peptide which catalyses the ADP-ribosylation of the membrane-associated stimulatory G-subunit of adenylate cyclase. Then overproduction and disturbance of ion and fluid balance in the intestinal mucosae cause severe diarrhoe⁴⁰. Finally, children suffered from infection by *V. cholera* die of shock and acidosis because of deficits of water and electrolytes at rapid progression, if they have no proper medical treatments. Patients infected by *V. cholera* biovar eltor (El Tor, 1905) show diarrhoe resembled to that seen in ones infected by *S. dysentery*. *Vibrio parahaemolyticus*, *Clostridium perfringens*, *Staphylococci* and *Yersinia enterocolitica* have been established as bacterial pathogens of infantile diarrhoe. Furthermore, pseudo-

40. Arbuthnott J.P.: *Virulence mechanism, In. Oxford Textbook of Pathology*. Ed. McGee J. O'D., Isaacson P.G., Wright N.A. Oxford University Press. 1992, 1: Chap.6:pp.422-428.

monas aeruginosa, Aeromonas hydrophilia, Edwardsiella tarda, Bacillus cereus and subtilis, Vibrio fetus are also thought as its possible pathogens⁴¹.

II. Chronic infantile diarrhoe

Chronic infantile diarrhoe is derived from many kind of diseases mentioned formerly at classification of this paper. Children with acute infantile diarrhoe can easily shift to chronic phase by their nutrition, medication and other many causes. Crohn's disease, ulcerative colitis and ischemic colitis are seen in adult patients and rare in infants.

Microvillous inclusion disease(MID) of gastrointestinal canal is a rare disease showing poor prognosis without curative therapies. MID-children show intractable diarrhoe after birth and continue. Long-term hyperalimentation is necessary for them. Biopsies from the stomach, duodenum, jejunum, ileum, colon, rectum and liver but not the gallbladder, reveal inclusion bodies positively stained by alkaline phosphatase stain. Ultrastructural finding of intracytoplasmic inclusions shows the structure lined by intact microvilli, which are present in the absorptive surface epithelial cells of the intestine⁸⁻¹¹.

Tuberculosis of the intestine, primary or secondary, occurs in children of developing countries. Affected site is terminal ileum and colon with ulcer formation, later forming circular shrinkage of the affected canal. Patients with amebic dysentery infection are mostly in adult and rarely in infants. Giardiasis is also rare disease causing enteritis and chronic diarrhea¹².

Infantile diarrhoe is seen in many children suffered from congenital metabolic disorders, such as glucose-galactose malabsorption, sucrose intolerance, enterokinase deficiency and lactose intolerance¹³ and so forth. Calvin R.T. examined children with chronic diarrhea for their carbohydrate tolerance and compared to the biopsy results from the intestine. Results indicated about 70% of all abnormal biopsy had specific disaccharidase activity¹⁵. Glucose and water absorption and disaccharidase activities are closely correlated to the villous morphology of the intestine, and human milk did not accelerate functional recovery of the small intestinal mucosa¹⁴.

Many drugs such as antibiotics or prostaglandin and others trigger the occurrence of infantile diarrhoe same as adults. Antibiotics induce microbial substitution in the in-

41. Tripp J.H., Harries J.T.: *Infective diarrhoe and vomiting. In. Essentials of paediatric gastroenterology*. Ed. Harries J.T., Churchill Livingstone, London, 1977, Chap.10:pp.164-198.

testinal canal¹⁶. Lincomycin is apt to cause pseudomembranous colitis and diarrhoe, Neomycin causes moderate degree of malabsorption of fat and protein from the intestinal canal.

Short bowel syndrome, less than 50cm in length of the intestinal canal at birth, or secondary after operation, remains a challenging problem to be cured. These children have intractable diarrhoe and difficult to nourish. Galeano N.F., et al used them specially designed protein hydrolysate formulas¹⁷. Children with congenital diabetes mellitus (IDDM) show severe secretory diarrhoe with stool volumes of more than 100ml/kg/day. Two unrelated male infants were died of septicaemia and malnutrition without poor control of hyperglycemia. Autopsy revealed the alimentary tract lined entirely by secretory-type glands, without Lieberkühn glands and villi, showing diffuse intestinal dysphasia¹⁹. For the examination of infants with unexplained protracted diarrhoe autoantibody tests against insulin should be performed²².

Congenital microvillous atrophy is a distinct disorder within the intractable diarrhoe syndrome which has an extremely poor diagnosis. In theses children, microvillous involutions were found in the entire bowels²³. Diarrhoe and disorganization of the brush border assembly occur as a cosequence of a more fundamental defect but of accumulation of secretory granules²⁴.

Familial occurrence of protracted diarrhea of infancy is reported also²⁰, but showing negative stool cultures but persistent enteritis, with rather good prognosis. Savage M.O., et al reported specific complement-fixing autoantibodies reacting by immunofluorescence with human duodenal, jejunal, colonic epithelium²¹.

Bile juice is correlated to the surveillance system of the intestinal mucosae, since it contains secretory type IgA with J-chain, then children with distorted excretion of bile juice such as congenital biliary atresia⁴², show often enteritis and diarrhoe. Other many children with immuno-insufficiency are easily affected by many kinds of pathogens followed to enteritis and diarrhoe, finally die of septicaemia if some proper therapies are not done for them.

42. Rossi T.M., Lebenthal E.: Pathogenic mechanism of protracted diarrhea. *Adv. Pediatr.* 1983, 30:pp.595-633.