Persistent diarrhea

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Abstract

Introduction: persistent diarrhea has high impact on infantile morbidity and mortality rates in developing countries. Several studies have shown that 3 to 20% of acute diarrheal episodes in children under 5 years of age become persistent.

Definition: persistent diarrhea is defined as an episode that lasts more than 14 days.

Etiology: the most important agents isolated in persistent diarrhea are: Enteropathogenic E. coli (EPEC), Salmonella, Enteroaggregative E. coli (EAEC), Klebsiella and Cryptosporidium.

Clinical aspects: in general, the clinical characteristics of patients with persistent diarrhea do not change with the pathogenic agent. Persistent diarrhea seems to represent the final result of a several insults a infant suffers that predisposes to a more severe episode of diarrhea due to a combination of host factors and high rates of enviromental contamination. Therefore, efforts should be made to promptly treat all episodes of diarrhea with appropriate follow-up.

Therapy: the aim of the treatment is to restore hydroelectrolytic deficits and to replace losses until the diarrheal ceases. It is possible in the majority of the cases, using oral rehydration therapy and early an appropriate type of diet.

Prevention: it is imperative that management strategies also focus on preventive aspects. The most effective diarrheal prevention strategy in young infants worldwide is promotion of exclusive breast feeding.

It is estimated that 3 to 20% of the acute diarrhea episodes among children younger than 5 years old become persistent, and that over 50% of the deaths provoked by diarrhea are associated to persistent episodes.5,6

Definition

In 1987, the World Health Organization (WHO) defined persistent diarrhea as a diarrheal episode with a presumably infectious cause that starts as an acute episode and lasts in an unusual way, causing the aggravation of the nutritional
STATE AND A HIGH LIFE RISK CONDITION. THE TERM DOES NOT INCLUDE CHRONIC OR RECURRENT FORMS OF DIARRHEA, SUCH AS TROPICAL SPRUE, CELIAC DISEASE, CYSTIC FIBROSIS, AND OTHER HEREDITARY DISORDERS WITH DIARRHEAL MANIFESTATIONS. IN THE BULLETIN PUBLISHED BY WHO, PERSISTENT DIARRHEA WAS ESTABLISHED AS THE DIARRHEAL EPISODE LASTING 14 DAYS OR MORE.

Epidemiology

Lanata et al. followed 677 children below 3 years of age for a period of 27 months, in Peru, and they found an incidence of 8.1 episodes of acute diarrhea per child per year, and 0.25 episodes of persistent diarrhea. In this work, 3.2% of the diarrheal episodes became persistent. Henry et al., in Bangladesh, evaluated 363 children for a period of 24 months. The evaluated children had, on average, 1.5 episodes of acute diarrhea and 0.5 episodes of persistent diarrhea per year, seeing that 23% of the diarrheal episodes became persistent. Fang et al., evaluating children younger than 3 years old in the Northeast of Brazil for a period of 3 years, showed that 10% of the diarrheal episodes evolved for more than 14 days. In 1999, Sarti et al., in Mexico, evaluated 1,034 episodes of diarrhea in children below 5 years of age, out of which 19 were persistent, with a prevalence of 1.8/100 children with diarrhea (2%). A study performed in Tunisia investigated 380 children hospitalized because of diarrhea for a period of 2 years, and, out of them, 74 (19.5%) evolved to persistent diarrhea. In Nairobi, Kenya, 384 children with diarrhea were evaluated, and, out of them, 16.5% evolved persistently in the diarrheal status. In 1999, in Guinea-Bissau, 319 children with diarrhea below 5 years of age were studied, and, out of them, 40 (12.5%) evolved for more than 14 days.

However, we still observe, in regions of low income in Brazil, that persistent diarrhea presents high prevalence, reaching levels over 50%. Recently, in February 2000, Lins & Silva showed that out of 246 children younger than 2 years old considered to have diarrheal disease in Recife, 140 (56.9%) evolved for more than 2 weeks.

Risk factors

The identification of risk factors for the persistence of diarrhea contributed to the development of prophylactic and therapeutic measures against the perpetuation of the diarrheal process. In 1995, Gonzalez et al. identified the following risk factors, in order of importance: early episodes of persistent diarrhea, malnutrition, time of lactation shorter than 1 month, use of antibiotics, mixed infections, early episodes of acute diarrhea and identification of enteropathogens in the feces. In Kenya, other possible risk factors were mentioned, such as presence of blood in the feces, pneumonia, malnutrition, severe dehydration, artificial suckling and treatment with antibiotics. These authors report that out of the children with persistent diarrhea, 63% were younger than 1 year old, suggesting that this age group would be more vulnerable to the persistence of the process. In Brazil, Pinto et al., in 1998, pointed out the relation between malnutrition and incidence, duration and gravity of the diarrheal process. Decrease of the immune function, poverty, lack of motherly suckling, inadequate feeding and environmental contamination do all have a role in the persistence of the diarrheal process.

Lethality

It is well established that the risk of mortality because of acute diarrhea increases significantly along the duration of the disease. The persistent diarrhea, for its turn, appears as a much more important cause of morbidity and mortality than the acute one, mainly after the introduction of an oral rehydration therapy. The identification of risk factors related to the death of patients in which the diarrheal process has already perpetuated is of great importance. Through this, it is determined what group of children needs special attention, in order to avoid a fatal evolution.

Victora et al. compared data obtained from children below 5 years of age that died of diarrhea in Brazil, Senegal, Bangladesh and India. Persistent diarrhea occurred in more than 62% of the deaths for diarrhea in Brazil, 47% in India, 36% in Senegal, and 26% in Bangladesh. These findings are probably due to the low rates of mortality for acute diarrhea in countries that use oral rehydration therapy (ORT) largely. Faveau et al. demonstrated that 49% of the deaths for diarrhea presented association between persistent diarrhea and malnutrition. Victor et al. verified that in metropolitan areas of the state of Rio Grande do Sul, during 1 year of...
observation, out of the total number of deaths for diarrhea among children with less than 1 year of age, persistent diarrhea was responsible for 62% of the dysfunctions, while 28% were due to acute diarrhea, and 10% to “dysentery”. In this study, the authors suggested that infections acquired during hospitalization would be associated with 2/3 of the fatal cases, and reinforced the importance of the protector role of motherly suckling, which was also reinforced in the study of Lins & Silva, in 2000. In 1995, in Kenya, the percentage of death among children with persistent diarrhea was of 31.7%. In 1998, in Brazil, Andrade et al. analyzed the risk factors to death among children with persistent diarrhea. In this study, 189 children hospitalized because of persistent diarrhea were evaluated, out of which 21 (11.1%) died. The factors that showed a significant association with death were: 6 months of age or less, provenance from other hospitals, dehydration of III degree during hospitalization, presence of classic enteropathogenic Escherichia coli (EPEC) in the feces and the use of total parenteral nutrition (TPN). Systemic infection was considered the most important probable cause of death among infants hospitalized with persistent diarrhea.

**Etiology**

Several studies have shown that the excretion of pathogens in the feces of children with persistent diarrhea is common, with isolation rates higher than 40%. In 1998, Andrade et al. had 57.1% of positivity in the etiologic research. The excretion of pathogens in the feces of asymptomatic children in developing countries is common, what makes the interpretation of epidemiological studies become difficult.

The agents most frequently isolated in the feces of children with persistent diarrhea are classic enteropathogenic E. coli (EPEC), Salmonella, enteroaggregative E. coli (EAEC), Klebsiella and Cryptosporidium. Some species of EPEC constitute an important predisposing factor to persistent diarrhea factor. Several researches have studied infants with acute and persistent diarrhea, showing a high concomitance of isolation of EPEC serum groups in the feces and in the jejunal juice. Cruz et al. concluded that EPEC favors the bacterial proliferation in the small intestine.

Black, in 1993, evaluated 4 studies carried out in India, Nepal and Bangladesh about persistent diarrhea, and did not find any association of rotavirus with persistent diarrhea. Besides, in this geographic regions, EPEC, Aeromonas, Campylobacter and Shigella did not seem to be particularly associated with persistent episodes of the diarrhea.

Several authors have suggested that EAEC is an important pathogen causative of diarrhea in children, and it has been found more frequently in episodes of persistent diarrhea than in controls. In 1992, in the Northeast of Brazil, a high incidence of enteroadherent E. coli was verified in the feces and in the jejunal juice of children with persistent diarrhea (36% with aggregative adherence, 29% with diffuse adherence, and 13% with local adherence to Hep-2 cells). In the same year, Henry et al., in Bangladesh, isolated EAEC in the feces of 27.4% of the diarrhea cases that persisted for more than 14 days and in the feces of 17.9% of the acute episodes, while Shigella, Aeromonas, Giardia and ETEC appeared more frequently in acute episodes than in persistent ones. In 1993, Bhatnagar et al., in India, studying 284 children younger than 2 years old with nonsanguineous diarrhea and 107 controls, found EAEC in 21.4% of the persistent diarrhea cases, in 9.9% of the acute diarrhea cases, and in 3.7% of the controls. The isolation of EAEC in persistent diarrhea was significantly higher than in patients with acute diarrhea and in controls, but with no statistical significance. In 1995, Fang et al. reviewed 4,800 cases of diarrheal disease in Brazil, and 56 children with persistent diarrhea, 52 with acute diarrhea and 42 controls were selected for the investigation. EAEC was isolated in 68% of the persistent diarrhea cases, in 46% of the acute diarrhea cases, and in 31% of the controls. In 1998, Bardhan et al. studied 195 children, out of which 135 had persistent diarrhea, 42 had acute diarrhea, and 15 were controls. EAEC was isolated in the feces of 25.4% of the children with persistent diarrhea. Other organisms also significantly associated with persistent diarrhea were Aeromonas and Klebsiella. These authors also concluded that EAEC is an important pathogen associated with persistent diarrhea.

On the other hand, in 1993, Levine et al., in Chile, studying children with diarrhea, isolated EAEC at the same frequency both in children with diarrhea and in controls. Out of the 1,081 episodes of diarrhea evaluated, 103 were persistent, and, out of these, 17 were associated with EAEC (16.5%). Out of the 96 controls evaluated, EAEC was isolated in 24 (25%). Among the newborns, 77 out of the 662 episodes of diarrhea evaluated were persistent, and 12 of these (15.6%) were associated with EAEC. However, this agent was also isolated in 10 out of the 77 controls without diarrhea. Therefore, in this study, EAEC was not significantly associated with persistent diarrhea.

**Pathophysiology**

The pathophysiologic mechanisms that may be present and that determine the perpetuation of the diarrheal process, with compromising of the nutritional status, are multiple and complex.

Great part of the patients with persistent diarrhea had as onset an episode of acute diarrhea. It is known, nowadays, that some factors resulting from acute diarrhea may propitiate the installation of persistent diarrhea. The enteropathogens,
According to its virulence mechanisms, provoke lesions in the intestinal mucosa. So, the status of the mucosa barrier and the host’s microbial clearing capacity may influence the vulnerability to the persistence of those lesions. This way, during the diarrheal process, aggression to the mucosa and to the enterocyte brush border occurs, altering its morphology.\textsuperscript{1,33} The malabsorption of carbohydrates depends on the mucosa level of desquamation, considering that the loss of mature epithelial cell provokes a reduction of enzymes in the enteric membrane and increases, in the lumen, the subtract of carbohydrates, which then promote an osmotic phenomenon. Initially, loss of the capacity to hydrolyze and absorb the disaccharides occurs, because of deficiency in the disaccharidases.\textsuperscript{34} With the extension of the lesion, glucose and galactose absorption mechanisms and the facilitated fructose absorption may also be affected.\textsuperscript{35} The lesions in the small intestine favor the passage of alimentary proteins, intact or partially hydrolyzed by the mucosa, having, as a consequence, allergy to the proteins of the diet (cow milk, soybean protein).\textsuperscript{36,37}

Besides, due to some level of incapacity on the host’s part to keep the mechanisms that regulate the bacterial flora effective, a bacterial overgrowth may occur in the superior portions of the small intestine.\textsuperscript{29,38} As a direct consequence to this alteration in the microecology of the small intestine, a series of pathologic events will start to occur in chain, such as disconjugation and \textgreek{7}µ-dehydroxylation of bile salts,\textsuperscript{39} morphologic alterations in the intestinal mucosa,\textsuperscript{40-42} provoking decrease in the absorption surface,\textsuperscript{43} and functional lesions with deficiency of enterokinase\textsuperscript{44} and of the ATPase (Na+K+) enzym.\textsuperscript{45} Besides, desconjugated bile salts and dehydroxylated \textgreek{7}µ are able to provoke alterations in the permeability barrier of the intestinal mucosa.\textsuperscript{46,47} On the other hand, dysfunction in the terminal ileum has been described\textsuperscript{48} in patients with persistent diarrhea and malnutrition, leading not only to deficiency of the B12 vitamin, but also to the inadequate absorption of bile salts. The consequent decrease of bile salts pool will lead, first, to the malabsorption of fats of the diet,\textsuperscript{49} having as result the steatorrhea, which will deprive the patient of an important caloric offer. Secondly, the excretion of bile salts will induce the appearance of choleric diarrhea, because of the direct toxic action of the bile salts on the colonic mucosa.\textsuperscript{50}

Another factor that perpetuates the diarrheal process is related to the lack of regeneration of the intestinal mucosa morphology. The determining factor regarding absence of intestinal mucosa recuperation is the energetic-protean malnutrition, besides specific deficiencies of micronutrients, which determine abnormalities in the structure and function of the small intestine.\textsuperscript{51}

The synergic actuation of all these pathophysiologic factors becomes responsible for the perpetuation of the diarrheal process and for the aggravation of the nutritional state, if therapeutic measures are not taken.

Because of this series of events, several morphologic alterations have been described in the intestinal mucosa in patients with persistent diarrhea. Studies carried out at light microscopy confirm that patients with persistent diarrhea present important abnormalities in the mucosa of the small intestine. Some authors do not associate them with specific enteropathogens.\textsuperscript{52} Others conclude that either the total extension of the mucosa, the height of the villus or the villus-crypt relation are significantly decreased in the group of patients in whose feces EPEC was isolated, in relation to the control group.\textsuperscript{53} Fagundes Neto et al., in 1984, evaluating intestinal mucosa in patients with persistent diarrhea, through transmission electron microscopy (TEM), showed several structural alterations, specially the flattening of microvilli, besides the increased number of multivesicular bodies and the vacuolization of mitochondria and of the endoplasmic reticulum.\textsuperscript{42} Other authors demonstrated tissue lesions, such as the increased thickness of the enterocytes basal lamina and of the vases endothelium, as well as the deposit of collagen in lamina propria. These alterations seem to be related to the presence of adherent and non-adherent bacter.\textsuperscript{55} At scanning electron microscopy, intense and unspecific to the enteropathogenic agent lesions were demonstrated, such as decrease of the number and size of microvilli, structural disarrangement of enterocytes, and, in half of the cases, presence of mucous material covering part of the epithelium.\textsuperscript{56}

**Diagnosis**

In 1989, Kleinman et al. suggested that the malabsorption syndrome and malnutrition are common factors of persistent diarrhea. Malabsorption was defined as the presence of nutrients in the feces, followed by loss or insufficient gain of weight, with an appropriate to the age diet. The authors proposed several tests to evaluate the absorption of many nutrients of the diet, and concluded that, in order to judge the efficacy of a determined formula, it is necessary to measure the serum levels of the various elements of the diet, and, mainly, to monitor the retaking of ponderal gain during the adequate caloric offer.\textsuperscript{57}

**Clinical aspects**

In general, the clinical characteristics of patients with persistent diarrhea do not vary significantly according to the causative agent. Most of the times, these children did not receive motherly suckling or were weaned very early.\textsuperscript{17,18} The diarrheal status is similar to the acute episode, but it is associated with the malabsorption syndrome, which, if not controlled with an adequate dietetic management, leads to malnutrition and its fatal consequences. Among them, we emphasize a higher vulnerability of the immunological capacity, favoring the installation of infectious processes
that may disseminate systematically, causing a high life risk. With repeated diarrheal episodes or with the persistence of them, the nutritional damage gets aggravated. This phenomenon becomes more serious when the nutritional support remains deficient in the convalescence phase, what usually happens due to anorexia and inadequate realimentation practices.

Persistent diarrhea seems to represent the final result of a variety of insults to a child who is predisposed to frequent and serious episodes of diarrhea because of a combination between the host’s factors and environmental contamination. As a consequence, all the efforts have to be done in the sense of treating the diarrheal episodes efficiently, with an adequate follow-up.18

Therapeutical management

The objective of the treatment is to restore the hydroelectrolytic deficits and to restitute the fecal losses until the diarrheal process ceases. In almost all of the cases, this is possible through oral rehydration and early realimentation, using an appropriate dietetic scheme.30

Concerning the type of alimentation, the risks involving the use of parenteral feeding are known, specially in developing countries. Parenteral feeding shall be left as a last resource, in those patients with multiple alimentary intolerance, even to monosaccharides.32 As a consequence, most part of the recent studies on nutritional intervention during persistent diarrhea have focused the importance of the use of enteral feeding.18

In developed countries, there is a wide range of formulas commercially prepared, but their number is limited in third-world countries, where these formulas are also very expensive. Thus, it is necessary to select provisions that are of easy digestion, proportionate an adequate nutritional support, have low cost and are hypoallergenic and of easy acceptance.17,30 WHO proclaims a nutritional therapy with cheap and available provisions, containing mineral and vitamin supply (WHO, 1996). Vitamin A, other micronutrients, such as folic acid, iron and B12 vitamin, for its action on the intestinal mucosa and on the immune response, should be given to patients with persistent diarrhea.17 Roy et al., in 1998, emphasize that zinc supplementation in children with persistent diarrhea decreases significantly the recuperation time among underfed children, preventing the loss of weight and the decrease of serum concentrations of zinc.58

In general, underfed children with persistent diarrhea should receive an initial caloric offer of at least 75 kcal/kg/day, which should be increased in 25 kcal/kg/day, until it reaches 250 kcal/kg/day. The lesion in the intestinal mucosa present in the persistent diarrhea leads to lactase deficiency, incapacitating the hydrolysis of lactose into glucose and galactose. The use of lactose-free formulas reduces the duration of diarrheal processes in in-patients. So, the initial dietetic treatment for persistent diarrhea cases in developing countries is based on the use of lactose-free formulas. Bhutta & Hendricks suggest the use of diets based on cereals or vegetables, such as the rice formulas, which should be prepared with the addition of vegetal oil in order to increase the caloric offer. In the impossibility of achieving the adequate caloric and protein offer, these authors suggest the use of sour milk as a complement.18 Though, a substantial proportion of children do not respond to this dietetic proposal, and should be investigated in relation to other alterations, such as intolerance to monosaccharides and allergy to proteins of the diet. The presumptive diagnosis of alimentary allergy is carried out with suppression and provocation tests using the mentioned proteins, specially the cow milk protein.17 Harrison,59 in 1974, and Lyngkaram,60 in 1978, emphasized the importance of the intolerance to cow milk protein in the perpetuation of the diarrheal process. In these cases, formulas free from the aggressive protein are necessary. Some alternatives may be used when protein hydrolyzates are not available. Human milk proceeding from the milk bank showed to be efficacious when used by McFarlane & Miller in the treatment of children with persistent diarrhea.61 In spite of the consensus that the soybean protein may be the cause of alimentary allergy,62 some studies have shown good results with the use of soybean formulas in the treatment of these pathology.63,64 Other authors published studies reporting good results with the use of chicken formulas in the treatment of children with prolonged diarrhea.65,66

Clinical experiences with the use of antimicrobials in patients with persistent diarrhea are limited. In a case-control study carried out in South Africa, using oral gentamicin, metronidazole and cholestyramine in patients with persistent diarrhea, the use of oral gentamicin showed a significant decrease in the fecal losses, what did not happen with metronidazole.67 This result was not confirmed in later studies carried out in Guatemala68 and in India.69 Bahl et al., in 1996, did not find any benefic effect with the use of metronidazole in persistent diarrhea episodes that were not dysenteric and not associated with giardiasis and amebiasis.70 Alam et al., in 1995, using sulfamethoxazole-trimethoprim in patients with persistent diarrhea, showed a decrease in the fecal volume, a shorter duration of the diarrhea and a higher rate of recuperation within 7 days of treatment, besides a probable protector role concerning the occurrence of hospital infections in relation to the control group.71

Our experience along 25 years has shown clearly that the use of antibiotics and/or any other medicine in a routine way does not have any benefic action regarding the control of diarrhea. On the other hand, emphasis on the nutritional support, respecting the needs of each patient and using formulas that fulfill the digestive-absorptive needs and
capacities, preferably those with a protein hydrolyzate base, through oral or enteral feeding, represents the basic pillar in the exit regarding clinical recuperation of the patient with persistent diarrhea.

Prophylaxis

Taking into consideration the risks that persistent diarrhea involves, it is very important that prevention strategies are established. The most effective strategy used among young infants is the incentive to the exclusive motherly suckling. The protector role of motherly suckling in relation to the infectious processes of the gastrointestinal tract are known.

References

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