

# Spectrum of chronic diarrhoeal diseases - A cross sectional study

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## Abstract

Protracted diarrhoea is the most severe form of diarrhoea in infancy and has also been defined as intractable diarrhoea. Its etiology is poorly defined. We have retrospectively evaluated the etiology, the outcome, and the risk factors of 38 children, admitted with protracted diarrhoea and need for hospitalization from 5 January 2013 to 10 January 2016. Children with anatomic abnormalities and/or primary immunodeficiency were excluded. There was an inverse relationship between the number of patients and the age of diarrheal onset (mean age,  $2.9 \pm 3.5$  months). Etiology of protracted diarrhoea was an enteric infection in 18 cases (eight Salmonella, three Staphylococcus, five rotavirus, one adenovirus, one Cryptosporidium), multiple alimentary intolerance (eight cases), familial microvillous atrophy (two), autoimmune enteropathy (two), celiac disease, lymphangectasia, eosinophilic enteropathy, intestinal pseudoobstruction, and intestinal neurodysplasia (1 case each). Etiology was not detected in three cases. Overall, 12 children died, five are presently being treated, and 21 had full remission. Comparative evaluation of risk factors between children with protracted diarrhoea and a control population of children with diarrhoea but without the need for hospitalization showed that low birth weight, no breast feeding, history of fatal diarrhoea in a relative and early onset of diarrhoea had a significantly higher incidence in the former. Social background was similar in the two populations. We conclude that a specific etiology can be identified in the majority of cases of chronic diarrhoea. The etiologic spectrum of chronic diarrhoea is broad, but an enteric infection is the most common cause of chronic diarrhoea. The severity of this condition is related, at least in part, to establish risk factors.

**Key Word:** Intractable diarrhea- Parenteral nutrition-Enteric infection- Food intolerance – Congenital enteropathy.

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## INTRODUCTION

Severe and chronic protracted diarrhoea has become a relatively common disease in developing countries in recent years, especially low socio-economic children. Some authors refer to this condition as intractable diarrhoea, a term proposed in 1968 by Avery *et al.* to define a diarrhoea that lasts > 2 weeks in an infant younger than 3 months, with three negative stool

cultures<sup>1</sup>. There is no agreement on this definition. Some authors prefer the term protracted or persistent diarrhoea, defined as the syndrome of chronic protracted diarrhoea and malnutrition<sup>2,3</sup>. This may be confusing, as chronic, protracted, or persistent diarrhoea refers to the duration of diarrhoea (not <2 weeks), rather than to its severity. The opportunity to limit the definition of intractable diarrhoea to younger infants is also uncertain. Several authors included infants up to 1 year of age<sup>4-6</sup> and even older children<sup>7</sup>. Finally, the opportunity to exclude children with infectious diarrhea or with another established etiology has been questioned. Rossi and Lebenthal suggested including in the definition of intractable diarrhoea syndrome all cases of prolonged diarrhoea, even though a specific etiology is identified<sup>8</sup>. Others included also infants with documented intestinal infections<sup>9,10</sup>. Whatever the etiology of the diarrhea and the age of patient, diarrhea is always severe and usually requires total hospitalization. Thus we have defined our patients as affected by chronic diarrhoea requiring

hospitalization. We have reviewed the clinical records of children admitted in the years from 5 January 2013 to 10 January 2016, with chronic protracted diarrhoea and need for hospitalization, to see the pattern of etiology. We also examined the risk factors for chronic diarrhoea and the patients' outcome.

## PATIENTS AND METHODS

The clinical records of patients of low socio-economic status were admitted in the period from 5 January 2013 to 10 January 2016 with diarrhoea and need for hospitalization at the Department of Pediatrics of the RAMA Hospital and Research Centre were reviewed. The Department has a special unit for children with diarrhoea needed isolation, with established experience and advanced technology in diarrhoeal diseases. Children with anatomic abnormalities and those with primary immune deficiency, including human immunodeficiency virus (HIV) infection, were excluded from this study. Diarrhoea was defined as three or more loose or liquid stools per day. Consideration for employing hospitalization was based on the persistence of the diarrhoea, its worsening with oral or enteral feeding, and the failure of pharmacologic therapy, but virtually in the cases, hospitalization was started because of the life-threatening condition of the patient. All children were severely malnourished as a consequence of the diarrhoeal disease when they were admitted to the hospital. We refer to these children as patients with chronic protracted diarrhoea. The main diagnostic tools are Intestinal endoscopy and abdominal ultrasound. Microbiological analysis depended on the time of admission, too. In all cases it included search for Salmonella, Shigella, enteropathogenic E. coli, Giardia lamblia, and Entamoeba histolytica, Rotavirus, Tersinia enterocolitica and Campylobacter jejuni, Clostridium difficile and enterotoxigenic E.coli, Cryptosporidium and enteric viruses. Microbiological methods have been described or referred to in previous works<sup>17,18</sup>. Assessment of intestinal function included xylose oral load and the determination of fat, nitrogen, and carbohydrate fecal excretion. The secretory or the osmotic nature of the diarrhoea was assessed by the osmolal gap<sup>19</sup> or by the persistence of large fecal volumes while during hospitalization. Blood parameters were systematically monitored. Radiographs, ultrasounds, and computed tomography (CT) scan were performed in selected patients, if needed. According to the etiology of the diarrhoea, the patients were divided into four groups: (a) children with infectious diarrhoea; (b) those with multiple alimentary intolerance (MAI); (c) those having a primitive intestinal disease other than infections or food intolerance; and (d) those in which the etiology remained

undetermined. The important risk factors for chronic diarrhoea was considered: low birth weight, no breast milk feeding, early (before 1 and 3 months of age) onset of diarrhoea, early introduction of cow milk/topfeed, malnutrition, recording of fatal intestinal disease and of atopy in first and second degree relatives. The social background of the family was also considered as a risk factor for chronic protracted diarrhoea. The incidence of these features was compared with that of children with diarrhoea, but without the need for hospitalization, matched for the time of hospital admission, but otherwise randomly selected. This was done by reviewing the clinical records of patients admitted with diarrhoea. The statistical difference between children with the need of hospitalization and those not needing hospitalization was assessed by the  $\chi^2$  test.

## RESULTS

Overall, 38 patients were admitted with chronic protracted diarrhoea and were hospitalized from 5 January 2013 to 10 January 2016. Approximately one to three new cases were admitted each year. All but three children had already been hospitalized elsewhere before being admitted to our unit. Fifteen children came from slums with mean age at the onset of symptoms was  $2.9 \pm 3.5$  months, median age was 2 months (range, 1 to 14 months). The number of patients admitted with chronic protracted diarrhoea was inversely related to age in the first 12 months of life. Onset of diarrhoea after 12 months of age was recorded only in one of the 38 cases, who were seen with eosinophilic enteropathy at 14 months. Most patients had diarrhoea for at least 1 month before being hospitalized: mean duration of diarrhoea before hospitalization was  $2 \pm 2$  months (median, 1 months; range, 15 days to 9 months). Mean duration of hospitalization was  $3 \pm 5$  months (median duration, 2 months; range, 1 month to 3 years).

**Etiologic Diagnosis:** An etiologic diagnosis was established in all but three patients. The first group of patients included those with infectious enteritis. In all 18 cases diagnosed as infectious diarrhoea, the responsible microorganism was repeatedly detected during the course of the illness, and its disappearance from stools was associated with full and permanent recovery of the patient. The following enteric pathogens were detected. Salmonella (eight cases), coagulase-positive Staphylococcus (three), rotavirus (five), adenovirus (one) and Cryptosporidium (one). The second group includes eight children classified as having MAI, because they were not able to tolerate milk or elemental diets without a clear worsening of the diarrhoea. No enteric pathogen or other specific intestinal disease was detected in these children. Children with MAI were challenged with cow's

milk after several months of elimination diet, and all showed positive reaction to milk protein, thereby confirming the diagnosis according to the ESPGAN protocol (20). Afterwards, each of them did well on an elimination diet, and eventually all patients but one (who died) were able to return to a free diet. The third group of patients included nine children with various primitive intestinal diseases other than infections or food intolerance. There were two cases of familial microvillous atrophy. Two children had disorders of intestinal motility: one case of idiopathic intestinal pseudo obstruction and one of neuronal intestinal dysplasia. The other five children had a primitive intestinal disease related to an immune/inflammatory disorder. The fourth group included three children in whom the etiology of the diarrhoea was not detected.

**Outcome:** Twenty-one of the 38 children (55%) fully recovered. Two children leave suddenly. Two children are presently maintained on restricted diets. One is taking chronic anti-inflammatory treatment. Twelve children (32%) died: death was associated with overwhelming infections (most of which related to the central line) in eight children, with the lack of vascular access in two and

with liver failure in two. Overall, the worst outcome was in children with a primitive intestinal disease. Indeed, in these children, the mean duration of hospitalization was significantly more protracted than in children with other diarrheal etiology, and the fatality rate was increased. Incidence of Risk Factors in Children with Severe Chronic protracted Diarrhoea and in Those with Diarrhoea without the Need for Hospitalization The comparative evaluation of risk factors between the 38 children with chronic protracted diarrhoea and 76 children (two for each case of chronic protracted diarrhoea) with diarrhoea but without the need for hospitalization is reported. Among the risk factors considered familial history of fatal enteropathy, low birth weight, no breast feeding, and early onset of diarrhoea showed a significantly greater prevalence in children with chronic protracted diarrhoea than in those with diarrhoea without the need for hospitalization. On the contrary, the prevalence of familial atopy was significantly greater in control children. Finally, the social background was similar in the two groups considered.

**Table 1:** Etiological diagnosis and outcome in children with severe and chronic protracted diarrhoea

Etiology	Total cases	Full remission	Dead	Presently on treatment
ENTERIC INFECTION *	18	13	4	1-recurrent hospitalization
Food intolerance	8	7	1	
Autoimmune enteropathy	2	-	1	1(azathioprine)
Familial microvillous atrophy	2	-	2	
Celiac disease	1	-	-	1(Gluten-free diet)
Eosinophilic enteropathy	1	-	1	
Lymphangectasia	1	-	-	1(fat-restricted diet)
Pseudoobstruction	1	-	-	1(home food)
Neurodysplasia	1	-	1	
Unknown	3	1	2	
Total	38	21	12	5

\*responsible microorganism were salmonella(eight Cases), Coagulase-positive staphylococcus (three), rotavirus(five), Adenovirus(one) and Cryptosporidium(one)

**Table 2:** Comparative evaluation of risk factors in 38 children with severe and chronic diarrhea and in 76 controls with diarrhea but without the need for hospitalization

Risk factor	Cases		Controls		P
	N	%	N	%	
Low birth weight	9	24	2	3	0.001
No breast feeding	27	71	27	35	0.0007
Atopy	9	24	36	47	0.02
Familial fatal diarrhea	6	16	-	-	0.001
Early onset(<1 month)	17	45	22	29	NS
Early onset(<3 month)	29	76	26	34	0.0005
Social class I – III	11	29	20	26	NS
Social class IV-VI	24	63	43	56	NS
Social class unknown	3	8	13	17	NS

\*NS, not significant

## DISCUSSION

Severe chronic protracted diarrhoea of infancy is a syndrome rather than a disease. We have defined the children with chronic protracted diarrhoea as patients with an extremely severe diarrhoeal disease, which threatened their survival and required long-term hospitalization. Some authors refer to those children having intractable diarrhoea<sup>1,2,4,8</sup>. Each of our patients had unsuccessfully received several therapeutic or dietetic trails (including continuous enteral nutrition) before being hospitalized, which indicates that our population included only children with a most severe form of diarrhoea. This is probably the reason that the fatality rate in our series was greater than that reported in other recent works. Indeed, it has been shown that the fatality rate decreased from 45-70 to 0-10% from the original reported of children with intractable diarrhoea<sup>1,21,22</sup> to other more recent series<sup>2,8</sup>. However, the outcome may be greatly affected by the criteria of patients' enrollment. We have shown that the risk for chronic protracted diarrhoea decreases with increasing age in the first year of life. However, selected cases of chronic protracted diarrhoea may be seen beyond 1 year of age, shown by our and other observations<sup>7,10</sup>. It is well known that persistent diarrhea is related to poor socioeconomic background, at least in developing countries<sup>23</sup>. This may explain the lack of association between low social background and chronic protracted diarrhoea. The probability that diarrhoea may become severe and protracted was related to each of the risk factors considered, with the exception of social background and of familial atopy. These markers could be therefore used to evaluate the risk of developing chronic protracted diarrhoea. In most patients, the etiology of the diarrhoea had not been identified before admission to our unit. We showed that the accuracy of etiological diagnosis was related to the availability of advanced techniques. Indeed, when the etiology is investigated by a more thorough diagnostic approach, a broad spectrum of specific intestinal diseases is observed. When series of children with chronic protracted diarrhoea were reviewed, it was found that food intolerance and enteric infections were the most common etiologies of chronic protracted diarrhoea, whereas other rarer specific intestinal diseases were usually not detected<sup>1,3,5,10, 11, 24</sup>. However, in the population studied by us, infectious enteritis was the single most frequent cause of chronic protracted diarrhoea, being responsible for approximately half of the cases of chronic protracted diarrhoea. Several children had MAI. However, the diagnosis of MAI, even if proved by a pathologic<sup>20</sup>, does not necessarily mean that intolerance to food is the basis cause of the diarrhoea. The postulated mechanism of food intolerance involves an

immune response to food antigens, triggered by an increased absorption of macromolecules through damaged intestinal epithelium<sup>26,27</sup>. Therefore, food intolerance may be secondary to a primitive, not detected, intestinal disease. This further supports the need for a comprehensive diagnostic approach to decrease the number of children inappropriately diagnosed as having primitive MAI. The third group of patients included three major classes of primitive intestinal diseases: familial enteropathies, disorders of intestinal motility, and immune/inflammatory diseases. This group included a broad spectrum of enteric disease, for whose identification a combined approach with sophisticated instrumental and laboratory techniques was usually required. Each of the etiologies described has been previously reported as a cause of chronic diarrhoea<sup>12,13,28,32</sup>, but their relative importance in inducing chronic protracted diarrhoea was unknown. An increasing number of observations suggest that the frequency of both familial enteropathy and disorders of intestinal motility is greater than previously recognized<sup>12,14,21,29</sup>. Children in this group had the longest duration of hospitalization and the worst outcome. It is likely that many cause of really intractable diarrhea are due to congenital enteropathies or to permanent intestinal diseases such as those we have described. In these cases, there is no treatment, and survival depends on hospitalization<sup>30</sup>. A fourth group of children included three children without an etiologic diagnosis. The prevalence of cases of chronic diarrhea of undetermined etiology ranges from 0 to 100% in published series<sup>1,7</sup>. The difference depends largely on the enrollment criteria and on the availability of diagnostic techniques. Overall, our data show that an etiology diagnosis can be achieved in the majority of cases of chronic protracted diarrhoea. Because the number of children with chronic protracted diarrhoea is relatively low, these patients should be referred to centers in which the experience in clinical nutrition is associated with the availability of advanced technology for the diagnosis of diarrhoeal diseases. Finally, the definition of intractable diarrhoea appears to be confounding and inappropriate in the light of the progress in this field. We believe that an operational definition of this syndrome should include children with a severe and protracted diarrhoea and chronic nutritional failure, for whom the common pharmacologic and dietetic treatment had been unsuccessful and who need long-term hospitalization.

**Epilogue:** Diarrhea in children continues to pose a major public health challenge despite significant advances in interventions. Reducing mortality rates largely depends on life-saving treatment with ORS and zinc to all the children suffering with diarrhoea, whereas main tools of



prevention are cleanliness and vaccination. As pediatricians, we endorse the move to introduce the rotavirus vaccine into the national immunization schedule of India. The vaccine is a cost-effective intervention poised to make a much needed positive impact on public health in India. It will go a long way to ensure that Indian infants and children are protected against diarrhea, the second largest killer of Indian children.

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