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Clinical Evaluation of Severe and Chronic Diarrhea: A Study

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Abstract

Introduction: Severe and chronic diarrhea is the most severe form of diarrhea in infancy and has also been defined as intractable diarrhea. Its etiology is poorly defined. *Objective:* Retrospectively evaluated the etiology, the outcome, and the risk factors of 38 children, admitted with chronic diarrhea and need for hospitalization from 2010 to 2014. *Methods:* 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±3.5 months). *Results:* Etiology of chronic diarrhea was an enteric infection in 18 cased (eight Salmonell, there Staphylococcus, five rotavirus, one adenovirus, one Cryptosporidium), multiple alimentary intolerance (eight cases), familial microvillour atrophy (two), autoimmune enteropathy (two), celiac disease, lymphangectasia, eosinophilic enteropathy, intestinal pseudoobstructiopn, 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. *Conclusion:* Comparative evaluation of risk factors between children with chronic diarrhea and a control population of children with diarrhea but without the need for hospitalization showed that low birth weight, no breast feeding, history of fatal diarrhea in a relative and early onset of diarrhea had a significantly higher incidence in the former. Social background was similar in the two populations. We conclude that at specific etiology can be identified in the majority of cases of chronic diarrhea. The etiologic spectrum of chronic diarrhea is broad, but an enteric infection is the most common cause of chronic diarrhea. The severity of this condition is related, at least in part, to establish risk factors.

Keywords: Intractable Diarrhea; Parenteral Nutrition; Enteric Infection; Food Intolerance; Congenital Enteropathy.

Introduction

Severe and chronic diarrhea has become a relatively common disease in developing countries in recent years. Some author's refer to this condition as intractable diarrhea, a term proposed in 1968 by Avery et al. to define a diarrhea that lasts > 2 weeks in an infant younger than 3 months, with three negative stool cultures [1]. There is no agreement on this definition. Some authors prefer the term protracted or persistent diarrhea, defined as the syndrome of chronic diarrhea and malnutrition [2,3]. This may be confusing, as chronic, protracted, or persistent diarrhea refers to the duration of diarrhea (not <2 weeks), rather than to its severity. The opportunity to limit the definition of intractable diarrhea to younger infants is also uncertain. Several authors included infants up to 1 year of age [4,5,6] and even older children [7]. Finally, the opportunity to exclude children with infectious

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diarrhea or with another established etiology has been questioned. Rossi and Lebenthal suggested including in the definition of intractable diarrhea syndrome all cases of prolonged diarrhea, even though a specific etiology is identified [8]. Others included also infants with documented intestinal infections [9,10].

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 diarrhea requiring hospitalization.

We have reviewed the clinical records of children admitted in the years 2010-2014, with chronic diarrhea and need for hospitalization, to see the pattern of etiology. We also examined the risk factors for chronic diarrhea and the patients' outcome.

Methods

The clinical records of patients admitted in the period 2010-2014 with diarrhea and need for hospitalization at the Department of Pediatrics of the RAMA Hospital & Research Centre were reviewed. The Department has a special unit for children with diarrhea needed isolation, with established experience and advanced technology in diarrheal diseases.

Children with anatomic abnormalities and those with primary immune deficiency, including human immunodeficiency virus (HIV) infection, were excluded from this study. Diarrhea was defined as three or more loose or liquid stools per day. Consideration for employing hospitalization was based on the persistence of the diarrhea, it's 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 diarrheal disease when they were admitted to the hospital. We refer to these children as patients with chronic diarrhea.

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 [11,12]. 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 diarrhea was assessed by the osmolal gap [13] or by the persistence of large fecal volumes while during hospitalization. Blood parameters were systematically monitored. Radiographs, ultra sounds, and computed tomography (CT) scan were performed in selected patients, if needed.

According to the etiology of the diarrhea, the patients were divided into four groups:

a. Children with infectious diarrhea.
b. Those with multiple alimentary intolerance (MAI.)
c. Those having a primitive intestinal disease other than infections or food intolerance.
d. Those in which the etiology remained undetermined.

The social background of the family was also considered as a risk factor for chronic diarrhea. The incidence of these features was compared with that of children with diarrhea, 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 diarrhea. The statistical difference between children with the need of hospitalization and those not needing hospitalization was assessed by the χ^2 test.

Results

Overall, 38 patients were admitted with chronic diarrhea and were hospitalized from 2010 to 2014. 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±3.5 months, median age was 2 months (range, 1 to 14 months). The number of patients admitted with chronic diarrhea was inversely related to age in the first 12 months of life. Onset of diarrhea 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 diarrhea for at least 1 month before being hospitalized: mean duration of diarrhea before hospitalization was 2±2 months

(median, 1 months; range, 15 days to 9 months). Mean duration of hospitalization was 3 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 diarrhea, 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). (Table1).

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 diarrhea. 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 [14]. Afterwards, each of them did well on a 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 diarrhea 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 Diarrhea and in Those with Diarrhea without the Need for Hospitalization

The comparative evaluation of risk factors between the 38 children with chronic diarrhea and 76 children (two for each case of chronic diarrhea) with diarrhea 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 diarrhea showed a significantly greater prevalence in children with chronic diarrhea than in those with diarrhea 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 2).

Table 1: Etiological diagnosis and outcome in children with severe and chronic diarrhea

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)
Neurodysplasi	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 3: 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 n	%	Controls n	%	P value
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	Not Significant
Early onset (<3 month)	29	76	26	34	0.0005
Social class I – III	11	29	20	26	Not Significant
Social class IV-VI	24	63	43	56	Not Significant
Social class unknown	3	8	13	17	Not Significant

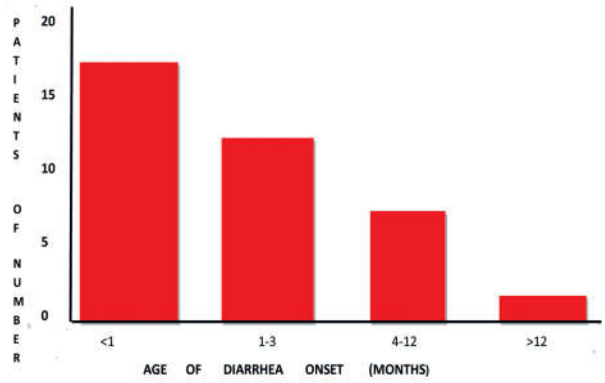

Table 1: Age of onset of severe protracted diarrhea. A clear inverse relationship between the number of patients and increasing age is observed.

Discussion

Severe chronic diarrhea of infancy is a syndrome rather than a disease. We have defined the children with chronic diarrhea as patients with an extremely severe diarrheal disease, which threatened their survival and required long-term hospitalization. Some authors refer to those children having intractable diarrhea [1,2,4,6-8]. 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 diarrhea. This is probably the reason that the fatality rate in our series was greater than that reported in other recent works (Table 3).

Indeed, it has been shown that the fatality rate decreased from 45-70 to 0-10% from the original reported of children with intractable diarrhea [1,15,16] to other more recent series [2,8]. However, the outcome may be greatly affected by the criteria of patients' enrollment.

We have shown that the risk for chronic diarrhea decreases with increasing age in the first year of life. However, selected cases of chronic diarrhea may be seen beyond 1 year of age, shown by our and other observations [7,10].

It is well known that persistent diarrhea is related to poor socioeconomic background, at least in developing countries.[17]This may explain the lack of association between low social background and chronic diarrhea.

The probability that diarrhea 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 diarrhea.

In most patients, the etiology of the diarrhea 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 diarrhea were reviewed, it was found that food intolerance and enteric infections were the most common etiologies of chronic diarrhea, whereas other rarer specific intestinal diseases were usually not detected [1-3,5,10,18,19]. However, in the population studied by us, infectious enteritis was the single most frequent cause of chronic diarrhea, being responsible for approximately half of the cases of chronic diarrhea.

Several children had MAI. However, the diagnosis of MAI, even if proved by a pathology [14], does not necessarily mean that intolerance to food is the basis cause of the diarrhea. The postulated mechanism of food intolerance involves an immune response to food antigens, triggered by an increased absorption of macromolecules through damaged intestinal epithelium [20,21]. 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 diarrhea [22-28] but their relative importance in inducing chronic diarrhea 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 [22,31,15,25]. 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 [26]. 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 [1-7]. The difference depends largely on the enrollment criteria and on the availability of diagnostic techniques.

Conclusion

Overall, our data show that an etiology diagnosis can be achieved in the majority of cases of chronic diarrhea. Because the number of children with chronic diarrhea 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 diarrheal diseases.

Finally, the definition of intractable diarrhea 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 diarrhea and chronic nutritional failure, for whom the common pharmacologic and dietetic treatment had been unsuccessful and who need long-term hospitalization.

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