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Etiology and Risk Factors of Severe and Protracted Diarrhea

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Summary: Severe and protracted diarrhea (SPD) is the most severe form of diarrhea in infancy and has also been defined as intractable diarrhea. Its etiology is poorly defined. We have retrospectively evaluated the etiology, the outcome, and the risk factors of 38 children, admitted with protracted diarrhea and need for total parenteral nutrition (TPN) from 1977 to 1993. 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). Etiology of SPD 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 SPD and a control population of children with diarrhea but without the need for TPN 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 a specific etiology can be identified in the majority of cases of SPD. The etiologic spectrum of SPD is broad, but an enteric infection is the most common cause of SPD. The severity of this condition is related, at least in part, to established risk factors. **Key Words:** Intractable diarrhea—Parenteral nutrition—Enteric infection—Food intolerance—Congenital enteropathy.

Severe and protracted diarrhea (SPD) has become a relatively uncommon disease in industrialized countries in recent years. Some authors 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 (4–6) and even older children (7). 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 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 a patient, diarrhea is always severe and usually requires total parenteral nutrition (TPN) (8,11).

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Thus we have defined our patients as affected by an SPD requiring TPN.

The improvement in the techniques of TPN has led to a longer survival of children with life-threatening diarrhea and, overall, to a better outcome. The availability of novel diagnostic tools over the past several years has expanded our knowledge of the various etiologies and pathophysiologies of this condition. A number of new diarrheal diseases have been identified, such as familial microvillous atrophy (12), autoimmune enteropathy (13), and chronic intestinal pseudoobstruction syndrome (14), which usually require TPN. Furthermore, new enteric pathogens, such as *Cryptosporidium* (15) or enteroaggregative *Escherichia coli* (16), have been discovered, which may be responsible for SPD.

We have reviewed the clinical records of children admitted in the years 1977–1993, with SPD and need for TPN, to see the pattern of etiology. We also examined the risk factors for SPD and the patients' outcome.

PATIENTS AND METHODS

The clinical records of patients admitted in the period 1977–1993 with diarrhea and need for TPN at the Department of Pediatrics of the University of Naples were reviewed. The Department has a special unit for children with diarrhea needing 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 TPN was based on the persistence of the diarrhea, its worsening with oral or enteral feeding, and the failure of pharmacologic therapy, but virtually in all cases, TPN 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 SPD.

Technical procedures for TPN depended on the time of admission. Intravenous administration of lipids and of oligoelements (W3000, Baxter, Trieste, Italy) was started in 1983 and in 1984, respectively. Broviac Silastic catheters were used since 1984 for delivering the intravenous nutrient.

The main diagnostic tools also changed over the course of the years. Peroral intestinal biopsy was initially performed in selected patients, but it gradually became a routine procedure even in patients in critical general condition. Intestinal endoscopy became available in 1981, intestinal manometry in 1984, and intestinal ultrastructure in 1985. 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 has been searched for since 1981, *Yersinia enterocolitica* and *Campylobacter jejuni* since 1982, *Clostridium difficile* and enterotoxigenic *E. coli* since 1984, *Cryptosporidium* and enteric viruses other than rotavirus since 1986, and enteroaggregative *E. coli* since 1992. Microbiological methods have been described or referred to in previous works (17,18). Searches for intestinal hormone peptides and for antiintestinal epithelium antibodies have been performed since 1986. 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 (19) or by the persistence of large fecal volumes while on TPN. Blood parameters were systematically monitored. Radiographs, ultrasounds, and computed tomography (CT) scans 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; and (d) those in whom the etiology remained undetermined.

The incidence of the following risk factors for SPD was considered: low birth weight, no breast milk feeding, early (before 1 and 3 months of age) onset of diarrhea, 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 SPD. The incidence of these features was compared with that of children with diarrhea, but without the need for TPN, 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 TPN and those not needing TPN was assessed by the χ^2 test.

RESULTS

Overall, 38 patients were admitted with SPD to receive TPN from 1977 to 1993. 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 Naples area. 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 SPD was inversely related to age in the first 12 months of life (Fig. 1). Onset of diarrhea after 12 months of age was recorded only in one of the 38 cases, who was seen with eosinophilic enteropathy at 14 months. Most patients had diarrhea for at least 1 month before being started on TPN: mean duration of diarrhea before TPN was 2 ± 2 months (median, 1 month; range, 15 days to 9 months). Mean duration of TPN 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 (Table 1). 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).

The second group included 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 (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 pseudoobstruction and one of neuronal intestinal dysplasia. The other five children had a primitive intestinal disease related to an immune/inflammatory disorder (Table 1). The fourth group included three children in whom the etiology of the diarrhea was not detected.

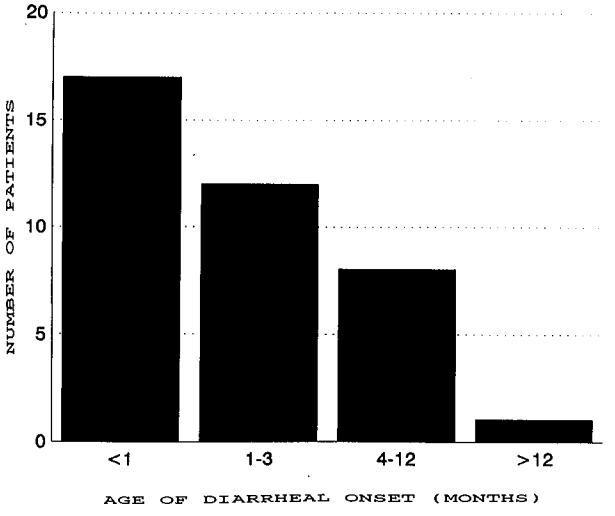

FIG. 1. Age of onset of severe protracted diarrhea. A clear inverse relationship between the number of patients and increasing age is observed.

Outcome

Twenty-one of the 38 children (55%) fully recovered (Table 1). Two children are currently receiving TPN. Two children are presently maintained on restricted diets. One is taking chronic antiinflammatory 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 TPN was significantly more protracted than in children with other diarrheal etiology (Fig. 2), and the fatality rate was increased (Table 1).

TABLE 1. *Etiologic diagnoses and outcome in children with severe and protracted diarrhea*

Etiology	Total cases	Full remission	Dead	Presently on treatment
Enteric infection[a]	18	13	4	1 (TPN)
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 TPN)
Neurodysplasia	1	—	1	
Unknown	3	1	2	
Total	38	21	12	5

TPN, total parenteral nutrition.
[a] Responsible microorganisms were *Salmonella* (eight cases), coagulase-positive *Staphylococcus* (three), rotavirus (five), adenovirus (one), and *Cryptosporidium* (one).

Incidence of Risk Factors in Children with Severe Protracted Diarrhea and in Those with Diarrhea without the Need for TPN

The comparative evaluation of risk factors between the 38 children with SPD and 76 children (two for each case of SPD) with diarrhea but without the need for TPN, is reported in Table 2. 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 SPD than in those with diarrhea without the need for TPN. 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.

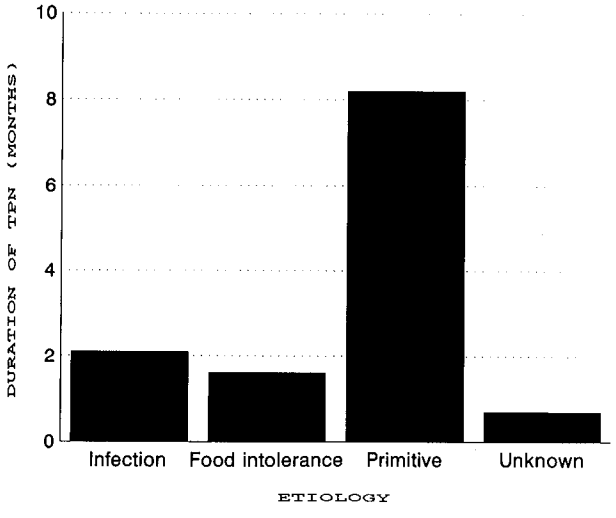

FIG. 2. Duration of total parenteral nutrition (TPN) according to the etiology. Patients were grouped by etiological diagnosis. Primitive are intestinal diseases other than enteric infections or food intolerance. Duration of TPN in children with primitive intestinal disease was significantly longer than that of children belonging to each of the other groups ($p < 0.01$).

DISCUSSION

Severe protracted diarrhea of infancy is a syndrome rather than a disease. We have defined the children with SPD as patients with an extremely severe diarrheal disease, which threatened their survival and required long-term parenteral nutrition. Some authors refer to those children as having intractable diarrhea (1,2,4–8). Each of our patients had unsuccessfully received several therapeutic or dietetic trials (including continuous enteral nutrition) before being started on TPN, 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

TABLE 2. *Comparative evaluation of risk factors in 38 children with severe and protracted diarrhea and in 76 controls with diarrhea but without the need for TPN*

	Cases		Controls		
Risk factor	*n*	%	*n*	%	*p*
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 mo)	17	45	22	29	NS
Early onset (<3 mo)	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

TPN, total parenteral nutrition; NS, not significant.

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 reports of children with intractable diarrhea (1,21,22) 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 SPD decreases with increasing age in the first year of life. However, selected cases of SPD may be seen beyond 1 year of age, as 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 (23). This was not the case in our population. It should be noted that health care in public hospitals is totally free in Italy, and this may explain the lack of association between low social background and SPD.

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 SPD.

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 SPD were reviewed, it was found that food intolerance and enteric infections were the most common etiologies of SPD, whereas other rarer specific intestinal diseases were usually not detected (1–3,5,10,11,24). However, in the population studied by us, infectious enteritis was the single most frequent cause of SPD, being responsible for approximately half of the cases of SPD. The etiology of infectious diarrhea changed with time, in that there was a clear-cut shift from bacterial to viral agents. The recently reported immunologic treatment of viral diarrhea may be effective in the prevention of SPD due to rotavirus (25).

Several children had MAI. However, the diagnosis of MAI, even if proved by a pathologic challenge, according to the diagnostic protocol (20), does not necessarily mean that intolerance to food is the basic 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 (26,27). 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 diseases, 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 SPD (12,13,28–32), but their relative importance in inducing SPD was unknown. An increasing number of observations suggests that the frequency of both familial enteropathy and disorders of intestinal motility is greater than previously recognized (12,14,21,29). Children in this group had the longest duration of TPN and the worst outcome. It is likely that many cases 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 TPN (30). A fourth group of children included three children without an etiologic diagnosis. The prevalence of cases of SPD 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.

Overall, our data show that an etiologic diagnosis can be achieved in the majority of cases of SPD. Because the number of children with SPD 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 TPN. This condition could be redefined as diarrhea with the need for TPN, rather than intractable diarrhea.

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