

Long-Term Parenteral Nutrition in Pediatric Autoimmune Enteropathies

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ABSTRACT

Severe and protracted or persistent diarrhea (SPD) is the most severe form of diarrhea in infancy and has also been defined as intractable diarrhea when it leads to dependence on total parenteral nutrition (TPN). One of the rare causes of SPD is represented by autoimmune enteropathy that is characterized by life-threatening diarrhea mainly occurring within the first years of life, persistent villous atrophy in consecutive biopsies, resistance to bowel rest, and evidence of antigut autoantibodies. We evaluated 10 patients (seven boys, mean age at diagnosis 18 months; range: 0 to 160 months) fulfilling criteria of autoimmune enteropathy to assess dependence on TPN. TPN was first required in all patients to avoid dehydration and electrolytic imbalance. All patients were dependent on immunosuppressive therapy (steroid, azothioprine, cyclosporine, tacrolimus). Three patients died of sepsis: two during TPN while in the hospital, and one at home after he was weaned off TPN. Five patients are weaned off TPN after a mean period of 18 months; they are actually on oral alimentation with a cow milk-free diet after a period of enteral nutrition with elemental formula. One underwent total colectomy and bone marrow transplantation and one developed an IPEX syndrome. One patient is still dependent on TPN for 24 months. She is on home parenteral nutrition. Patients with diagnosis of IPEX syndrome require parenteral support with three or four infusion per week. TPN represents a fixed step in the management of autoimmune enteropathy, but it may be considered as an interim treatment while waiting for intestinal adaptation, at least in some selected case of autoimmune enteropathy. Bone marrow transplantation should be considered and reserved for those patients with severe complications due to home parenteral nutrition, or in those that are really dependent on parenteral nutrition.

SEVERE AND PROTRACTED or persistent diarrhea (SPD) is the most severe form of diarrhea in infancy and has also been defined as intractable diarrhea when it leads to dependence on total parenteral nutrition (TPN). Potential causes of protracted diarrhea in infants and young children are postinfectious or food-sensitive enteropathy, misdiagnosis of primary immunodeficiency, inflammatory enteropathy or colitis dysmotility syndromes, metabolic diseases, and true intractable diarrhea.^{1,2} Among this last group we found, beside primary epithelial defects and syndromic diarrhea, four types of immune-mediated/autoimmune enteropathies: with known antigens, mutations of known immunoregulatory genes (IPEX and APCED syndromes), failure of lymphocyte negative selection, and unclassified autoimmune enteropathies.³ The Working Group of the Italian Society of Pediatric Gastroenterology and Hepatology estimated SPD incidence rate in Italy to be 0.64 to 0.92×10^{-5} infants per year; autoimmune

enteropathy represented the most common cause among the rarest.⁴

Autoimmune enteropathy (AIE) is a life-threatening, chronic disease of the small bowel and sometimes of colonic mucosa, characterized by chronic secretory diarrhea, villous atrophy, and associated autoantibodies. While diarrhea is not responding to bowel rest, TPN is required for rehydration and nutritional support. Furthermore, treatment requires long-term immunosuppression. However, currently available therapy (including steroids and cyclosporine) has

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resulted in remission in only a subset of patients.^{5,6} In this article we considered management of intractable diarrhea in children affected by AIE. Their diarrhea is characteristically watery, abundant, rich in sodium, resistant to bowel rest, and rapidly becoming life-threatening, requiring long-term TPN. Bone marrow transplantation (BMT) represents a new therapeutic option for patients who do not respond to immunosuppression.⁷ The aim of the study was to retrospectively evaluate dependency on TPN in our population of children affected by AIE.

METHODS

The main diagnostic criteria for diagnosis of AIE is severe life-threatening diarrhea that mainly occurs within the first years of life and requires TPN with persistent villous atrophy in consecutive biopsies, resistance to bowel rest, and evidence of gut autoantibodies. All children who met criteria for the diagnosis of AIE were included in the study. All patients were submitted to biochemical evaluation to exclude other causes of persistent diarrhea: RBC, ESR, CRP, total IGE, specific IgE, AST, ALT, amylases, lipases, antitransglutaminase, and antiendomysium antibodies, antigut antibodies, sweat test, fecal leukocytes, eosinophils, parasites, bacteria, and viruses. All patients then underwent at least one endoscopic examination with multiple biopsies to evaluate the upper and lower gastrointestinal tracts.

Exclusion criteria were the presence of other causes for chronic diarrhea, such as metabolic, infectious, postinfectious, allergic gastrointestinal, or systemic diseases. The therapeutic approach was standardized for all patients: TPN and immunosuppressive therapy.

RESULTS

Since 1990, we evaluated 56 patients with protracted diarrhea including 35 boys and an overall mean age at diagnosis of 12 months (range 0 to 160 months). The previous diagnosis had been: severe food allergy in 29 patients, metabolic diseases in five, primary epithelial defects in four, immunodeficiency in five, protein-wasting enteropathy in three (5%), and finally in 10 patients (seven boys, mean age at diagnosis 18 months; range: 0 to 160 months), autoimmune enteropathies, including two boys with IPEX syndrome. Antigut autoantibodies were present in 2 of 10 patients. Histological examination of upper endoscopy specimens showed villous atrophy in all cases, with activated T cells entering into the lamina propria. TPN was initially required in all patients to avoid dehydration and electrolyte imbalance. All patients were dependent on immunosuppressive therapy (steroid, azathioprine, cyclosporine, or tacrolimus). In particular all patients required steroid therapy and azathioprine; three also needed cyclosporine; and two, tacrolimus. Three patients died due to sepsis—two during TPN while in hospital, and one at home after he was weaned off TPN. Five patients were weaned off TPN at a mean period of 18 months. They are now on oral alimentation with a cow milk-free diet after a period of enteral nutrition with elemental formula. Among these patients, one underwent total colectomy and subsequently BMT, and one developed a clinical picture compatible with IPEX syndrome. All five patients are on immunosuppressive

therapy. One patient is still dependent on TPN for the past 24 months. She is on home parenteral nutrition (HPN). Patients with the diagnosis of IPEX syndrome require parenteral support with three or four infusions per week.

DISCUSSION

Long-term parenteral nutrition is effective treatment of intestinal failure due to AIE but, in these patients, we generally do not observe total dependency on TPN; therefore, there are no real indications for small bowel transplantation. BMT may represent an important therapeutic alternative to TPN. So far the choice of BMT is dependent on personal clinical condition and is to be considered in each patient on the basis of clinical picture, response to therapy, type of therapy needed, and eventual dependence/complications related to prolonged parenteral nutrition. Previous experience seems to not indicate BMT in IPEX patients because of the high rate of fatal complications over a short time interval.⁸ To avoid complications of TPN, intestinal rehabilitation must also be considered before BMT. If well-tolerated enteral nutrition represents the best option for patients with AIE, at least to reduce dependency on TPN.

TPN represents an important step in the management of AIE, but it may be considered as an interim treatment while waiting for intestinal adaptation, at least in some selected cases of AIE. BMT should be reserved for patients with severe complications due to HPN or those really dependent on PN. PN and BMT should be considered as complementary treatments in the management of AIE in infancy, but decision making must be referred to specialized centers with advanced diagnostic and therapeutic facilities.

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