Acta Pædiatr 86: 1077–81. 1997

Immune deficiencies in chronic intestinal pseudo-obstruction

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Forchielli ML, Young MC, Flores AF, Richardson D, Lo CW. Immune deficiencies in chronic intestinal pseudo-obstruction. Acta Pædiatr 1997; 86: 1077–81. Stockholm. ISSN 0803–5253

Aim: Chronic intestinal pseudo-obstruction has been associated with urinary disorders, myopathy, and ophthalmoplegia in adults and cholelithiasis in children. We observed a high percentage of total-parenteral-nutrition-dependent patients with pseudo-obstruction and recurrent infections requiring gammaglobulin infusions. *Methods*: All records for 23 children with chronic intestinal pseudo-obstruction (10 females and 13 males, mean age 9.8 y ± 4.9 y, range 4–24 y) referred for a nutritional evaluation from 1992 to 1995 were reviewed. Chronic intestinal pseudo-obstruction was diagnosed by clinical, radiographic findings and antroduodenal manometry. Intestinal full-thickness biopsies were performed in seven children. *Results*: Hypogammaglobulinemia was diagnosed in 18 patients (78%): 16 patients had various immunoglobulin deficiencies and 2 had selective antibody deficiency. Intravenous gammaglobulin was administered in 14 patients. Other medical conditions affecting the children are summarized as follows: autonomic dysfunction in 10 patients (43%), recurrent hypoglycemia in 9 (39%), asthma in 9 (39%), cholecystitis in 7 (30%), low serum carnitine level in 6 (26%), urinary dysfunction in 6 (26%), pancreatitis in 5 (22%), behavioral problems in 5 (22%), myopathy in 2 (9%), idiopathic thrombocytopenia in 2 (8%), velopharyngeal insufficiency in 1 (4%), oculocutaneous albinism in 1 (4%), Pierre-Robin syndrome in 1 (4%), and protein C deficiency in 1 (4%). Munchausen syndrome was suspected in two patients. *Conclusions*: Chronic intestinal pseudo-obstruction appears to be associated with immune deficiencies. It is unclear if the immune deficiencies, intestinal pseudo-obstruction, and the other medical conditions have a common underlying etiology. Repeated infections may be due to impaired immune function in children with chronic intestinal pseudo-obstruction. We recommend screening for immune deficiencies in children with chronic intestinal pseudo-obstruction. □ *Children, gut, immunity, motility disorders, parenteral nutrition*

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Chronic intestinal pseudo-obstruction (CIP) is characterized by neuropathic or myopathic degeneration of part or all of the gastrointestinal tract (1–3). Recurrent abdominal pain, distention and either vomiting or diarrhea in the absence of mechanical obstruction are common events in CIP. Malabsorption due to bacterial overgrowth is a common occurrence and children with CIP may develop failure to thrive (FTT). Total parenteral nutrition (TPN) is often required by children with CIP who may become dependent on it for growth. CIP may also be associated with urinary disorders (4) as well as myopathy (5, 6), ophthalmoplegia (7), and ovarian tube (8) dysmotility in adults and cholelithiasis (9, 10) in children. Children with CIP often require a multidisciplinary approach due to involvement of many organ systems. In particular, it appears that many children with CIP have recurrent infections associated with hypogammaglobulinemia. This paper will review the associated medical disorders seen in our patients with CIP in an attempt to identify an underlying systemic etiology.

Patients and methods

All patients with CIP referred to the Nutrition Support Service (NSS) of Children's Hospital, Boston from 1992 to 1995 for a nutritional evaluation were included in the study, which was approved by the hospital Committee on Clinical Investigation. In total, 23 children were identified and their medical records were collected and reviewed. The patients were followed from the entry into the study to the present. Children with CIP had clinical and radiographic findings of delayed gastric emptying, dilated loops of bowel with air–fluid levels, and abnormal barium transit in absence of mechanical obstruction on several occasions. Overall, gastrointestinal distension, either intermittent or persistent, became chronic and tended to worsen with time, especially after fundoplication. Neither multiple therapeutic trials nor various surgical procedures appeared to improve the gastrointestinal dysfunction in these patients.

All patients had antroduodenal manometries performed at least once by one of the authors (AF). Recordings were carried out for an average time of 6 h in fasting, postprandial periods, and with pharmacological testing with cisapride. Neuropathic abnormalities mainly consisted in the absence or reduced occurrence of migrating motor complexes, long or very short intervals between intestinal phase 3, non-propagating, slow-propagating, or retrograde

phase 3s, tonic contractions during clusters of phasic contractions, monotonous pattern of variable amplitude contractions unaffected by meals, severe post-prandial duodenal hypomotility, and eventually, post-prandial phase 3 persistence. Very low amplitude or absent contractions were considered indicative of myopathy. Duodenal contractions improved after pharmacological testing. In 7 patients full thickness biopsies of the gut were *performed and histologic abnormalities of gastrointestinal nerve and muscle were recorded.* Any children with conditions leading to malabsorption such as celiac disease or pancreatic insufficiency were excluded, as well as children with gastrointestinal dysmotility with a defined primary cause.

Onset of symptoms, age at time of diagnosis, type of diagnostic tests as well as the presence of other medical problems were considered. Many concomitant medical problems affected these children, requiring multidisciplinary involvement. Abnormalities in quantitative immunoglobulin levels (by nephelometry or radial immunodiffusion), IgG subclasses (by radial immunodiffusion and ELISA), and specific antibody titers such as tetanus titer (by hemagglutination) and PRP (polyribosylphosphate by radial immunodiffusion) titer were measured for evidence of immune deficiencies. A specific antibody titer was considered valid only after vaccination or proven infection. At the time of immune function determination, no patient was receiving immunoglobulin infusions. Results are presented as mean ± SD (standard deviation) with range. An attempt was made to reconstruct the sequence of events in each patient's clinical history.

Results

Medical records of the 23 children were investigated. All patients (10F and 13M, mean age 9.8 ± 4.9 y, range 4–24 y) carried the diagnosis of CIP. From a nutritional standpoint, 10 patients met criteria for malnutrition and all the 23 patients recovered from an initial weight loss. All patients required tube enteral feedings at some points, and 17 required TPN. All patients on TPN also received intravenous lipid infusions during home-TPN. These children were maintained between the 50th and 95th percentile weight for age during the course of TPN. There were no fatalities nor developments of TPN-related cholestasis in any patient.

The diagnosis of CIP was made at a mean age of 4.2 y ± 4 y (range 4 months–18 y), while the mean age at onset of symptoms was 1.1 y ± 2.8 y (range birth–11 y). In two-thirds of the patients, the gastrointestinal symptoms began in the neonatal period. Before being diagnosed, CIP was mostly misidentified with gastroesophageal reflux, malnutrition, or intractable diarrhea. *Twenty-one patients were considered to have a visceral neural-type disorder, based on uncoordinated contractions with generally normal amplitude on antroduodenal manometry and/or histologic abnormalities in number and in pattern of ganglion nodes, glial cells, or argyrophilic neurons, when biopsies were available.* Another had evidence of a visceral myopathy based on a muscle biopsy showing a relative disproportion in fiber dimension with possible focal fibrosis. In the remaining child the gastrointestinal defect was not defined and was classified as intermediate between a neural and muscular disorder. Gastrointestinal hormones were investigated in three children: in two gastrin, polypeptide P, and substance P were increased.

Immune deficiencies were diagnosed in 18 (78%) patients. Sixteen had various immunoglobulin (IgG) deficiencies and two had selective antibody deficiency. In these patients, IgG levels ranged from −2.3 to −2.9 SD of the normal levels for age. Initial IgA and IgM levels were usually within the normal range with a few minor exceptions. Subsequent IgA and IgM levels were all within the normal range, and substantially increased during gammaglobulin infusions. Four of 8 patients had decreased numbers of natural killer cells. In 10 patients immunologic abnormalities were detected before CIP was diagnosed, while in the remaining eight the diagnosis of CIP was made first. Six of the seven patients who underwent full thickness biopsies were discovered to be immune deficient (in two before CIP was diagnosed, and in four afterwards). At the time of immune deficiencies detection 4 patients were on enteral feedings, 9 on TPN, and 5 were receiving neither. In these five patients total protein values were slightly decreased with the lowest at 5 g/dl (normal range 6.5–8). Albumin values and total lymphocyte count were in the normal range in all patients except one, whose albumin value was 3.4 g/dl (normal range 3.8–4.5) during TPN infusion.

Nutritional parameters such as weight for height, height for age and mid-arm circumference were normal in all 18 immune-deficient patients, whereas weight for age was lower than the 5th percentile in 3 patients (in 2 before beginning TPN). These patients suffered multiple infectious episodes consisting of upper respiratory infection, otitis media, urinary tract infection, and central venous line-related sepsis. To reduce infections, gammaglobulin was administered in regular infusions (every 2–3 weeks, for periods ranging from 1 to 10 y) to 14 of the 18 patients. During gammaglobulin infusions, IgG and IgG subclasses were normal, to decrease again during the gammaglobulin suspension trials. The laboratory abnormalities clinically coincided with increased infectious episodes. A preliminary report on seven of these patients documented a 33.5–55.4% ($p < 0.01$) decrease in CVL-related infections during gammaglobulin therapy (11). Table 1 summarizes the immunological abnormalities.

In two patients, Munchausen syndrome was suspected even though for one an intestinal full thickness biopsy confirmed the diagnosis of CIP. Both patients had immune deficiencies.

Concomitant abnormalities in these children are summarized in Table 2.

Discussion

Our study suggests that immune deficiencies may often be present in CIP although the causal relationship is unclear. No immune defects were reported in the literature with the exception of autoantibodies against neuronal tissue in myenteric plexus in carcinoma-associated pseudo-obstruction (12, 13).

Immune deficiencies may be primary or secondary. In our group, the immunologic abnormalities appear mainly humoral, although in four of the eight patients screened, natural killer cells were decreased. In two children the immune deficiencies were consistent with an impaired functional response to antigen, based on the low specific antibody production after immunization. In our group, the immune defects may be secondary to malnutrition resulting in decreased antibody production and/or to recurrent infections with increased antibody consumption and turnover. Prolonged starvation may be either the result or the cause of abnormal motility. Five patients were diagnosed with immune deficiencies before becoming TPN dependent and were mildly malnourished. On the contrary, TPN dependency and CIP itself may be two factors involved in the immune deficiencies detected in the nine patients on TPN at time of diagnosis with normal weight for age, normal albumin and total protein. Although TPN may reverse immune deficiencies secondary to malnutrition, it may lead to gastrointestinal mucosal atrophy (14) and induce bacterial translocation (15). Long-term TPN could also be responsible for specific nutritional deficiencies with indirect effects on the gut. Lipid infusions may also alter immune function. Finally, repeated central venous line related sepsis might be an outcome of an already impaired immune response as well as a cause of antibody consumption. Nevertheless, in CIP bacteria overgrowth (16) with mucosal damage and lymphangiectasia occurring after surgical procedures, fibrosis of the bowel wall, and severe bowel dilatation may lead to protein losing enteropathy (17) with both immunoglobulin and T-cell losses (18).

Many of these patients were affected by other medical conditions, so it was decided to further investigate whether these disorders may be linked to CIP and immune deficiencies. It is known that gastrointestinal dysmotility can result from derangement of the central nervous system, the immune system, the endocrine function, and nerve and muscle located in the gut (19). In our study eight children with CIP and immune deficiencies experienced autonomic dysfunction, based on altered sympathetic skin response and cardiovascular reflex tests. Autonomic dysfunction may cause neuropathic gastrointestinal abnormalities. At the same time, the sympathetic nervous system has been shown to inhibit natural killer-cell activity, and sequestrate lymphocytes (20). In addition, mucosal immune response (21, 22) and colonic phasic contraction (23) can be regulated by neuropeptides. The neuropeptides [i.e. nitric oxide, substance P, enkephalin and vasoactive intestinal

Table 1. List of patients with immune alteration at first detection.

Patient No.	Age	IgG (SD)	IgG1 (SD)	IgG2 (SD)	IgG3 (SD)	PRP (normal = >1200 ng/ml)	Tet Ab normal > 0.5 U/ml)	T Subsets (SD)	IV IgG
1	14 months	normal	low§	low§	low§	43; 40; 370	0.36, 0.4	NA	Yes
2	6 y	normal	normal	normal	−2.2	390	normal	NA	Yes
3	4 y	−2.4	NA	NA	NA	NA	normal	NA	No
4	13 months	−2.3	−3	normal	normal	4.5	normal	normal	Yes
5	3 y	normal	normal	normal	−2.7	Normal	normal	−3.6	Yes
6	13 months	−2.4	NA	NA	NA	NA	normal	normal	Yes
7	19 y	normal	normal	low§	normal	90	normal	NA	Yes
8	5 months	−2.6	NA	NA	NA	62	0.2	NA	Yes
9	3 y	−2.8	−2.3	−2.4	normal	300	normal	NA	Yes
10	3 y	−2.5	normal	−2.2	normal	NA	low§	−2.8	Yes
11	7 y	normal	normal	normal	−2.2	Normal	normal	−3.2	Yes
12	1 y	−2.5	−2.1	−2.1	normal	NA	normal	NA	Yes
13	4 months	−2.9	NA	NA	NA	NA	normal	normal	Yes
14	3 months	−2.9	NA	NA	NA	NA	normal	NA	Yes
15	4 months	−2.8	NA	NA	NA	NA	normal	normal	Yes
16	3 y	−2.5	−2.2	normal	normal	NA	normal	−2.4	No
17	7 y	normal	−2.7	normal	normal	NA	normal	NA	No
18	6 y	−2.3	NA	NA	NA	Normal	normal	NA	No
Abnl (%)		12/18 = 67	6/11 = 54	5/11 = 45	4/11 = 36	6/9 = 67	3/18 = 17	4/8 = 50	14/18 = 78

SD: standard deviation from the age specific normal mean.
§: described as being below the normal range. Exact value was not available.
NA: not available.
Tet Ab: tetanus antibody.
PRP: polyribosophosphate reaction.
Abnl: total of abnormal values.
IV IgG: intravenous gammaglobulin infusions.

polypeptide (VIP)] are influenced by external agents such as infection, type of food, radiation, and vascular insufficiency (24, 25). Unfortunately, our data on altered gut hormones were limited to two patients, but both had immune deficiencies and CIP.

All patients with autonomic dysfunction also suffered from behavioral problems, consisting of depression, attention deficit disorder and anxiety, which like stress may affect the immune response (19).

CIP can also be a result of muscle degeneration (5–7), which sometimes is secondary to mitochondria abnormalities. No studies have shown an underlying autoimmune process able to explain the presence of CIP and immune function. The only patient with mitochondrial dysfunction however, had both CIP and immune dysfunction.

Infections may be more frequent because of immune deficiencies. The hypothesis of a viral infection responsible for CIP has been raised in several reports (26–28). In this study, one patient developed gastrointestinal obstruction after varicella. It was not possible, however, to establish a causal link between the infection and CIP onset, and besides, the patient did not have any measurable immune deficiencies.

CIP is frequently misdiagnosed, often resulting in multiple surgical procedures and medical therapies. Both surgical procedures and medical interventions in turn may obscure the true diagnosis. It is unclear how neural, muscular, metabolic, hormonal degeneration, failure of development of the gastrointestinal system or even psychological factors may be related to CIP and immune deficiencies. The similarities in the clinical histories of many of our patients are suggestive of a common underlying process. Given the high occurrence of recurrent infections and immune deficiencies in our patients with CIP, evaluation of immune function should be included in the work up of these patients. An ongoing study is trying to characterize the type of immune deficiencies present in these children to better define the role of gammaglobulin infusion.

Table 2. List of associated conditions in children with CIP.

Patients	Mitochondrial dysfunction	Total parenteral nutrition	Gastroesophageal reflux	Fundoplication	Behavioral problems	Carnitine deficiency	Urinary dysfunction	Immune dysfunction	Autonomic dysfunction	Cholecystitis	Munchausen syndrome	Asthma	Dumping syndrome	Hypotonia	Pierre-Robin syndrome	Protein C deficiency	Vasculitis	Limb pain	Idiopathic thrombocytopenia	Velopharyngeal insufficiency
1	x		x		x			x												
2		x	x			x	x	x												
3		x	x		x			x	x	x			x							
4		x	x	x		x			x	x		x	x					x	x	
5		x	x			x		x	x											
6		x						x		x	x	x								
7					x															
8			x					x												
9		x	x	x		x		x	x				x			x				
10		x	x	x2			x	x		x		x	x						x	
11		x	x			x	x	x	x	x			x				x			
12			x					x	x			x	x							
13			x					x	x											
14		x	x	x2	x		x	x	x			x	x							x
15		x	x	x				x	x			x	x							
16		x	x				x		x			x	x							
17			x							x				x						
18		x					x	x												
19		x	x					x												
20		x	x																	
21		x	x	x2				x			x	x								
22		x	x		x	x		x		x					x					
23		x	x	x				x				x								
Total	1	17	20	7	5	6	6	18	10	7	2	9	9	1	1	1	1	1	2	1
%	4	74	87	30	22	26	26	78	43	30	8	39	39	4	4	4	4	4	8	4

x2: fundoplication done twice.

Acknowledgements.—Acknowledgements to Allan Walker and his brilliant suggestion and to Eugenio Anessi-Pessina and his patience.

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Received Nov. 15, 1996. Accepted in revised form June 12, 1997