Defining DIOS and Constipation in Cystic Fibrosis With a Multicentre Study on the Incidence, Characteristics, and Treatment of DIOS

*Roderick H. Houwen, *Hubert P. van der Doef, †Isabelle Sermet, ‡Anne Munck, §Bruno Hauser, ||Jaroslaw Walkowiak, ¶Eddy Robberecht, #Carla Colombo, **Maarten Sinaasappel, and ††Michael Wilschanski, on behalf of the ESPGHAN Cystic Fibrosis Working Group

ABSTRACT

Objectives: Various definitions for distal intestinal obstruction syndrome (DIOS), meconium ileus equivalent, and constipation in patients with cystic fibrosis (CF) are used. However, an unequivocal definition for DIOS, meconium ileus equivalent, and constipation is preferred. The aims of this study were, therefore, to seek consensus on the definitions for DIOS and constipation in patients with CF and to determine the incidence, characteristics, and treatment of DIOS in a cohort of paediatric patients with CF.

Methods: During the 2005 European Society for Paediatric Gastroenterology, Hepatology, and Nutrition meeting in Porto a group of paediatric gastroenterologists discussed the definition of DIOS and constipation in CF. Subsequently, all patients younger than or equal to 18 years with complete DIOS according to the definition agreed upon and diagnosed during the years 2001 to 2005 in 8 CF centres were studied.

Results: Distal intestinal obstruction syndrome was defined as an acute complete or incomplete faecal obstruction in the ileocaecum, whereas constipation was defined as gradual faecal impaction of the total colon. Fifty-one episodes of DIOS in 39 patients were recorded, giving an overall incidence of 6.2 (95% confidence interval, 4.4–7.9) episodes per 1000 patient-years. Of the 39 patients with DIOS, 20% experienced a relapse, 92% were pancreatic insufficient, 44% had a history of meconium ileus at birth, and 82% had a severe genotype. Conservative treatment was effective in 49 of 51 DIOS episodes (96%).

Conclusions: The European Society for Paediatric Gastroenterology, Hepatology, and Nutrition CF Working Group definitions of DIOS and constipation in CF are specific and make a clear distinction between these 2 entities. The incidence of DIOS in the present study was considerably higher than reported previously.

Key Words: constipation, cystic fibrosis, distal intestinal obstruction syndrome, incidence, meconium ileus equivalent

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In patients with cystic fibrosis (CF), a syndrome of postneonatal distal small bowel obstruction caused by meconium-like stool plugs was first described in 1945. At that time this condition was named meconium ileus equivalent (MIE) (1). Later the term ''distal intestinal obstruction syndrome'' (DIOS) was introduced, referring to a range of clinical conditions due to partial or complete bowel obstruction (2). Subsequently, DIOS and MIE were sometimes used as interchangeable terms (3), but more commonly DIOS also encompassed a variety of other intestinal symptoms, including palpable caecal masses, abdominal pain, intussusception, and volvulus (4,5). The definition of DIOS sometimes also included constipation, which is a common condition in CF that also causes abdominal pain and distension, and responds to conservative medical treatment (6). Because of these varied definitions, comparing studies on incidence and other characteristics of these conditions is difficult.

Consequently, consensus on the definition for DIOS, MIE, and constipation in CF is essential. The aims of this report were, therefore, to seek consensus on the definitions for these conditions in patients with CF. Subsequently, the incidence, characteristics, and treatment results of DIOS in a paediatric CF cohort from 8 centres was investigated.

METHODS

European Society for Pediatric Gastroenterology, Hepatology and Nutrition CF Working Group

A group of paediatric gastroenterologists with an interest in gastrointestinal manifestations of CF, convened at the 38th annual meeting of the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) in Porto in June 2005 to seek consensus on the definition of DIOS and constipation in patients with CF.

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From the *Wilhelmina Children's Hospital, University Medical Center, Utrecht, the Netherlands, the †Hopital Necker-Enfants-Malades, the ‡Hopital Robert Debre, Paris, France, the §Universitair Ziekenhuis Brussel, Brussels, Belgium, the ||Poznan University of Medical Sciences, Poznan, Poland, the ¶University Hospital of Ghent, Ghent, Belgium, the #Fondazione IRCCS Policlinico, Mangiagalli, Regina Elena, University of Milan, Italy, the **Erasmus MC, University Medical Center, Rotterdam, the Netherlands, and the ††Hadassah University Hospitals, Hebrew University Jerusalem, Israel.

Address correspondence and reprint requests to H.P.J. van der Doef, Department of Pediatric Gastroenterology [KE.01.143.0], University Medical Center, Postbox 85090, 3508 AB Utrecht, The Netherlands (e-mail: H.P.J.vanderdoef@umcutrecht.nl).

Drs Houwen and van der Doef contributed equally to the work.

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The ESPGHAN CF Working Group suggested that the term MIE is redundant because both MIE and DIOS, as defined in Porto, refer to the same condition. The ESPGHAN CF Working Group also made a distinction between complete and incomplete DIOS. Complete DIOS was defined as the combination of (1) complete intestinal obstruction, as evidenced by vomiting of bilious material and/or fluid levels in small intestine on an abdominal radiography with (2) a faecal mass in ileo-caecum and (3) abdominal pain or distension or both. Incomplete or impending DIOS was defined as (1) a short history (days) of abdominal pain or distension or both and (2) a faecal mass in ileocaecum, but without signs of complete obstruction. Constipation was defined as (1) abdominal pain or distension or both or (2a) a decline in the frequency of bowel movements in the last few weeks to months or (2b) increased consistency of stools in the last few weeks or months or both, whereas (3) the symptoms are relieved by the use of laxatives. If a plain abdominal radiography is performed, the faecal content of the total colon should be increased. These 2 sets of definitions also make a distinction between the fairly acute onset of symptoms as seen in complete and impending DIOS, and the more gradual onset of symptoms as usually seen in constipation (summarized in Tables 1 and 2).

Patients

At the 38th annual meeting of the ESPGHAN, questionnaires to determine frequency, risk factors, and treatment of complete DIOS were given to members of the ESPGHAN CF Working Group. Information was obtained from 8 medical centres: Wilhelmina Children's Hospital, University Medical Center Utrecht, Utrecht, The Netherlands; Hopital Necker-Enfants-Malades, Paris, France; Hopital Robert Debre, Paris, France; Universitair Ziekenhuis Brussel, Brussels, Belgium; University Hospital of Ghent, Ghent, Belgium; Poznan University of Medical Sciences, Poznan, Poland; Fondazione IRCCS Policlinico, Mangiagalli, Regina Elena, University of Milan, Milan, Italy, and the Hadassah University Hospitals, Hebrew University Jerusalem, Israel/Sheba Medical Center, Tel Aviv-University, Tel Hashomer, Israel.

The following parameters were recorded: number and characteristics (pancreatic status, meconium ileus at birth) of patients with CF with a DIOS episode that was diagnosed at an age younger than or equal to 18 years between 2001 and 2005, the treatment instituted, as well as the mean number of patients with CF younger than or equal to 18 years enrolled in each of the participating medical centres between 2001 and 2005.

Genetic Classification

Cystic fibrosis transmembrane conductance regulator (CFTR) mutations were classified into 5 classes (class I–class V) on the basis of primary mechanism of defective CFTR function. Cystic fibrosis transmembrane conductance regulator mutations class I, II, and III were considered severe mutations and CFTR mutations class IV and V were considered mild mutations (7–10). With this classification, the patients were classified into 3 groups according to the probable effect of their mutations on CFTR function, regardless of clinical severity. The first group consisted of patients with a severe genotype, defined as 2 severe CFTR mutations. Within this group, DF508 homozygous patients were also analysed separately. The second group consisted of patients with a mild genotype, defined as at least 1 mild mutation. The third group consisted of patients with an undetermined genotype, defined as 1 undetermined mutation and 1 severe mutation.

TABLE 1. ESPGHAN CF Working Group definition for DIOS in cystic fibrosis

No. 1	Complete intestinal obstruction as evidenced by vomiting of bilious material and/or fluid levels in small intestine on an abdominal radiography
No. 2	Faecal mass in ileo-caecum
No. 3	Abdominal pain and/or distension
Complete DIOS: no. 1, no. 2, and no. 3	
Incomplete/Impending DIOS: no. 2 and no. 3, without no. 1	

CF = cystic fibrosis; DIOS = distal intestinal obstruction syndrome; ESPGHAN = European Society for Paediatric Gastroenterology, Hepatology, and Nutrition.

TABLE 2. ESPGHAN CF Working Group definition for constipation in cystic fibrosis

No. 1	Abdominal pain and/or distension
No. 2a	Reduced frequency of bowel movements in the last few weeks or months
No. 2b	Increased consistency of stools in the last few weeks or months
No. 3	Symptoms 1 and 2 are relieved by the use of laxatives
Constipation: no. 1 or no. 2a or no. 2b and no. 3	

CF = cystic fibrosis; ESPGHAN = European Society for Paediatric Gastroenterology, Hepatology, and Nutrition.

Clinical Manifestations

Pancreatic insufficiency was defined as abnormal faecal fat excretion in stool samples collected during a 72-hour period (11). When these results were not available patients with faecal elastase-1 concentrations lower than 100 μg/g of stool were considered to have pancreatic insufficiency (12,13). Also, a history of meconium ileus at birth was recorded.

Diagnosis of CF

The diagnosis of CF had been established on the basis of characteristic clinical findings (typical pulmonary or gastrointestinal disease) in combination with an elevated sweat chloride concentration of more than 60 mmol/L (quantative pilocarpine iontophoresis) or 2 disease-causing mutations within the CFTR gene (14,15).

Statistical Analysis

The incidence of DIOS was given in episodes per 1000 patient-years with 95% confidence limits.

RESULTS

During a 5-year period (2001–2005), 51 episodes of complete DIOS were diagnosed in 39 patients. The overall incidence of DIOS in the 8 participating centres was 6.2 episodes per 1000 patient-years (95% confidence interval, 4.5–7.9) (Table 3). The mean age of the patients during an episode was 9.0 years (range 0.1–17.9 years). A subdivision into 6 age categories was made (Table 4) and the frequency of DIOS episodes among these categories ranged from 10% to 22%.

The CFTR genotypes in patients are shown in Table 5. The vast majority, 32 patients (82%), had a severe genotype, of which 21 patients were homozygous for DF508. One patient had a mild

TABLE 3. Incidence of DIOS in cystic fibrosis in the medical centres

Centre	Patient-years	DIOS (episodes/patients)	Incidence (episodes/1000 patient-years)
UMCU	1165	9/8	7.7
Necker-Enfants-Malades	1750	13/9	7.4
Robert Debre	900	5/5	5.6
Universitair Ziekenhuis Brussel	396	5/5	12.6
University Hospital of Ghent	750	1/1	1.3
Poznan University of Medical Sciences	450	5/3	11.1
Hadassah Medical Organization/Sheba Medical Centre	1250	5/3	4.0
University of Milan	1600	8/5	5.0
Total	8261	51/39	6.2 (95% CI 4.5–7.9)

CI = confidence interval; DIOS = distal intestinal obstruction syndrome; UMCU = University Medical Center Utrecht.

genotype (3%), whereas the genotype was unknown in 6 patients (15%). Among the 39 patients with DIOS, 8 (20%) experienced more than 1 episode during the 5-year period (2001–2005); 5 patients experienced 2 episodes, 2 patients experienced 3 episodes, and 1 patient experienced 4 episodes. Thirty-six patients (92%) were pancreatic insufficient and 17 (44%) had a history of meconium ileus (Table 5).

Most patients were treated with meglumine diatrizoate (Gastrografin; Schering AG, Berlin, Germany) enema (33%), polyethylene glycol (PEG) lavage (20%), an enema with or without an oral laxative (22%), or oral laxatives (16%). Although the participating centres differed widely in the treatment of DIOS all were effective; only 2 patients (4%) needed surgery in the treatment of a DIOS episode (Table 6). One patient with pancreas insufficiency and a history of meconium ileus was treated surgically at age 2.9 years and experienced 2 more episodes of DIOS at age 3.3 and 3.6 years, whereas the other patient with pancreas insufficiency and without a history of meconium ileus was treated surgically at age 0.24 years and did not experience a relapse.

TABLE 4. Age categories of the 51 DIOS episodes in the 8 medical centres

Age categories DIOS episodes, y	Frequency of DIOS episodes
0–3	10 (20%)
3–6	8 (16%)
6–9	9 (18%)
9–12	5 (10%)
12–15	11 (22%)
15–18	8 (16%)

DIOS = distal intestinal obstruction syndrome.

DISCUSSION

The ESPGHAN CF Working Group definitions for DIOS and constipation in CF are specific, which should simplify future comparison of different aspects of these conditions. Previous definitions of DIOS sometimes included constipation, which overestimated the incidence of genuine obstruction, whereas the real incidence of constipation in CF was difficult to estimate. Therefore, a distinction between constipation and DIOS was made in the current ESPGHAN CF Working Group definitions.

In this study, the overall incidence of DIOS in paediatric patients with CF was 6.2 episodes per 1000 patient-years (95% confidence interval, 4.5–7.9). Andersen et al (4) reported a lower incidence of DIOS (2.15 per 1000 patient-years) in patients with CF ages 0 to 20 years using a definition identical to ours. The patients in the present study, encompassing 2001 to 2005, were probably treated with a higher dose of pancreas enzyme replacement therapy than in the 1976 to 1986 period (4). Littlewood et al (16) indeed suggests that the current more aggressive treatment with pancreas

TABLE 5. Clinical features associated with DIOS in cystic fibrosis in the 8 medical centres

	UMCU	Enfants-Malades	Robert Debre	Brussels	Ghent	Poznan	Hadassah/Sheba	Milan	Total
DIOS patients	8	9	5	5	1	3	3	5	39
Patients with >1 episode of DIOS	1	4	0	0	0	1	1	1	8 (20%)
Genotype									
Severe	8	8	3	5	1	1	3	3	32 (82%)
DF508/DF508	6	6	2	4	0	0	0	3	21 (54%)
Mild	0	0	1	0	0	0	0	0	1 (3%)
Undetermined	0	1	1	0	0	2	0	2	6 (15%)
Clinical manifestations									
Exocrine PI	8	8	5	5	0	2	3	5	36 (92%)
Meconium ileus	7	1	4	2	0	1	0	2	17 (44%)

DIOS = distal intestinal obstruction syndrome; UMCU=University Medical Center Utrecht.

TABLE 6. Treatment of DIOS episodes in the 8 medical centres

Treatment	UMCU	Enfants-Malades	Robert Debre	Brussels	Ghent	Poznan	Hadassah/Sheba	Milan	Total
Conservative	2	0	0	0	0	0	0	0	2 (4%)
Oral laxatives	0	0	0	0	0	0	1	7	8 (16%)
Polyethylene glycol lavage + oral laxatives	2	2	0	0	1	0	4	1	10 (20%)
Enema + oral laxatives	3	0	0	1	0	4	0	0	8 (16%)
Enema – oral laxatives	1	0	0	2	0	0	0	0	3 (6%)
Gastrografin enema ± oral laxatives	0	10	5	2	0	0	0	0	17 (33%)
Barium enema + oral laxatives + polyethylene glycol lavage	1	0	0	0	0	0	0	0	1 (2%)
Surgery	0	1	0	0	0	1	0	0	2 (4%)

DIOS = distal intestinal obstruction syndrome; UMCU = University Medical Center Utrecht.

supplements may result in less undigested food in the intestine and thus promote faecal impaction, which seems to be in agreement with our results. Nevertheless the role of pancreas enzyme replacement therapy and steatorrhea in the pathogenesis of DIOS remains controversial. Pancreatic insufficiency or poorly controlled steatorrhea is also thought to induce more sticky intestinal mucus and DIOS (17–19). In addition, Rosenstein and Langbaum (20) and Andersen et al (4) reported that the incidence of DIOS did not change after the introduction of the more efficient acid resistant, enteric-coated, encapsulated microspheres of pancreatic enzymes.

The present study found a higher frequency (44%) of meconium ileus at birth in patients with DIOS than the 15% to 28% found in other studies (1,17,21). This could be because of the stricter definition of DIOS in the present multicentre study compared with the reviewed studies (1,17,21). The relation between MI at birth and the subsequent development of DIOS is also corroborated by Blackman (22), who reported a significant correlation between these 2 entities. In 2 smaller studies a similar trend was observed, which did not reach statistical significance (23,24). Additionally, similar pathological defects, such as slow intestinal transit (25) and impaired intestinal secretion, may contribute both to the development of intestinal obstruction in DIOS and to meconium ileus.

Treatment with Gastrografin enema, PEG lavage, oral laxatives, or an enema with or without laxatives was effective in almost all of our patients with DIOS. Interestingly, although treatment schedules differed widely between centres, the preferred treatment in each centre was effective. This seems to indicate that removal of the sticky intestinal contents from the ileocaecum can be obtained effectively through different medical methods. In general, we prefer a step-up approach starting with oral laxatives with or without an enema: Treat the patient with PEG lavage, when this is not effective. Consider surgery if these conservative treatments are not successful.

The low frequency of mild genotype in patients with DIOS (3%) in our study is in concordance with the reported association between severe genotype and DIOS (17,22). This may indicate that a severely impaired intestinal chloride secretion, as a result of major CFTR dysfunction, plays an important role in this condition. However, the relation between severe genotype and DIOS is not absolute, because patients with a mild genotype may still develop DIOS. Genes other than the CFTR gene, modifier genes, may also influence the severity of the gastrointestinal phenotype of CF and thus DIOS (26,27), although the CF Twin and Sibling Study in the United States (22) reported no significant differences in concordance rates between monozygotic twins and siblings, indicating that genetic factors other than CFTR genotype do not play a major role in DIOS. Nevertheless, meconium ileus was clearly influenced by modifier genes, so DIOS, which is associated, may still have a small genetic component. Clearly, further studies are necessary to investigate the role of modifier genes in the gastrointestinal phenotype in patients with CF.

In conclusion, the current definitions of DIOS and constipation in CF are specific and make a strict distinction between DIOS and constipation, which should make comparison for different aspects of these conditions between centres straightforward. Using the newly established definition for DIOS, we could already establish that the current incidence is higher than previously estimated, which could be caused by the more aggressive treatment with pancreatic enzymes used. We also found that conservative treatment was effective in almost all patients with DIOS.

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