World Journal of Gastroenterology

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.3748/wjg.v21.i1.318

World J Gastroenterol 2015 January 7; 21(1): 318-325
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

ORIGINAL ARTICLE

Observational Study

Long-term follow-up of distal intestinal obstruction syndrome in cystic fibrosis

Moran Lavie, Tzipora Manovitz, Daphna Vilozni, Sarina Levy-Mendelovich, Ifat Sarouk, Ilana Weintraubv, David Shoseyov, Malena Cohen-Cymberknoh, Joseph Rivlin, Ori Efrati

Moran Lavie, Tzipora Manovitz, Daphna Vilozni, Sarina Levy-Mendelovich, Ifat Sarouk, Ilana Weintraubv, Ori Efrati, Pediatric Pulmonary Unit and the National Center for Cystic Fibrosis, Edmond and Lily Safra Children's Hospital, Sheba Medical Center, Tel Hashomer 52621, Israel
David Shoseyov, Malena Cohen-Cymberknoh, Cystic Fibrosis Center and Pediatric Pulmonary Unit, Hadassah Hebrew University Medical Center, Jerusalem 91120, Israel
Joseph Rivlin, Cystic Fibrosis Center, Carmel Medical Center, Haifa 34362, Israel
Author contributions: Lavie M, Vilozni D and Efrati O designed the study, analyzed the data and wrote the manuscript; Manovitz T, Levy-Mendelovich S and Sarouk I collected the medical data and performed the statistical analysis; Weintraubv I, Shoseyov D, Cohen-Cymberknoh M and Rivlin J provided the medical data, analyzed the data and were also involved in the writing and editing of the manuscript.

Correspondence to: Dr. Moran Lavie, Pediatric Pulmonary Unit and the National Center for Cystic Fibrosis, Edmond and Lily Safra Children's Hospital, Sheba Medical Center, Derech Sheba 2, Tel Hashomer 52621, Israel. moran.lavie@sheba.health.gov.il
Telephone: +972-3-530-2884
Fax: +972-3-534-5914
Received: June 16, 2014
Peer-review started: June 20, 2014
First decision: July 21, 2014
Revised: August 27, 2014
Accepted: September 29, 2014
Article in press: September 30, 2014
Published online: January 7, 2015

Abstract

AIM: To investigate the long-term follow-up of distal intestinal obstruction syndrome (DIOS) in Israeli cystic fibrosis (CF) patients.

METHODS: This is a multi-center, comparative, retrospective study in which we reviewed the medical records of all CF patients from three major CF centers in Israel who were treated in the period from 1980 to 2012. Patients diagnosed with DIOS were defined as the study group. The patients were diagnosed with DIOS based on their clinical presentation and typical findings on either abdominal X-ray or computerized tomography scan. For the control group, CF patients with no DIOS were matched to the patients in the study group for age, sex, and cystic fibrosis transmembrane conductance regulator (CFTR) mutations. For both groups, the collected data included age, sex, CFTR genotype, weight, height, and body mass index. Clinical data included respiratory function tests in the last five years prior to the study, respiratory function test immediately before and after the DIOS event, number of hospitalizations, sputum culture results, and CF-related conditions diagnosed according to the CF clinical practice guidelines. In the study group, data on the DIOS treatment and tendency for DIOS recurrence were also analyzed.

RESULTS: The medical charts for a total of 350 CF patients were reviewed. Of the 350 CF patients, 26 (7.4%) were diagnosed with DIOS. The control group included 31 CF patients with no DIOS diagnosis. The mean follow-up period was 21.6 ± 8.2 years. The total of DIOS episodes in the follow-up period was 60. The distribution of DIOS episodes was as follows: 6/26 (23.1%) study patients had one episode of DIOS in

their lifetime, 7/26 (26.9%) had two episodes, 7/26 (26.9%) had three episodes, and 6/26 (23.1%) had four or more episodes. Compared to the control group, DIOS patients had a significantly higher incidence of meconium ileus in the past (65.4% *vs* 0%, respectively, $P < 0.02$), more *Aspergillus* spp. colonization (34.6% *vs* 3.2%, respectively, $P < 0.02$), and a higher number of hospitalizations due to respiratory exacerbations (8.6 *vs* 6.2 mean total hospitalizations per follow-up period, respectively, $P < 0.02$). No other significant differences were found between the control and study groups. The conservative treatment of DIOS, which mainly includes hydration and stool softeners, was successful in 82% of the episodes. The survival rate was similar for both groups.

CONCLUSION: CF patients with DIOS suffer from recurrent hospitalizations and airway pathogen acquisition. Although recurrence of DIOS is common, conservative treatment is successful in most patients.

Key words: Distal intestinal obstruction syndrome; Cystic fibrosis; Meconium ileus; Treatment; Recurrence

Core tip: Distal intestinal obstruction syndrome (DIOS) is a gastrointestinal complication of cystic fibrosis (CF). This study reviews the long-term follow-up of DIOS across two decades in Israeli CF patients. The DIOS patients were more prone to meconium ileus, *Aspergillus* spp. airway colonization and frequent hospitalizations then the DIOS-negative CF patients. DIOS recurrence was observed in 77% of patients. Conservative treatment was successful in 82% of the episodes, which makes it the treatment of choice for DIOS management. The survival rate was similar to the CF patients without DIOS.

Lavie M, Manovitz T, Vilozni D, Levy-Mendelovich S, Sarouk I, Weintraubv I, Shoseyov D, Cohen-Cymberknoh M, Rivlin J, Efrati O. Long-term follow-up of distal intestinal obstruction syndrome in cystic fibrosis. *World J Gastroenterol* 2015; 21(1): 318-325 Available from: URL: http://www.wjgnet.com/1007-9327/full/v21/i1/318.htm DOI: http://dx.doi.org/10.3748/wjg.v21.i1.318

INTRODUCTION

Cystic fibrosis (CF) is an autosomal recessive disease caused by mutation of the cystic fibrosis transmembrane conductance regulator (CFTR) protein, which is a cell membrane channel for transport of chloride ions[1]. The systems usually affected by this disease are respiratory, gastrointestinal, and reproductive[2]. The prevalence of CF-related gastrointestinal complications has been on the rise in recent years, a fact that can partly be attributed to an increase in the average age of CF patients[3]. The two gastrointestinal manifestations in CF that lead to intestinal obstruction are meconium ileus (MI) and distal intestinal obstruction syndrome (DIOS). MI is a condition specific to infants, who in most cases are also diagnosed with CF, strongly suggesting that MI may be the first clinical marker of the disease. The MI appears in 10%-21% of CF patients[4-6]. The meconium in the MI neonates is viscous, dry and thick, consequently causing intestinal obstruction. DIOS, a similar phenomenon of intestinal obstruction, occurs later in life. DIOS is characterized by the accumulation of viscous intestinal contents within the bowel lumen involving the terminal ileum, cecum and ascending colon, potentially causing complete or partial intestinal obstruction[7]. The DIOS incidence rate ranges from 2.3% to 41.3%[8]. A recent study in European children showed complete obstruction incidence rate ranging 5-12 episodes per 1000 CF patients per year[9].

Some of the indications of the presence of acute complete obstruction are bilious vomiting, a mass in the ileocecal area, abdominal pain and distention, and air-fluid level in the small intestine on abdominal X-ray. The incomplete fecal obstruction is characterized by abdominal pain and a mass in the ileocecal area[9]. Although the pathogenesis of DIOS is unknown, the underlying assumption is that DIOS is a combination of a few factors, including pancreatic insufficiency (PI) with abnormal secretion of pancreatic enzymes and abnormal digestion, insufficient secretion of bicarbonate, viscous and mucoid secretions of the intestinal mucosa, and impaired intestinal motility[9]. Various DIOS treatment options are available[3,9]. In most cases, patients with incomplete DIOS respond well to oral rehydration combined with stool softeners or laxatives. When DIOS presents with more severe intestinal obstruction characterized by bilious vomiting or when washout therapy has failed, hospitalization is recommended, and intravenous rehydration and nasogastric aspiration should be commenced. With early aggressive medical management, surgery is seldom required; laparotomy with washout *via* enterostomy should supersede resection of the ileocecum.

There is a lack of consensus in the literature on the different aspects of DIOS in CF patients. Correlation between DIOS and the pulmonary and nutritional status was found to be either non-significant[7] or positive[3]. On the other hand, DIOS patients suffered from a lower forced expired volume in 1 s (FEV1) and had more severe morbidity than patients without DIOS[9,10]. The correlation between pancreatic enzyme replacement therapy (PERT) and DIOS is still not fully understood. Some reports suggest a positive correlation between PERT and an increased risk of obstruction[9,11]. Others found that the pancreatic failure and uncontrolled steatorrhea led to an increase in intestinal obstruction frequency that did not improve even after the introduction of a more efficient pancreatic enzyme treatment[3,10,12-14]. The correlation between DIOS and MI also remains inconclusive, ranging

from positive[2,8,9] to non-significant[10]. Contradictory evidence exists for the correlation between severity of the CFTR mutation and the chance of developing DIOS, as well[8-10]. Additional DIOS risk factors include dehydration, CF-related diabetes, and organ transplantation[15].

The objective of the current study was to assess clinical characteristics, risk factors, morbidity and mortality among Israeli CF patients with and without DIOS during a 20-year follow-up period. Furthermore, the treatments used by the three CF centers for DIOS-positive CF patients were also assessed. A more comprehensive understanding of DIOS and a development of a clear treatment strategy will help create an all-encompassing management plan to be used by patients and doctors to manage this complicated disease.

MATERIALS AND METHODS

Subjects

The subjects included in the study were patients from three major CF centers in Israel: (1) Pediatric Pulmonary Unit and the National Center for Cystic Fibrosis, Edmond and Lily Safra Children's Hospital, Sheba Medical Center, Tel Hashomer, affiliated with Sackler Medical School, Tel-Aviv University; (2) Cystic Fibrosis Center and Pediatric Pulmonary Unit, Hebrew University of Jerusalem Hadassah Medical Center, Jerusalem; and (3) Cystic Fibrosis Center, Carmel Medical Center, Haifa, affiliated with Technion Faculty of Medicine, Haifa.

The Cystic Fibrosis Foundation's consensus statement was used to diagnose CF in all of the patients based on the clinical characteristics, identified CFTR alteration mutation, and/or pathological sweat chloride test (performed on two occasions)[16].

Study design

A retrospective review of the CF patients' medical records during 1980-2012 was performed. CF patients were divided into either the study group (DIOS-positive) or the control group (DIOS-negative). Patients in both groups were matched based on age, sex, and CFTR mutations. Data collected from medical files included age, sex, CFTR genotype, weight, height, and body mass index (BMI). The study group was composed of 26 CF patients and the control group was composed of 31 CF patients, for a total of 57 patients. The clinical data included respiratory function tests in the 5 years prior to data collection, respiratory function test immediately prior to and following the DIOS episode, number of hospitalizations, and sputum culture results. CF-related conditions (diagnosed according to the CF clinical practice guidelines[17]) were also collected, and included rectal prolapse, gastritis, PI, CF-related diabetes, portal hypertension, percutaneous endoscopic gastrostomy, cholelithiasis, cholestasis, cholecystitis, sinusitis, hemoptysis, nasal polyps, organ transplantation, malignancy, and mortality. The study group data also included information of the treatment for DIOS and propensity for recurrence. The study was approved by the Institutional Ethics Committees of all three institutions.

Diagnosis and management of DIOS

The diagnosis of DIOS was performed based on the clinical manifestations, such as abdominal pain, constipation, bilious vomiting, a mass in the ileocecal area, and abdominal X-ray or computerized tomography scan showing distention and air-fluid level in the small intestine[15]. The treatment included (1) hydration with intravenous or feeding tubes; (2) stool softeners (polyethylene glycol) administered either per os or *via* a feeding tube; (3) continuation of oral pancreatic enzymes; or (4) surgical management[15]. The stool softeners used were Meroken™ (Taro Pharmaceutical Industries Ltd., Haifa, Israel), mineral oil, lactulose, N-acetylcysteine or Gastrografin® solution (sodium meglumine diatrizoate; Bracco Diagnostics Inc., Monroe, NJ, United States). For the treatment of adults, 100 mL of Gastrografin was added to 400 mL of drinking water per dose; for the treatment of children < 6-years-old, 50 mL of Gastrografin was added to 200 mL of drinking water per dose.

Statistical analysis

Data was analyzed using the IBM SPSS Statistics for Windows software (version 21.0; IBM Corp., Armonk, NY, United States). Categorical parameters were analyzed using the Pearson's chi-square and Fisher's exact tests. Continuous variables were analyzed using the paired *t*-test and the Mann-Whitney *U* test. A *P*-value less than 0.05 were considered significant.

RESULTS

The study encompassed 350 patients, accounting for about 60% of all CF patients in Israel. Of the 350 patients, 26 (7.4%) were diagnosed with DIOS. The average length of the follow-up period for the entire cohort was 21.6 ± 8.2 years. Twenty (76.9%) DIOS patients and 26 (83.8%) control patients underwent follow-up for > 15 years, and 17 (65.3%) DIOS patients and 19 (61.3%) control patients were followed for ≥ 20 years (Table 1). The average age for occurrence of the first DIOS episode was 9.7 ± 8.5-years-old. Following this first episode, 13 patients (50.0%) were followed for at least 10 years and 6 (23.1%) patients were followed for at least 15 years. The average follow-up period after the first DIOS episode was 9.5 ± 7.7 years. Six (23.1%) study patients had one episode of DIOS in their lifetime, 7 (26.9%) had two episodes, 7 (26.9%) had three episodes, and 6 (23.1%) had four or more episodes. The control group included 31 CF patients not diagnosed with DIOS matched by age, sex, and CFTR genotype to the study group. The clinical characteristics of the 57 patients included in the study are presented in Table 2.

From the DIOS group, 13 (50.0%) patients were homozygous and 8 patients (30.7%) were compound

Table 1 Long-term follow-up of the cohort *n* (%)

Follow-up length in years	Study group	Control group
10	23 (88.4)	29 (93.5)
15	20 (76.9)	26 (83.8)
20	17 (65.3)	19 (61.3)
25	13 (50.0)	9 (35.4)
30	5 (19.2)	1 (3.2)
Total number of patients per group	26	31

Study group: Cystic fibrosis patients diagnosed with distal intestinal obstruction syndrome; Control group: Cystic fibrosis patients.

heterozygous for the CFTR gene. In the control group, 12 (38.7%) patients were homozygous and 9 (35.4%) patients were compound heterozygous for CFTR gene. The rest of the patients in both groups had unknown mutations. The two prominent alleles were DeltaF508 and W1282X. DeltaF508 was found in 46.2% of the DIOS patients and 58.1% of the control group patients. W1282X was found only in 46.2% of the DIOS group patients. Other mutations included: T360K, 3849+10KBC→T, G85E, D952H, R334W, 405+1G→A, S549R, 5T, Q359K, N1303K, 3120del, e92x, and I1234V. There was no statistical difference between the DIOS and control group in the severity of mutations or mutation class. In the DIOS group, the BMI was slightly lower than that in the control group but the difference was not significant (18.4 *vs* 19.3, respectively, $P = 0.301$). The percentage of patients who received percutaneous endoscopic gastrostomy tube insertion, to improve nutritional status, was similar between the DIOS group and the control group (7.7% *vs* 6.5%, respectively, $P = 1.00$). In the DIOS group, 18 patients had pancreatic insufficiency and were treated with an enzyme replacement therapy. There was no statistical difference in PI between the DIOS group and the control group [18 (69.2%) *vs* 27 (87.1%), respectively, $P = 0.97$]. The incidence of MI in the medical history of DIOS group patients compared to the control group was 65.4% *vs* 0.0%, respectively ($P = 0.001$).

The incidence rate and diversity of bacterial colonization by *Pseudomonas aeruginosa, Staphylococcus aureus, Burkholderia cepacia,* and nontuberculous *Mycobacterium* was similar between the DIOS and control groups (84.6% *vs* 90.3%, $P = 0.691$; 53.8% *vs* 41.9%, $P = 0.431$; 7.7% *vs* 0%, $P = 0.204$; and 7.7% *vs* 16.1%, $P = 0.436$, respectively). In contrast, patients suffering from DIOS had significantly more infections with *Aspergillus* spp. then the control group (34.6% *vs* 3.2%, $P = 0.003$, respectively).

The patients who developed intestinal obstruction did not suffer from an increase in the number of CF-related complications (42.3% *vs* 58.1% in the controls, $P = 0.292$). There was an upward trend in the number of organ transplantations in the DIOS group (15.4% *vs* 3.2%, respectively, $P = 0.167$) and an increase in rectal prolapse in the control group (0.0% *vs* 6.5%, respectively, $P = 0.0495$).

In order to evaluate the severity of lung disease,

Table 2 Characteristics of the cohort *n* (%)

	Study group	Control group	*P*-value
Patients	26	31	NS
Sex			
Male	19 (73.1)	20 (64.5)	NS
Female	7 (26.9)	9 (35.5)	NS
Age, mean ± SD (years-old)	9.7 ± 22.5	6.7 ± 20.9	NS
Genotype			
Homozygote	13 (50.0)	12 (38.7)	NS
Heterozygote	8 (30.8)	9 (35.5)	NS
Unknown	5 (19.2)	8 (25.8)	NS
DeltaF508	12 (46.2)	18 (58.1)	NS
BMI, weight/height	18.4	19.3	NS
PI	18 (69.2)	27 (87.1)	NS
MI in the past	17 (65.4)	0 (0.0)	< 0.02[1]
Lung colonization			
Pseudomonas aeruginosa	22 (84.6)	28 (90.3)	NS
Staphylococcus aureus	14 (53.8)	13 (41.9)	NS
Burkholderia cepacia	2 (7.7)	0 (0.0)	NS
MOTT	2 (7.7)	5 (16.1)	NS
Aspergillus spp.	9 (34.6)	1 (3.2)	< 0.02[1]

[1]Statistically significant. Study group: Cystic fibrosis patients diagnosed with distal intestinal obstruction syndrome; Control group: Cystic fibrosis patients; *n*: Number of patients; SD: Standard deviation; BMI: Body mass index; MI: Meconium ileus; MOTT: Mycobacteria other than tuberculosis; PI: Pancreatic insufficiency; NS: Not significant.

pulmonary function tests (PFTs) performed during the 5-year period prior to the study (2007 - 2011) were reviewed. The average value of each PFT parameter was calculated from all the yearly PFTs. There were no significant differences between the DIOS and control groups, as seen in Table 3. Further evaluation of the effect of an intestinal obstruction episode on lung disease included comparison of the PFTs of DIOS patients collected up to 2 mo before, and PTFs collected 2 to 4 wk after an obstruction. There was no significant difference between PFTs in the period prior to or following the bowel obstruction. The average FEV1 was 68.6% before *vs* 70.2% after obstruction ($P = 0.979$), the average forced vital capacity was 76.35% before *vs* 76.4% after obstruction ($P = 0.759$), and the average forced expiratory flow between 25% and 75% of forced vital capacity was 54.9% before *vs* 50.0% after obstruction ($P = 0.418$). The patients in the study group had significantly more hospitalizations due to respiratory exacerbations than those in the control group (8.6 *vs* 6.2 mean total hospitalizations per follow-up period, respectively, $P = 0.018$). In order to exclude age bias, the average number of hospitalizations per year for a 20-year follow-up period was measured. Even with this correction, our results still show a significantly higher number of hospitalizations in the DIOS group compared to the control group (0.4 *vs* 0.3 mean total hospitalizations per year, respectively, $P = 0.008$).

Overall, the DIOS group included 26 patients who suffered 60 episodes of intestinal obstruction during the 20-year follow-up period. The treatment distribution for the 60 episodes was as follows: 75.0% of episodes were managed conservatively, 18.3% surgically, and

Table 3 Forced expired volume in 1 s (% predicted) comparing study patients and controls in the 5-year period prior to the study

FEV1	Study group		Control group		*P*-value
	n	Mean % predicted ± SD	*n*	Mean % predicted ± SD	
1st yr	17	68.8 ± 19.5	22	70.0 ± 16.9	0.837
2nd yr	21	66.6 ± 19.1	29	71.0 ± 16.3	0.386
3rd yr	21	69.7 ± 21.0	25	69.9 ± 18.2	0.978
4th yr	21	67.7 ± 20.4	29	68.5 ± 18.6	0.876
5th yr	22	70.7 ± 20.1	17	68.5 ± 19.8	0.691

Study group: Cystic fibrosis patients diagnosed with distal intestinal obstruction syndrome; Control group: Cystic fibrosis patients; *n*: Number of patients; SD: Standard deviation; FEV1: Forced expired volume after 1 s of blowing out; SD: Standard deviation. A $P < 0.05$ is considered statistically significant.

Table 4 Management strategies for the intestinal obstruction in the study group

Type of treatment	*n* (%)
Conservative	45 (75.0)
Gastrografin PO	15 (33.3)
Enema	12 (26.6)
Combination of Gastrografin PO + enema and/or Gastrografin enema and/or N-acetylcysteine PO	11 (24.4)
Gastrografin enema	4 (8.8)
N-acetylcysteine enema	3 (6.6)
Surgical	11 (18.3)
Laparotomy with milking	3 (27.2)
Other	8 (72.7)
No intervention	4 (6.6)
Total	60 (100)
Supportive	37 (61.6)
Antibiotics	10 (27.0)
IV fluids	13 (35.1)
Feeding tube	6 (16.2)
Peglax	6 (16.2)
Laxatives	2 (5.4)

n: Number of treatments; PO: Per os; IV: Intravenous.

6.7% resolved without any intervention. The most often used drug for the treatment of intestinal obstruction was oral administration of Gastrografin, and the least used drug was N-acetylcysteine (Table 4). As part of supportive treatment, 61.6% of the DIOS patients received antibiotics and fluids. There was one mortality case in each group. In the study group, death was due to complications related to liver transplantation, not associated with DIOS; the patient in the control group died due to the end-stage lung disease.

DISCUSSION

This study followed Israeli CF patients who suffered from DIOS for an average follow-up period of 21.6 ± 8.2 years after the first bout of bowel obstruction. In the 60% of all Israeli CF patients, the DIOS incidence rate was 7.4%. This rate most likely represents the actual rate of the entire CF patient population in Israel, and it falls within the wide range of DIOS incidence worldwide of 2.4%-41.3%[8]. This incidence can be due to mutations, the hot climate, and/or food that are specific to Israel.

In our study, none of the patients in the control group had a prior history of MI, while 65.4% of the patients in the study group did have it ($P = 0.001$). The intestinal obstruction in the neonate, which is frequently managed surgically, leaves a diseased intestine, increasing the possibility for future adhesions and subsequent obstructions. MI may be the primary indication of intestinal susceptibility that makes the intestine prone to recurrent obstructions. Of the 26 DIOS patients, 20 (76.9%) had more than one episode of intestinal obstruction in their lifetime, supporting these two possible explanations. Several groups reported a significant correlation between DIOS and a history of MI[8]. O'Halloran *et al*[18] showed MI incidence of 28% in patients with DIOS. Houwen *et al*[9] found an even higher incidence of MI in DIOS patients (44%). A significant positive correlation was also supported by the findings from a study by Efrati *et al*[2] that used the same unique CF population in Israel as our study. Since both MI and DIOS probably share similar pathophysiology, this association seems logical. However, Dray *et al*[10] found no significant correlation between DIOS and a history of MI. In our study, DIOS patients had a significantly higher hospitalization rate mostly due to respiratory exacerbations, although some of the hospitalizations were due to intestinal obstructions.

Despite the increased number of hospitalizations, the results of our study show that morbidity and mortality rates of the DIOS patients were similar to those of the control group. This finding is surprising since one would expect every hospitalization to be related to the patient's baseline deteriorating. Similar results have been shown by Koletzko *et al*[7] who found no correlation between DIOS and severity of lung disease, with the respiratory function of DIOS patients being similar to CF patients without DIOS in terms of the severity spectrum. Khoshoo *et al*[3] showed that DIOS is related to a less severe pulmonary disease. It appears that the administration of the immediate treatment to resolve the acute DIOS event, as well as the long-term supportive care given to these patients, contributed to these good results. Treatments that demonstrated beneficial properties in decreasing the damage and increasing recovery of the patients to their pre-hospitalization state include antibiotic treatment, Gastrografin, long-term laxative treatment, stool softeners, fluids, nutritional support, and chest physiotherapy. Still, other studies have found an association between DIOS and higher morbidity[9,10].

The survival rate was similar for the two groups in this study, suggesting that DIOS does not increase the mortality rate of CF patients. In addition, as shown previously, there are similarities between the DIOS patients and the control regarding the respiratory function tests and nutritional status. An interesting result is that the study patients were not sicker in the long run and did not deteriorate more than the control patients, despite their need for more treatments and recurrent hospitalizations. A potential explanation of this observation is that the majority of DIOS patients suffered from MI as neonates and were diagnosed early as CF patients, therefore receiving close medical attention and aggressive treatment very early in life. This early diagnosis gave them an advantage by preventing or postponing irreversible lung damage. Indeed, several studies have shown that an early diagnosis of CF improves prognosis in the long run[2,19,20]. Moreover, Efrati *et al*[2] showed that patients with MI showed no differences regarding PFTs in comparison to patients who did not suffer from MI after a 25-year follow-up.

CF patients suffer from recurrent respiratory tract infections, in part due to dehydration of the airway surface and decreased mucociliary clearance which may lead to chronic lung infections[21]. As a result, various bacterial pathogens such as *Pseudomonas aeruginosa* or *Staphylococcus aureus* colonize the respiratory airways in all of the CF patients regardless of DIOS diagnosis. However, *Aspergillus* spp. colonization is seen more frequently in patients who suffer from DIOS. We hypothesize that frequent hospitalizations expose DIOS patients to a higher number of antibiotic treatments, creating an optimal microenvironment for fungal infections.

The majority of CF patients, who participated in our study, suffered from pancreatic insufficiency and their condition was managed with PERT. Furthermore, there was no statistical difference in the PI prevalence and use of PERT between the DIOS group and the control group. These findings contradict previous studies that showed a connection between the aggressive use of PERT during the years and an increased risk of DIOS[9,22]. Others have shown an increase in intestinal obstruction and the DIOS incidence due to pancreatic failure and uncontrolled steatorrhea despite the introduction of more efficient pancreatic enzyme treatment[3,10,13-15].

The current study was not able to establish a clear link between CFTR mutations and DIOS as demonstrated in prior studies. The Cystic Fibrosis Genotype-Phenotype Consortium[23] and others[24-26] showed a strong association between severe mutations and pancreatic insufficiency. DIOS is mainly seen in patients with severe CFTR-related phenotypes[8,10]. Houwen *et al*[9] showed that 82% of DIOS patients had severe CFTR mutations *vs* 3% who had non-severe mutations. However, even patients with a mild phenotype developed DIOS, which suggests that not only CFTR but other modifier genes may have an effect on the severity of the gastrointestinal phenotype[9]. The results from a study by Blackman *et al*[8] did not support this statement and the authors argued that modifier genes do not contribute to DIOS, as opposed to MI.

In our study, the two most-prominent mutations in the patients suffering from DIOS were DeltaF508 and W1282X. Among the study patients, 46.2% carried at least one DeltaF508 allele, and 36.5% of the alleles of the entire cohort carried this mutation. Prior studies reported this mutation as the most-common within the CF patient population worldwide, being found in 67% of chromosomes[23]. In addition, the correlation between DeltaF508 and pancreatic insufficiency has previously been reported[23]. Indeed, 45 (78.9%) patients from the entire cohort suffered from PI. The second most-prominent mutation in the study group was W1282X, found in 46.2% of our DIOS patients in at least one allele. This mutation is almost exclusively found in the Jewish Ashkenazi population, which constitutes 1% of CF patients in the world[27]. Although morbidity and mortality of the W1282X mutation have not been studied in depth, the mutation is considered to be a Class I stop mutation. Our study found that the respiratory, nutritional and morbidity status, as well as the mortality of the study patients, were all similar to that of the control group. The unique W1282X mutation, more prevalent in our patient population, compared to the world CF population, may be contributing to this fact. It is unlikely that this severe mutation would have a protective effect on the patients. Most likely, the W1281X mutation enables modifier genes to affect the clinical presentation of DIOS, consequently providing a protective effect. In light of our study results, one can concede that modifier genes or the mutation itself may indeed be a factor affecting the clinical presentation of DIOS.

In this study we demonstrated the efficacy of supportive and conservative management of intestinal obstruction with rare need for surgical treatment. Oral Gastrografin was the most commonly used treatment. Indeed, of the 45 episodes managed in a conservative manner, 15 (33.3%) were resolved solely by Gastrografin and 9 (20%) were resolved by Gastrografin with an additional oral agent or enema as part of a combined therapy. Combined therapy was initiated either as the first choice or when Gastrografin alone did not resolve the obstruction. If the combined therapy was initiated as a second line after the failure of Gastrografin to resolve the obstruction, then the success rate of the Gastrografin treatment was 57.7%. However, since combined therapy was initiated as the first choice in some cases, usually due to severe obstruction, then the actual success rate of Gastrografin was even higher. In the past, N-acetylcysteine treatment either orally or *via* enema, was highly accepted[7,28-30]. However, some investigators have shown that treatment with N-acetylcysteine either has a high failure rate[7] or that a high dose increases the risk of liver damage[7,31]. Furthermore, N-acetylcysteine is cost-prohibitive and due to offensive taste patients often fail to comply with the treatment[32]. In comparison,

Gastrografin, a hyperosmolar dye (1500-2000 mOsm/kg), has a success rate of up to 81% with a single oral dose, and patients prefer this treatment over other available treatments[18]. However, the potential risks associated with taking Gastrografin orally are vomiting or coughing while drinking, resulting in aspiration of the drug[7], causing pulmonary edema and acute inflammation with alveolar damage and bleeding, due to the high osmolality of the drug[6,7]. Houwen *et al*[9] related the use of Gastrografin to enema. The group emphasized the importance of the substance as both a diagnostic and therapeutic tool (radiopaque and hyperosmolar) followed with caution regarding the danger of translocation of large quantities of water from the circulation to the intestine. Their conclusion was that this procedure should be administrated to older children with appropriate monitoring[9]. Our study refutes these concerns regarding Gastrografin. Indeed, being the most-common treatment, the study patients did not have lower respiratory function tests in comparison to the control, the mentioned complications were not observed during the treatment, and the treatment had a high success rate for resolving the obstruction. In contrast, the previously popular treatment involving the use of enema with N-acetylcysteine was rarely used. Surgical treatment, which was the only definitive treatment in the past, is associated with high morbidity and mortality and was rarely used and required in the current study. The high morbidity and mortality rates associated with surgical treatment are related to bleeding, delayed healing of surgical wounds, and postoperative infections[29]. Therefore, as of recently the application of surgical treatment has been decreasing and in most cases conservative treatment is the primary choice. However, researchers like Speck *et al*[33] suggest that with an increase in the incidence of DIOS in the adult CF population, the need for surgical intervention will rise; but this did not seem to be the case in our study population.

Our study has a few limitations. Primarily, the data were taken from three different centers, each using different follow-up and report systems. On the other hand, these three centers are all located in Israel; therefore, the treatment strategies were not significantly different in terms of drug choice and treatment regimen. A prospective study would be the best approach for determining the efficacy of different treatment strategies in the management of intestinal obstruction. However, our study is retrospective and was based on a review of the treatments given through the years to treat different episodes and could, therefore, be affected by different habits or tendencies of centers to offer one agent over another as a primary treatment option. Nonetheless, oral Gastrografin was the most-common agent used by all three centers and showed very high success rates in each. Because Gastrografin has few side effects and forms of administration, we strongly recommend this compound as the primary choice for treating intestinal obstruction in CF patients diagnosed with DIOS. Despite the above-mentioned limitations, we believe that these results can be implemented for the entire CF patient population worldwide.

In conclusion, CF patients, both pediatric and adult, who suffer from recurrent intestinal obstruction either in the form of MI or DIOS, have similar pulmonary and nutritional status, survival rates and associated morbidities compared to CF patients who do not. This finding is encouraging considering that DIOS patients often suffer from high rates of hospitalization and respiratory tract infections. Conservative treatment, especially with oral Gastrografin, is very successful in these patients. The combination of early diagnosis, appropriate treatment, and close follow-up all lead to successful results in CF patients of older age. The more we expand the knowledge regarding the treatment of DIOS in CF patients, the more efficient the clinical management approach will become, potentially significantly improving the life expectancy and the quality of life for these patients.

COMMENTS

Background

Distal intestinal obstruction syndrome (DIOS) is a gastrointestinal complication commonly associated with cystic fibrosis (CF). Long-term clinical implications of DIOS regarding the morbidity and mortality of CF patients have not been thoroughly investigated.

Research frontiers

Currently, no strong consensus exists in the literature regarding the different aspects of CF patients' medical history (morbidity, mortality, and DIOS reoccurrence rate) and the most beneficial treatment for DIOS. The purpose of the current study was to assess clinical characteristics, risk factors, morbidity and mortality in Israeli CF patients with and without DIOS during a 20-year follow-up period. In addition, the different DIOS treatments used were also assessed.

Innovations and breakthroughs

Long-term follow-up of DIOS patients has shown DIOS patients having more frequent airway colonization by *Aspergillus* spp., as well as more hospitalizations due to respiratory exacerbations. The DIOS patients had significantly higher incidence of meconium ileus in their medical history compared to the control patients. Although recurrence of DIOS was common, the administration of conservative treatment was successful in most of the cases. The occurrence of DIOS did not alter the survival of these patients compared to that of the control group.

Applications

The results imply that the conservative approach is the treatment of choice with a good outcome. Meconium ileus may be a risk factor for the development of DIOS as CF patients get older. Patients with a history of DIOS are prone to recurrent intestinal obstruction.

Terminology

Distal intestinal obstruction syndrome is an intestinal obstruction caused by an accumulation of viscous intestinal contents within the bowel lumen that may cause complete or partial intestinal obstruction in cystic fibrosis patients. Despite the lack of knowledge regarding the specifics of the pathogenic mechanism of DIOS, the assumption is that the condition is a combination of pancreatic insufficiency, insufficient bicarbonate secretion, viscous and mucoid secretions of the intestinal mucosa, impaired intestinal motility, and chronic inflammation. Different therapeutic options are available for use in the treatment of DIOS, and they mainly include oral rehydration combined with stool softeners or laxatives.

Peer review

This paper presents a very interesting multi-center, comparative, retrospective study showing a promising prognosis for cystic fibrosis patients with a history of DIOS using conservative treatment as the treatment of choice in management of DIOS.

REFERENCES

1 **Proesmans M**, De Boeck K. Evaluation of dietary fiber intake in Belgian children with cystic fibrosis: is there a link with gastrointestinal complaints? *J Pediatr Gastroenterol Nutr* 2002; **35**: 610-614 [PMID: 12454573]

2 **Efrati O**, Nir J, Fraser D, Cohen-Cymberknoh M, Shoseyov D, Vilozni D, Modan-Moses D, Levy R, Szeinberg A, Kerem E, Rivlin J. Meconium ileus in patients with cystic fibrosis is not a risk factor for clinical deterioration and survival: the Israeli Multicenter Study. *J Pediatr Gastroenterol Nutr* 2010; **50**: 173-178 [PMID: 19668004 DOI: 10.1097/MPG.0b013e3181a3bfdd]

3 **Khoshoo V**, Udall JN. Meconium ileus equivalent in children and adults. *Am J Gastroenterol* 1994; **89**: 153-157 [PMID: 8304294]

4 **Cystic Fibrosis Foundation**. Patient Registry 2000 Annual Data Report. Bethesda, MD: Cystic Fibrosis Foundation, 2001

5 **Munck A**, Gérardin M, Alberti C, Ajzenman C, Lebourgeois M, Aigrain Y, Navarro J. Clinical outcome of cystic fibrosis presenting with or without meconium ileus: a matched cohort study. *J Pediatr Surg* 2006; **41**: 1556-1560 [PMID: 16952591]

6 **Friedman BI**, Hartenberg MA, Mulroy JJ, Tong TK, Mickell JJ. Gastrografin aspiration in a 3 3/4-year-old girl. *Pediatr Radiol* 1986; **16**: 506-507 [PMID: 3774397]

7 **Koletzko S**, Stringer DA, Cleghorn GJ, Durie PR. Lavage treatment of distal intestinal obstruction syndrome in children with cystic fibrosis. *Pediatrics* 1989; **83**: 727-733 [PMID: 2717290]

8 **Blackman SM**, Deering-Brose R, McWilliams R, Naughton K, Coleman B, Lai T, Algire M, Beck S, Hoover-Fong J, Hamosh A, Fallin MD, West K, Arking DE, Chakravarti A, Cutler DJ, Cutting GR. Relative contribution of genetic and nongenetic modifiers to intestinal obstruction in cystic fibrosis. *Gastroenterology* 2006; **131**: 1030-1039 [PMID: 17030173]

9 **Houwen RH**, van der Doef HP, Sermet I, Munck A, Hauser B, Walkowiak J, Robberecht E, Colombo C, Sinaasappel M, Wilschanski M. Defining DIOS and constipation in cystic fibrosis with a multicentre study on the incidence, characteristics, and treatment of DIOS. *J Pediatr Gastroenterol Nutr* 2010; **50**: 38-42 [PMID: 19525866 DOI: 10.1097/MPG.0b013e3181a6e01d]

10 **Dray X**, Bienvenu T, Desmazes-Dufeu N, Dusser D, Marteau P, Hubert D. Distal intestinal obstruction syndrome in adults with cystic fibrosis. *Clin Gastroenterol Hepatol* 2004; **2**: 498-503 [PMID: 15181619]

11 **Evans AK**, Fitzgerald DA, McKay KO. The impact of meconium ileus on the clinical course of children with cystic fibrosis. *Eur Respir J* 2001; **18**: 784-789 [PMID: 11757628]

12 **di Sant'agnese PA**, Davis PB. Cystic fibrosis in adults. 75 cases and a review of 232 cases in the literature. *Am J Med* 1979; **66**: 121-132 [PMID: 420238]

13 **Rosenstein BJ**, Langbaum TS. Incidence of distal intestinal obstruction syndrome in cystic fibrosis. *J Pediatr Gastroenterol Nutr* 1983; **2**: 299-301 [PMID: 6553601]

14 **Andersen HO**, Hjelt K, Waever E, Overgaard K. The age-related incidence of meconium ileus equivalent in a cystic fibrosis population: the impact of high-energy intake. *J Pediatr Gastroenterol Nutr* 1990; **11**: 356-360 [PMID: 2246718]

15 **Colombo C**, Ellemunter H, Houwen R, Munck A, Taylor C, Wilschanski M. Guidelines for the diagnosis and management of distal intestinal obstruction syndrome in cystic fibrosis patients. *J Cyst Fibros* 2011; **10** Suppl 2: S24-S28 [PMID: 21658638 DOI: 10.1016/S1569-1993(11)60005-2]

16 **Rosenstein BJ**, Cutting GR. The diagnosis of cystic fibrosis: a consensus statement. Cystic Fibrosis Foundation Consensus Panel. *J Pediatr* 1998; **132**: 589-595 [PMID: 9580754]

17 **Marshall BC**, Campbell PW. Improving the care of infants identified through Cystic Fibrosis newborn screening. *J Pediatr* 2009; **155**: S71-S72 [PMID: 19914444 DOI: 10.1016/j.jpeds.2009.09.004]

18 **O'Halloran SM**, Gilbert J, McKendrick OM, Carty HM, Heaf DP. Gastrografin in acute meconium ileus equivalent. *Arch Dis Child* 1986; **61**: 1128-1130 [PMID: 3789794]

19 **Farrell PM**, Kosorok MR, Laxova A, Shen G, Koscik RE, Bruns WT, Splaingard M, Mischler EH. Nutritional benefits of neonatal screening for cystic fibrosis. Wisconsin Cystic Fibrosis Neonatal Screening Study Group. *N Engl J Med* 1997; **337**: 963-969 [PMID: 9395429]

20 **Hudson I**, Phelan PD. Are sex, age at diagnosis, or mode of presentation prognostic factors for cystic fibrosis? *Pediatr Pulmonol* 1987; **3**: 288-297 [PMID: 3670904]

21 **Flume PA**, Mogayzel PJ, Robinson KA, Rosenblatt RL, Quittell L, Marshall BC. Cystic fibrosis pulmonary guidelines: pulmonary complications: hemoptysis and pneumothorax. *Am J Respir Crit Care Med* 2010; **182**: 298-306 [PMID: 20675678]

22 **Littlewood JM**, Wolfe SP, Conway SP. Diagnosis and treatment of intestinal malabsorption in cystic fibrosis. *Pediatr Pulmonol* 2006; **41**: 35-49 [PMID: 16288483]

23 Correlation between genotype and phenotype in patients with cystic fibrosis. The Cystic Fibrosis Genotype-Phenotype Consortium. *N Engl J Med* 1993; **329**: 1308-1313 [PMID: 8166795]

24 **Schechter MS**. Non-genetic influences on cystic fibrosis lung disease: the role of sociodemographic characteristics, environmental exposures, and healthcare interventions. *Semin Respir Crit Care Med* 2003; **24**: 639-652 [PMID: 16088580]

25 **Kulczycki LL**, Kostuch M, Bellanti JA. A clinical perspective of cystic fibrosis and new genetic findings: relationship of CFTR mutations to genotype-phenotype manifestations. *Am J Med Genet A* 2003; **116A**: 262-267 [PMID: 12503104]

26 **Millar-Jones L**, Goodchild MC. Cystic fibrosis, pancreatic sufficiency and distal intestinal obstruction syndrome: a report of four cases. *Acta Paediatr* 1995; **84**: 577-578 [PMID: 7633158]

27 **Abeliovich D**, Lavon IP, Lerer I, Cohen T, Springer C, Avital A, Cutting GR. Screening for five mutations detects 97% of cystic fibrosis (CF) chromosomes and predicts a carrier frequency of 1: 29 in the Jewish Ashkenazi population. *Am J Hum Genet* 1992; **51**: 951-956 [PMID: 1384328]

28 **Hanly JG**, Fitzgerald MX. Meconium ileus equivalent in older patients with cystic fibrosis. *Br Med J* (Clin Res Ed) 1983; **286**: 1411-1413 [PMID: 6404483]

29 **Hodson ME**, Mearns MB, Batten JC. Meconium ileus equivalent in adults with cystic fibrosis of pancreas: a report of six cases. *Br Med J* 1976; **2**: 790-791 [PMID: 974611]

30 **Perman J**, Breslow L, Ingal D. Nonoperative treatment of meconium ileus equivalent. *Am J Dis Child* 1975; **129**: 1210-1211 [PMID: 1190145]

31 **Bailey DJ**, Andres JM. Liver injury after oral and rectal administration of N-acetylcysteine for meconium ileus equivalent in a patient with cystic fibrosis. *Pediatrics* 1987; **79**: 281-282 [PMID: 3808803]

32 **Cleghorn GJ**, Stringer DA, Forstner GG, Durie PR. Treatment of distal intestinal obstruction syndrome in cystic fibrosis with a balanced intestinal lavage solution. *Lancet* 1986; **1**: 8-11 [PMID: 2867297]

33 **Speck K**, Charles A. Distal intestinal obstructive syndrome in adults with cystic fibrosis: a surgical perspective. *Arch Surg* 2008; **143**: 601-603 [PMID: 18559755 DOI: 10.1001/archsurg.143.6.601]

P- Reviewer: Berkane S, Maria Streba LA, Vasilescu A
S- Editor: Qi Y **L- Editor**: A **E- Editor**: Wang CH

Published by **Baishideng Publishing Group Inc**
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com

ISSN 1007-9327