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Long-term intestinal obstruction sequelae and growth in children with cystic fibrosis operated for meconium ileus: expectancies and surprises☆

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ABSTRACT

Background/purpose: In the few studies on intestinal complications and growth of cystic fibrosis (CF) patients with a history of meconium ileus (MI), operated MI has not been investigated separately. We aimed to investigate the incidence of long-term intestinal obstruction sequelae [constipation, distal intestinal obstruction syndrome (DIOS)] and growth in CF patients operated for MI.

Methods: Retrospective study (1989–2016) including operative diagnoses and procedures, constipation and DIOS events, yearly Body Mass Index (BMI) measurements. Outcomes were examined in subgroups operated for MI only and for MI with atresia and/or volvulus.

Results: Of 49 patients followed-up for 15 (mean) years, 5 (10.2%) developed constipation and 14 (28.6%) DIOS. BMI was within normal percentiles in 53 patients over a 10-year follow-up. MI only and MI with atresia and/or volvulus did not differ in constipation and/or DIOS incidence (11/34 vs. 7/15, $p = 0.39$) or in BMI ($p = 0.47$). Cases with ileocecal valve resection (ICV-R) showed lower constipation and/or DIOS incidence than those without ICV-R (0/6 vs. 11/28, $p = 0.02$) and no different BMI ($p > 0.05$).

Conclusions: CF patients operated for MI were in long-term risk for constipation/DIOS; their growth was normal. Interestingly, underlying atresia/volvulus neither increased constipation/DIOS risk nor affected growth. Strikingly, ICV-R showed no constipation/DIOS risk and no impact on growth.

Type of study: Retrospective comparative study.

Level of evidence: III.

Meconium ileus (MI) is characterized by viscid, inspissated meconium causing intraluminal obstruction in the distal ileum and ileocecal valve at birth [1]. It is most often the earliest clinical manifestation of cystic fibrosis (CF) [1], and occurs in 13%–17% of patients with CF [2]. Intestinal atresia and volvulus complicate about 17% and 29% of MI cases respectively [3]. Contrast enemas successfully release MI in 36%–39% of patients in contemporary series [3,4]. Surgery is required in failure of contrast enemas, in persistent obstruction owing to an associated intestinal atresia, or in peritonitis owing to perforation and/or volvulus [1,5].

It remains unclear whether MI is a significant risk factor among patients with CF for long-term complications. Some authors suggested that MI is associated with an increased risk of malnutrition [6] and distal intestinal obstruction syndrome [3,7] (DIOS, acute obstruction of the distal ileum and right colon by viscid mucofeculent material in postneonatal life [8]). On the contrary, others did not confirm significant differences between CF patients with and without MI in growth [9] or in the incidence of constipation (chronic gradual fecal impaction of the total colon [8]) and DIOS in the long-term [10,11–13]. Moreover, there is a lack of data about the impact of surgery on the long-term outcome of patients with MI and about the severity of long-term complications in the particular group of patients with MI who underwent surgery for an underlying intestinal atresia and/or volvulus.

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The purpose of this study is to investigate the incidence of long-term intestinal obstruction sequelae—i.e., constipation and DIOS—and growth in CF patients with a history of operated MI. The impact of surgery for an associated atresia and/or volvulus on the long-term outcome of these patients is also examined.

1. Patients and methods

Charts of all patients with CF who were operated for MI between 1989 and 2015 and were subsequently followed in the CF Center of our Hospital until the end of 2016 were retrospectively reviewed. Patients with MI managed successfully with contrast enemas were excluded. "Aghia Sophia" Children's Hospital CF Center has been the only pediatric reference center for CF in Greece for the study period, and, thus, the number of CF patients with operated MI followed as outpatients in this Center is representative of the total number of CF patients with a history of operated MI in Greece.

MI diagnosis was confirmed on contrast studies (identification of microcolon with inspissated meconium in right colon [1]) in stable cases initially managed conservatively, and intraoperatively (identification of terminal ileum obstruction owing to inspissated meconium with proximal perforation and/or volvulus [1]) in cases taken to theater early owing to signs of peritonitis. CF diagnosis was confirmed with DNA analysis (identification of two CF-producing mutations [14]) in all cases.

For each patient, the following were recorded: date of birth, gender, birth weight, age at surgery for MI, operative diagnosis (MI associated with atresia and/or volvulus or MI nonassociated with atresia and/or volvulus), operative procedure undertaken (enterotomy, stoma formation or primary anastomosis), age at stoma closure, events of constipation and/or DIOS and respective management, and, finally, height, weight and Body Mass Index (BMI), as those were measured at the annual clinic appointments.

Patients with operated MI who developed constipation and DIOS have been managed in accordance with the guidelines for the care of children with CF by Royal Brompton Hospital, London [15]. As a general rule, management of constipation included improvement of oral fluid intake, compliance with pancreatic enzymes supplementation and administration of lactulose and, in some cases, of oral N-acetylcysteine. Management of DIOS included nasogastric decompression if obstruction was complete, intravenous hydration, oral Gastrografin, N-acetylcysteine in some cases, and rarely Klean-prep. No special diet plan was employed in cases with constipation or DIOS; a high-calorie diet with avoidance of nuts and grains was recommended to all CF patients. The above protocols have remained relatively unchanged and with the same key interventions during the study period.

1.1. Statistics

Differences in the frequency of complications between groups were tested by Chi-square test; Likelihood Ratio Chi-square or Fisher's exact test was utilized when the dataset did not meet the sample size assumption for Pearson's Chi-square [16,17]. Relative Risk (RR) and respective 95% Confidence Intervals (CI) were utilized as a measure of association between an intervention and the occurrence of complications; RR > 1 indicated an increased risk of complications.

Independent samples t-test or one-way Analysis of Variance (ANOVA) followed by Games–Howell post-hoc was used to assess differences in BMI between two or three, respectively, groups at distinct time points (e.g., year 4). Differences in BMI between groups over a follow-up period (e.g., 10-year follow-up including 10 annual measurements) were tested using ANOVA for repeated measures (rANOVA). Normal distribution was confirmed using Shapiro–Wilk test. Data are presented as mean and standard deviation (SD). BMI-for-age percentiles corresponding to the mean BMI values on the basis of the Centers for Disease Control and Prevention growth charts for boys [18] and girls [19] are also provided. Follow-up is presented as mean ± SD and range or median and range when the sample size was small.

Statistical analysis was performed using the SPSS V.20 software.

2. Results

2.1. Operative diagnosis and management

A total of 53 patients with CF operated for MI were included in the study. Male to female ratio was 29:24 (1.2:1). Birth weight of the patients was 2.9 ± 0.5 (mean ± SD) kg. Age at surgery was 2.7 ± 1.4 days [3 ± 1.5 days for uncomplicated MI cases initially managed with Gastrografin enemas (n = 35), and 2.2 ± 1.2 days for cases with MI complicated by peritonitis owing to perforation or volvulus, in whom conservative treatment was not attempted (n = 18)].

The diagnosis at surgery and respective operative management are shown in Table 1. Of the 53 patients, 38 (72%) suffered MI only, while 15 (28%) cases had MI associated with intestinal atresia and/or volvulus; two of the atresia cases had been diagnosed on antenatal ultrasound scans. A total of 11 cases (21%) had bowel perforation (6 with MI only, 3 with MI associated with atresia, 1 with MI associated with volvulus and 1 with MI associated with atresia and volvulus). Of all 53 patients, 39 (74%) underwent stoma formation. Bowel resection was performed in 27 patients (followed by stoma in 18 or primary anastomosis in 9 patients). In cases with MI only (nonassociated with atresia and/or volvulus), enterotomy was performed in 3 cases (8.3%), stoma in 29 (80.6%) and limited resection and primary anastomosis in 4 (11.1%). The bowel resection performed in the 13 cases with MI only (followed by stoma in 9 and primary anastomosis in 4 patients) was segmental, limited to a small segment of terminal ileum which looked unhealthy.

Stoma was closed at an age of 5.2 ± 3.5 months. Six cases with MI only underwent ICV resection and ileoascending anastomosis at the stoma closure.

2.2. Constipation and DIOS

Our 53 patients had a follow-up of 15 ± 7.2 (mean ± SD) years (range 1–26 years) for constipation and DIOS. Four cases had missing data in follow-up.

Five out of the remaining 49 patients (10.2%) developed constipation, which required regular medical management. One out of the five patients developed rather refractory constipation, which led to two episodes of constipation and a DIOS episode over a period of six months; the rest four patients were managed successfully since the first episode of constipation and no further events occurred. Age at presentation of constipation was 7.6 ± 6.5 years (range 4 months to 15 years).

Fourteen out of the 49 patients (28.6%) developed DIOS, of whom only one had previously been diagnosed with constipation. Ten patients developed only one DIOS episode (at the age of 6.2 ± 5.4 years, range 1–16 years), two patients had two episodes (one at the age of 4 and 7 months, and one at the age of 10 and 16 years), one had three (at ages 1, 4 and 12 years) and one had four episodes (ages 1, 5, 13 and 14 years). Mean age at DIOS occurrence was 6.5 years (range 4 months to 16 years). All DIOS episodes, apart from one, were treated successfully with conservative measures; one patient with a single DIOS episode at the age of 1 year required surgery and was managed with enterotomy and bowel irrigation.

The frequency of long-term intestinal obstruction sequelae (constipation and/or DIOS episodes) was not related to the patients' age; no significant differences were found between age groups 0–6 years, 6–12 years and 12–18 years (Fisher's exact tests, $p > 0.05$).

2.2.1. MI only versus MI associated with atresia and/or volvulus

The frequency of constipation and DIOS in MI only as well as in MI associated with intestinal atresia and/or volvulus is shown in Table 2. The incidence of overall intestinal obstruction sequelae, i.e., the total