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Effect of meconium ileus on the clinical prognosis of patients with cystic fibrosis

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Abstract

The objective of the present study was to determine the possible prognostic factors which may explain the difference in the survival of patients with cystic fibrosis (CF) with and without meconium ileus. Over a period of 20 years, 127 patients with CF, whose diagnosis was confirmed by typical clinical characteristics and altered sweat chloride levels, were studied retrospectively. The patients were divided into two groups: group 1 consisted of patients who presented CF and meconium ileus (N = 9), and group 2 consisted of patients with CF without meconium ileus (N = 118). The characteristics studied were based on data obtained upon admission of the patients using a specific protocol. Demographic, clinical, nutritional and laboratory data were obtained. The genotype was determined in 106 patients by PCR. Survival was analyzed using the Kaplan-Meier method. The median follow-up period was 44 months. A statistically significant difference was observed between the groups studied regarding the following variables: age at diagnosis and weight and height z scores. The presence of meconium ileus was associated with an earlier diagnosis; these patients had greater deficits in height and weight at the time of diagnosis and at the end of the study. The estimated probability of survival for patients with CF without meconium ileus was 62 ± 14% and for those with meconium ileus 32 ± 18%. Patients with CF and meconium ileus presented a poor nutritional status at diagnosis and a lower survival rate compared to the general CF population.

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Key words
• Cystic fibrosis
• Meconium ileus
• Survival
• Nutrition
• Genotype

Introduction

Meconium ileus is the earliest clinical manifestation of cystic fibrosis (CF), a genetically recessive lethal disorder (1). A relation between meconium ileus and CF has been reported since the beginning of the century (2). Meconium ileus seems to be more the result of the presence of viscous mucus in the bowel than of pancreatic insufficiency itself (3); however, it occurs almost exclusively in patients with pancreatic insufficiency (4). In this condition, the meconium contains a high amount of protein and becomes extremely thick, causing obstruction of the terminal ileum which is responsible for approximately 20% of the cases of intestinal obstruction during the neonatal period (5).

In the past, early mortality of CF patients was associated, in part, with elevated morbidity and low survival rates of patients with

meconium ileus (6). Mortality rates ranged from 65 to 79% in 1940 (7,8) and the long-term survival rate was 57% in 1970 (9). However, improvement in survival of these patients has been recently demonstrated. In 1987, Hudson and Phelan (10) reported that survival of patients with meconium ileus was the same as that observed for the general CF population. Thus, estimated patient survival after 6 months of surgical treatment rose from 33% in the 1960s to 100% in the 1980s (2). Various factors have contributed to the higher survival rate such as earlier diagnosis, the introduction of better surgical techniques and intensive postoperative care with adequate nutritional support (11,12), and efficient antimicrobial therapy (13).

Based on the improvement in the survival of patients with meconium ileus, this condition is now considered to be of minor relevance as a prognostic factor. Corey and Farewell (14) reported that meconium ileus is not a significant prognostic factor for survival. In our unit, however, patients with meconium ileus still have an increased risk of dying as compared to patients without meconium ileus. In order to determine the possible prognostic factors which may explain the difference in the survival of patients with and without meconium ileus, we conducted a retrospective study on patients admitted to the CF outpatient clinic of the Pulmonology Unit, Hospital das Clínicas, UFMG, Belo Horizonte, MG, Brazil.

Material and Methods

Patients

The sample consisted of 127 patients admitted to the Pediatric Pulmonology Unit, Cystic Fibrosis Service, Hospital das Clínicas, UFMG, between 1977 and 1997, with a diagnosis of CF confirmed by typical clinical characteristics (chronic lung and/or gastrointestinal manifestations) and who had two determinations of sweat chloride of 60 mEq/l or higher. Median follow-up was 44 months (2 to 313 months). The patients were divided into two groups. Group 1 consisted of patients with CF and meconium ileus (N = 9) and group 2 of patients with CF without meconium ileus (N = 118). Meconium ileus was defined by the lack of excretion of meconium during the first 48 h of life, associated with clinical signs of intestinal obstruction and characteristic radiological findings (15). Group 2 consisted of CF patients with signs and symptoms of the disease such as chronic pulmonary and gastrointestinal manifestations without signs of intestinal obstruction during the first days after birth.

Informed consent for genotype determination and for the study to be performed was obtained from the parents or persons responsible and the study was approved by the Ethics Committee of UFMG.

Variables analyzed

The characteristics analyzed were based on data obtained upon admission of the patients to the unit using a specific protocol consisting of demographic (sex, color), clinical (age at diagnosis, Shwachman-Kulczycki clinical score), nutritional (birth weight, weight and height z scores upon admission) and laboratory data (sweat chloride, fecal fat, pulmonary colonization) and genotype. Continuous variables were stratified using cut-off points established in the literature; for those variables for which the cut-off point has not been established, such as age at diagnosis, the likelihood ratio test was used.

Genotype

Genetic analysis was performed using 10 ml of total blood in EDTA collected from 103 patients and their parents. In addition, a sample was obtained from the parents of three children who died during the study; thus it was possible to determine the genotype of these three children. The five most

frequent mutations in the CFTR gene were analyzed: F508, G542X, G551D, R553X and N1303K. DNA was extracted by the method of Lemna et al. (16) and amplified by PCR and mutations were analyzed using specific oligonucleotide alleles or by restriction enzyme digestion and polyacrylamide gel electrophoresis.

Statistical analysis

The data bank was created with the public domain program EPI INFO (version 6) (17). The chi-square test was used to compare proportions and the Kruskal-Wallis test for comparison of median values. For nutritional factors, the weight and height z scores upon admission and at the end of the follow-up period were calculated using the EPINUT program included in EPI INFO. Survival was determined by limited-product estimation using the method of Kaplan-Meier and the estimate was constructed using the KMSURV program (18). The following parameters were added to this analysis: the date of diagnosis was considered as time zero, an adverse effect was defined as the occurrence of death during follow-up, and the probability of survival was calculated for the first 12 follow-up years.

Results

A total of 127 patients with CF were followed up between 1977 and 1997. Table 1 shows the characteristics of patients with CF and meconium ileus upon admission and at the end of the follow-up period. Meconium ileus was observed in 9 children (5 boys and 4 girls), corresponding to a 7% incidence in our service. Seven patients had a non-surgical form of meconium ileus characterized by thick meconium in the terminal ileum. Clinical presentation included abdominal distention, vomiting and delay in meconium excretion. In one case, fetal intestinal obstruction was detected by prenatal ultrasound. A family history of CF was present in only one case. Two neonates presented jejunal atresia as a complication of meconium ileus.

Median patient follow-up was 36 months. The nutritional status, determined by weight and height z scores, showed undernutrition upon admission of all patients with meconium ileus. As shown in Table 1, these children showed a lower weight z score upon admission than patients without meconium ileus. The median weight z score was -3.58 for the group with meconium ileus and -2.04 for the others ($P<0.001$). In contrast, the

Table 1. Clinical data at admission and at the end of the follow-up period for 9 patients with cystic fibrosis and meconium ileus.

Patients	Follow-up (months)	At admission					At the end of the follow-up period				
		Zweight	Zheight	SK	Genotype	Age at dignosis (months)	Zweight	Zheight	SK	Oxygen	Death
1	60	-2.56	-1.72	73	F508/other	1	-2.23	-1.98	60	yes	yes
2	25	-2.58	-3.61	86	Other/other	11	0.09	0.27	89	no	no
3	36	-4.63	-3.94	75	F508/other	1	-2.31	-2.01	72	no	no
4	68	-4.44	-3.55	45	Other/other	5	-2.45	-1.92	49	yes	yes
5	4	-1.89	-2.97	70	#	2	-1.67	-1.44	70	no	yes
6	77	-3.99	-3.75	67	F508/F508	4	-1.94	-1.41	59	no	no
7	31	-3.94	-3.65	55	F508/F508	2	-4.50	-3.07	60	no	yes
8	22	-3.11	-4.30	75	#	2	-1.80	-1.81	#	yes	yes
9	114	-3.58	-3.79	75	F508/F508	3	-2.06	-2.10	82	no	no
Median	36	-3.58	-3.65	73	-	2.1	-2.06	-1.92	93	-	-

Zweight, weight z score; Zheight, height z score; SK, Shwachman-Kulczycki clinical score. #Not obtained.

median Shwachman-Kulczycki clinical score was 73, indicating a good clinical situation. Regarding the genotype, the F508 mutation, which is considered to be a severe mutation, was identified in 5 patients. Of the 5 patients who died, 3 (60%) had used oxygen previously, whereas the 4 patients who survived showed preserved pulmonary function.

At the end of the follow-up period patients with meconium ileus weighed less and were shorter, with median z scores of -2.06 and -1.19 for weight (P = 0.02) and of -1.92 and -1.05 for height (P = 0.05) for patients with and without meconium ileus, respectively.

Table 2 shows the variables analyzed in

Table 2. Analysis of differences between cystic fibrosis patients with and without meconium ileus.

Factors	Meconium ileus (N = 9)	Other (N = 118)	Chi-square test	P
Gender				
Male	5	72	0.00	0.73
Female	4	46		
Race				
White	6	65	0.11	0.37
Non-white	3	53		
Genotype (1)				
Homozygous F508	3	14		
Heterozygous F508	2	28	-	-
Other	2	57		
Genotype (2)				
F508	5	42	1.21	0.23
Other	2	573		
Age at diagnosis				
≤3 months	5	10	13.6	0.001
>3 months	4	108		
SK				
≤70	4	44	0.00	0.73
>70	5	73		
Birth weight				
<2500 g	2	18	0.01	0.63
≥2500 g	7	100		
Zweight				
<-1.88	9	67	4.50	0.01
≥-1.88	0	48		
Zheight				
<-1.88	8	56	3.91	0.03
≥-1.88	1	59		
Sweat chloride				
≤95 mEq/l	4	53	0.10	1
>95 mEq/l	5	65		
Fecal fat loss				
≥3 g/24 h	5	49	0.14	0.71
<3 g/24 h	3	51		
Respiratory colonization				
Yes	3	51	0.05	0.73
No	6	67		

SK, Shwachman-Kulczycki clinical score; Zweight, weight z score; Zheight, height z score.

the two groups. Note that three characteristics were significantly different between groups: age at diagnosis and nutritional status (weight and height z scores).

In patients with meconium ileus (group 1) CF was diagnosed earlier than in group 2 patients (χ^2 = 13.6, P = 0.001), with the median age at diagnosis being 2.1 months for group 1 and 44 months for group 2 (Kruskal-Wallis = 18, P<0.001).

No significant difference in birth weight was observed between groups (χ^2 = 0.01, P = 0.63). Most of the patients of either group did not present a low birth weight. There was a statistically significant difference between groups in the distribution of weight z score upon admission at a cut-off point of -1.88 (χ^2 = 4.5, P = 0.01). All patients with meconium ileus presented a weight z score lower than -1.88, and among those without meconium ileus, 67 (56.7%) showed a weight z score lower than -1.88. The same was observed for the height z score variable, with a statistically significant difference between groups (χ^2 = 3.9, P = 0.03). Only one patient with meconium ileus (11%) showed a height z score equal to or higher than -1.88, whereas 59 patients (50%) without meconium ileus presented a height z score equal to or higher than -1.88. Thus, there was a statistically significant difference between groups regarding nutritional variables upon admission.

No significant difference regarding the other factors studied was observed between groups. The Shwachman-Kulczycki clinical score was obtained for 126 patients upon admission. Using a cut-off point of 70, 55% of the patients from group 1 and 62% of those from group 2 presented a clinical score above the cut-off point, corresponding to a good clinical condition.

Genetic analysis was performed on 106 patients. In the group of patients with meconium ileus, 3 were homozygous and 2 were heterozygous for the F508 mutation. Two patients died before genetic analysis could be performed; in two other patients, none of the five mutations analyzed was observed. Of the patients without meconium ileus, 14 (12%) were homozygous and 28 (24%) were heterozygous for the same mutation. In the other 57 (48%) patients without meconium ileus, none of the five mutations analyzed was detected.

During the follow-up period of the study, 20 (16%) of the 127 patients died, including 5 (25%) patients with CF and meconium ileus. Meconium ileus constituted a significant factor for predicting the risk of death. The estimated probability of survival was 62 ± 14% for patients without meconium ileus at clinical presentation, and 32 ± 18% for those with meconium ileus. Figure 1 shows the survival curve stratified by the occurrence of meconium ileus.

Discussion

The incidence of meconium ileus in pa-

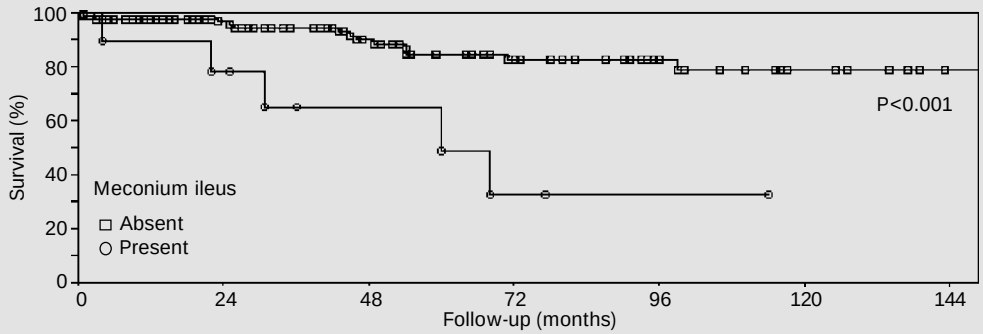

Figure 1. Cumulative survival curves (Kaplan-Meier estimates) comparing cystic fibrosis patients with and without meconium ileus.

tients with CF ranges from 7% (19) to 20% (1), being around 10 to 15% in most series (20). According to the Registry of the US National Cystic Fibrosis Foundation, the incidence was 16% among 17,857 patients registered (21). In the present study, however, the incidence was 7%, a value similar to that also reported in studies from Italy and Brazil (19,22). These data may suggest either a lower incidence of meconium ileus in our patients with CF or a failure to identify the patients with this severe intestinal obstructive condition in the State of Minas Gerais.

Poor results in terms of survival of patients with this problem were reported between 1950 and 1970, before improvement in surgical techniques for these cases. Recent studies have shown that meconium ileus was responsible for only 1 to 2% of deaths from CF between 1979 and 1991 in the United States (23). According to Fuchs and Langer (24), the prognosis for patients with CF and meconium ileus is similar to that reported for the general CF population. Our data show that, in spite of the low incidence of meconium ileus in our unit, this condition was responsible for 25% of deaths occurring during the study.

Some studies determined possible factors associated with meconium ileus, which may explain the difference in the survival of patients with and without this condition. Other studies demonstrated that children with meconium ileus generally present a lower birth weight than those without meconium ileus (20); however, Holsclaw et al. (25) observed that children with CF and meconium ileus have a higher birth weight than those without meconium ileus. This finding was not confirmed by our study; no statistically significant difference was observed between groups regarding this variable. The increased death risk for patients with meconium ileus observed in the present study may be related to poor nutritional status. As shown in Table 1, patients presenting with meconium ileus showed a higher deficit in both weight and height at diagnosis and at the end of follow-up. This long-term repercussion on nutritional status was not observed by other authors (2,20).

The association between genotype and meconium ileus in CF is uncertain. Usually, meconium ileus only occurs in patients with pancreatic insufficiency, and even among these patients it is only observed in 15% of cases (26). Some authors suggest that this condition occurs in patients carrying severe mutations (4,27); however, this situation is not always observed (28). In the present study, of the 9 patients with meconium ileus, 5 presented the F508 mutation which is considered to be severe.

Several authors have reported an increase in survival of CF patients and meconium ileus in the last decades (9,29). The death of patients with this intestinal obstructive condition was attributed to a generalized infection following prolonged hospitalization, due to extensive intestinal resection and consequent malabsorption and undernutrition (30). The improved outcome in patients with meconium ileus was attributed to the better surgical techniques employed and immediate postoperative care (31). A recent study showed that the main cause of morbidity and mortality in these children are pulmonary complications of CF (24). This finding is consistent with other studies showing that early diagnosis of CF improves the short-term prognosis but does not affect progression of the deterioration of the pulmonary condition in the long term (10,32). It is important to note that, in our study, the mean age of survival was 9 years for patients without meconium ileus, and 3.2 years for patients with meconium ileus. In other words, patients with this condition have a proportionally lower survival rate and die at a younger age. Therefore, in our unit there seems to be a combination of factors contributing to a worse prognosis. The persistence of the compromised nutritional status and the early deterioration of

the pulmonary condition, demonstrated by the fact that 3 children received oxygen therapy before death, may act in a synergistic way to reduce survival.

We should also mention the delay in the diagnosis of CF in patients with meconium ileus referred to our unit. In the present study, the mean age at diagnosis of children with meconium ileus was 3.6 months, an age much higher than that at other centers. Of the 37 patients with meconium ileus followed up by Kraemer et al. (33), all were diagnosed during the first days of life. This calls attention to the fact that the diagnosis of meconium ileus is being made late in the State of Minas Gerais, given that it is an important cause of intestinal obstruction which might be still detected *in utero* by ultrasound of the pregnant mother. Unfortunately, most of these patients were born in hospitals without neonatal intensive care units or other facilities like parenteral nutritional therapy. Besides, the patients were referred later to our unit and this fact probably affected negatively their clinical condition. Several authors have shown that early diagnosis prevents the serious respiratory complications responsible for the early death of these patients. Therefore, although most of our patients presented an uncomplicated form of meconium ileus, at diagnosis they were already affected and presented a seriously compromised nutritional status.

Thus, we believe that the survival of children admitted to our unit may be improved by the participation of a multidisciplinary group, including neonatologists and pediatric surgeons, which could provide early diagnosis and adequate treatment for this condition within a reasonable period of time.

References

1. Wood RE, Boat TF & Doershuk CF (1976). Cystic fibrosis. *American Review of Respiratory Disease*, 113: 833-878.
2. Del Pin CA, Czyrko C, Ziegler MM, Scanlin TF & Bishop HC (1992). Management and survival of meconium ileus. A 30-year review. *Annals of Surgery*, 215: 179-185.
3. Heymans HS (1989). Gastrointestinal dysfunction and its effects on nutrition in CF. *Acta Paediatrica Scandinavica*, 363 (Suppl): 74-78.
4. Kerem B, Rommens JM, Buchanan JA, Markiewicz D, Cox TK, Chakravarti A, Buchwald M & Tsui LC (1989). Identification of the cystic fibrosis gene: genetic analysis. *Science*, 245: 1073-1080.
5. Caniano DA & Beaver BL (1987). Meconium ileus: a fifteen-year experience with forty-two neonates. *Surgery*, 102: 699-703.
6. Gurwitz D, Corey M, Francis PW, Crozier D & Levison H (1979). Perspectives in cystic fibrosis. *Pediatric Clinics of North America*, 26: 603-615.
7. Hiatt RB & Wilson PE (1948). Celiac syndrome: therapy of meconium ileus. *Surgery Gynecology and Obstetrics*, 87: 317-327.
8. Dey DL (1963). The surgical treatment of meconium ileus. *Medical Journal of Australia*, 121: 179-180.
9. McPartlin JF, Dickson JA & Swain VA (1972). Meconium ileus. Immediate and long-term survival. *Archives of Disease in Childhood*, 47: 207-210.
10. Hudson I & Phelan PD (1987). Are sex, age at diagnosis, or mode of presentation prognostic factors for cystic fibrosis? *Pediatric Pulmonology*, 3: 288-297.
11. Heird WC, Driscoll Jr JM, Schullinger JN, Grebin B & Winters RW (1972). Intravenous alimentation in pediatric patients. *Journal of Pediatrics*, 80: 351-372.
12. Wilmott RW, Tyson SL, Dinwiddie R & Matthew DJ (1983). Survival rates in cystic fibrosis. *Archives of Disease in Childhood*, 58: 835-836.
13. Hill DJ, Martin AJ, Davidson GP & Smith GS (1985). Survival of cystic fibrosis patients in South Australia. Evidence that cystic fibrosis centre care leads to better survival. *Medical Journal of Australia*, 143: 230-232.
14. Corey M & Farewell V (1996). Determinants of mortality from cystic fibrosis in Canada, 1970-1989. *American Journal of Epidemiology*, 143: 1007-1017.
15. Park RW & Grand RJ (1981). Gastrointestinal manifestations of cystic fibrosis: a review. *Gastroenterology*, 81: 1143-1161.
16. Lemna WK, Feldman GL, Kerem B, Fernbach SD, Zevkovich EP, O'Brien WE, Riordan JR, Collins FS, Tsui LC & Beaudet AL (1990). Mutation analysis for heterozygote detection and the prenatal diagnosis of cystic fibrosis. *New England Journal of Medicine*, 322: 291-296.
17. Dean AG, Dean JA & Coulombier D (1994). *Epi Info, Version 6: A Word Processing, Database, and Statistics Program for Epidemiology on Microcomputers*. Centers for Disease Control and Prevention, Atlanta, GA, USA.
18. Campos-Filho N & Franco EL (1988). Microcomputer-assisted univariate survival data analysis using Kaplan-Meier life table estimators. *Computer Methods and Programs in Biomedicine*, 27: 223-238.
19. Bettinelli ME, Civardi A, Constantini D, Padoan R, Giunta A, Cesana B, Greco L, Salvatore D, Santamaria F, Castro M, Lucid V & Scarpa P (1990). Survival in cystic fibrosis: preliminary report from an Italian multicenter study. *Acta Universitatis Carolinae Medica*, 36: 215-216.
20. Kerem E, Corey M, Kerem B, Durie P, Tsui LC & Levison H (1989). Clinical and

genetic comparisons of patients with cystic fibrosis, with or without meconium ileus. *Journal of Pediatrics*, 114: 767-773.
21. Wood BP (1997). Cystic fibrosis. *Radiology*, 204: 1-10.
22. Farias L, Rosario-Filho NA & Kovalhuk L (1997). Aspectos clínicos da fibrose cística: Experiência no Hospital das Clínicas da UFPR, 1980-1996. *Pediatria*, 19: 241-246.
23. Halliburton CS, Mannino DM & Olney RS (1996). Cystic fibrosis deaths in the United States from 1979 through 1991. An analysis using multiple-cause mortality data. *Archives of Pediatrics and Adolescent Medicine*, 150: 1181-1185.
24. Fuchs JR & Langer JC (1998). Long-term outcome after neonatal meconium obstruction. *Pediatrics*, 101: 1-7.
25. Holsclaw DS, Eckstein HB & Nixon HH (1965). Meconium ileus: Twenty-year review of 109 cases. *American Journal of Diseases of Children*, 109: 101-113.
26. Tsui LC & Durie P (1997). Genotype and phenotype in cystic fibrosis. *Hospital Practice*, 32: 115-134.
27. Feingold J & Guilloud-Bataille M (1999). Genetic comparisons of patients with cystic fibrosis with or without meconium ileus. Clinical Centers of the French CF Registry. *Annales de Genetique*, 42: 147-150.
28. Johansen HK, Nir M, Hoiby N, Koch C & Schwartz M (1991). Severity of cystic fibrosis in patients homozygous and heterozygous for delta F508 mutation. *Lancet*, 337: 631-634.
29. Docherty JG, Zaki A, Coutts JA, Evans TJ & Carachi R (1992). Meconium ileus: a review 1972-1990. *British Journal of Surgery*, 79: 571-573.
30. Robinson MJ & Norman AP (1975). Life tables for cystic fibrosis. *Archives of Disease in Childhood*, 50: 962-965.
31. Mabogunje OA, Wang CI & Mahour H (1982). Improved survival of neonates with meconium ileus. *Archives of Surgery*, 117: 37-40.
32. Phelan PD, Allan JL, Landau LI & Barnes GL (1979). Improved survival of patients with cystic fibrosis. *Medical Journal of Australia*, 1: 261-263.
33. Kraemer R, Hadorn B & Rossi E (1977). Classification at time of diagnosis and subsequent survival in children with cystic fibrosis. *Helvetica Paediatrica Acta*, 32: 107-114.