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ORIGINAL ARTICLE

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The impact of cystic fibrosis on neonatal intestinal obstruction: the need for prenatal/neonatal screening

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Abstract To determine the incidence of cystic fibrosis (CF) in neonates with intestinal obstruction (NIO) secondary to meconium ileus (MI), jejunoileal atresia (JA), meconium plug syndrome (MPS), volvulus (V), and meconium peritonitis (MP) and analyze the correlation of ultrasonographic (US) signs with CF in NIO with a prenatal diagnosis of intestinal anomaly, a prospective analysis of different types of NIO from 1990 to 1998 was undertaken. Immunoreactive trypsin measurement, genetic studies, and sweat tests were performed to confirm or rule out CF. Cases with prenatal diagnosis were analyzed for gestational age, dilated bowel, ascites, hyperechoic bowel, and calcifications. Of 80 neonates, 19 (24%) had CF: 2/33 (6%) JA, 6/14 (43%) MPS, 1/14 (7.1%) MP, 10/10 (100%) MI, and 0/9 V. Thirty (37.5%) had a prenatal diagnosis of an intestinal anomaly. The overall incidence of CF in NIO with a prenatal diagnosis of intestinal anomaly was 4/30 (13%), or 333 times the estimated risk of CF in the general population. A hyperechoic pattern with dilated bowel was associated with higher specificity for CF: 3/3 cases (100%), followed by hyperechoic bowel with ascites: 3/4 cases (75%). All babies with any type of NIO should thus be screened for CF. Prenatal screening for CF should be indicated in all pregnancies with US patterns of specific intestinal disorders.

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Introduction

Meconium ileus (MI) is the earliest clinical manifestation of cystic fibrosis (CF) and occurs in 10% to 20% of infants with the condition. The inheritance of CF is autosomal recessive; the disease occurs in approximately 1/2,500 live Caucasian births and approximately 1/20 Caucasians are estimated to be heterozygous [3]. The disease is less frequent in the Black and Oriental populations. In the African-origin population, the incidence of CF is 1/1,7000 and 1/70 African–American infants are heterozygotes [15], while 1/5,000 Oriental babies are affected and 1/50 are heterozygotes. Other obstructive bowel disorders such as MI, jejunoileal atresia (JA), meconium plug syndrome (MPS), volvulus (V), and meconium peritonitis (MP) have also been described in association with CF in the prenatal and/or neonatal period [1, 5, 6, 16–18]. To date, these intestinal anomalies can be detected accurately by prenatal ultrasound (US), although antenatal diagnosis is difficult owing to the changing appearance of the bowel throughout gestation and the different manifestations of the obstructive process.

To determine the incidence of CF in different types of neonatal intestinal obstruction (NIO) and analyze the correlation with CF in cases with prenatal detection of an intestinal anomaly, we reviewed our experience with neonatal cases of MI, JA, MPS, V, and MP.

Materials and methods

A prospective study of neonates treated for NIO secondary to MI (defined as ileal obstruction due to abnormally viscid meconium resolving only with enterotomy and irrigation), JA, MPS (defined as colonic meconium obstruction relievable after a hydrosoluble

and hyperosmolar enema), V (defined as intestinal torsion with obstruction of the small bowel but without viscid meconium in the distal ileum), and MP at Bambino Gesù Children's Hospital during the 8-year period January 1990–December 1998 was carried out. Patients were selected exclusively on the basis of a clinical-radiologic picture of intestinal obstruction.

All patients underwent evaluation for CF by measuring immunoreactive trypsin and a quantitative pilocarpine iontophoresis sweat chloride test according to Gibson and Cooke's technique [9]. Before December 1997 a genetic study was performed if at least two sweat tests were positive; after that time it was done after one positive test because of its unreliability in the neonatal period. In cases with prenatal detection of an intestinal anomaly the following clinical and echographic findings were recorded for each scan: gestational age, dilated bowel, ascites, hyperechoic bowel, and calcifications. The bowel was defined as hyperechoic when its echogenicity appeared similar to surrounding bone. The correlation between isolated and associated prenatal US patterns of intestinal anomalies and the incidence of CF diagnosed after birth were also studied. A minimum of 1 year follow-up was required for each patient in order to confirm or exclude CF, with at least two sweat tests done.

Results

A total of 80 neonates with NIO were identified; 42 males and 38 females. A total of 19/80 (24%) CF cases were confirmed at birth (Table 1).

At an average age of 6 days, a blood sample was obtained in all cases for neonatal CF screening using immunoreactive trypsin. Babies with hypertrypsinemia (normal immunoreactive trypsin value: 80 ng/ml) were referred for a second sample. Ten patients (12.5%) had increased two-stage hypertrypsinemia and 60% (6/10) had CF. On the other hand, 68% (13/19) of CF patients had normal results. All affected neonates showed either a homozygote or a heterozygote Δ F508 mutation; 14% were compound heterozygotes for CF mutation Δ F508 and G512 X.

Thirty of the 80 neonates (37.5%) had prenatal echography suspicious for a bowel anomaly; no cases of MPS and V were detected prenatally. No fetus had a prenatal diagnosis of CF. Pregnant women were referred to us only for counselling. The antenatal US findings of small-bowel obstructions are summarized in Table 2. The average gestational age at the first pathological scan was 29 weeks (range 21–39 weeks). Neither medically-induced nor spontaneous abortions occurred during the study period in pregnant women whose fetuses had intestinal anomalies. Dilated bowel was observed in all but 3 fetuses. In 3 cases where hyperechoic bowel together with dilated bowel or ascites was observed, CF was confirmed after birth. A total of 4/30 (13%) babies with prenatal diagnosis of an intestinal anomaly had CF confirmed after birth. In Table 3 the prenatal US patterns, either isolated or associated, are correlated with the incidence of CF. Hyperechoic bowel in conjunction with dilated bowel was associated with a higher specificity for CF: 3/3 cases (100%), followed by hyperechoic bowel and ascites: 3/4 fetuses (75%). Eight of the 30 (27%) prenatally detected cases were scanned before 24 weeks, the deadline indicated for pregnancy termination in Italy.

Table 1 Incidence of cystic fibrosis (CF) in patients with neonatal intestinal obstruction

Diagnosis at birth	No. of cases of CF	Percentage
Jejunoileal atresia	2/33	6%
Meconium plug syndrome	6/14	43%
Meconium peritonitis	1/14	7.1%
Volvulus	0/9	0
Meconium ileus	10/10	100%
Total	19/80	(24%)

Discussion

The incidence of NIO due to meconium abnormalities in neonates with CF is 13% [17]. Therefore, no studies on the incidence of CF in each type of NIO have been published.

MI is typically reported as a manifestation of CF. In our series CF was present in 10/10 (100%) neonates with MI, 3 of them (30%) had antenatal diagnosis of an intestinal disorder. All 3 fetuses showed dilated bowel; 2 of them also had hyperechoic bowel, ascites, and calcifications. In no case was prenatal screening for CF proposed. Genetic studies allow diagnosis of CF during pregnancy, but not all mutations responsible for the disease have been identified as yet. Detection of a CF modifier locus of MI was performed studying sibpairs [21]; MI could be detected during the 2nd trimester of gestation, and fetal US diagnosis is suggested by either dilated bowel or hyperechoic bowel [10]. However, these

Table 2 Diagnosis at birth of cystic fibrosis (CF) and correlation with prenatal ultrasonographic patterns in 30 cases (*JA* jejunoileal atresia, *MP* meconium peritonitis, *MI* meconium ileus, *V* volvulus)

Diagnosis at birth	No. of cases	Mean gestational age at diagnosis (weeks)	Dilated bowel	Ascites	Calcifications	Hyperechoic bowel	CF
JA	20	29 (21–39)	20	1	0	1	1
MP	5	26 (21–31)	2	3	1	1	0
MI	3	28 (26–30)	3	2	2	2	3
V	2	26 (25–27)	2	0	0	0	0
Total	30	29 (21–39)	27/30	6/30	3/30	4/30	
CF			4/27	3/6	2/3	3/4	4/30

Table 3 Prenatal US findings, either isolated or associated with one or more intestinal abnormalities and correlation with incidence of cystic fibrosis (CF)

Antenatal US pattern	No. of patients (n = 30)	No. of CF cases (n = 4)
Dilated bowel	27	4/27 (14%)
Isolated	24	1/24 (4%)
Plus hyperechoic bowel and ascites	1	1/1 (100%)
Plus hyperechoic bowel, ascites, and calcifications	2	2/2 (100%)
Ascites	6	3/6 (50%)
Isolated	1	0/1
Plus hyperechoic bowel	1	0/1
Plus calcifications	1	0/1
Calcifications[a]	3	2/3 (66%)
Isolated	0	
Hyperechoic bowel[a]	4	3/4 (75%)
Isolated	0	

[a]US patterns reported above in Table

US patterns have a low specificity and have also been noted in fetuses with JA, V, and MP [6].

No studies on the incidence of CF in MPS have been reported. The association with CF is known [16]. Additionally, MPS has been described as either a benign disease or a manifestation of Hirschsprung's disease. In the presented series 6/14 (43%) babies with MPS had CF and none had prenatal diagnosis. Two isolated cases of prenatal diagnosis of MPS have been published; no association with CF was observed [18].

In neonatal JA, CF has an incidence reported between 5% and 12.2% [14, 19]. Roberts et al. quantified the magnitude (4/38, 11%) of JA associated with CF in Atlanta using population-based data [15]. Familial occurrence was also described by Blanck et al. [1], suggesting other genetic factors involved in the expression of the intestinal obstruction. CF was revealed in 2/33 (6%) neonates with JA in our series; 20 of them had prenatal diagnosis of an intestinal anomaly. One (5%) was identified as having CF after birth, but no prenatal screening for CF was proposed. JA is more commonly detected during the 3rd trimester of gestation; hyperechoic bowel, transient ascites, and progressive bowel dilatation are the typical antenatal US patterns.

The incidence of CF in neonates with MP is reported as between 15% and 40% [5]. Prenatal US findings include ascites, intra-abdominal cystic masses, dilated bowel, and calcifications. The incidence of CF (8% to 13.5%) in prenatally-detected MP is lower than in newborns with a diagnosis of MP [2, 13]. This difference is probably due to the following factors: (1) intra-abdominal calcifications, suggestive in the fetus, could be asymptomatic in the newborn and consequently underdiagnosed; (2) calcifications could be an US pattern of fetal infection such as Parvovirus B19, Herpesvirus, Cytomegalovirus, and Toxoplasmosis infections; and (3) the negative correlation between calcifications and CF [2–6, 8]. In fact, MP produces calcifications less commonly in CF because of the high (80%) deficiency of pancreatic enzymes [7]. The incidence of CF in our neonatal series of MP was 7.1% (1/14); 5/14 had antenatal diagnosis of an intestinal anomaly and in no case was CF diagnosed after birth.

Isolated midgut V was noted only occasionally as a manifestation of CF [11]. Antenatal echographic findings of isolated V show either upper or mid-abdominal dilated bowel. None of the 9 neonates with isolated V had a diagnosis of CF after birth. Two (22%) had antenatal suspicion of an intestinal disorder (Table 2).

Although the prenatal diagnosis of NIO is difficult owing to the changing appearance of the bowel throughout gestation, dilated bowel is the most frequent US sign of an obstructive process. In a perspective study Corteville et al. [4], correlating antenatal echographic findings with postnatal outcome, reported that hyperperistalsis and progressive fetal bowel dilatation were accurate predictors of small-bowel obstruction with a sensitivity of 100%. In the same study, 4 of 20 (18.2%) fetuses with dilated bowel had CF confirmed after birth and 3 of the 4 also showed hyperechoic bowel. Isolated hyperechoic bowel was observed in 33 fetuses, only 1 of whom had CF (3%).

Recently, Muller et al. [12] reported an incidence of CF of 3.3% (7/209 fetuses) in isolated hyperechoic bowel diagnosed by a fetal screening. In the literature, hyperechoic bowel in association with dilated bowel is more predictive for CF than isolated hyperechoic bowel (18.2% [4], vs 3% [4]–3.3% [12]). Our prenatal observation confirms this higher correlation between CF and dilated bowel in conjunction with hyperechoic bowel; the presence of ascites can strengthen the suspicion. In fact, the incidence of CF increases from 4% to 100% if more than one echographic pattern is present; the highest specificity for CF was seen in the group with dilated bowel and hyperechoic bowel (3/3, 100%), the lowest in isolated dilated bowel (1/24, 4%) (Table 3).

The selected prenatal population presents a risk of CF 333 times (4/30, 13%) as high as the estimated risk in the general population (1/2,500, 0.04%), but lower compared with the risk of CF in the population with NIO (19/80, 24%), which is 600 times as high as the estimated risk! MPS was present in 32% (6/19) of cases

with CF in neonatal series and no case in prenatal series. The discrepancy probably explains the difference in the incidence of CF between the neonatal and prenatal groups.

Finally, our results point to three main conclusions: (1) all babies with intestinal obstruction should be tested to confirm or rule out CF on the basis of a significant association of NIO and CF (24%); (2) prenatal screening for CF is probably performed too infrequently in fetuses with echographic signs of intestinal disorders (dilated bowel, ascites, hyperechoic bowel, and calcification as either an isolated or associated pattern); and (3) prenatal and neonatal screening for CF in these selected groups should be recommended to improve prenatal counselling and early medical treatment.

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