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Published in:
Archives of Disease in Childhood

DOI:
[10.1136/archdischild-2013-304159](https://doi.org/10.1136/archdischild-2013-304159)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2014

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Leeuwen, L., Magoffin, A. K., Fitzgerald, D. A., Cipolli, M., & Gaskin, K. J. (2014). Cholestasis and meconium ileus in infants with cystic fibrosis and their clinical outcomes. *Archives of Disease in Childhood*, 99(5), 443-447. <https://doi.org/10.1136/archdischild-2013-304159>

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Cholestasis and meconium ileus in infants with cystic fibrosis and their clinical outcomes

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Received 27 March 2013

Revised 21 December 2013

Accepted 23 December 2013

Published Online First

16 January 2014

ABSTRACT

Objective To identify the incidence and outcomes of cholestasis and meconium ileus (MI) in infants with cystic fibrosis (CF).

Design Retrospective cohort study.

Setting Single-centre study.

Patients From January 1986 to December 2011, 401 infants with CF (69 with MI) presented to our centre.

Main outcome measurements (1) incidence of cholestasis, (2) identification of risk factors for cholestasis, (3) association between the presence of cholestasis and MI and the development of clinically significant CF-associated liver disease (CFLD) defined as multilobular cirrhosis with portal hypertension.

Results Cholestasis occurred in 23 of 401 infants (5.7%). There was a significantly higher incidence of cholestasis in infants with MI (27.1%) compared to those without MI (1.2%) ($p < 0.001$). Infants with MI had a 30.36-fold increased risk of developing cholestasis compared to those without MI ($p < 0.001$). Cholestasis resolved in all children, at a median (range) age of 9.2 (0.8–53.2) months in the MI group and 10.2 (2.0–19.4) months in the non-MI group. The majority of cholestatic infants (87.0%) and infants with MI (92.8%) did not develop clinically significant CFLD, not significantly different than either the 93.9% of non-cholestatic infants nor the 93.7% infants without MI.

Conclusions Cholestasis is an uncommon condition in CF affecting only 5.7% of the screened newborn CF population. The greatest risk factor for developing cholestasis is the presence of MI. However, the presence of MI appears not to be associated with the development of CFLD. An effect of neonatal cholestasis on the development of CFLD cannot be excluded by this study.

INTRODUCTION

Cystic fibrosis (CF) is the most common life-limiting autosomal recessive disorder in the Caucasian population, with an incidence of approximately 1 in every 3000 live births in Australia.¹ Survival of CF patients has progressively improved since the introduction of the diagnostic sweat test in the 1950s. Recently, CF newborn screening (NBS) programmes have further reduced the morbidity and mortality associated with CF.^{2–6} With the median survival age of patients now approaching 40 years of age,⁷ non-respiratory complications such as liver disease have become increasingly important.

The earliest manifestation of liver involvement in CF is neonatal cholestasis which appears uncommon, described in only two retrospective studies and several case reports.^{8–14} In addition, the outcome of neonatal cholestasis has varied from full recovery to liver failure and death^{13 14} but the exact

What is already known

- ▶ As the life expectancy of patients with cystic fibrosis (CF) has progressively improved, non-respiratory complications such as liver disease have become increasingly important.
- ▶ Neonatal cholestasis is the first hepatobiliary complication in patients with CF, which is poorly described in the current literature.

What this study adds

- ▶ Cholestasis is an uncommon occurrence in cystic fibrosis with an incidence of 5.7% in infants.
- ▶ Infants with meconium ileus (MI) have a significantly increased risk for the development of cholestasis.
- ▶ In this study, the presence of MI in infants with CF was not associated with the later development of CF-associated liver disease.

incidence, course and effects of the cholestasis remain uncertain. Specifically, studies are needed to ascertain whether the neonatal cholestasis in CF leads to the development of multilobular cirrhosis (MBC) with its clinically significant complications of portal hypertension (PH), liver failure and encephalopathy and the need for transplantation, that is, clinically significant CF-associated liver disease (CS CFLD) described in several recent studies^{15–19} and the global gene modifier study.²⁰ The latter studies are important contributions as MBC and PH can be recognised clinically and confirmed by non-invasive imaging. Moreover, literature in the last two decades has indicated that MBC is a phenomenon of childhood with de novo occurrence in adult CF patients being very uncommon,^{17 19 21 22} and thus, longitudinal studies should be able to determine the true outcome of those originally with neonatal cholestasis within a 20-year span from birth.

Considering also neonatal cholestasis appears to occur mainly in infants with meconium ileus (MI), and the latter has been associated with a fivefold increased risk of developing CFLD,^{21 23–25} a longitudinal study from neonatal diagnosis would help to determine the contribution of these factors to the development of CS CFLD. The State of New South Wales has undertaken NBS for CF since July 1981

To cite: Leeuwen L, Magoffin AK, Fitzgerald DA, et al. *Arch Dis Child* 2014;**99**:443–447.

and has a documented occurrence of MI of 15.4%.²⁶ In addition, annual assessments from birth of liver function have been undertaken since 1986.

The aims of the current longitudinal study over an interval of 26 years therefore were:

1. to determine the incidence of cholestasis in infants with CF
2. to identify risk factors for developing cholestasis
3. to determine whether cholestasis and/or MI in infancy are associated with the later development of CS CFLD.

METHODS

Patients and methods

In this retrospective cohort study, we included all infants with CF referred to the Children's Hospital at Westmead (CHW), previously known as the Royal Alexandra Hospital for Children, over a 26-year period between 1 January 1986 and 31 December 2011. The diagnosis of CF was suggested either by a positive NBS result on the New South Wales NBS Programme or by the presence of MI and confirmed by sweat testing or genotyping. A two-step immunoreactive trypsinogen (IRT) protocol was used between January 1986 and January 1993 for the NBS process. From January 1993 to December 2011, an IRT and DNA test (screening only for $\Delta F508$ mutation) two-step profile was used. The diagnosis of CF was confirmed by a sweat chloride value greater than 60 mmol/L or genotyping showing two known CF mutations (retrospective prior to 1993). The infants were referred usually on a geographic basis or by the patient's paediatrician to our centre, which receives over 60% of the CF patients diagnosed in New South Wales annually.

We identified all CF infants with cholestasis based on their liver function tests (LFTs) in early infancy. Cholestasis was defined as a conjugated bilirubin level of greater than 17 $\mu\text{mol/L}$ and/or at least 20% of total bilirubin level.²⁷ Each infant underwent a complete work-up according to the 'Neonatal cholestasis protocol' used at CHW, a tertiary centre for the investigation and management of paediatric liver disease in New South Wales. The protocol includes: LFTs, serum albumin, renal function, full blood counts, coagulation screening, fat soluble vitamin serum levels, metabolic screening including serum lactate and pyruvate, α -1 antitrypsin phenotyping, checking NBS results, viral serology, and baseline imaging with ultrasound (U/S) and DISIDA hepatobiliary scintigraphy. Other tests for example, cholangiography and liver biopsy are undertaken as a result of initial results and clinical context and progress. After identification of CF infants with cholestasis, two cohorts were formed: (1) infants with cholestasis diagnosed with MI (MI group) and (2) infants with cholestasis without MI (non-MI group). Additionally, all CF infants diagnosed after presentation with MI were identified in order to determine risk factors for the development of cholestasis in infants with MI. Infants with MI were divided into two cohorts: (1) infants with MI and cholestasis and (2) infants with MI but without cholestasis. Complicated MI was defined as MI in

combination with segmental volvulus, intestinal atresia, mucosal necrosis, intestinal perforation, meconium peritonitis or giant meconium pseudocyst formation.

All medical charts of patients were reviewed and relevant clinical data were collected. LFTs were performed at diagnosis and at least annually thereafter. LFTs of included infants and clinical outcomes regarding the development of CFLD and complications of CFLD were obtained. CFLD was defined as MBC with PH. In all children, the diagnosis of CFLD with PH was confirmed by ultrasonography. Complications of CFLD included ascites, hypersplenism (splenomegaly with thrombocytopenia and/or leukopenia), oesophageal or gastric variceal haemorrhages, hepatic encephalopathy and synthetic liver failure.

Statistical analysis

Data were analysed using SPSS V20.0 for Windows (SPSS Inc., Chicago, Illinois, USA). Data were expressed as mean \pm SD, median (range) or number (percentage), as appropriate. Categorical variables were compared using χ^2 test or Fisher's exact test. The Student t test was used for continuous normally distributed variables and non-parametric tests for non-normally distributed continuous variables. Logistic regression analyses were performed to find predictive associations. A p value < 0.05 was considered significant.

RESULTS

Infants with cholestasis

During the 26-year period, 403 patients with CF were initially referred to CHW. Seventy-one (17.6%) infants were diagnosed following a presentation of MI and 314 (77.9%) children were diagnosed by NBS. Eighteen (4.5%) infants were missed by the NBS programme and presented with clinical symptoms (figure 1).

One cholestatic infant in the MI group who was born overseas was excluded from statistical analyses since there were minimal data available on her baseline anthropometric data, LFTs, investigations and treatments in the first 2 months of life prior to transfer to our CF centre. Further, one infant with MI but without cholestasis was lost to follow-up and was therefore excluded from statistical analyses regarding the development of CFLD and the comparisons between infants with MI.

The overall incidence of cholestasis in our cohort was 5.7%. Cholestasis occurred in 19 (27.1%) infants with MI and in 4 (1.2%) infants without MI (figure 1, $p < 0.001$). Logistic regression showed an OR of 30.36 (95% CI 9.93 to 92.86) for developing cholestasis in infants with MI compared to those without MI ($p < 0.001$).

Patient characteristics of both groups are shown in table 1. Not surprisingly, children in the MI group were diagnosed at an earlier age than children in the non-MI group. All four (100%) patients in the non-MI group were male, whereas eight (42.1%) patients in the MI group were male. All cholestatic infants were diagnosed with pancreatic insufficiency by 72-h faecal fat

Figure 1 Flowchart: mode of diagnosis and presence of cholestasis in infants with cystic fibrosis (CF). *One cholestatic infant who was born overseas was excluded from statistical analyses. MI, meconium ileus.

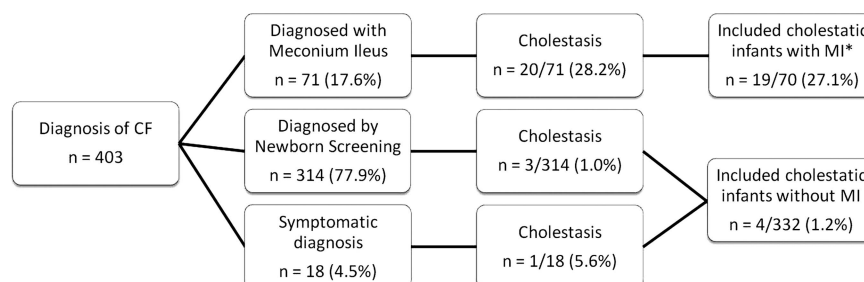


Table 1 Patient characteristics of infants with cholestasis

Variables	MI group (n=19)	Non-MI group (n=4)	p Value
Birth weight (g)	3181±425.7	2855±382.8	0.17
Male	8 (42.1%)	4 (100%)	0.09
Genotype			
Homozygous ΔF508	13 (68.4%)	2 (50.0%)	0.36
Heterozygous ΔF508	5 (26.3%)	1 (25.0%)	
Unknown	1 (5.3%)	1 (25.0%)	
Age at CF diagnosis (days)	1.0 (1.0–5.0)	54.5 (47.0–63.0)	<0.001

Data are presented as mean±SD, median (range) or number of patients (percentage). CF, cystic fibrosis; MI, meconium ileus.

collections. Eighteen children (94.7%) in the MI group required surgical treatment and total parenteral nutrition (TPN) compared to none of the children in the non-MI group ($p=0.001$). The children in the MI group received TPN for a median period of 15.5 (3.0–74.0) days. None of the infants with cholestasis were found to have a confounding non-CF diagnosis, and in the absence of such, none underwent a liver biopsy.

Course of cholestasis

Results of LFTs are shown in table 2. Cholestasis was diagnosed between 1 and 26 days of age in the MI group (median: 8.0) and between 48 and 57 days of age in the non-MI group (median: 49.5), which was significantly different ($p<0.001$). Further, the highest level of conjugated bilirubin occurred at an earlier age in the MI group. However, there were no significant differences in the peak levels of conjugated and total bilirubin between both groups.

Cholestasis resolved in all children. The resolution of cholestasis occurred at a median age of 9.2 (0.8–53.2) months in the MI group and 10.2 (2.0–19.4) months in the non-MI group. Five children in the MI group were commenced on therapy with ursodeoxycholic acid (UDCA). Four of these children received UDCA treatment for a short period ranging from 8 to 24 weeks, and one child remains on UDCA treatment at the age of 5 years.

Outcomes of infants with cholestasis

The outcome of infants with cholestasis varied but the majority of patients did not develop CFLD. The overall incidence of CFLD was 13.0% (3/23) in infants with cholestasis with a total follow-up of 282 patient-years, which was not significantly different from the 6.1% (23/378) of infants without cholestasis who developed CFLD ($p=0.18$).

In the non-MI group, two (50.0%) patients developed CFLD compared to one (5.3%) child in the MI group, which was not a significant difference ($p=0.07$). One child in the non-MI group developed CFLD at 6.5 months of age, but did not develop any complications of his CFLD except for an episode of hepatic encephalopathy in his teens, as reported recently.²⁸ The other child in the non-MI group developed CFLD at 3.0 years of age and required a liver transplant at 6.9 years of age for liver synthetic dysfunction.

In the MI group, only one child developed CFLD at the age of 10.9 years. CFLD in this child has remained stable until now, at the follow-up age of 17.1 years. One infant in the MI group, born in 1987, died from sepsis at 7 weeks of age, 2 days after closure of his ileostomy. None of the children who were treated with UDCA have developed clinically relevant CFLD to date (observation period: 1.6–7.5 years).

MI and cholestasis

Cholestasis occurred in 27.1% of infants diagnosed with MI. During this study, we found no significant changing pattern in the proportion of MI infants with cholestasis observed over 5-year intervals. The rate of cholestatic infants varied from 15.4% to 35.0% over the six intervals and was between 33.3% and 35.0% in four of the intervals. We compared infants with MI and cholestasis to infants with MI but without cholestasis.

Patient characteristics of both groups are shown in table 3. Complicated MI was significantly higher in the cholestasis group ($p=0.004$). Further, there was a trend towards a significant difference in the requirement for surgical treatment and treatment with TPN between both groups ($p=0.05$ for both). Other clinical variables were not significantly different between both groups.

In the univariate logistic regression analysis, surgical treatment and TPN were not significant risk factors for cholestasis ($p=0.06$ and $p=0.07$, respectively). However, the presence of complicated MI was found as a risk factor for cholestasis ($p=0.004$), with an unadjusted OR of 5.43 (95% CI 1.74 to 16.90) and an OR adjusted for surgery of 3.83 (95% CI 1.15 to 12.77). The OR could not be adjusted for surgical treatment and TPN due to co-linearity of both variables.

In our total cohort, 7.2% of 69 patients with MI developed CFLD compared to 6.3% of 332 CF patients without MI ($p=0.79$). Additionally, no significant difference was found between the later development of CFLD within the MI group. In the MI group, 5.3% of patients with cholestasis developed CFLD compared to 8.0% of the children without cholestasis ($p=1.00$).

Table 2 Results of liver function tests in cholestatic infants

Variables	MI group (n=19)	Non-MI group (n=4)	p Value
Age at diagnosis of cholestasis (days)	8.0 (1.0–26.0)	49.5 (48.0–57.0)	<0.001
Age at highest bilirubin level (days)	20.0 (1.0–80.0)	49.5 (48.0–57.0)	0.04
Highest conjugated bilirubin level ($\mu\text{mol/L}$)*	64.0 (18.0–284.0)	30.0 (17.0–117.0)	0.56
Highest total bilirubin level ($\mu\text{mol/L}$)†	105.0 (28.0–471.0)	45.5 (40.0–130.0)	0.12
Age at resolution of cholestasis (months)	9.2 (0.8–53.2)	10.2 (2.0–19.4)	0.90

Data are presented as median (range).

*Normal value conjugated bilirubin: 1–10 $\mu\text{mol/L}$.

†Normal value total bilirubin: 1–15 $\mu\text{mol/L}$.

MI, meconium ileus.

Table 3 Patient characteristics of infants with meconium ileus (MI)

Variables	MI with cholestasis (n=19)	MI without cholestasis (n=50)	p Value
Birth weight	3181±425.7	3108±588.3	0.62
Male	8 (42.1%)	22 (44.0%)	0.89
Genotype			0.60
Homozygous ΔF508	13 (68.4%)	33 (66.0%)	
Heterozygous ΔF508	5 (26.3%)	10 (20.0%)	
Other/unknown	1 (5.3%)	7 (14.0%)	
Complicated MI	12 (63.2%)	12 (24.0%)	0.004
Surgical treatment	18 (94.7%)	35 (70.0%)	0.05
Total parenteral nutrition (TPN)	18 (94.7%)	36 (72.0%)	0.05
Duration TPN (days)	15.5 (3.0–74.0)	14.0 (2.0–54.0)	0.32
Outcome			
No CFLD	18 (94.7%)	46 (92.0%)	1.00
CFLD	1 (5.3%)	4 (8.0%)	

Data are presented as mean±SD, median (range) or number of patients (percentage). CFLD, cystic fibrosis (CF)-associated liver disease.

DISCUSSION

With reference to the three aims of this study, we have clearly demonstrated a low incidence (5.7%) of neonatal cholestasis in a large group of over 400 infants with CF diagnosed over 26 years within a Statewide NBS programme. As such, it represents the largest cohort and longest follow-up study to date, and as the total number of CF patients within the population was documented, it provides an accurate assessment of the incidence of neonatal cholestasis in a CF population. Secondly, it has identified MI and complicated MI as the only significant risk factors for the development of cholestasis in these infants, noting, however, that with a total of 23 infants with cholestasis the sample size is not adequate to assess other factors including TPN, surgery or gene modifier effects. Finally, the study clarifies the role of MI regarding the later onset of CFLD. In those with MI 7.2% developed CFLD with PH, a proportion virtually identical to the 6.3% of CF infants without MI, indicating that MI is unlikely to have had a contributing role to the later development of CFLD. This is in contrast with earlier reports suggesting infants with MI have an increased risk of developing CFLD.^{18 21 29–32} However, broad definitions and criteria for the diagnosis of CFLD have been used in previous studies, which could explain these different results.

There was no significant difference between the proportion of infants with neonatal cholestasis and without cholestasis (13.0% vs 6.1% respectively) who developed CFLD with PH, but, as above, the sample size of the cholestatic subgroup is small and does not have the power to determine non-significance. However, since a large majority with cholestasis (87.0%) did not develop CFLD, it is unlikely to be a major contributing factor to the development of CFLD. As alluded to above, TPN, neonatal surgery, sepsis and even bile duct disease have been suggested as other risk factors for the development of neonatal cholestasis in CF infants.^{33 34} While the numbers of cholestatic infants are insufficient to address these issues, it is apparent from our data that over 50% of our infants with MI who underwent surgery and received TPN never developed cholestasis. Moreover, no difference was found in genotype (all had class I, II or III mutations), they were all pancreatic insufficient and there was no gender difference. Thus, besides the effects of MI and complicated MI which were the only significant findings contributing to the development of cholestasis, the other possibility would be a gene modifier effect similar to the *SERPINA1*

Z allele associated with CFLD.²⁰ In this regard it will be interesting to see whether the current North American gene modifier study²⁰ elucidates further modifiers which may contribute to the development of CFLD and whether, in turn, such modifiers are applicable to the occurrence of neonatal cholestasis.

An important observation of the current study is the uncommon occurrence of neonatal cholestasis (5.7%) even after including over 400 consecutive infants diagnosed by neonatal screening over an interval of 26 years. Moreover, the study has evaluated the occurrence of CFLD with PH and demonstrated a childhood/adolescent occurrence of only 6%–7%. Such data are essential when considering planning of any future prospective studies regarding neonatal cholestasis or CFLD, in terms of their incidence, diagnosis, cause or therapy, as the lower occurrence of either complication would require multicentre studies to provide adequate sample sizes.

Limitations of this study include its retrospective study design and the relatively small sample size of cholestatic infants and children with CFLD, which increases the risk of type II errors. Cholestasis and CFLD with PH are rare complication in CF patients. Therefore, despite our large cohort of 403 CF patients, we were not able to include more patients with cholestasis in this study. Analyses in large CF data registries are suggested to further explore this issue.

CONCLUSION

Cholestasis is an uncommon occurrence in CF affecting only 5.7% of the newborn CF population. The greatest risk factor for developing cholestasis is the presence of MI and it is statistically associated with the coexistence of complicated MI. Clinically significant CFLD with PH occurs in childhood/adolescence but is also an uncommon event, and the current study clearly demonstrates it is not associated with the occurrence of MI. An effect of neonatal cholestasis on the later development of CFLD with PH cannot be excluded by the current study due to the small sample size of cholestatic infants.

Contributors LL: contributed to the study design, data collection and data analysis, drafted the initial manuscript and approved the final manuscript as submitted. AKM: contributed to the data collection, reviewed and critically revised the manuscript and approved the final manuscript as submitted. DAF: contributed to the study design, reviewed and critically revised the manuscript and approved the final manuscript as submitted. MC: responsible for setting up the original database, reviewed and critically revised the manuscript and approved the final manuscript as

submitted. KJG: contributed to the study design, reviewed and critically revised the manuscript and approved the final manuscript as submitted.

Competing interests None.

Ethics approval Children's Hospital at Westmead (Activity N3984).

Provenance and peer review Not commissioned; externally peer reviewed.

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