Received: October 9, 2025
Accepted: October 26, 2025

Acad Med J 2025;5(3):189-193
UDC: 616-056.7-053.31
https://www.doi.org/10.53582/AMJ2553189k
Case report

MECONIUM ILEUS AS INITIAL PRESENTATION OF CYSTIC FIBROSIS: A RETROSPECTIVE CASE SERIES FROM A MACEDONIAN PEDIATRIC CYSTIC FIBROSIS CENTER

Krsteska Elena[1], Spirevska Lidija[1], Andreevska Stepanovska Andrijana[1, 2], Anastasovska Violeta[3], Jordanova Olivera[4], Cvejoska Cholakovska Valentina[1, 2], Fushtikj Naceva Stojka[1]

[1]Department of Cystic Fibrosis, University Children's Clinic, Faculty of Medicine, Ss. Cyril and Methodius University in Skopje, Republic of North Macedonia
[2]Department of Pulmonology and Allergology, University Children's Clinic, Faculty of Medicine, Ss. Cyril and Methodius University in Skopje, Republic of North Macedonia
[3]Department of Neonatal Screening, University Children's Clinic, Faculty of Medicine, Ss. Cyril and Methodius University in Skopje, Republic of North Macedonia
[4]Department of Clinical Laboratory, University Children's Clinic, Faculty of Medicine, Ss. Cyril and Methodius University in Skopje, Republic of North Macedonia
e-mail: ekrsteska90@gmail.com

Abstract

Introduction: Meconium ileus (MI) is often the earliest clinical sign of cystic fibrosis (CF), caused by intestinal obstruction due to thickened meconium from CFTR dysfunction. MI is commonly associated with severe CFTR mutations (classes I-III), which impair chloride and bicarbonate transport.

Case report: We report a retrospective case series of six neonates with MI, diagnosed with CF at Pediatric CF Center at University Children's Clinic, Skopje, over the last eight years. During this period, newborn bloodspot screening (NBS) program for CF was conducted, based on two sequential measurements of immunoreactive trypsinogen (IRT) and IRT-IRT protocol. All infants presented with early intestinal obstruction requiring surgical intervention, including enterotomy and ileostomy. Postoperative care included pancreatic enzyme therapy and nutritional support. CF diagnosis was confirmed via sweat chloride testing and genetic analysis, which showed a predominant presence of the F508del mutation in homozygous or compound heterozygous forms. Despite timely surgical intervention, three infants experienced severe complications and early mortality. It is noteworthy that one of these cases had false-negative NBS result, highlighting limitations of the IRT-IRT protocol in MI cases. The remaining patients showed varied recovery and nutritional outcomes.

Conclusions: MI is a known cause of false-negative results in CF NBS, as IRT levels may be low in affected neonates. Therefore, any newborn presenting with MI should be presumed to have CF until proven otherwise. Confirmation requires sweat chloride testing and genetic analysis. These findings support the need for revised CF NBS protocols in all MI cases to ensure timely diagnosis and management.

Keywords: cystic fibrosis, immunoreactive trypsinogen, meconium ileus, newborn screening

Introduction

Cystic fibrosis (CF) is a life-threatening autosomal recessive disorder caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene located on the long arm of chromosome 7. This gene encodes the CFTR protein, a chloride and bicarbonate channel expressed on epithelial surfaces. Dysfunction or deficiency of CFTR protein disrupts salt and water regulation, leading to thickened secretions and progressive damage in organ systems where fluid transport is essential[1,2].

CF is a multisystem disease with variable clinical presentation. The respiratory system is most commonly affected, resulting in chronic bronchiectasis, recurrent sinusitis, and progressive pulmonary insufficiency. Lung disease is the most important reason for morbidity and mortality in people with CF ($_{pw}$CF). Pancreatic involvement includes exocrine insufficiency with malabsorption and endocrine dysfunction leading to CF-related diabetes. Gastrointestinal complications range from meconium ileus (MI) in neonates to distal intestinal obstruction syndrome and biliary liver disease. The reproductive system is also impacted, with congenital bilateral absence of the *vas deferens* in males and reduced fertility in females. Electrolyte imbalances and metabolic disturbances further contribute to morbidity[3].

Newborn screening (NBS) has become a cornerstone of early CF diagnosis, enabling timely initiation of multidisciplinary care and preventive treatment. Advances in molecular diagnostics, nutritional support, and mutation-specific therapies, such as CFTR modulators, have significantly improved survival and quality of life[4,5].

One of the earliest and most specific manifestations of CF is meconium ileus, a neonatal intestinal obstruction caused by abnormally thick meconium in the terminal ileum. MI is strongly associated with severe CFTR mutations, particularly F508del, and is considered a clinical hallmark of CF in infancy[6]. The pathophysiology involves impaired bicarbonate secretion, acidic intestinal environment, and dehydrated mucus, resulting in mechanical obstruction. MI may present as “simple” (isolated obstruction) or “complicated” (associated with perforation, volvulus, or meconium peritonitis)[7-9].

Despite advances in prenatal diagnostics and surgical techniques, MI remains a clinical challenge due to its variable presentation and the genetic heterogeneity of CF. Moreover, MI can lead to false-negative results in IRT-based CF screening protocols, as IRT levels may be paradoxically low in affected neonates. Therefore, any newborn presenting with MI should be presumed to have CF until confirmed otherwise through sweat chloride testing and/or CFTR genetic analysis[10-12].

This study presents a case series of neonates with MI and confirmed CF in North Macedonia, highlighting diagnostic challenges within the national IRT-IRT screening protocol and emphasizing the need for revised strategies to ensure early and accurate diagnosis.

Case report

This retrospective case series included six neonates with MI as the first manifestation of CF, diagnosed during the national screening program in North Macedonia that was introduced in 2019, after one year pilot study[13]. Data from the medical records included NBS results, CFTR mutation profile, prenatal ultrasound findings, sweat chloride levels, gestational age and birth weight, age at surgical intervention, and survival outcome (Table 1).

Table 1. Characteristics of patients

Case	Genotype	Mutation Class	IRT1 ng/ml / IRT2 ng/ml	GA & BW	Sweat Chloride Test
1	F508del /F508del	Class II / Class II	**88.1 / 63.2**	38 GA, 2680 g	85 mmol/L
2	F508del/457TAT>G	Class II / Class I	40.6	40 GA, 3050 g	110 mmol/L
3	F508del / N1303K	Class II / Class II	58.1	39 GA, 3560 g	76 mmol/L
4	F508del /621+1G>T	Class II / Class I	**185.8**	37 GA, 2250 g	80 mmol/L
5	F508del / G542X	Class II / Class I	41.9	26 GA, 2180 g	83 mmol/L
6	F508del / F508del	Class II / Class II	**113.7 / 263.8**	41 GA, 3160 g	75 mmol/l

Immunoreactive trypsinogen (IRT), Gestational Age (GA), & Birth Weight (BW).

The patient cohort predominantly exhibited genotypes involving the F508del mutation, including homozygous and compound heterozygous. All patients presented with intestinal obstruction within the first days of life, requiring prompt surgical intervention. Surgical approaches included enterotomy with meconium evacuation and temporary ileostomy formation in severe cases. Postoperative management was standardized and included pancreatic enzyme replacement therapy, aggressive nutritional support with specialized formula feeding, and fat-soluble vitamin supplementation to address malabsorption. Follow-up included monitoring for postoperative complications such as anastomotic leaks, sepsis, electrolyte imbalances, and the timing of ileostomy closure. Sweat chloride testing in all cases yielded values above diagnostic thresholds (>60 mmol/L), and CF was confirmed through genetic testing. Notably, three of the neonates had false-negative NBS results (cut-off value: IRT1 <70 ng/ml at 36-48 hours after birth, IRT2 <45 ng/ml at 21st day after birth). Two neonates, despite timely surgical and medical interventions, experienced poor postoperative recovery and died due to severe complications within the first year of life, at five and nine months, respectively. The remaining patients had variable recovery trajectories, with differences in hospital stay duration and nutritional outcomes. Prenatal diagnosis was made in two cases, highlighting the need for improved prenatal screening strategies in high-risk pregnancies.

Discussion

This case series underscores the diagnostic and management challenges associated with meconium ileus as an early and often severe presentation of cystic fibrosis. Meconium ileus remains one of the most specific neonatal signs of CF and typically necessitates surgical intervention within the first days of life. In our cohort, all patients required surgery, emphasizing the urgency and severity of this presentation.

The predominance of F508del-associated genotypes in this cohort aligns with established genotype-phenotype correlations in CF, particularly those linked to severe disease. Most patients were either homozygous for F508del or compound heterozygotes with another class I-III mutation, consistent with literature indicating that MI is more common in patients with minimal or absent CFTR function[6,14].

A significant observation was the occurrence of false-negative NBS results in three patients. This is a well-documented phenomenon in MI cases, likely due to reduced levels of

IRT caused by prenatal pancreatic destruction or dilution from thick meconium. This finding supports existing recommendations that all newborns with MI should be presumed to have CF until proven otherwise, with diagnostic confirmation via sweat chloride testing and/or CFTR mutation analysis, irrespective of NBS results[10-12].

Postoperative outcomes varied. Two infants died from severe complications, highlighting the vulnerability of this patient group, even with timely diagnosis and adherence to standard of care. These outcomes emphasize the importance of multidisciplinary approach involving pediatric surgeon, neonatologist, gastroenterologist, and CF subspecialists. The lack of prenatal diagnosis in all but two cases underscores the need to enhance prenatal detection strategies, especially in at-risk families. Although prenatal genetic testing is not routine in many settings, greater awareness and accessibility could allow for earlier diagnosis and improved postnatal planning.

Nutritional management is vital in CF patients with MI due to pancreatic insufficiency-related malabsorption. Our approach involved early initiation of pancreatic enzyme replacement, high-calorie formula feeds, and fat-soluble vitamin supplementation, implemented consistently in patients. Overall, this case series reinforces the need for immediate CF evaluation in any neonate presenting with MI, regardless of NBS results. Timely surgical intervention, clinical vigilance, and standardized multidisciplinary postoperative care are critical to improve outcomes in this high-risk group.

Conclusions

MI is suspected if a baby fails to pass meconium shortly after birth and develops symptoms of bowel obstruction, such as distention of the abdomen or vomiting. MI must be treated immediately to prevent complications such as bowel perforation, a twisting of the bowel, or inflammation and infection of the abdominal cavity. All babies with MI should be tested for CF because more than 90 percent of full-term babies with MI have CF. MI is a known cause of false-negative results in CF NBS, as IRT levels may be low in affected neonates. Therefore, any newborn presenting with MI should be presumed to have CF until proven otherwise. Confirmation requires sweat chloride testing and/or CFTR genetic analysis. These findings support the need for revised CF NBS protocols in all MI cases to ensure timely diagnosis and management.

Conflict of interest statement. None declared.
Written informed consent for publication was obtained from the patient

References

1. Riordan JR, Rommens JM, Kerem B, Alon N, Rozmahel R, Grzelczak Z, *et al*. Identification of the cystic fibrosis gene: cloning and characterization of complementary DNA. *Science* 1989; 245(4922): 1066-73. doi: 10.1126/science.2475911.
2. Sathe M, Houwen R. Meconium ileus in Cystic Fibrosis. *J Cyst Fibros* 2017; 16 (Suppl 2): S32-S39. doi: 10.1016/j.jcf.2017.06.007.
3. Ratjen F, Bell SC, Rowe SM, Goss CH, Quittner AL, Bush A. Cystic fibrosis. *Nat Rev Dis Primers* 2015; 1: 15010. doi: 10.1038/nrdp.2015.
4. Elborn JS. Cystic fibrosis. *Lancet* 2016; 388(10059): 2519-2531. doi: 10.1016/S0140-6736(16)00576-6.
5. Lopez A, Daly C, Vega-Hernandez G, MacGregor G, Rubin JL. Elexacaftor/tezacaftor/ivacaftor projected survival and long-term health outcomes in people with cystic fibrosis homozygous for F508del. *J Cyst Fibros* 2023; 22(4): 607-614. doi: 10.1016/j.jcf.2023.02.004
6. Weerakkody Y, Kogan J, Foster T, et al. Meconium ileus. *Radiopaedia.org*. Accessed 28 Jul 2025. Available from: https://radiopaedia.org/articles/meconium-ileus

7. Tobias J, Tillotson M, Maloney L, Fialkowski E. Meconium ileus, distal intestinal obstruction syndrome, and other gastrointestinal pathology in the cystic fibrosis patient. *Surg Clin North Am* 2022; 102(5): 873-882. doi: 10.1016/j.suc.2022.07.016.
8. Padoan R, Cirilli N, Falchetti D, Cesana BM; Meconium Ileus Project Study Group. Risk factors for adverse outcome in infancy in meconium ileus cystic fibrosis infants: a multicentre Italian study. *J Cyst Fibros* 2019; 18(6): 863-868. doi: 10.1016/j.jcf.2019.07.003.
9. Rescorla FJ. Meconium ileus and the role of surgery. *Semin Pediatr Surg* 1999; 8(4): 264-271.
10. Grosse SD, Boyle CA, Botkin JR, Comeau AM, Kharrazi M, Rosenfeld M, *et al*. Newborn screening for cystic fibrosis: evaluation of benefits and risks and recommendations for state newborn screening programs. *MMWR Recomm Rep* 2004; 53(RR-13): 1-36. PMID: 15483524.
11. Lumertz MS, Rispoli T, Murieli da Rosa K, Pinto LA. False-negative newborn screening result for immunoreactive trypsinogen: a major problem in children with chronic lung disease. *J Bras Pneumol* 2019; 45(3): e20180062. doi: 10.1590/1806-3713/e20180062.
12. Dupuis A, Keenan K, Ooi CY, et al. Prevalence of meconium ileus marks the severity of mutations of the cystic fibrosis transmembrane conductance regulator (CFTR) gene. *Genet Med* 2016; 18(4): 333-340. doi: 10.1038/gim.2015.85.
13. Fustik S, Anastasovska V, Plaseska-Karanfilska D, Stamatova A, Spirevska L, Pesevska M, *et al*. Two years of Newborn screening for cystic fibrosis in North Macedonia: First experience. *Balkan J Med Genet* 2021; 24(1): 41-46. doi: 10.2478/bjmg-2021-0015.
14. Donos MA, Ghiga G, Trandafir LM, Cojocaru E, Țarcă V, Butnariu LI, *et al*. Diagnosis and Management of Simple and Complicated Meconium Ileus in Cystic Fibrosis, a Systematic Review. *Diagnostics (Basel)* 2024; 14(11): 1179. doi: 10.3390/diagnostics14111179.