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JSM Gastroenterology and Hepatology

Review Article

# Meconium Ileus in the Cystic Fibrosis Patients of Russia

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**Submitted:** 09 February 2016

**Accepted:** 28 March 2016

**Published:** 29 March 2016



**Keywords**
- Meconium Ileus
- Cystic Fibrosis
- Neonatal Screening

**Abstract**

The influence of meconium ileus (MI) on cystic fibrosis (CF) progression attracts steady interest due to high MI prevalence and widespread practice of neonatal screening.

**Study:** The aim of this study was to investigate MI prevalence in the Russian population and describe the clinical characteristics of patients with MI in the neonatal period in different age groups based on the Russian Federal Registry data as of 2014. One hundred forty two MI patients were analyzed. The patients were included in the registry, which contains 2131 CF patients from Russia.

**Results:** In 2014, the registry contained 6.6% CF patients who had experienced MI. Within the first year of life 22.1% of children were diagnosed, among them 10,7% of the children aged between 1 year and 7 years old, 5,6% of the children from 7 to 18 years old, and 1,5% of patients over 18. The age of diagnosis in patients with ileus was 5-fold lower than the age of diagnosis of the patients without ileus. It was 0.76±2.01 years old versus 3.72±6.16, $p<0.0001$. The sweat chlorides determined by sweat test were significantly higher in the group with ileus than in the group without ileus. Significant clinical differences were identified in the body mass index (BMI) only. The BMI was higher in the group of patients without MI. Electrolyte impairments, aspergillosis and hepatic cirrhosis were more frequent in MI group. The survival rate and age of death were lower for the patients with MI.

**Conclusion:** The frequency of MI was 6,6% among the patients with CF according to the Russian Federal Registry data (2014). The affect of MI on survival and quality of life still requires further discussion.

## ABBREVIATIONS

MI : Meconium Ileus ; CF : Cystic fibrosis ; CFTR: Cystic Fibrosis Trans membrane conductance Regulator; SD: Standard Deviation; Me: Median; IR: Interquartile Range; BMI : Body mass index ; ECFS : European Cystic Fibrosis Society; CFRD: Cystic fibrosis related diabetes; FVC : Forced Vital Capacity ; FEV1 : Forced Expiratory Volume in 1 second; ABPA : Allergic Broncho Pulmonary Aspergillosis

## INTRODUCTION

Meconium ileus (MI), which is defined as intestinal obstruction of abnormal meconium at the level of the terminal ileum, is diagnosed in 15-20% of newborns with cystic fibrosis (CF) [1-3]. In a number of countries, including the Russian Federation, this diagnosis was considered fatal for the patients during the first months of life before the neonatal screening for CF was introduced. The National CF newborn screening program was launched in 2007. The Russian Federation national registry was organized in 2011. These two events enable us to estimate the prevalence and outcome of MI [3].

The aim of the current study was to investigate MI prevalence in the Russian population and describe MI features in various age groups, based on the Russian Federal registry of 2014.

## MATERIALS AND METHODS

### Patients and techniques

The research was retrospective. The analysis of MI prevalence was based on the national registry of CF patients of 2014. The registry contained 2131 CF patients. There were 1509 children (78 of those under 1 year, 708 of those 1 to 7 y. o., 723 of those 7 to 18 y. o.), while the number of adults was 662 (338 of those 18-25 y. o., 216 of those 25-32 y. o., and 68 patients older than

32). There were determined clinical, laboratory and instrumental data related to the requirements of the ECFS (European Cystic Fibrosis Society) Patient Registry (https://www.ecfs.eu/projects/ecfs-patient-registry/information-about-ecfspr-cf-patients). Only the patients meeting the diagnostic criteria were included in the registry. The following data were analyzed: the age of diagnosis, double-check sweat chloride test, the presence of pancreatic insufficiency, extra pulmonary and pulmonary complications (cirrhosis with portal hypertension, cystic fibrosis related diabetes [CFRD] with fasting hyperglycemia, osteoporosis, forced vital capacity [FVC], forced expiratory volume in 1 second ([FEV1], height, weight, and body mass index (BMI). We studied the frequency of Staphylococcus aureus, Haemophilus influenzae, Streptococcus pneumonia, Pseudomonas aeruginosa, Burkholderia cepacia, nontuberculous Mycobacteria and other respiratory infections.

The multiplex amplification (insertion/deletion mutation test) method was applied for identifying CFTR mutations. The technique of allele-specific ligation with a subsequent amplification was used for the registration of mutations points (single nucleotide polymorphism). For a number of patients, the nucleotide sequence was determined by the procedure of direct automatic sequence with the help of the sequenator unit produced by 'Applied Biosystems' in accordance with the manufacturer's protocol.

The statistical data processing was performed by STATISTICA v.10 (StatSoft, Inc., USA) software pack. Depending on the kind of distribution, the measures of central tendency and scattering were either mean (M) ± standard deviation (SD) or median (Me)±IR (interquartile range). Means or medians were compared by using the Student t-test or Mann-Witney test. Survival rate analysis was performed by the Kaplan-Meier survival curve. The log-rank test was applied to assess the difference of survival rates between the groups. The difference was registered as significant at $p < 0.05$.

## RESULTS

Clinic and genetic analyses were performed for children and adults who had MI according to the Russian Federal Registry as of 2014. The number of patients with MI was 141 (6.6% of the total number of patients), including 117 patients (5.49%), who had surgical treatment, and 24 (1.13%) patients, who received conservative treatment.

In the registry of 2014, MI was diagnosed in 17 cases (22.1%) among the CF patients of the first year of life. As for the children aged 1 to 7 years, MI was registered in 75 cases (10.7%) while in the group of the patients aged 7 to 18 y. it was registered in 40 cases (5.6%). In anamnesis MI prevalence among adults was 1.5%. The age of diagnosis for CF patients with MI was 0.76±2.01 y.o. compared to 3.72±6.16 y.o. in the group without MI, p<0.0001 (Table 1). The sweat chlorides determined by sweat test were significantly higher in the group with ileus than in the group without ileus (107±21 vs 101±24, p=0.0052). Significant difference in clinical parameters was registered for BMI only. BMI was higher for the patients without MI in the general group. However, pulmonary function was better within the MI group. All the children with MI had pancreatic insufficiency.

In the group of children from birth to 18 years, significant difference was registered in patient's age, age of diagnosis, and sweat test results in the same way as in the whole group of patients (Table 2).

The patients' health was assessed in different age groups. The diagnosis of CF in children register aged under 1 year at MI was set before birth or in the first days. CF diagnosis by means neonatal screening was established in patients under 2 months of age. Children born in 2014 did not differ from group to group (MI-group and MI-free group) in any parameter tested. In the age group from 1 to 7 years old, there were differences in the age of diagnosis (0.19±0.29 y.o. [MI-group] vs 0.52±0.85 y.o. ([MI-free group], $p$=0.0011) and sweat test results (106.07±19,81 mM/l [MI-free group] vs 112.13± 18,57 mM/l ([MI-group], p=0.0157). In the group of ages from 7 to 18 years old (born when neonatal screening was not available in Russia), there were differences in the age of diagnosis (1.47±3.06 y.o. [MI-group]) vs 2.89±3.42 y.o. ([MI-free group], p=0.0101), body weight (28.8±9.8 kg [MI-group] vs 33.7±12.9 kg [MI-free group], p=0.0203) and height (134.4±17.8 cm [MI-group] vs 140.9±17.5 cm [MI-free group], p=0.0269). Only the introduction of a national program of neonatal screening in Russia drew attention to the problem of CF as a whole and this has enabled early diagnosis. This has led

**Table 1**: General characteristics of patients with meconium ileus and without ileus in common group.

| Index | Patients without MI (MI-free group) | Patients with MI (MI-group) | P-value |
|---|---|---|---|
| Mean age, years | 13.16±9.69 | 6.4±5.64 | <0.0001 |
| Age of diagnosing, years | 3.72±6.16 | 0.76±2.01 | <0.0001 |
| Sweat test 1, mM/l | 100.88±23.86 | 106.94±20.58 | 0.0052 |
| Sweat test 2, mM/l | 101.76± 22,51 | 112.24 ±21,16 | 0,0001 |
| BMI | 16.96±3.13 | 15.82±2.02 | <0.0001 |
| FEV1 | 73.33±27.54 | 84.71±25.33 | 0.0103 |
| Mild CFTR mutations | 23,3% | 4,4% | 0,00002 |
| Homozygous for the F508del mutation | 25,5% | 40,8% | 0,00673 |

Abbreviations: BMI: Body Mass Index; FVC: Forced Vital Capacity; FEV1: Forced Expiratory volume in 1 second; MI - Meconium ileus.

**Table 2:** General characteristics of children with meconium ileus and without ileus.

| Index | Children without MI (MI-free group) | Children with MI (MI-group) | P-value |
|---|---|---|---|
| Mean age, years | 7.73±4.88 | 5.45±4.42 | 0.0000 |
| Age of diagnosing, years | 1.68±2.75 | 0.57±1.79 | 0.0000 |
| Sweat test 2, mM/l | 103.69±21.49 | 112.12±20.23 | 0.0018 |
| Abbreviations: MI- Meconium Ileus | | | |

**Table 3:** Characteristic of CF patients with MI in anamnesis in different ages of life.

| Index | Patients without MI (MI-free group) | Patients with MI (MI-group) | p* |
|---|---|---|---|
| Common group | | | |
| Electrolite disorder | 3,54% | 7.97% | 0,00911 |
| ABPA | 1,38 | 2,16 | 0,0091. |
| Group from 1 to 7 y. o. | | | |
| Sweat test results | 106.07±19,81 mM/l | 112.13± 18,57 mM/l | p=0.0157 |
| Group of age from 7 to 18 y. o. | | | |
| Body weight | 33.7±12.9 kg | 28.8±9.8 kg | 0.0203 |
| Height | 140.9±17.5 cm | 134.4±17.8 cm | p=0.0269 |
| Group from 18 to 25 y.o | | | |
| ABPA | 0,99 0% | 11,1% | 0,0083 |
| Cirrhosis with portal hypertension | 6,8% | 33,3% | 0,0033 |
| Group adult | | | |
| Cirrhosis with portal hypertension | 5,09% | 33,3% | 0,0002 |
| Abbreviations: p - Mann-Witney test; ABPA: Allergic Broncho Pulmonary Aspergillosis; MI: meconium ileus | | | |

to the understanding of professionals that patients with MI are primarily CF patients.

The Patients with MI were also more susceptible to the progression of hepatic cirrhosis, allergic bronchopulmonary aspergillosis (ABPA), and electrolyte impairments (Table 3). The electrolyte impairments occurred more frequently in patients who had experienced MI, at the rate of 7.97% versus 3.54% for those without MI, p=0.0091. ABPA was registered in 3 cases (2.16%) versus 26 cases (1.38%) without MI in the general group. In the group of adults with MI, ABPA was

For the groups of children with and without MI, hepatic cirrhosis with portal hypertension was registered with the same frequency (3.15% and 3.05% respectively). Among adults with MI (9 patients), 3 patients (33.3%) had cirrhosis with portal hypertension. In the group without MI, cirrhosis was identified in 29 patients (5.09%) of 570 persons (p=0.0002, Mann-Witney test.).

In the group of patients without MI, 127 mutations in the *CFTR* gene were registered, while in the group with MI, there were 25 mutations, as: delta F508 – 59%, CFTRdele2, 3 – 9,4%, G542X - 2,7%, W1282X- 2,2%, 394delTT -1,8%, N1303K -1,3% , 3821delT-1,3%, 2143delT-0,9%, S1196X-0,89%. 15 mutations (2184insA, 1677delTA, R553X, 3849+ 10kbC- >T, E92K, L1335P, L138ins, R1158X, 712- 1G- >T, R1066C, S466X, R1070Q, Dup ex 6b- 10, 1898+ 2T- >C, 583delC, W496X) occurred at a frequency of – 0,45%/

No difference was found in the frequency of allele F508 del between MI-group and MI-free group in the general group of patients. MI patients differed in the rate of mild mutations, which was 4.39% vs. 23.85% in the group without MI (p=0.00192). The CFTR dele 2, 3 (21 kb) mutation was distributed as follows: 9.4% for the patients with MI versus 5.7 % for the patients without ileus. The Patients with ileus were identified with such mutations as G542X (2.50% compared to 1.08%) and 3821delT (1.25% compared to 0.37%) more frequently than without MI.

In the group with MI, 4 patients died in 2014 (2.84%, mean age 1.44±1.59 years old) and 137 patients (mean age 6.54±5.66 y.o.) were alive as of December 31, 2014. As to the other group (CF MI-free patients), 34 patients (1.73%, mean age 16.83±9.69 y.o.) died and 1937 (mean age 13.09±9.69 y.o.) were alive. Comparing the survival rate (figure 1) between the two groups (applying survival analysis and log-rank test) the following distinction was identified: the survival rate for patients with ileus was significantly lower than for patients without ileus (p=0.04624).

The group of the patients with MI was also compared with the group of those without MI in the frequency of other indicators, including the cystic fibrosis related diabetes [CFRD] with fasting hyperglycemia, osteoporosis, forced vital capacity [FVC], Staphylococcus aureus, Haemophilus influenzae, Streptococcus pneumonia, Pseudomonas aeruginosa, Burkholderia cepacia, nontuberculous Mycobacteria. The groups did not show statistically significant differences in the above indicators.

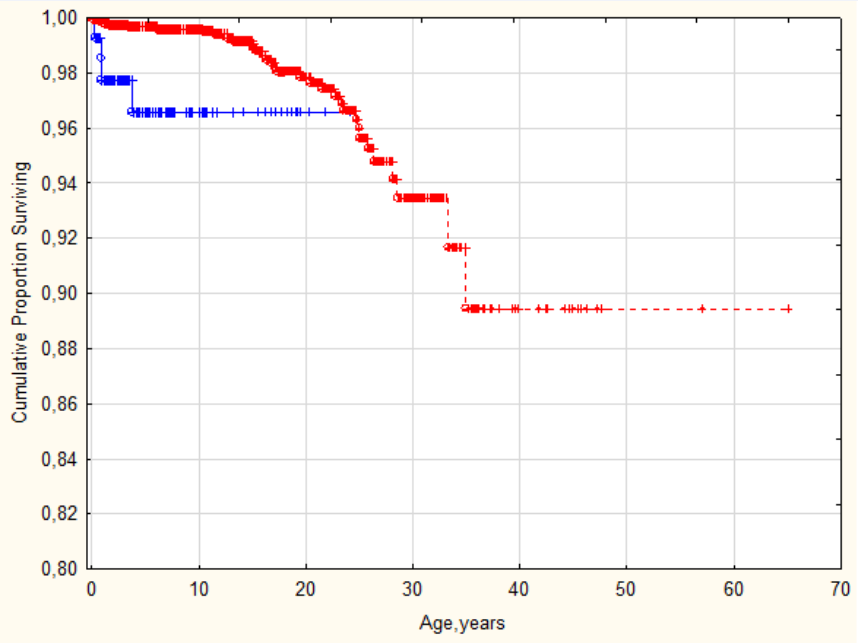


**Figure 1** Survival rates (Kaplan-Meier plots): the blue curve is for MI-phenotype (group 1) and the red one is for MI-free phenotype (group 0). Axis Y shows the cumulative proportion surviving (dimensionless), axis X shows the patient's in years.

## DISCUSSION

The prevalence of MI and the problem of the health of patients with MI in cystic fibrosis continues to be discussed by researchers (all) [1-9]. The frequency of MI was 6,6% of the patients with CF according Russian Federal Registry data (2014). MI prevalence varies among different registers US, Italy, Germany from 13 to 21% [3,7].MI prevalence in children below the age of 1 year was 22.1% and decreased in the group of adults to 1 5% in anamnesis MI prevalence of in the early years of life is the real agrees with reports [3].

The health of children during the early years of life is practically the same in the groups with and without MI [7,8]. The number of patients with MI in older age groups decreased. This can be explained by the absence of neonatal screening in Russia until 2007, late diagnosis, the death of infants due to electrolyte disturbances and possibly other complications, such as cirrhosis of the liver. Age of death of the patients from the registry in 2014 with MI (within the first three years of life) confirm this hypothesis.

The common pathophysiology is the inspissation of secretions in the hollow structures of the gastrointestinal tract. [9]. Breach of chlorine intestinal mucosa channel function before child birth led to high rates of sweat test, chronic pancreatic insufficiency in 100% of cases, as well as high frequency electrolyte disorders in the first years of life patients with MI. Later after 7 years children with MI had low figures of the growth and weight [8]. Since that time BMI was lower in all age groups.

The adult patients probably died due to some of reasons, such as cirrhosis of the liver. Liver dysfunction at an early age in children with MI was observed in the report [8]. The data about the frequency of homozygous for the F508 del mutation and mild mutations agreement with the results of research [3]. We found a high frequency of mutations CFTR dele 2, 3 (21 kb) and G542X, The last mutation discussed also in this report [3].

## CONCLUSION

The prevalence of MI was 6.6% of CF patients according to Russian data of the Federal Register (2014). MI prevalence in children below the age of 1 year is 22.1%. It is valid. MI problem needs further investigation.

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**Cite this article**

*Kondratyeva E, Sherman V, Kapranov N, Amelina E, Cherniak A, et al. (2016) Meconium Ileus in the Cystic Fibrosis Patients of Russia. JSM Gastroenterol Hepatol 4(2): 1058.*