

Katarzyna Zybert[1], Ewa Mierzejewska[2], Dorota Sands[1]

CLINICAL STATUS AND SOMATIC DEVELOPMENT OF PATIENTS WITH OR WITHOUT MECONIUM ILEUS DIAGNOSED THROUGH NEONATAL SCREENING FOR CYSTIC FIBROSIS

STAN KLINICZNY I ROZWÓJ SOMATYCZNY PACJENTÓW Z NIEDROŻNOŚCIĄ SMÓŁKOWĄ LUB BEZ NIEDROŻNOŚCI SMÓŁKOWEJ U PACJENTÓW, U KTÓRYCH MUKOWISCYDOZĘ ROZPOZNANO W OPARCIU O BADANIE PRZESIEWOWE NOWORODKÓW

[1]Institute of Mother and Child, Cystic Fibrosis Centre, Warsaw, Poland
[2]Department of Epidemiology and Biostatistics, Institute of Mother and Child, Warsaw, Poland

Abstract

The aim of the study *was to compare the patients with abnormal result of newborn screening for cystic fibrosis (CF NBS), with or without meconium ileus (MI), in regard to their clinical status at the diagnosis and early childhood somatic development.*

Material and methods: *The survey comprised patients with abnormal results of CF NBS which was carried out during years 2006-2011. Cohort of 92 children remaining under care of Institute of Mother and Child was followed in the period 09.2006-12.2011. In our study there were two groups compared: 19 children with MI and 73 children without MI. Clinical characteristics and genotype were evaluated and biochemical tests assessing pancreatic insufficiency and hepatic dysfunction were performed at the time of diagnosis, then annual weight and height Z-scores as well as clinical status based on Shwachman-Kulczycki score were collected. Cox proportional hazards regression model was used to assess the effect of MI and genotype on development of pancreatic insufficiency.*

Results: *MI was observed in 19 (20.6%) of 92 CF infants. MI and non-MI patients did not differ in respect of sex, gestational age and birth weight. The presence of severe genotype was more frequent in MI than non-MI group (94.7 and 64.4% respectively), whereas no significant difference was found in F508del mutation distribution. At the time of diagnosis inadequate weight gain and hepatic function disturbances prevailed more often in MI (68.4% and 31.6%) than non-MI group (39.7% and 9.6%). Pancreatic insufficiency was diagnosed in all children in MI group and in 76.1% of non-MI group and the risk of PI development was 2.3 (1.4-4.0) times higher in MI than in non-MI patients. MI children had smaller weight-for-age Z-score at the age of 12 months (-0.95) when compared to non-MI children (-0.13). Weight Z-scores compared at the age of 2 and 3 years as also height-for-age Z-scores did not differ significantly between groups. No statistically significant difference in clinical status according to Shwachman-Kulczycki score was found between MI and non-MI groups at the age of 12 months, 2 years and 3 years.*

Conclusions: *Our results suggest that the history of MI in children with CF may predispose them to more severe clinical course of disease in early childhood: insufficient weight gain and liver disturbances at the time of diagnosis, higher risk of developing pancreatic insufficiency and smaller weight at the age of 12 months, although clinical status according to Shwachman-Kulczycki score did not differ from non-MI group. Patients with MI, may require more intensive care and supervision in treatment. Further research is needed to asses MI impact on development of CF children in subsequent years.*

Key words: newborn screening, meconium ileus, pancreatic insufficiency, *CFTR* gene mutation

Streszczenie

Cel pracy: *Celem pracy było porównanie stanu klinicznego w momencie diagnozy oraz rozwoju somatycznego we wczesnym dzieciństwie pacjentów z nieprawidłowym wynikiem badania przesiewowego noworodków w kierunku mukowiscydozy (CF NBS), u których wystąpiła lub nie wystąpiła niedrożność smółkowa (MI).*

Materiał i metody: *Kohorta 92 dzieci z nieprawidłowym wynikiem CF NBS pozostawała pod opieką IMiD w okresie od 09.2006 do 12.2011. Przy rozpoznaniu oceniano stan kliniczny, genotyp, oraz wykonywano testy biochemiczne oceniające funkcję wątroby i wydolność zewnątrzwydzielniczą trzustki. Raz w roku przeprowadzano pomiary masy i długości ciała wyrażając je w wartościach znorma-lizowanych, a także oceniano stan kliniczny według skali Shwachmana-Kulczyckiego. W celu oszacowa-nia wpływu MI oraz genotypu na rozwój niewydolności trzustki zastosowano model proporcjonalnego ryzyka Coxa.*

Wyniki: *MI wystąpiła u 19 (20,6%) z 92 badanych noworodków. Dzieci z grupy MI i bez MI nie różniły się pod względem płci, wieku ciążowego oraz urodzeniowej masy ciała. Stwierdzono, że ciężki genotyp występował częściej w grupie MI niż w grupie bez MI (odpowiednio 94,7% oraz 64,4%), natomiast nie stwierdzono różnic w rozkładzie mutacji F508del. W momencie rozpoznania w grupie dzieci z MI częściej występowały niezadawalające przyrosty masy ciała oraz objawy zaburzenia funkcji wątroby (68,4% i 31,6%) niż w grupie bez MI (39.7% oraz 9.6%). Niewydolność zewnątrzwydzielniczą trzustki stwierdzono u wszystkich dzieci z MI natomiast u dzieci bez MI w 76.1%, a ryzyko wystąpienia PI było 2,3 (1,4-4,0) razy wyższe w grupie MI. W grupie MI u dzieci w wieku 12 miesięcy stwierdzono mniejszą masę ciała wyrażoną w wartościach znormalizowanych (-0.95) w porównaniu z grupą dzieci bez MI (-0,13). Nie wykazano istotnych statystycznie różnic masy ciała w wieku 2 i 3 lat oraz długości ciała pomiędzy badanymi grupami. Nie stwierdzono istotnych statystycznie różnic w stanie klinicznym ocenianym według skali Shwachmana-Kulczyckiego pomiędzy grupami z MI oraz bez MI.*

Wnioski: *Nasze badania sugerują, że wystąpienie MI u dzieci z CF może predysponować do cięższego przebiegu choroby w okresie niemowlęcym, niezadawalających przyrostów masy ciała i zaburzeń funkcji wątroby w momencie rozpoznania, wyższego ryzyka wystąpienia zewnątrzwydzielniczej niewydolności trzustki oraz niższej masy ciała w wieku 12 miesięcy jakkolwiek stan kliniczny pacjentów badanych grup nie różnił się. Dzieci z MI wymagają intensywniejszej terapii i monitorowania CF. Wskazane są dalsze badania w celu oceny konsekwencji MI na rozwój dzieci z CF w kolejnych latach.*

Słowa kluczowe: badanie przesiewowe noworodków w kierunku mukowiscydozy, niedrożność smółkowa, niewydolność zewnątrzwydzielnicza trzustki, mutacje genu *CFTR*

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INTRODUCTION

Meconium ileus (MI) is the earliest symptom of CF and it appears in about 6-20% CF affected newborns [1, 2]. In these cases, meconium is characteristic for high thickness and stickiness which results in intestinal passage disturbances and gastrointestinal tract mechanical obstruction. Clinical manifestation is observed in the first 48 hours of life. A newborn baby does not pass meconium, his abdomen is distended and the lower right quadrant reveals palpable mass. Feeding is uneasy and cholemesis appears. Abdominal cavity radiogram usually presents intestinal loop widening and granular mass in right lower quadrant. Contrast medium application may visualise bead shaped masses in a small intestine distal part as well as a stricture of the large intestine.

In a number of cases, MI symptoms are observed even during obstetric ultrasonography. Among them, there are hydramnion, hyperechogenic masses in small intestine distal part dilatation and peritoneum calcification.

MI formation pathomechanism is not absolutely clear. There are reports claiming that MI development is largely influenced by environmental disturbances in small intestine lumen. In normal conditions, during mucous production, HCO_3^-, provoke mucins loosening by Ca^{2+} ions chelation so that mucus is less thick and better hydrated. In the case of abnormal structure of CFTR albumin, in CF patients HCO_3^- secretion is disturbed. Intestinal pH is smaller and water content decreased. These features lead to bigger adhesion to intestinal walls [3, 4]. Correlation is found between *CFTR* gene mutations and frequency of MI [1]. However, significantly higher frequency of MI prevalence in monozygotic twins than in dizygotic ones or siblings points at an important role of modifying genes in this pathology formation [5, 6, 7]. In families, where MI was diagnosed in one child, there is 39% risk of finding it in another one [8].

Up to the 70ties, mortality of CF patients with diagnosed MI exceeded 70% [9, 10, 11, 12]. Survival improvement rate was largely influenced by introduction of Gastrografin used in non-operative treatment as well as by operative

techniques and postoperative procedures modification. Available literature from the centre in Pennsylvania shows that in the 60ties, 6 month survival amounted to 33%, in the 70ties to 60% and after 1979, it was 100% [13].

THE AIM OF THE STUDY

The aim of the study was to compare the patients with abnormal result of newborn screening for cystic fibrosis (CF NBS), with or without meconium ileus (MI), in regard to their clinical status at the diagnosis and early childhood development.

MATERIAL AND METHODS

The survey comprised patients with abnormal results of CF NBS (newborn screening for cystic fibrosis) born in the voivodships of Masovian, Warmian-Masurian, Podlaskie and Lublin Districts, the diagnosis and treatment of whom were carried out in Mother and Child Institute (IMiD). In years 2006-2011 582 693 newborns were examined, CF diagnosis was established in 100 children. Ninety two of them are under care of our centre and were followed longitudinally from September 2006 to December 2011, with the mean time of follow-up 33 months.

Nineteen of these children developed MI so in our study there were two groups compared: 19 children with MI (MI group) and 73 children without MI (non-MI group).

CF NBS strategy was modified over time [14]. Children with CF NBS abnormal result were called to IMiD for consultation visit in order to verify the diagnosis. Disease diagnosis was established in accordance with criteria included in national and international diagnostic standards [15, 16, 17, 18]. On specialist consultation visit, medical history was taken, physical examination and sweat tests with the use of pilocarpine iontophoresis by Gibson and Cook as well as with conductivity method were performed [19], provided medical documentation was analysed with special concern of CF typical symptoms – body mass increase, diet, diarrhoea and respiratory tract symptoms (cough, respiratory tract infections) as well as hepatic functions disturbances (based on biochemical tests). Data concerning course of pregnancy were collected and early anthropometric measurements were made. In order to assess hepatic function, biochemical test were made (total protein, albumins, aspartate aminotransferase, alanine transaminase, gamma-glutamyltranspeptidase, alkaline phosphatase, bilirubin). Pancreatic insufficiency (PI) was diagnosed on the basis of the clinical symptoms (presence of fat in stools, diarrhoea, failure to thrive) and faecal elastase 1 activity. Subsequent specialist visits were scheduled depending on patient's clinical status, initially every 1-3 months and then usually four times in a year. Once a year, closely to the date of birth, patient's clinical status was assessed basing on Shwachman-Kulczycki score.

Infant gestational age- and gender-specific birth weight Z-scores were calculated by using Fenton's intrauterine growth chart [20]. Age- and gender-specific Z-scores for weight and height were computed by using the Institute of Mother and Child's growth reference [21].

Two classification systems were used in genotype analysis, the first – based on F508del mutation (homozygous, heterozygous or neither mutation) and the second – on the basis of their functional effect on CFTR production. Genotypes with two class I, II or III mutations were classified as „severe" type, genotypes with at least one class IV or V mutation, associated with some residual CFTR function – as "mild". "Unidentified" genotype group comprised patients with only one „severe" mutation and the second or both mutations, which could not be assigned to a functional class [22, 23, 24].

Statistical analysis

Patients characteristics are presented as means ± standard deviation (SD) for normally distributed variables or medians and range for non-normally distributed data. Normality was assessed by Kolmogorov-Smirnov test and graphical inspection of data. Differences in characteristics, results of sweat tests and physical development of MI and non-MI patients were assessed using Student's t-test for normally distributed variables and Mann-Whitney test for non-normally distributed data. Group comparisons of categorical variables (patients' characteristics, clinical manifestations at the time of diagnosis, clinical status according to Shwachman-Kulczycki score) were performed using Pearson X^2 test and Fisher exact test, as appropriate. Cox proportional hazards regression model was used to assess the effect of MI and genotype on development of pancreatic insufficiency. P-value<0.05 was accepted as statistically significant. Statistical analyses were performed using IBM SPSS v.18 and StatXact-3, version 3.1.

RESULTS

Characteristics of examined groups – MI and non-MI patients are presented in Table I.

No statistically significant differences was found between both groups in respect of sex, gestational age, frequency of twins and birth weight. Age of children at assessment did not differ between groups.

In all patients, DNA analysis was made as an integral part of CF NBS. The analysis enabled identification of mutation in *CFTR* gene alleles in every examined child. *CFTR* gene most common mutation in both examined groups was *F508del* variation prevailing with the frequency close to 60% of examined alleles. Prevalence of *dele2,3(21kb), N1303K, R553X, 2143delT* mutations exceeded 2% in both groups. The second most frequent mutation in non-MI group – *3849+10kbC>T* (8.2%) was not observed in MI patients (Table II).

Between both examined groups, no significant difference was found in genotype distribution based on *F508del* mutation. However statistically significant difference was observed in the distribution of genotypes analysed in respect of their functional class. Mild genotype appeared in 23.3% of children from non-MI and did not occur in MI group, while severe genotype was detected in 94.7% of patients of MI group and 64.4% of patients of non-MI group (Table III).

The results of sweat tests performed at diagnosis did not differ significantly in MI as compared with non-MI

Table I. Characteristics of the CF patients, who developed and did not develop meconium ileus.
Tabela I. Charakterystyka pacjentów z mukowiscydozą, z niedrożnością smółkową lub bez niedrożności smółkowej.

		MI (n=19)	Non-MI *Bez MI* (n=73)	p-value
Gender *Płeć*	**Male** *Męska*	9 (47.4%)	35 (47.9%)	0.950
	Female *Żeńska*	10 (52.6%)	38 (52.1%)	
Gestational age (weeks)* *Wiek ciążowy (Hbd)**		40 (30 – 41)	39 (35 – 42)	0.235
Birth weight *Urodzeniowa masa ciała*	**(g)#**	3072 (±907)	3320 (±454)	0.097
	Z-score#	0.009 (±1.186)	-0.276 (±0.892)	0.251
Pregnancy *Ciąża*	**Single** *Pojedyncza*	16 (84.2%)	71 (97.3%)	0.058
	Twin *Bliźniacza*	3 (15.8%)	2 (2.7%)	
Age at assessment (months)* *Wiek w momencie ukończenia obserwacji (miesiące)**		33 (9 – 62)	33 (0 – 64)	0.526

*Data are presented as median values (min – max) – *Dane są przedstawione jako mediany (minimum – maksimum).*
#Data are presented as mean values ±SD – *Dane są przedstawione jako średnie ±SD.*

Table II. Frequencies of the most common mutations of CFTR gene in MI and non-MI patients.
Tabela II. Częstość występowania najczęstszych mutacji genu CFTR w grupach pacjentów z MI i bez MI.

CFTR mutation *Mutacja CFTR*	**MI** (n=38)	**Non-MI** *Bez MI* (n=146)	**All patients** *Ogółem* (n=184)
F508del	23 (60.5%)	87 (59.6%)	110 (59.8%)
3849+10kbC>T	–	12 (8.2%)	12 (6.5%)
dele2,3(21kb)	3 (7.9%)	5 (3.4%)	8 (4.4%)
N1303K	2 (5.3%)	6 (4.1%)	8 (4.4%)
R553X	1 (2.6%)	6 (4.1%)	7 (3.8%)
2143delT	1 (2.6%)	4 (2.7%)	5 (2.7%)
2184insA	2 (5.3%)	2 (1.4%)	4 (2.2%)
W1282X	–	3 (2.1%)	3 (1.6%)
R334W	–	3 (2.1%)	3 (1.6%)
2183AA>G	–	3 (2.1%)	3 (1.6%)
G542X	1 (2.6%)	1 (0.7%)	2 (1.1%)
1898+1G>C	1 (2.6%)	1 (0.7%)	2 (1.1%)
3272-26A>G	–	2 (1.4%)	2 (1.1%)
Others *Pozostałe*	4 (10.6%)	11 (7.4%)	15 (8.1%)

group. Average values amounted to 73.9 mmol/l in MI group and 76.9mmol/l in non-MI group for pilocarpine iontophoresis whereas for conductivity method they were 101.8 and 100.6 mmol/l respectively (Table IV).

Median of diagnosis age in MI group amounted to 34 days (11-147 days) and in non-MI group – 36 days (11-90 days) and the difference between groups was not significant (p=0.923).

In the period when the observation was completed, PI referred to all children in MI group and 76.1% of non-MI group. In MI group the risk of PI development was over two times higher than in non-MI group. Additionally, lower risk of PI was observed in children who were not homozygotes of *F508del* mutation (Table V).

In the period of diagnosis, insufficient weight gain referred mainly to MI (68.4%) than to non-MI (39.7%) children and the difference was statistically significant. In MI children, hepatic function disturbances prevailed more often – in 31.6% of patients, while in non-MI group this symptom was presented by 9.6% of patients. Among examined children, no difference was found in clinical respiratory symptoms (Fig. 1).

At the age of 12 months in MI group, mean weight-for-age Z-score was significantly lower in comparison with non-MI group (-0.95 and -0.13 respectively, p=0.004). This trend was observable also at the age of 2 and 3 years, but the differences were not significant (Fig. 2a and 2b).

Mean height-for-age Z-score at the age of 1, 2 and 3 years did not differ between groups.

Table III. Distribution of CFTR genotypes according to presence of F508del mutation and to the functional class in MI and non-MI patients.

Tabela III. Rozkład genotypów CFTR według obecności mutacji F508del i według klasy funkcjonalnej w grupach pacjentów z MI i bez MI.

	MI	Non-MI *Bez MI*	p-value
F508del/F508del *F508del/F508del*	7 (36.8%)	25 (34.2%)	0.967
F508del/other *F508del/inna*	9 (47.4%)	37 (50.7%)	
Other/other *Inna/inna*	3 (15.8%)	11 (15.1%)	
All *Ogółem*	19 (100.0%)	73 (100.0%)	
Severe *Ciężki*	18 (94.7%)	47 (64.4%)	0.018
Mild *Łagodny*	–	17 (23.3%)	
Unidentified *Nieokreślony*	1 (5.3%)	9 (12.3%)	
All *Ogółem*	19 (100.0%)	73 (100.0%)	

Table IV. Quantitative pilocarpine iontophoresis and conductivity in MI and non-MI patients.

Tabela IV. Wartości ilościowej jontoforezy pilokarpinowej oraz testu konduktometrycznego w grupach pacjentów z MI i bez MI.

	MI	Non-MI *Bez MI*	p-value
Pilocarpine iontophoresis [mmol/l]* *Jontoforeza pilokarpinowa [mmol/l]**	73.9 (±16.7)	76.9 (±22.3)	0.595
Conductivity test [mmol/l]# *Metoda konduktometryczna [mmol/l]#*	101.8 (±19.8)	100.6 (±21.5)	0.987

*performed in 19 MI patients and 72 non-MI patients – *wykonano u 19 pacjentów z MI oraz u 72 bez MI.*
#performed in 18 MI patients and 69 non-MI patients – *#wykonano u 18 pacjentów z MI oraz u 69 bez MI.*

Table V. Risk factors of pancreatic insufficiency in CF patients.

Tabela V. Czynniki ryzyka wystąpienia niewydolności zewnątrzwydzielniczej trzustki w grupie pacjentów z mukowiscydozą.

		β	p-value	HR	95%CI
Group *Grupa*	**Non-MI** *Bez MI*	–	–	Ref.	–
	MI	0.846	0.002	2.33	1.36 – 4.00
Genotype *Genotyp*	**F508del/ F508del**	–	–	Ref.	–
	F508del/other *F508del/inna*	-0.858	0.001	0.42	0.25 – 0.71
	Other/other *Inna/inna*	-1.377	0.001	0.25	0.11 – 0.57

HR – hazard ratio; 95%CI – 95% confidence interval – HR – *współczynnik ryzyka*; 95%CI – *95% przedział ufności.*

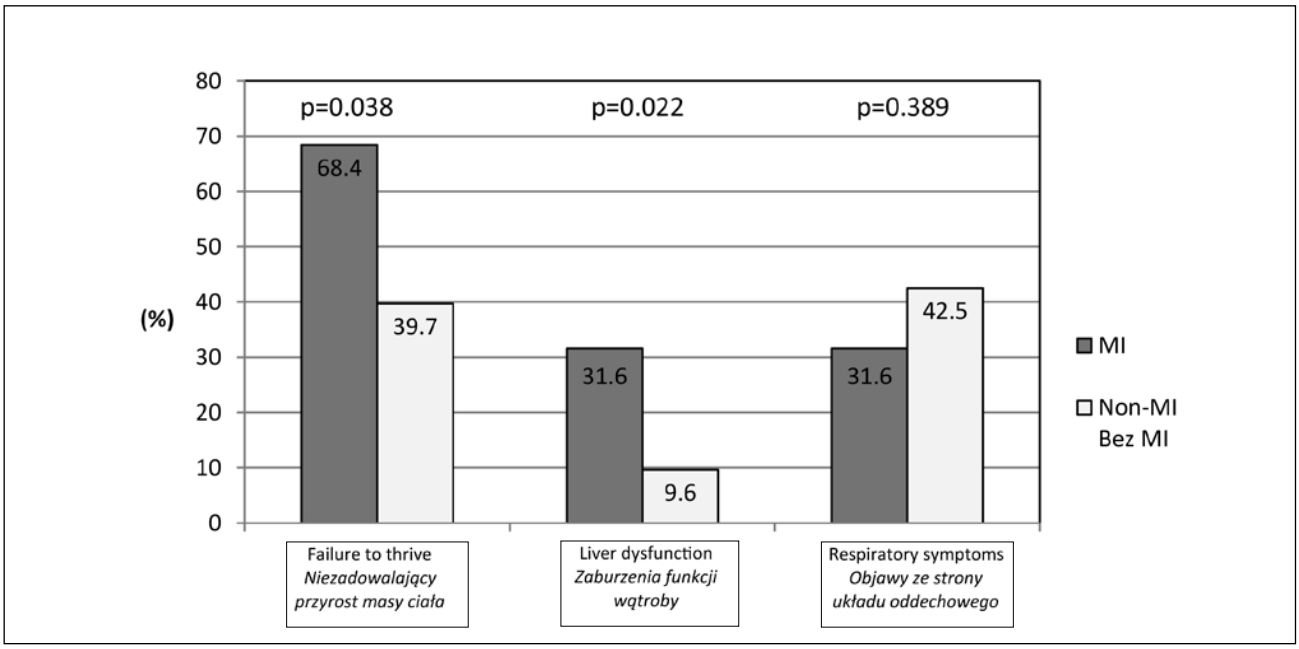

Fig. 1. Clinical manifestations at the time of diagnosis in MI and non-MI patients.

Ryc. 1. Objawy kliniczne w momencie rozpoznania w grupach pacjentów z MI i bez MI.

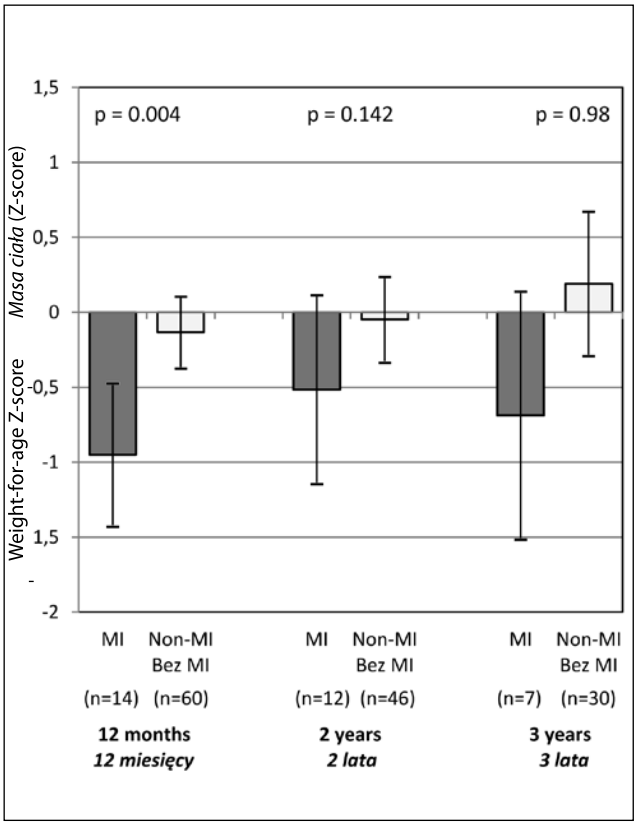

Fig. 2a. Mean weight-for-age Z-score at age of 12 months, 2 and 3 years in MI and non-MI patients (error bars represent 95% confidence intervals).

Ryc. 2a. Średnia masa ciała (Z-score) w wieku 12 miesięcy, 2 i 3 lat w grupach pacjentów z MI i bez MI (słupki błędu reprezentują 95% przedziały ufności).

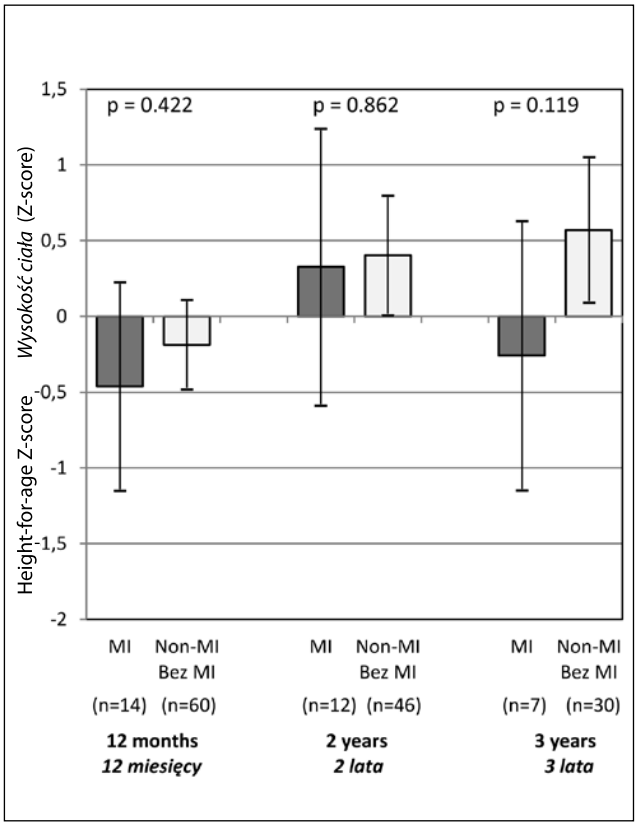

Fig. 2b. Mean height-for-age z-score at age of 12 months, 2 and 3 years in MI and non-MI patients (error bars represent 95% confidence intervals).

Ryc. 2b. Średnia wysokość ciała (Z-score) w wieku 12 miesięcy, 2 i 3 lat w grupach pacjentów z MI i bez MI (słupki błędu reprezentują 95% przedziały ufności).

wyrównać

Table VI. Patients clinical status according to Shwachman-Kulczycki score in MI and non-MI patients.

Tabela VI. Ocena kliniczna według skali Shwachmana-Kulczyckiego w grupach pacjentów z MI i bez MI.

	MI ***n (%)***	**Non-MI** ***Bez MI n (%)***	**p-value**
12 months ***12 miesięcy***	n=14	n=60	
very good *bardzo dobry*	4 (28.6%)	33 (55.0%)	0.077
good *dobry*	8 (57.1%)	25 (41.7%)	
moderate *średni*	2 (14.3%)	2 (3.3%)	
2 years ***2 lata***	n=12	n=46	
very good *bardzo dobry*	7 (58.3%)	32 (69.6%)	0.595
good *dobry*	5 (41.7%)	13 (28.3%)	
moderate *średni*	-	1 (2.2%)	
3 years ***3 lata***	n=7	n=30	
very good *bardzo dobry*	2 (28.6%)	19 (63.3%)	0.150
good *dobry*	5 (71.4%)	9 (30.0%)	
moderate *średni*	-	2 (6.7%)	

Patients clinical status was compared according to Shwachman-Kulczycki score. No statistically significant differences was found between MI and non-MI groups at the age of 12 months, 2 years and 3 years (table VI).

DISCUSSION

In the presented paper, MI prevalence frequency amounts to 20.6% and does not differ considerably from the ones described in other studies. In the examined material no statistically significant difference in mean birth weight Z-score was found between MI and non-MI newborns. Reports including birth weight values comparison present various results. In Wisconsin, the group of 82 CF patients was examined among whom 39% were MI individuals. In that population, smaller birth mass was found in MI neonates in contrast with non-MI neonates [25, 26, 27]. In turn, French clinical follow up survey including groups pairing which comprised 52 patients (26 pairs) did not confirm any relation between MI and birth veight [28].

Mutation *F508del*, which is the most frequent in CF patients in Poland and in the world, was the most commonly diagnosed mutation in the examined population. There are some reports of an increased prevalence of some mutations in MI patients. Among them, there are: *F508del, G542X, W1282X, R553X, G551D* [1, 2]. In the presented material, in MI patients , apart from F508del, only *R553X* and *G542X* were identified. In non-MI group, except for *F508del*, the mutation *3849+10kbC>T* was the next frequent one as it occurred in 8.2% of cases in non-MI patients. It is important from the clinical point of view, as this mutation is strictly concerned with preserved pancreas exocrine functions and decreased and sometimes even normal sweat tests results.

In the examined groups, no statistically significant difference was found in genotypes distribution based on F508del mutation (homozygous, heterozygous or neither mutation). These results are concurrent with the ones elicited by Munck et al. [28]. In turn, examinations carried out within The Wisconsin CF Neonatal Screening revealed difference in genotypes distribution according to MI development. In MI group, there were fewer *F508del* homozygotes – 50% and more patients with no *F508del* mutations – 12% than in non-MI group where these indices were 62% and 0% respectively [25]. The difference in cited reports result both from dissimilarities in *CFTR* gene prevalence in particular countries and modifying genes influence on CF phenotype.

IMiD patients with diagnosed MI in 94.7% presented severe genotype (mutations in both alleles of *CFTR* gene belonged to class I-III mutations) whereas in non-MI group severe genotype was presented by 64.4% of patients. This result is in accordance with Van der Doef et al. observations of patients from the Netherlands, Italy and Germany, where MI seemed to prevail in patients with severe genotype, but also *F508del* mutation homozygotes [29].

In all MI children PI was diagnosed, whereas among non-MI patients it was observed significantly less often – in 76.1% and the risk of developing PI was over two times higher in MI in comparison to non-MI group. Although pancreatic *failure* does not influence MI prevalence [2], MI children should be considered as pancreatic insufficient. In the group examined by Munck, 100% of MI patients had pancreatic failure versus 88% on non-MI patients, but in this study patient's average age was higher (12.5 years) as in ours [28], so the higher proportion of non-MI patients could develop PI. In the group of Israeli patients, during 20-year-long study, 100% of MI patients presented PI. Among our patients, average age at the moment of observation completion was 33 months. It is a younger group and it is quite probable that in some children with sufficient pancreas PI may develop later. Elicited result was also largely influenced by high prevalence of *3849+10kbC>T* mutation which is related to preserved pancreas exocrine sufficiency.

At the time of diagnosis in MI children hepatic dysfunctions were observed more frequently – 31.6% than in non-MI group – 9.6%. Apart from basing disease, parenteral nutrition during perioperative period is a predisposing factor of these disturbances. They subsided after nutritional therapy onset and ursodeoxycholic acid administration. However, the question whether cystic fibrosis liver disease (CFLD) will develop in MI children

needs further investigation. In accordance to long term studies of a French centre, hepatic pathologies in the form of fatty degeneration visible in ultrasound examination or hepatic values increase were found more often in MI patients (42%) than in control group (19%) [28]. Contrary Israeli studies did not reveal higher frequency of portal hypertension and liver cirrhosis in MI patients [30].

Among IMiD patients, in MI group insufficient weight gain was observed more often at the diagnosis time. Our results are similar to those originating from Wisconsin centre, which point at worse parameters of MI children somatic development. These studies demonstrated that at the diagnosis time, MI children presented smaller weight in comparison with non-MI children [25].

Among children treated in IMiD, no statistically significant difference was found in respiratory tract functioning. In Wisconsin, convergent results were elicited, where similarly to IMiD, the presence of respiratory symptoms was observed in physical examination and on the basis of medical history taken from parents [31].

At the age of 12 months MI group presented smaller weight stated in normalized values than non-MI group. Such trend was observed between MI and non-MI patients at the age of 2 and 3 years, but the differences were not statistically significant. Also differences in height between groups were not significant. Similarly to our study, worse development of MI children was reported from Wisconsin centre [25], where Z-scores for body mass and height for MI and non-MI groups were compared from infancy to 12 years of age. Contrary Munck at al. did not observed differences in Z-score weight and hight between MI and non-MI patients at age from 1 to 15 years [28]. Also Efrati et al. observed that BMI at the age of 1, 5, 10 and 20 years as well as Z-score for BMI at the age of 5, 10, 20 years did not differ significantly in MI population in comparison with non-MI patients [30]. However in these surveys, patients were not included into CF NBS and in non-MI groups diagnosis average age was higher. Maybe due to the earlier age of diagnosis in our non-MI group, somatic development parameters would differ significantly as in such cases earlier nutritional intervention is possible.

Somatic development comparisons in our study were possible by 2011 at the first three years of patient's life and the groups of children compared at the age of 2 and 3 years were small. Further observation and evaluation of larger groups is required to find possible differences in subsequent years.

On assessing clinical status of patients according to Shwachman-Kulczycki score no statistically significant difference was detected between the examined groups. In Australian study, comprising 39 pairs of MI children and non-MI children diagnosed in the course of CF NBS, differences were found between groups in radiologic and general activity components of the Shwachman-Kulczycki score only [32]. MI children obtained smaller score, although the fact, that average age of patients in Australian study was higher – above 9 years, has to be taken into consideration.

The study carried out in IMiD enabled to assess MI influence on clinical status and development of children in whom the diagnosis was established in the course of CF NBS. The patients were diagnosed at similar age and therapeutic procedures were made in one centre which allowed to minimize the differences between examined groups. The survey comprises early childhood only and should be continued in order to define MI influence on further development of observed population of CF patients.

CONCLUSIONS

Suffering from MI in children with CF may predispose them to more severe clinical course of disease in early childhood. In our study severe genotype occurred more frequently in these children. MI children more often presented insufficient weight gain and liver disturbances at the time of diagnosis. They had a higher risk of developing pancreatic insufficiency than non-MI children. At the age of 12 months MI group presented smaller weight than non-MI group although clinical status according to Shwachman–Kulczycki score did not differ between groups. Children with history of MI may require more intensive care and supervision in monitoring and treatment of CF. Further research is needed to asses MI impact on development of CF children in subsequent years.

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Conflicts of interest/Konflikt interesu
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Address for correspondence:
Katarzyna Zybert
Cystic Fibrosis Centre
Institute of Mother and Child
Kasprzaka Street 17a, 01-211 Warsaw, Poland
Phone: +48 22 32-77-371
e-mail: zybertka@wp.pl