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MECONIUM ILEUS IN NEWBORNS WITH CYSTIC FIBROSIS – RESULTS OF TREATMENT IN THE GROUP OF PATIENTS OPERATED ON IN THE YEARS 2000-2014

NIEDROŻNOŚĆ SMÓŁKOWA U NOWORODKÓW Z MUKOWISCYDOZĄ – WYNIKI LECZENIA PACJENTÓW OPEROWANYCH W LATACH 2000-2014

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Abstract

Aim: Evaluation of diagnostic and treatment procedures in children with cystic fibrosis (CF) operated on because of meconium ileus (MI).

Material and methods: The authors retrospectively reviewed the documentation of 10 CF newborn patients operated on in the years 2000-2014 because of MI. In prenatal ultrasound (US) examinations, suspicion of bowel abnormalities was raised in 2 cases, even though all the 10 mothers had a minimum of 3 US examinations during pregnancy. The mean gestational age of the newborns was 39.2 weeks (36-41 weeks), their mean birth weight 3472g (2560-4550 g). Family history of CF was positive in two patients. Genetic testing was performed in all the children operated on.

Results: In all the children operated on, mutations in both alleles of the CFTR gene were found. Five patients were F508del homozygotic, 4 were heterozygotic for this mutation, one had another mutation. Sweat tests were positive in all the children.

Abdominal distention was observed in 9 patients, vomiting and retention of gastric contents in 5. In 8 children meconium was not passed at all. 2 children passed a small amount of viscid meconium. Before the operation, rectal saline washouts were done in 5 newborns. Five patients were operated on during the first day of life, four on the second day and one on the third day of life. Intra-operatively a simple form of MI was diagnosed in 8 cases, a complicated form in 2 cases. In patients with the simple form of MI, a Bishop-Koop stoma was created after the evacuation of meconium. Two of these children needed a resection of some centimetres of dilated terminal ileum with doubtful viability. In newborns with the complicated form of MI, the treatment was individualized, always with stoma formation.

The time of postoperative meconium evacuation through enterostomy ranged from 6 to 15 days. Enteral feeding was started on average on the 9th day postoperatively. The mean hospital stay was 22.9 days.

In 8 children the stoma was taken out at the mean age of 19.4 months, in one patient the stoma closed spontaneously. No disturbances in electrolyte balance or excessive fluid loss, nor any body weight deficits connected with the stoma were observed. There were no complications during stoma closure. All the patients are alive. The time of observation ranges from 7 to 146 months (average 95 months).

All the patients currently present respiratory symptoms, have pancreatic insufficiency and need pancreatic enzyme supplementation. Seven do not, however, have body weight and height deficits. All the children with weight and height deficits have abnormal liver function tests. During observation two patients had MI equivalent symptoms, which was resolved by conservative treatment.

Conclusions: 1. In every case of intra-operative diagnosis of MI, it is necessary to perform genetic testing and sweat tests to confirm or exclude CF. 2. Mechanical intra-operative decompression of the bowel from inspissated meconium with a temporary stoma, which makes the continuation of bowel decompression possible in the postoperative period, is an effective treatment in children with MI. 3. The Bishop-Koop stoma, permitting the passage through the whole gastrointestinal tract, is a safe option. In our material, no complications of this stoma, such as stoma care problems or dyselectrolythemia were observed. 4. The decision of stoma closure in children with MI and CF should be delayed until the moment of introducing a broadened diet and should be undertaken together with a pediatrician who is a specialist in CF therapy.

Key words: meconium ileus, cystic fibrosis, Bishop-Koop stoma

Streszczenie

Cel pracy: Ocena postępowania diagnostyczno-terapeutycznego u dzieci z mukowiscydozą (CF), operowanych z powodu niedrożności smółkowej (MI).

Materiał i metody: Badaniami objęto 10 noworodków z CF, operowanych w latach 2000-2014 z powodu MI. Podejrzanie nieprawidłowości jelit w prenatalnym badaniu ultrasonograficznym matek wysunięto w 2 przypadkach, choć u wszystkich 10 matek wykonywano minimum 3 badania w okresie ciąży. Średni wiek ciążowy noworodków wynosił 39,2 Hbd (36-41 Hbd), średnia masa urodzeniowa 3472 g (2560-4550 g). Wywiad rodzinny w kierunku CF był dodatni u 2 pacjentów. Badania genetyczne w kierunku CF wykonano u wszystkich operowanych dzieci.

Wyniki: U wszystkich operowanych noworodków wykryto mutacje w obu allelach genu CFTR. Pięciu pacjentów było homozygotami F508del, 4 było heterozygotami w odniesieniu do tej mutacji, u jednego stwierdzono inne mutacje. Próby potowe wypadły pozytywnie u wszystkich dzieci.

Wzdęcie brzucha obserwowano u 9 pacjentów, wymioty i zalegania treści pokarmowej u 5; 8 dzieci nie wydalilo smółki po urodzeniu, 2 wydalilo jedynie niewielką ilość lepkiej smółki. Próby leczenia zachowawczego (wlewki doodbytnicze) wykonano u 5 noworodków. Pięciu pacjentów operowano w pierwszej dobie życia, czterech w drugiej i jednego w trzeciej dobie życia. Śródoperacyjnie prostą postać MI rozpoznano w 8 przypadkach, złożoną w 2 przypadkach. U pacjentów z prostą postacią MI ewakuowano zalegającą smółkę i wytworzono przetokę Bishop-Koop'a. Dwoje z tych dzieci wymagało resekcji kilku centymetrów jelita krętego o wątpliwej żywotności. U noworodków ze złożoną postacią MI postępowanie było zindywidualizowane, zawsze jednak z wytworzeniem przetoki jelitowej.

Czas pooperacyjnej ewakuacji smółki poprzez dreny pozostawione w przetoce wynosił od 6 do 156 dni. Żywnienie dojelitowe wprowadzano średnio w 9 dobie po zabiegu. Średni okres hospitalizacji wynosił 22,9 dni (12-53).

Przetokę zamknęto u 8 dzieci w wieku średnio 19,4 miesięcy, u jednego pacjenta zamknęła się ona samodzielnie. U pacjentów nie obserwowano żadnych zaburzeń równowagi wodno-elektrolitowej ani niedoborów masy ciała związanych z istnieniem przetoki. Nie wystąpiły też powikłania związane z operacją zamknięcia przetoki jelitowej. Wszyscy pacjenci przeżyli. Czas obserwacji wynosi od 7 do 146 miesięcy (średnio 95 miesięcy). U wszystkich występują objawy ze strony układu oddechowego, wszyscy mają zewnątrzwydzielniczą niewydolność trzustki i wymagają suplementacji enzymów trzustkowych. U siedmiorga dzieci nie stwierdzono niedoboru masy ciała i wysokości. U trojga pacjentów z niedoborem masy ciała i wysokości występują zaburzenia funkcji wątroby. W okresie obserwacji u dwojga dzieci wystąpił ekwiwalent niedrożności smółkowej, który ustąpił po leczeniu zachowawczym.

Wnioski: 1. W każdym przypadku śródoperacyjnego rozpoznania niedrożności smółkowej konieczne jest potwierdzenie lub wykluczenie współistnienia mukowiscydozy. 2. Mechaniczne śródoperacyjne odbarczenie jelita z zalegającej lepkiej smółki z wytworzeniem czasowej przetoki jelitowej, umożliwiającej pooperacyjne płukanie jelit, jest skutecznym postępowaniem u dzieci z niedrożnością smółkową. 3. Przetoka Bishop-Koop'a jest bezpiecznym rozwiązaniem. Wśród leczonych pacjentów nie obserwowano żadnych powikłań związanych z tym typem przetoki. 4. Decyzja o zamknięciu przetoki u dzieci z MI i CF powinna być opóźniona do momentu wprowadzenia rozszerzonej diety i podejmowana wspólnie z pediatrą- specjalistą leczenia dzieci z mukowiscydozą.

Słowa kluczowe: niedrożność smółkowa, mukowiscydoza, przetoka Bishop-Koop'a

Meconium ileus (MI) is defined as an intestinal obstruction caused by the impaction of thick, inspissated, protein-rich, adhesive and dessicated meconium filling the distal part of the terminal ileum [1, 2, 3].

Cystic fibrosis (CF) coexists in 75% of neonates with MI and in 20% of patients it is the earliest manifestation of CF [1, 2, 3, 4, 5, 6]. The deficiency of exocrine pancreatic enzymes and abnormal mucin production are responsible for the abnormal, protein-rich composition of meconium [3, 7, 8]. Some percent of patients with MI are preterm very-low-birth-weight babies, in whom intestinal obstruction, caused by the impaction of the

bowel lumen by meconium results from immature or ineffective peristalsis of the fetal intestine, followed by excessive water absorption (7).

Impaction of meconium may compromise blood perfusion in the bowel, inducing necrosis and perforation. Therefore, MI can be classified into two forms, which exist with similar (50-58%) frequency. The simple form is caused only by the intraluminal ileal obstruction. Intra-operatively terminal ileum is grossly distended and filled with green, viscid, plastic meconium. Proximally the meconium is fluid. In the terminal ileum, just proximal to Bauhin's valve, there are pellets of sticky, inspissated, pale-grey

meconium. There is also a microcolon. In complicated MI, in spite of intestinal obstruction, a prenatal volvulus of heavy loops of bowel or bowel distention may cause ischemic necrosis, intestinal atresia or perforation with the formation of meconium peritonitis or a peritoneal pseudocyst. The complicated form of MI can be the reason for the short bowel syndrome [1, 2, 3, 5, 9, 10, 11, 12].

Now, with the advances in anaesthesia and intensive care, new treatment strategies and close cooperation with pediatricians, specialists in CF, the survival of the children with MI approaches 100% [2, 6, 12, 13, 14].

AIM

Evaluation of treatment procedures of children operated on because of meconium ileus in mucoviscidosis.

MATERIAL AND METHODS

We retrospectively reviewed the medical documentation of patients operated on in the years 2000-2014 because of MI

According to the protocol treatment of newborns with the simple form of MI, if the rectal washout fails, the patient is referred for an operation. During laparotomy the terminal ileum is opened at the border of the dilated and narrow part and meconium is manually evacuated with the help of diluted ambroxol (Mucosolvan). In cases with uncertain intestinal viability, resection of this part of the bowel is performed, and exteriorization of the ileum according to the Bishop-Koop method (or another kind of stoma) is created. Two drains are passed to the proximal and to the distal limb of the stoma in order to facilitate meconium evacuation in the postoperative period.

A Mucosolvan solution is used for bowel irrigation through these drains (Mucosolvan diluted 1:5; 2-3ml of the solution is instilled through each drain twice daily, and the drain is then closed for 30-60 minutes), and is also administered through a nasogastric tube. Bowel cleaning is continued till the moment when the child starts to pass stools spontaneously and enteral feeding can be started.

In the cases of complicated MI, the intra-operative treatment is individualized. Most often resection of the pseudocyst, resection of an obstructed or necrotic bowel, are performed, all of them followed by a stoma formation. Post-operative treatment is the same as in the simple form of MI.

Early after the operation, children are consulted by a pediatrician who is a specialist in CF therapy. The diagnosis of CF is tentatively established by an immunoreactive trypsinogen assay and subsequently confirmed by sweat tests (performed using 2 methods) and by genetic analysis. Pancreatic enzyme supplementation (Kreon) is started when enteral feeding begins. In the case of cholestasis, ursodeoxycholic acid (Ursofalk) therapy is ordered.

After discharge, children stay under the care of the Outpatient Surgical Clinic and the CF Center. The decision about closing the stoma is undertaken together with the pediatrician, after introducing a broadened, post-infant diet and ensuring the normal function of the gastrointestinal tract.

Appendix 1. Rules of proceedings applied in the case of MI in the Clinical Department of Children's and Adolescents' Surgery, IMC

in the Clinical Department of Children's and Adolescents' Surgery, the Institute of Mother and Child. Children with VLBW with MI were excluded. All the patients were treated according to one protocol (appendix 1).

Data collected from medical documentation included the following: family history, the presence of prenatal diagnosis, the time and mode of delivery, birth weight, the time of the beginning of clinical symptoms and their kind, the day of life on which the operation was done, the form of MI, the kind of intra- and postoperative treatment, the total length of hospital stay. The results of genetic testing and sweat tests, as well as complications and late results of treatment were also analysed.

In the years 2000-2014, 12 patients were operated on because of meconium ileus. Among them in 10 cases (6 girls and 4 boys), the diagnosis of cystic fibrosis was confirmed and this was the group that was analysed.

The family history of cystic fibrosis was positive in two patients. In prenatal ultrasound, the suspicion of bowel abnormalities was raised in two cases (1-suspicion of intestinal obstruction, 1-hyperechogenic bowel), even though all the 10 mothers had a minimum of 3 US examinations during pregnancy. The mean gestational age was 39.2 weeks (range 36-41 weeks). The birth weight ranged from 2560 to 4550 g, (an average of 3472 g), the mean Apgar score was 9.4 points (range 6-10). Two of the children (one with prenatal suspicion of intestinal obstruction) were born by cesarean section.

The symptoms, observed in the patients analysed, and the time when they started, as well as the correlation with the form of MI are shown in table I. Six patients were fed after delivery. In all of them clinical symptoms of bowel obstruction started in the second or at the end of the first day of life.

RESULTS

Before the operation, efforts to evacuate meconium with the help of a rectal washout (saline), were made in 5 newborns in good general condition. They failed in all the cases. A Gastrografin enema was not used in any patients. Five children in a bad general condition with the suspicion of complicated MI were referred for operative treatment at once. Five patients were operated on during the first day of life, four on the second day and one on the third day of life. Intra-operatively a simple form of MI was diagnosed in 8 cases and a complicated form in 2 cases. In the patients with a simple form of MI, a Bishop-Koop stoma was created (as described in appendix 1) after the intra-operative evacuation of meconium. Two of the children needed a resection of some centimetres of grossly dilated terminal ileum with doubtful viability. In one newborn with a complicated form of MI, resection of the volvulus followed by intestinal anastomosis and the creation of appendicocostomy were performed. In the second child, a meconium pseudocyst was resected and a Bishop-Koop stoma created. This patient was re-operated on at the age of 1 month because of adhesive intestinal obstruction.

The time of postoperative meconium evacuation through enterostomy ranged from 6 to 15 days. Enteral feeding was started between the 7th and 14th day postoperatively

Table I. Characteristics of patients operated on because of meconium ileus in cystic fibrosis in the Institute of Mother and Child.

Tabela I. Charakterystyka pacjentów operowanych w Instytucie Matki i Dziecka z powodu niedrożności smółkowej związanej z mukowiscydozą.

Patient Pacjent	Symptoms post delivery Objawy po urodzeniu			Feeding post delivery Karmienie po urodzeniu	Day of life when symptoms started Dzień rozpoczęcia objawów	Form of MI Postać MI
	Meconium post delivery Smółka po porodzie	Regurgitation/ vomiting/ retention of gastric contents Ulewania/wymioty/ zalegania treści żołądkowej	Abdominal distention Wzdęcie brzucha			
1	-	-	+	-	1	simple prosta
2	-	-	+	-	1	simple prosta
3	-	+	-	+	1	complicated powikłana
4	-	+	+	+	2	simple prosta
5	-	-	+	-	1	simple prosta
6	+	+	+	+	2	simple prosta
7	-	-	+	+	1	simple prosta
8	+	+	+	+	2	simple prosta
9	-	-	+	-	1	complicated powikłana
10	-	+	+	+	2	simple prosta

(average 9th day). The child with the meconium pseudocyst was fed only enterally from the age of 15 months, in spite of extensive bowel resection.

For the whole group, the mean hospital stay was 22.9 days (range 12-53), for simple MI 19.7 days (range 12-40), for two children with complicated MI: 18 and 53 days.

In 8 children the stoma was taken out at the age of 12-30 months (an average of 19.4 months), in one patient the stoma closed spontaneously. No disturbances in electrolyte balance or excessive fluid loss, nor any body weight deficits connected with the stoma were observed. There were no complications during stoma closure. All the patients are alive. The time of observation ranges from 7 to 146 months (an average of 95 months).

The family history of cystic fibrosis was positive in two patients with a simple form of MI. Genetic testing was performed in all the twelve children operated on. In 10 of them mutations in both alleles of the CFTR gene were found (80%) (Table II).

Five of those patients are F508del homozygotic, 4 are heterozygotic for this mutation, one had other mutations (dele 2,3(21kb)/E822X). Sweat tests using the quantitative

pilocarpine iontophoresis and/or conductometric method (WESCOR) were positive in all the children with genetically proven CF (Table III).

All the CF patients currently present with respiratory symptoms, have pancreatic insufficiency and need pancreatic enzyme supplementation (Table III). The majority (seven) do not, however, have body weight and height deficits (defined as body weight and height below the 10th percentile). All the children with weight and height deficits have abnormal liver function tests.

During the observation period, two patients had meconium ileus equivalent symptoms, which were resolved by conservative treatment.

DISCUSSION

Meconium ileus is the earliest clinical manifestation of CF and occurs in 15%-27% of the patients with CF [1, 2, 8, 10]. Patients homozygotic for the F508del mutation have a 24.9% chance of MI, F508del plus any other mutation in the CFTR gene have a 16.9% chance of the disease. Two other CFTR mutations confer to a 12.5% chance of MI [1].

Table II. Mutations of patients operated on because of meconium ileus in cystic fibrosis in the Institute of Mother and Child.

Tabela II. Mutacje u pacjentów operowanych w Instytucie Matki i Dziecka z powodu niedrożności smółkowej związanej z mukowiscydozą.

Patient Pacjent	Mutations Mutacje	Remarks Uwagi
1	F508del/dele2,3(21kb)	
2	F508del/F508del	
3	dele 2,3(21kb)/E822X	
4	F508del/F508del	(+) family history (+) wywiad rodzinny
5	F508del/F508del	
6	F508del/F508del	
7	F508del/2143delT	(+) family history (+) wywiad rodzinny
8	F508del/R553X	
9	F508del/F508del	
10	F508del/W1292X	

Table III. Sweat tests and symptoms during the follow-up of patients operated on because of meconium ileus connected with cystic fibrosis in the Institute of Mother and Child.

Tabela III. Testy potowe oraz objawy występujące podczas obserwacji u pacjentów operowanych w Instytucie Matki i Dziecka z powodu niedrożności smółkowej związanej z mukowiscydozą.

Patient Pacjent	WESCOR (mmol/l)	Pilocarpine iontophoresis (mEq/l) Jontoforeza pilocarpinowa	Symptoms during follow-up Objawy podczas obserwacji				
			Body weight deficit Niedobór masy ciała	Body height deficit Niedobór wysokości ciała	Respiratory tract Ze strony układu oddechowego	Cholestasis Cholestaza	Liver disease Choroby wątroby
1	117.0	100.7	-	-	+	-	-
2	117.0	55.1	-	-	+	-	+
3	105.0	79.2	+	-	+	-	+
4	74.8	n.e.	-	-	-	+	-
5	112.1	130.0	-	-	+	-	+
6	109.0	55.6	-	-	+	-	-
7	n.e.	44.1	-	+	+	+	+
8	96.0	53.3	+	+	+	+	+
9	106.0	75.5	-	-	+	+	+
10	n.e.	122.0	-	-	+	-	+

In nine of the 10 presented newborns with MI and CF, the F508del mutation was identified. Four of them were heterozygotic and five homozygotic for this mutation. Other identified mutations were: dele2,3(21kb), E822X, 2143delT, R553X, W1292X. All of these are classified as "severe" types (class I, II or III). This confirms the reports of other authors [1, 4, 7, 17].

The reported family history of patients with MI and CF ranges from 8 to 33% [2, 3, 5, 8, 12]. In our material, family history of CF was present in 2 patients (20%).

Prenatal diagnosis is difficult, as symptoms of MI on prenatal ultrasonograms are variable and not specific for this disorder [1, 5, 10, 11, 13, 15, 16, 18] (appendix 2.). In our material, prenatal diagnosis was suspected only in two children with cystic fibrosis and MI. Neither of those children were born in our Institute.

Before laparotomy, differentiation between the simple and complicated form of MI may be difficult, but is very important, because of distinct therapeutic options in each of them. Whereas complex MI presents a surgical

The possible features of MI on a prenatal ultrasonogram include hyperechoic masses consisting of inspissated meconium in the terminal ileum, dilated bowel loops and nonvisualisation of the gallbladder. Polyhydramnios may also be present with the incidence of 20-22%. Complicated meconium ileus can present as fetal ascites, echogenic bowel, polyhydramnios, fetal bowel dilatation, an intra-abdominal calcified mass or an echogenic intra-abdominal cyst in prenatal US and cause fetal or neonatal distress.

Appendix 2. Features of MI on prenatal ultrasonogram

emergency, in simple MI, attempts at conservative treatment can be used at first [1, 9, 12, 19].

In the study presented, 8 out of ten patients (80%) had a simple form of MI, which is a proportion which cannot be precisely explained. It is perhaps because we analysed only patients with CF and some authors consider that the incidence of CF in neonates with the complicated form (MP) is lower than in the simple form and ranges from 15 to 40% [11, 16].

The clinical presentation described in the literature includes: abdominal distention in 96-100%, bilious vomiting in 49-91%, delayed passage of meconium for more than 24 h or lack of meconium in 36-83% and visible or palpable loops of the bowel in 15-44% of newborns. Symptoms begin earlier in complicated cases, abdominal distention may be present at birth, as well as visible, or there can be palpable loops of the bowel or abdominal mass [1, 2, 3, 5, 8, 10, 12, 14]. The patients presented had abdominal distention in 90% of the cases, bilious vomiting in 50% and a lack of the passage of meconium in 80%. Data regarding the visible loops of the bowel are not complete, so they were not analysed.

There is very little information in the literature about the timing of the beginning of symptoms and about the moment when neonates are referred to the surgeon, though this fact seems to be important in the planning of treatment. The symptoms of intestinal obstruction in 6 of our patients were observed from the first day of life, and in 4 - from the 2nd day of life.

We found information about feeding before transferring to the surgical centre only in the work of Nagar H., where 9/10 patients received oral feeding before starting to vomit and of Rescorla F., most of whose patients were fed before admission [8, 17]. Among our patients, six out of ten were fed after delivery, surprisingly two of them had symptoms from the first day of life and one had a positive family history and bowel abnormalities on prenatal ultrasonographic examination.

After birth, both the simple and the complicated form of MI have to be treated as intestinal obstruction with resuscitation, gastric decompression, intravenous fluid replacement, antibiotic coverage.

In the simple form of MI, non-operative treatment in the form of hyperosmotic (Gastrografin) enemas, first

described by Helen Noblett in 1969, is recommended by most authors [1, 20]. After the enema, there should be a rapid passage of meconium pellets and later semiliquid meconium, which continues over 24 to 48 hours. Attempts at an enema can be repeated 2-3 times. The possible risks of a hyperosmotic enema include early and late rectal or colonic perforation (3%-23%), ischemic enterocolitis, hepatotoxicity and hypovolemic shock [2, 9, 14, 21]. Historical data show the success rate can be as high as 56-83% [2, 17, 20, 21]. Contemporary studies of this treatment report a lower success rate – from 5.5% to 40%, [1, 6, 9, 10, 11, 17, 21, 22]. Copeland et al. suggest that this lower success rate is connected with fewer attempts at enema per patient before referral for surgical treatment, the use of lower osmolarity solutions rather than Gastrografin as used in some institutions, changes in radiologist's experience and concludes that enema attempts are less aggressive [21]. Karimi et al. suggest that Gastrografin enema was less effective in patients with MI in CF [9].

This treatment option has the advantage of avoiding the operation. Moreover, the length of hospital stay is shorter compared with cases requiring an operation. On the other hand, the referral of a patient is usually delayed and obstruction is well established at presentation. Therefore, since the obstruction is in the terminal ileum, it is difficult to achieve satisfactory decompression. Another problem is the time needed for the complete evacuation of meconium – 48 hours and the fear of serious complications connected with delaying the operation [1]. The high rate of the complicated form of MI (50%) may further explain diminishing the utilisation of radiologic decompression [6]. It seems that good results of Gastrografin enema treatment are in part the result of incorporating patients with the meconium plug syndrome among those with true meconium ileus [12, 14].

We performed rectal washouts in 5 patients, in 5 others there was a suspicion of a complicated form of MI. We manage simple MI using deep rectal washouts (like Jawaheer et al. [19]). If the obstruction is not relieved in 6 hours, the child is qualified for laparotomy.

In the case of failure of a Gastrografin enema or in the complicated form of MI, operative treatment is performed. Now, with the advances in anaesthesia and intensive care, new treatment strategies and close cooperation with the pediatric-specialist in CF, survival approaches 100% [2, 12, 13, 14]. Therefore, all our patients survived. The optimal surgical technique still remains controversial. Each centre has its own preferred technique, based on their individual experience [2, 3, 5, 6, 9, 10, 14, 17, 19, 22, 23, 24].

The aim of surgical treatment is the evacuation of meconium from the intestine, thus relieving the obstruction, in simple MI, and also the establishment of intestinal continuity and preservation of maximal intestinal length in complicated MI.

There are some operative options. The first one to be introduced was the Mikulicz double-barrelled enterostomy (appendix 3.).

The results of surgical treatment improved significantly after introducing the Bishop-Koop distal chimney

Mikulicz double-barrelled enterostomy, first reported by Gross, is preferred by some surgeons as safe, because complete intra-operative evacuation of inspissated meconium is then not necessary and intra-abdominal anastomosis is avoided. The bowel is opened after complete closure of the abdomen, thereby reducing the risk of intraperitoneal contamination. The disadvantages of this technique are problems with stoma care, the presence of high output stoma and the inherent risk of dehydration and serious dyselektrolytemia. This stoma should be closed as soon as possible (1, 5, 9).

Appendix 3. Mikulicz double-barrelled enterostomy

enterostomy in 1957, which involves resection with anastomosis between the end of the proximal segment and the side of the distal segment of the bowel /Roux-en-Y ileostomy/ with exteriorisation of the distal limb [1, 25]. The normal passage of stool till the anus is preserved. This kind of anastomosis solves the problem of diameter differences between the proximal and distal bowel segment. Then resection of the dilated but viable ileum is not necessary. Postoperative distal bowel irrigation is possible through drains placed in the proximal and distal limb of the intestine. Mucous fistula can close spontaneously. If not, the B-K stoma is easily closed [2, 5, 11, 14, 23]. Proximal enterostomy described by Santulli and Blanc in 1961 is similar [1]. However, in these two procedures, anastomosis is made intraperitoneally.

Other therapeutic options are T-tube enterostomy with postoperative distal bowel irrigation proposed by O'Neill and al. in 1970 and modified by Harberg in 1981, and appendicostomy described by Fitzgerald and Conlon with a cecostomy catheter inserted by the appendiceal stump for irrigation and the evacuation of impacted meconium [1, 6, 24].

The main advantage of enterostomy is that postoperative intestinal lavage can be performed in order to evacuate remaining meconium, and then manual manipulation during surgery can be minimized. The disadvantages of the enterostomies by Mikulicz, Bishop-Koop and Santulli are: the necessity of stoma care, the need for an extra surgical procedure, prolonged hospital stay (if you close the stoma early), the risk of high output diarrhea and dyselektrolytemia [1, 9, 10, 24].

In recent years, popularity was gained by resection and primary anastomosis, first proposed by Swenson in 1962, used both in the simple as well as in some cases of the complicated form of MI [1, 6, 9, 10, 14, 19]. The important issues connected with this option are the necessity of adequate resection of the compromised bowel, complete proximal and distal evacuation of meconium, the technical difficulty connected with the disproportion of proximal and distal ends and the necessity of preserving an adequate blood supply to the anastomosis.

In the opinion of many authors, there is no difference in the results of patients who had primary anastomosis

and those who had resection with enterostomy, apart from the duration of hospital stay – all these authors take out the stoma during initial hospitalization [1, 2, 8, 10, 11, 23]. The advocates of Swenson's technique emphasize the advantage of avoiding a second anesthetic and surgical procedure in infants with a potentially compromised respiratory function.

There are, however, also reports by Jawaheer et al. and Karimi et al. that primary anastomosis gives a 21-31% complication rate [1, 9].

The simplest operative intervention is enterotomy, "washout" and closure of the enterotomy, used in the simple form of MI not responding to conservative management. But it takes a lot of time, which can be dangerous to a neonate [8, 10, 11, 14, 17, 22].

In the Institute of Mother and Child, surgical treatment of the simple form of MI consisted of the evacuation of meconium, sometimes resection of some centimeters of grossly distended terminal ileum, and the creation of a Bishop-Koop stoma. In 2 complicated cases of MI, different kinds of operations were performed, all of them followed by a stoma formation. The Bishop-Koop stoma ensured the normal passage through the gastrointestinal tract till the anus and served as a safety valve. This made the anastomosis devoid of tension, which reduced the risk of dehiscence. Catheters were instilled through the proximal and distal limb of the stoma, which made it possible to conduct intestinal irrigation and evacuation of residual meconium in the postoperative period. Instillation of ambroxol (Mucosolvan) via the nasogastric tube additionally helped solubilize residual meconium. Our opinion about the value and safety of a Bishop-Koop stoma is shared by many authors [3, 5, 9, 13, 14, 25].

In recent works, early postoperative complications are described in 4-31% cases, and more in those with primary anastomosis. These include wound infection, anastomosis leak, peritonitis, adhesive intestinal obstruction [2, 6, 9, 10, 12].

We had one surgical complication – a child with a meconium pseudocyst developed adhesive obstruction at the age of 1 month, and needed a re-operation. None of the children developed peritonitis or died.

In the literature, the time of hospitalization for cases treated by resection and primary anastomosis ranges from 17 to 202 days, and for cases treated by stoma formation and closure from 23 to 49 days [2, 6, 9, 12, 19]. Our patients stayed in the hospital for an average of 22.9 days; in simple MI this time was even shorter – 19.7 days. The duration of hospital stay for stoma closure was 8.5 days.

In most publications the authors propose taking out of the stoma at the age of 2-3 months or even after 5 days from the initial operation, mainly prior to initial discharge, to help avoid prolonged problems with fluid, electrolyte and nutritional losses – but not all of those publications mentioned the type of stoma in detail [1, 2, 6, 12, 14]. In the Bishop-Koop stoma there is no need for early closure. Once the bowel lumen is cleaned, the ileostomy which is against the peristaltic stream often stops functioning [25]. In our patients no problems with

excessive fluid losses, dyselectrolytemia or failure to gain weight and no stoma care problems were observed. Our policy was to close the Bishop-Koop stoma after the first year of life, between 12 and 22 months, always after a consultation with a CF specialist and after the assurance that there was a normal function of the digestive tract and the child had an established pancreatic replacement therapy, corresponding with a post-infant diet and reached satisfactory weight gain. We did not observe either any surgical or anesthesiological complications during stoma closure, nor were there any problems with stoma care, which is in agreement with Holsclaw's experience [5]. Some authors describe complications during early stoma closure [2, 23]. That is an argument in favour of delaying the stoma closure till the time when the child is in good health.

Each patient with fetal or neonatal bowel obstruction should be suspected to have CF. Therefore, diagnostic tests (sweat tests, molecular analysis) should be performed as soon as possible. Sweat-tests/sweat chloride concentration can in theory be done after the first 48 h of life, but practically an adequate quantity of sweat (75 mg or 15 ml) is difficult to obtain during the first weeks of life, especially in preterm infants [1, 15]. After discharge, the patient should be referred to a CF Center for counselling and education.

Patients with CF and MI should be treated as having pancreatic insufficiency, and a pancreatic enzyme replacement therapy should be withheld once oral feeding is started. The dosage is 2000 to 5000 lipase units per 120 ml of full strength formula [1].

Infants with MI are at risk for cholestasis, particularly if they have had or are receiving TPN. Although neonatal cholestasis and later liver disease are different entities, Colombo et al. (1994) found that 35% of the patients with CF and MI had liver disease, whereas only 12% of patients with CF without MI had liver disease [1, 26]. The recent work of Leeuwen et al. shows that there is a significantly higher incidence of cholestasis in infants with MI (27.1%) compared to those without MI (1.2%). The highest percentage of cholestasis was observed in the group with complicated MI. The reasons for that are also surgical treatment and TPN. Cholestasis resolved in all the patients, and neither cholestasis nor MI were risk factors of developing serious liver disease later in life. This is in contrast with previous reports suggesting a higher incidence of developing liver disease in infants with MI [4, 26]. In our material, cholestasis was present in 4 newborns and resolved in all. Abnormal liver function tests are now observed in 7 children, who do not have signs of portal hypertension or multilobular cirrhosis, signs of liver failure or encephalopathy.

With improved non-operative and operative treatment, the use of total parenteral nutrition and advances in anaesthesiology, the prognosis for children with both simple and complicated MI is good. Short-term survival rates approaching 100% are reported [10, 11, 14, 23]. Moreover, all of our patients survived.

The described frequency of MI equivalent symptoms in patients with MI and CF was 20-29%, 7-12.5% needed

an operation [6, 11, 27]. Two of our patients presented symptoms of MI equivalent, which were resolved using conservative treatment.

Most recent studies show that long-term nutritional, pulmonary and mortality outcomes of children with CF treated because of MI are the same as the outcomes of patients with CF without MI, especially when there is a long-term follow-up, although height and weight percentiles may be lower. The type of therapy – conservative or surgical – is irrelevant [1, 10, 23, 27, 28, 29].

Only Lai et al. stated that patients with CF presenting with MI have greater risks of shortened survival than those diagnosed through neonatal screening [30].

All of our children with CF present with the signs of pulmonary disease, all need pancreatic enzyme supplementation. However, seven of them do not have any weight and height deficiencies, although the mean follow-up is relatively short – 95 months (8 years). All the children with body height and weight deficiency have abnormal liver function tests. Only one child had the signs of a short bowel syndrome, as a result of a complicated form of MI (pseudocyst), which needed excessive bowel resection. That was also the only child who was re-operated on, because of adhesive obstruction at the age of 1 month. Now this girl is on enteral feeding only and has no height and weight deficits.

In our opinion therapeutic treatment used in the Institute of Mother and Child: rectal washouts in place of Gastrografin enema, and in cases of failure of such therapy intra-operative evacuation of meconium and creation of a Bishop-Koop stoma and postoperative bowel irrigation provides a good approach to newborns with MI and CF, which is moreover the safest one. Appropriate antibiotic prophylaxis, implementation of chest therapy, the use of TPN in the early postoperative period and close cooperation with a specialist in CF therapy, delayed closure of the Bishop-Koop stoma after ensuring the normal function of the gastrointestinal tract and normal physical development of the child, are significant in ensuring a favourable outcome.

CONCLUSIONS

1. In every case of intra-operative diagnosis of meconium ileus it is necessary to perform genetic testing and sweat tests to confirm or exclude cystic fibrosis.

2. Mechanical operative decompression of the bowel from inspissated meconium by means of a temporary stoma making it possible to continue bowel decompression in the postoperative period is an effective treatment in children with MI.

3. The Bishop-Koop stoma, permitting the passage through the whole gastrointestinal tract, is a safe option. In our material no complications of this stoma, such as stoma care problems or dyselectrolytemia were observed.

4. The decision of stoma closure in children with MI and CF should be delayed till the moment of introducing a broadened diet and should be undertaken together with a pediatrician who is a specialist in CF therapy.

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Conflicts of interest/Konflikt interesu

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