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FEATURES OF THE COURSE OF HIRSCHSPRUNG'S DISEASE IN PATIENTS WITH DOWN SYNDROME AND OTHER GENETIC ANOMALIES

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Abstract. *Introduction.* The incidence of Hirschsprung's disease (HD) in patients with Down syndrome (DS) is significantly higher than in the population and ranges from 2.76 to 16%. The article examines the features of the course of the disease in patients with HD and DS, risk factors for complications and ways to prevent and treat them. *Objective*. The objective of the presented work was to analyze the prevalence of Hirschsprung's disease in children with Down syndrome, as well as to identify risk factors for the development of complications, and to develop strategies for the prevention and treatment of this group of patients.*Materials and methods.* During the period from 2016 to 2024, 14 children (3.8%) with concomitant genetic diseases were operated on at the Filatov Children's Hospital for Pediatric Surgery: Down syndrome — 10 (2.7%), Moyatt–Wilson — 2 (0.54%), Sturge–Weber — 1 (0.27%) and ondine syndrome — 1 (0.27%). The average age was 1.8 years (from 1 month to 6 years). The total form was diagnosed in 2 cases (14.2%), subtotal — in 2 (14.2%), in other children — recto-sigmoid form (71.6%). Three children (21.4%) had a stoma — ileostomy previously applied to two children with extended agangliosis (14.2%) and a sigmostomy to the 1 child. *Results.* The majority of children had early (7–50%) or late (3–21.4%) complications: 4 children had a failure of the colorectal anastomosis (CRA). The treatment outcomes were as follows: permanent stoma in 2 (14.2%) children, fecal incontinence in 5 patients (35.7%), rectal stenosis developed in 2 cases (14.2%). One child died on the background of persistent peritonitis with concomitant primary immunodeficiency syndrome (7.1%). A favorable long-term result was achieved in 6 cases (42.8%). *Conclusions.* Given the higher risk of developing CRA failure in patients with HD+DS, preventive stomas or 2-stage interventions should be more widely used, which can significantly reduce the risk of inflammatory complications in the postoperative period.

Keywords: *Hirschsprung's disease, Down syndrome, prevention of complications, treatment tactics*

ОСОБЕННОСТИ ТЕЧЕНИЯ БОЛЕЗНИ ГИРШПРУНГА У ПАЦИЕНТОВ С СИНДРОМОМ ДАУНА И ДРУГИМИ ГЕНЕТИЧЕСКИМИ АНОМАЛИЯМИ

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Резюме. *Введение.* Частота болезни Гиршпрунга (БГ) у пациентов с синдромом Дауна (СД) значительно выше, чем в популяции, и составляет от 2,76 до 16%. В статье рассматриваются особенности течения заболевания у пациентов с БГ в сочетании с СД, факторы риска развития осложнений и пути их профилактики и лечения. *Цель* представленной работы заключалась в анализе распространенности болезни Гиршпрунга у детей с синдромом Дауна, а также выявлении факторов риска развития осложнений, выработке стратегий профилактики и лечения данной группы пациентов. *Материалы и методы.* За период с 2016 по 2024 г. в клинике детской хирургии ДГКБ им. Н.Ф. Филатова оперированы 14 детей (3,8%) с сопутствующими генетическими заболеваниями: синдромом Дауна — 10 (2,7%), Моятт–Вильсона — 2 (0,54%), Стурге–Вебера — 1 (0,27%) и синдром «ундины» — 1 (0,27%). Средний возраст составил 1,8 года (от 1 месяца до 6 лет). Тотальная форма диагностирована в двух случаях (14,2%), субтотальная — в двух (14,2%), у остальных детей — ректосигмоидная форма (71,6%). Трем детям (21,4%) предварительно была наложена стома — илеостома двум детям с протяженным аганглиозом (14,2%) и одному ребенку — сигмостома. *Результаты.* У большинства детей имели место ранние (7–50%) или поздние (3–21,4%) осложнения: у четырех детей наблюдалась несостоятельность колоректального анастомоза (КРА). Исходы лечения были следующими: постоянное стомаконосительство — 2 (14,2%) ребенка, недержание кала — у 5 пациентов (35,7%), стеноз прямой кишки развился в 2 случаях (14,2%). Один ребенок погиб на фоне некупирующегося перитонита при сопутствующем синдроме первичного иммунодефицита (7,1%). Благоприятный отдаленный результат удалось достичь в 6 случаях (42,8%). *Выводы.* Учитывая высокий риск развития несостоятельности колоректального анастомоза (КРА) у пациентов с СД+БГ, следует шире использовать превентивные стомы или двухэтапные вмешательства, что может существенно снизить риск воспалительных осложнений в послеоперационном периоде.

Ключевые слова: *болезнь Гиршпрунга, синдром Дауна, профилактика осложнений, тактика лечения*

INTRODUCTION

According to the literature, the incidence of Hirschsprung's disease (HD) in Down syndrome (DS) ranges from 2.76 to 16% (1.4), and the incidence of DS in patients with HD ranges from 1 to 9% (2.4), that is, the combination of HD+SD in the population is significantly higher than the overall incidence of HD. Numerous studies have proved that the severity of clinical manifestations and the frequency of various complications are higher in patients with DS. The article is devoted to the analysis of HD treatment in patients with DS and some other hereditary syndromes.

AIM

The aim of the study is to analyze the prevalence of Hirschprung's disease in children with Down syndrome, as well as to identify risk factors for the development of complications, to develop strategies for prevention and treatment of this group of patients.

MATERIALS AND METHODS

In the period from 2016 to 2024, 367 patients underwent laparoscopic assisted surgery for Hirschprung's disease by means of the Soave-

Georgeson technique. The surgeries took place in the paediatric surgery clinic of the N.F. Filatov Children's Hospital. All patients were older than the neonatal period. Among these patients, 14 children (3.8%) had concomitant genetic diseases: Down syndrome — 10 (2.7%), Moyatt–Wilson syndrome — 2 (0.54%), Sturge–Weber syndrome — 1 (0.27%) and 'Ondine's curse' syndrome — 1 (0.27%). Undoubtedly, these syndromes have fundamental differences, however, the majority of children had similar features of the postoperative period, thus, we decided to analyze the case histories of all the above-mentioned patients as well. The patients' data are summarized in Table 1.

TREATMENT RESULTS

Most of the children were male, only one girl had Down syndrome and another had Sturge–Weber syndrome. The HD was diagnosed at a median age of 1.8 years (1 month to 6 years), which is now considered relatively late, taking into account that alertness for HD should be high in this group of patients. The distribution by length of agangliosis did not differ compared to general population — the total form was diagnosed in two cases (14.2%), subtotal — in two cases (14.2%), the remaining children had the rectosigmoid form (71.6%).

Three children (21.4%) had a preliminary stoma applied: two children with extended agangliosis were iliostomized (14.2%) and one child was sigmostomized.

The overall complication rate in this group of patients was very high. Postoperative period proceeded without any peculiarities in three cases (21.4%), the rest of the children had early (7–50%) or late (3–21.4%) complications. Early postoperative complications were represented by cases of colorectal anastomosis (CRA) failure: four children had CRA failure of grade III-IV according to our classification (Figs. 1, 2) and were accompanied by pelvic (3–21.4%) and spilled (1–7.1%) peritonitis. One child had a 60 mm circular necrosis of the descended intestine, while the other had CRA failure with normal fixation of the descended intestine and necrosis of perineal soft tissues.

The most severe late complications included the development of paraproctitis and rectoperineal fistula in 1 year after surgery (Fig. 3), which required colostomy. Taking into account the severe degree of mental deficit and difficulties in care, the parents refused to close the stoma afterwards. The child is a permanent stoma carrier. A life-threatening complication in the form of severe Hirschprung-associated colitis of clostridial etiology developed 9 years after the initial operation. Hirschprung-associated enterocolitis (HAEC) had a severe course, complicated by fibrinous purulent peritonitis and multiorgan failure. The child was operated: lavage and drainage of the abdominal cavity and ileostomy were performed. On the background of treatment, including powerful antibacterial therapy, constant lavage of

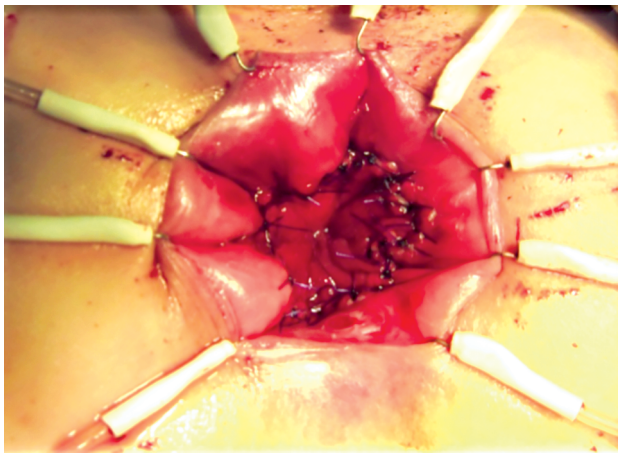

Fig. 1. Appearance of the colorectal anastomosis in child G., 6 years old, the reduced intestine is bright pink, the blood supply is beyond doubt

Рис. 1. Внешний вид колоректального анастомоза у ребенка Г., 6 лет, низведенная кишка ярко-розового цвета, кровоснабжение не вызывает сомнений

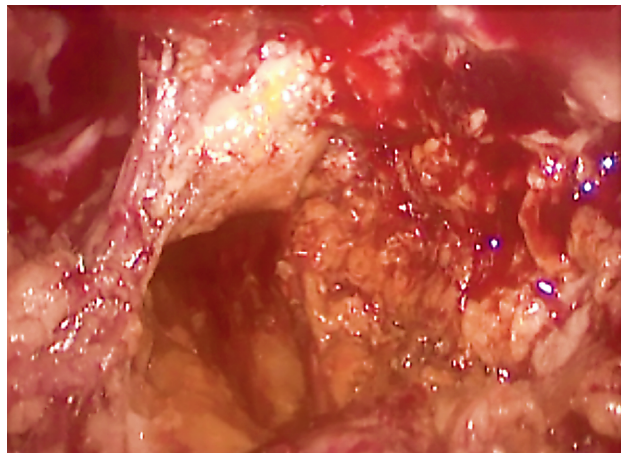

Fig. 2. Laparoscopic picture: 6 days after colon reduction in child G., 6 years old — retrorectal abscess, ischemic circular necrosis of the colon reduction, pelvic peritonitis

Рис. 2. Лапароскопическая картина: 6-е сутки после низведения толстой кишки у ребенка Г., 6 лет — ретроректальный абсцесс, ишемический циркулярный некроз низведенной кишки, тазовый перитонит

Table 1. Characteristics of patients with Hirschsprung disease and associated genetic syndromes

Таблица 1. Характеристика пациентов с болезнью Гиршпрунга и сопутствующими генетическими синдромами

№ п/п	Пол ребенка и возраст на момент операции на момент рождения / Gender of the child and age at the time of reduction surgery	Генетический синдром и сопутствующие врожденные пороки развития (ВПР) и заболевания / Genetic syndrome and associated congenital malformations (CMF) and diseases	Форма заболевания / Form of the disease	Предварительное стомирование / Pre- ostomy	Осложнения / Complications	Сроки развития осложнений / Time frame for the development of complications from the moment of surgery	Стомирование на этапах коррекции осложнений / Ostomy at the stages of correction of complications	Исход / Exodus
1	Мальчик, 1 месяц / Boy, 1 month	С-м Моятт–Вильсона / Moyatt-Wilson S-m	Ректосигмоидная / Rectosigmoid	–	Парапроктит, ректопериневальный свищ / Rectoperineal fistula	1 год / 1 year	+	Постоянная стома / Permanent stoma
2	Мальчик, 3 месяца / Boy, 3 month	С-м Моятт–Вильсона / Moyatt-Wilson S-m	Ректосигмоидная / Rectosigmoid	–	ГАЭК, псевдомембранозный колит, сепсис / GAEC, pseudomembranous colitis, sepsis	9 лет / 9 years	+	Благоприятный / Favorable
3	Девочка, 1 год / Girl, 1 year	С-м Стурге–Вебера / Sturge-Weber S-m	Ректосигмоидная / Rectosigmoid	–	Стеноз КРА, ятрогенный разрыв НАС / CRA stenosis, iatrogenic rupture of the EAS	6 месяцев / 6 months	+	Реконструктивная операция на промежности, стеноз КРА, недержание кала / Reconstructive surgery of the perineum, cranial stenosis, fecal incontinence
4	Мальчик, 3 года / Boy, 3 years old	С-м Дауна / Down S-m	Ректосигмоидная / Rectosigmoid	–	–	–	–	Благоприятный / Favorable
5	Мальчик, 3 месяца / Boy, 3 month	С-м Дауна (острый лейкоз) / S-m Down (acute leukemia)	Тотальная / Total	Илеостома / Ileostomy	Несостоятельность илеоилеоанастомоза, абсцесс брюшной полости, сепсис / Failure of ileo-ileoanastomosis , abdominal abscess, sepsis	1 месяц / 1 month	+	Недержание кала / Fecal incontinence
6	Мальчик, 6 лет / Boy, 6 years old	С-м Дауна / Down S-m	Ректосигмоидная / Rectosigmoid	–	Циркулярный некроз низведенной кишки, газовый перитонит / Circular necrosis of the reduced intestine, pelvic peritonitis	6-е сутки / 6th day	+	Стеноз КРА I степени Недержание кала II степени / 1st degree CRA stenosis Stage 2 fecal incontinence
7	Мальчик, 5 лет / Boy, 5 years old	С-м Дауна / Down S-m	Субтотальная / Subtotal	–	Несостоятельность КРА / Insolvency of the CRA	12-е сутки / 12th day	+	Постоянная стома / Permanent stoma

№ п/п	Пол ребенка и возраст на момент операции ин-вмешательства / Gender of the child and age at the time of reduction surgery	Генетический синдром и сопутствующие врожденные пороки развития (ВПР) и заболевания / Genetic syndrome and associated congenital malformations (CMF) and diseases	Форма заболевания / Form of the disease	Предварительное стомирование / Pre- ostomy	Осложнения / Complications	Сроки развития осложнений / Time frame for the development of complications from the moment of surgery	Стомирование на этапах коррекции осложнений / Ostomy at the stages of correction of complications	Исход / Exodus
8	Девочка, 1 год / Girl, 1 year	С-м Дауна / Down S-m	Ректосигмоидная / Rectosigmoid	Сигмостома / Sigmostoma	–	–	–	Благоприятный / Favorable
9	Мальчик, 8 месяцев / Boy, 8 months	С-м Дауна / Down S-m	Ректосигмоидная / Rectosigmoid	–	Некроз мягких тканей промежности / Necrosis of soft tissue of the perineum	8-е сутки / 8th day	+	Наложение вторичных швов. Ректальный пролапс. Недержание кала / Application of secondary sutures. Rectal prolapse. Fecal incontinence
10	Мальчик, 3 года / Boy, 3 years old	С-м Дауна / Down S-m	Ректосигмоидная / Rectosigmoid	–	Несостоятельность КРА, разлитой каловый перитонит / CRA failure, diffuse fecal peritonit	6-е сутки / 6th day	+	Благоприятный / Favorable
11	Мальчик, 1 год / Boy, 1 year	С-м Дауна / Down S-m	Ректосигмоидная / Rectosigmoid	–	–	–	–	Благоприятный / Favorable
12	Мальчик, 3 года / Boy, 3 years old	С-м Дауна / Down S-m	Ректосигмоидная / Rectosigmoid	–	Несостоятельность КРА, тазовый перитонит / CRA failure, pelvic peritonitis	5-е сутки / 5th day	+	Благоприятный / Favorable
13	Мальчик, 11 месяцев / Boy, 11 months	С-м «ундины» / S-m "undines"	Субтотальная / Subtotal	Илеостома / Ileostomy	Стеноз КРА / CRA stenosis	1 месяц / 1 month	–	Недержание кала II степени / Stage 2 fecal incontinence
14	Мальчик, 9 месяцев / Boy, 9 months	С-м Дауна / Down S-m	Тотальная / Total	–	Деструктивный аппендицит, лизис аппендикса, заворот подвздошной кишки / Destructive appendicitis, appendix lysis, ileal volvulus	5-е сутки / 5th day	+	Разлитой перитонит на фоне первичного иммунодефицита, внутрибрюшные абсцессы. Летальный исход / Diffuse peritonitis against the background of primary immunodeficiency, intra-abdominal abscesses. Death

Note: CMA — congenital malformations; HAEC — Hirschsprung-associated enterocolitis; CRA — colorectal anastomosis; EAS — external anal sphincter.
Примечание: ВПР — врожденные пороки развития; ГАЭК — Гиршпрунг-ассоциированный энтероколит; КРА — колоректальный анастомоз; НАС — наружный анальный сфинктер.

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the colon with metronidazole, use of methods of extracorporeal detoxification, the condition was finally stabilized. A year after the colitis, the child was examined, biopsy of the lowered intestine was performed and its normal ganglionic structure was confirmed, and the ileostomy was closed with subsequent favorable outcome. It was not possible to convincingly prove the obstructive nature of GAEC, as the child had no history of constipation before the development of this complication. Interestingly, both children with this complication had Moyatt-Wilson syndrome. It was not possible to convincingly prove the obstructive nature of Hirschprung associated enterocolitis (HAEC), as the child had no history of constipation before the development of this complication. Interestingly, both children with this complication had Moyatt–Wilson syndrome.

In order to correct the complications, 10 children (71.4%) had to undergo stoma surgery. Two patients (14.2%) became permanent stoma carriers. One child had iatrogenic damage of the external anal sphincter (NAS), the patient underwent reconstructive intervention on the perineum: sphincter plasty was performed. One child underwent secondary suturing due to colorectal anastomosis (CRA) failure on the background of perineal soft tissue necrosis. In all other cases, no additional interventions on the rectum were performed, and no secondary sutures were placed.

Among the comorbidities that could affect the treatment outcomes were: acute leukaemia (1–7.1%), primary immunodeficiency (1–7.1%). It is interesting to note that both children with blood disorders had total HD. Only one child had overweight, it was a patient with advanced extended necrosis of the lower intestine.

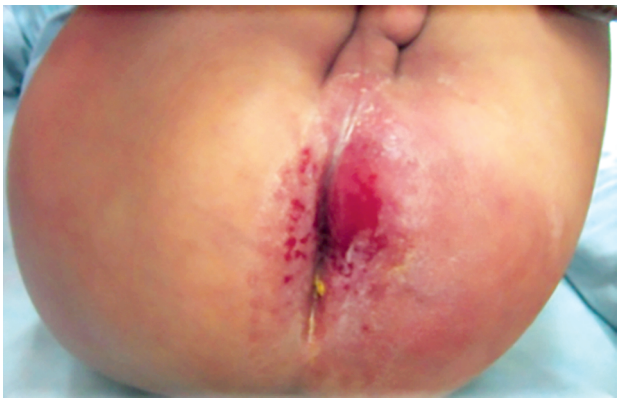


Fig. 3. Acute purulent paraproctitis in a patient after colon resection for Hirschsprung's disease

Рис. 3. Острый гнойный парапроктит у пациента после резекции толстой кишки по поводу болезни Гиршпрунга

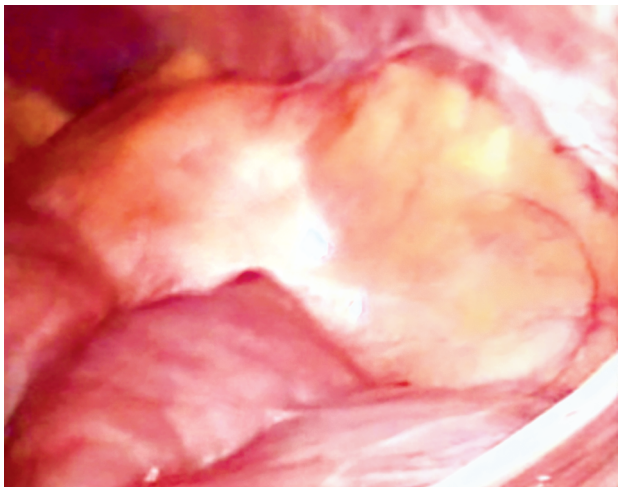
Anatomical peculiarities of the colon structure were revealed in three cases — retroperitoneal location of the left colon, scattered type of blood supply of the left colon, and excessive amount of adipose tissue making it difficult to verify angioarchitectonics in the mesentery of the sigmoid colon. It can be assumed that such anatomical prerequisites contributed to ischemic disorders in the descended colon (Fig. 4).

The outcomes of treatment were as follows: permanent stoma carrier — 2 (14.2%) children, fecal incontinence — 5 patients (35.7%), rectal stenosis developed in 2 cases (14.2%). One child died against the background of unrelieved peritonitis with concomitant primary immunodeficiency syndrome (7.1%). Favorable long-term outcome was achieved in 6 cases (42.8%).

DISCUSSION

The problem of treating surgical diseases in patients with various genetic syndromes is widely discussed in the literature, since these patients have peculiarities that affect the results of treatment at the stages of diagnosis, treatment and a postoperative period. Although there is due caution in the diagnosis of HD in DS patients, many authors indicate that the diagnosis is established later than in children without concomitant genetic syndromes. According to R.A. Saberi et al., during the neonatal period patients with DS are diagnosed with HD later ,(6th and 4th day after birth), and the duration of treatment is longer (22 and 15 days, respectively) [1, 2]. Due to the more severe course of the disease, up to 43% of patients with a combination of DS+HD require ostomy in the newborn period [4–6].

According to the summary data, the frequency of repeated operations in children with DM+BG ranges from 10 to 29% [7–9] due to the development of complications. Thus, according to A. Pini Prato et al., the probability of HAEC is 32% even before the surgery[4]. Similar data are published by D.R. Halleran et al. who analyzed the cases of HAEC on a large sample of patients, 14% of which were patients with DS. The severity of HAEC manifestations in these children was higher (7.1 and 5.6 points on the HAEC assessment scale), the frequency of tachycardia on admission was 75 and 19%, respectively, hypotension — 33 and 7%, the need for treatment in the intensive care unit — 58 and 12% [3]. Moreover,



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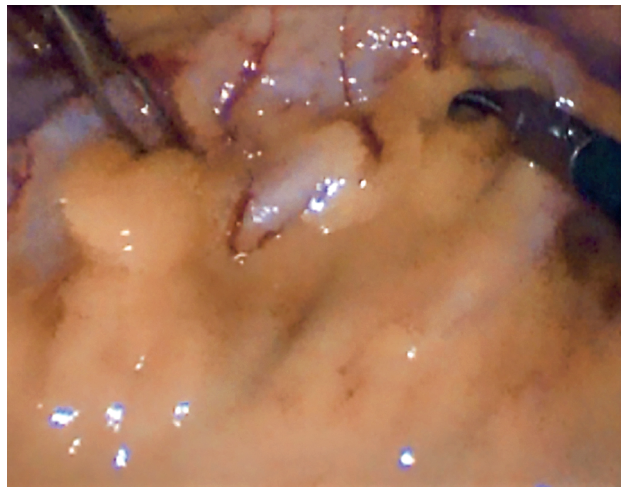

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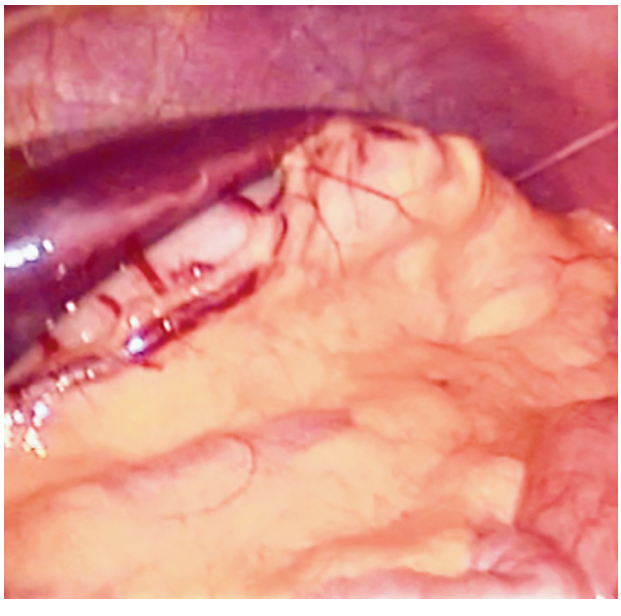

в / c

Fig. 4. Laparoscopic picture of the abdominal cavity in a child with Down syndrome and Hirschsprung disease — an excessive amount of visceral fat around the colon: *a* — retroperitoneal location of the left parts of the colon, the intestine is in a "fat sheath"; *b* — an excessive amount of visceral fat in the sigmoid colon; *c* — fatty sheath around the transverse colon

Рис. 4. Лапароскопическая картина брюшной полости у ребенка с синдромом Дауна и болезнью Гиршпрунга — избыточное количество висцерального жира вокруг толстой кишки: *а* — забрюшинное расположение левых отделов толстой кишки, кишка в «жировом футляре»; *б* — избыточное количество висцерального жира в сигмовидной кишке; *в* — «жировой футляр» вокруг поперечного отдела ободочной кишки

the duration of illness before admission was almost 3 times longer (84 and 24 hours, respectively). The authors believe that this is due to the fact that children with mental deficits start complaining later. This may also explain the severity of manifestations. In addition, recent studies on the pathogenesis of HAEC show that susceptibility to HAEC in HD patients is partly due to impaired immune function of the intestinal mucosa, in particular impaired intestinal B-cell function and impaired IgA production [10, 11]. This dysfunction probably results in an inadequate respond to an infectious lesion, predisposing the patient to bacterial invasion and HAEC. Children with DS have a previously described predisposition to many infectious diseases and cancers. Moreover, specific studies have shown that patients with DS have an initial deficiency in both humoral and cellular immunity, resulting in profound B-lymphocytopenia and alterations in IgA production. However, a study by A.J.M. Dingemans et al. showed that the incidence of HAEC in HD patients does not depend on concomitant DS [10].

In addition to HAEC, numerous publications indicate a higher risk of surgical complications, according to R.A. Saberi et al. children with DS have a higher incidence of wound complications (12 and 3%) compared to patients without DS and ulcerative necrotizing enterocolitis (UNEEC) (14 and 5%) [2].

Patients with DM have a high risk of mortality. Thus, R.A. Saberi et al. reported that the mortality rate for HD in the newborn period is more than 4 times higher in children with DS (5 and 0.8%) [2]. In 2013, these rates were significantly higher — 12 and 4.2–5.5%, respectively [5]. These data are

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confirmed by studies of the Japanese Association of Paediatric Surgery conducted in 2009, according to which preoperative mortality of children with DS+HD decreased from 10 to 3%, and overall mortality decreased from 26 to 8% [6]. However, despite the positive trends, the mortality rate is still very high, as the overall mortality rate in HD does not exceed 1% according to the American Association for Paediatric Surgery [9–11].

Possible explanations include: less precise control of body dynamics and greater difficulty in maintaining balance when walking, which may be the result of documented cerebellar deficits, muscle hypotonia and ligament laxity in people with DS; co-activation of agonist-antagonist muscle groups; mitochondrial dysfunction and very low aerobic fitness. The oxygen uptake efficiency index, which determines an individual's exercise capacity, is lower in these patients, inevitably leading to poor adaptation to exercise. Arterial resistance in response to maximal exercise is reduced in people with DS.

Three cases revealed peculiarities of the anatomical structure of the left colon, which determine specific features of its blood supply and contribute to ischemia of the descending colon. No discussions of the issue were found in the literature. However, taking into account that patients with DS are more often overweight, the literature focuses on the influence of obesity and the development of complications after surgical interventions in these patients. Patients with DS have a specific constitutional type characterized not only by an overall excess of adipose tissue but also by an increased amount of visceral fat, a phenomenon observed even in malnourished children. Visceral fat is concentrated in the mesentery of the intestine, often with a scattered type of blood supply to the intestine, which directly affects the peculiarities of the blood supply to the descending colon. Overweight and obesity in DS are caused by slow metabolism, abnormal leptin concentration in blood and low level of physical activity. Patients with DS appeared to have significantly higher leptin levels than their siblings, and this is more pronounced than the body fat percentage would suggest. This may explain the increased risk of obesity. Leptin levels are higher in children with DS than in children without DS but with the same body mass index (BMI), whether or not obesity is present. This fact demonstrates leptin resistance in DS.

The tendency to apnea in patients with Down syndrome may play a role, as sleep apnea may precede obesity. Thus, A. Ravel et al. reported that 62% of obese children had a higher prevalence of large lingual tonsils and more often underwent palatine tonsillectomy [1].

The high incidence of inflammatory complications is probably due to the higher frequency of immunological abnormalities in children with DM. Recent studies on the pathogenesis of HAEC suggest that susceptibility to HAEC in patients with DS is partly due to impaired immune function of the intestinal mucosa, in particular impaired intestinal B-cell function and impaired production IgA.23–26. This dysfunction probably results in an inability to respond to infectious lesions, predisposing the patient to bacterial invasion and HEC. Children with DS have a well-described predisposition to many infectious diseases and cancers, and specific studies have shown that patients with DS have an initial deficiency in both humoral and cellular immunity, resulting in profound B-lymphocytopenia and alterations in IgA production [3, 11].

CONCLUSION

It is clear that children with DS suffering from symptoms such as constipation, abdominal bloating, regurgitation and vomiting during the newborn period and the first months of life should not receive conservative treatment before HD is excluded with the help of rectal biopsy. Earlier diagnosis may help to reduce the proportion of decompensated forms of the disease and reduce the risk of complications.

Given the higher risk of CRA failure in patients with diabetes, obesity, immunological disorders and other additional risk factors, preventive stomas or two-stage interventions should be more widely used in relegation surgery, which may significantly reduce the risk of inflammatory complications in the postoperative period.

The high incidence of CRA failure may be due to ischemic disorders in the lowered intestine associated with the peculiarities of angioarchitectonics in patients with DS. The use of hyperbaric oxygenation in the early postoperative period may be a promising way to prevent ischemic complications in patients of this group.

Patients with diabetes and HD should be examined to exclude immunological disorders, as the presence of the latter may lead to the development of life-threatening complications after surgery.

ADDITIONAL INFORMATION

Author contribution. Thereby, all authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

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Consent for publication. Written consent was obtained from legal representatives of the patient for publication of relevant medical information within the manuscript.

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Вклад авторов. Все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Авторы заявляют об отсутствии внешнего финансирования при проведении исследования.

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