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ABSTRACT

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A CLINICAL CASE OF RECURRENT CLOSTRIDIUM DIFFICILE-ASSOCIATED DIARRHEA IN A CHILD

Introduction. Clostridium difficile is the most important infectious aetiology of antibiotic-associated diarrhea. Today, in the era of pandemics and numerous epidemics that have faced the humanity, antibiotic therapy is one of the most common medical practices. However, the careless use and irrational prescription of antibiotics increase the risk of their negative impact on the human body and steadily approach antibiotic resistance. American Academy of Pediatrics reports an increase in the incidence of Clostridium difficile infection in children; a wide spectrum of disease severity can occur, ranging from asymptomatic carriage to severe recurrent diarrhea. Annually 20 thousand cases of Clostridium difficile infection are registered among patients in the pediatric cohort according to the American Academy of Pediatrics. The relevance of the topic is due to the increase in the incidence of Clostridium difficile-associated diarrhea, which is a result of irrational antibiotic therapy.

The aim of the study: to increase the awareness and vigilance of medical workers regarding the possibility of recurrent Clostridium difficile-associated diarrhea in children based on the demonstration of a clinical case.

Materials and methods. The results of examination, clinical observation and analysis of clinical case of enterocolitis caused by Clostridium difficile in a 5-year-old child are given.

Results and discussion. A 5-year-old patient was hospitalised with complaints of increased body temperature, blood-tinged stools, abdominal pain, lethargy, and decreased appetite. Clostridium difficile toxin A and toxin B were detected by the PCR method during stool analysis for the detection of clostridia. The patient was discharged from the clinic with an improvement in his general condition after the treatment, on the background of clinical recovery. But later he was hospitalized twice to the the Kyiv City Children's Clinical Infectious

Hospital with a recurrence of Clostridium difficile-associated diarrhea and positive Polymerase chain reaction test results.

Conclusions. Circumspection of the possibility of recurrent Clostridium difficile-associated diarrhea is important in the diagnosis of infectious diseases.

Keywords: Clostridium difficile, diarrhea, enterocolitis, recurrent course, diagnosis, children.

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КЛІНІЧНИЙ ВИПАДОК РЕЦИДИВУЮЧОГО ПЕРЕБІГУ CLOSTRIDIUM DIFFICILE-АСОЦІЙОВАНОЇ ДІАРЕЇ У ДИТИНИ

Clostridium difficile є найвагомішою інфекційною етіологією діареї, пов'язаної з прийомом антибіотиків. Сьогодні, в еру пандемій та численних епідемій, що припали на досвід людства, антибіотикотерапія є одним з найпоширеніших лікувальних практик. Проте, недбале використання та нераціональне призначення антибіотиків підвищує ризик їхнього негативного впливу на організм людини та невпинно наближають до антибіотикорезистентності. Американська академія педіатрії повідомляє про зростання захворюваності на інфекцію Clostridium difficile у дітей та широкий спектр тяжкості захворювання, починаючи від безсимптомного носійства до тяжкої рецидивуючої діареї. Так, за даними Американської академії педіатрії, щорічно реєструється 20 000 випадків серед пацієнтів педіатричної когорти. Актуальність теми обумовлена підвищенням частоти захворюваності на Clostridium difficile-асоційовану діарею, що часто є наслідком нераціональної антибіотикотерапії.

Мета дослідження: підвищити обізнаність та настороженість медичних працівників щодо можливості виникнення рецидивуючого перебігу Clostridium difficile-асоційованої діареї у дітей на основі демонстрації клінічного випадку.

Матеріали і методи. Наведено власні результати обстеження, клінічного спостереження й аналізу випадку захворювання на ентероколіт, викликаного Clostridium difficile у дитини 5 років.

Результати та їх обговорення. Пацієнт, 5 років, надійшов до стаціонару зі скаргами на підвищення температури тіла, випорожнення з домішками крові, біль в животі, в'ялість, знижений апетит. Методом ПЛР при аналізі калу на виявлення клостридій було виявлено Clostridium difficile токсин А та токсин В. Після проведеного лікування, на фоні клінічного одужання пацієнт був виписаний з поліпшенням загального стану, проте згодом був двічі повторно госпіталізований до дитячої лікарні міста Києва з рецидивом Clostridium difficile-асоційованої діареї та позитивними результатами тесту ПЛР.

Висновки. Настороженість щодо можливості виникнення рецидивуючого перебігу Clostridium difficile-асоційованої діареї має важливе значення в діагностиці інфекційних хвороб.

Ключові слова: Clostridium difficile, діарея, ентероколіт, рецидивуючий перебіг, діагностика, діти.

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ABBREVIATIONS

COVID-19 – Coronavirus disease
SARS-CoV-2 – Severe acute respiratory syndrome coronavirus 2
AAD – Antibiotic-associated diarrhea
CDAD – Clostridium difficile-associated diarrhea
ESR – Erythrocyte sedimentation rate
INR – International normalized ratio
APTT – Activated partial thromboplastin time
PT – Prothrombin time
PCR – Polymerase chain reaction
CRP – C-reactive protein

INTRODUCTION / ВСТУП

Today, in the era of pandemics and numerous epidemics that have faced the humanity, antibiotic therapy is one of the most common medical practices. However, the careless use and irrational prescription of antibiotics increase the risk of their negative impact on the human body and steadily approach antibiotic resistance. Antibiotic-associated diarrhea (AAD) is one of the most frequent consequences of antibiotic therapy, which can have minimal clinical manifestations and can cause death [1, 2].

According to the American Academy of Pediatrics (AAP), Clostridium difficile is the most important infectious cause of AAD worldwide and the leading cause of healthcare-associated infection in the United States. AAP reports an increase in the incidence of Clostridium difficile infection in children. 20 thousand cases of Clostridium difficile infection are registered annually among patients in the pediatric cohort. A wide spectrum of disease severity can occur, ranging from asymptomatic carriage to severe recurrent diarrhea [3].

Due to the enormous frequency of antibiotic prescription during the COVID-19 pandemic and the immunological features caused by the SARS-CoV-2 virus, the relevance of Clostridium difficile-associated diarrhea (CDAD) infection has increased and requires the development of new approaches. Because of the massive spread of SARS-CoV-2, the lack of many treatment options, and the high rates of both recurrence and mortality, Clostridium difficile poses a serious challenge to the health care system [4].

Clostridium difficile is a gram-positive spore-forming anaerobic bacterium in the form of a rod up to 4–5 micrometers in size. It was first discovered in 1935 as part of the normal flora of healthy people and was named Bacillus difficile due to problematic cultivation, and later renamed Clostridium difficile. Later, with the introduction of antibiotic therapy, scientists discovered a correlation between the microorganism and antibiotic-associated diarrhea and pseudomembranous colitis [4, 5, 6].

The main pathogenic factor of Clostridium difficile is the production of toxins [7, 8]. Clostridium difficile was included in the list of microorganisms with an "urgent" level of threat by the Centers for Disease Control and Prevention. Due to the difficulty of controlling this infection, Clostridium difficile colonization can be observed in 20–50% of hospitalized patients. In addition, there has been an increase in community-acquired CDAD, which may not always be related to antibiotic use or recent hospitalization [6, 9].

Diarrhea associated with Clostridium difficile accounts for 10-25% of all cases of AAD. However, Clostridium difficile is isolated in 50-75% of patients with antibiotic-associated colitis and in almost 100% of patients with pseudomembranous colitis. In cases of AAD, when the infectious agent cannot be isolated, it is called idiopathic AAD (IAAD) [10, 11].

The development of AAD is caused by a violation of the qualitative and quantitative composition of the intestinal microflora, as well as the pharmacological, toxic, and allergic effect of the antibacterial drug. According to the leading pathogenetic mechanism, the following types of diarrhea are distinguished: osmotic, secretory, hypermotor and infectious. Osmotic (hyperosmolar) diarrhea against the background of antibiotic therapy can develop due to impaired carbohydrate metabolism and increased deconjugation of bile acids (against taking Ampicillin, Clindamycin, Metronidazole, Erythromycin). Hypermotor diarrhea develops due to impaired motility of the gastrointestinal tract and is caused mainly by the pharmacological properties of the drugs. Secretory diarrhea develops due to impaired hepatic circulation of bile acids (on the background of taking Clindamycin, Ampicillin), the number of 7-adehydroxylating lactobacilli decreases, which leads to the accumulation of primary bile acids, which can stimulate the secretion of chlorine and water

into the cavity of the large intestine. Infectious diarrhea is caused by a violation of the qualitative and quantitative composition of the intestinal microflora, which is accompanied by a decrease in the protective functions of the intestinal mucosa and contributes to the growth of pathogenic and opportunistic microorganisms (Clostridium spp., Candida spp., Salmonella, Staphyloccus aureus) [11].

According to the recent updates published by the AAP, the diagnosis of CDAD can be difficult because currently available diagnostic methods detect either the presence of the microorganism or the pathogenic toxin, but cannot distinguish between colonization and infection. Because colonization can be high in certain pediatric populations, such as infants and young children, clear diagnostic methods are critical. Among treatment metods, Metronidazole has long been considered the mainstay of CDAD therapy in children. However, new evidence supports safety and efficacy of the oral Vancomycin and Fidaxomicin as additional treatment options [3]. Our research work corresponds to the current guidelines, as in the present clinical case the patient was prescribed Metronidazole and Vancomycin.

Objective: to increase the awareness and vigilance of medical workers regarding the possibility of recurrent CDAD in children based on the demonstration of a clinical case.

Materials and Methods. The results of the examination, clinical observation and analysis of a case of enterocolitis caused by Clostridium difficile in a 5-year-old child who was hospitalized three times at the Kyiv City Children's Clinical Infectious Hospital of with recurrence of the disease are given.

Results. We present our own clinical case. Patient M., 5 years old, was hospitalised with complaints of increased body temperature, stools with blood impurities, abdominal pain, lethargy, decreased appetite. From the anamnesis, it was known that the child was born full-term, the growth and development of the child proceeded according to age. Vaccinations were carried out according to the National calendar of preventive vaccinations. Hereditary, allergological and epidemiological anamnesis were not burdened. In the anamnesis, there was information about the disease two weeks before (pneumonia), and Amoxicillin was prescribed for treatment.

During admission to the hospital, the patient's condition was of moderate severity due to intoxication, dehydration, abdominal and enterocolitis syndromes. The consciousness was clear, the position was passive, the skin was pale, the mucous membranes were dry, the turgor of soft tissues was reduced. The tongue was dry with a white coating. The heart rate was 100 per minute, blood pressure – 110/70 mm Hg. The abdomen was soft on palpation, painful in all areas. Excretions were frequent (10–15 times a day), liquid, with impurities of blood.

Laboratory studies. Complete blood count during the hospitalization: erythrocytes – 5,05 × 10^{12}/l, hemoglobin – 138 g/l, leukocytes – 33,3 × 10^{9}/l, platelets – 286 × 10^{9}/l, eosinophils – 1%, rod-shaped neutrophils – 29%, segmented neutrophils – 64%, lymphocytes – 3%, monocytes – 2%, ESR – 3 mm/h. In the clinical blood analysis, attention was drawn to significant neutrophilic leukocytosis with a shift of the formula to the left, relative lympho- and monocytopenia. Index of the coagulation system: PT – 11,.8; prothrombin activity according to Kwik 99,4; INR – 1,03; Fibrinogen – 3,2; fibrin – 14; APTT – 33,9.

General analysis of urine without features. In the coprogram, neutral fat was detected in a moderate amount, fatty acids were not observed, Gregersen's reaction was negative. Single muscle fibers, a lot of mucus and 10-20 leukocytes in the field of the view were detected. Fecal calpoprotein <12 μg/g; 25-Hydroxyvitamin D – 22,15 ng/ml; ANA – 0,64; CRP – 2 mg/l.

Protein fractions – total protein – 68,3 g/l; A/G ratio – 1,63; α1 globulin – 4,0%; α2 globulin – 9,0%; β-globulin – 9,0%; γ-globuly – 16; fractional albumin – 62,0%.

Microbiological research and determination of the sensitivity of selected cultures to antibiotics: E. coli – 10^{8}; Candida fungi – 10^{6}; Klebsiella – 10^{2}. Bacteriological examination of mucus from the pharynx for flora and culture of feces during the hospitalization did not reveal pathogenic and opportunistic flora. Clostridium difficile toxin A and toxin B were detected by the PCR method (qualitative determination) during stool analysis for the detection of clostridia.

Complete blood count in dynamics after 7 days: erythrocytes – 5,07 × 10^{12}/l, hemoglobin – 136 g/l, leukocytes – 16,8 × 10^{9}/l, platelets – 454 × 10^{9}/l, myelocytes, metamyelocytes – 8% , eosinophils – 2%, rod-shaped neutrophils – 7%, segmented neutrophils – 35%, lymphocytes – 340%, monocytes – 13%, ESR – 3 mm/h. In the dynamics, there is a decrease in leukocytosis with a shift in the formula to young forms, relative monocytosis.

The treatment: Metronidazole, Ceftazidime, oral rehydration, infusion therapy with glucose-salt solutions, symptomatic treatment (antipyretics in age-related doses, antiemetics, sorbents, Simethicone). On the background of treatment, the child's condition was improved and stabilized. The patient was discharged with improved health and given recommendations for follow-up with a paediatrician, a dairy-free diet, probiotics and enzyme supplements intake. **The full**

diagnosis was Enterocolitis caused by Clostridium difficile, exicosis of I degree, moderate severity.

After 9 days after discharge, the patient was re-hospitalised with complaints of increased body temperature up to 39℃ and loose stools. From the data of the objective examination, the condition was of medium severity due to intoxication and colitis.

Laboratory studies. Complete blood count during the re-hospitalization: erythrocytes – 4,47 × 10^{12}/l, hemoglobin – 124 g/l, leukocytes – 6 × 10^{9}/l, platelets – 192 × 10^{9}/l, eosinophils – 0%, rod-nuclear neutrophils – 6%, segmented neutrophils – 70%, lymphocytes – 14%, monocytes – 9%, ESR – 15 mm/h. In the clinical blood analysis, attention was paid to relative lymphocytopenia and an increase in ESR. In dynamics, during the week, all laboratory parameters of the general blood test have stabilized. Biochemical analysis of blood and general analysis of urine was without features. CRP - 9 mg/l. A small amount of muscle fibers, starch, a small amount of vegetable fibers, 2-3 leukocytes in the field of vision, yeast-like fungi covered the entire field of vision were found in the coprogram. Pathogenic and intestinal flora were not detected during the bacterial culture of feces twice. Clostridium difficile toxin A and toxin B were detected by the PCR method during stool analysis for the detection of clostridia.

The treatment: oral rehydration, infusion therapy with glucose-saline solutions, oral Metronidazole and Vancomycin. Against the background of treatment, the condition of the child was improved. The patient was discharged with clinical recovery on the 10th day of the hospitalisation. Follow-up by a pediatrician, diet and probiotic intake were recommended. **The full diagnosis was enterocolitis caused by Clostridium difficile**, **moderate severity.**

5 days after the previous hospitalization, the child was admitted to the hospital again with complaints of abdominal pain and loose, frequent bowel movements. From the data of the objective examination, the condition was of medium severity due to intoxication and colitis.

Laboratory studies. Complete blood count during the last hospitalization: erythrocytes – 4,66 × 10^{12}/l, hemoglobin – 130 g/l, leukocytes – 6,22 × 10^{9}/l, platelets – 286 × 10^{9}/l, eosinophils – 1% , rod- nuclear neutrophils – 4%, segmented neutrophils – 47%, lymphocytes – 38%, monocytes – 9%, ESR – 3 mm/h.

General analysis of urine without features. In the coprogram, neutral fat was found in moderate amount, fat acids were not observed, Gregersen's reaction was negative. Fecal calpoprotectin <12 μg/g; 25-Hydroxyvitamin D – 22,15 ng/ml; ANA – 0,64; CRP – 2 mg/l. Protein fractions – total protein – 68,3 g/l; A/G ratio – 1,63; α1 globulin – 4,0%; α2 globulin – 9,0%; β-globulin – 9,0%; γ-globulin -16; fractional albumin – 62,0%. Biochemical analysis of blood – without specific changes. Clostridium difficile toxins A and B were detected by the PCR method during stool analysis for the detection of clostridia.

Instrumental studies. During ultrasound of abdominal organs – liver dimensions: anteroposterior dimension of the right lobe – 104 mm, left lobe – 45 mm, contours were even, clear, echogenicity of the parenchyma has not changed, the structure was homogeneous, portal vein – 7 mm. In the hepatoduodenal ligament, lymph nodes were visualized, up to 15 mm in size with a normal structure. The gallbladder was S-shaped, not enlarged, the wall was compacted, not thickened, the contents were anechoic. Pancreas: fully visualized, slightly enlarged: head – 20 mm, body – 14 mm, tail – 20 mm, tissue echogenicity was normal, structure was homogeneous. The left kidney was located typically, oval in shape, the contour was even, clear, the dimensions were not increased, the echogenicity, the parenchyma were normal, the calyx system was slightly compacted. With color doppler mapping, the blood flow was traced to the kidney capsule. Free fluid was visualized: under the visceral edge of the liver – 4 mm; in the right flank with a height of 9 mm, above the urinary bladder with a height of 11 mm. With energy Doppler mapping examination, the wall of the cecum was slightly thickened – 2,8 mm, layer-by-layer differentiation was not disturbed, vascularization was moderately enhanced. The walls of the ascending colon, descending colon, and sigmoid colon were not thickened, the differentiation of the layers was not disturbed, the haustration was preserved, and the vascularization was not enhanced. Multiple mesenteric lymph nodes up to 13 mm in size were visualized, in the right iliac region up to 20 mm in size, of normal structure, blood flow was moderately increased. Conclusion: ultrasound signs of reactive changes in the pancreas, lymphadenopathy. During the ECG, moderate metabolic changes in the myocardium were detected. The valves – without changes. Defects of partitions were not observed. The general contractility of the myocardium of both ventricles was good.

The treatment: symptomatic drugs (antipyretics, antiemetics, sorbents, Simethicone) and medications with Saccharomycetes boulardi. Dietary, vitamin, omega-3 and probiotic recommendations were provided. The patient was discharged with an improvement in his general condition and a negative test result for Clostridium dificile toxins**. The full diagnosis was recurrent Clostridium Difficile-associated diarrhea, moderate severity.**

Discussion. The research is devoted to the demonstration of a clinical case of CDAD in a 5-year-

old child who was hospitalized three times to the Kyiv City Children's Clinical Infectious Hospital with recurrence of the disease. AAP indicated that recurrence of this disease in pediatric practice was common like in adults. This disease can affected children in 20-23% of cases [3].

The US Centers for Disease Control and Prevention (CDC) has identified Clostridium difficile as an urgent threat, and marked it as one of the top 5 drug-resistant pathogens. According to published sources, Clostridium difficile is the leading cause of healthcare-associated infection in the United States, with approximately half a million confirmed cases each year, with 223,900 requiring hospitalization and more than 12,000 deaths [5, 6, 8].

Diagnosis of CDAD in children is difficult, and detection of the causative agent cannot always confirm the diagnosis. There are several commercial tests available for diagnosis that detect the presence of Clostridium difficile or toxin production, but these have limitations and are the gold standard. Tests that detect the toxin are specific but not sensitive enough for diagnosis. Detection of the toxin does not always correlate with the severity of symptoms in children, and the concentration of the toxin in the stool cannot reliably distinguish carriage from infection [10].

The importance of diagnosis was demonstrated by scientists from Zaporizhia. The clinical case of CDAD in a 65-year-old female patient with chronic concomitant pathology of the gastrointestinal tract in the form of chronic atrophic gastritis, chronic pancreatitis, chronic noncalculous cholecystitis, as well as the postoperative period after resection for sigmoid colon cancer was presented. After the treatment of CDAD, the patient was discharged with positive dynamics. Despite the improvement of well-being during the treatment and a satisfactory condition at the time of discharge, several weeks later complaints of general weakness, frequent loose stools, swelling of the face and limbs, and abdominal pain appeared at home. However, the patient did not seek medical help again, and without adequate treatment, this case has fatal outcome [1]. Compared with the described clinical case, our own clinical case concerned a pediatric patient without accompanying chronic pathology and was characterized by a mild course; patient was hospitalized and examined for clostridial infection three times.

The positive effect of treatment in represented clinical case was observed after the administration of Saccharomycetes boulardi probiotics. This is consistent with literature data from Goldenberg J.Z., et al. (2017). In their research study, scientists decided to evaluate the effectiveness and safety of probiotics in prevention of diarrhea caused by Clostridium difficile in adults and children. The study included a systematic review and meta-analysis of 31 randomized controlled trials involving 8,672 patients. The data obtained by the authors indicate the effectiveness of probiotics in the prevention of CDAD and demonstrated a 60% reduction in the risk of diarrhea after using of probiotics [12].

The benefit of Saccharomycetes boulardi probiotics in prevention of Clostridium difficile infection was also demonstrated in the studies of Koon H.W. et al. (2016). Researchers used hamster models infected with Clostridium difficile strains to determine the probability of prevention of cecal tissue damage and inflammation in hamsters by oral administration of live or heat-inactivated non-pathogenic yeast Saccharomyces boulardii CNCM I-745 (S.b). In the study, it was found that per os consuming of live, but not heated, S.b. with a help of gastric tube, starting 5 days before infection with Clostridium difficile, significantly reduced cecal tissue damage in hamsters. The medium conditioned by S.b also inhibited the destruction of Clostridium difficile mediated by toxins A and B. Therefore, the authors concluded that Saccharomycetes boulardi is effective in preventing Clostridium difficile infections by inhibiting the cytotoxic effects of its toxins and may be useful in CDAD [13].

CONCLUSIONS / ВИСНОВКИ

Circumspection of the possibility of recurrent Clostridium difficile-associated diarrhea is important in the diagnosis of infectious diseases. Dynamic observation, the use of a wide range of laboratory-instrumental means and treatment approaches can be useful in avoiding diagnostic mistakes and can prevent possible consequences.

AUTHOR CONTRIBUTIONS / ВКЛАД АВТОРІВ

Liudmyla Palatna – diagnostic and therapeutic work, analysis of the results, conclusions, article editing of the manuscript for publication.

Iryna Shpak – literature review, analysis, design and editing of the work, English translation of the manuscript for publication.

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CONFLICT OF INTEREST / КОНФЛІКТ ІНТЕРЕСІВ

The authors declare no conflict of interest.

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