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Possibilities of using intestinal microflora transplantation in the treatment of gastrointestinal diseases

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ABSTRACT

The number of *Clostridium difficile* infections (CDI) has significantly increased in Poland and throughout Europe. Their treatment involves the administration of metronidazole, vancomycin or fidaxomicin as indicated in current recommendations. Despite proper approach to the treatment, numerous recurrences of *Clostridium difficile* are reported. Fecal microflora transplant (FMT) is an alternative yet effective method of treatment of CDI. Moreover, this method is increasingly implemented in other disease entities.

DESCRIPTION OF THE PROBLEM:

Fecal microflora transplant (FMT) is a safe method of treating intestinal dysbiosis. The therapy is based on transferring the stool suspension from a healthy human (donor) to the patient (recipient). The transplant can be performed by oral route (through the gastric/duodenal probe) or via the rectal route (colonoscopy). The donor of the FMT material must give an informed consent to have performed

numerous blood and stool tests that are included in the donor selection procedures. The day before transplant, the recipient has to take the last dose of vancomycin taken in the 14-day treatment.

INTRODUCTION

Fecal microflora transplant is based on transferring the stool suspension from a healthy human (donor) to the patient (recipient) in order to sustain the natural colon microflora [1-2]. The transplant can be performed by oral route (through the gastric/duodenal probe) or via the rectal route (colonoscopy). In recent years the increased interest in FMT followed both - the growing number of cases of CDI as well as increasing awareness of the importance of intestinal microbiota for human health [1]. The number of bacteria in human body is ten times higher than number of its cells. A digestive tract is colonized by around 500-1000 species of microorganisms that have positive effect on digestion process and immune system. Moreover, microorganisms protect against penetration of pathogen and diminish the development of tumors. In spite of various studies, the composition of microbiota is still undiscovered - currently only 30% of microbiome species were grown [1]. The history of FMT method starts in the 4th century in China, yet it was introduced to modern medicine in second half of 20th century. Since the first premises of successful fecal transplant, the literature was enriched in numerous studies of application of this method in different diseases entities including bacterial diarrhea, irritable bowel syndrome, constipation or inflammatory bowel states. What is more, there are many reports showing effectiveness and safety of FMT. This method of treatment of CDI was assessed as efficient in two randomized studies [1-2]. The FMT is also used in treatment of ulcerative colitis (UC) yet the further research needs to be introduced to confirm the efficacy of this method. Still, current results are promising [2]. So far, it has also been proven that people with FMT have an increased insulin sensitivity.
Microflora transplant intestinal tract has been included in the canon of Evidence Based Medicine (EBM) and is no longer an experimental methodbut a commonly used and often life-saving method. Furthermore, FMT is willingly chosen method by patients due to its low invasiveness and rare side effects [3]. Microflora transplant involves administering several doses of faecal suspension by the oral route (gastric / duodenal probe) or rectal (colonoscopy). The donor can be any healthy person both from the family and non-relatives. Technique and method associated with FMT are constantly evolving standardized preparations of frozen stool or tablets enable oral therapy.

DESCRIPTION OF THE ISSUE

Clostridium difficile is a gram-positive anaerobic bacteria belonging to a group of opportunistic pathogens [4].
Its virulence is determined by the two types of exotoxins: A (TcdA) and B (TcdB) which inactivate Rho protein in GTPase enzyme by glycosylation [5]. The process leads to impaired absorption of water and electrolytes due to acute colitis. Spores produced by the bacteria can survive in a wide range of temperature and pH. They are resistant to commonly used disinfectants [5-6]. Clostridium difficile strain B1/NAP1/027 (North American Pulsed Field Type I),

also known as a rybotype PCR 0027, secrete 10 to 20 times more exotoxine A and exotoxine B. Futhermore they produce extra amount of spores and also release binar toxine (ADP-rybosylotransferase) [4,6]. These special features determine high virulency with the frequent relapses and increased mortality [6, 8].

Symptomatic C. difficile infections are termed as disease associated with Clostridium difficile infection - CDI (Clostridium difficile-associated disease CDAD) and include antibiotic-associated diarrhea, post-antibiotic colitis and pseudomembranous colitis [6]. C.difficile is the most common cause of antibiotic-associated diarrhea- it concerns from 15 to 25% of all cases [7]. Antibiotic therapy is a common contributor to Clostridium difficile infection. The highest risk of CDI is linked to using antibiotics with a broad spectrum of activity, including 2nd and 3rd generation cephalosporins, clindamycin, fluoroquinolones and penicillins with beta-lactamase inhibitors. The occurrence of C.difficile infection is often triggered by the hospitalization, surgical interventions, endoscopic procedures within the gastrointestinal tract and other invasive medical procedures, including: nasogastric tube feeding or percutaneous endoscopic gastrostomy [6,8]. Most often C. difficile infection affects people over 65 years old, among whom it is 20 times more frequent than in people under 20 years old [9]. This is probably related to the weakness of the immune system and the occurrence of numerous comorbidities in this age group [8]. There is no doubt about relationship between the use of proton pump inhibitors or H2 receptor antagonists and increased frequency of Clostridium difficile infections. It is associated with reduction of gastric acid secretion [6-7]. This fact was mentioned in the recommendations of numerous scientific societies. In addition, the factors that increase the risk of CDAD are: chemotherapy, immunosuppressive treatment and vitamin D deficiency [4].

The reservoir of Clostridium difficile infection includes hospitalized patients, medical staff hands and medical furniture and equipment (bedding, bathroom equipment or reusable medical equipment, eg. stethoscopes) [10, Rośko-Ochojska and others 2014). Despite of using disinfectants, spores of bacteria can persist on objects for a long time, even up to several months. C. difficile infection is transmitted via the fecal-oral route with an incubation period up to 2 months (Gajewski et al. 2017). C. difficile carriage affects 3% of general population and 20-40% of hospitalized people (increases depending on the length of hospital stay) [9]. Frequency of Clostridium difficile infections in Poland is approximately 76/10000 hospitalized patients [4]. This number is much higher than the statistics of Western European countries, where the average is about 23/10000 patients [4]. Data on mortality related to CDI are differentiated depending on the severity of the course range from 2% to 30% [4].

Commonly used screening test for Clostridium difficile infection is based on detection of glutamate dehydrogenase (GDH) in the stool [6]. GDH is an enzyme that can be produced by toxicogenic and non-toxicogenic Clostridium difficile strains [10]. The test is characterized by high sensitivity at the level of 96 – 100 percent but does not enable to differentiate between Clostridium difficile infection and permanent carriage [9]. Positive screening test result requires confirmation test which detects exotoxin A and exotoxin B in the stool [10]. Confirmation test is characterized by high specificity (95-98%) but significantly lower sensitivity (60-70%) [9]. In case of positive screening test result combined with negative

confirmation test result stool culture is conclusive. Tests based on detection of bacteria genetic material are significant step forward in diagnostics of Clostridium difficile infection. NAAT (nucleic acid amplification test) or PCR (polymerase chain reaction) are considered as the most accurate and reliable methods.

The first step in treatment of CDI is a cesation of antibiotic therapy that caused a disease [4]. This is sufficient to relieve symptoms within 48-72 hours in 23% of patients with mild infection [9]. The first-line of pharmacologic therapy during the first CDI episode is the use of metronidazole or vancomycin [4]. Fidaxomicin has also been registered for use in CDI, but its high price is a significant limitation for using this medicament [4, 6]. In case of CDI relapse intestinal microflora transplantation should be considered as an effective and safe method in therapy of the disease [6].

SUMMARY AND CONCLUSIONS:

Intestinal microflora transplantation has many applications in modern medicine.
The presented research results prove that in the disease associated with Clostridium difficile fecal microflora transplantation is a safe and efficient method, often more effective than standard antibiotic therapy. Further research are needed on the use of this method in treatment of ulcerative colitis and irritable bowel syndrome however recent reports are promising.

REVIEW OF THE LITERATURE

BENEFITS

The biggest benefit observed in the researches sacrificed to gut microbiota graft in CDI treatment, is significantly higher effectiveness of this method comparing to the standard antibiotic therapy. The study entitled „Randomised clinical trial: faecal microbiota transplantation by colonoscopy vs. vancomycin for the treatment of recurrent Clostridium difficile infection" patients suffering from pseudomembranous enteritis were divided into two groups. The first one was treated according to regular scheme with vancomycin, and in the second one the scientists have combined different methods: gut microbiota graft and vancomycin infusion but shorter comparing to the first group. After a year observed a 26% decrease in diarrhea occurence the first group and 90% decrease in the second one [11]. The scientific work "Duodenal infusion of donor feces for recurrent clostridium difficile" showed that the cure rate after fecal microbiota transplantation (FMT) was 94% comparing to the 31% of cured patients obtaining only vancomycin [12].

SAFETY

The method of FMT is considered as a safe one. The most frequent negative effects of this therapy are: sore throat, flatulence, winds, nausea, transient increase of body temperature.
In 2014 there was noted a case of a young female patient obtained FMT from her obese daughter. Woman gained more than 25 kg despite lack of change in her lifestyle [13]. Modifications of diet and physical activity did not result in weight loss. Presented case is not unique in literature although that issue requires further researches.

COSTS

Potential cost of antibiotic treatment of diarrhea caused by Clostridium difficile infection in Europe was estimated for 3 billions euro in 2008, and it is predicted that this sum would double in 40 years [14]. In the simulation test in 2015 proved that FMT therapy is more than 2,5 times less expensive comparing to the standard vancomycin treatment of recurrent CDI [15].

ETHIC ASPECTS

The need of wider use of FMT method is signalized by many articles occurring in the Internet about "homemade" ways to perform graft of gut microbiome. Although "web tips" are not in accordance to guidelines or standardized protocols providing security of transplantation in contrast to the procedure completed in the in accredited health care facilities [14]. In 2018 made an analysis of information appearing in the popular services and social media about FMT method. Proved that 9 to 50 contents showing up in Google contained spurious information. Similar results obtained after analysis of matters coming from Facebook and Youtube - respectively 8% and 14% [16]. Cited data underline the role of education and increasing public awareness about Fecal Microbiota Transplantation.

OTHER USE

Currently FML is world-wide use to treat ulcerative colitis or irritable bowel syndrome. In the meta-analysis from 2016 titled "Fecal Microbiota Transplantation for Ulcerative Colitis: A Systematic Review and Meta-Analysis" comparing 25 different researches carried out on a total 234 people, patient's ratio with remission after FMT was 41,58% [17]. In the research "Can fecal microbiota transplantation cure irritable bowel syndrome?" obtained promising results about irritable bowel syndrome. 52,7% of patients, after gut microbiota transplantation, were cured or the symptoms have alleviated [18]. Nowadays multiple researches are conducted considering the application of FMT in the treatment of chosen neurological disturbances (e.g. multiple sclerosis, Parkinson's disease, autism or chronic fatigue syndrome) in which etiology seem to be connected with gut microbiota disorders [14].

CONCLUSIONS

Fecal microflora transplant may be successfully applied in treatment of CDI in case of patients who fail after treatment with metronidazole or vancomycin and patients with recurrent infections of *C. difficile*. Additionally, FMT is the method used in therapy of ulcerative colitis and irritable bowel syndrome.

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