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PREVALENCE OF *SUTTERELLA WADSWORTHENSIS* IN THE FECAL MICROBIOTA OF OBESE CHILDREN

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Abstract. *Sutterella wadsworthensis* are Gram-negative, non-spore-forming, bile-resistant, microaerophilic bacteria. IgA-specific serine endopeptidase is among one of the crucial biochemical traits of *S. wadsworthensis.* In scientific publications, *Sutterella* spp. has been linked to ulcerative colitis, autism spectrum disorder, and obesity in children. Moreover, after analyzing various clinical complications in obese patients, it was found that Sutterella spp. influences an increase in insulin resistance, which subsequently leads to the development of type 2 diabetes. Here, the fecal microbiome from 156 patients in the pediatric department was analyzed, of which 23 children comprised control group, 23 children — with obesity lacking concomitant pathology, 110 children — with obesity and concomitant pathology. The study was aimed at determining a correlation between microorganism *S. wadsworthensis* and types of obesity in children as well as its role in developing this pathology. As a result, a direct relationship was revealed between the isolated bacillus and obesity without concomitant pathology in girls vs boys aged 14 to 17 years, and data were also obtained that *S. wadsworthensis* was isolated significantly more often. In addition, it was decided to analyze microorganisms associated with *S. wadsworthensis* in order to identify microbiome members characteristic of obese people. Statistical processing revealed a marked significant positive correlation with the isolation of *Streptococcus* spp., *S. anginosus*, *C. perfringens*, *S. aureus* and *W. confusa*. In addition, the ability of *S. wadsworthensis* to reduce the functionality of the intestinal antibacterial immune response due to the enzyme IgA-specific serine endopeptidase can lead to developing inflammation and penetration of various pathobionts into enterocytes. Thus, our and others study results indicate the controversial importance and a need to further investigate *S. wadsworthensis* both in obesity and other gastrointestinal diseases.

Key words: *Sutterella wadsworthensis, children, obesity, fecal microbiota, inflammatory bowel disease, anaerobes.*

РАСПРОСТРАНЕННОСТЬ *SUTTERELLA WADSWORTHENSIS* В ФЕКАЛЬНОЙ МИКРОБИОТЕ ДЕТЕЙ С ОЖИРЕНИЕМ

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Резюме. *Sutterella wadsworthensis* является грамотрицательной, неспорообразующей, желчеустойчивой, микроаэрофильной бактерией. Одним из важнейших биохимических свойств *S. wadsworthensis* является наличие фермента IgA-специфической сериновой эндопептидазы. В научной литературе *Sutterella* spp. связывают с язвенным колитом, расстройством аутистического спектра и ожирением у детей. Более того, проанализировав

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различные клинические осложнения у пациентов с ожирением, было установлено, что *Sutterella* spp. влияет на увеличение резистентности к инсулину, что впоследствии ведет к развитию сахарного диабета 2 типа. В данном исследовании был проанализирован фекальный микробиом 156 пациентов педиатрического отделения, из которых 23 ребенка составляют контрольную группу, 23 — группу с ожирением без сопутствующей патологии, 110 детей с ожирением и сопутствующей патологией. Целью исследования было определить корреляцию микроорганизма *S. wadsworthensis* с типами ожирения у детей и его роль в развитии данного заболевания. В результате выявлена прямая взаимосвязь между выделенной палочкой и ожирением без сопутствующей патологии у девочек в возрасте от 14 до 17 лет, также получены данные о том, что *S. wadsworthensis* достоверно чаще высевалась у мальчиков. Кроме того, было решено провести анализ микроорганизмов, ассоциированных с *S. wadsworthensis*, с целью выявления представителей микробиома, характерных для людей с ожирением. При статистической обработке найдена достоверно значимая положительная корреляция с выделением *Streptococcus* spp., *S. anginosus*, *C. perfringens*, *S. aureus* и *W. confusa*. К тому же способность *S. wadsworthensis* снижать функциональность кишечного антибактериального иммунного ответа за счет фермента IgA-специфической сериновой эндопептидазы может приводить к развитию воспаления и проникновению к энтероцитам различных патобионтов. Таким образом, итоги нашего и других исследований в научном сообществе говорят о противоречивом значении и необходимости дальнейшего изучения *S. wadsworthensis* как в контексте ожирения, так и других заболеваний желудочно-кишечного тракта.

Ключевые слова: *Sutterella wadsworthensis, дети, ожирение, фекальная микробиота, воспалительные заболевания кишечника, анаэробы.*

Suturella wadsworthensis belongs to the *Sutterella* spp., family *Sutterellaceae*, order *Burkholderiales*, class *Betaproteobacteria*. Microorganisms of this species are gram-negative, non-spore-forming, bile-resistant, microaerophilic bacteria. They have two main forms: bacilli and coccobacilli. Spiral and filamentous morphotypes are also found [4].

Chocolate or brucella agars are used for cultivation of *Sutterella* spp. Incubation requires anaerobic or microaerophilic conditions and 48–72 hours of time [7]. *Sutterella* spp. are not saccharolytic. They show negative results for catalase, urease and oxidase, and are also capable of reducing nitrates to nitrites. These bacteria have enzymes such as esterase, L-arginine-arylamidase and L-aspartate-arylamidase [4, 7].

S. wadsworthensis is able to attach to mucus and proteins of extracellular matrix, such as laminin, type 1 collagen, fibronectin. Such adhesion factors, along with resistance to the bile acids, determine their localization in the duodenum and bile ducts [1]. According to this fact, the preferred material for collection in order to detect *S. wadsworthensis* will be a biopsy material of the mucous membrane, rather than feces samples.

One of the most important biochemical properties of *S. wadsworthensis* is the presence of the enzyme called IgA-specific serine endopeptidase [2]. The main function of IgA is to protect the epithelial cells of the mucous membranes from the pathogenic microorganisms by hindering adhesion, so its destruction can lead to infection of epithelial cells. In 2015 a study was published, in which the authors observed a low level of IgA in animals with a high content of *Sutterella* spp., and a high level of IgA in animals with a low content of *Sutterella* spp. It was also found in that research that the ability of bacteria to destroy IgA components leads to an increase in intestines ulceration in animals with the injection of sodium dextran sulfate [3].

A study of the microbiota in patients with ulcerative colitis, published in 2020, revealed the influence of *S. wadsworthensis* on the development of this disease. According to its results, patients with a high content of *Sutterella* spp., who underwent fecal microbiota transplantation, did not have endoscopic remission, while patients with low content of these microorganisms achieved it without taking corticosteroids [2]. In addition, *Sutterella* spp. is found in the material of patients with appendicitis and peritonitis. At the same time, in 2018, a study of patients with Crohn's disease showed a small biodiversity of the intestinal microbiota and a reduced number of *Sutterella* spp. [6]. There is a connection between *Sutterella* spp. and autism spectrum disorder (ASD). In a study, conducted in 2012, an analysis using a protein immunoblot revealed the reactivity of IgG or IgM to *Sutterella* spp. antigens in 11 patients with ASD, while in the control group only one individual had weak IgG reactivity. Despite the fact that already in 2013 the assumption about the specificity of these microorganisms for children with ASD was refuted, the question of immunoreactivity in patients with this disorder requires further study [8].

In July 2023 an article was published, in which the authors established a direct connection between *Sutterella* spp. and obesity in pediatric patients, as well as an inverse connection in adult patients. Moreover, after analyzing various clinical complications in patients with obesity, the effect of *Sutterella* spp. was claimed to increase insulin resistance, which subsequently leads to the emergence of type 2 diabetes mellitus. The effect of the microbiome on insulin resistance was also confirmed after transplantation of fecal microbiota from lean donors to patients with metabolic syndrome. Transplantation caused

an increase in the sensitivity of cells to insulin, as well as an increase in the diversity of various taxa of microorganisms [5].

All of the above data indicate the contradictory role of *S. wadsworthensis* in the pathogenesis of various human diseases, therefore further studies in this direction are required.

The purpose of this work is to analyze the frequency of *S. wadsworthensis* in children with various types of obesity, as well as to find an answer whether *Sutterella* spp. is an etiological factor in the development of this pathology or is a part of the normal human microbiome.

Materials and methods

The study involved 156 children, aged from 7 to 17 years. 23 children were included in the control group, 23 children — in the group with obesity without concomitant pathology, and 110 children — in the group with obesity and concomitant pathology. 63 (40.4%) of included individuals were girls and 93 (59.6%) were boys.

To analyze the species diversity of the intestinal microbiota in children, 156 feces samples were seeded on 7 different nutrient media: Rogosa SL Agar (HiMedia, India), Urinary Tract Infections Chromogenic Agar (CondaLab, Spain), Bifidobacterium Agar (HiMedia, India), Clostridial Agar (HiMedia, India), Anaerobic Agar (HiMedia, India), Brucella Agar (HiMedia, India) with the addition of 10% mutton blood, Veillonella Agar (HiMedia, India). Cultivation was carried out using the "BACTRON 300-2" anaerobic station (Sheldon, USA) during 7 days. Identification of cultivated microorganisms was performed using a MALDI-ToF mass-spectrometer (Bruker, Germany).

Statistical analysis was carried out using the Stat Tech v. 3.1.8 program (Stattech LLC, Russia). Quantitative indicators were evaluated for compliance with the normal distribution using the Shapiro–Wilk criterion (with the number of subjects less than 50) or the Kolmogorov–Smirnov criterion (with the number of subjects more than 50). Quantitative data were described using median (Me) and lower and upper quartiles (Q_1–Q_3) in the absence of a normal distribution. Categorical data were described with absolute values and percentages. The percentages in the analysis of four-field conjugacy tables were compared using Pearson's chi-squared criterion (with values of the expected phenomenon greater than 10) and Fisher's exact criterion (with values of the expected phenomenon less than 10).

Results and discussion

According to the results of the intestinal microbiota analysis, *S. wadsworthensis* was detected in 18 (11.5%) children out of 156. In the control group, this microorganism was isolated in 2 (8.7%) cases, in group of children with obesity without concomitant pathology in 3 (13%) cases, and in children with obesity and with concomitant pathology in 13 (11.8%) cases.

Having divided all the examined children by gender and age (7–9 years old; 10–13 years old; 14–17 years old) we analyzed the results of the study for reliable correlations with the isolation of *S. wadsworthensis*. Statistical processing showed that *S. wadsworthensis* was significantly more often isolated from boys ($p = 0.029$). In addition, a direct connection was found between the isolation of microorganism and obesity without concomitant pathology in girls aged from 14 to 17 years ($p = 0.006$). However, further analysis of the correlation between the phenotype of the examined children and the isolation of *S. wadsworthensis* showed no significant results in any age group.

Considering the fact that in the scientific community obesity is assumed to correlate with various representatives of the intestinal microbiota, it was decided to conduct a statistical analysis to find out associations of *S. wadsworthensis* with other microorganisms. In general, *S. wadsworthensis* was isolated in samples along with such bacteria as *Clostridium perfringens*, *Clostridioides difficile*, *Clostridium ramosum*, *Clostridium innocuum*, *Bacteroides fragilis*, *Bacteroides ovatus*, *Parabacteroides distasonis*, *Staphylococcus aureus*, *Streptococcus gallolyticus*, *Streptococcus anginosus*, *Streptococcus mutans*, *Streptococcus agalactiae*, *Streptococcus constellatus*, *Candida albicans*, *Weissella confusa* and less often along with other microorganisms. During statistical processing, a significant positive correlation with the *Streptococcus* spp. was found ($p = 0.036$). In addition, a significant connection with *S. anginosus* was found ($p = 0.018$), the isolation of which was also positively correlated with *S. wadsworthensis*. A statistically significant positive correlation was also found for such microorganisms as *C. perfringens* ($p = 0.006$), *S. aureus* ($p = 0.003$) and *W. confusa* ($p = 0.035$).

A large number of data that have appeared in the scientific community claim ambiguous facts about the participation of *S. wadsworthensis* in various pathologies. In this study, we tried to find a reliable correlation of this microorganism with obesity in children, as well as to determine its possible role in the development of the disease. Statistical processing of our results showed that *S. wadsworthensis* was found mainly in boys. However, unlike the study in 2023, we were unable to find a statistically significant connection with obesity and concomitant diseases in the entire group of examined children. Nevertheless, after dividing the children into age groups, the results showed a reliable association of *S. wadsworthensis* with obesity without concomitant pathology in girls aged from 14 to 17 years. Although the statistical search for further correlations in children of other age groups did not reveal any significant connections, in our opinion, it is impossible to claim unequivocally whether

S. wadsworthensis is not an etiological factor involved in the development of obesity in children. In addition, it is important to consider the ability of *Sutterella* spp. to reduce the functionality of the intestinal antibacterial immune response. Due to disruption of the barrier function provided by IgA, *S. wadsworthensis* contributes to the emergence of inflammation, providing the penetration of various pathogens to enterocytes, such as, for example, *C. perfringens*, *S. aureus* and *S. anginosus*. These bacteria in our study were statistically associated with the isolation of *S. wadsworthensis*. Overall, the results of the accumulated scientific data, as well as the results of our study, indicate the requirement for further study of *S. wadsworthensis* both in the context of obesity and other diseases of the gastrointestinal tract.

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