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UNDERSTANDING THE LINK BETWEEN EARLY ANTIBIOTIC EXPOSURE AND NEURODEVELOPMENTAL DISORDERS: IMPLICATIONS FOR MEDICAL AND PHARMACEUTICAL EDUCATION

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The gut microbiota has emerged as a crucial determinant of neurodevelopmental processes. Early colonization of the gastrointestinal tract is essential for immune system maturation, metabolic regulation, and the establishment of the gut–brain axis, which collectively influence cognitive and behavioral outcomes. An increasing body of evidence demonstrates strong associations between gut microbial composition and neurodevelopmental disorders such as autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD). Experimental studies suggest that microbiota alterations can modulate stress responses and social behavior, even when microbial balance is later restored. Human epidemiological research indicates that early antibiotic exposure can disrupt gut microbial diversity, thereby heightening susceptibility to neuropsychiatric conditions. Preventive use of probiotics during infancy has shown potential in reducing later-life risks of such disorders. A large Swedish cohort study revealed that both prenatal and early-life antibiotic exposure are associated with increased odds of ASD and ADHD. Additional evidence supports the link between antibiotic administration and impaired cognitive performance, executive functioning, and language development. Microbiota-based interventions, including probiotic supplementation and fecal microbiota transplantation, have demonstrated improvements in gastrointestinal and behavioral symptoms in children with ASD. Furthermore, environmental exposures – such as to triclosan – may contribute to adverse neurodevelopmental outcomes. These findings underscore the role of early microbial modulation as a potential preventive or therapeutic strategy for neurodevelopmental disorders. From an educational standpoint, integrating microbiome science into medical and pharmaceutical curricula could enhance professionals' understanding of the gut–brain connection and foster evidence-based approaches to early-life health interventions. Future interdisciplinary research is required to clarify causal mechanisms, optimize microbiota-targeted therapies, and evaluate their long-term effectiveness.

Key words: antibiotics, attention-deficit/hyperactivity disorder, autism spectrum disorder, gut microbiota, neurodevelopment, probiotics, medical education.

Чала Єлизавета, Адамчук-Чала Надія. Розуміння зв'язку між раннім впливом антибіотиків і нейророзвитковими розладами: наслідки для медичної та фармацевтичної освіти

Мікробіота кишечника дедалі більше визнається важливим чинником, що впливає на формування та функціонування нервової системи. Раннє заселення шлунково-кишкового тракту мікроорганізмами відіграє ключову роль у розвитку імунних і метаболічних процесів, які визначають когнітивні та поведінкові результати в подальшому житті. Низка сучасних досліджень виявила тісний зв'язок між складом кишкової мікробіоти та виникненням нейророзвиткових розладів, зокрема розладу спектра аутизму (РАС) і синдрому дефіциту уваги з гіперактивністю (СДУГ). Експериментальні моделі показують, що зміни у складі мікробіоти можуть впливати на реакції на стрес і поведінку навіть після її відновлення. Дані клінічних досліджень свідчать, що ранній вплив антибіотиків може порушувати баланс мікробіоти кишечника, підвищуючи ризик розвитку нейропсихіатричних розладів. Профілактичне застосування пробіотиків у ранньому віці демонструє потенціал у зниженні ризику розвитку таких порушень у майбутньому. Зокрема, когортне дослідження у Швеції встановило, що як пренатальний, так і післяпологовий вплив антибіотиків асоціюється з підвищеними шансами розвитку РАС і СДУГ. Інші наукові дані вказують на зв'язок між використанням антибіотиків і зниженням когнітивних функцій, виконавчих здібностей і мовленнєвого розвитку у дітей. Доведено, що терапії, спрямовані на мікробіоту кишечника, зокрема пробіотики та трансплантація фекальної мікробіоти, можуть покращувати як шлунково-кишкові симптоми, так і поведінкові показники у дітей із РАС. Крім того, екологічні чинники, як-от вплив триклозану, також можуть відігравати роль

у зміні нейророзвиткових процесів. Ці результати вказують на перспективність ранньої модуляції мікробіоти як підходу до профілактики або лікування нейророзвиткових розладів. Подальші дослідження мають визначити причинно-наслідкові зв'язки та довготривалу ефективність терапій, орієнтованих на мікробіоту. У контексті медичної та фармацевтичної освіти важливо формувати у майбутніх фахівців розуміння взаємозв'язку між мікробіомом, фармакологічними впливами та психонейрологічним здоров'ям людини, що сприятиме розвитку превентивних стратегій у клінічній практиці.

Ключові слова: антибіотики, синдром дефіциту уваги з гіперактивністю, розлад спектра аутизму, мікробіота кишечника, нейророзвиток, пробіотики, освітні підходи.

Introduction. The gut microbiota as a potential regulator of neurodevelopment has been a highly relevant subject of research in recent decades in the fields of biomedicine, immunology and nutrition. The formation of the gut microbiota in the immediate postnatal period has a decisive impact on the development and functioning of many immune and metabolic systems, which is an integral part of the health and well-being of living organisms 1, 2, 3, 4. Recent studies revealed a link between the gut microbiome and autism spectrum disorder (ASD), which was validated in a mouse model of ASD where the microbiome was mechanistically linked to abnormal metabolites and behavior 5. How the presence of intestinal microbiota regulates the activity of the Hypothalamic-Pituitary-Adrenal (HPA) system is shown in the article 6. The authors experiments on rodents provide convincing evidence that the microorganisms inhabiting the gut affect neurodevelopment. The researchers aimed to find out whether there are other changes in brain function, such as behavioral changes in germ-free (GF) mice, and if so, to compare them with the behavior of mice with a normal gut microbiota. They also noted the effect of reducing anxiety-like behavior in the Elevated Plus Maze (EPM) in adult GF mice compared to traditionally raised specific pathogen-free (SPF) mice. They also presented data collected when adult GF mice were subsequently colonized with SPF feces, thereby reintroducing normal gut microbiota, and then re-evaluated for anxiety-like behavior. Interestingly, the anxiolytic behavioral phenotype observed in GF mice was preserved after colonization with the SPF gut microbiota. These data show that gut-brain interactions are important for the development of central nervous system (CNS) stress responses and that there may be a critical period after which microbiota and immune system recovery does not normalize the behavioral phenotype. Early work in transferring animal data to the clinic was initiated by studies 7, that demonstrated the link between gut microbiota and cognitive processes in infants. The first years of human life are a dynamic time of gut colonization and brain development, but our knowledge of the relationship between these two processes is still fragmented. In particular, it is known that experimental manipulations that alter the gut microbiota affect learning, communicative behavior, and cognitive abilities. In study 7, the authors tested whether microbial composition at age 1 was associated with cognitive outcomes using the Mullen Early Learning Scale, as well as with global and regional brain volumes using structural magnetic resonance imaging at ages 1 and 2. Fecal samples were collected from 89 normally developing 1-year-old children. The sequencing of 16S ribosomal RNA amplicons was used to identify and quantify bacterial taxa. Based on the results of the cluster analysis, 3 groups of infants were identified that differed in bacterial composition. Scores on the Mullen scale at the age of 2 years differed significantly between clusters. In addition, higher alpha diversity was associated with lower scores on the Total Comprehensive Assessment, Visual Reception Scale, and Expressive Language Scale at age 2. Previous analyses of neuroimaging data suggest that the gut microbiome has minimal impact on regional brain volumes at 1 and 2 years of age.

Antibiotics are often prescribed to infants. In addition to the growing concern about antibiotic resistance, there is also a concern about the potential negative impact of antibiotics on gut microbiota and health and developmental outcomes. Following this line of research, a study was conducted to examine antibiotic exposure in the first 24 months of life and neurocognitive outcomes at age 11 years 8. The authors wanted to determine the relationship between early antibiotic exposure and later neurocognitive outcomes. Participants were infants born to mothers who had participated in a probiotic study. The original study was designed to evaluate the effects of two different probiotics on allergy outcomes in childhood. Antibiotic exposure was based onparental reports and was categorized according to the following time of first exposure: 0–6 months, 6–12 months, 12–24 months, or none at all. At age 11 years, childrens neurocognitive outcomes were assessed using a psychological interview, parental questionnaire, and self-assessment. The association between the time of antibiotic exposure and neurocognitive outcomes was investigated using regression models. Among the 474 participants who

were initially enrolled in the study, 342 (72%) children passed the neurocognitive assessment at the age of 11 years. According to the findings, after adjusting for mode of delivery, probiotic therapy group assignment, income, and breastfeeding, children who received antibiotics in the first 6 months of life had significantly lower overall cognitive ability and verbal comprehension, and an increased risk of problems with metacognition, executive function, impulsivity, hyperactivity, attention deficit hyperactivity disorder (ADHD), anxiety, and emotional problems. It is well known that antibiotic therapy affects the gastrointestinal (GI) microbiome, and antibiotic use may also play a role .linked to neurodevelopmental disorders such as autism spectrum disorder (ASD) and attention-deficit/ hyperactivity disorder (ADHD) in the etiology of autism and ADHD. Current experimental evidence suggests that the gut microbiota can alter the functions of the nervous system, which provides new insights into the mechanism of neuropsychiatric disorders [1, 2, 3]. This problem has become particularly relevant because antibiotics are the most common type of medication used during pregnancy and childhood. However, the results of studies on the link between antibiotic exposure and ADHD have been controversial 9, 2, 3. A population-based retrospective cohort study was conducted 9. To collect data on children, the National Health Insurance Research Database of Taiwan was used. The prevalence of antibiotic use in children (age 2 years) included in this study was analyzed. There were 1,601,689 children enrolled in this study between 2004 and 2012. The risk of developing ADHD was assessed using the Cox proportional hazards model. 71.25% of children took at least one antibiotic, and the average follow-up period was 7.07 years. After controlling for other comorbidities, children who took antibiotics had a 1.12 times higher risk of developing ADHD than those who did not take antibiotics. The risk of ADHD was increased by penicillin and cephalosporin, regardless of the duration of antibiotic use. A Swedish population-based cohort study was also conducted 2, which identified the impact of antibiotics during pregnancy and early life and the risk of autism and attention deficit hyperactivity disorder in childhood. Participants in this population-based cohort study from Sweden included all first live singleton births (N = 483,459) between January 2006 and December 2016. The association between antibiotic use and autism and ADHD in children aged ≤ 11 years was assessed using multivariable logistic regression models and generalized estimating equations (GEE). Among mothers, 25.9% (n = 125,106) received ≥1 antibiotic during the exposure period (3 months before conception to delivery), and 41.6% (n = 201,040) of children received ≥1 antibiotic in early life (aged ≤ 2 years). Penicillin was the most common class of antibiotics (17.9% of mothers, and 38.2% of children). Maternal antibiotic use was associated with an increased risk of autism [odds ratio (OR) = 1.16, 95% confidence interval (CI) 1.09-1.23] and ADHD (OR = 1.29, 95% CI 1.21-1.36) in childhood. Exposure to antibiotics in early life showed an even stronger association [autism (OR = 1.46, 95% CI 1.38-1.55); ADHD (OR = 1.90, 95% CI 1.80-2.00)]. Sub-analyses of both maternal and child exposure indicate a dose-response relationship. Seventy-five infants were studied, randomized to receive Lactobacillus rhamnosus GG (ATCC 53103) or placebo during the first 6 months of life and then followed for 13 years. The gut microbiota of the study children was assessed at 3 weeks, 3, 6, 12, 18, 24 months, and 13 years of age by fluorescein in situ hybridization (FISH) and qPCR, and indirectly by blood group secretor type at 13 years of age. The diagnoses of ADHD and Asperger's syndrome (AS) were made by a pediatric neurologist or psychiatrist based on ICD-10 diagnostic criteria. At the age of 13 years, 6/35 (17.1%) children in the placebo group were diagnosed with ADHD or ASD, and none in the probiotic group (p-value = 0.008). The mean (S.D.) number of Bifidobacterium bacteria in feces during the first 6 months of life was lower in sick children (8.26 (1.24) log cells/g) than in healthy children (9.12 (0.64) log cells/g); p = 0.03. Researchers proved that the use of antibiotics during pregnancy and early childhood is associated with an increased risk of developing autism and ADHD in childhood. Differences were noted, however, depending on the period of exposure and classes of antibiotics. The above-mentioned studies evidenced a link between the use of antibiotics during pregnancy and early childhood, as well as autism and ADHD in childhood. The findings indicated that antibiotic use during pregnancy may be associated with an increased risk of ADHD in children. However, there was insufficient evidence of a link between antibiotic use after birth and ADHD risk. Further studies using more valid methods were required before a conclusion could be drawn over a long period. A more in-depth study of the effects of antibiotics and the onset of attention- deficit/hyperactivity disorder in children was conducted in study 3 , using a systematic approach and meta-analysis. On January 1, 2021, the authors searched several databases (PubMed, APA PsycINFO, EMBASE) to identify relevant studies. A random effects model was used to calculate the

pooled risk score. Statistical heterogeneity was tested using the chi-square test and the I2 statistic. Four risk estimates of antibiotic use during pregnancy and eight risk estimates of antibiotic use after birth were made. The pooled odds ratio was for the ADHD score. The authors suggested that antibiotic exposure depended on the type of antibiotic and the number of antibiotic doses, which in turn may influence the association between antibiotic exposure and ADHD. However, a systematic understanding of the etiology of Neurodevelopmental Disorders (NDD) and their association with other conditions in childhood and adolescence was not complete. More detailed analytical work is presented in a paper on the meta-analysis of genetic effects associated with neurodevelopmental disorders (NDD) and related conditions in children [10]. The researchers synthesized the literature on the contribution of genetic and environmental factors to the development of NDD, the intersection of genetic and environmental factors between different NDDs, and the combination of NDD with disruptive disorders, impulse control, and conduct disorders (DICC). The search was conducted on three platforms: Web of Science, Ovid Medline, and Ovid Embase. Studies were included only if 75% or more of the sample consisted of children and/or adolescents, and the etiology of NDD and DICC was determined using single-generation family designs or genomic methods. Studies in which participants were selected based on unrelated diagnoses or trauma were excluded. A multilevel random-effects meta-analysis of 296 independent studies involving more than four million (partially overlapping) individuals was performed. Thus, they found that all NCDs were significantly heritable (family-based heritability, 0.66 (s.e. = 0.03); SNP-based heritability, 0.19 (s.e. = 0.03)). The meta-analytic genetic correlations between the NDDs were moderate (large genetic correlation based on family heritability – 0.36 (s.e. = 0.12); large genetic correlation based on SNPs – 0.39 (s.e. = 0.19)) but differed significantly between pairs of disorders. Genetic overlap between NPD and DICD was strong (large family-based genetic correlation, 0.62 (s.e. = 0.20)). In general, microbiota transfer therapy changes the gut ecosystem and improves gastrointestinal symptoms. Some open studies have highlighted its impact on autism symptoms 5, 11 and related effects in humans 8, 12, 13, 14, 15. ASDs are complex neurobiological disorders that impair social interaction and communication and lead to restricted, repetitive, and stereotyped patterns of behavior, interests, and activities 5 . The causes of these disorders remain poorly understood, but the gut microbiota, the 1013 bacteria that live in the human gut, is thought to be involved, as children with ASD often suffer from gastrointestinal disorders that correlate with ASD severity. Several previous studies have reported abnormal gut bacteria in children with ASD. This small, open-label clinical trial evaluated the effect of microbiota transfer therapy (MTT) on gut microbiota composition and ASD symptoms in 18 children diagnosed with ASD. The MTT included 2-week antibiotic treatment, bowel cleansing, and then advanced fecal microbiota transplantation (FMT) using a high initial dose followed by daily dosing and smaller maintenance doses for 7-8 weeks. The Gastrointestinal Symptom Rating Scale revealed an approximately 80% reduction in gastrointestinal symptoms at the end of treatment, including significant improvement in symptoms of constipation, diarrhea, indigestion, and abdominal pain. The improvement was maintained 8 weeks after treatment. Similarly, clinical assessments showed that behavioral symptoms of ASD improved significantly and remained improved 8 weeks after treatment. Bacterial and phage sequencing analysis showed successful partial engraftment of the donor microbiota and positive changes in the intestinal environment. In particular, the total bacterial diversity and the number of Bifidobacterium, Prevotella, and Desulfovibrio among other taxa increased after MTT, and these changes persisted after treatment was discontinued (follow-up was conducted for 8 weeks). It is known that viral diseases in children are common and often treated with antibiotics. The age of first exposure to antibiotics and the consequences of neurological development in childhood are particularly important 12. The authors showed the ability of antibiotics to reduce the diversity and composition of the gut microbiota, which leads to a deterioration in the cognitive and behavioral development of children aged 4.5 years. The researchers controlled numerous risk factors, including otitis media. The study included 5589 children enrolled in the broadly generalized Growing Up in New Zealand cohort study with data on antibiotic exposure, antenatal maternal information, and behavioral and cognitive outcomes at 4.5 years of age. Children were classified as having been exposed to antibiotics for the first time according to the following mutually exclusive age categories: 0–2 months; 3–5 months; 6–8 months; 9–11 months; 12–54 months; or not exposed to antibiotics before 54 months. Developmental assessments included the Strengths and Difficulties Questionnaire, the Lurie Handclap Test, and the Peabody Picture Vocabulary Test-III. In a univariate analysis, a clear dose-response relationship was

found, where earlier exposure to antibiotics during the first year of life was associated with behavioral difficulties, lower executive function scores, and lower receptive language ability. After adjusting for confounding factors, pairwise comparisons showed that the first exposure to antibiotics between birth and 3 months or between 6 and 9 months was associated with lower receptive vocabulary. Exposure to antibiotics at any age before 12 months was associated with increased behavioral difficulty scores at 4.5 years of age. A systematic review 13 shows the impact of microbiome composition on impulsive and violent behavior. It shows the influence of microbiomes on brain function and human behavior. The authors focused on critical factors that influence the formation of microbiomes that can affect human health in later life, such as the method of delivery, early feeding, and early exposure to antibiotics. They searched PubMed, Web of Science, and the Cochrane Library, and included original human studies that examined adults and children with impulsive and/or aggressive behavior, assessed the composition of the participants' gut microbiota, delivery method, infant feeding regimen, or early exposure to antibiotics. The bibliographic search yielded 429 articles, of which 21 met the eligibility criteria. Two studies presented data on patients with schizophrenia with aggressive behavior, and 19 studies presented data on patients with ADHD. The results showed that several bacterial taxa are associated with ADHD symptoms and aggressive behavior in patients with schizophrenia. No association was found between the method of delivery and impulsive behavior, and no article was found linking the way babies are fed to aggressive behavior. A large-scale study conducted in China 14 (reported exposure to triclosan from everyday antimicrobials in early life with the effect of increasing the potential risk of developing autism spectrum disorders. Maternal exposure to triclosan (TCS) significantly increases autistic behavior in rats, possibly due to disruption of retinoic acid neuronal signaling. Although environmental endocrine disruptors (EDs) have been linked to autism in humans, little attention has been paid to the link between TCS, one of the EDs found in commonly used antibacterial care products, and autism. A total of 1345 children with ASD and 1183 children with typical development (TD) from 13 cities in China were registered. Childrens ages ranged from 2 to 7 years. A questionnaire was used to investigate maternal use of antibacterial products of daily use (APDU) during pregnancy. The main symptoms of ASD were assessed using the Autism Behavior Checklist (ABC), Childhood Autism Rating Scale (CARS), Social Response Scale (SRS), and the Child Neurobehavioral Scale-Revised 2016 (CNBS-R2016). The concentration of TCS was measured by LC-MS/MS. Maternal TCS during pregnancy can be an unrecognized potential environmental risk factor for ASD (OR = 1.267, p-value = 0.023). Maternal use of antibacterial daily necessities (UADN) TCS levels during pregnancy were strongly correlated with TCS levels in offspring (adjusted β = 0.277, p-value = 0.001). TCS concentrations were higher in children with ASD (p-value = 0.005) and positively correlated with ABC scale scores (sensory subscales: p-value = 0.03; social self-help subscales: p-value = 0.011) and SRS scale (social awareness subscales: p-value = 0.045; social communication subscales: p-value = 0.001; autism behavioral subscales: p-value = 0.006; total SRS score: p-value = 0.003) in children with ASD. This relationship was more significant in boys than in girls. Another systematic review 15 proved the effect of gut microbe-based treatment on gut microbiota, behavioral symptoms, and gastrointestinal symptoms in children with autism spectrum disorders. Many studies have identified some abnormalities in gastrointestinal (GI) physiology (e.g., increased intestinal permeability, generalized microbiota changes, and intestinal infection) in children with ASD. According to the authors, changes in the intestinal flora may be associated with the severity of GI and ASD symptoms. The current evidence from the Cochrane Library, EBSCO PsycARTICLES, PubMed, Web of Science, and Scope databases was analyzed until July 12, 2020. The analysis included experimental studies that used gut microbe-based treatments in children with ASD. Independent data extraction and quality assessment of the studies were conducted by PRISMA. As a result, 16 articles were selected, and found that some interventions (e.g., prebiotics, probiotics, vitamin A supplementation, antibiotics, and fecal microbiota transplantation) can alter the gut microbiota and improve behavioral and GI symptoms in patients with ASD.

Conclusions. Taking probiotics at an early age may reduce the risk of developing neuropsychiatric disorders in later childhood, possibly through mechanisms beyond the composition of the gut microbiota. Researchers have shown that taking probiotics at an early age can reduce the risk of developing neuropsychiatric disorders in later childhood, most likely through mechanisms beyond the gut microbiota. The use of antibiotics in children especially penicillin and cephalosporin has been associated with an increased risk of ADHD. Evidence is provided to inform and potentially guide clinical

and educational diagnostic procedures and practice. The imbalance in research efforts that characterizes developmental genetics research is highlighted. A research protocol for long-term treatment is presented as a promising approach to altering the gut microbiome and gut vermis and improving gut and behavioral symptoms of ASD. Improvements in GI symptoms, ASD symptoms, and microbiome were maintained for at least 8 weeks after treatment was completed, suggesting a long-term impact. Similarly, a study of children with ASD found that oral treatment with non-absorbable antibiotics improved GI and ASD symptoms, but only temporarily. After adjusting for socioeconomic factors and otitis media, there is evidence that antibiotic exposure during potentially sensitive developmental periods is associated with receptive language and behavior in later childhood. The potential involvement of microbiomes in the pathophysiology of impulsive and violent behavior in humans is considered. The gap in knowledge about the relationship between the gut microbiome and these extreme behaviors is filled. For the first time, a case-control study was performed to investigate the correlation between TCS and ASD. The results suggest that maternal UADN during pregnancy may be a potential risk for ASD in children. Further determination of TCS levels showed that maternal UADN during pregnancy may be associated with excessive TCS exposure. In addition, TCS levels in children with ASD are higher than in children with TD. Higher TCS levels in children with ASD may be significantly associated with more severe core symptoms, and this association was more significant in male children with ASD. The gut microbiota may become a new target for individuals with ASD in the future. It is suggested that interventions on the gastrointestinal tract and behavioral symptoms in patients with ASD can be effective. The findings support the implication of microbiota alterations in psychiatric diseases, and fecal bacteria may be a potential new marker of gut microbiota in ADHD. Future research is needed to confirm these findings and to clarify the temporal and causal relationships between these variables.

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