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ORIGINAL ARTICLE

Investigation of Plasma TMAO Levels in Children and Adolescents with ADHD: A Cross-Sectional Study

DEHB Tanılı Çocuk ve Ergenlerde Plazma TMAO Seviyelerinin İncelenmesi: Kesitsel Bir Çalışma

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ABSTRACT

Introduction: Attention Deficit Hyperactivity Disorder (ADHD) is a common neurodevelopmental disorder in children and adolescents. Recent research has suggested a potential link between gut microbiota-derived metabolites, such as Trimethylamine N-oxide (TMAO), and neuropsychiatric disorders. This study aims to investigate plasma TMAO levels in children and adolescents with ADHD and explore the relationship between TMAO levels and the severity of ADHD symptoms.
Methods: This cross-sectional study included 96 participants aged 7 to 15 years, consisting of 50 patients diagnosed with ADHD and 46 healthy controls. Plasma TMAO levels were measured using the Enzyme-Linked Immunosorbent Assay (ELISA) method. ADHD symptom severity was assessed using the T-DSM-IV-TR scale.
Results: Plasma TMAO levels were significantly higher in the ADHD group compared to the control group (p=0.02). Additionally, a positive correlation was found between TMAO levels and the total T-DSM-IV-TR scores (p<0.001), indicating that higher TMAO levels are associated with more severe ADHD symptoms. No significant correlations were observed between TMAO levels and other subscale scores.
Conclusion: The findings suggest that elevated plasma TMAO levels in children and adolescents with ADHD may be indicative of the disorder's biochemical characteristics. Furthermore, TMAO could be linked to the severity of ADHD symptoms, highlighting its potential role in the pathophysiology of ADHD.

Keywords: ADHD, Trimethylamine N-oxide, gut microbiome, neurotoxicity, child and adolescent psychiatry

ÖZ

Giriş/Amaç: Dikkat Eksikliği ve Hiperaktivite Bozukluğu (DEHB), çocuklar ve ergenler arasında yaygın görülen bir nörogelişimsel bozukluktur. Son dönemlerde yapılan çalışmalar, bağırsak mikrobiyotasına bağlı metabolitler, özellikle Trimetilamin N-oksit (TMAO) ile nöropsikiyatrik bozukluklar arasında olası bir bağlantı olabileceğini öne sürmektedir. Bu çalışmanın amacı, DEHB tanısı alan çocuk ve ergenlerde plazma TMAO seviyelerini incelemek ve bu seviyeler ile DEHB semptom şiddeti arasındaki ilişkiyi değerlendirmektir.
Yöntemler: Bu kesitsel çalışmaya, yaşları 7 ile 15 arasında değişen toplam 96 kişi katılmıştır. Katılımcılar, 50 DEHB tanılı hasta ve 46 sağlıklı kontrol bireyinden oluşmaktadır. Plazma TMAO seviyeleri, Enzim Bağlı İmmünosorbent Analizi (ELISA) yöntemi ile ölçülmüştür. DEHB semptom şiddeti, T-DSM-IV-TR ölçeği kullanılarak değerlendirilmiştir.
Bulgular: DEHB grubunda plazma TMAO seviyeleri, kontrol grubuna kıyasla anlamlı derecede yüksek bulunmuştur (p=0.02). Ayrıca, TMAO seviyeleri ile toplam T-DSM-IV-TR puanları arasında pozitif bir korelasyon saptanmıştır (p<0.001), bu da daha yüksek TMAO seviyelerinin daha şiddetli DEHB semptomlarıyla ilişkili olduğunu göstermektedir. Ancak, TMAO seviyeleri ile diğer alt ölçek puanları arasında anlamlı bir ilişki bulunmamıştır.
Sonuçlar: Bu çalışma, DEHB tanılı çocuk ve ergenlerde yüksek plazma TMAO seviyelerinin, bozukluğun biyokimyasal bir özelliğini yansıtıyor olabileceğini göstermektedir. Ayrıca, TMAO seviyeleri ile DEHB semptom şiddeti arasındaki ilişki, TMAO'nun DEHB'nin patofizyolojisinde rol oynayabileceğini düşündürmektedir.

Anahtar Kelimeler: DEHB, Trimetilamin N-oksit, bağırsak mikrobiyomu, nörotoksisite, çocuk ve ergen psikiyatrisi.

Introduction

Attention Deficit Hyperactivity Disorder (ADHD) is a highly prevalent neurodevelopmental disorder that can affect 5-7% of children and adolescents worldwide (1). ADHD is characterized by developmentally inappropriate inattention, hyperactivity, and impulsivity (2). These symptoms are associated with dysfunctions in the dopaminergic neurotransmitter system and fronto-striatal brain functions. However, the exact pathogenesis of ADHD remains difficult to understand due to its complex and multifactorial nature (3-5). Recent studies suggest that alterations in the gut microbiome may contribute to the development of ADHD (6, 7). These studies hypothesize that the gut microbiota can produce neuroactive molecules such as gamma-aminobutyric acid (GABA), serotonin, dopamine, noradrenaline, acetylcholine, and histamine, which can influence the gut-brain axis network (8, 9). A study by Aarts et al. (2017) supports the hypothesis that gut microbiome-related dopamine dysregulation in individuals with ADHD may potentially contribute to the etiology of ADHD through the gut-brain axis (10). Similarly, Prehn-Kristensen et al. (2018) reported

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decreased alpha diversity of the microbiome in young patients with ADHD, suggesting promising potential for ADHD prevention and treatment interventions (5). However, Bundgaard-Nielsen et al. (2020) reported heterogeneous results regarding the relationship between the gut microbiome and ADHD, highlighting the uncertain nature of this relationship and the need for further research to better understand the role of the gut microbiome in ADHD (11).

Trimethylamine N-oxide (TMAO), a microbial-derived metabolite, is obtained through the digestion of dietary foods such as choline, phosphatidylcholine, and carnitine (12, 13). This process begins with the enzymatic activation of gut microbes, leading to the production of a compound called trimethylamine (TMA). Subsequently, TMA is oxidized in the liver by the enzyme flavin-containing monooxygenase, resulting in the formation of TMAO (14, 15). Recent studies have linked TMAO with cardiovascular diseases (CVD), chronic kidney disease, vascular cognitive impairment, and neurodevelopmental disorders (16, 17). A recent study on children with autism found that elevated plasma levels of TMAO were associated with autism. This finding suggests that TMAO could potentially serve as a biomarker for autism and assist in early intervention strategies for prevention (15).

The potential role of TMAO in the etiology of ADHD may be related to its ability to cross the blood-brain barrier (BBB) and lead to neuroinflammation (18-20). This neuroinflammation can compromise the integrity of the BBB, allowing harmful substances to enter the central nervous system and increasing the release of pro-inflammatory cytokines (TNF-α, IL-1β) (21, 22). Increased neuroinflammation and oxidative stress can exacerbate dysfunctions in the dopaminergic system, which plays a critical role in the pathophysiology of ADHD (23). This process can further worsen ADHD symptoms (inattention, hyperactivity, impulsivity) (24). Additionally, TMAO is thought to impair synaptic plasticity in the brain, negatively affecting cognitive functions and attention processes (25). These mechanisms suggest that TMAO could play a significant biochemical role in the etiology of ADHD and could be used as a potential biomarker.

The observed alterations in gut microbiota in individuals with ADHD, along with the reported associations between TMAO levels and autism, have played a pivotal role in shaping the rationale for this study. Accordingly, this study aims to quantify plasma TMAO levels in children and adolescents diagnosed with ADHD and to examine their potential correlation with ADHD symptom severity. Given the established links between gut microbiota and neuropsychiatric conditions, we hypothesize that plasma TMAO levels will be significantly elevated in individuals with ADHD compared to healthy controls. Furthermore, we propose that higher TMAO levels will be positively correlated with greater ADHD symptom severity, thereby suggesting a potential biochemical interplay between the gut microbiome and ADHD pathophysiology. By elucidating this relationship, the study seeks to advance our understanding of the neurobiological underpinnings of ADHD and contribute to future diagnostic and therapeutic strategies.

Materials and Methods

Subjects and Study Design

This cross-sectional study was conducted on children and adolescents aged 7-15 years. The study was carried out in two different groups. The first group consisted of children and adolescents who were first-time diagnosed with ADHD and presented to the Selçuk University Child and Adolescent Psychiatry Department Clinic as outpatients. The ADHD diagnosis was made by a specialist child and adolescent psychiatrist using the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version-Turkish Adaptation (K-SADS-PL-T) (26) and DSM-5 (27) diagnostic criteria. The second group consisted of healthy children and adolescents aged 7-15 years, who presented to the same clinic and were evaluated by a specialist child and adolescent psychiatrist as having no psychiatric disorders according to the K-SADS-PL-T and DSM-5 diagnostic criteria. Informed consent was obtained from the participants before joining the study, and sociodemographic information was collected using special forms. The severity of ADHD symptoms was measured using the Turgay DSM-IV-Based Screening and Assessment Scale for Disruptive Behavior Disorders in Children and Adolescents (T-DSM-IV-S). The study included 50 patients diagnosed with ADHD who presented to the clinic and 46 healthy individuals randomly selected from the control group. Exclusion criteria included intellectual disability, substance use disorder, other psychiatric disorders (e.g., depression, anxiety disorders), neurological disorders (e.g., epilepsy, brain tumors), chronic inflammatory diseases, cardiovascular diseases, diabetes, and kidney diseases. Ethical approval for this study was obtained from the Selçuk University Local Ethics Committee

(decision no: 2023/419, dated 12.09.2023).

Socio-Demographic Data Form

To analyze the socio-demographic characteristics of the participants, various questions were asked about variables such as age, gender, educational level, parental occupations, socioeconomic status, and family structure. These variables were collected to create a general profile of the participants and to better understand the context of the study. The data obtained were classified according to the hunger and poverty thresholds in Turkey for the year 2023. This classification was done to evaluate the socioeconomic status of the participants more objectively and to enhance the comparability of the study results with the general population. Socio-demographic data were collected for descriptive purposes but were not included in the statistical analyses.

Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version-Turkish Version (K-SADS-PL-T)

This is a semi-structured interview tool developed by Kaufman and colleagues (26). It was used to diagnose patients in the study group. After the patients and one of their parents were interviewed by the responsible assistant researcher, a diagnosis was made, followed by a clinical evaluation by the lead researcher. The Turkish validity and reliability study was conducted by Gökler and colleagues (28).

Turgay DSM-IV-Based Screening and Assessment Scale for Disruptive Behavior Disorders in Children and Adolescents (T-DSM-IV-S)

This scale was developed by Turgay and its Turkish validity and reliability study was conducted by Ercan and colleagues (29, 30). It is a screening tool for disruptive behavior disorders. To exceed the threshold score on this 41-item scale, at least 6 out of the 9 items querying inattention, at least 6 out of the 9 items querying hyperactivity/impulsivity, at least 4 out of the 8 items querying oppositional defiant disorder, and at least 3 out of the 15 items querying conduct disorder need to be scored as 2 or 3.

Blood Samples

Blood samples of 5 milliliters were collected from the antecubital vein of participants between 8:30 and 10:00 a.m. after overnight fasting. These blood samples were centrifuged at 3,000 rpm for 10 minutes after clotting was complete. The resulting serum was transferred to Eppendorf tubes and stored at -80°C. The plasma TMAO level in the blood samples was measured using the Enzyme-Linked Immunosorbent Assay (ELISA) method at the Medical Biochemistry Research Laboratory of Selçuk University Faculty of Medicine after 8 hours of fasting.

Statistical Analysis

The data were analyzed using the SPSS-22 statistical software package. The Chi-Square test was used to show differences between groups for categorical data. The Shapiro-Wilk and Kolmogorov-Smirnov tests were used to determine whether the data had a normal distribution. To compare measurements of a specific variable between two different groups, the Student's t-test was used for data with normal distribution, while the Mann-Whitney U test was used for data not showing a normal distribution. A significance level of $p<0.05$ was accepted. To prevent Type II errors that may arise from comparing multiple variables, covariates were determined, and a univariate ANCOVA analysis was conducted. The Spearman test was used for correlation analysis. A significance level of $p<0.05$ was accepted. Correlation results were shown using a Scatter Plot graph.

Results

There was no statistically significant difference in age, weight, height, and body mass index (BMI) values between individuals diagnosed with ADHD and the control group; both groups were similar in these demographic characteristics. However, T-DSM-IV-S scores were found to be significantly higher in the ADHD group compared to the control group ($p<0.001$). Additionally, a significant difference was found in plasma TMAO levels between individuals with ADHD and the control group ($p=0.02$). This result shows that plasma TMAO levels are higher in individuals with ADHD compared to the control group, suggesting that TMAO may be associated with ADHD (Table 1, Figure 1).

Table 1. Demographic and Clinical Characteristics of ADHD Patients and Healthy Controls

Variables	ADHD (n=50)	Control (n=46)	p Değeri	t/x²
Age	10.76 ± 1.95	10.34± 1.71	0.379	-1.09[a]
Weight (kg)	43.1 ± 11.9	42.3 ± 11.2	0.423	0.86[a]
Height (cm)	148.8 ± 10.84	146.76 ± 9.33	0.946	0.06[a]
BMI (kg/m²)	20.5± 4.94	19.4 ± 4.91	0.365	1.18[a]
Gender			0.066	3.378[b]
- Female	21 (%42.0)	28 (%60.9)		
- Male	29 (%58.0)	18 (%39.1)		
T-DSM-IV-S	54.48± 10.25	9.22± 4.05	<0.001	-27.3[a]
TMAO (ng/mL)	429.16±64.65	263.83±18.73	<0.02	-2.36[a]

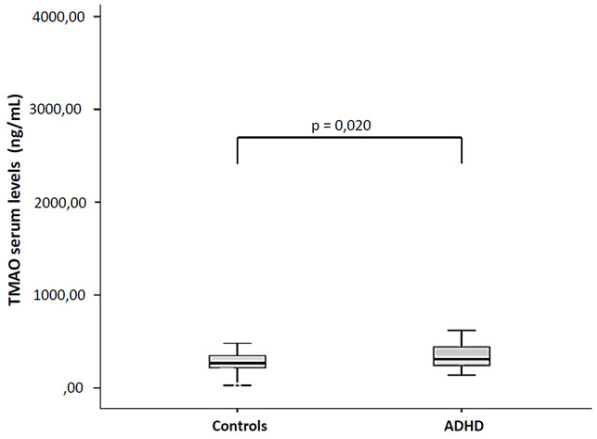

Figure 1. Serum TMAO Levels in ADHD Patients and Healthy Controls

To avoid Type II errors that may arise from multiple analyses, ANCOVA was conducted with age and BMI as covariates to compare serum TMAO levels. Serum TMAO levels were found to be significantly higher ($F(3,96) = 3.116$, $p = 0.03$, $\eta p^2 = 0.92$). The comparison of serum TMAO levels after controlling for age and BMI is presented in Table 2.

Table 2. Comparison of Serum TMAO Levels Between ADHD Patients and Healthy Controls According to ANCOVA

ANCOVA	ADHD n (50)		Control n (46)		F(3,96)	p	η_p^2
	Mean	SD	Mean	SD			
TMAO (ng/mL)	429.16	64.65	263.83	18.73	3.116	0.03	0.92

Spearman correlation coefficient was used in the correlation analysis conducted to determine the relationship between TMAO levels and the T-DSM-IV-S total score. According to the analysis results, a positive and statistically significant correlation was found between TMAO levels and the T-DSM-IV-S total score ($r=0.462$, $p<0.001$). (Figure 2.)

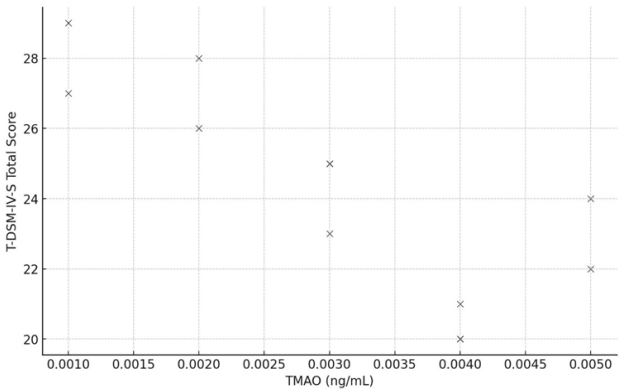

Figure 2. Scatter Plot Correlation Graph Between TMAO and T-DSM-IV-S Total Score

The scatter plot clearly illustrates the positive relationship between the two variables. This relationship indicates that as TMAO levels increase, the T-DSM-IV-S total score also increases. In the scatter plot created for the visual representation of the correlation, TMAO levels are shown on the x-axis (in ng/mL), and the T-DSM-IV-S total score is shown on the y-axis. Each point represents an individual participant's TMAO level and T-DSM-IV-S total score values.

Discussion

The aim of this study is to investigate the relationship between plasma TMAO levels and the severity of ADHD symptoms by comparing plasma TMAO levels in patients diagnosed with ADHD to those in a control group. It was found that plasma TMAO levels were significantly higher in children with ADHD compared to the control group, independent of age and BMI. Our study observed a positive correlation between plasma TMAO levels and T-DSM-IV-S total scores in children with ADHD. To our knowledge, this study is the first in the literature to evaluate plasma TMAO levels between individuals with ADHD and a control group. Our findings may represent an important step towards linking ADHD with biochemical changes. However, further research is necessary, and the clinical significance of these findings should be better understood.

The proposed link between ADHD and the gut microbiome is based on the interaction between the gastrointestinal system and the central nervous system (CNS). This interaction, commonly referred to as the "gut-brain axis," is now widely accepted (31). Components involved in this crucial axis include the autonomic nervous system (ANS), the vagus nerve, the enteric nervous system (ENS), the hypothalamic-pituitary axis (HPA), neurotransmitters, hormones, metabolites, and, of course, the gut microbiota (32). Recent research indicates changes in the gut microbiome of individuals with ADHD. For example, Jiang et al. analyzed the composition of the gut

microbiota in 51 adolescent patients with ADHD and 32 healthy controls from China, reporting a significant reduction in Faecalibacterium in patients with ADHD (33). In another study, Prehn-Kristensen et al. highlighted a decrease in alpha diversity of the gut microbiota in adolescent patients with ADHD and a negative correlation between ADHD symptom scores and alpha diversity (34). Considering that plasma TMAO levels are thought to reflect the gut microbiome, our study's findings of significant differences in plasma TMAO levels between patients and controls support the literature. This contributes to the understanding of the complex interaction between ADHD and the gut microbiome.

Plasma TMAO levels have been investigated in previous studies as an indicator of neurodegeneration in various diseases (13). A recent study examining the relationships between the gut microbiota and Alzheimer's disease (AD) suggested that the gut microbial metabolite TMAO is strongly correlated with AD (35). Another study on dementia patients by Vogt et al. (2018) showed high levels of TMAO in cerebrospinal fluid (CSF) (36). Additionally, Nguyen et al. (2021) explored altered functional pathways related to immune modulation and found changes in TMAO reductase and Kdo2-lipid A biosynthesis pathways in schizophrenia (37). These data further elaborate on the potential of TMAO to enhance neurodegeneration. Considering the neurodevelopmental differences observed in ADHD (38), it is hypothesized that the elevated TMAO levels observed in our study may trigger the manifestation of ADHD symptoms by promoting neurodegeneration. Further research is needed to understand the underlying mechanisms of this phenomenon.

ADHD is a disorder linked to imbalances in dopamine levels (39). Deficiencies in dopamine-rich regions, such as the prefrontal cortex and striatum, can contribute to ADHD symptoms (40). Dopamine also plays an important role in regulating the integrity and permeability of the gut mucosa. This regulation can lead to increased gut permeability and changes in interactions with the microbiota (41). Increased gut permeability due to dopamine can elevate the production of TMA, resulting in higher levels of TMAO (42). This complex relationship may offer new perspectives on the etiology and treatment of ADHD. Further research and clinical studies in this area could evaluate the potential of therapeutic interventions aimed at regulating dopamine levels for the treatment of ADHD.

Study Limitations

This study has several limitations. First, the dietary habits of the patients were not standardized. This may influence the results due to dietary differences between the patient and control groups. The lack of standardization of dietary habits is a common limitation in studies examining the gut-brain axis and ADHD relationship, which may limit the generalizability of the findings. Second, there are various confounding factors that could affect plasma TMAO levels, including infections, chronic inflammation, and cardiovascular variables. The presence of such confounding factors may prevent plasma TMAO levels from accurately reflecting CNS levels, thus reducing the accuracy of the findings. Third, the sample size is quite limited, and our study has a cross-sectional design. The small sample size reduces the generalizability of the findings and limits the power of statistical analyses. The cross-sectional design makes it difficult to determine causal relationships. Fourth, a more detailed analysis is needed to determine whether participants in the ADHD group have gut symptoms. The lack of evaluation of gut symptoms and probiotic use makes it challenging to fully elucidate the relationship between ADHD and the gut microbiome. Fifth, although socio-demographic data were collected, these data could not be effectively completed by the patient and control groups, and thus were not used in statistical analyses. The absence of socio-demographic data in statistical analyses may overlook the potential effects of these variables on ADHD and plasma TMAO levels, limiting the overall validity of the study. Excluding socio-demographic variables in analyses reduces the comparability of results across different demographic groups. Sixth, only a single molecule, TMAO, was measured in this study. To fully understand the complex biochemical and neurological mechanisms of ADHD, it is necessary to evaluate various biomarkers and molecules. The lack of assessment of the lipid profile and the absence of inquiries regarding smoking are significant limitations of the study. The exclusion of these factors may limit the scope and accuracy of the findings.

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Statement of Ethics

The study was approved by the Selçuk University Local

Ethics Committee and conducted in accordance with international ethical standards (approval no: E-70632468-050.01.04-587822). Permission was obtained from the participants with an informed consent form.

Conflict of Interest Statement

The authors have no conflict of interest to disclose.

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No financing used

Declaration of Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Authorship and Contributions

The conception of the study was led by A.G. The study design was developed by A.G. and S.T. Data collection and processing were carried out by S.T. and R.K. M.E.T. was responsible for data analysis and interpretation. The manuscript was written by A.G., while S.T. and R.K. conducted the critical review of the study.

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